Pre-pregnancy Obesity, Pre-existing Diabetes, and the Risks of Serious Adverse Fetal Outcomes

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DECLARATION

I declare that this Doctoral Statement is my own work. I have correctly acknowledged the work of others, in accordance with University and Institute guidance on good academic conduct. No part of the material offered has been previously submitted for a degree or other qualification in this or any other university. For joint works, my independent contributions have been outlined in the appropriate co-authorship forms.

SIGNATURE

DATE

27 June 2016

ABSTRACT

The epidemics of obesity and diabetes are two of the leading threats to health in the 21st century. Maternal obesity complicates a large and increasing minority of pregnancies, and pre-existing diabetes is one of the most common maternal chronic health complications of pregnancy. This Doctoral Statement presents a portfolio of six published articles that draw on the North of England's long-standing population-based registries of maternal and perinatal health to investigate the effects of pre-pregnancy obesity and diabetes on a range of serious adverse pregnancy outcomes.

The first two articles examined a cohort of pregnant women who delivered in five of the region's hospitals during 2003-2005 to explore the associations between maternal body mass index and the risks of, 1) congenital anomaly and 2) fetal and infant death. The next three examined a cohort of pregnant women with pre-existing diabetes who delivered during 1996-2008 to explore the effects of the condition on, 1) congenital anomaly, 2) birth weight, and 3) fetal and infant death. The final article examined women with pre-existing diabetes who had delivered two successive pregnancies to explore the influences of recurrent adverse pregnancy outcome. Maternal pre-pregnancy obesity and diabetes were both associated with increased risks of congenital anomaly, stillbirth, and infant death, with stronger effects for diabetes than obesity. In diabetes, peri-conception glycaemic control was strongly associated with birthweight and the risks of congenital anomaly, stillbirth, and infant death, and previous adverse outcome was associated with a doubled risk in the second pregnancy.

For each article I provide a contemporary analysis of its contribution to the literature and critique of the methodology. The wider relevance of the research is also considered by discussing the evidence for causality, potential mechanisms, and implications for public health. Finally, I reflect on my individual contributions and my development towards an independent epidemiologist.

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Section 2·3 **Tennant PWG**, Rankin J, Bell R. Maternal body mass index and the risk of fetal and infant death; a cohort study from the North of England. *Human Reproduction*, 2011; 26(6): 1501-1511. DOI: **10.1093/humrep/der052**

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Appendix B(iv) **Tennant PWG**, Glinianaia SV, Bilous RW, Rankin J, Bell R. Should women with diabetic nephropathy considering pregnancy continue ACE inhibitor or angiotensin II receptor blocker therapy until pregnancy is confirmed? Reply to Lewis G and Maxwell AP [letter]. *Diabetologia,* 2014; 57(5): 1084-5. DOI: **10.1007/s00125-014-3191-2**

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LIST OF ABBREVIATIONS

A1c	Glycated haemoglobin – *see also* HbA_{1c}
ADA	American Diabetes Association
aOR(s)	Adjusted odds ratio(s)
aSHR(s)	Adjusted sub-distribution hazard ratio(s)
ASD(s)	Atrial septal defect(s)
BINOCAR	British and Irish Network of Congenital Anomaly Registers
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CI(s)	Confidence interval(s)
CHD	Congenital heart disease
DCCT	Diabetes Control and Complications Trial
DHAP	Dihydroxyacetone phosphate
DH	(UK) Department of Health
DNA	Deoxyribose nucleic acid
EUROCAT	European Surveillance of Congenital Anomalies
FFA(s)	Free fatty acid(s)
FPG	Fasting plasma glucose
GADPH	Glyceraldehyde 3-phosphate dehydrogenase
GRADE	Grades of Recommendation, Assessment, Development and Evaluation
HbA_{1C}	Glycated haemoglobin – *see also A1c*
ICD(-10)	International statistical classification of diseases and related health problems (version 10)
ID	Indices of Deprivation – *see also IMD*
IDF	International Diabetes Federation

IMD	Index of Multiple Deprivation – *see also ID*
IQR	Interquartile range
LADA	Latent autoimmune diabetes of adults
LGA	Large for gestational age
LMP	Last menstrual period
LOWESS	Locally-weighted scatterplot smoothing
MeSH	Medical Subject Heading
MICE	Multivariate imputation by chained equations
MODY	Maturity onset diabetes of the young
NADPH	Nicotinamide adenine dinucleotide phosphate
NFE2L2	Nuclear factor (erythroid-derived 2)-like 2
NFκB	Nuclear factor κB
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIH	National Institutes for Health
NorCAS	Northern Congenital Abnormality Survey
NorDIP	Northern Diabetes in Pregnancy Survey
NTD(s)	Neural tube defect(s)
OGGT(s)	Oral glucose tolerance test(s)
ONS	(UK) Office for National Statistics
OR(s)	Odds ratio(s)
PARP	Poly((adenoside diphosphate)-ribose) polymerase
PHE	Public Health England
PMS	Perinatal Mortality Survey

PMMS	Perinatal Morbidity and Mortality Survey – *see also PMS*
PR(s)	Prevalence Ratio(s)
RAAS	Renin-angiotensin-aldosterone system
RCT(s)	Randomised Controlled Trial(s)
RMSO	Regional Maternity Survey Office
ROS	Reactive oxygen species
RR(s)	Relative risk(s)
SGA	Small for gestational age
SHR(s)	Sub-distribution hazard ratio(s)
TNF-α	Tumour necrosis factor α
USA	United States of America
UK	United Kingdom
VSD(s)	Ventricular septal defect(s)
WHO	World Health Organization

CHAPTER 1: INTRODUCTION

1·1 OVERVIEW

The following serves as the Doctoral Statement for my PhD by Published Works. The research uses epidemiological methods to explore and quantify the effects of maternal pre-pregnancy obesity and maternal pre-existing diabetes on the risks of serious adverse fetal outcomes, predominantly congenital anomalies, stillbirths, and infant deaths. The submission includes six peer-reviewed original articles, published between April 2010 and April 2015.

Chapter 1 (p1) serves as a comprehensive overview of the research setting. It introduces the exposures and the outcomes that lie at the heart of the research, before summarising the current state of knowledge concerning the risks of each serious adverse pregnancy outcome in pregnant women with obesity and diabetes specifically.

Chapter 2 (p36) details the six constituent articles that form the submission. For each, a brief overview is provided along with a summary of 'what was known' and 'what this study added'. The published versions of each article, along with any supplementary materials, are included directly in the submission, to minimise repetition and provide the most unbiased account of the research. An additional discussion is nevertheless provided to examine each paper in light of subsequent advances in the field.

Chapter 3 (p144) summarises the key narrative themes and overall contribution to the literature, the common methodological strengths and limitations, the biological implications, the implications for policy and practice, and the opportunities future research.

Finally, **Chapter 4** (p170) provides a personal account of my contributions to this programme of research and reflects on my growth and development over the course of the research portfolio.

1·2 EXPOSURES

1·2·1 The burden of non-communicable disease

Infectious diseases are humanity's primordial scourge, causing more deaths than any other influence throughout history.[12] For now however they are in decline.[13] Improvements in sanitation, nutrition, and hygiene, as well as the development of antimicrobial agents and vaccinations, have reduced transmission and transformed treatment.[13] Though the biggest benefits have been confined to high-income countries,[13] the world has nevertheless undergone a radical transition, with global life-expectancy now surpassing 70-years.[14] But with the declining burden of infectious disease, there has been a corresponding rise in the non-communicable diseases.[15]

Until recently considered '*diseases of the rich*',[16] the non-communicable diseases have traditionally attracted relatively little attention from the global health community,[17] despite accounting for 38 million deaths per year, or 68% of all-cause mortality.[18] Though partly compensatory – a numerical trade-off for lower infectious disease mortality – they are not an inevitable consequence of prolonged life.[19] On the contrary, comparisons with hunter-gatherer communities suggest that the non-communicable diseases, like the nutritional deficiencies before them, may reflect a simple evolutionary mismatch.[20] Humans are poorly suited to the 'Western' diet and lifestyle of sedentary living and abundant high-calorie but low-nutrient food.[21] Thus, as these exposures have spread, so too has the average human waistline, resulting not only in a dramatic rise in the prevalence of obesity,[22] but to an 'epidemic' of diabetes.[23]

1·2·2·1 Definition

The World Health Organization (WHO) describes obesity as a state of *'abnormal or excessive fat accumulation that may impair health*'.[24] This aptly reflects both the term's ambiguity and its historical nature. What was once abnormal is now commonplace,[25] and what counts as excessive, or even discernibly more harmful to health, is a matter of ongoing conjecture.[26]

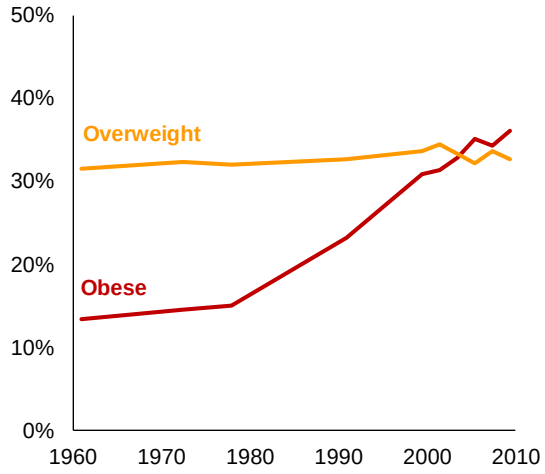
While obesity may be theoretically defined using a range of anthropometric measures, in practice it is almost always identified by body mass index (BMI), with both the WHO and National Institutes of Health (NIH) now agreeing on a diagnostic threshold of ≥30kg/m^2.[24,27] The ubiquity of BMI however is probably more a reflection of its simplicity - both in terms of measurement and calculation - than its accuracy for discriminating risk. In fact, BMI has a number of limitations (see **Section 3·2·4**, p148) that support perennial calls for its replacement.[28] Nevertheless, in a suitably large and varied sample, it correlates well with more direct measures of adiposity, making it a reasonable tool for population-based research.[29]

1·2·2·2 Prevalence

Obesity is the first and most obvious health consequence of the Western diet and lifestyle.[30] Increasing calorie consumption - particularly from refined carbohydrates and saturated fats - and decreasing levels of physical activity have led to greater and greater numbers exposed to the persistent energy excess that promotes fat storage and ultimately obesity.[31]

For the individual, obesogenesis is hence usually a gradual process, characterised by creeping but unrelenting weight gain.[31] In contrast, the growth in the global prevalence of obesity has been anything but gradual.[22] Rare for most of human history, obesity became considerably more commonplace during the 20th century, particularly in post-industrial settings.[32] It was not however until 1980, generally considered the start of the 'obesity epidemic', that the most dramatic growth began (**Figure 1**, p4).[33] In the 28 years between then and 2008, the global prevalence doubled from approximately 6% to 12%.[22] This surge is expected to continue, with estimates predicting a global prevalence of 20% by 2030.[34] Although mostly driven by increases among middle-income countries, such as Egypt and Mexico, growth is expected in all settings.[34]

Figure 1 Trends in overweight and obesity among adults (20–74 years) living in the United States of America during 1960–2010. Data from Fryar *et al* 2012.[35]



In the United Kingdom (UK), the increase has been particularly stark.[25] In 1980, the National Heights and Weights Survey estimated that 6% of men and 8% of women were obese.[36] Thirteen years later, at the start of the Health Survey for England, the prevalence had doubled (13% and 16% respectively).[37] Another twenty years and it had doubled again (26% and 24% respectively).[37] It is now markedly more common (67% and 57% for men and women respectively) to be either overweight (BMI: 25-30kg/m^2)[i] or obese than what was once termed 'normal' weight (now described as either 'healthy' or 'recommended', BMI: 18.5-25kg/m^2)[ii].[37] By 2050, some models anticipate that the majority of the UK adult population will be obese.[38] Though perhaps pessimistic, given the rate of increase has slowed since 2000,[37] it is fair to assume that obesity will remain obstinately prevalent for many years to come.

1·2·2·3 Risk factors

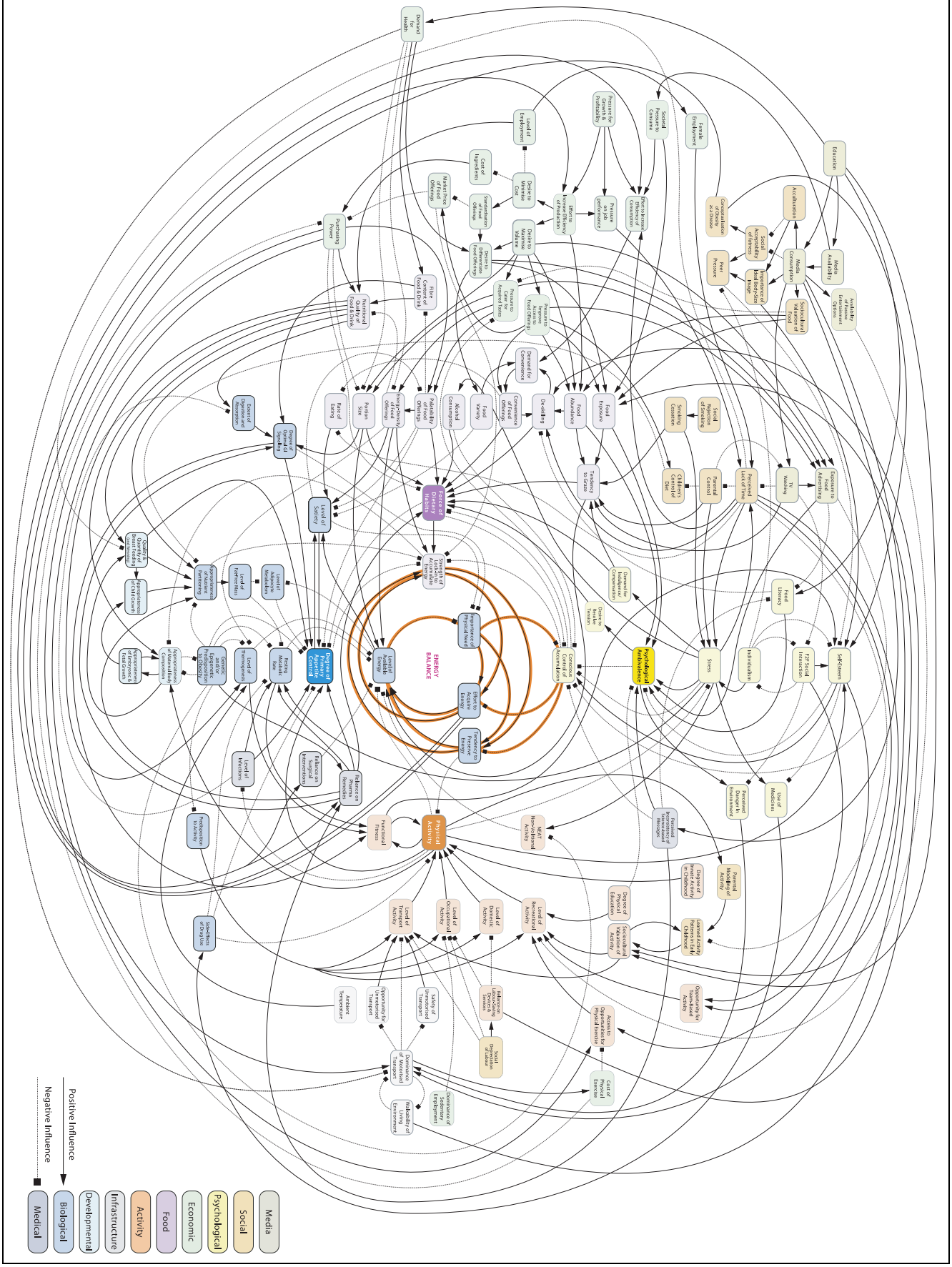
Despite common assertions that obesity stems from a simple matter of '*eating too much and moving too little*',[39] the underlying causes are tremendously complex, with genetic, physiological, psychological, social, and cultural factors all implicated in its pathogenesis (**Figure 2**, p5).[38] To discuss these in their entirety would be a burdensome task, but some aspects are particularly noteworthy.

In low income settings, and for much of human history, obesity was a marker of opulence that was outside the reach of all but the most economically fortunate.[40] But wherever high calories, particularly from refined carbohydrates, are available for low costs, that association is reversed.[41] In the UK, obesity is now twice as common among women living in the lowest quintile of household income than the highest.[37] Underlying this trend is a complex mix of educational, financial, and social factors that offer insight into what has been termed the 'obesogenic environment'.[42]

[i] According to WHO and NIH criteria.[24,27]

[ii] *Idem*.

Figure 2 Conceptual map of the causes of obesity. Reproduced from Butland *et al* 2007[38]



Healthier foods – in other words high-nutrient, low-sugar foods that are less associated with obesity – simply cost more.[43] In fact, per calorie, the cost difference between more healthy and less healthy foods is as much as threefold.[44] Maintaining a diet that meets all the criteria of the UK Department of Health (DH) Eatwell Plate[iii] is hence over 50% more expensive than the traditional British diet of 'meat, chips, and pudding'.[43] This economic incentive is further reinforced by the food environment.[46] Low-income areas for example have more fast-food stores and fewer supermarkets, both of which are associated with increased prevalence of obesity.[47,48]

Similar barriers discourage physical activity. Cultural and economic changes to transport, communication, entertainment, and employment have made exercise in leisure time an increasingly important component of total physical activity.[49] But recreational exercise brings a number of financial barriers, such as gym membership fees and specialist clothing.[50] The opportunity costs are even greater, with lack of leisure time and competing work commitments both cited as prominent hurdles.[51] Deprived areas typically have fewer 'green-spaces', which promote greater physical activity, and bigger problems with traffic and crime, which dissuade it.[52,53] Obese and disadvantaged individuals are also more likely to experience comorbid health problems, which further inhibit physical activity.[54,55]

Together, these factors support and sustain social norms, which themselves further maintain the obesogenic environment.[41] Perhaps the clearest example are the unique dietary habits of some minority ethnic groups.[56] Though confounded by socioeconomic deprivation, these may partly explain some of the ethnic differences in obesity.[57] Such comparisons are however complicated by differences between ethnic groups in the association between BMI and body composition.[58] Ethnic-specific BMI categories are therefore under ongoing debate,[59,60] although the majority of scientific studies continue to use standard WHO BMI categories.[61]

1·2·2·4 Pathophysiology

The clinical significance of obesity has been recognised since antiquity,[40] and few modern physicians would probably disagree with Hippocrates' view that, '*corpulence is not only a disease itself, but the harbinger of others*'.[62] As it stands, the list of known consequences reads like the contents of a textbook on chronic disease. Coronary artery disease, stroke, type 2 diabetes, hypertension, osteoarthritis, chronic kidney disease, fatty liver disease,

[iii] The Eatwell Plate recommends '*plenty of fruit and vegetables*', '*plenty of potatoes, bread, rice, pasta and other starchy foods*', '*some milk and dairy foods*', '*some meat, fish, eggs, beans and other non-dairy sources of protein*', and '*just a small amount of food and drink that is high in fat or sugar*'.[45]

depression, and various cancer subtypes are all known to be associated with obesity.[63] Whether and to what extent these are causal is complicated by obesity's relationship with so many other relevant exposures and behaviours.[64] Nevertheless, increasing understanding of the metabolic role of adipose has revealed a number of mechanisms through which obesity might directly cause non-communicable disease.[65]

Though traditionally viewed as little more than a site of inert energy storage,[66] adipose tissue - particularly white adipose tissue located in the abdominal cavity - is now recognised as a highly active endocrine organ.[66] The total number of adipocytes however are largely fixed during early life.[67] A prolonged energy excess thus creates increasing demand on existing adipocytes, resulting in pathological hypertrophy, impaired metabolic function, and increased cell death.[68]

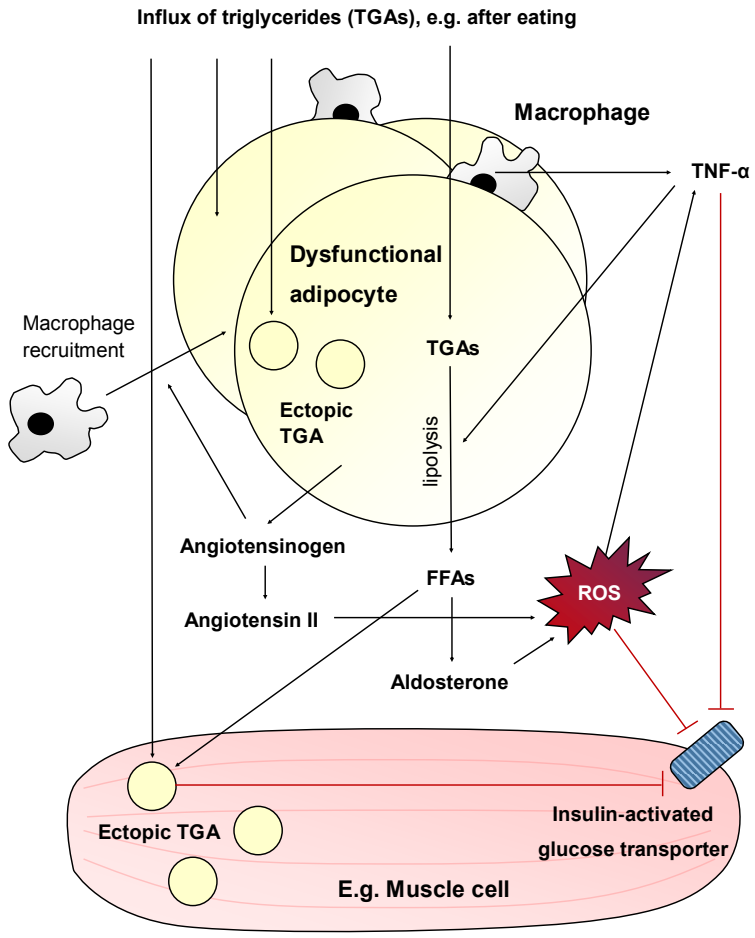
The first implication of this 'dysfunctional adipose' is the tendency to leak free fatty acids (FFAs),[68] which are transformed by the liver into triglycerides.[68] These either accumulate in the liver, the pancreas, and muscles as ectopic fat, or are incorporated into very low density lipoproteins (vLDLs) for transport.[69] Compared with high-density lipoproteins (HDLs), low density lipoproteins (LDLs) are considerably more likely to adhere to nascent vascular lesions and provoke inflammation.[69] This is exacerbated by the release of pro-inflammatory cytokines such as TNF-α[iv] from macrophages that amass in dysfunctional adipose and promote a state of chronic low-grade inflammation.[70] As well as contributing to the development of cardiovascular disease,[71] this inflammation is thought to be the principal mechanisms through which obesity increases the risk of cancer.[72]

Elsewhere, adipose tissue is also involved in regulation of the renin-angiotensin-aldosterone system (RAAS);[73] known foremost for its role in influencing blood pressure;[74] a well-known risk factor for cardiovascular disease.[75] Circulating FFAs stimulate the release of aldosterone, which increases water retention to raise blood pressure.[76] This is reinforced by increases in angiotensin II produced from angiotensinogen that is released directly by dysfunctional adipocytes.[73]

Taken together, this cluster of obesity, dyslipidaemia, inflammation, and hypertension are typical of what has been dubbed the 'metabolic syndrome',[77] lest for one additional feature of particular relevance to diabetes; obesity - or dysfunctional adiposity at least – also appears to cause insulin resistance (**Figure 3**, p8).[78,79]

[iv] Tumour necrosis factor α

Figure 3 Schematic representation of mechanisms through which dysfunctional adipose tissue is thought to cause insulin resistance



FFAs = Free fatty acids. ROS = Reactive oxygen species. TGA(s) = Triglyceride(s). TNF- α = Tumour necrosis factor α.

The accumulation of ectopic fat in liver cells and skeletal muscle trigger a signalling cascade that inhibits the activity of cell surface insulin receptors.[79] This same pathway is disrupted by several of the inflammatory mediators released by macrophages in dysfunctional adipose, most notably TNF-α, which also increases the supply of FFAs.[79] Elsewhere, insulin resistance is further exacerbated by modifications to the RAAS.[80] Though the exact mechanisms have not been established, both angiotensin II and aldosterone stimulate the production of reactive oxygen species (ROS),[73] which appear to inhibit insulin signalling by indirectly activating stress-sensitive kinases.[81]

Regardless of the mechanism, the consequences of this increasing insulin resistance are well recognised. As insulin receptors become increasingly inert, so too do the glucose transport molecules that they control. Without a corresponding increase in insulin secretion, made less likely by ectopic fat deposition in the pancreas,[82] then blood glucose levels increase, commencing the path to type 2 diabetes.

1·2·2·5 Obesity in pregnancy

By virtue of youth, obesity is typically less common in women of childbearing age than the population as a whole. In most populations however this difference is relatively modest. In England during 2014 for example an estimated 20% of women aged 16-44 were obese compared with 26% of adults generally.[37] Although the true prevalence of obesity in the obstetric population may be slightly lower, there are nevertheless close parallels with secular

trends. In the 19-years between 1989 and 2007, the estimated prevalence of obesity in pregnant women in England doubled from 8% to 16%;[83] the same proportion as in the general population over a similar period.[37] This has placed enormous pressure on maternity services, as obese pregnant women bring a range of additional care needs,[84] estimated to cost at least £1000 per mother.[85]

Before pregnancy, obesity is associated with an increased risk of infertility and sub-fecundity,[86] a problem that is exacerbated by increases in the risks of early and recurrent miscarriage.[87,88] Beyond the first-trimester, the principal implications of maternal obesity - for the mother - consist of a three-fold increase in the risk of pre-eclampsia and a four-fold increase in the risk of gestational diabetes.[89,90] These likely contribute to the increased rates of induction of labour and delivery by caesarean section (twice as common for both elective and emergency sections),[91,92] although they may also be explained by the increased risk of macrosomia.[93] After delivery, obese mothers are less likely to initiate breastfeeding,[94] typically breastfeed for a shorter time-period,[94] and experience an increased risk of post-partum mental health problems.[95]

For the offspring, the full implications of maternal obesity remain unknown, but evidence from animal models suggests that the effects may extend throughout the lifecourse to a range of physiological outcomes.[96] In humans, the dominant evidence consists of an increased risk of obesity and insulin resistance in the offspring,[97,98] although maternal obesity has also been associated with earlier adult mortality in the offspring.[99] It is the association with mortality in early life however that is arguably of foremost concern. Indeed, apart from the higher risk of maternal death,[100] the most severe complications of pregnancy are serious adverse fetal outcomes such as stillbirths, infant deaths, and congenital anomalies.[7,101,102] Further details of these, and their associations with both pre-pregnancy obesity and diabetes, are discussed in **Section 1·3·2·4** (p25), **Section 1·3·3·4** (p30), and **Section 1·3·4·4** (p33).

1·2·3·1 Definition

Diabetes mellitus, herein simply diabetes[v], is the name for a group of metabolic disorders characterised by enduring hyperglycaemia, the most common varieties of which are type 1 diabetes (T1DM), type 2 diabetes (T2DM), and gestational diabetes (GDM).

Type 1 diabetes consists of an acquired deficiency in the production of insulin following the destruction of an individual's pancreatic beta cells, either by injury, infection, chemical toxicity, or – most commonly - idiopathic autoimmunity.[103] The condition usually presents in childhood and was hence traditionally referred to as juvenile-onset diabetes.[104] Without regular treatment with insulin (or an insulin receptor ligand) type 1 diabetes is lethal, giving rise to the condition's other historic name; insulin dependent diabetes mellitus (IDDM).[105]

Type 2 diabetes, in contrast, is not necessarily characterised by an absolute lack of insulin, but by a *relative* deficiency, resulting from insufficient beta-cell function to overcome a backdrop of insulin resistance.[106] Unlike type 1 diabetes, where the onset is usually relatively sudden, type 2 diabetes typically develops over many years or decades. It was hence classically referred to as adult-onset diabetes.[107] The division of type 1 and type 2 diabetes into juvenile and adult onsets has fallen out of favour due to the identification of maturity-onset diabetes of the young (MODY), a familial variant of type 2 diabetes caused by constitutionally poor beta-cell function,[108] and latent autoimmune diabetes of adults (LADA), a slowly-developing variant of type 1 diabetes.[109] Historically, type 2 diabetes has also been referred to as non-insulin dependent diabetes (NIDDM), but this is potentially confusing, since individuals with type 2 diabetes may also receive insulin therapy.[107]

Gestational diabetes is persistent and severe hyperglycaemia that arises during pregnancy. It is analogous to type 2 diabetes, in that it is characterised by a relative – not absolute – lack of insulin.[110] In this instance, the insulin resistance is caused, or at least exacerbated, by metabolic features of pregnancy, such as human placental lactogen (hPL; a hormone that dramatically reduces insulin sensitivity).[110] Although most women with gestational diabetes will experience a resolution of their hyperglycaemia once pregnancy has ended,[111] the condition is associated with a substantially increased risk of overt type 2 diabetes later in life.[112]

[v] 'Diabetes' may also refer to diabetes insipidus, an unrelated condition characterised by excess urination. In the current document, and all constituents, the term diabetes refers only to diabetes mellitus.

1·2·3·2 Diagnosis

Historical descriptions of diabetes make reference to one symptom – glycosuria – that formed the hallmark of its diagnosis for centuries.[113] These days, a formal diagnosis requires at least one blood test (**Table 1**, p12).[114]

As with any physiological characteristic, it is improbable that the harmful effects of raised plasma glucose appear abruptly at a particular threshold.[115] Much effort has therefore been devoted to agreeing on the point at which detectable hyperglycaemia represents clinical diabetes.[116] This is further complicated by the natural variation in plasma glucose levels, which fluctuate throughout the day according to the frequency and composition of food consumed.[117]

The fasting plasma glucose (FPG) test and the 75mg 2-hour oral glucose tolerance test (OGTT) both aim to circumvent this issue. An FPG result above 7.0mmol/l or an OGTT result (two hours after consumption of 75g anhydrous glucose) above 11.1mmol are considered diagnostic of diabetes by both the WHO/International Diabetes Federation (IDF) and the American Diabetes Association (ADA) (**Table 1**, p12).[114,118] In pregnancy, the ADA deem an FPG above 5.1mmol/L or 75mg 2-hour OGTT above 8.5mmol/L to indicate gestational diabetes,[114] while the UK's National Institute for Health and Care Excellence (NICE) currently advise corresponding values of 5.6 mmol/L and 7.8 mmol/L respectively (**Table 1**, p12).[119]

Alternatively, the average blood glucose concentration over the previous few months can be inferred from the quantity of glycated haemoglobin (HbA_{1c}).[120] Indeed, HbA_{1c} concentrations above 48mmol/mol are now widely considered diagnostic of diabetes in non-pregnant individuals,[121] and is the ADA's recommended approach (**Table 1**, p12).[114,120] Since it does not require prior fasting and is robust to temporary fluctuations in control, testing for HbA_{1c} offers clear benefits for reduced intrusiveness. Despite this, it is not yet strictly approved for the diagnosis of diabetes in pregnancy (although preliminary studies from India, North America, and New Zealand, suggest first-trimester values of 41-43mmol/mol may identity women with gestational diabetes as reliably as OGTT).[122-124]

Despite the numerous efforts to provide a reliable and reproducible test for diabetes, formal diagnosis is still a conservative process, requiring either two serial blood tests or, more commonly, the presence of clinical signs.[114,118] For many with type 2 diabetes however visible signs may not be evident until several years after the disease onset.[125] As many as 1-2% of the UK population may therefore have undiagnosed diabetes,[126] with a further 10-20% probably living with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) short of overt diabetes.[127] This defined state of subclinical hyperglycaemia (**Table 1**, p12),

sometimes called 'pre-diabetes' or 'borderline diabetes', is a core symptom of the metabolic syndrome and a critical indicator of diabetes risk.[128] Although the health consequences are considerably smaller on an individual basis than for overt diabetes, pre-diabetes may still be responsible for significant morbidity at the population level; perhaps even greater, given the higher prevalence proportion.[129]

Table 1 Criteria for the diagnosis of diabetes, impaired glucose tolerance, and impaired fasting glucose.[114,118-120] In the absence of clinical signs (polyuria, polydipsia, unexplained weight loss etc.), a second confirmatory test is required.

	WHO/IDF[118,120]	**ADA**[114]	**NICE**[119]
Pre-existing diabetes			
HbA_{1c}	≥48mmol/mol	**≥48mmol/mol**[a]	
	or	*or*	
FPG	≥7.0mmol/L	≥7.0mmol/L	
	or	*or*	
75mg OGTT (2-hour)	**≥11.1mmol/L**[a]	≥11.1mmol/L	
Gestational diabetes			
FPG	-	5.1 mmol/L[b]	5.6 mmol/L[b]
		or	*or*
75mg OGTT (2-hour)	-	8.5 mmol/L[b]	7.8 mmol/L[b]
Impaired Glucose Tolerance			
FPG	<7.0mmol/L	<7.0mmol/L	
	and	*and*	
75mg OGTT (2-hour)	≥7.8 to <11.1mmol/L	≥7.8 to <11.1mmol/L	
Impaired Fasting Glucose			
FPG	**6.1 to 6.9mmol/L**[a]	5.6 to 6.9mmol/L	
	And (if measured)		
75mg OGTT (2-hour)	<7.8mmol/L	-	

Criteria are for concentration in plasma. WHO = World Health Organization. IDF = International Diabetes Federation. ADA = American Diabetes Association. NICE = National Institute for Health and Care Excellence. FPG = Fasting Plasma Glucose. OGTT = Oral Glucose Tolerance Test. [a]Recommended test. [b]At 24-28 weeks' gestation.

1·2·3·3 Prevalence

Although descriptions of diabetes can be traced to the very beginnings of written history,[130] the condition has likely spent most of human existence as a rare, if tragic, occurrence. Aretaeus of Cappadocia – credited for naming the disease - described diabetes as '*not very frequent among men*',[113] an observation that is apparently corroborated by his illustrious contemporary Galen of Pergmanon, who reports having only ever encountered two cases of the condition.[113]

Until the discovery of insulin in 1921,[131] many with type 1 diabetes are likely to have died before ever achieving a diagnosis. In the years afterwards, the prevalence of type 1 diabetes no doubt increased with improving prognosis, but contemporary estimates of both incidence and prevalence were extraordinarily low, presumably due to under-ascertainment.[132] In the most prominent longitudinal data, Westlund (1966) identified a steady incidence of around 1 per 10,000 person-years for those under 30 years of age in Oslo during 1925-1954.[133] From the middle of the 20th century however there was a clear trend upwards, with the incidence of type 1 diabetes increasing steadily throughout 1960-1996 in most populations.[134] But as stark as this increase may be, it is a relative side show in an 'epidemic' dominated by type 2 diabetes.[135]

Historical data on the incidence and prevalence of type 2 diabetes is complicated by a backdrop of low diagnosis and misclassification. The modern biological definitions of type 1 and type 2 diabetes was not widely adopted until several years after Berson and Yalow (1960) demonstrated the role of insulin resistance in type 2 diabetes.[136] Even today, many studies of the epidemiology of diabetes fail to clearly differentiate between the two types, making it difficult to identify the contribution of each. Westlund's hospital study in Oslo during 1925-1954 nevertheless demonstrates the most important determinate of diabetes incidence; the exponential association with age.[133] Compared to under 30 year-olds, Westlund found the incidence was three times higher among 30-59 year-olds and twelve times higher among over 60 year-olds.[133]

The ageing global population has hence had a dramatic impact on the absolute number of people living with diabetes, which is thought to have doubled in the 28 years between 1980 to 2008.[23] Although the estimated prevalence varies between data sources (partly depending on how they account for those with undiagnosed diabetes) all agree the trends are set continue.[135,137,138] The sixth edition of the IDF Diabetes Atlas pooled data from a variety of sources to estimate that 8.3% of the global adult population were living with diabetes in 2013, with as many as 80% of these living in low- or middle-income countries.[135] By 2035 the authors predict the prevalence will increase to 10.1%,[135] although this may be conservative, as it does not account for predicted changes in the prevalence of obesity.[139]

In the UK, estimates derived from general practice data predict that 6% of the adult population – or 3.2 million adults – had diagnosed diabetes during 2013,[126] with an additional 0.5-1.0 million undiagnosed.[140] This stark increase from just 2.8% in 1996 and 4.3% in 2005, is mostly attributable to increases in the prevalence of type 2 diabetes.[141] Although the trend in the prevalence of type 1 diabetes shows no sign of abating,[142] the numbers are greatly surpassed by increases in type 2, which now account for 90% of people

living with the condition.[126] If trends continue, it is estimated that as many as five million people in the UK will be living with diabetes by 2025; a prevalence of approximately 9.0%.[143]

1·2·3·4 Risk factors

Though the pathophysiologies of type 1 and type 2 diabetes have many similarities (see **Section 1·2·3·5**, p17), the aetiologies are quite distinct. Both are partly hereditary.[144,145] The offspring of parents with type 1 diabetes experience a 5-10% risk of developing the condition (compared with less than 0.5% in the general population),[104] with a larger effect for an affected father than mother.[146] Over 50 candidate genes for type 1 diabetes have been identified in the human leukocyte antigen (HLA) system, indicating the autoimmune component of the disease.[147] The rare MODY follows a Mendelian inheritance pattern, the most common gene culprits being *HNF1A* (which codes for a transcription factor involved in regulating a number of liver proteins) and *GCK* (which codes for glucosekinase, the so-called 'pancreatic glucose sensor').[148] The heritability of type 2 diabetes appears to be polygenic, but while several gene candidates have been identified – mostly influencing beta-cell function - the individual effects are modest.[149,150]

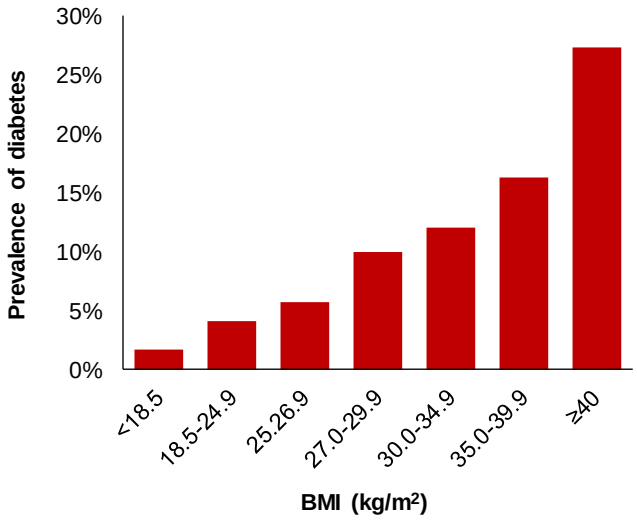
The incidence of both type 1 and type 2 diabetes are strongly associated with age, albeit entirely uniquely. Most cases of type 1 diabetes arise during childhood, with the incidence peaking during ages 10-14 years.[104] LADA is rarely diagnosed, but is likely commonly misclassified as type 2.[151] The risk of type 2 diabetes itself increases exponentially with advancing years until levelling beyond 65 years, reflecting a possible negative survival bias.[152]

There are few other known risk factors for type 1 diabetes, the aetiology of which remains largely a mystery. On an ecological level, the prevalence has been associated with increasing distance from the equator,[153] leading to speculation that the risk of type 1 diabetes, like other idiopathic autoimmune diseases,[154] may be partly determined by sun exposure and/or intake of vitamin D.[155]

The risk of type 2 diabetes, in contrast, has been associated with a range of physiological and psychosocial factors, the most prominent of which is obesity (**Figure 4**, p15).[139] This may be due to a number of shared risk factors. Both obesity and diabetes have for example been associated with low levels of physical activity, high levels of sedentary behaviour, and increased consumption of obesogenic foods and drinks.[156-159] The strength of the association between obesity and diabetes however remains considerable even accounting for these shared exposures.[160] In the Nurses' Health Study – which followed 70,000 women

yet to develop diabetes – the risk of developing diabetes after adjusting for age, physical activity, smoking, and alcohol consumption was monotonic with increasing BMI, reaching 28 times higher for those with a BMI over 40kg/m^2 compared with those below 21kg/m^2.[160] Further stratification by physical inactivity showed that, while this too influenced diabetes risk, it only modestly explained the effect of obesity.[160] In fact, Qin *et al*'s 2010 meta-analysis of the interaction between BMI and physical activity suggests that it is obesity, not lack of physical activity *per se*, that is the key determinant of diabetes risk.[162] This may reflect the apparently distinct contributions of total adiposity and abdominal adiposity,[163] with the proportion of abdominal adiposity being a more potent indicator of diabetes risk.[164] Abdominal adipose is especially associated with dysfunctional metabolic mechanisms such as ectopic fat deposition,[165] a stark predictor of diabetes risk.[166]

Figure 4 Prevalence of diabetes by body mass index (BMI) among adults living in the USA during 1999-2002. Data are from the National Health and Nutrition Examination Surveys (NHANES).[161]



Cigarette smoking also has a complex association with diabetes, because of its apparently paradoxical correlation with both higher diabetes risk and lower body weight.[167,168] In fact, this simply demonstrates the limitations of weight and BMI as measures of abdominal adiposity.[169] Whilst smoking is correlated with lower overall body mass it is also correlated with higher levels of visceral fat.[170] Elsewhere, smoking further promotes insulin resistance by increasing the release of FFAs from adipose tissue,[171] systematic inflammation,[172] and oxidative stress.[173]

Metabolic differences may also explain ethnic variations in the prevalence of type 2 diabetes. Although complicated by clustering of cultural and socio-economic risk factors,[174] individuals from South Asian or African/Caribbean backgrounds experience two-to-three times greater risk of diabetes than those from white ethnic groups.[175] The NICE and ADA thus recommend a lower BMI threshold of 23kg/m^2 for screening Chinese and South Asians for type 2 diabetes.[176,177] The high prevalence of diabetes among indigenous populations (three to five times higher than in non-indigenous comparisons),[178] suggests a possible genetic legacy relating to exposure, or lack thereof, to refined carbohydrates.[179] In high-risk ethnic groups,

a greater proportion of fat is stored centrally, and adipose dysfunction and ectopic fat deposition occur at lower absolute levels of adiposity.[180]

1·2·3·5 Pathophysiology

Before the advent of insulin therapy, those with overt diabetes faced a bleak prognosis. Areteus of Capadoccia described it thus,

> '*Life is short, unpleasant and painful, thirst unquenchable…death inevitable*'.[113]

With timely diagnosis and treatment, such a fate is now rare outside of low income settings.[181] Yet diabetes remains a serious and life-threatening illness that brings a tremendous burden of mortality and morbidity.[182] In 2012, 1.5 million people died as a direct consequence of diabetes, making it the eighth leading cause of death worldwide.[183] But for every year of life lost, an additional two-to-four are also lived with disability.[184] Indeed, in 2013, diabetes was the seventh leading global cause of years lived with disability, and the fifth leading cause in the UK.[185]

Although an acute hyperglycaemic crisis represents the most serious diabetic event – bringing a risk of coma and death – most of the disease burden results from progressive damage to both small and large blood vessels.[186] At the macrovascular level, diabetes is thus associated with markedly increased risks of coronary artery disease and stroke.[187] This applies equally in both type 1 and type 2 diabetes,[186] and is independent of the many co-morbid risk factors.[188]

At the microvascular level, the most common complications are neuropathy (present in around half of those living with diabetes),[189] retinopathy (present in around a third),[190] and nephropathy (present in up to a quarter),[189] the implications of which can include blindness, kidney failure, and limb loss.[191] The landmark Diabetes Control and Complications Trial (DCCT) proved these to be a direct consequence of hyperglycaemia, observing much lower risks in those who achieved strict glucose control.[192] The 'unifying mechanism' through which these outcomes are thought to occur is oxidative stress (**Figure 5**, p15).[193]

Following glycolysis, excess pyruvate is metabolised through the tricarboxylic acid cycle (TCA) to create an abundance of electron donors. This influx stalls the electron transport chain, resulting in the expulsion of electrons to molecular oxygen to create ROS. These cause DNA[vi] damage, the repair of which leads to the recruitment and activation of PARP[vii], which in turn inhibits the activity of the key glycolytic enzyme, GAPDH[viii]. Deactivation of GAPDH impedes transit through the glycolysis pathway, leading to glucose being

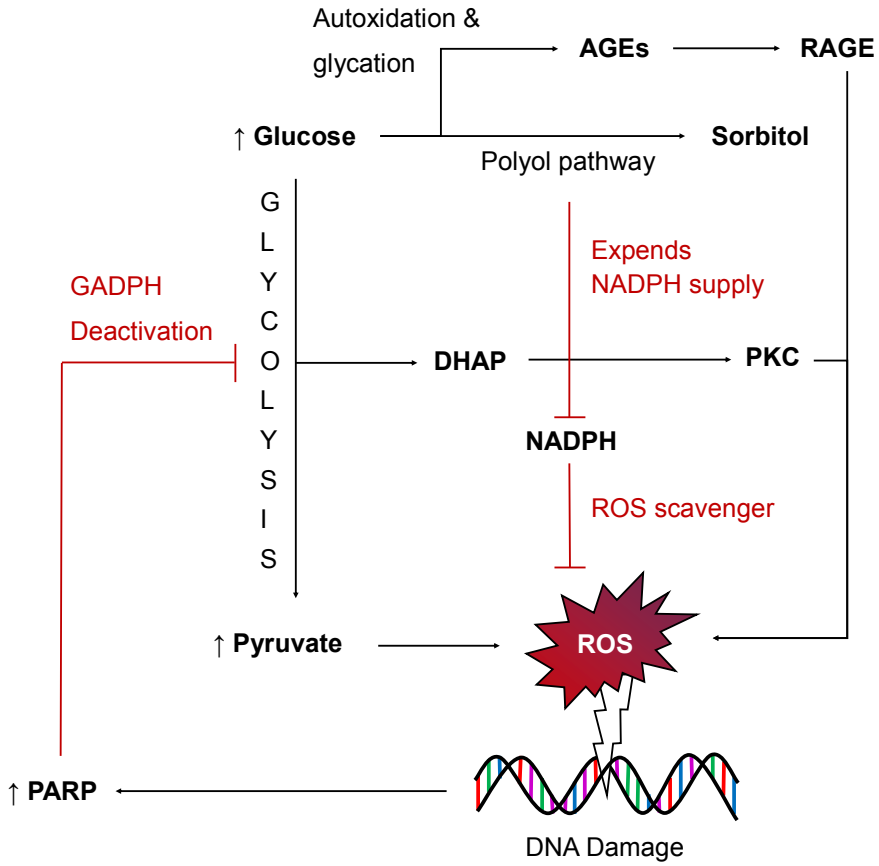
[vi] Deoxyribonucleic acid

[vii] Poly((adenoside diphosphate)-ribose) polymerase

[viii] Glyceraldehyde 3-phosphate dehydrogenase

metabolised through a series of deleterious mechanisms that themselves further increase oxidative stress (**Figure 5**, below).[194]

Figure 5 'Unifying mechanism' of the pathobiology of diabetes complications.[193]



AGEs = Advanced glycated end-product(s). DHAP = dihydroxyacetone phosphate. DNA = Deoxyribosenucleic acid. GADPH = Glyceraldehyde 3-phosphate dehydrogenase. PARP = Poly((adenoside diphosphate)-ribose) polymerase PKC = Protein kinase C. RAGE = Receptor of advanced glycated end-products. ROS = Reactive oxygen species.

In the polyol-pathway, glucose is converted into sorbitol, expending the supply of NADPH[ix], an important scavenger of ROS.[195] Since sorbitol cannot pass through the cell membrane it accumulates, altering the osmotic potential, and causing a potentially harmful increase in cytosolic-pressure.[196]

Advanced glycated end-products (AGEs) are created when an auto-oxidised product of glucose becomes bonded to a protein; HbA_{1c} being the most prominent example.[197] Glycated proteins may form rigid polymers by cross-linking, causing pathology wherever flexibility is required for healthy function (e.g. in vascular stiffening).[197] AGEs also trigger an

[ix] Nicotinamide adenine dinucleotide phosphate

inflammatory response and the production of ROS by activating the receptor of advanced glycated end-products (RAGE).[198]

Finally, one of the most well-studied metabolic implications of hyperglycaemia is the activation of protein kinase C (PKC) by diglyceride (made from the glycolysis intermediate DHAP[x]).[199] Protein kinase C has a number of implications - including inflammation, oxidative stress, and decreased vessel flexibility – which Brownlee summarises succulently as thus, '*the things that are good for normal function are decreased and the things that are bad are increased*'.[193]

1·2·3·6 Diabetes in pregnancy

Diabetes is the UK's most common serious pre-existing health complication of pregnancy,[200] but it was not always so. The first case of diabetes in pregnancy was not recorded until as late as 1824[xi],[201] and studies from the turn of the 20th century indicate the maternal mortality ratio was 25-50%.[202] Since then, three things have changed. Insulin has not only offered life to women with type 1 diabetes, but transformed their prospects during pregnancy. Indeed, by 1940-50 the maternal mortality ratio for those with overt (most likely type 1) diabetes had fallen to 1%.[203] Though still an order of magnitude greater than in the general population, this was nevertheless low enough to shift the focus towards morbidity and the health of the offspring. More recently, the obesity epidemic, together with steady increases in the age of childbirth,[204] have led to a surge in the number of pregnant women with type 2 diabetes.[205]

Pregnancy presents a unique risk to women with diabetes by triggering a number of metabolic changes, including increased insulin resistance, hyperlipidaemia, and systemic inflammation (including higher levels of TNF-α).[110] Alongside the already precarious profile of pre-existing diabetes, this makes the maintenance of optimum glycaemic control – and indeed the entire experience of pregnancy – particularly demanding and stressful.[206] The immediate consequence is an increase in the risk of diabetes complications, including nephropathy, retinopathy, and ketoacidosis.[207,208] At the other extreme, fluctuating insulin sensitivity, reductions in counter-regulatory hormones, changes in diet and appetite, and a lack of awareness also lead to an increase in the incidence of hypoglycaemia.[209] Although the long term impact of these episodes are poorly understood, severe hyperglycaemia is potentially life-threatening, bringing risks of unconsciousness, coma, and serious injury.[209]

[x] Dihydroxyacetone phosphate

[xi] The author (Bennewitz) describes a 22-year old mother living in Berlin who experienced 'unquenchable thirst' and glycosuria during her fourth and fifth pregnancies. Though unclear whether she had pre-existing or gestational diabetes, the report is regardless the first recorded description of any form of the condition during pregnancy.

In terms of the obstetric implications, both pre-eclampsia and delivery by caesarean section are around five times more common in women with pre-existing diabetes,[210] with approximately 10% of women with diabetes in the UK experiencing pre-eclampsia and over 50% now delivering by caesarean section.[205] These striking rates of delivery by caesarean section reflect not just the maternal risks associated with pre-existing diabetes, but the unparalleled risks for the offspring.

First posited in the 1920s, but largely attributed to Jorgan Pedersen's 1952 PhD thesis,[211] the Pederson hypothesis outlines how maternal hyperglycaemia crosses the placenta to induce fetal hyperglycaemia, promote fetal insulinaemia, and ultimately stimulate a sustained uptake of glucose.[212] Though other mechanisms are now also recognised,[213] the consequence is nevertheless a dramatic surge in fetal growth, particularly in fetal adipose.[214] In the short term, this results in nearly half of all affected offspring being large-for-gestational-age (LGA).[215] In the longer term the effects includes higher risks of obesity and diabetes.[216,217] These however arguably represent some of the more favourable outcomes, since diabetes in pregnancy is also strongly associated with the risks of both fetal death and congenital anomaly; further details of which are described in **Section 1·3·2·5** (p26) **Section 1·3·3·5** (p30), and **Section 1·3·4·5** (p33).

1·3 OUTCOMES

1·3·1 Serious adverse fetal outcomes

Pregnancy and childbirth are prominent within the framework of every known human culture, with the birth of a healthy infant marked by ritual and celebration.[218] Much of this has probably evolved from the intimate link between reproduction and survival,[218] and the heritage of childbirth as a life crisis event.[219]

For most of human history, pregnancy, childbirth, and the immediate postnatal period have been hazardous, with best estimates suggesting that around 1% of mothers died as a consequence of pregnancy and up to 30% of infants died during the first month of life.[220,221] Since the early-to-mid twentieth century however these risks have fallen dramatically and most pregnant women living in high-income settings - including the UK - can now expect a healthy live-born child.[222]

Despite these advances, the perinatal period - defined variably as the time immediately around birth[xii] - remains one of the riskiest and most critical periods of life. Over a quarter of human embryos are lost before achieving viability,[223] and the risk of mortality during the first four weeks of life is higher than at any point until old age.[224] The loss of a wanted child, whether during pregnancy, infancy, or resulting from a major congenital anomaly is associated with both profound and prolonged parental distress, and serious adverse fetal outcomes are hence some of the most feared events among perinatal health professionals.[225-228]

[xii] The exact definition of the 'perinatal period' varies between settings, but typically spans from the locally-defined border of viability (~24 weeks gestational age in the UK) up to either 7 or 28 days post birth (the latter sometimes being termed the 'extended perinatal period')

1·3·2·1 Definition

Major congenital anomalies - herein simply congenital anomalies[xiii] - describe a diverse group of chromosomal, genetic, and structural abnormalities with serious physical, intellectual, or cosmetic consequences that present before birth. Though recognised since antiquity,[229] congenital anomalies have historically been poorly defined, inconsistently classified, and subject to countless changes in nomenclature;[230] in part due to an enduring legacy of pejorative language use.[xiv]

In the broadest sense, congenital anomalies can be divided by their aetiopathologies into those that result from a known genetic abnormality – ranging from karyotype anomalies to single gene mutations - and those that arise during embryonic or fetal development - commonly known as structural anomalies. Because of the range of unique presentations, structural anomalies are usually divided into groups, which describe the organ system most prominently affected.[231] Both these and the genetic anomalies are then typically further subdivided into subtypes, which define the broad phenotype or genotype.[231] In Europe, the European Surveillance of Congenital Anomalies (EUROCAT) - a consortium of 43 population-based registers of congenital anomaly - maintains a set of guidelines for the classification of congenital anomaly groups and subtypes, which are annually reviewed and updated by a multidisciplinary panel of experts.[232]

Assigning a diagnosis for cases of congenital anomaly however is complicated by the fact that around a quarter present with more than one structural anomaly.[233] Some of these syndromic cases are explained by an underlying chromosomal or genetic disorder, while others may belong to a previously recognised pattern of anomalies. The 2008 EUROCAT syndrome guide classifies these according to their suspected aetiology as either

[xiii] Minor congenital anomalies are those abnormalities that do not present with serious physical, intellectual, or cosmetic consequences. Examples include balanced chromosomal rearrangements, undecended testes (cryptorchidism), and facial asymmetry. The prevalence proportions of minor congenital anomalies are usually found to be considerably greater than of major anomalies, although they are also more likely to be under-ascertained, if at all. Congenital anomaly registries belonging to the EUROCAT, for example, actively exclude cases of minor anomaly. In the current document, and all constituents, the term ‘congenital anomalies’ refers only to major congenital anomalies.

[xiv] Although the primary Medical Subject Heading (MeSH) is 'congenital abnormalities' the WHO now favour the term 'congenital anomalies', which is also preferred throughout this document. Other MeSH entry terms - some of which remain in-use in the literature - are congenital- or birth-: disorders, malformations, defects, or deformities. Teratology - the term for the field incorporating the study of congenital anomalies – is itself derived from the Greek *teratos,* meaning 'monster', a word that somehow endured into the International statistical Classification of Diseases and related health problems (ICD) version 10 (ICD-10) (codes Q89.7 and Q89.8).

syndromes,[234] which are those with a suspected single cause, sequences, which are thought to arise from a prior anomaly or mechanical factor,[235] or associations, which are those where the aetiopathology is entirely unknown.[236] Cases with more than one structural anomaly that are not part of a known syndrome, sequence, or association are considered multiple anomalies.

1·3·2·2 Prevalence

Reliable estimates of congenital anomaly prevalence require detailed surveillance systems that collect information from multiple sources and on cases ending in elective terminations of pregnancy.[237,238] Such estimates are thus only currently available in higher-income areas, such as the United States of America (USA), Europe, and Australia.[233,239,240] Even among these regions, the prevalence proportions vary significantly, although most estimates indicate that around 15-30 per 1,000 births are affected.[233,239-241] The most common congenital anomaly groups are congenital heart disease (CHD) (comprising 25-35% of cases), those belonging to the urinary system (10-15%), nervous system (10-15%), and digestive system (5-10%), limb anomalies (10-20%), and chromosomal anomalies (15-25%).[233,239-241]

From 1st April 2016, all births in the UK will be monitored by the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS). The NCARDRS includes several former regional population-based registers of congenital anomaly belonging to the British and Irish Network of Congenital Anomaly Registers (BINOCAR).[241] During 2012, around a quarter of congenital anomaly cases in these areas resulted in a termination of pregnancy for fetal anomaly - equivalent to 45% of those that were prenatally diagnosed - and the estimated total prevalence was 22.7 per 1,000 total births (95% confidence interval, CI: 22.1 to 23.2). [241] For the most common anomaly groups the prevalence proportions, per 1,000 total births, were 6.0 (95% CI: 5.7 to 6.3) for CHD, 4.3 (95% CI: 4.1 to 4.6) for chromosomal syndromes, 3.5 (95% CI: 3.3 to 3.7) for limb anomalies, 2.8 (95% CI: 2.6 to 3.0) for urinary anomalies, 2.6 (95% CI: 2.5 to 2.9) for nervous system anomalies, and 1.8 (95% CI: 1.7 to 2.0) for digestive system anomalies. [241]

Temporal trends in the prevalence of congenital anomaly are somewhat difficult to assess. Regional registers may show increases due to improving methods of ascertainment while data from national or international collaborations may ironically mask genuine changes at smaller levels. In the 43 EUROCAT registers between 1999 and 2008 however significant decreases in prevalence were identified for a large minority of anomaly subtypes, at rates of 1-8% per year.[242] Similarly, in the former BINOCAR regions a significant if modest decrease, equivalent to 1.5% per year, was observed during 2007-2011. [241]

1·3·2·3 General risk factors

The aetiology of congenital anomalies is largely unknown. In an often quoted figure, Brent suggests that 15-25% of anomalies are genetic in origin, 10% are environmental, and the remaining 65-75% are of unknown cause, most likely resulting from complex and multifactorial interactions between genetic and environmental factors.[243] Since the causes of most chromosomal and genetic syndromes are however equally unclear, this essentially argues that little over 10% of anomaly cases are actually understood. This likely reflects the huge practical challenges of examining outcomes that are 'hidden' by pregnancy.[244] Most congenital anomalies arise during the first few weeks of gestation, before many women may be aware of their pregnancy.[245] Prospective data collection therefore requires following a cohort of non-pregnant women; an impractical approach given the rarity of the outcomes. Almost all existing knowledge of congenital anomaly aetiology has therefore been derived from studies using retrospective designs.

Theoretically, high-dose exposure to any generic genotoxin - such as a heavy metal or ionising radiation - may increase the risk of congenital anomalies.[246,247] Such exposures however are relatively rare; especially in high-income countries where regulations govern the shipment and disposal of toxic material. Perhaps more common are medications and infections with high teratogenic potential. Thalidomide - subject of one of the world's greatest pharmaceutical scandals - remains the most prominent such exposure,[248] but peri-pregnancy exposure to diethylstilbestrol, retinoids, antifolates, certain anticonvulsants, warfarin, and lithium are all recognised as potential causes of congenital anomaly.[249] Maternal infections with cytomegalovirus, herpes simplex, parvovirus B19, rubella, syphilis, toxoplasmosis, and, varicella-zoster are also known to be potentially teratogenic,[250] although most, except syphilis ,[251]rarely coincide with pregnancy. The 2015-2016 epidemic of Zika fever in South America and the Pacific Islands has also identified the Zika virus as a prominent teratogen. Although the full details remain unclear, infection with the virus has been firmly linked with congenital anomalies of the brain, including microcephaly.[252] With the disease spreading 'explosively',[253] and no vaccine yet available, the Zika virus may soon become – if it is not already - the world's leading single cause of congenital anomaly.

Smaller associations are known for a range of more common environmental, genetic, and phenotypic exposures. Congenital anomalies are approximately 15% more common among males than females, albeit with large variation between subtypes.[254] Consanguineous parents are more likely to have offspring affected by congenital anomaly, with a doubling in the risk among first-cousins.[255] The prevalence of congenital anomalies is significantly higher in twin pregnancies, particularly monochorionic twins,[256] as well as being generally more common among siblings, particularly for anomalies from the same group.[257] Advancing

maternal age dramatically increase the risks of chromosomal and genetic anomalies,[258] and may also have a small effect on structural anomalies.[259] Use of assisted reproductive technologies may increase the risk of congenital anomalies, though the effect may be exaggerated by correlation with other risk factors including maternal age.[260] Consumption of folic acid supplements significantly reduces the risk of neural tube defects (NTDs), CHD, and (more tentatively) orofacial clefts.[261] Smoking during pregnancy is associated with very small increased risks of CHD, digestive system anomalies, nervous system anomalies, limbs anomalies and orofacial clefts.[262] Finally, some types of air pollution,[263] drinking water constituents,[264] and anti-hypertensive medications,[265] may marginally increase the risks of certain anomaly groups and subtypes, but the current evidence is weak or inconclusive.

1·3·2·4 Obesity and the risk of congenital anomalies

The idea that maternal obesity might be associated with an increased risk of structural congenital anomalies emerged during the 1980s, but did not hit prominence until Waller *et al*'s seminal study in the *American Journal of Obstetrics and Gynecology*.[266] Published in 1994, this first investigation of the association between BMI and the risk of congenital anomaly, found an apparent doubling in the risk of NTDs for obese mothers (BMI≥31kg/m^2) compared with those of recommended BMI (19-27kg/m^2).[266] Taken alone however Waller *et al* 1994 was not completely convincing, in part due to concerns that the mother's pre-pregnancy weight had been recalled many months, even years, after the pregnancy had concluded.[266] In fact, this was not uncommon among contemporary studies, many of which were also hampered by low statistical power - especially for the less-common groups and subtypes - and/or a failure to identify cases ending in termination of pregnancy.[267-270]

By the time of Waller's own follow-up study in 2007,[271] some consensus was beginning to emerge, [272-275] but discordant hypotheses tests maintained a perception of uncertainty. The first meta-analysis appeared in 2008, in which Rasmussen *et al* estimated that the odds of a NTDs were 1.70 (95% CI: 1.34 to 2.15) higher among obese women compared with women of 'normal weight'.[276] Stothard *et al* 2009 (**Appendix B(i)**, p191) followed shortly afterwards, bringing a larger scope, more rigorous selection criteria, and extensive sensitivity analyses.[7] The odds ratio (OR) for NTDs was nevertheless extremely similar [OR=1.87 (95% CI: 1.62 to 2.15)], although a larger effect was found for spina bifida [OR=2.24 (95% CI: 1.86 to 2.69)] than anencephaly [OR=1.39 (95% CI: 1.03 to 1.87)].[7] Stothard *et al* 2009 also identified that obesity was associated with significantly increased odds of CHD [OR=1.30 (95% CI: 1.12 to 1.51)], including septal anomalies specifically [OR=1.20 (95% CI: 1.09 to 1.31)], cleft palate [OR=1.23 (95% CI: 1.03 to 1.47)], cleft lip and palate [OR=1.20 (95% CI: 1.03 to 1.40)] and hydrocephalus [OR=1.68 (95% CI: 1.19 to 2.36)].[7] The review found similar, albeit smaller,

effects for overweight women, suggesting that the associations might follow a dose-response with increasing BMI.[7]

Since then, there have been a steady stream of relevant observational studies, some of which are particularly worthy of note. In 2010, Blomberg and Källén updated their analysis of the Swedish Register of Birth Defects to examine the association between pre-pregnancy BMI and the risk of congenital anomaly in over a million births.[277] The results were fairly consistent with Stothard *et al* 2009, although the homogenous classification system allowed the authors to examine several important subtypes, with significant associations observed for cystic kidney disease, diaphragmatic hernia, and omphalocele.[277] Additional analyses separated obesity into class I (BMI: 30-34.9kg/m_2), class II (BMI: 35-39.9kg/m^2) and class III (BMI≥40kg/m^2), which revealed clear evidence of a dose-response effect with increasing BMI.[277]

Three large studies from the USA clarified the relationship between obesity and CHD, which had previously been affected by heterogeneity.[7] All three identified remarkably similar effects, albeit consistently smaller than estimated by Stothard *et al* 2009.[278-280] Cai *et al*'s 2014 meta-analysis of these, and others, found a dose response, with the OR of CHD compared with recommended BMI increasing from 1.08 (95% CI: 1.02 to 1.15) in overweight (BMI: 25-29.kg/m^2) to 1.15 (95% CI: 1.11 to 1.20) in moderate obesity (BMI: 30-39.9kg/m^2) and 1.39 (95% CI: 1.31 to 1.47) in severe obesity (BMI: ≥40kg/m^2)[281] The effect of obesity appeared fairly consistent among CHD subtypes, with significant ORs of between 1.22 and 1.51 identified for hypoplastic left heart, pulmonary valve stenosis, outflow tract defects, atrial septal defects, tetralogy of Fallot, conotruncal defects, and coarctation of the aorta.[281]

In 2015, Blanco *et al* conducted a meta-analysis of the association between maternal obesity and the risk of orofacial clefts.[282] Despite a large increase in the pooled sample-size over Stothard *et al* 2009 (due to two new studies from the USA)[283,284] the pooled odds ratios for cleft lip and palate [OR=1.13 (95% CI: 1.04 to 1.23)] and cleft palate [OR=1.22 (95% CI: 1.09 to 1.35)] were virtually indistinguishable from what had been estimated previously.[282]

1·3·2·5 Diabetes and the risk of congenital anomalies

In 1949, White published the first major study of the natural history of diabetes in pregnancy in the context of low maternal mortality.[285] Of the many complications for both mother and child, White considered, '*the most harmful of the tragic consequences… (to be) the occurrence of congenital fetal defects*'.[285] Since then, and especially since Pedersen *et al*'s seminal cohort study in 1964,[286] it has been widely recognised that congenital anomalies are more common in women with pre-existing diabetes.[287] Until recently however the finer

details of this association, have proved persistently elusive. For a start, there have been wide differences in the estimated effect size. Becerra *et al* 1990 for example estimated that women with diabetes experienced 15-20 times the odds of CHD or nervous system anomalies,[287] while Garne *et al* 2012 – the largest study of its type but notably lacking a normally-formed comparison group – found equivalent ORs of just 1.2-2.5.[288] In a recent meta-analysis, Zhoa *et al* 2015 estimated the summary risk of congenital anomaly to be 2.4 (95% CI: 1.9 to 3.1) times greater in women with pre-existing diabetes,[289] but there was substantial heterogeneity between the included studies (I^2=78), despite the exclusion of all studies published before 1990.

Meta-analysing CHD specifically, Simeone *et al* 2015 estimated a summary OR of 3.8 (95% CI: 3.0 to 4.9) for pre-existing diabetes, with tentatively less heterogeneity (60%[xv]) between the constituent 14 studies.[290] This may however simply reflect the greater uncertainty around each individual study estimate. Few studies prior to Bell *et al* 2012 (**Section 2·4**, p68)[3] had sufficient power to reliably estimate the effect of diabetes on individual groups and subtypes with precision.[291,292]

[xv] Calculated from data presented in Appendix Table 1 of Simone *et al* 2015[290]

1·3·3·1 Definition

A stillbirth is the delivery of a fetus showing no signs of life at a gestational age where independent life is conventionally thought possible.[293] These comprise both antepartum stillbirths, where the fetus dies before labour, and intrapartum stillbirths, where the fetus dies during labour.[294] Fetal deaths occurring earlier – i.e. before the point where independent life is thought possible - are considered miscarriages.[294] Since this threshold is heavily influenced by the availability and quality of neonatal care, the distinction between miscarriages and stillbirths have changed over time, and there remain notable differences between countries.[294] In the USA for example stillbirths comprise any fetal death occurring at or after 20-weeks' gestation, while in parts of Northern Europe the definition only applies at 28-weeks'.[295] In the UK, the definition of stillbirth was changed from 28-weeks' to 24-weeks' by the 1992 Stillbirth (Definition) Act.[296]

All stillbirths in the UK are legally registered and recorded by the Office for National Statistics (ONS), but worldwide the majority go uncounted.[297] The WHO 'Every Newborn' action plan hope this will change, calling for all countries to start recording all births, including stillbirths.[298] Because of the challenges of ascertainment, the WHO's international stillbirth definition includes fetal deaths occurring at or after 28 weeks' and – since gestational age is often unknown - births with a birthweight under 1000g.[293]

1·3·3·2 Prevalence

Though the label has been applied to a number of maladies, stillbirths are perhaps the ultimate 'silent killer'.[294] By convention, death before the legal definition of life is no death at all.[299] Thus, while an estimated 2.5 million stillbirths are believed to be delivered worldwide every year (equivalent to 2% of all recorded births)[300] these are entirely absent from the WHO's global burden of disease.[301] Given this, it is unsurprising that definitive details of the prevalence of stillbirth are lacking, particularly as more than 98% of stillbirths occur in low- or middle-income countries,[302] where they are not collected routinely or consistently.[297]

Despite their relative rarity in high-income settings, stillbirths – particularly antepartum stillbirths - remain endemic in all populations.[303] In the UK, the prevalence of stillbirth is currently around 4.5-5.0 per 1,000 total births, having fallen by approximately 20% since 1992, when the 24 weeks' threshold was adopted.[204] Compared with other high-income countries however this decline has been somewhat modest.[303] In the 2010 EURO-Peristat project, which compared stillbirth rates in the continent of Europe, the estimate (from 28-

weeks') of 3.8 per 10,000 births for England and Wales was closer to the table-topping 4.3 per 1,000 births in France than the 1.5 per 1,000 births observed in the Czech Republic.[304] Although less dramatic, similar variations are apparent at regional level within the UK.[305]

1·3·3·3 General risk factors

Since 1927, when the UK began the statutory registration of stillbirths, the prevalence has fallen ten-fold.[204] Much of this success can be attributed to improvements in the availability and quality of obstetric care, which have led to dramatic falls in the prevalence of intrapartum stillbirth.[306] Thus, while intrapartum deaths comprise around 10% of stillbirth cases in the UK,[305] they still account for a third of all stillbirths worldwide.[307] In poor rural areas, many women give birth without any healthcare assistance, and deliveries by Caesarean section are especially rare, leading to higher rates of intrapartum stillbirth than even antepartum stillbirth.[294]

After obstetric factors, infectious diseases are likely to be next biggest global cause of stillbirth.[308] One in four women who give birth in sub-Saharan Africa show evidence of infection with malaria,[309] which is associated with five-times the risk of antepartum stillbirth.[310] Infection with syphilis – endemic in many low-income countries – causes stillbirth in 25% of affected pregnancies,[311] and is thought to explain up to a quarter of all stillbirths in sub-Saharan Africa.[312] Most stillbirths with an infectious origin however are thought to result from contamination by commensal organisms, such as *Escherichia coli*, group B streptococci or *Ureaplasma urealyticum*.[313] Although inevitably more common in countries with poorer sanitation and access to antibiotic medication, such infections are nevertheless thought to explain between 10-25% of stillbirths even in more affluent areas.[314]

The leading determinates of stillbirth in high-income settings are derived from the social environment.[315] Women from minority ethnic groups generally experience higher risks of stillbirth than women of white ethnicity.[316-318] Although this may partly be explained by constitutional factors, a large component is explained by correlation with socio-economic disadvantage,[319,320] itself a strong and enduring predictor of stillbirth.[321] Cigarette smoking during pregnancy, which is associated with a doubling in the risk of stillbirth,[322] is considerably more common in more deprived socio-economic groups.[323] Similarly, exposure to second-hand smoking is both correlated with socio-economic disadvantage and with risk of stillbirth.[324,325] The only prominent risk factor for stillbirth in high-income settings that operates against the social gradient is maternal age, with older age at birth – particularly first birth – being associated with an increased risk of stillbirth.[326,327]

1·3·3·4 Obesity and the risk of stillbirth

> '*Obesity… should be recognized as a disease… which during the reproductive phase of a woman's life may have disastrous results both to the mother and to her child*.'

So wrote Emerson in 1962, after finding a four-time greater prevalence of 'fetal loss' in women who 'weighed more than 10% above ideal weight for height'.[328] It has since taken nearly half a century for this early observation to be confirmed. The only notable epidemiological study published before the year 2000 was Little and Weinberg's (1993) exploratory investigation of various potential risk factors for stillbirth, which found a significantly increased risk associated with maternal obesity.[329] Since then, several observational studies have reported significantly increased risks.[91,330-332] Chu *et al*'s meta-analysis in 2007 summarised nine studies to estimate that maternal overweight and maternal obesity were associated with 1.47 (95% CI: 1.08 to 1.94) and 2.07 (95% CI: 1.59 to 2.74) increased odds of stillbirth respectively.[101] More recently, Aune *et al* 2014 combined data from 18 studies across the continuum of BMI to find that the risk of stillbirth increased linearly by 1.24 (95% CI: 1.18 to 1.30) for every 5kg/m^2 increase in BMI above 20kg/m^2.[333] Heterogeneity was apparent between studies that adopted different definitions of stillbirth, with a larger effect (relative risk, RR=1.45, 95% CI: 1.25 to 1.68) among those studies with late (>28 weeks') definitions of stillbirth, than among those studies that using earlier definitions (20-24 weeks) (RR=1.18, 95% CI: 1.11 to 1.25).[333]

1·3·3·5 Diabetes and the risk of stillbirth

As with congenital anomalies, the effect of diabetes on the risk of stillbirth has long been recognised. In White's 1949 cohort of women with pre-existing diabetes, nearly 8% of pregnancies ended in stillbirth.[285] Since then, advances in healthcare have led to increasing optimism, such that in 1989 the St Vincent Declaration set a 5-year goal for women with diabetes to achieve the same pregnancy outcomes as those without the condition.[334] Although the original timeframe proved optimistic,[335] it is nevertheless believed that parity of outcomes can be achieved in, 'well-controlled diabetic patients who attend high-risk clinics'.[336] Much of the recent interest in the association between diabetes and stillbirth has thus focussed on the size and nature of the relationship in routine practice. Observational studies from the last 20-years however have demonstrated little - if any - change in the RR of fetal death.[210,336-343] Pre-existing diabetes thus remains one of the leading causes of stillbirth in high-income countries, with Flenady *et al*'s abridged meta-analysis from 2011 reporting a three times (OR=2.90, 95% CI: 2.05 to 4.09) increase in odds; albeit with some evidence of heterogeneity (I^2=49%, p=0.099).[315]

1·3·4·1 Definition

An infant death is the death of a live born child at any time between birth and aged one year.[344] These comprise neonatal deaths, which consist of deaths up to aged 28 days, and post neonatal deaths, which include all deaths between 28 days and one year.[344] Neonatal deaths are also commonly divided into early neonatal deaths (between 0 and 7 days) and late neonatal deaths (between 7 and 28 days).[344] Perinatal deaths (from which the population-level 'perinatal mortality rate' is derived) includes stillbirths and neonatal deaths.[344]

1·3·4·2 Prevalence

At the end of the 20th century, the USA's Centers for Disease Control and Prevention (CDC) reflected on the country's greatest successes in population health during the preceding hundred years.[345] At the forefront was infant mortality, the decline of which was deemed, '*unparalleled by other mortality reduction this century*'.[346] Outside of high-income settings however there was far less triumphalism.[347] Indeed, such was the burden of child death – the majority of which occur during infancy - that the United Nations (UN) made its reduction – by a factor of two-thirds - their fourth Millennium Development Goal.[348] Although the target was missed, the global incidence of both child death and infant death did fall by around half between 1990 and 2014-15[348] Nevertheless, there remain around 4.5 million infant deaths worldwide per year, a prevalence of 3.4 per 10,000 live births and a ten-fold difference in infant mortality rates between low- and high-income counties.[349,350]

In England and Wales, the prevalence of infant death is currently around 4.0 per 10,000 total births, itself having halved since 1990.[351] This is relatively high among high-income countries. In the 2010 EURO-Peristat project for example the England and Wales ratio of 3.8 per 1,000 births was around the middle of the group; similar to Germany (3.7 per 1,000), France (3.5 per 1,000), and the Netherlands (3.8 per 1,000), but notably behind Iceland (2.3 per 1,000), Finland (2.3 per 1,000), and Sweden (2.3 per 1,000).[304] Similar variations are apparent between regions within the UK.[351]

1·3·4·3 General risk factors

As with stillbirth, the causes of infant death are strongly varied by region. Up to a quarter of global neonatal deaths are due to asphyxia, arising from some of the same complications and deficiencies in obstetric care that underlie the high burden of intrapartum fetal death.[352]

Infectious diseases are also particularly prominent.[353] Up to two million infants die each year from either pneumonia or diarrhoea, a large proportion of which are due to vaccine-preventable infections such as rotavirus, cholera, *streptococcus pneumoniae*, and *Haemophilus influenzae* type b.[354] An additional half a million infants die from sepsis, usually due to infection with commensal bacterial organisms, such as *Escherichia coli*, group B streptococci, and *staphalococcus aureus.*[355] Despite a huge vaccination programme, and an aim to eliminate the condition before 2005, up to 60,000 infants still die every year from tetanus.[356] Similarly, although Mother-to-Child-Transmission programmes have revolutionised pregnancy in HIV, many infants still die from early-life infection with the virus.[357]

The leading cause of infant death in high-income settings is pre-term birth, defined as those births occurring before 37 weeks of gestation.[358] This is however somewhat disingenuous, since preterm birth is itself an outcome with a complex, varied, and unclear aetiology.[359] In low-income areas, a lack of high-quality antenatal and postnatal care – such as prophylactic steroid injections or access to antibiotics – means as many as three-quarters of pre-term infants die from potentially preventable complications.[360] Nevertheless, even with the best available treatment, pre-term infants are still highly susceptible to infection.[361] In a similar manner, congenital anomalies are also one of the world's leading cause of infant death,[362] and account for as many as a third of infant deaths in England and Wales.[351] Although some subtypes are irreparably lethal, others are entirely compatible with survival, even long-term survival, given adequate healthcare provision.[363]

A number of socio-environmental factors are also associated with the risk infant death. The association between material deprivation and the risk of infant death has been long recognised in the UK.[364] Indeed, the socioeconomic gap in infant mortality was the UK government's chosen benchmark for reducing health inequalities during 2001-2010.[365] Regardless, the infant mortality ratio is currently around five times greater among single-parent households from the most deprived occupational social class (7.2 per 1,000 births) than among married households from the least deprived (1.6 per 1,000 births).[351] Though less extreme, similar inequalities are also observed between ethnic groups, with the ratio among Asian Pakistani (6.7 per 1,000 births) and Black African (6.6 per 1,000 births) for example being double the ratio among White British (3.3 per 1,000 births).[366] A range of socially-determined behaviours are known contribute to these differences, including variations in smoking[322,367] alcohol use,[368] and breastfeeding.[369]

1·3·4·4 Obesity and the risk of infant death

The association between maternal obesity and the risk of infant death has not received much attention until relatively recently. In the most prominent investigation published before the year 2000, Cnattingius *et al* 1998 found no significant evidence of association between maternal BMI and the risk of *early* neonatal death, although they did notice a (non-significant) 'doubling' in risk among primiparous women.[370] Three years later, Baeten *et al* 2001 found a corresponding 1.59 (95% CI: 1.18 to 2.13) times increase of infant death in a sample of primiparous women.[371]

There has since been a string of relevant studies,[332,372-378] the results of which were summarised in two systematic reviews published in April 2014.[102,333] Meehan *et al* 2014 pooled the results of 11 observational studies to estimate that the odds of neonatal or infant death were 1.42 (95% CI: 1.24 to 1.63) times greater among obese women than those of recommended BMI.[102] There was some evidence of a dose repose, with the OR increasing to 2.03 (95% CI: 1.61 to 2.56) when the risk threshold was raised to 35kg/m^2 and falling to 1.27 (95% CI: 1.14 to 1.42) when it was lowered to 25kg/m^2.[102] Aune *et al* 2014 examined increasing BMI as a continuum of risk from underweight upwards. [333] Their pooled analysis of 12 cohort studies estimated that the risk of neonatal death and infant death increased by 1.15 (95% CI: 1.07 to 1.23) and 1.18 (95% CI: 1.09 to 1.28) respectively for each 5kg/m^2 increase in pre-pregnancy BMI.[333] More recently, a large study of nearly two million pregnancies in Sweden confirmed that the effect of increasing BMI on infant mortality did not appear to differ between primiparous and multiparous women.[379]

1·3·4·5 Diabetes and the risk of infant death

During the initial decades after the introduction of insulin, high neonatal mortality was a common consequence of diabetes in pregnancy. Miller *et al*'s (1946) cohort of women with diabetes from the USA during 1928-1944 for example found that the prevalence of neonatal death was over four times greater than in those without the condition.[380] Though not formally confirmed by systematic review, this excess appears to have persisted over time. Studies from Sweden, Denmark, Norway, and the UK have all found consistent RRs and ORs for neonatal death of between two and four.[210,336,338-340,343,381]

The notable exception comes from a small Australian cohort study, which reported an apparently flat OR of 1.03 (95% CI: 0.51 to 2.11), although without adjustment for the large number of model variables[xvi], the result is a more consistent 1.87 (95% CI: 1.01-3.48).[341]

[xvi] In their 'multiple logistic regression analysis', Mohsin *et al* 2006 conditioned on maternal age, maternal country of birth, maternal aboriginal heritage, maternal smoking in pregnancy, maternal socioeconomic circumstances, maternal diabetes, maternal hypertension, gravidity, gestational age at the first antenatal appointment, amniocentesis investigation, booking for antenatal care, maternal death at discharge, fetal sex, plurality of pregnancy, birth setting, mode of delivery, and birth weight.[341] Several of these variables (most notably maternal hypertension, amniocentesis investigation, booking for antenatal care, mode of delivery, and birthweight) are likely to act on the causal pathway between maternal pre-existing diabetes and infant death. The interpretation of the conditional association between diabetes and the risk of neonatal death is therefore unclear.

1·4 SUMMARY

Obesity and diabetes are serious and related disorders of metabolism with complex aetiologies. The proportions of people living with these conditions, whether in the UK or the throughout the world, have increased dramatically over the past thirty years, and most estimates suggest these trends are set to continue. The public health implications of this 'epidemic' are profound, since both obesity and diabetes are associated with a range of severe and costly health problems.

Though less affected than older age groups, obesity and diabetes are increasingly common in women of childbearing age and hence complicate an increasing proportion of pregnancies. During pregnancy, both conditions have been associated with higher risks of serious adverse fetal outcomes including congenital anomalies, stillbirths and infant deaths; although previous studies have lacked certain details or been limited by methodological issues. Though relatively rare, these events are responsible for a substantial population burden of misery and mortality, particularly in low- and middle-income countries.

Among high-income nations, the UK has a relatively high prevalence of stillbirth and infant death, despite a declining proportion of births complicated by congenital anomaly. Although potentially due to a number of social factors, such as smoking, the UKs high prevalence of obesity[xvii] and incidence of type 1 diabetes[xviii] are likely contributors. The following chapter describes six individual investigations which sought to clarify and explore the effects of maternal pre-pregnancy obesity and pre-existing diabetes on the risks of serious adverse pregnancy outcomes within the UK.

[xvii] In 2012, the prevalence of obesity among adults living in the UK was estimated to be 24.7%, compared with a European average of 16.7%. This was higher than in all other European nations, except Hungary.[382]

[xviii] In 2013, the incidence of type 1 diabetes among children aged 0-14 years was estimated to be 28.2 per 100,000, compared with a European average of 18.4 per 100,000. This was higher than in all other European nations, except Finland, Sweden, and Norway.[382]

CHAPTER 2: SUBMITTED PUBLISHED WORKS

2·1 OVERVIEW

This chapter presents the six original articles that form the basis of my submission for a PhD by Published Works. For each, I made a substantial independent contribution to the conduct of the research and content of the manuscript, details of which have been provided and approved by all co-authors.

The submitted articles have been incorporated directly into the Doctoral Statement to minimise repetition and provide the most unbiased account of the research. Each has nevertheless been accompanied by a summary of its contribution to the literature in the style of a BMJ article synopsis, albeit modified into past tense ('what *was* known', and 'what this study *added*') to better convey the contemporary impact. An additional commentary is also provided, to evaluate the methods and results of each investigation in the context of subsequent changes to knowledge and practice.

The first two articles (Rankin *et al* 2010, **Section 2·2**, p38; and Tennant *et al* 2011, **Section 2·3**, p53) describe a retrospective cohort of approximately 30,000 pregnant women who booked and delivered in one of five hospitals in the North of England during 2003-2005. Electronic maternity records were linked with perinatal outcome data from the Northern Congenital Abnormality Survey (NorCAS)[xix] and Northern Perinatal Mortality Survey (PMS)[xx] to examine the associations between maternal BMI and the risks of congenital anomaly and fetal and infant death respectively.

The next three articles (Bell *et al* 2012, **Section 2·4**, p68; Glinianaia *et al* 2012, **Section 2·5**, p84; and Tennant *et al* 2013, **Section 2·6**, p108) describe a population-based cohort of approximately 1500 pregnant women with pre-existing diabetes who delivered in the North of England during 1996-2008 and consented to participate in the Northern Diabetes in Pregnancy Survey (NorDIP)[xxi]. Detailed sociodemographic and clinical information notified to the NorDIP were linked with outcome data from the NorCAS and PMS to examine the risks

[xix] The NorCAS was a population-based register of congenital anomaly. All cases delivered in the North of England during 1985-2015 were notified to the register, whether occurring in live birth, stillbirth, late miscarriage, or termination of pregnancy for fetal anomaly (any gestation).

[xx] The PMS was a population-based register of late miscarriage, stillbirth, and infant death. All cases delivered in the North of England during 1981-2015 were notified to the register.

[xxi] The NorDIP was a population-based survey of pre-existing diabetes in pregnancy. All pregnant women with type 1 or type 2 diabetes (diagnosed at least six months prior to the start of pregnancy) that booked for delivery in the North of England during 1996-2015 were invited to participate in the audit.

and predictors of congenital anomalies, birth weight, and fetal and infant death in women with diabetes.

The final article (Tennant *et al* 2015, **Section 2·7**, p127) describes a longitudinal cohort of 220 women with pre-existing diabetes who booked a first and successive second singleton pregnancy in the North of England during 1996-2008 and consented to participate in the NorDIP. The article examined the risk, and predictors, of serious adverse pregnancy outcome in the first and second pregnancy specifically, including the effect of adverse outcome in the first pregnancy.

Five additional publications have been included as supporting evidence in **Appendix B** (p191) without further comment or analysis. These include one systematic review which was ineligible for primary inclusion in this submission[xxii], one published letter, and three original articles towards which I made a secondary contribution.

[xxii] Stothard *et al* 2009 (**Appendix B(i)**, p187) was published over six years prior to the date of submission for examination and was therefore not eligible for consideration.

2·2 RANKIN *et al* 2010 (MATERNAL BMI & CONGENITAL ANOMALIES)

Title: Maternal body mass index and congenital anomaly risk: a cohort study

Authors: Rankin J, **Tennant PWG**, Stothard KJ, Bythell M, Summerbell C, and Bell R

Journal: International Journal of Obesity (Volume 34 Issue 9 Pages 1371-1380)

Date of publication: 06 April 2010

2·2·1 Overview

This article describes the results of a retrospective cohort study that sought to examine the association between maternal pre-pregnancy BMI and the prevalence of congenital anomaly, by group and subtype. Information on maternal BMI at booking - as well as a number of pre-hypothesised potential confounding factors - were obtained from the electronic records of five maternity units in the North of England for deliveries occurring during 2003-2005 and linked with outcome data on the occurrence of congenital anomalies from the NorCAS.

The publication has a corrigendum, which corrects for minor discrepancies in the footnotes to **Table 2** (**Section 2·2·6**, p50).

2·2·2 What was known

- Several studies from the USA had shown an association between maternal obesity and increased risks of NTDs, CHD, and orofacial clefts, but the association with other anomaly groups and for all individual subtypes was unclear
- Some of the excess risk was thought to be due to differences in the rates of termination of pregnancy for congenital anomaly or from confounding by factors such as maternal age, smoking, ethnicity, and socioeconomic status
- Maternal underweight had also been associated with a higher risk of gastroschisis, but little was known about the potential association with congenital anomalies as a whole, or for other individual groups or subtypes.

2·2·3 What this study added

- In the first UK cohort study to examine this question, the overall prevalence of congenital anomaly (all groups) was found to be significantly greater in women who were either underweight [aOR=1.60 (95% CI: 1.09 to 2.36)] or obese [aOR=1.30 (95% CI: 1.03 to 1.63)] pre-pregnancy compared with women of recommended BMI.

- Relative and absolute risks of congenital anomaly, overall and by group and subtype, were presented by WHO BMI category, with obesity being significantly associated with cleft lip, ventricular septal defects (VSDs), and eye anomalies and maternal underweight associated with atrial septal defects (ASDs), hypospadias, and genital anomalies.

- The proportion of terminations of pregnancy for congenital anomaly was no different between obese women and women of recommended BMI, suggesting that differences in live born prevalence are not likely to be explained by differential termination rates.

- None of maternal age, smoking, ethnicity, or socioeconomic circumstances had any perceptible effect on the association between obesity and the odds of congenital anomaly, suggesting that these are unlikely to be acting as confounding factors (at least in similar populations).

2·2·4 Contribution of the candidate to this work

I performed the cleaning and merging of the five hospital datasets, coded the individual congenital anomaly diagnoses into groups and subtypes, conducted the data analysis, drafted the methods, results, tables, produced Figure 1, and critically-reviewed the draft produced by JR. A copy of the Newcastle University Co-Authorship form for this publication can be found in **Appendix A(i)** (p179).

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ORIGINAL ARTICLE

Maternal body mass index and congenital anomaly risk: a cohort study

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Objective: To investigate the association between maternal body mass index (BMI) and major, structural congenital anomalies.
Design: Cohort study using prospectively collected data.
Methods: Data on all singleton pregnancies booked at five maternity units in the north of England between 01 January 2003 and 31 December 2005 and data on congenital anomalies notified to the Northern Congenital Abnormality Survey were linked using key variables. Maternal pre-gestational diabetic status was derived from the Northern Diabetes in Pregnancy Survey. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were estimated by maximum-likelihood logistic regression models, with missing values modelled as explicit categories.
Results: There was a total of 41 013 singleton pregnancies during the study period, of which 682 were affected by a structural congenital anomaly, a total prevalence of 166 (95% CI: 154, 179) per 10 000 registered births. Overall, the risk of a congenital anomaly was significantly increased among the maternal underweight (BMI $\leqslant 18.5\,kg\,m^{-2}$; aOR = 1.60, 95% CI: 1.09, 2.36; $P = 0.02$) and maternal obese groups (BMI $\geqslant 30\,kg\,m^{-2}$; aOR = 1.30, 95% CI: 1.03, 1.63; $P = 0.03$), but not for maternal overweight (BMI = 25–29.9 $kg\,m^{-2}$; aOR = 0.85, 95% CI: 0.68, 1.06; $P = 0.15$), compared with mothers of recommended BMI. Maternal obesity was associated with significantly increased risk of ventricular septal defect (aOR = 1.56, 95% CI: 1.01, 2.40; $P = 0.04$), cleft lip (aOR = 3.71, 95% CI: 1.05, 13.10; $P = 0.04$) and eye anomalies (aOR = 11.36, 95% CI: 2.25, 57.28; $P = 0.003$). Maternal underweight was associated with significantly increased risks of atrial septal defect (aOR = 2.86, 95% CI: 1.18, 6.96; $P = 0.02$), genital anomalies (aOR = 6.30, 95% CI: 1.58, 25.08; $P = 0.009$) and hypospadias (aOR = 8.77, 95% CI: 1.42, 54.29; $P = 0.02$).
Conclusions: We found an overall increased risk of congenital anomalies in women who are obese and women who are underweight compared with women of recommended weight. Women should be made aware of these risks and supported to optimize their weight before pregnancy.
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Keywords: underweight; body mass index; congenital abnormalities; pregnancy

Introduction

Obesity is a major public health and economic concern. Globally, 1.6 billion adults age 15 or above were overweight (body mass index (BMI) $\geqslant 25\,kg\,m^{-2}$) and over 400 million adults were obese (BMI $\geqslant 30\,kg\,m^{-2}$) in 2005.[1] In the United Kingdom, almost a quarter of adults (24%), both men and women, were obese in 2007.[2]

The prevalence of overweight and obesity among women of childbearing age (16–44 years) is also increasing. Within the United Kingdom, there has been an increase in obesity among women of childbearing age from 12.0% in 1993 to 18.5% in 2006.[3]

Obesity in pregnancy is known to be associated with a number of adverse clinical outcomes for both the mother and baby. Health implications for the mother include increased risk of insulin resistance and gestational diabetes, hypertensive disorders, and increased caesarean section rates.[4–6] For the infant, the health implications of maternal obesity include increased birthweight, stillbirth and neonatal death, and shoulder dystocia during delivery.[7–9] (see Box 1 for definitions of obstetric terminology).

Congenital anomalies are a diverse range of conditions present at birth that affect approximately 2–4% of all deliveries. They are a leading cause of stillbirth and infant mortality as well as being important contributors to preterm

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Box 1 Glossary of obstetric terminology

- Anencephaly—a neural tube defect that occurs when the cephalic (head) end of the neural tube fails to close.
- Association—the nonrandom occurrence in two or more individuals of a pattern of multiple anomalies not known to be a malformation syndrome (such as Down's syndrome), a malformation sequence (of events) or what is called a polytopic field defect (in which all of the defects are concentrated in one particular area of the body).
- Atrial septal defect—a hole in the septum, the wall, between the atria, the upper chambers of the heart.
- Hydrocephalus—an abnormal buildup of cerebrospinal fluid (CSF) in the ventricles of the brain.
- Hypertensive disorders—having abnormally high blood pressure.
- Hypospadias—a birth defect of the penis involving the urethra (the transport tube leading from the bladder to discharge urine outside the body).
- Microdeletion—The loss of a tiny piece of a chromosome, a piece so small its absence is not apparent on ordinary examination (using a regular light microscope to look at chromosomes prepared in the usual fashion).
- Monogenic syndrome—pertaining to one gene. As opposed to polygenic.
- Shoulder dystocia—halt to spontaneous delivery because the baby's shoulder is wedged behind the mother's pubis, owing usually to the baby being too big to fit through the birth canal.
- Ventricular septal defect—a hole in the septum (the wall) between the lower chambers of the heart (the ventricles).

Taken from http://www.medterms.com.

birth and morbidity in the first year of life and beyond. Studies, mainly from the United States of America also suggest an association between maternal obesity and congenital anomalies, in particular neural tube defects,[10–12] and cardiac anomalies.[13–16] Although maternal obesity has been associated with other congenital anomaly subtypes, the evidence for these links is less consistent.[17] Maternal underweight has also been linked with the occurrence of specific congenital anomalies, for example, gastroschisis.[18] A recent systematic review and meta-analysis also suggested that maternal overweight may also be implicated.[17]

The aim of this cohort study is to investigate whether maternal BMI at the first antenatal visit is associated with the occurrence of major, structural (non-chromosomal) congenital anomalies in the northeast region of the United Kingdom.

Materials and methods

Study population

Data on all singleton pregnancies occurring between 01 January 2003 and 31 December 2005, booked and delivered in five maternity units in the northeast of England, were included in the study. Multiple pregnancies were excluded as they are known to have a higher congenital anomaly risk than singletons.[19] The five hospitals were chosen as they have electronically stored maternity care information for recent years.[20] The five participating maternity units included both tertiary referral centres in major urban areas and smaller district general hospitals. Overall, they account for around half of all deliveries in the northeast region of England. The women delivering in these units are likely to be typical of the regional population as a whole.

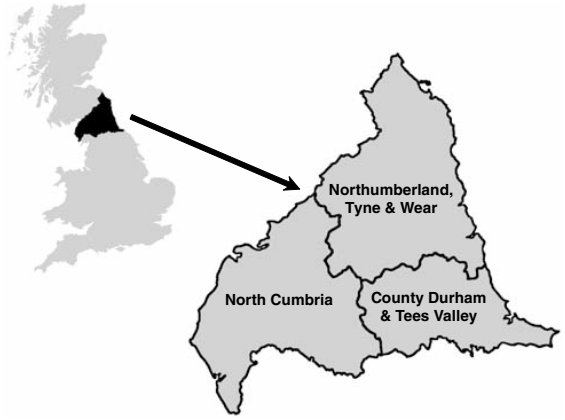

Figure 1 Map of the geographical area covered by the Northern Congenital Abnormality Survey (NorCAS).

Congenital anomaly data

Congenital anomaly data were extracted from the Northern Congenital Abnormality Survey (NorCAS), a population-based register of congenital anomalies that has been operating since 1985. The NorCAS is a voluntary collaborative survey, which collects data prospectively on congenital anomalies arising within the population of approximately three million living in the former Northern Health region, which includes the catchment populations of the five participating hospitals and an average of 30 000 total annual births during the study period.[21] The geographical area covered by NorCAS is shown in Figure 1.

Case definition, classification and ascertainment

The NorCAS collects data on congenital anomalies whether occurring as late miscarriages (gestational age $\geqslant$20 weeks), terminations of pregnancy for fetal anomaly after prenatal diagnosis, or registered births (live and stillbirths), and whether diagnosed antenatally or not. Cases born to mothers resident at birth within the boundaries of the former Northern health region, even if they were delivered outside the region, are captured by the NorCAS. Cases are notified to the register from multiple sources including antenatal ultrasound, fetal medicine records, cytogenetic laboratories, the regional cardiology centre, pathology departments and pediatric surgery to ensure a high case ascertainment. All cases of congenital heart disease are confirmed by autopsy, surgery, echocardiography or cardiac

catheterization. Once notified, cases are verified for duplication and then entered onto the register. Further details of data collection have been published previously.[22] The NorCAS has a high case ascertainment as evidenced by the regular cross-validations carried out with the UK Office for National Statistics and with regional cytogenetic and pediatric cardiology databases.[23,24]

The age limit for registration onto NorCAS during the study period was 12 years. NorCAS records up to six congenital anomalies per case and adopts the exclusion criteria for minor anomalies used by the European Surveillance of Congenital Anomalies (EUROCAT).[25] NorCAS is a member of the British Isles Network of Congenital Anomaly Registers[26] and EUROCAT. All anomalies are coded using the WHO International Classification of Diseases version 10 (ICD 10).

Congenital anomalies were categorized by congenital anomaly group (the organ system affected), subtype (the individual condition) and syndrome (where applicable) according to the EUROCAT guidelines.[25]

Cases included all singleton deliveries (including terminations of pregnancy for fetal anomaly at any gestation, stillbirths of $\geqslant$24 weeks gestation and live births) with at least one EUROCAT-classified congenital anomaly notified to the NorCAS with a date of delivery between 01 January 2003 and 31 December 2005 and delivered in one of the five hospitals. Cases associated with a known teratogen, chromosomal anomaly, monogenic syndrome, microdeletion, association or sequence were excluded.

Information on diabetes status of the mother

Information on maternal pre-gestational diabetes status was derived from the Northern Survey of Diabetes in Pregnancy (NorDIP),[27] a collaborative survey of all pregnancies in women with diabetes diagnosed at least 6 months before the index pregnancy. NorDIP coordinators in each hospital notify pregnancies in women with pre-gestational diabetes, and data collection is undertaken by clinicians within the unit.

The NorDIP and NorCAS are maintained on a central database held at the Regional Maternity Survey Office in Newcastle upon Tyne.[21]

Data linkage

The hospital data were matched to the data held by the NorCAS and the NorDIP by staff in the information departments in each of the five hospitals. Data linkage was achieved by fuzzy matching using five key variables: mother's surname, mother's postcode at booking, infant date of birth, infant sex and birthweight. 'Fuzzy' matching involved first linking the data sets using all five variables, then by matching four variables, three, two and finally by using one variable.

The index of multiple deprivation, a UK census-derived area-based measure of socioeconomic deprivation, was determined from the mother's residential postcode and was added to the linked data set by staff at the NorthEast Public Health Observatory. The index of multiple deprivation is based on seven census domains: income deprivation, employment deprivation, health deprivation and disability, education, skills and training deprivation, barriers to housing and services, living environment deprivation, and crime.[28]

Ethical approval

The NorCAS has exemption from the National Information Governance Board for Health and Social Care from a requirement for consent for inclusion on the register and has ethics approval (04/MRE04/25), as part of the British Isles Network of Congenital Anomaly Registers network, to undertake studies involving the use of the data. This study was given a favourable ethical opinion from the Northumberland Research Ethics Committee (07/Q0902/2) and Research and Development approval from each of the participating hospitals.

Analyses

Variables were treated as categorical to account for potentially non-linear relationships. BMI was categorized according to the WHO classification: underweight BMI $\leqslant 18.5\,kg\,m^{-2}$; recommended weight BMI = 18.5–$24.9\,kg\,m^{-2}$; overweight BMI = 25–$29.9\,kg\,m^{-2}$; and obese BMI $\geqslant 30\,kg\,m^{-2}$. Maternal age at delivery was separated into three categories: $<$20 years, 20–29 years and $\geqslant$30 years. Cigarette smoking status was dichotomized into current smokers and non/ex-smokers. The index of multiple deprivation was ranked and divided into tertiles for this study.

Unadjusted odds ratios (ORs), adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were estimated by maximum-likelihood logistic regression models, with missing values modelled as explicit categories.[29] Adjusted models included maternal age at delivery, ethnicity, maternal BMI at the first antenatal visit, maternal history of pre-gestational diabetes, cigarette smoking status at the first antenatal visit and index of multiple deprivation. ORs for the risk of a structural congenital anomaly were calculated for all maternal and fetal factors and for maternal BMI. ORs were calculated for all congenital anomaly groups and subtypes with five or more recorded cases. This cut-off was chosen to comply with current disclosure guidance.[30] Interactions between maternal BMI and other maternal variables in predicting a structural congenital anomaly were examined by the inclusion of cross-product terms. Prevalence estimates for the total population, and stratified by BMI, were calculated for congenital anomaly groups and subtypes with five or more recorded cases.

As a smaller proportion of the cases had missing BMI than the non-cases, stratified prevalence estimates were weighted

to correct for the resultant under-representation of the denominator. Weighting was determined for each congenital anomaly group and subtype as the ratio of all case pregnancies (or non-case pregnancies) to case pregnancies (or non-case pregnancies) with non-missing BMI multiplied by the ratio of all pregnancies (case and non-case) to pregnancies with a non-missing BMI.

Statistical analyses were performed using Stata 10 1 (StataCorp, College Station, TX, USA) and $P<0.05$ was considered statistically significant.

Results

There was a total of 40 934 singleton pregnancies identified during the 3-year study period, of which 682 were affected by a structural congenital anomaly, a total prevalence of 166 (95% CI: 154, 179) per 10 000 registered births (Table 1). Cardiovascular anomalies were the most common congenital anomaly group identified, being present in half of the case pregnancies (341), followed by urinary anomalies (113; 16.6%), nervous system anomalies (71; 10.4%), digestive system anomalies (63; 9.2%) and orofacial clefts (59; 8.7%) (Table 1). In all, 585 (85.8%) of the case pregnancies ended in live birth, 84 (12.3%) in termination of pregnancy for fetal anomaly and 12 (1.8%) in fetal death (>20 weeks gestation).

Table 2 shows the distribution of maternal and fetal variables among cases (that is, pregnancies affected by a congenital anomaly) and non-cases. Mothers with pre-gestational diabetes and mothers who smoked cigarettes during pregnancy were both at significantly greater odds of a pregnancy affected by a congenital anomaly (diabetes: $P<0.001$, smoking: $P=0.02$).

Of the fetal factors, indeterminate sex ($P<0.001$), very low gestational age at delivery ($P<0.001$) and low birth weight ($P<0.001$) were significantly more common among pregnancies affected by a congenital anomaly, although fetal sex was not significant when cases of indeterminate sex were excluded ($P=0.38$).

Maternal BMI was missing for one-quarter of the participants (23.5% of cases; 25.0% of non-cases), resulting in 30 703 singleton pregnancies with known BMI, which included 522 cases. Those with missing BMI were older ($P<0.001$), less likely to smoke ($P<0.001$), less likely to live in a deprived area ($P<0.001$) and delivered smaller infants or fetuses ($P<0.001$) of a shorter gestational age ($P<0.001$). Table 3 shows the estimated prevalence of congenital anomaly by BMI category, correcting for unbalanced missing values.

Table 4 presents the ORs of a pregnancy being affected by a structural congenital anomaly by maternal BMI. There were no differences between the unadjusted ORs and the adjusted ORs for any of the comparisons examined, hence only adjusted ORs are presented (Table 4). The overall risk of a congenital anomaly were significantly increased among the mothers who were underweight (aOR = 1.60, 95% CI: 1.09–2.36; $P=0.02$) and obese (aOR = 1.30, 95% CI: 1.03–1.63; $P=0.03$), but not for those who were overweight (aOR = 0.85, 95% CI: 0.68–1.06; $P=0.16$), compared with mothers of recommended BMI (Table 4). Considering the congenital anomaly groups and subtypes, maternal obesity was associated with a significantly increased risk of

Table 1 Total prevalence (per 10 000 singleton deliveries and 95% confidence intervals) of selected structural congenital anomaly groups and subtypes[a]

Congenital anomaly[b]	*Total*	*Total prevalence per 10 000 singletons*[c] *(95% CI)*[d]
All structural anomalies	682	166 (154–179)
Nervous system anomalies	71	18 (14–22)
Neural tube defects	42	10 (8–14)
Anencephaly	18	4 (3–7)
Spina bifida	22	5 (3–8)
Hydrocephalus	14	3 (2–6)
Microcephaly	9	2 (1–4)
Eye	11	3 (1–5)
Congenital cataract	6	1 (1–3)
Cardiovascular anomalies	341	84 (75–93)
Transposition of the great vessels	16	4 (2–6)
Ventricular septal defect	155	38 (33–45)
Atrial septal defect	77	19 (15–24)
Atrioventricular septal defect	11	3 (1–5)
Tetralogy of Fallot	18	4 (3–7)
Ebstein anomaly	5	1 (<1–3)
Pulmonary valve stenosis	55	14 (10–18)
Aortic valve atresia/stenosis	9	2 (1–4)
Hypoplastic left heart	6	1 (1–3)
Coarctation of the aorta	17	4 (2–7)
Respiratory	17	4 (2–7)
Cystic adenomatoid malformation	6	1 (1–3)
Orofacial clefts	59	15 (11–19)
Cleft lip	19	5 (3–7)
Cleft lip and palate	22	5 (3–8)
Cleft palate	18	4 (3–7)
Digestive system	63	16 (12–20)
Anorectal atresia/stenosis	11	3 (1–5)
Hirschsprung disease	6	1 (1–3)
Diaphragmatic hernia	7	2 (1–4)
Abdominal wall	15	4 (2–6)
Gastroschisis	12	3 (2–5)
Omphalocele	6	1 (1–3)
Urinary	113	28 (23–34)
Bilateral renal agenesis	6	1 (1–3)
Cystic kidney disease	31	8 (5–11)
Genital	21	5 (3–8)
Hypospadias	9	2 (1–4)
Indeterminate sex	6	1 (1–3)
Limb	24	6 (4–9)
Limb reduction anomalies	11	3 (1–5)
Polydactyly	9	2 (1–4)
Musculo-skeletal	11	3 (1–5)
Other congenital anomalies	7	2 (1–4)

Abbreviation: CI, confidence interval. [a]Classified according to EUROCAT guidelines. [b]Only subtypes with greater than five cases are shown due to UK disclosure guidelines at time of submission. [c]Includes those occurring in fetal deaths (>20 weeks gestation), terminations of pregnancy for fetal anomaly following prenatal diagnosis, and live births. [d]Binomial exact confidence intervals.

Table 2 Maternal and fetal characteristics among cases and non-cases

Variable	*Cases (%)* N = *682*[a]	*Non-cases (%)* N = *40 260*	*Adjusted odds ratio (95% CI)*[b]	*Adjusted P-value*[b]
Maternal characteristics				
Maternal age				
<20 years old	79 (11.6)	4089 (10.2)	1.08 (0.84–1.39)	
20–29.9 years old	333 (48.8)	19 454 (48.3)	Reference	0.68
⩾30 years old	270 (39.6)	16 709 (41.5)	0.96 (0.81–1.13)	
Maternal ethnicity				
White	519 (76.1)	33 634 (83.6)	Reference	0.63
Non-white	53 (7.8)	3301 (8.2)	1.07 (0.80–1.44)	
Missing	110 (16.1)	3317 (8.2)		
BMI (kg m^{-2})				
<18.5 (underweight)	30 (4.4)	1060 (2.6)	1.60 (1.09–2.36)	
18.5–24.9 (recommended)	274 (40.2)	16 214 (40.3)	Reference	0.002
25–29.9 (overweight)	113 (16.6)	7975 (19.8)	0.85 (0.68–1.06)	
⩾30 (obese)	105 (15.4)	4932 (12.3)	1.30 (1.03–1.63)	
Missing	160 (23.5)	10 071 (25.0)		
Maternal pre-gestational diabetes				
No	672 (98.5)	40 067 (99.5)	Reference	<0.001
Yes	10 (1.5)	185 (0.5)	3.22 (1.68–6.15)	
Cigarette smoking status				
None/ex-smoker	360 (52.8)	25 251 (62.7)	Reference	0.02
Current smoker	165 (24.2)	9137 (22.7)	1.28 (1.05–1.57)	
Missing	157 (23.0)	5864 (14.6)		
Index of multiple deprivation				
Tertile 1 (most deprived)	247 (36.2)	13 386 (33.3)	0.86 (0.71–1.04)	
Tertile 2	214 (31.4)	13 375 (33.2)	Reference	0.28
Tertile 3 (most advantaged)	220 (32.3)	13 297 (33.0)	0.95 (0.78–1.16)	
Missing	1 (0.2)	194 (0.5)		
Fetal characteristics				
Sex of infant/fetus[c]				
Male	352 (51.6)	20 498 (50.9)	Reference	<0.001 (0.38[b])
Female	316 (46.3)	19 745 (49.1)	0.93 (0.80–1.09)	
Indeterminate	9 (1.3)	8 (0.0)	52.62 (19.90–139.81)	
Missing	5 (0.7)	1 (0.0)		
Gestational age				
<24 weeks	88 (12.9)	69 (0.2)	73.52 (52.15–103.65)	<0.001
24–36 weeks	111 (16.3)	2636 (6.6)	2.93 (2.36–3.62)	
⩾37 weeks	483 (70.8)	34 481 (85.7)	Reference	
Missing	0 (0.0)	3066 (7.6)		
Birth weight				
<2.5 kg	188 (27.6)	2704 (6.7)	5.18 (4.32–6.20)	<0.001
2.5–3.99 kg	429 (62.9)	32 697 (81.2)	Reference	
⩾4.0 kg	54 (7.9)	4828 (12.0)	0.84 (0.63–1.12)	
Missing	11 (1.6)	23 (0.1)		

Abbreviations: BMI, body mass index; CI, confidence interval. [a]Includes those occurring in fetal deaths (>20 weeks gestation), terminations of pregnancy for fetal anomaly following prenatal diagnosis and live births. [b]Adjusted for maternal age, ethnicity, BMI, pre-gestational diabetes, cigarette smoking status and index of multiple deprivation. [c]Comparison between males and females only, that is, excluding those of indeterminate sex.

ventricular septal defect (aOR = 1.56, 95% CI: 1.01, 2.40; $P = 0.04$), cleft lip (aOR = 3.71, 95% CI: 1.05, 13.10; $P = 0.04$) and eye anomalies (aOR = 11.36, 95% CI: 2.25, 57.28; $P = 0.003$). Maternal underweight was associated with a significantly increased risk of both atrial septal defect (aOR = 2.86, 95% CI: 1.18, 6.96; $P = 0.02$) and genital anomalies (aOR = 6.30, 95% CI: 1.58, 25.08; $P = 0.009$), in particular hypospadias (aOR = 8.77, 95% CI: 1.42, 54.29; $P = 0.02$). There was no significant increased risk for maternal overweight (Table 4). No significant evidence of interaction was observed between maternal BMI and any of the other variables in the adjusted model.

Table 3 Total prevalence (per 10 000 singleton deliveries and 95% confidence intervals) of selected structural congenital anomaly groups and subtypes stratified by maternal BMI

Congenital anomaly[a]	*Total with BMI*	*Prevalence per 10 000 singletons (95% CI)*[b,c,d]			
		Underweight: BMI <18.5	*Recommended: BMI 18.5–24.9*	*Overweight: BMI 25.0–29.9*	*Obese: BMI 30.0*
All structural anomalies	522	270 (179–380)	163 (144–183)	137 (112–164)	204 (165–245)
Nervous system anomalies	42	37 (6–82)	13 (8–20)	5 (1–11)	24 (11–40)
Neural tube defects	23	18 (<1–52)	7 (3–11)	5 (1–11)	12 (3–24)
Anencephaly	7	9 (<1–35)	1 (<1–3)	4 (<1–9)	2 (<1–7)
Spina bifida	15	9 (<1–35)	5 (2–9)	1 (<1–5)	10 (2–21)
Hydrocephalus	12	9 (<1–35)	4 (1–8)	<1 (<1–5)	8 (<1–18)
Microcephaly	5	9 (<1–35)	1 (<1–3)	<1 (<1–5)	4 (<1–11)
Eye	9	<1 (<1–35)	1 (<1–3)	1 (<1–5)	12 (3–24)
Cardiovascular	272	137 (71–218)	89 (75–105)	67 (49–86)	104 (76–134)
Transposition of the great vessels	15	18 (<1–52)	5 (2–10)	<1 (<1–5)	8 (1–18)
Ventricular septal defect	123	37 (6–82)	40 (31–51)	26 (15–39)	61 (41–86)
Atrial septal defect	60	55 (15–109)	18 (12–26)	16 (8–26)	22 (10–37)
Atrioventricular septal defect	10	<1 (<1–35)	6 (3–11)	<1 (<1–5)	<1 (<1–7)
Tetralogy of Fallot	14	<1 (<1–35)	5 (2–10)	5 (1–11)	2 (<1–7)
Pulmonary valve stenosis	35	18 (<1–52)	12 (7–18)	7 (2–15)	14 (4–26)
Aortic valve atresia/stenosis	7	<1 (<1–35)	2 (<1–4)	2 (<1–7)	4 (<1–11)
Coarctation of the aorta	15	<1 (<1–35)	5 (2–9)	4 (<1–9)	8 (1–18)
Respiratory	12	<1 (<1–35)	4 (1–7)	4 (<1–9)	6 (<1–15)
Cystic adenomatoid malformation	6	<1 (<1–35)	2 (<1–5)	2 (<1–7)	<1 (<1–7)
Orofacial clefts	45	28 (2–68)	13 (8–20)	11 (4–20)	22 (10–37)
Cleft lip	12	<1 (<1–35)	3 (1–6)	2 (<1–7)	10 (2–21)
Cleft lip and palate	19	9 (<1–35)	6 (3–11)	5 (1–11)	8 (1–18)
Cleft palate	14	18 (<1–52)	4 (1–8)	4 (<1–9)	4 (<1–11)
Digestive system	45	18 (<1–52)	14 (8–21)	13 (6–23)	18 (7–32)
Anorectal atresia/stenosis	9	<1 (<1–35)	4 (1–7)	4 (<1–9)	<1 (<1–7)
Hirschsprung disease	6	9 (<1–35)	<1 (<1–2)	4 (<1–9)	4 (<1–11)
Abdominal wall	7	9 (<1–35)	2 (<1–5)	2 (<1–7)	<1 (<1–7)
Gastroschisis	6	9 (<1–35)	2 (<1–4)	2 (<1–7)	<1 (<1–7)
Urinary	86	46 (10–96)	28 (21–38)	27 (16–40)	24 (11–40)
Bilateral renal agenesis	6	<1 (<1–35)	2 (<1–5)	2 (<1–7)	<1 (<1–7)
Cystic kidney	24	9 (<1–35)	10 (5–15)	4 (<1–9)	8 (1–18)
Genital	16	28 (2–68)	4 (1–8)	6 (1–13)	2 (<1–7)
Hypospadias	8	18 (<1–52)	2 (<1–4)	2 (<1–7)	2 (<1–7)
Limb	17	18 (<1–52)	5 (2–10)	6 (1–13)	2 (<1–7)
Limb reduction anomalies	10	9 (<1–35)	4 (1–7)	4 (<1–9)	<1 (<1–7)
Polydactyly	6	<1 (<1–35)	2 (<1–4)	2 (<1–7)	2 (<1–7)
Musculo-skeletal	6	<1 (<1–35)	1 (<1–3)	4 (<1–9)	2 (<1–7)
Other congenital anomalies	5	<1 (<1–35)	2 (<1–5)	1 (<1–5)	<1 (<1–7)

Abbreviations: BMI, body mass index; CI, confidence interval. [a]Only subtypes with greater than five cases are shown. [b]Corrected for unbalanced missing values. [c]Includes those occurring in fetal deaths (>20 weeks gestation), terminations of pregnancy for fetal anomaly following prenatal diagnosis and live births. [d]Binomial exact confidence intervals.

Discussion

This cohort study describes the relationship between maternal BMI at the first antenatal visit and the risk of a pregnancy being affected by a structural congenital anomaly over a 3-year period using data from the northeast of England. Only two previous studies from the United Kingdom have considered maternal weight and congenital anomaly risk, and both predate the current rise in obesity levels. Richards[31] found an increased risk of anencephaly in women who were heavier than controls, and Wald *et al.*[32] found that maternal serum alpha-fetoprotein, a marker for neural tube defects, was higher in lighter women. This is the first UK study to examine the relationship between maternal BMI and risk of congenital anomaly. After adjustment for available risk factors, we found that the overall risk of a structural congenital anomaly was greater for women who were obese or underweight at the start of pregnancy compared with women of recommended weight, but not for women who were overweight. More specifically, maternal obesity was associated with an increased risk of ventricular septal defects, cleft lip and eye anomalies while maternal underweight was associated with atrial septal defect, genital anomalies and hypospadias. No other significant associations were found between maternal BMI and any other congenital anomaly group or subtype. We analysed 23 congenital anomaly groups/subtypes and four categories of BMI. However, with such a large number of comparisons, we expect some

Table 4 Relative odds of a pregnancy affected by a structural congenital anomaly group and subtype by maternal BMI

Congenital anomaly[a]	*Total with BMI*	*Underweight: BMI <18.5*		*Overweight: BMI 25.0–29.9*		*Obese: BMI⩾30.0*	
		Adjusted odds ratio (95% CI)[b]	P-*value*	*Adjusted odds ratio (95% CI)*[b]	P-*value*	*Adjusted odds ratio (95% CI)*[b]	P-*value*
All structural anomalies	522	1.60 (1.09–2.36)	0.02	0.85 (0.68–1.06)	0.15	1.30 (1.03–1.63)	0.03
Nervous system anomalies	42	2.44 (0.82–7.22)	0.11	0.38 (0.13–1.11)	0.08	1.88 (0.91–3.86)	0.09
Neural tube defects	23	2.18 (0.47–10.11)	0.32	0.78 (0.25–2.49)	0.68	1.85 (0.66–5.21)	0.24
Anencephaly	7	5.18 (0.44–60.28)	0.19	3.39 (0.55–20.83)	0.19	2.07 (0.18–23.55)	0.56
Spina bifida	15	1.52 (0.19–12.49)	0.70	0.27 (0.03–2.19)	0.22	2.22 (0.70–7.01)	0.18
Hydrocephalus	12	2.28 (0.27–18.97)	0.45	[c]	[c]	1.93 (0.55–6.72)	0.30
Microcephaly	5	6.40 (0.57–72.56)	0.13	[c]	[c]	3.54 (0.47–26.82)	0.22
Eye	9	[c]	[c]	1.17 (0.11–13.00)	0.90	11.36 (2.25–57.28)	0.003
Congenital heart disease	270	1.55 (0.90–2.66)	0.11	0.75 (0.55–1.02)	0.06	1.16 (0.84–1.59)	0.36
Transposition of the great vessels	15	3.80 (0.80–18.06)	0.09	[c]	[c]	1.41 (0.43–4.64)	0.58
Ventricular septal defect	123	0.95 (0.34–2.63)	0.93	0.64 (0.39–1.04)	0.07	1.56 (1.01–2.40)	0.04
Atrial septal defect	59	2.86 (1.18–6.96)	0.02	0.87 (0.45–1.66)	0.67	1.13 (0.56–2.28)	0.73
Tetralogy of Fallot	14	[c]	[c]	0.83 (0.25–2.70)	0.75	0.34 (0.04–2.70)	0.31
Pulmonary valve stenosis	35	1.46 (0.34–6.30)	0.62	0.59 (0.24–1.47)	0.26	1.02 (0.43–2.45)	0.96
Aortic valve atresia/stenosis	7	[c]	[c]	1.19 (0.20–7.17)	0.85	1.75 (0.29–10.72)	0.55
Coarctation of the aorta	15	[c]	[c]	0.75 (0.20–2.84)	0.67	1.66 (0.49–5.57)	0.42
Respiratory	12	[c]	[c]	0.96 (0.24–3.85)	0.95	1.59 (0.39–6.42)	0.52
Cystic adenomatoid malformation	6	[c]	[c]	1.02 (0.19–5.59)	0.98	[c]	[c]
Orofacial clefts	44	1.84 (0.55–6.25)	0.32	0.87 (0.40–1.89)	0.72	1.76 (0.84–3.66)	0.13
Cleft lip	12	[c]	[c]	0.89 (0.17–4.61)	0.89	3.71 (1.05–13.10)	0.04
Cleft lip and palate	18	1.41 (0.18–11.21)	0.75	0.85 (0.26–2.70)	0.78	1.48 (0.46–4.76)	0.51
Cleft palate	14	3.90 (0.79–19.25)	0.10	0.86 (0.22–3.34)	0.82	0.87 (0.18–4.24)	0.86
Digestive system	45	1.30 (0.30–5.57)	0.72	0.99 (0.48–2.04)	0.98	1.35 (0.62–2.94)	0.45
Anorectal atresia/stenosis	9	[c]	[c]	0.96 (0.24–3.90)	0.96	[c]	[c]
Abdominal wall	7	2.32 (0.25–21.34)	0.46	1.37 (0.25–7.64)	0.72	[c]	[c]
Gastroschisis	6	3.01 (0.31–29.56)	0.35	1.86 (0.31–11.36)	0.50	[c]	[c]
Urinary	86	1.54 (0.61–3.90)	0.37	0.99 (0.60–1.65)	0.97	0.92 (0.48–1.74)	0.80
Bilateral renal agenesis	6	[c]	[c]	0.95 (0.17–5.27)	0.95	[c]	[c]
Cystic kidney	24	0.96 (0.13–7.31)	0.97	0.41 (0.12–1.40)	0.15	0.91 (0.30–2.74)	0.86
Genital	16	6.30 (1.58–25.08)	0.009	1.36 (0.43–4.31)	0.60	0.41 (0.05–3.39)	0.41
Hypospadias	8	8.77 (1.42–54.29)	0.02	1.26 (0.21–7.59)	0.80	0.90 (0.09–8.87)	0.93
Limb	17	2.86 (0.60–13.56)	0.19	1.23 (0.41–3.70)	0.71	0.44 (0.06–3.47)	0.43
Limb reduction anomalies	10	2.68 (0.31–23.11)	0.37	1.11 (0.28–4.45)	0.88	[c]	[c]
Polydactyly	6	[c]	[c]	1.45 (0.24–8.80)	0.69	1.20 (0.12–11.82)	0.88
Musculo-skeletal	6	[c]	[c]	3.22 (0.53–19.46)	0.20	1.77 (0.16–19.98)	0.64
Other congenital anomalies	5	[c]	[c]	0.49 (0.05–4.42)	0.53	[c]	[c]

Abbreviations: BMI, body mass index; CI, confidence interval. [a]Only subtypes with greater than five cases are shown due to current UK disclosure guidelines. [b]Adjusted for maternal age, ethnicity, BMI, pre-gestational diabetes, cigarette smoking status and index of multiple deprivation. [c]Insufficient cases.

significant association to occur by chance. In addition, as the number of cases in certain groups was small, the study had limited statistical power in these groups to detect a difference, for example, for limb reduction defects.

There are now a number of studies, mainly from the United States, suggesting an association between maternal obesity and congenital anomaly risk, particularly for neural tube defects and cardiovascular anomalies.[10–16] In a recent meta-analysis, Stothard *et al.*[17] showed increased risks in obese women for cleft palate, hydrocephaly and limb anomalies in addition to neural tube defects and cardiovascular anomalies. In this study, we found an increased risk of ventricular septal defects among women who were obese. Cedergren and Kallen[15] also found an association between maternal obesity and ventricular septal defects.

Maternal underweight was associated with significantly increased odds of both atrial septal defects (ASDs) and genital anomalies. Although few previous studies have shown associations between maternal underweight and congenital anomalies, there are exceptions. Watkins *et al.*[16] found an increased risk of ASDs in women who were underweight, while the study by Waller *et al.*[12] found a raised OR for septal defects (ASDs were not specifically reported) although this did not reach statistical significance. Maternal underweight has also been associated with the occurrence of gastroschisis.[18] To our knowledge, the risk of genital anomalies has not previously been examined with respect to maternal underweight.

Our study has several strengths. We have used data on congenital anomalies from a long-standing, high-quality register rather than that recorded in the hospital data. The

NorCAS contributes to established United Kingdom and European networks that use similar inclusion criteria, and have a consistent approach to data collection, coding and recording. We have included congenital anomalies arising within live births, stillbirths, termination of pregnancy for fetal anomaly after prenatal diagnosis and late miscarriages, thus reducing ascertainment bias. Twelve percent of cases reported here resulted in a termination of pregnancy, highlighting the importance of including these cases in similar studies. As the NorCAS includes cases diagnosed beyond the first year of life, those congenital anomalies that are only detectable well after birth have also been captured. We have analysed a range of selected, major congenital anomalies that are well defined and ascertained. We were able to subdivide the congenital anomalies into groups and subtypes, thus anomalies with potentially different aetiologies were not being combined. When the same exclusion criteria were applied to the NorCAS data for the whole region, the total prevalence figure found in this study is similar to that reported by NorCAS. Further, with accurate data on maternal pre-gestational diabetes status from the NorDIP, we were able to take account of this confounder in our analyses.

However, there were also a number of study limitations. The BMI data were routinely collected by the five hospitals and, at the time of the data collection, is likely to have been derived from self reported height and, in some cases, weight. Fattah *et al*.[33] showed that approximately a fifth of women booking for antenatal care in their sample underestimated their BMI, mainly because of underreporting of weight. BMI was missing for almost a quarter of our sample. It is not clear whether these data are missing because they were not collected at the time of the first antenatal visit, or whether they were recorded in the notes, but were not added to the hospital information systems. The loss of such a proportion of the sample reduced study power. This explains the wide CIs on many of the results, particularly for individual subtypes and indicates why this study was unable to confirm some of the findings of a recent systematic review,[17] in spite of achieving similar point estimates for both neural tube defects and cardiovascular anomalies. Thus, as for many congenital anomaly studies, a lack of significant association should not be taken as evidence of no relationship.

We have presented risks associated with maternal BMI category by individual subtype where possible. While congenital anomalies are frequently associated within the same infant, we have not attempted to account for such clustering because of the relatively small number of cases. This approach is consistent with that of other studies in the field.[16]

As a smaller proportion of the cases had missing BMI than the non-cases, stratified prevalence estimates were weighted to correct for the resultant under-representation of the denominator. Although this process will have corrected for the numerator–denominator bias, there may still be bias if the BMI profile of the women with missing BMI was different to the women with known BMI.

As our study was limited to routinely collected data, information on some key data items, which are known to increase the risk of congenital anomalies, was not available. For example, we were not able to include information on maternal diet. The nutritional status of a woman during pregnancy is an established risk factor for many reproductive outcomes. In particular, the link between folic acid intake during the periconceptional period and the occurrence of neural tube defects is well established.[34] Some of the hospitals did collect information on maternal folic acid status but, disappointingly, the data were too limited to be included in our analyses. The collection of such data on all pregnancies needs urgently to be improved if we are to gain important information on whether such factors influence the association of maternal BMI and congenital anomaly risk and to understand whether, and how, public health messages are acted on.

Finally, this study estimated standard errors using maximum-likelihood methods, which can provide biased results when the case and comparison groups are highly unbalanced.[35] While exact methods offer a potential solution, these could not be used because of prohibitive computational requirements.

Several mechanisms linking maternal obesity to the occurrence of congenital anomalies have been suggested. Maternal pre-gestational diabetes is a known risk factor for congenital anomalies, especially nervous system and cardiac anomalies.[36] Thus, undiagnosed diabetes and dysglycaemia in obese pregnant women is one potential explanation for the increased risk of congenital anomalies. Wentzel[37] has suggested that diabetes-induced congenital anomalies result from disturbance in micronutrient metabolism and oxidative stress. However, including data on known maternal diabetes status in our study only fractionally reduced the ORs, most likely because of the very small number of cases.

Maternal obesity has also been associated with reduced folate levels,[38] and the protective effect of folic acid in reducing the risk of a neural tube defect may not be observed in obese women.[39] Similar nutritional deficiencies may explain the association between maternal underweight and congenital anomalies. Unfortunately, we did not have sufficient data on folate consumption, or any other vitamin or mineral supplementation, to test this hypothesis further.

It has previously been suggested that difficulties in the antenatal detection of congenital anomalies by ultrasound in obese women may explain the higher prevalence of congenital anomalies.[40,41] However, as our study includes terminations of pregnancy for fetal anomaly, this is an unlikely explanation for our findings. Furthermore, we found no significant difference in the proportion of terminations between mothers who were underweight, normal weight, overweight or obese ($P = 0.71$).

Our study found an overall increased risk of congenital anomalies in women who are obese and women who are underweight, compared with women of recommended BMI. These findings suggest that interventions are needed to

support women to achieve a healthy weight before becoming pregnant, not only for women who are obese but also for women who are underweight. We would suggest that future studies should consider the complete BMI range, as the effect of overweight remains unclear and all congenital anomaly subtypes as information on risk is still lacking for many. Further research on mechanisms is also essential if potential interventions, especially for those women who are unable to optimize their weight before pregnancy, are to be developed.

Conflict of interest

The authors declare no conflict of interest.

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CORRIGENDUM

Maternal body mass index and congenital anomaly risk: a cohort study

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After the publication of the article, the authors noticed a couple of minor errors in Table 2, in *Fetal characteristics* section. The correct table is reproduced below.

The authors would like to apologize for this mistake.

Table 2 Maternal and fetal characteristics among cases and non-cases

Variable	*Cases (%) N = 682*[a]	*Non-cases (%) N = 40 260*	*Adjusted odds ratio (95% CI)*[b]	*Adjusted P-value*[b]
Maternal characteristics				
Maternal age				
<20 years old	79 (11.6)	4089 (10.2)	1.08 (0.84–1.39)	
20–29.9 years old	333 (48.8)	19 454 (48.3)	Reference	0.68
⩾30 years old	270 (39.6)	16 709 (41.5)	0.96 (0.81–1.13)	
Maternal ethnicity				
White	519 (76.1)	33 634 (83.6)	Reference	0.63
Non-white	53 (7.8)	3301 (8.2)	1.07 (0.80–1.44)	
Missing	110 (16.1)	3317 (8.2)		
BMI (kg m^{-2})				
<18.5 (underweight)	30 (4.4)	1060 (2.6)	1.60 (1.09–2.36)	
18.5–24.9 (recommended)	274 (40.2)	16 214 (40.3)	Reference	0.002
25–29.9 (overweight)	113 (16.6)	7975 (19.8)	0.85 (0.68–1.06)	
⩾30 (obese)	105 (15.4)	4932 (12.3)	1.30 (1.03–1.63)	
Missing	160 (23.5)	10 071 (25.0)		
Maternal pre-gestational diabetes				
No	672 (98.5)	40 067 (99.5)	Reference	<0.001
Yes	10 (1.5)	185 (0.5)	3.22 (1.68–6.15)	
Cigarette smoking status				
None/ex-smoker	360 (52.8)	25 251 (62.7)	Reference	0.02
Current smoker	165 (24.2)	9137 (22.7)	1.28 (1.05–1.57)	
Missing	157 (23.0)	5864 (14.6)		
Index of multiple deprivation				
Tertile 1 (most deprived)	247 (36.2)	13 386 (33.3)	0.86 (0.71–1.04)	
Tertile 2	214 (31.4)	13 375 (33.2)	Reference	0.28
Tertile 3 (most advantaged)	220 (32.3)	13 297 (33.0)	0.95 (0.78–1.16)	
Missing	1 (0.2)	194 (0.5)		
Fetal characteristics				
Sex of infant/fetus				
Male	352 (51.6)	20 498 (50.9)	Reference	<0.001 (0.38[c])
Female	316 (46.3)	19 745 (49.1)	0.93 (0.80–1.09)	
Indeterminate	9 (1.3)	8 (0.0)	52.62 (19.90–139.81)	
Missing	5 (0.7)	1 (0.0)		
Gestational age				
<24 weeks	88 (12.9)	69 (0.2)	73.52 (52.15–103.65)	<0.001
24–36 weeks	111 (16.3)	2636 (6.6)	2.93 (2.36–3.62)	
⩾37 weeks	483 (70.8)	34 481 (85.7)	Reference	
Missing	0 (0.0)	3066 (7.6)		
Birth weight				
<2.5 kg	188 (27.6)	2704 (6.7)	5.18 (4.32–6.20)	<0.001
2.5–3.99 kg	429 (62.9)	32 697 (81.2)	Reference	
⩾4.0 kg	54 (7.9)	4828 (12.0)	0.84 (0.63–1.12)	
Missing	11 (1.6)	23 (0.1)		

Abbreviations: BMI, body mass index; CI, confidence interval. [a]Includes those occurring in fetal deaths (>20 weeks gestation), terminations of pregnancy for fetal anomaly following prenatal diagnosis and live births. [b]Adjusted for maternal age, ethnicity, BMI, pre-gestational diabetes, cigarette smoking status and index of multiple deprivation. [c]Comparison between males and females only, that is, excluding those of indeterminate sex.

Before Rankin *et al* 2010, there were no UK cohort studies of the association between maternal BMI and the risk of congenital anomaly. Although previous studies had been performed in similar high-incomes settings with large white populations, several weaknesses were common, including retrospective self-reporting of weight and lack of information for cases ending in termination of pregnancy.[266-275] By linking prospective exposure information from hospital records with high-quality information from the NorCAS (the strengths of which are discussed further in **Section 3·2·1**, p145), this study sought to address these methodological concerns.

Unfortunately, unlike our prior systematic review (Stothard *et al* 2009),[7] Rankin *et al* 2010 was substantially hindered by low statistical power. This was particularly apparent when I updated the NTD and CHD meta-analyses from Stothard *et al* 2009 to include the results of Rankin *et al* 2010 for a chapter in Gillman and Poston's 'Maternal Obesity'.[383] For both outcomes, the CIs from Rankin *et al* 2010 were some of the widest of all contributing studies. Perhaps more striking however was the similarity between the study's points estimates (NTDs: aOR=1.85, 95% CI: 0.66 to 5.21, CHD: aOR=1.16 (95% CI: 0.84 to 1.59) and those of the meta-analysis [NTDs: OR=1.80 (95% CI: 1.60 to 2.02); CHD: OR=1.20 (95% CI: 1.15 to 1.25)]. Given the focus on reducing systematic error, the agreement between Rankin *et al* 2010, Stothard *et al* 2009, and the recent meta-analysis from Cai *et al* 2014[281] provides reassurance that the observed associations are consistent and generalizable (at least in predominantly-white populations in high-income countries).

In terms of hypothesis testing, Rankin *et al* 2010 reported statistically significant associations between obesity and VSDs [aOR=1.56 (95% CI: 1.01 to 2.40)], cleft lip, and eye anomalies and between underweight and ASDs [aOR=2.86 (95% CI: 1.18 to 6.96)], genital anomalies, and hypospadias [aOR=8.77 (95% CI: 1.42 to 54.29)]. In contrast, Cai *et al's* recent (2014) meta-analysis did not find statistically significant associations between obesity and VSDs [OR=0.98 (95% CI: 0.90 to 1.07)] or between underweight and ASDs [OR=1.11 (95% CI: 0.85 to 1.45)].[281] Given the overlapping confidence intervals, the original findings of statistical significance were therefore probably due to normal sampling variation. Similarly, in over 2000 cases with hypospadias, Adams *et al* 2011 found no evidence of association between maternal underweight and the risk of hypospadias [OR=1.07 (95% CI: 0.95 to 1.21)].[384]. Although this estimate is significantly smaller than reported by Rankin *et al* 2010, such disagreements are not unexpected given the vast number of associations examined. In hindsight, I do not agree with my contemporary decision to report p-values – never mind conduct formal hypothesis tests – for every anomaly group and subtype, given the study was not sufficiently powered to do so.

As one of very few cohort studies in the area, I was keen for Rankin *et al* 2010 to include absolute risks of congenital anomaly by BMI-category. Producing these estimates however was complicated by an imbalance in the proportion of missing BMI between cases and non-cases. As standard at the time, I attempted to correct for this bias by up-weighting the denominator and down-weighting the numerator to reflect the average proportion of missing data across the whole sample. Unfortunately, this approach requires the data are missing *completely* at random, i.e. that the true BMI distribution was identical between those with known and unknown BMI.[385] Given those women with missing BMI were known to be significantly different to the rest of the sample, this was clearly somewhat optimistic, and the results are unlikely to have avoided bias.[385] Multiple imputation methods would have offered a more robust solution,[385] but I was unaware of their existence, and they had not been implemented into routine statistical software.

My decision to analyse BMI in WHO categories is also questionable. Although categorical analyses were virtually ubiquitous,[266-275] a continuous examination of BMI would have provided an important boost to the study's statistical power. I decided against this approach in order to maximise the comparability and clinical interpretability and because of suspicion that the association was curvilinear (a fact confirmed by our own results in maternal underweight). In hindsight, a combination of locally-weighted scatterplot smoothing (LOWESS) and segmented regression methods, as used later in Bell *et al* 2012 (**Section 2·4**, p68), Glinianaia *et al* 2012 (**Section 2·5**, p84), Tennant *et al* 2013 (**Section 2·6**, p108) and Tennant *et al* 2015 (**Section 2·7**, p127), would have offered a superior solution.

2·3 TENNANT *et al* 2011 (MATERNAL BMI & FETAL & INFANT DEATH)

Title: Maternal body mass index and the risk of fetal and infant death; a cohort study from the North of England.

Authors: **Tennant PWG**, Rankin J, and Bell R

Journal: Human Reproduction (Volume 26 Issue 6 Pages 1501-1511)

Date of Publication: 05 April 2011

2·3·1 Overview

This article examined the same retrospective cohort of pregnant women described in Rankin *et al* 2010 (albeit excluding cases of congenital anomaly) to examine the association between maternal pre-pregnancy BMI and the risk of fetal and infant death. Outcome data on the occurrence of late miscarriages, stillbirths, and infants deaths and information on the cause of death were obtained from the PMS.

2·3·2 What was known

- Several studies - mainly from Scandinavia - had shown an association between maternal obesity and increased risks of third-trimester stillbirth, but there was limited evidence of association with either fetal deaths in earlier pregnancy or infant deaths.
- Few studies had explored the potential causes of death, with only one previous study discounting the putative contribution of congenital anomalies.
- Although maternal overweight had also been associated with a modestly increased risk of stillbirth, the association between BMI as a continuous variable and the risk of fetal or infant death had not been examined.

2·3·3 What this study added

- Maternal pre-pregnancy obesity was found to be associated with doubled odds of spontaneous fetal death [aOR=2.32 (95% CI: 1.64 to 3.28)] and infant death [aOR=1.97 (95% CI: 1.13 to 3.45)] in normally-formed offspring. This did not appear to be explained by any of maternal age, smoking, ethnicity, or socio-economic circumstances, adjustment for which had negligible impact on the effect of obesity.

- The association between BMI as a continuous variable and the probability of fetal and infant death was found to follow a J-shaped pattern, with the lowest prevalence (6.1 per 1000 total births) among women with a pre-pregnancy BMI of 23kg/m^2, and the probability increasing linearly by 6-7% for each additional 1kg/m^2 thereafter.

- No evidence was found that the association between maternal obesity and the odds of spontaneous fetal death was confined to a specific gestational age. The effect was instead similar for both late miscarriages (20-23 weeks' gestation) and antepartum stillbirths (≥24 weeks' gestation).

- A significantly higher proportion of stillbirths among obese women were observed to be attributed to pre-eclampsia, although the association between maternal obesity and the odds of stillbirth remained significant even when all deaths due to pre-eclampsia were removed.

2·3·4 Contribution of the candidate to this work

I performed the cleaning and merging of the five hospital datasets, designed and conducted the statistical analysis, drafted the introduction, methods, results, tables and discussion, produced the figures, compiled the references, and edited the manuscript following critical-review from JR and RB. A copy of the Newcastle University Co-Authorship form for this publication can be found in **Appendix A(ii)** (p181).

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human reproduction

ORIGINAL ARTICLE ***Reproductive epidemiology***

Maternal body mass index and the risk of fetal and infant death: a cohort study from the North of England

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BACKGROUND: Early pregnancy obesity (body mass index, BMI, ≥30 kg/m^2) carries significant health implications. This cohort study investigates the association between early pregnancy BMI and the risk of fetal and infant death in pregnancies not affected by congenital anomalies or pre-gestational diabetes.

METHODS: Data on singleton pregnancies delivered during 2003–2005 at five hospitals were linked with data from three regional registers: the Northern Perinatal Mortality Survey, the Northern Diabetes in Pregnancy Survey and the Northern Congenital Abnormality Survey. Logistic regression models were used to determine the crude and adjusted odds ratios (aOR) of a spontaneous fetal death (≥20 weeks gestation) and infant death (aged up to 1 year), among underweight (BMI <18.5 kg/m^2), overweight (BMI 25–29.9 kg/m^2) and obese women compared with women of recommended BMI (18.5–24.9 kg/m^2).

RESULTS: Obese women were at significantly increased risks of both fetal death [aOR = 2.32 (95% confidence interval: 1.64–3.28), $P <$ 0.001] and infant death [aOR = 1.97 (1.13–3.45), $P = 0.02$]. Continuous analyses revealed a V-shaped relationship between BMI and the risk of fetal and infant death, with a minimum risk at 23 kg/m^2, and significantly increased risk thereafter for both fetal death [aOR, per unit = 1.07 (1.05–1.10), $P <$ 0.001] and infant death [aOR, per unit = 1.06 (1.02–1.10), $P = 0.007$]. No significant excess risks, however, were identified for either maternal underweight [fetal death: aOR = 0.98 (0.42–2.25), $P = 0.96$; infant death: aOR = 1.89 (0.73–4.88), $P = 0.19$] or maternal overweight [fetal death: aOR = 1.34 (0.94–1.89), $P = 0.10$; infant death: aOR = 1.35 (0.79–2.32), $P = 0.27$] as categories. Except for higher rates of pre-eclampsia among stillbirths, no specific cause of death could explain the increased odds of fetal and infant death among the obese.

CONCLUSIONS: Early pregnancy obesity is significantly associated with fetal and infant death, independent of the known relationships with congenital anomalies and maternal pre-gestational diabetes.

Key words: obesity / miscarriage / stillbirth / perinatal mortality / neonatal mortality

Introduction

In 2007, an estimated 24% of adults in England were obese (body mass index, BMI, of 30 kg/m^2 or above), compared with 19% in 2000 (Joint Health Surveys Unit, 2008). This pattern is reflected in the population of pregnant women (Heslehurst *et al*., 2010), where raised BMI carries significant health implications including increased risks of gestational diabetes, hypertensive disorders, thromboembolic disorders, Caesarean delivery, wound infection (Sebire *et al*., 2001; Abdollahi *et al*., 2003; O'Brien *et al*., 2003; Ehrenberg *et al*., 2004b; Chu *et al*., 2007a) and, for the infant, congenital anomaly, macrosomia and low Apgar score (Sebire *et al*., 2001; Ehrenberg *et al*., 2004a; Stothard *et al*., 2009).

A recent meta-analysis indicated that maternal obesity may also increase the risk of stillbirth (Chu *et al*., 2007b), while other studies suggest similar associations for neonatal and infant death (Cedergren 2004; Kristensen *et al*., 2005; Nøhr *et al*., 2007; Thompson *et al*., 2008; Chen *et al*., 2009), and for miscarriages <20 weeks gestation among obese women undergoing fertility treatment (Metwally *et al*., 2008). In contrast, there remains limited information regarding the association with fetal deaths before 24 weeks gestation in the general population, and with post-neonatal deaths (Baeten *et al*., 2001; Frøen *et al*., 2001; Nøhr *et al*., 2005; Salihu *et al*., 2007; Thompson *et al*., 2008). Moreover, few studies have adequately accounted for the potential confounding influences of congenital anomalies. In addition to their association with maternal obesity (Stothard *et al*., 2009),

congenital anomalies are a leading cause of fetal and infant death (American College of Obstetrics and Gynecology Committee on Genetics, 2009). Maternal obesity also has a complex relationship with fetal growth (Schaefer-Graf et al., 2003), but any adjustment needs to account for the impact of gestational age.

The pregnancy population of the North of England is uniquely surveyed by several population-based registers, including registers of fetal and infant mortality, congenital anomaly and maternal pre-gestational diabetes. This study combined data from a cohort of pregnancies drawn from five hospitals in the region with outcome and pre-gestational diabetes data from three population-based registries, to investigate the association between early pregnancy BMI and fetal and infant death, in pregnancies not affected by congenital anomalies or pre-gestational diabetes.

Methods

Study population

The North of England (UK) is a geographically distinct area with a stable population of 3 million and ~30 000 deliveries per year (Rankin et al., 2010). This study includes data from singleton pregnancies occurring between 1 January 2003 and 31 December 2005 stored on the information systems of five maternity units in the region. The hospitals were chosen as they have well-established electronic maternity records that include maternal booking BMI (Heslehurst et al., 2007), account for around half of all deliveries in the region and the women who deliver in them reflect the pregnancy population of the region as a whole.

Definitions

Late miscarriages are the spontaneous loss of a fetus at 20–23 completed weeks of gestation. *Stillbirths* are deliveries of a fetus showing no signs of life at 24 or more completed weeks of gestation. *Antepartum stillbirths* are stillbirths where there was no evidence of life during labour. *Intrapartum stillbirths* are stillbirths where the fetus died during labour. *Spontaneous fetal deaths* comprise miscarriages and stillbirths. *Neonatal deaths* are deaths, following live birth, of a baby before aged 28 days. *Early neonatal deaths* are neonatal deaths occurring before aged 7 days. *Perinatal deaths* comprise stillbirths and early neonatal deaths. *Post-neonatal deaths* are deaths, following live birth, of an infant aged 28 days or more, but less than 1 year of age. *Infant deaths* comprise neonatal deaths and post-neonatal deaths.

Information on fetal and infant deaths

The Northern Perinatal Mortality Survey (PMS) collects data on all late miscarriages, terminations of pregnancy for congenital anomaly following prenatal diagnosis at 20 or more completed weeks of gestation, stillbirths and infant deaths that occur within the region (Hey et al., 1984).

Data linkage

The hospital data were matched to the data held by the PMS, by staff in the information departments in each of the five hospitals. Data were linked by fuzzy matching on five key variables: mother's surname, mother's postcode at booking, infant date of birth, infant sex and birthweight. Fuzzy matching is an iterative procedure that matches on progressively less data, perfect matches being matched first, followed by matches on four variables, three variables, etc. A total of 449 out of 487 (92%) cases were matched to a hospital record. The majority of unmatched cases [36 out of 38 (95%)] had a gestational age <24 weeks.

Analysis

Prevalence rates for fetal outcomes and perinatal mortality were estimated as the number of cases per 1000 total births. Prevalence rates for infant outcomes were estimated as the number of cases per 1000 live births. 95% CIs (confidence intervals) for prevalence rates were derived from the binomial distribution.

Birthweight was standardized for gestational age (predominately estimated from ultrasound examination) using sex and parity-specific fetal growth curves. Expected weight for gestational age was estimated by applying a customizable fetal growth formula to reference values for the region (Gardosi et al., 1995; Tin et al., 1997). For the 12 636 pregnancies (41%) with missing parity, term values were estimated as the mean of the primiparous and multiparous references. BMI, derived from height and weight at booking, was categorized according to the WHO classification: underweight <18.5 kg/m^2; recommended BMI of 18.5–24.9 kg/m^2; overweight of 25–29.9 kg/m^2 and obese >30 kg/m^2. The median gestational age at booking was 10 weeks (inter-quartile range: 8–13). The indices of deprivation (ID), a UK census-derived area-based measure of socio-economic deprivation (Noble et al., 2008), was determined from the mother's residential postcode at booking and divided into tertiles. Maternal ethnicity and cigarette smoking status, both self-reported at booking, were also divided into categories; ethnicity into white and non-white, smoking into never-smokers and current/ex-smokers.

Odds ratios (ORs) and associated 95% CIs for maternal obese compared with maternal recommended BMI were estimated for each outcome using maximum-likelihood logistic regression. ORs and 95% CIs for maternal underweight and overweight, compared with maternal recommended BMI, were also estimated for combined fetal death and combined infant death outcomes. To investigate the shape of the relationship between continuous BMI and the risk of fetal and infant death, locally weighted scatter plot smoothing (LOWESS) was performed (with smoothing parameter of 0.5), revealing a V-shaped relationship with a minimum at BMI = 23 kg/m^2 (Fig. 1). Spline logistic regression models, with knots at BMI = 23 kg/m^2, were hence used to estimate the per-unit ORs and 95% CIs for a fetal or infant death. Pregnancies associated with a congenital anomaly, as notified to the Northern Congenital Abnormality Survey (NorCAS) (Richmond and Atkins, 2005), or with maternal pre-gestational diabetes (types I and II), as notified to the Northern Diabetes in Pregnancy Survey (NorDIP) (Hawthorne et al., 1994; Bell et al., 2008), were excluded, due to their established associations with both maternal obesity and fetal and/or infant mortality (Becerra et al., 1990; Hu et al., 2004; American College of Obstetrics and Gynecology Committee on Genetics, 2009; Stothard et al., 2009). To estimate the crude effect of BMI on each outcome, unadjusted models were constructed including BMI as the only predictor. To estimate the influence of BMI, independent of potential confounders, terms were added for maternal age, ethnicity, smoking status and ID—adjusted ORs (aORs) reported in the text refer to these models. Additional models were constructed to adjust for standardized birthweight (and gestational age for mortality after live birth) to examine potential mediating influences on the association between maternal BMI and fetal and infant death. Interactions between maternal BMI and all other variables (maternal age, ethnicity, smoking status, ID, standardized birthweight and gestational age) were examined by the inclusion of cross-product terms in categorical models. This method was also used to assess whether the effect of obesity on spontaneous fetal death varied with respect to gestational age. Differences in cause of death among obese women compared with women of recommended BMI were examined by equality of proportion and chi-squared tests. Obstetric classification categories were compared among fetal deaths (Cole et al., 1986), and clinico-pathological categories among infant deaths (Hey et al., 1986). Women with unknown BMI were omitted

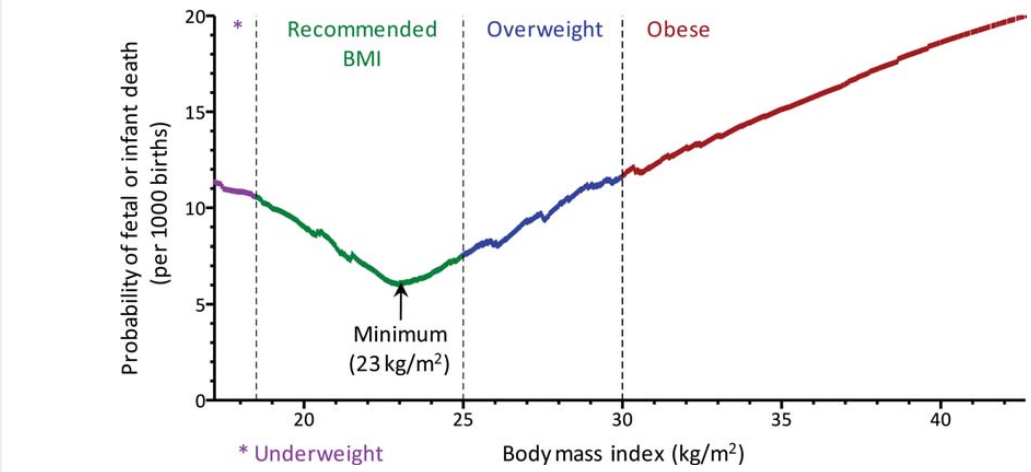

Figure 1 The association between maternal body mass index and the risk of a fetal or infant death, as estimated by locally weighted scatter plot regression.

from all analyses concerning BMI. To examine if this approach introduced any bias, primary outcome results were recalculated on imputed data, with missing BMI values being estimated by multiple imputation (using a predictive mean matching method over 100 imputations) from delivery unit, maternal age, ethnicity, parity, ID, smoking status, infant sex, standardized birthweight, gestational age and fetal/infant outcome (Moons *et al*., 2006). Statistical analyses used Stata 10.1 (StataCorp, TX). $P < 0.05$ was considered statistically significant.

Ethical approval

This study was given approval from the Northumberland Research Ethics Committee (07/Q0902/2) and Research & Development approval from each of the participating hospitals.

Results

Figure 2 shows the flow of cases through the study. Of the 40 932 singleton pregnancies identified during the 3-year period, 75 ended in late miscarriage, 65 in termination of pregnancy for congenital anomaly, 200 in stillbirth and 40 592 in live birth. Of the live births, there were 92 neonatal deaths and 55 post-neonatal deaths. The prevalence rates of each fetal and infant outcome are shown in Table I.

In summary, 897 pregnancies were associated with a congenital anomaly, 184 with pre-gestational diabetes and 11 with both a congenital anomaly and pre-gestational diabetes. Congenital anomaly was significantly more common among fetal deaths [OR = 6.94 (95% CI: 4.79–10.05), $P < 0.001$] and infant deaths [OR = 26.92 (95% CI: 18.99–38.15), $P < 0.001$]. Pre-gestational diabetes was also significantly more common among fetal deaths [OR = 3.99 (95% CI: 1.63–9.78), $P = 0.002$], but no post-natal deaths were recorded among live born infants whose mothers had pre-gestational diabetes.

From the remaining cohort, maternal BMI was missing for approximately one-quarter of pregnancies [cases = 57 (17.1%), non-cases = 9927 (25.1%)]. Those with missing BMI were older ($P < 0.001$), less likely to smoke ($P < 0.001$), less likely to live in deprived areas ($P < 0.001$) and delivered smaller infants/fetuses ($P < 0.001$) of shorter gestational ages ($P < 0.001$). Table II details the characteristics of the remaining 29 856 pregnancies with known maternal BMI, stratified by outcome; 53.8% had a recommended BMI, 3.5% were underweight, 26.4% were overweight and 16.3% were obese. Compared with women of recommended BMI, obese women were more likely to be white ($P < 0.001$), live in a deprived area ($P < 0.001$), older ($P < 0.001$) and deliver heavier infants/fetuses ($P < 0.001$) of slightly longer gestational ages ($P < 0.001$).

Table III shows the relative odds of each outcome for obese women compared with those of recommended BMI, after excluding pregnancies affected by congenital anomaly or pre-gestational diabetes. Maternal obesity was associated with significantly increased odds of all mortality outcomes, with the exception of intrapartum stillbirth and post-neonatal death. Adjustment for maternal age, ethnicity, smoking status and ID did not materially change any of the ORs. Additional adjustment for gestational age and/or standardized birthweight increased the apparent effect for all outcomes except late miscarriages. Of the possible interactions with maternal obesity, none were statistically significant, including gestational age, with the effect of maternal obesity on the odds of spontaneous fetal death appearing constant throughout gestation. When the results were reanalysed to include those with unknown but imputed BMI, the point estimates did not materially change [aOR for fetal death with imputed BMI data = 2.22 (95% CI: 1.57–3.14, $P < 0.001$), for infant death with imputed BMI data = 1.73 (95% CI: 1.00–3.01, $P = 0.05$)].

Table IV shows the relative odds of a fetal or infant death for underweight and overweight women, compared with those of recommended BMI. Maternal underweight was not significantly associated with either outcome. Before adjustment, maternal overweight was also not associated with either outcome, although a significant association with spontaneous fetal death emerged after adjusting for potential confounders and standardized birthweight. Table IV

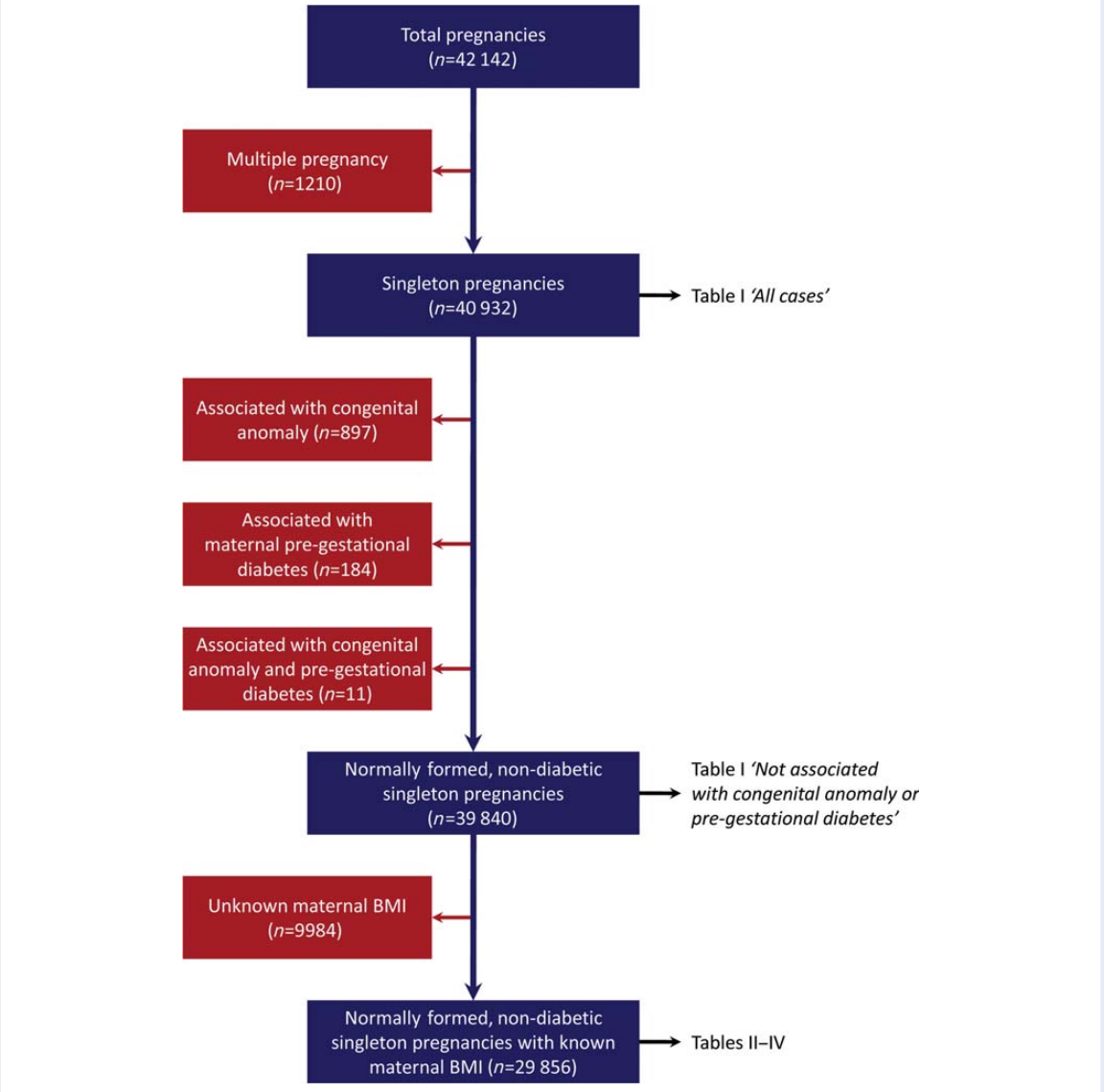

Figure 2 The flow of cases through the study.

additionally shows the relative odds of a fetal or infant death for each unit of BMI, separately for women <23 kg/m^2 and for women >23 kg/m^2. The results are consistent with the categorical analyses, with no significant evidence of association <23 kg/m^2 and significantly raised odds of both outcomes as BMI increases >23 kg/m^2.

A higher proportion of fetal deaths and stillbirths (both intrapartum and antepartum) were attributed to pre-eclampsia among obese women than among women of recommended BMI (spontaneous fetal deaths: 15% versus 1%, $P = 0.003$; stillbirths: 19% versus 2%, $P = 0.002$). Nevertheless, the relative odds of spontaneous fetal death remained significantly elevated when deaths attributed to pre-eclampsia were excluded [aOR = 1.99 (95% CI: 1.38–2.87), $P < 0.001$]. No other cause of death, for any of the outcomes measured, was found to be significantly more, or less, common among obese women, compared with those of recommended BMI.

Discussion

This study describes the relationship between early pregnancy maternal BMI and the odds of fetal and infant death in a cohort of pregnancies, drawn from across the North of England, over a 3-year period. After excluding pregnancies affected by a congenital

Table 1 Prevalence rates of selected fetal and infant outcomes.

Outcome	All cases		Not associated with congenital anomaly or pre-gestational diabetes	
	n	Prevalence (95% CI) Per 1000 total births	*n*	Prevalence (95% CI) Per 1000 normally formed, non-diabetic births
Spontaneous fetal death[a]	275	6.7 (6.0–7.6)	237	5.9 (5.2–6.7)
Late miscarriage[b]	75	1.8 (1.4–2.3)	70	1.8 (1.4–2.2)
Antepartum stillbirth[c]	184	4.5 (3.9–5.2)	152	3.8 (3.2–4.5)
Intrapartum stillbirth[d]	16	0.4 (0.2–0.6)	15	0.4 (0.2–0.6)
Perinatal death[e]	259	6.3 (5.6–7.1)	206	5.2 (4.5–5.9)
Stillbirth[f]	200	4.9 (4.2–5.6)	167	4.2 (3.6–4.9)
		Per 1000 live births		Per 1000 normally formed, non-diabetic live births
Early neonatal death[g]	59	1.5 (1.1–1.9)	39	9.8 (0.7–1.3)
Infant death[h]	147	3.6 (3.1–4.3)	97	2.4 (2.0–3.0)
Neonatal death[i]	92	2.3 (1.8–2.8)	62	1.6 (1.2–2.0)
Post-neonatal death[j]	55	1.4 (1.0–1.8)	35	0.9 (0.6–1.2)

[a]Late miscarriages and stillbirths.
[b]Spontaneous loss of a fetus at 20–23 completed weeks of gestation.
[c]Stillbirths where the fetus died before the onset of labour.
[d]Stillbirths where the fetus died after the onset of labour.
[e]Stillbirths and early neonatal deaths.
[f]Deliveries of a fetus showing no signs of life at 24 or more completed weeks of gestation.
[g]Neonatal deaths occurring before aged 7 days.
[h]Neonatal deaths and post-neonatal deaths.
[i]Deaths, following live birth, of a baby before aged 28 days.
[j]Deaths, following live birth, of an infant aged 28 days or more, but less than aged 1 year.

anomaly or pre-gestational diabetes, and adjusting for other potential confounding factors, this study found that the odds of fetal death and infant death were two to three times greater for women who were obese at the start of pregnancy compared with women of recommended BMI. Further adjustment for standardized birthweight and gestational age slightly (but not significantly) increased the observed effect size for all outcomes except late miscarriages. Compared with recommended BMI, neither underweight nor overweight were significantly associated with either fetal or infant death, however when BMI was examined as a continuous variable, the odds of both fetal death and infant death increased consistently by 6–7% for each additional unit above 23 kg/m^2, thus acting throughout the overweight and obese range. Finally, pre-eclampsia was significantly more commonly attributed as a cause of death in fetal deaths among obese women than among women of recommended BMI.

Strengths and weaknesses

This study used data from three high-quality population-based registries. The PMS is one of the longest standing surveys of fetal and infant mortality and has a record of high ascertainment (Hey *et al*., 1984). Furthermore, the study was able to investigate both late miscarriages and post-neonatal deaths, which have rarely been examined previously. The high ascertainment of both the NorCAS and NorDIP also reassures that the majority of cases of congenital anomaly and pre-gestational diabetes will have been accounted for (Richmond and Atkins, 2005; Bell *et al*., 2008).

Our findings should be generalizable to any predominately white population where body fat distributions are analogous for a given BMI, and with similar causes of fetal and neonatal death.

By standardizing birthweight for sex and gestational age by applying a fetal growth to regional standards, this study was able to examine the impact of maternal obesity on the risk of fetal and infant death, independent of fetal growth and gestational age. This contrasts with most previous studies (Little and Weinberg, 1993; Baeten *et al*., 2001; Frøen *et al*., 2001; Sebire *et al*., 2001; Stephansson *et al*., 2001; Cedergren 2004; Kristensen *et al*., 2005; Nøhr *et al*., 2005; Salihu *et al*., 2007; Hauger *et al*., 2008; Leung *et al*., 2008; Chen *et al*., 2009; Khashan and Kenny, 2009), which either have not adjusted for birthweight or have resorted to stratification or subgroup analysis, hindering comparisons at low gestational ages.

Including categorical and continuous analyses of BMI imparts the strengths of both approaches, including aiding comparisons with the literature whilst providing novel information about the nature of the relationship between BMI and fetal and infant death.

This study has a number of limitations. Height and, in some cases, weight are likely to have been self-reported. Since pregnant women have been shown to differentially underreport their weight (Fattah *et al*., 2009), the observed associations may be biased towards a larger effect. This study was only able to analyse BMI at booking and not the possible influence of gestational weight gain, or at other time points, such as pre-pregnancy. Even at booking, BMI was missing for almost a quarter of the sample. To predict any resulting bias we estimated the BMI values for those with missing data and recalculated the results. For all outcomes, there were only small

Table II Maternal and fetal characteristics, by cases and non-cases.

Variable	Number (%)	
	Cases[a] ($n = 277$)	Non-cases ($n = 29\,579$)
Maternal		
Body mass index (kg/m^2)		
<18.5 (underweight)	11 (4.0)	1041 (3.5)
18.5–24.9 (recommended)	116 (41.9)	15 956 (53.9)
25–29.9 (overweight)	75 (27.1)	7806 (26.4)
≥30 (obese)	75 (27.1)	4776 (16.2)
Age (years)[b]		
<20 years	42 (15.2)	3042 (10.3)
20–29.9 years	134 (48.4)	14 534 (49.1)
≥30 years	101 (36.5)	12 000 (40.6)
Cigarette smoking status		
None	131 (47.3)	17 860 (60.4)
Ex/current smoker	96 (34.7)	8411 (28.4)
Missing	*50 (18.1)*	*3308 (11.2)*
Ethnicity		
White	203 (73.3)	25 353 (85.7)
Non-white	35 (12.6)	2439 (8.3)
Missing	*39 (14.1)*	*1787 (6.0)*
Index of multiple deprivation		
Tertile 1 (most deprived)	108 (39.0)	10 296 (34.8)
Tertile 2	109 (39.4)	9786 (33.1)
Tertile 3 (least deprived)	60 (21.7)	9360 (31.6)
Missing	*0 (0.0)*	*137 (0.5)*
Fetal		
Sex		
Male	156 (56.3)	14 994 (50.7)
Female	114 (41.2)	14 585 (49.3)
Indeterminate	7 (2.5)	0 (0.0)
Gestational age (weeks)[b]		
20–23	57 (20.6)	1 (0.0)
24–30	69 (24.9)	98 (0.3)
30–36	51 (18.4)	1542 (5.2)
≥37	100 (36.1)	26 035 (88.0)
Missing	*0 (0.0)*	*1903 (6.4)*
Birthweight (z-score)[b,c,d]		
$Z \leq -1$	97 (35.0)	3726 (12.6)
$-1 < Z < 1$	157 (56.7)	19 516 (66.0)
$Z \geq 1$	16 (5.8)	4342 (14.7)
Missing	*7 (2.5)*	*1995 (6.7)*

[a]Includes late miscarriages, stillbirths and infant deaths up to aged 1 year.
[b]These variables were treated as continuous (units in brackets) but are presented here in categories to aid transparency.
[c]Standardized against expected fetal weight for sex, gestational age and parity (where possible) (Gardosi *et al.*, 1995; Tin *et al.*, 1997).
[d]The mean standardized birthweight for the total non-missing sample ($n = 27\,935$) was $z = 0.03$ with standard deviation 1.03.

changes to the point estimates with no affect on the conclusions of significance. Regardless, the loss of nearly a quarter of the sample will have reduced the statistical power. Consequently, the non-significant associations between obesity and post-neonatal death and between obesity and intrapartum stillbirths should not be considered as evidence of no effect. Similarly, our study is unlikely to have had sufficient power to detect potential relationships between fetal and infant death and either underweight, where the available sample was small, or overweight, where the difference in odds, relative to recommended BMI, is likely to be less pronounced. This problem was exacerbated by the observed non-uniformity of the recommended BMI category, within which the risk of a fetal or infant death varied from 6.1 per 1000 at BMI = 23 kg/m^2 to 10.6 per 1000 at BMI = 18.5 kg/m^2—the same value as was estimated for an overweight woman with BMI = 28.4 kg/m^2 (Fig. 1).

This study was unable to match 8% of known cases to a hospital entry. All except two of these were deliveries <24 weeks that were probably missing from their corresponding hospital data set. Some, however, may have been present and not linked, resulting in duplicate non-cases. These will not have materially affected the prevalence estimates, as the numerator included unmatched cases and the denominator would overwhelm such small numbers. The BMI results are also unlikely to have been biased, as this would require matching to be associated with maternal BMI.

While this study was able to account for several potential confounders, including socio-economic status, the analysis was limited to variables that were routinely collected at booking No information was thus available on maternal alcohol consumption or caffeine intake, both of which are potentially predictive of infant and/or fetal death (Kesmodel *et al.*, 2002; Wisborg *et al.*, 2003). Similarly, this study was unable to examine a number of potentially explanatory factors such as quality of antenatal care, baseline blood pressure and vascular risk factors, which may lie on the causal pathway between maternal obesity and fetal and infant death. However, previous studies that have adjusted for pre-eclampsia and/or other hypertensive disorders, have reported negligible changes to the associations between maternal obesity and fetal and/or infant death (Baeten *et al.*, 2001; Stephansson *et al.*, 2001; Kristensen *et al.*, 2005; Nøhr *et al.*, 2005, 2007; Chen *et al.*, 2009). Some of the included variables also had shortcomings; smoking status was not known for over a tenth of the sample, while our indicator of socio-economic status was based on residential area information rather than individual level, although no measure of socio-economic status is without limitation (Galobardes *et al.*, 2006). Most disappointing, however, was the incomplete parity information, which may also influence the risk of infant and/or fetal death (Raymond *et al.*, 1994). Nevertheless, adjusting for parity among those with available data had negligible impact on the adjusted ORs.

Finally, our study estimated standard errors using maximum-likelihood methods, which can provide biased results when the case and comparison groups are highly unbalanced (King and Ryan, 2002). Although exact methods offer a potential solution, these are currently computationally prohibitive.

Comparison with other studies

Several studies have examined the relationship between early pregnancy obesity and the risk of fetal or infant death. For stillbirths, the majority of

Table III Relative odds of a fetal or infant death for maternal obesity, compared with recommended BMI.

Outcome	Model 1 (unadjusted)			Model 2 (adjusted for maternal age, ethnicity, smoking status, and index of multiple deprivation)			Model 3 (as Model 2, also adjusted for standardized birthweight[a] and/or gestational age[b])		
	Cases	OR (95% CI)	*P*-value	Cases	OR (95% CI)	*P*-value	Cases	OR (95% CI)	*P*-value
Spontaneous fetal death[c]	196	2.24 (1.59–3.16)	<0.001	196	2.32 (1.64–3.28)	<0.001	189	2.65 (1.82–3.87)	<0.001
Late miscarriage[d]	50	2.55 (1.24–5.26)	0.01	50	2.81 (1.35–5.85)	0.006	44	2.74 (1.06–7.05)	0.04
Antepartum stillbirth[e]	134	2.24 (1.49–3.37)	<0.001	134	2.25 (1.49–3.40)	<0.001	133	2.69 (1.76–4.12)	<0.001
Intrapartum stillbirth[f]	12	1.43 (0.37–5.54)	0.60	12	1.68 (0.43–6.60)	0.46	12	1.88 (0.47–7.47)	0.37
Perinatal death[g]	179	2.22 (1.56–3.16)	<0.001	179	2.26 (1.58–3.23)	<0.001	178	2.47 (1.65–3.68)	<0.001
Stillbirth[h]	146	2.16 (1.46–3.18)	<0.001	146	2.19 (1.48–3.25)	<0.001	145	2.63 (1.75–3.94)	<0.001
Early neonatal death[i]	33	2.57 (1.13–5.86)	0.03	33	2.61 (1.13–6.01)	0.02	33	3.05 (1.14–8.13)	0.03
Infant death[j]	81	1.97 (1.13–3.42)	0.02	81	1.97 (1.13–3.45)	0.02	81	2.47 (1.33–4.58)	0.004
Neonatal death[k]	52	2.07 (1.03–4.13)	0.04	52	2.07 (1.03–4.18)	0.04	52	2.58 (1.13–5.89)	0.02
Post-neonatal death[l]	29	1.80 (0.72–4.51)	0.21	29	1.80 (0.71–4.56)	0.21	29	2.21 (0.87–5.64)	0.10

[a]Standardized against expected fetal weight for sex, gestational age and parity (where possible) (Gardosi *et al*., 1995; Tin *et al*., 1997).
[b]Gestational age was included in models of perinatal death, early neonatal death, infant death, total neonatal death and post-neonatal death.
[c]Late miscarriages and stillbirths.
[d]Spontaneous loss of a fetus at 20–23 completed weeks of gestation.
[e]Stillbirths where the fetus died before the onset of labour.
[f]Stillbirths where the fetus died after the onset of labour.
[g]Stillbirths and early neonatal deaths.
[h]Deliveries of a fetus showing no signs of life at 24 or more completed weeks of gestation.
[i]Neonatal deaths occurring before aged 7 days.
[j]Neonatal deaths and post-neonatal deaths.
[k]Deaths, following live birth, of a baby before aged 28 days.
[l]Deaths, following live birth, of an infant aged 28 days or more, but less than aged 1 year.

existing studies comprise analyses of deaths occurring from 28 weeks of gestation among Scandinavian populations (Frøen *et al*., 2001; Stephansson *et al*., 2001; Cedergren, 2004; Kristensen *et al*., 2005; Nøhr *et al*., 2005). Chu *et al.* meta-analysed these, and other studies (Little and Weinberg, 1993; Sebire *et al*., 2001; Djrolo *et al*., 2002) to report a summary OR of 2.07 (95% CI: 1.59–2.74) for obese women compared with women of recommended BMI (Chu *et al*., 2007b). This is very similar to the crude stillbirth OR from our study [2.16 (95% CI: 1.46–3.18)], despite differences in parity, stillbirth definition and in the exclusion of congenital anomalies and pre-gestational diabetes. In contrast, a more recent study by Salihu *et al.* (2007), derived from over 1.5 million births in Missouri, USA, found a significantly smaller crude OR of 1.5 (95% CI: 1.4–1.6). The lowest effect sizes were reported by Khashan and Kenny (2009) [aOR = 1.05 (95% CI: 0.80–1.37)] and Hauger *et al*. (2008) [OR = 1.07 (95% CI: 0.74–1.56)]. Salihu *et al*. (2007) suggested that one possible reason for their own lower effect size might be their inclusion of fetal deaths occurring at or after 20 weeks gestation, although this is not supported by the current study, which identified similar ORs for miscarriages (20–23 weeks gestation) and stillbirths (24 weeks or more).

Research examining the relationship between maternal BMI and the risk of miscarriage predominately concerns women receiving fertility treatment (Metwally *et al*., 2008). In 2008, Metwally *et al.* meta-analysed the association between maternal overweight and obesity and the risk of miscarriage before 20 weeks gestation and reported a summary OR of 1.67 (95% 1.25–2.25). This is not significantly different from the ORs for both late miscarriage and stillbirth obtained from the current study when overweight and obese women are combined [late miscarriage: OR = 2.16 (95% CI: 1.19–3.94), stillbirth: OR = 1.54 (95% CI: 1.11–2.14)]. Given the similarity between these values, and the absence of a significant interaction between maternal obesity and gestational age in the current study, it seems possible that the effect of maternal obesity on the risk of antepartum fetal death might be consistent throughout pregnancy.

The majority of existing studies of infant death examine the neonatal period only. Two studies among Scandinavian populations found significant associations between maternal obesity and neonatal death. In the earliest, Kristensen *et al.* (2005) reported an adjusted OR of 2.7 (95% CI: 1.2–6.1), similar to our adjusted OR [2.07 (95% CI: 1.03–4.18)], and from Roman *et al*.'s (2007) study from the Reunion ('two-fold'). In contrast, Nøhr *et al.* (2005) reported a slightly lower adjusted OR of 1.6 (95% CI: 1.0–2.4), although the difference is within normal sampling error. Two studies, including Khashan and Kenny's study from North West England, found no evidence of association between maternal obesity and neonatal death (Leung *et al*., 2008; Khashan and Kenny, 2009). For Leung *et al.* (2008), this is likely due to low statistical power (the prevalence of obesity was only 2.3%), while Khashan and Kenny's (2009) result may be explained by a higher risk reference group, given they observed a protective effect of maternal overweight relative to recommended BMI.

Examining early neonatal death in the Swedish Medical Birth Registry, Cedergren (2004) reported adjusted ORs ranging from 1.59 (95% CI: 1.25–2.01) among obese women with BMI <35 kg/m^2 to 3.41 (95% CI: 2.07–5.63) among morbidly obese women (BMI > 40 kg/

Table IV **Relative odds of a fetal or infant death for maternal underweight and overweight, compared with recommended BMI, and for each additional unit of BMI for women <23 kg/m^2 and for women >23 kg/m^2.**

Outcome	Model 1 (unadjusted)			Model 2 (adjusted for maternal age, ethnicity, smoking status, and index of multiple deprivation)			Model 3 (as Model 2, also adjusted for standardized birthweight[a] and/or gestational age[b])		
	Cases	OR (95% CI)	*P*-value	Cases	OR (95% CI)	*P*-value	Cases	OR (95% CI)	*P*-value
Maternal underweight versus maternal recommended BMI									
Spontaneous fetal death[c]	196	1.12 (0.49–2.57)	0.79	196	0.98 (0.42–2.25)	0.95	189	0.72 (0.31–1.67)	0.44
Infant death[d]	81	2.25 (0.88–5.78)	0.09	81	1.89 (0.73–4.88)	0.19	81	1.65 (0.61–4.49)	0.26
Maternal overweight versus maternal recommended BMI									
Spontaneous fetal death[c]	196	1.32 (0.93–1.87)	0.12	196	1.34 (0.94–1.89)	0.10	189	1.45 (1.00–2.09)	0.05
Infant death[d]	81	1.32 (0.77–2.26)	0.31	81	1.35 (0.79–2.32)	0.27	81	1.40 (0.78–2.53)	0.26
Maternal obese versus maternal recommended BMI									
Spontaneous fetal death[c]	196	2.24 (1.59–3.16)	<0.001	196	2.32 (1.64–3.28)	<0.001	189	2.65 (1.82–3.87)	<0.001
Infant death[c]	81	1.97 (1.13–3.42)	0.02	81	1.97 (1.13–3.45)	0.02	81	2.47 (1.33–4.58)	0.004
Per unit increase in BMI for maternal BMI <23 kg/m^2									
Spontaneous fetal death[c]	196	0.92 (0.83–1.02)	0.10	196	0.93 (0.84–1.04)	0.19	189	1.01 (0.90–1.12)	0.92
Infant death[d]	81	0.87 (0.75–1.01)	0.64	81	0.90 (0.77–1.04)	0.15	81	0.91 (0.78–1.07)	0.25
Per unit increase in BMI for maternal BMI >23 kg/m^2									
Spontaneous fetal death[c]	196	1.07 (1.04–1.10)	<0.001	196	1.07 (1.05–1.10)	<0.001	189	1.08 (1.05–1.11)	<0.001
Infant death[d]	81	1.06 (1.02–1.10)	0.004	81	1.06 (1.02–1.10)	0.007	81	1.08 (1.03–1.13)	0.001

[a]Standardized against expected fetal weight for sex, gestational age and parity (where possible) (Gardosi *et al.*, 1995; Tin *et al.*, 1997).
[b]Gestational age was included in models of perinatal death, early neonatal death, infant death, total neonatal death and post-neonatal death.
[c]Spontaneous loss of a fetus at 20–23 completed weeks of gestation or delivery of a fetus showing no signs of life at 24 or more completed weeks of gestation.
[d]Deaths, following live birth, of a baby before aged 1 year.

m^2), which is consistent with our adjusted OR for all obese women [2.61 (95% CI: 1.13–6.01)].

Three studies from the USA examined deaths beyond the neonatal period and identified significant associations between maternal obesity and infant death. Baeten *et al.* (2001) found an OR of 1.59 (95% CI: 1.18–2.13) for obese women compared with women with a BMI of 20–24.9 kg/m^2. Similarly, Thompson *et al.* (2008) reported adjusted ORs of 1.23 (95% CI: 1.03–1.48) and 1.70 (95% CI: 1.22–2.36) among infants whose mothers were mild/moderately obese and morbidly obese, respectively. The largest study, by Chen *et al.* (2009), again reported an OR for infant death of around 1.5 [1.46 (95% CI: 1.23–1.73)]. While these effects appear smaller than our observed effect [aOR = 1.97 (95% CI: 1.13–3.45)], the difference is not statistically significant.

Chen *et al.* (2009) also reported a significant OR for post-neonatal deaths [aOR = 1.28 (95% 1.02–1.61)]. While the current study identified a higher point estimate, the effect was not statistically significant [aOR = 1.80 (0.71–4.56)], indicating we may have had insufficient power for this outcome. To our knowledge, Chen *et al* is the only previous study to examine post-neonatal deaths specifically.

For underweight and overweight, the pattern is inconsistent. Chu *et al.*'s (2007b) meta-analysis previously confirmed an association between maternal overweight and the risk of stillbirth [OR = 1.47 (95% CI: 1.08–1.94)], a finding partly repeated by the current study, but only after adjusting for potential confounders and standardized birthweight [aOR, for all fetal deaths = 1.45 (95% CI: 1.00–2.09)]. None of the studies in Chu *et al.*'s (2007b) meta-analysis (Little and Weinberg, 1993; Frøen *et al.*, 2001; Stephansson *et al.*, 2001; Djrolo *et al.*, 2002; Kristensen *et al.*, 2005; Nøhr *et al.*, 2005), nor the others we identified (Hauger *et al.*, 2008; Leung *et al.*, 2008; Khashan and Kenny, 2009) found a significant relationship between underweight and fetal death. For most of these, as for the current study, this is likely due to inadequate power.

As in the current study, the majority of previous relevant studies (Baeten *et al.*, 2001; Kristensen *et al.*, 2005; Nøhr *et al.*, 2007; Leung *et al.*, 2008; Thompson *et al.*, 2008; Chen *et al.*, 2009; Khashan and Kenny, 2009) found no significant evidence of association between either maternal underweight or maternal overweight (as categories) and the risk of neonatal or infant death [the exceptions being Nøhr *et al.*, (2007) for overweight, and Chen *et al.*, (2009) for underweight and overweight]. However, this should not be taken as evidence of no effect. For both underweight and overweight, only one study (Khashan and Kenny and Leung *et al.*, 2008, respectively) reported point estimates below 1. Furthermore, our LOWESS plot (Fig. 1) suggests gradients of risk acting through both underweight

and overweight, with a notably steady trend above 23 kg/m^2, suggesting a continuous effect that may simply be masked by low power when the overweight and recommended BMI categories are directly compared (especially given the observed non-uniform risk pattern within the recommended BMI category). While no previous study of fetal and infant death have examined BMI using methods such as LOWESS, Kosa *et al*.'s (2010) study of the relationship between BMI and the risk of pre-term delivery identified a very similar V-shaped curve, with a minimum at 24 kg/m^2. Larger studies of fetal and infant death are required to investigate these patterns, and the effects of underweight and overweight, in more detail.

Potential mechanisms

A number of explanations have been proposed to explain the apparent association between maternal obesity and fetal and infant death, many of which are shared between both outcomes, potentially explaining the similarity in effect sizes. Both congenital anomalies and maternal pre-gestational diabetes are known to be associated with maternal obesity and with fetal and infant death (Becerra *et al*., 1990; Hu *et al*., 2004; American College of Obstetrics and Gynecology Committee on Genetics, 2009; Stothard *et al*., 2009). Although we excluded known cases of either congenital anomaly or pre-gestational diabetes, some risk may still be attributable to undiagnosed diabetes, gestational diabetes or pre-diabetic hyperglycaemia (Lau and Li, 1994).

Some of the effect of obesity on fetal death is likely attributable to hypertension and pre-eclampsia, which is more common among mothers of increased BMI (Galtier-Dereure *et al*., 2000; O'Brien *et al*., 2003). We found a higher proportion of stillbirths were attributed to pre-eclampsia among obese women compared with those of recommended BMI. Part of this may be due to the increased inflammatory profile of obese pregnant women (Ramsay *et al*., 2002), given the established association between systemic inflammation and pre-eclampsia (Redman and Sargent, 2003). In addition, the risk of vascular and endothelial dysfunction, and hence pre-eclampsia, may be increased by exaggerations in the normal pregnancy-related changes in lipid metabolism (Nelson *et al*., 2009). However, it is noteworthy that maternal obesity remained predictive of both fetal and infant death after cases of pre-eclampsia were excluded.

Alternative potential mechanisms include episodes of apnoea, differential ability to detect fetal movement and over-aggressive responses to infection. Maasilta *et al*. (2001) demonstrate that obese pregnant women experience significantly extended periods of snoring and hence more episodes of apnoea and oxygen desaturation than pregnant women of recommended BMI, potentially increasing risks to the fetus (Fraklin *et al*., 2000). Fretts (2005) suggests that thinner women may be better than obese women at recognizing decreased fetal movement, which may precede fetal demise. It is hypothesized that elevated concentrations of inflammatory mediators may pose a direct risk to the fetus if an infection reaches the amniotic cavity (Schmatz *et al*., 2009). Finally, the possibility of residual confounding, e.g. by socio-economic factors that are associated with obesity but not well explained by ID, should not be discounted.

The observed increase in the association between maternal obesity and the risk of fetal and infant death when adjusting for standardized birthweight suggests that birthweight acts as a reverse mediator in the relationship. In our study, this was because low birthweight, itself a predictor of fetal and infant death, was much less common among obese women. Nonetheless, this small protective influence was insignificant compared with the otherwise increased risk of fetal and infant death among the maternal obese.

Conclusions

This study found that the odds of both fetal death and infant death were significantly greater for women who were obese during early pregnancy compared with women of recommended BMI, and that each additional unit increase in BMI above 23 kg/m^2 was associated with an increase of 6–7% in the odds of both outcomes.

Among obese women, we estimate the absolute risk of a miscarriage, stillbirth or infant death to be 7.6 per 1000 singleton births (95% CI: 3.9–11.4) greater than among women of recommended BMI. This has significant implications on a population level. Given the rising prevalence of obesity in the population of pregnant women (Heslehurst *et al*., 2010), the rates of miscarriage, stillbirth and infant mortality can be anticipated to increase.

Further studies are required to investigate the specific mechanisms involved. In the meantime, women should be made aware of the risks of entering pregnancy with a high BMI, and supported to optimize their weight before pregnancy.

Author's roles

P.W.G.T.: data analysis, interpretation of results and drafting of manuscript. J.R.: study conception and design, interpretation of results and critical review of manuscript. R.B.: study conception and design, interpretation of results and critical review of manuscript.

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Although neither the first nor the largest UK study of the association between maternal obesity and the risk of stillbirth, Tennant *et al* 2011 is arguably still one of the most comprehensive. By combing routine maternity data with information from three population-based registers, the study remains noteworthy for including stillbirths before 28 weeks and infant deaths beyond 28 days, excluding cases affected by congenital anomaly, examining cause of death, and adjusting for a range of potential confounding influences.

With the same sample as Rankin *et al* 2010, it is unsurprising that Tennant *et al* 2011 likewise experienced problems with low statistical power, albeit moderated by higher prevalence proportions and larger effect sizes. No significant associations for example were identified between overweight and any of the outcomes under test. Despite this, the estimated OR for stillbirth [1.34 (95% CI 0.94 to 1.89)] was very similar to the summary OR reported in Chu *et al*'s meta-analysis from 2007 [1.45 (95% CI, 1.08 to 1.94)]. Similarly, the overweight OR for infant death [1.35 (95% CI: 0.79 to 2.32)] is statistically indistinguishable from the results of Johansson *et al*'s 2014 study of nearly two million births in Sweden [OR=1.25 (95% CI 1.16-1.35)].[379] Aune *et al's* 2014 meta-analysis in JAMA is notable for abandoning BMI categories completely, summarising the effects of BMI on stillbirth and infant death per 5kg/m^2 increase in BMI. The summary ORs of 1.24 (95% CI: 1.18 to 1.30) and 1.18 (95% CI: 1.09 to 1.28) respectively are slightly lower than the corresponding values for Tennant *et al* 2010 [OR=1.43 (95% 1.21 to 1.67) and OR=1.27 (95% CI: 1.06 to 1.53) respectively], but not beyond what is expected from sampling variation.

In hindsight, it is perhaps unfortunate that the final version of Tennant *et al* 2011 primarily focussed on overweight and obesity as distinct entities given the clear continuum in risk for values above 23kg/m^2. In conducting the analysis, I had initially adopted the same categorical approach as with Rankin *et al* 2010, for the same reasons of comparability, clinical interpretability, and concerns around non-linearity. Following peer-review, I extended this to include secondary analyses of BMI as a continuous variable, but still (somewhat cautiously) kept the categorical results as the headline findings. My decision to conduct and present a LOWESS analysis of the continuous relationship between BMI and the risk of fetal and infant death however did provide the study's most innovative and striking result (**Figure 1**, p57). Subsequently reproduced in the DH's '*Healthy Lives, Healthy People: A call to action on obesity in England*',[386] **Figure 1** (p57) strongly conveys both the linear risk for increasing BMI above 23kg/m^2 and the heterogeneity of the recommended category, with the same risk of fetal and infant death estimated for a pre-pregnancy BMI of 18.5kg/m^2 (considered 'healthy') as for 28.3kg/m^2 (considered at the upper extreme of 'overweight').

As one of just two studies to exclude cases complicated by congenital anomaly (the other being Nohr *et al* 2005)[332] it is curious that the ORs estimated by Tennant *et al* 2011 are consistently higher than the summary estimates produced by Chu *et al* 2007,[101] Meehan *et al* 2014,[102] and Aune *et al* 2014.[333] This could be explained by multiple factors, including superior case ascertainment, the use of clinically recorded data on BMI (even if some are likely to have been self-reported), higher mean BMI among the obese, sampling variation, and selection bias. With a larger sample, it might have been more informative to include cases of congenital anomaly and present stratified analyses, to delineate their contribution to the association between maternal obesity and fetal and infant death. The low absolute number of deaths with congenital anomaly, however, necessitated their exclusion. This is preferable to conflating such deaths with normally-formed fetal deaths, due to their divergent aetiologies and the complexities introduced by elective terminations of pregnancy (which compete as outcomes with spontaneous fetal and infant deaths).

As with Rankin *et al* 2010, the primary analysis excluded participants with missing BMI, despite being unrepresentative of the sample a whole. On this occasion however I chose to perform additional sensitivity analyses, imputing BMI using predictive mean matching. Although the results '*did not materially change*', there were small reductions in the effect sizes for both stillbirths and infant deaths. Given these are likely to have been the more accurate of the estimates; they arguably should have formed the primary results.

2·4 BELL *et al* 2012 (DIABETES, HbA_{1c}, & CONGENITAL ANOMALIES)

Title: Peri-conception hyperglycaemia and nephropathy are associated with risk of congenital anomaly in women with pre-existing diabetes: a population-based cohort study

Authors: Bell R, Glinianaia SV, **Tennant PWG**, Bilous RW, Rankin J

Journal: Diabetologia (Volume 55 Issue 4 Pages 936-947)

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2·4·1 Overview

This article describes the results of a population-based cohort study that sought to examine the association between maternal pre-existing diabetes and the prevalence of congenital anomaly, by group and subtype. Socio-demographic and clinical information for pregnant women with pre-existing diabetes in the North of England who delivered during 1996-2008 were obtained from the NorDIP and linked with outcome data on the occurrence of congenital anomalies from the NorCAS.

David Haddon was commissioned to write a commentary to accompany the release of this publication, which has been included in **Appendix C** (p234).

2·4·2 What was known

- Women with pre-existing (type 1 or type 2) diabetes were known to experience a substantially increased risk of congenital anomaly, but the exact size of the effect was unclear .
- Although significant associations had been consistently observed for the largest anomaly groups (e.g. congenital heart disease) and certain rare syndromes (e.g. causal regression sequence), the effects were unknown for most groups and subtypes.
- Pre-pregnancy glycaemic control was known to be a strong influence of the risk of congenital anomaly, but it was not known how completely this explained the association with diabetes.

2·4·3 What this study added

- The risk of non-chromosomal congenital anomaly in women with pre-existing diabetes was observed to be 7.2% (95% CI: 6.0 to, 8.5), nearly four times greater than among women without the condition [RR=3.8 (95% CI: 3.2 to 4.5)].

- Except for sequences, the relative risk of congenital anomaly associated with diabetes was found to be consistently between three- and six-times higher for all anomaly groups

- The odds of non-chromosomal anomaly were found to increase linearly by 2% for each 1mmol/mol increase in peri-conception HbA_{1c} above 45mmol/mol (6.3%), but even at this optimal level, the odds of non-chromosomal anomaly were around twice that observed in the general population.

- Pre-pregnancy nephropathy was observed to be associated with a doubling in the prevalence of congenital anomaly, but there was no apparent difference in the risk of congenital anomaly by diabetes type, or between male and female offspring.

2·4·4 Contribution of the candidate to this work

I assisted SVG with coding the individual congenital anomaly diagnoses into groups and subtypes, designed and conducted parts of the statistical analysis[xxiii], drafted parts of the methods[xxiv], parts of the results[xxv], and Table 5, produced Figure 1, and critically-reviewed the draft produced by RB. A copy of the Newcastle University Co-Authorship form for this publication can be found in **Appendix A(iii)** (p183).

[xxiii] I assisted with the multivariable regression (in particular calculating the beta-coefficients and performing interaction tests). I conducted the LOWESS analysis.

[xxiv] Particularly the sections entitled, '*Classification of congenital anomalies*' and '*Statistical analyses*'

[xxv] Particularly the section entitled, '*Predictors of non-chromosomal congenital anomalies in women with diabetes*'

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ARTICLE

Peri-conception hyperglycaemia and nephropathy are associated with risk of congenital anomaly in women with pre-existing diabetes: a population-based cohort study

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Abstract
Aims The aim of this study was to quantify the risk of major congenital anomaly, and to assess the influence of peri-conception HbA_{1c} and other clinical and socio-demographic factors on the risk of congenital anomaly occurrence in offspring of women with type 1 and type 2 diabetes diagnosed before pregnancy.
Methods This was a population-based cohort study using linked data from registers of congenital anomaly and diabetes in pregnancy. A total of 401,149 singleton pregnancies (1,677 in women with diabetes) between 1996 and 2008 resulting in live birth, fetal death at ≥20 weeks' gestation or termination of pregnancy for fetal anomaly were included.
Results The rate of non-chromosomal major congenital anomaly in women with diabetes was 71.6 per 1,000 pregnancies (95% CI 59.6, 84.9), a relative risk of 3.8 (95% CI 3.2, 4.5) compared with women without diabetes. There was a three- to sixfold increased risk across all common anomaly groups. In a multivariate analysis, peri-conception glycaemic control (adjusted OR [aOR] 1.3 [95% CI 1.2, 1.4] per 1% [11 mmol/mol] linear increase in HbA_{1c} above 6.3% [45 mmol/mol]) and pre-existing nephropathy (aOR 2.5 [95% CI 1.1, 5.3]) were significant independent predictors of congenital anomaly. Associations with gestation at booking (aOR 1.1 [95% CI 1.0, 1.1]) and parity (aOR 1.6 [95% CI 1.0, 2. 5]) were not significant. Unadjusted risk was higher for women from deprived areas or who did not take folate. Type and duration of diabetes, ethnicity, age, BMI, preconception care, smoking and fetal sex were not associated with congenital anomaly risk.
Conclusions Peri-conception glycaemia is the most important modifiable risk factor for congenital anomaly in women with diabetes. The association with nephropathy merits further study.

Keywords Congenital abnormalities · Diabetes · Hyperglycaemia · Nephropathy · Preconception

Abbreviations

aOR	Adjusted odds ratio
EUROCAT	European surveillance of congenital anomalies
ICD	International Classification of Diseases
IMD	Index of Multiple Deprivation
IQR	Interquartile range
LOWESS	Locally weighted scatter plot smoothing
NorCAS	Northern Congenital Abnormality Survey
NorDIP	Northern Diabetes in Pregnancy Survey

Introduction

Pregnancies complicated by pre-existing diabetes are at high risk of adverse outcome, including stillbirth, perinatal

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mortality, congenital anomaly, Caesarean section and macrosomia [1, 2]. The global prevalence of type 2 diabetes is increasing particularly at younger ages, resulting in an increasing proportion of pregnancies complicated by diabetes. Congenital anomalies are a major cause of stillbirth and neonatal death for babies born to women with diabetes [2, 3] and a substantial proportion end in termination of pregnancy. They are also important contributors to mortality and morbidity throughout infancy and childhood, and survivors may have considerable ongoing health and social care needs.

The risk of congenital anomaly in women with diabetes is strongly associated with glycaemic control, indicated by higher levels of HbA_{1c} in pregnancies affected by congenital anomaly [4–6]. However, similar rates of congenital anomaly have been reported in women with type 1 and 2 diabetes, despite generally lower HbA_{1c} levels in type 2 diabetes [1]. This may reflect differences in other variables that are associated with congenital anomaly risk, such as maternal age, BMI, smoking, ethnicity and socioeconomic status. Previous studies have not assessed the extent to which these factors may modify the effect of glycaemia in the development of congenital anomaly in women with diabetes.

This study combined data from established population-based registers with comprehensive ascertainment to quantify the risk of major congenital anomaly in pregnancy in women with type 1 and type 2 diabetes, and to assess the influence of clinical and sociodemographic risk factors in addition to peri-conception HbA_{1c}.

Methods

Study population The study area in the north of England (UK) has a population of about 3 million and 31,000 deliveries per year. This analysis included all singleton pregnancies to women resident in the region, resulting in live birth, stillbirth (≥24 weeks gestation), late fetal loss (20–23 weeks gestation), or termination of pregnancy following prenatal diagnosis of a fetal anomaly (any gestation), during the period 1996–2008.

Pregnancies in women with and without pre-existing diabetes The Northern Diabetes in Pregnancy Survey (NorDIP) records details of all known pregnancies, irrespective of outcome, in women resident in the study area and diagnosed with diabetes at least 6 months prior to conception [7]. Pregnancies in women with gestational diabetes (i.e. hyperglycaemia first diagnosed during pregnancy) are not included. Demographic and clinical variables are collected, including pre-pregnancy and antenatal HbA_{1c} (DCCT-aligned since 2000). The total number of registered singleton live and stillbirths was obtained from the UK Office for National Statistics.

Congenital anomaly cases The Northern Congenital Abnormality Survey (NorCAS) collects information on all cases of congenital anomaly (up to six anomalies for each case) diagnosed to age 12 years, including those arising in fetal loss or termination of pregnancy for fetal anomaly. The register uses multiple sources of ascertainment [8]. The NorDIP and NorCAS are held on a single linked database at the Regional Maternity Survey Office in Newcastle.

Classification of congenital anomalies All major congenital anomalies were coded according to the International Classification of Diseases 10th revision (ICD-10; www.who.int/classifications/icd/en/) and categorised using European surveillance of congenital anomalies (EUROCAT) criteria (www.eurocat@ulster.ac.uk), by group (the system affected), subtype (the individual disorder), and syndrome (where applicable). Chromosomal anomalies were defined as any anomaly in the number of chromosomes or in the structure of at least one chromosome resulting in a genetically unbalanced genotype (ICD-10 codes: Q90–92, Q93, Q96–99). Non-chromosomal anomalies are all remaining major congenital anomalies included in the EUROCAT classification scheme [9, 10].

Isolated cases (with one anomaly diagnosis only) were assigned to their primary anomaly group and subtype. Cases with two or more non-chromosomal anomalies were reviewed to identify a primary group or subtype, or to confirm a diagnosis of multiple anomalies. Cases were classified as multiple anomalies if they had two or more unrelated anomalies across separate organ systems. Individuals with several anomalies from the same organ system were included within that group but not classified by subtype. A congenital anomaly was classified as isolated if it occurred alone, or if all coexisting anomalies were commonly associated secondary anomalies. Chromosomal anomalies, syndromes (patterns of anomalies arising from a single cause, e.g. genetic disorders [11]), skeletal dysplasias (syndromes of skeletal development [10]), sequences (patterns of anomalies arising from a prior anomaly or mechanical factor [12]), associations (recognised patterns of anomalies of unknown cause [11]) and other microdeletions, were regarded as primary anomalies rather than instances of multiple anomalies.

Statistical analyses Prevalence rates of congenital anomaly, by group and subtype, were determined for women with and without diabetes and compared by calculating the RR, and 95% CIs for prevalence rates were calculated using exact methods. Numbers of cases are presented only for groups and subtypes where there was at least one case in pregnancies with diabetes. Rates and RRs (95% CI) for the subtypes of congenital anomalies are presented if there were three or more cases in pregnancies with diabetes. Heterogeneity of RRs between anomaly groups was examined using Cochran's Q test.

ORs and associated 95% CIs for non-chromosomal congenital anomalies among women with diabetes were estimated for various sociodemographic and clinical variables using logistic regression. Independent effects were estimated from an adjusted model, constructed using backwards stepwise regression. All variables with an unadjusted p value below 0.5 were entered into the model (maternal age at delivery, gestational age at booking, peri-conception HbA_{1c}, type of diabetes, preconception folic acid, nephropathy diagnosed pre-pregnancy, retinopathy diagnosed pre-pregnancy, fetal sex, parity, pre-pregnancy care, index of multiple deprivation, smoking during pregnancy). Variables were then iteratively removed until all remaining had $p<0.1$. The multivariate analysis had at least adequate power ($\beta=0.8$) to detect a medium effect (Cohen's d=0.5, equivalent to OR of 2.47) for any variable with a baseline exposure probability between 5% and 95% (which included type 2 diabetes, non-white ethnicity, preconception folate consumption, pre-pregnancy care, smoking during pregnancy). Greater power was available for the continuous variables (duration of diabetes, maternal age at delivery, maternal BMI at booking, gestational age at booking, and peri-conception HbA_{1c}).

Interaction terms were used to examine whether variables in the adjusted model had the same effect on the risk of congenital anomalies in women with type 2 compared with type 1 diabetes. The relative contributions of variables in the adjusted model were approximated by estimating the standardised β coefficients, which allow the importance of continuous and non-continuous variables to be directly compared [13]. HbA_{1c} was analysed as a single peri-conception variable, using measurement closest to conception (within three months of conception) where available (48.4% of pregnancies) and mean first trimester value (up to 14 weeks gestation) otherwise. BMI, determined from height and weight at booking, was included as a continuous variable, excluding underweight women due to potential curvilinearity [14]. The index of multiple deprivation (IMD), an area-based measure of socioeconomic status, was determined from maternal residential postcode at booking and grouped into tertiles [15]. Locally weighted scatter plot smoothing (LOWESS), with smoothing parameter 0.8, was used to investigate the shape of the relationship between HbA_{1c}, as a continuous variable, and the risk of congenital anomaly. CIs for the LOWESS plot were estimated by bootstrapping (50,000 iterations).

Statistical analyses were performed using SPSS for Windows version 17.0 (IBM Corporation, Somers, NY, USA) and Stata 11.1 (StataCorp, College Station, TX, USA). $P<0.05$ was considered statistically significant.

Ethics approval and research governance NorCAS, as part of the British Isles Network of Congenital Anomaly Registers, has exemption from the UK National Information and Governance Board (PIAG 2-08(e)/2002 20/06/2002) from a requirement for individual consent and has ethics approval (09/H0405/48) to undertake studies using the data. Newcastle Research Ethics Committee originally granted approval for the NorDIP in 1993, and data are now obtained and held with informed consent.

Results

Study population Overall, 401,149 singleton live births, stillbirths, late fetal losses, and terminations of pregnancy were recorded during the study period, including 1,677 in women with pre-existing diabetes, giving a prevalence of 4.2 per 1,000 (95% CI 4.0, 4.4) pregnancies.

Among women with diabetes, median (interquartile range, IQR) maternal age at delivery was 30 (25–24) years; 649 (40.1%) women were primiparous and the median (IQR) peri-conception HbA_{1c} was 7.9% (6.8–9.2). A total of 1314 (78.4%) women had type 1 and 363 (21.6%) had type 2 diabetes. There were significant differences in the characteristics of women with type 1 and type 2 diabetes (Tables 1 and 2). Overall reported preconception folate consumption was low, but not significantly different in women with type 1 and type 2 diabetes ($p=0.06$).

Risk of congenital anomaly A total of 9,488 singleton pregnancies were affected by at least one major congenital anomaly, including 129 in women with diabetes. The risk of a pregnancy affected by any major congenital anomaly in women with diabetes was over three times higher than the background population (RR 3.3 [95% CI 2.8, 3.9]; Table 3). There was no difference in the proportion of affected pregnancies ending in termination for fetal anomaly in women with and without diabetes: 23 (18%) vs 1,811 (19%); RR 0.9 (95% CI 0.6, 1.3).

The prevalence of major congenital anomaly per 1,000 pregnancies was 82.2 (95% CI 67.9, 98.3) in women with type 1 diabetes and 57.9 (95% CI 36.2, 87.1) in women with type 2. There was no significant difference in risk of congenital anomaly by type of diabetes (RR 1.4 [95% CI 0.9, 2.2] for type 1 vs type 2).

There was no evidence of increased risk of chromosomal anomalies in women with diabetes (RR 1.2 [95% CI 0.6, 2.4]). Excluding chromosomal anomalies, the relative risk of affected pregnancy for women with diabetes was 3.8 (95% CI 3.2, 4.5). There was significant variation in relative risk between different groups of non-chromosomal anomaly ($p=0.05$), attributable to a 12-fold increase for the sequence group (including caudal dysplasia sequence, sirenomelia and partial urorectal septum malformation sequence) among women with diabetes (Table 3).

Among pregnancies in women without diabetes, the rate of non-chromosomal anomaly was significantly higher in

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Table 1 Characteristics of mothers with type 1 and type 2 diabetes (continuous variables)[a]

Continuous variable	Type 1 (n=1314)			Type 2 (n=363)			p value
	n	Range	Median (IQR)	n	Range	Median (IQR)	
Duration of diabetes (years)	1,303	0.9–36	2 (6–18)	352	1–19	2 (1–4)	<0.001
Maternal age at delivery (years)	1,314	15–46	29 (24–33)	363	17–46	33 (29–37)	<0.001
BMI at booking (kg/m^2)	1,010	17–52	25.5 (23–29)	283	19–64	34.6 (29–40)	<0.001
Gestational age at booking (weeks)	1,308	1–34	8 (7–11)	358	2–34	9 (7–12)	0.009
Peri-conception HbA_{1c} (%)	1,146	5–16.4	8.1 (7.0–9.3)	291	4.6–15.3	7.0 (6.2–8.2)	<0.001
Peri-conception HbA_{1c} (mmol/mol)	1,146	31.1-155.7	65.0 (53.0-78.1)	291	26.8–143.7	53.0 (44.3-66.1)	<0.001

[a] Includes chromosomal and non-chromosomal anomalies

males (RR 1.2 [95% CI 1.1, 1.2]). This sex difference was not apparent among pregnancies in women with diabetes (RR 0.9 [95% CI 0.6, 1.2] for males vs females), although the risk ratio did not differ significantly from that observed in the general population.

Predictors of non-chromosomal congenital anomalies in women with diabetes Peri-conception HbA_{1c} and presence of pre-pregnancy nephropathy were significant independent predictors of congenital anomaly (Table 4). For each percentage (11 mmol/mol) increase in HbA_{1c}, the odds of a pregnancy being affected by congenital anomaly increased by 30% (adjusted odds ratio (aOR) 1.3 [95% CI 1.2, 1.4]). LOWESS indicated that this was a steadily increasing effect for HbA_{1c} values above 6.3% (45 mmol/mol) (Fig. 1 and Table 5). There was no evidence of risk reduction below this value, although there were very few cases in this range.

Pre-pregnancy nephropathy was associated with greater than two-fold increased risk of congenital anomaly (aOR 2.5 [95% CI 1.1, 5.3]). Gestation at booking in weeks (aOR 1.1 [95% CI 1.0, 1.1]) and parity (aOR 1.6 [95% CI 1.0, 2.5]) were also included in the final adjusted logistic regression model (p<0.1) although the associations did not quite reach the nominated significance level (p<0.05). Of the four variables that were retained in the adjusted model, the highest predictive contribution was attributable to HbA_{1c} (standardised beta coefficient, β=0.41), which was more than twice as important as parity (β=0.19), and over 2.5 times more important than gestational age at booking (β=0.16) and nephropathy (β=0.15).

In univariate analysis, socioeconomic status (OR 2.0 [95% CI 1.2, 3.2]) and lack of folic acid (OR 2.0 [95% CI 1.3, 3.3]) were significant predictors of pregnancy affected by congenital anomaly. However, these effects were attenuated below significance when adjustment was made for HbA_{1c}. There was no evidence that any of the associations between variables in the adjusted model and the risk of congenital anomalies was different in women with type 2 diabetes compared with women with type 1 diabetes.

Type and duration of diabetes, fetal sex, maternal ethnicity, early pregnancy BMI, smoking during pregnancy, pre-pregnancy retinopathy, and neuropathy were not significantly associated with the risk of congenital anomaly in either unadjusted or adjusted models.

Discussion

This population-based cohort study provides robust estimates of the risk of major congenital anomaly among offspring of women with pre-existing diabetes. Overall, one in 13 singleton deliveries (7.7%) was affected, and the rate of non-chromosomal anomaly was almost four times higher than in women without pre-existing diabetes. Peri-conception HbA_{1c} has previously been reported to be associated with congenital anomaly [4], but the association with pre-existing nephropathy is, to our knowledge, previously unreported. The risk of congenital anomaly increased linearly with increasing HbA_{1c} above 6.3% (45 mmol/mol), by nearly 30% for each 1% (11 mmol/mol) increase.

This study linked independently and robustly ascertained congenital anomaly cases with detailed clinical information on pregnancies in women with diabetes, notified to long-standing population-based registers. This minimised potential detection bias between pregnancies in women with and without diabetes, and enabled exploration of the independent effects of a wide range of clinical and sociodemographic risk factors. Ascertainment and coding of anomalies was consistent throughout, standardised according to internationally agreed criteria, and independent of diabetes status. We restricted our analysis to EUROCAT defined major anomalies, because these are consistently ascertained, and have the greatest impact on mortality and morbidity. Pregnancies in women with diabetes are subject to increased antenatal surveillance, leading to the potential for ascertainment bias unless, as in NorCAS, cases are notified whenever diagnosed in childhood (to age 12 years). This is particularly important for cardiovascular anomalies, many of which are only diagnosed in early

Table 2 Characteristics of mothers with type 1 and type 2 diabetes (categorical variables)[a]

Categorical variable	Type 1 (n=1314)		Type 2 (n=363)		p value
	n	%	n	%	
Complicated by a congenital anomaly	108	8.2	21	5.8	0.12
Preconception folic acid					
Yes	424	32.3	98	27.0	0.06
No	810	61.6	223	61.4	
Missing	80	6.1	42	11.6	
Nephropathy (pre-pregnancy)					
Yes	57	4.3	3	0.8	0.002
No	1,257	95.7	360	99.2	
Neuropathy (pre-pregnancy)					
Yes	28	2.1	0	0.0	0.01
No	1,286	97.9	363	100.0	
Retinopathy (pre-pregnancy)					
Yes	263	20.0	16	4.4	<0.001
No	992	75.5	323	89.0	
Missing	59	4.5	24	6.6	
Pre-pregnancy care					
Yes	583	44.4	106	29.2	<0.001
No	731	55.6	257	70.8	
Fetal sex					
Male	707	53.8	179	49.3	0.13
Female	601	45.7	182	50.1	
Uncertain/missing	6	0.5	2	0.6	
Smoking during pregnancy					
Yes	290	22.1	81	22.3	0.92
No	910	69.2	246	67.8	
Missing	114	8.7	36	9.9	
Parity					
Primipara (parity=0)	559	42.5	90	24.8	<0.001
Parity ≥1	710	54.0	243	66.9	
Missing	45	3.4	30	8.3	
Ethnicity					
White	1,278	97.3	286	78.8	<0.001
Other	31	2.4	70	19.3	
Missing	5	0.4	7	1.9	
IMD					
Tertile 1 (most deprived)	385	29.3	171	47.1	<0.001
Tertile 2	442	33.6	115	31.7	
Tertile 3 (least deprived)	481	36.6	76	20.9	
Missing	6	0.5	1	0.3	

[a]Includes chromosomal and non-chromosomal anomalies

childhood. Most previous cohort studies of anomalies in pregnancies complicated by diabetes include only those diagnosed antenatally or apparent shortly after birth, a major methodological limitation [2, 3, 5, 16–19].

This is one of the largest cohort studies to date, including 120 cases of major non-chromosomal anomaly in women with both type 1 and type 2 diabetes, and the only such study to include detailed clinical information. The north of England benefits from a long history of collaborative clinical networking within maternity and neonatal services, and the NorCAS and NorDIP surveys were initiated by pioneering clinicians in the 1980s and 1990s. The surveys are now supported by the Regional Maternity Survey Office (RMSO) which provides a focus for data collection and dissemination

Table 3 Rates (95% CI) of major groups and selected subtypes of congenital anomalies[a] in pregnancies of women with and without pre-existing diabetes per 1000 singleton pregnancies and RR (95% CI%)

Group (subtype)[a]	Pregnancies with diabetes		Pregnancies without diabetes		Relative risk(95% CI)
	n	Rate (95% CI)	*n*	Rate (95% CI)	
Nervous system	16	9.5 (5.4, 15.4)	769	1.9 (1.8, 2.1)	5.0 (3.0, 8.1)
Neural tube defects	10	6.0 (2.9, 10.9)	443	1.1 (1.0, 1.2)	5.4 (2.9, 10.1)
Hydrocephalus		2		115	
Microcephaly		1		55	
Holoprosencephaly		1		31	
Eye	2		98		
Cardiovascular system	44	26.2 (19.1, 35.1)	2919	7.3 (7.0, 7.6)	3.6 (2.7, 4.8)
Transposition of great vessels	3	1.8 (0.4, 5.2)	130	0.3 (0.3, 0.4)	5.5 (1.8, 17.2)
Single ventricle	1		13		
Ventricular septal defect	21	12.5 (7.8, 19.1)	1285	3.2 (3.0, 3.4)	3.9 (2.6, 6.0)
Atrial septal defect	1		217		
Atrioventricular septal defect	2		69		
Tetralogy of Fallot	4	2.4 (0.7 6.0)	95	0.24 (0.2, 0.3)	10.0 (3.7, 27.2)
Pulmonary valve stenosis	3	1.8 (0.4, 5.2)	244	0.6 (0.5, 0.7)	2.9 (0.9, 9.1)
Hypoplastic left heart	1		78		
Coarctation of aorta	2		101		
Total anomalous pulmonary venous return	1		35		
Orofacial clefts	1		437		
Digestive system	10	6.0 (2.9, 10.9)	421	1.05 (0.95, 1.15)	5.7 (3.0, 10.6)
Oesophageal atresia	2		43		
Duodenal atresia or stenosis	1		36		
Hirschprung's disease	1		51		
Atresia of bile ducts	1		15		
Diaphragmatic hernia	2		91		
Urinary	12	7.2 (3.7, 12.5)	974	2.4 (2.3, 2.6)	2.9 (1.7, 5.2)
Cystic kidney disease	2		200		
Congenital hydronephrosis	1		20		
Bladder exstrophy	1		14		
Genital	2		76		
Limb	2		234		
Musculoskeletal	3	1.8 (0.4, 5.2)	55	0.14 (0.1, 0.2)	13.0 (4.1, 41.5)
Syndrome (monogenic or unknown)	11	6.6 (3.2, 11.7)	439	1.1 (1.0, 1.2)	6.0 (3.1, 10.9)
Laterality syndrome (right/left atrial isomerism, situs inversus)	6	3.6 (1.3, 7.8)	25	0.06 (0.04, 0.09)	57.2 (23.5, 139.2)
Angelman syndrome	1		6		
Blepharophimosis-ptosis syndrome	1		3		
Laurence–Moon syndrome	1		2		
Prader–Willi syndrome	1		10		
Incontinentia pigmenti	1		6		
Associations	1		34		
Sequence	7	4.2 (1.6, 8.6)	139	0.35 (0.3, 0.4)	12.0 (5.6, 25.6)
Caudal dysplasia sequence	5	3.0 (0.9, 6.9)	7	0.02 (0.01, 0.03)	170.2 (54.1, 535.6)
Sirenomelia	1		6		
Partial urorectal septum malformation sequence	1		21		
Multiple anomalies	9	5.4 (2.5, 10.2)	440	1.1 (1.0, 1.2)	4.9 (2.5, 9.4)
Total non-chromosomal	120	71.6 (59.6, 84.9)	7613	19.1 (18.6, 19.5)	3.8 (3.2, 4.5)
Chromosomal anomalies	9	5.4 (2.5, 10.2)	1747	4.4 (4.2, 4.6)	1.2 (0.6, 2.4)
Grand total	129	76.9 (64.6, 90.8)	9359	23.4 (23.0, 23.9)	3.3 (2.8, 3.9)

[a] EUROCAT coding

Table 4 Association of maternal and fetal factors with non-chromosomal congenital anomalies in offspring of women with pre-existing diabetes (results of univariate and multivariate logistic regression)

Category	Number (%)			
	Total pregnancies (n=1668)	With congenital anomalies (n=120)	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)
Duration of diabetes (years)[b]	1,646	117	1.00 (0.97, 1.02	
Maternal age at delivery (years)[b]	1,668	120	0.98 (0.95, 1.01)	
BMI at booking (kg/m^2)[b]	1,277	95	1.00 (0.97, 1.03)	
Gestation at booking (weeks)[b]	1,657	120	1.04 (1.00, 1.08)	1.05 (1.00, 1.11)
Peri-conception HbA_{1c} (%)[b]	1,428	96	1.30 (1.18, 1.43)	1.30 (1.18, 1.43)
Type of diabetes				
Type 1	1,306	100 (7.7)	1.42 (0.86, 2.33)	
Type 2	362	20 (5.5)	1.00	
Preconception folate supplement				
Taken	518	22 (4.2)	1.00	
Not taken	1,028	85 (8.3)	2.03 (1.26, 3.29)	
Nephropathy diagnosed pre-preg				
No	1,609	110 (6.8)	1.00	1.00
Yes	59	10 (16.9)	2.78 (1.37, 5.64)	2.45 (1.14, 5.25)
Neuropathy diagnosed pre-preg				
No	1,640	118 (7.2)	1.00	
Yes	28	2 (7.1)	0.99 (0.23, 4.23)	
Retinopathy diagnosed pre-preg				
No	1,308	85 (6.5)	1.00	
Yes	277	24 (8.7)	1.37 (0.85, 2.19)	
Fetal sex				
Female	779	59 (7.6)	1.00	
Male	881	57 (6.5)	0.84 (0.58, 1.23)	
Parity				
Primipara (0)	648	43 (6.6)	1.00	1.00
Multipara (≥1)	945	76 (8.0)	1.23 (0.84, 1.81)	1.56 (1.00, 2.45)
Pre-pregnancy care				
Yes	683	41 (6.0)	1.00	
No	985	79 (8.0)	1.37 (0.92, 2.02)	
IMD (tertiles)				
1 (most deprived)	551	52 (9.4)	1.96 (1.22, 3.16)	
2 (middle)	555	40 (7.2)	1.46 (0.89, 2.41)	
3 (least deprived)	555	28 (5.0)	1.00	
Smoking during pregnancy				
No	11,48	80 (7.0)	1.00	
Yes	370	31 (8.4)	1.22 (0.79, 1.88)	
Ethnicity				
White	1,555	112 (7.2)	1.00	
Other	101	8 (7.9)	1.11 (0.53, 2.34)	
HbA_{1c} measurement recorded				
Pre-pregnancy	807	52 (6.4)	1.00	
1st trimester	621	44 (7.1)	1.11 (0.73, 1.68)	

[a]Adjusted model was constructed using backwards stepwise regression. All variables with an unadjusted p value below 0.5 were entered into the model (maternal age at delivery, gestational age at booking, peri-conception HbA_{1c}, type of diabetes, preconception folic acid, nephropathy diagnosed pre-pregnancy, retinopathy diagnosed pre-pregnancy, fetal sex, parity, pre-pregnancy care, IMD, smoking during pregnancy). Variables were then iteratively removed until all remaining had p<0.1, details of which are shown

[b]Continuous variable

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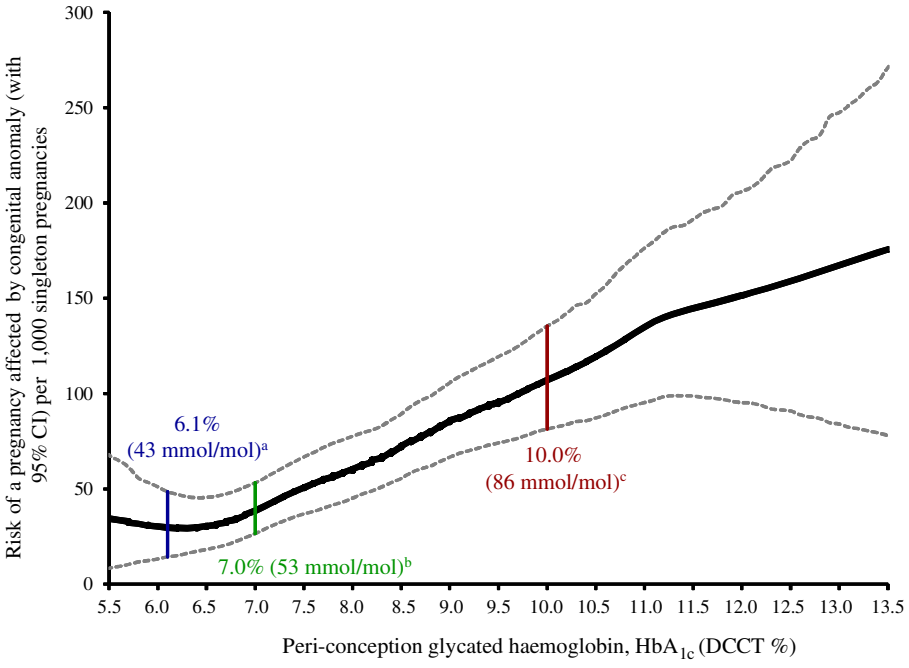

HbA_{1c}	5.5–6.4	6.5–7.4	7.5–8.4	8.5–9.4	9.5–10.4	10.5–11.4	11.5–12.4	12.5–13.5
Singleton pregnancies	195	322	346	220	158	70	32	24
Cases	6	10	21	19	17	10	4	5

Fig. 1 Association between peri-conception HbA_{1c} in women with pre-existing diabetes and the risk (with 95% CIs) of a pregnancy affected by major congenital anomaly. To convert values for HbA_{1c} in % into mmol/mol, subtract 2.15 and multiply by 10.929

[a]National Institute for Health and Clinical Excellence (UK), 2008: (1.1.4.2) 'If it is safely achievable, women with diabetes who are planning to become pregnant should aim to maintain their HbA_{1c} below 6.1%. Women should be reassured that any reduction in HbA_{1c} towards the target of 6.1% is likely to reduce the risk of congenital malformations.' [27]

[b]American Diabetes Association (USA), 2011: (VII.B) 'A_{1c} levels should be as close to normal as possible (<7%) in an individual patient before conception is attempted.' [26]

[c]National Institute for Health and Clinical Excellence (UK), 2008: (1.1.4.3) 'Women with diabetes whose HbA_{1c} is above 10% should be strongly advised to avoid pregnancy.' [27]

across a number of linked surveys of maternal and perinatal health outcome (www.rmso.org.uk).

HbA_{1c} was measured within three months prior to conception in nearly half of cases, and this is likely to reflect peri-conception glycaemia better than first trimester measurements. However, information on covariates such as maternal age and parity was not available for unaffected pregnancies in women without diabetes, and we were therefore unable to adjust our relative risk estimates. Few of the women with diabetes were of non-white ethnicity. Robust information about hypoglycaemic therapy was not available, so we were unable to investigate any potential association with congenital anomaly risk. The study may have lacked power to quantify the relative risk for anomalies with a small effect size, or where very few cases were reported. In the multivariate analyses, we estimated that we had adequate power to detect a medium effect size for almost all variables examined. The study may have missed some associations with smaller effect sizes.

We estimated the relative risk of non-chromosomal congenital anomaly in the offspring of women with existing diabetes to be nearly four-fold higher than the general population. Previously published estimates range from two- to threefold [2, 3, 16, 17, 20] to tenfold [21, 22]. Direct comparison with the current study is difficult due to differences in ascertainment and classification of anomalies, and lack of comparable risk estimates for offspring of women without diabetes. In a large cohort of births to women with diabetes from England, Wales and Northern Ireland (CEMACH enquiry), the prevalence of major non-chromosomal anomaly was 4.6%, compared with 7.2% in the current study. This difference may reflect the fact that CEMACH did not have access to a population-based register and only identified cases apparent within 28 days of delivery. Our study is population-based and draws on multiple sources to identify cases of anomaly diagnosed at any time up to age 12 years. Under-ascertainment is also likely to explain the CEMACH study's low reported prevalence ratio of 2.2 for congenital anomaly in

Table 5 Risk of a pregnancy affected by major congenital anomaly in women with pre-existing diabetes, by peri-conception HbA_{1c}

Peri-conception glycated haemoglobin (HbA_{1c})		Risk of a pregnancy affected by congenital anomaly (95% CI)	
DCCT (%)	IFCC (mmol/mol)	Per 1,000 singleton pregnancies	For individual singleton pregnancy
5.5	37	34.3 (8.3, 67.6)	1 in 29 (15, 121)
6.0	42	30.2 (13.1, 51.0)	1 in 33 (20, 76)
6.1[a]	43[a]	29.7 (14.3, 48.5)	1 in 34 (21, 70)
6.5	48	30.3 (18.1, 45.5)	1 in 33 (22, 55)
7.0[b]	53[b]	38.4 (26.5, 53.1)	1 in 26 (19, 38)
7.5	58	50.6 (36.8, 66.8)	1 in 20 (15, 27)
8.0	64	60.1 (45.1, 77.6)	1 in 17 (13, 22)
8.5	69	72.3 (55.5, 89.3)	1 in 14 (11, 18)
9.0	75	85.5 (66.7, 105.7)	1 in 12 (9, 15)
9.5	80	95.3 (74.1, 119.4)	1 in 10 (8, 13)
10.0[c]	86[c]	107.1 (81.4, 135.4)	1 in 9 (7, 12)
10.5	91	119.3 (87.2, 152.3)	1 in 8 (7, 11)
11.0	97	134.9 (95.3, 176.4)	1 in 7 (6, 10)
11.5	102	144.7 (98.7, 191.4)	1 in 7 (5, 10)
12.0	108	151.5 (95.2, 206.1)	1 in 7 (5, 11)
12.5	113	158.9 (90.8, 222.2)	1 in 6 (5, 11)
13.0	119	167.2 (84.0, 247.4)	1 in 6 (4, 12)
13.5	124	175.7 (77.8, 271.0)	1 in 6 (4, 13)

[a,b,c]For further explanation see Fig. 1

IFCC, International Federation of Clinical Chemistry and Laboratory Medicine

women with and without diabetes, as the comparison was with age-adjusted prevalence rates from the EUROCAT network of population-based registries [2]. The current study estimated a 3.8-fold increase, based on a direct comparison of the congenital anomaly rates in women with and without diabetes from the same source population, indentified independently of diabetes status.

Only two variables, higher peri-conception HbA_{1c} and pre-existing nephropathy, were significant independent predictors in multivariate analysis. Parity and gestational age at booking were retained in the multivariate model but the associations did not reach statistical significance. There was no evidence of an independent effect of maternal age, smoking, ethnicity and early pregnancy BMI, which have been associated with congenital anomaly risk in the general population. A higher rate of congenital anomaly was observed in women resident in more deprived areas; this was largely attributable to higher peri-conception HbA_{1c} in these women. We found no evidence that the increased risk of anomaly in women with diabetes was specific to males, in contrast with an earlier report [23], although we confirmed the increased risk for males in the general population [24, 25]. There was no evidence that any of the identified predictors of congenital anomaly were different in type 1 and type 2 diabetes.

Peri-conception HbA_{1c} was the most important independent predictor of congenital anomaly risk, confirming previous reports [4–6]. The current study identified a linear relationship with HbA_{1c} for values between 6.3% and 11% (45 and 97 mmol/mol). The odds were lowest for HbA_{1c}= 6.3% (45 mmol/mol), although still above background population levels, and increased by approximately 2% in absolute terms for each 1% (11 mmol/mol) increase, slightly lower than previous reports [5, 6]. We found no evidence of further reduction for values below 6.3% (45 mmol/mol), although there were few individuals in this range.

Current guidance from the American Diabetes Association recommends a target HbA_{1c} <7% (53 mmol/mol) prior to pregnancy [26]. In England, the National Institute for Health and Clinical Excellence (NICE) suggests a target for preconception HbA_{1c} <6.1% (43 mmol/mol), if safely achievable, and strongly discourages pregnancy at levels >10% (86 mmol/mol) [27]. Our results indicate that there appears to be no specific threshold for change in congenital anomaly risk, and hence do not provide support for particular peri-conception HbA_{1c} targets, but rather provide risk estimates across a range of HbA_{1c} levels. Our results further suggest that even achieving near normal levels of HbA_{1c} does not eliminate the increased risk of congenital anomaly attributable to diabetes. All women with diabetes should be encouraged to achieve as great a reduction in HbA_{1c} as possible prior to conception.

There was a greater than twofold increased risk of congenital anomaly in the offspring of women with pre-existing nephropathy. This group is known to be at increased risk of adverse pregnancy outcome [28, 29], but this is the first

study to suggest a specific increased risk of occurrence of congenital anomaly. This finding requires confirmation in other studies. Nephropathy may reflect a history of prolonged poor glycaemic control, including high variability in glucose levels, which may not be reflected by HbA_{1c} [30]; however, neither retinopathy nor neuropathy conferred increased risks of congenital anomaly. Women with nephropathy usually require antihypertensive medication and are often treated with ACE inhibitors, which have been associated with congenital anomaly risk [31]. Current guidance suggests that these and other potentially teratogenic medications should be discontinued prior to conception [27, 32] but many pregnancies are unplanned and the extent of peri-conception exposure to potentially teratogenic medications is unknown. We were unable to investigate this issue as the registers do not record details of peri-conception medications. There is evidence for a genetic influence on diabetic nephropathy, and it is possible that an association with congenital anomaly may have a genetic basis [33]. Oxidative stress is thought to play a role in the development of nephropathy as well as in congenital anomaly [34]. These potential shared mechanisms merit further research.

Type of diabetes was not independently associated with risk of congenital anomaly, and did not modify the association with other variables. There was a slightly higher unadjusted risk of non-chromosomal anomaly among women with type 1 diabetes (RR 1.4 [95% CI 0.9, 2.2]), which may have been significant with a larger sample size; however the effect was heavily attenuated by adjustment for HbA_{1c}, suggesting that this is the main driver for any difference in risk between type 1 and type 2. Women with type 2 diabetes had lower peri-conception HbA_{1c}, but were less likely to attend for preconception care, and had markedly different clinical and sociodemographic characteristics compared with women with type 1 diabetes, in line with previous reports [35, 36]. Specific approaches to improve pregnancy planning in women with type 2 diabetes may be required. Reported rates of preconception folate supplementation were generally low, suggesting poor awareness among women and/or low rates of planned pregnancies.

This study confirms the association of pre-existing diabetes with a wide range of non-chromosomal anomalies affecting most major organ systems [20, 37] and with the risk of anomalies affecting multiple systems [37, 38] Cardiovascular anomalies were the most common, reflecting their high frequency in the general population, and were not proportionally more frequent in women with diabetes. However, we confirmed very high relative risks for caudal regression sequence and laterality syndrome [38, 39], suggesting a specific effect of diabetes in the aetiology of these rare anomalies.

Given the diverse range of congenital anomalies associated with maternal diabetes, mechanisms that have a general effect on early organogenesis are likely [40, 41]. Hyperglycaemia may be directly implicated through induction of oxidative stress within the embryo [42]. Disruption of specific genetic pathways in this way has been described in animal models for neural tube and cardiac outflow tract development [43].

Blood glucose levels may fluctuate widely, even in the presence of apparently 'optimal' HbA_{1c} [30]. Multiple anomalies may arise from multiple episodes of hyperglycaemia during the critical windows of development for different organ systems. Hence, approaches to reducing peri-conception glucose variability using insulin pump therapy and continuous glucose monitoring may be valuable in the prevention of congenital anomaly and should be evaluated in this regard [44].

Implications Women with diabetes remain at greatly increased risk of offspring affected by major congenital anomaly. Achieving optimal glycaemic control prior to conception remains the most important modifiable risk factor, but is unlikely to eliminate the excess risk. Guidelines emphasise the provision of specialist preconception care to improve preparation and planning for pregnancy, but uptake remains low, and women from ethnic minority groups, socially deprived areas and with type 2 diabetes are less likely to attend. Awareness of the need for preparation for pregnancy should be incorporated into the routine care of young women with diabetes. Further research is needed to evaluate new approaches to improve the number of women with diabetes who are adequately prepared for pregnancy, and to reduce sociodemographic inequalities in outcome.

We found that women with pre-existing nephropathy were at particularly high risk of congenital anomaly. These women require specific care and support to achieve a planned pregnancy with a good outcome. Further investigation of the extent and consequences of exposure to potentially teratogenic factors in these women, including medications, is required. Interventions to reduce glucose variability and anti-oxidant therapies merit further assessment of their potential to reduce congenital anomaly risk in women with diabetes.

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Contribution statement RB and JR developed the study concept and supervised the research. SVG prepared the database and PWGT coded the anomalies. SVG and PWGT analysed the data, and with RWB, RB and JR, interpreted the findings. RB wrote the first draft of the report; all co-authors contributed to writing and agreed the final draft.

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In the accompanying commentary (**Appendix C**, p234), Haddon described Bell *et al* 2012 as a '*definitive epidemiological assessment*' and a '*final answer*' to those who question the primacy of pre-existing diabetes and hyperglycaemia on the risk of congenital anomaly.[387] Such hyperbole is admittedly typical for this sort of piece – written as they are by those with the greatest of interest – but is perhaps unusual when the subject is an observational study that delivers not the glamour of a new discovery, but the mundanity of confirmation.

Regardless, of the works included in this submission Bell *et al* 2012 is arguably the most significant. While many studies had previously examined the association between diabetes and congenital anomaly, all lacked detail and/or experienced methodological flaws.[210,287,288,340,343,388-391] Limited statistical power, in particular, had led to erroneous conclusions that the association might be restricted to certain anomaly groups[287] or subpopulations.[391] But low precision (i.e. high *random* error) is arguably less serious than low accuracy (i.e. high *systematic* error), as demonstrated by Garne *et al* 2012.[288] Despite benefitting from high-quality population-based data on the prevalence of congenital anomaly, this large pan-European study lacked accurate information on which pregnancies were affected by diabetes, leading to some implausible protective ORs.[288]

In their recent meta-analysis of the association between pre-existing diabetes and the risk of congenital heart disease, Simeone *et al* 2015 (who omitted Garne *et al* 2012) estimated a relative risk of 3.8 (95% credible interval, CrI: 3.0 to 4.9), strikingly similar to the 3.6 (95% CI: 2.7 to 4.9) estimated by Bell *et al* 2012 (though perhaps unsurprisingly, since Bell *et al* 2012 will have received the largest analytic weight). The results are also indistinguishable from the next largest study [OR=3.5 (95% CI: 2.7 to 4.7)], Eidem *et al's* 2011 Norwegian register-based cohort of women with type 1 diabetes.[343] For CHD, the association with pre-existing diabetes thus seems fairly consistent, at least among predominantly white populations in the northern hemisphere.

With detailed and reliable information on both congenital anomalies and maternal pre-existing diabetes, Bell *et al* 2012 was also able to examine the mediators of congenital anomaly within women with diabetes. The observed association between nephropathy and anomaly risk fits well into the accumulating evidence that anti-hypertensive medications, or hypertension itself, may be teratogenic.[392] The most informative result however again came from LOWESS, which I used to estimate the risk of congenital anomaly across the range of values of peri-conception HbA_{1c} (with the addition of bootrapped CIs). Although Nielsen *et al* 2006 had previously used LOWESS to explore the relationship between first-trimester HbA_{1c} and the risk of composite 'early adverse outcomes',[292] the results, as with Tennant *et al*

2011, were primarily illustrative. In producing **Figure 1** (p77) and **Table 5** (p78) for Bell *et al* 2012, I specifically aimed to maximise the relevance for pre-conception planning and decision-making, which Hadden speculated would, '*become a major educational demonstration for diabetic mothers-to-be, as well as all of their advisors*'.[387]

Bell *et al 2012*'s most prominent limitation is the incomplete information on pre-conception HbA_{1c}, which results from the current fact that around half of women with pre-existing diabetes do not attend for pre-conception care.[11] The research team considered several approaches to address this problem, the final choice being a direct substitution of missing pre-conception values with first-trimester ones to create a 'peri-conception' variable. Although both variables are closely correlated (Spearman's ρ=0.75), HbA_{1c} levels are systematically lower in pregnancy, possibly due to an increase in erythrocyte volume.[393]. Simply combining these variables will hence have increased the overall variance and overestimated the absolute risk for a given pre-conception HbA_{1c}. Although my original suggestion of multiple imputation was rejected on the grounds of complexity, a possible compromise might have been to add the systematic difference (regression intercept) between the two, the downside being this would still have underestimated the true variance.

2·5 GLINIANAIA *et al* 2012 (HbA_{1c} & BIRTHWEIGHT IN DIABETES)

Title: HbA_{1c} and birthweight in women with pre-conception type 1 and type 2 diabetes: a population-based cohort study

Authors: Glinianaia SV, **Tennant PWG**, Bilous RW, Rankin J, Bell R

Journal: Diabetologia (Volume 55 Issue 12 Pages 3193-3203)

Date of Publication: 27 September 2012

2·5·1 Overview

This article examined the same cohort of pregnant women with pre-existing diabetes described in Bell *et al* 2012 (albeit excluding cases of congenital anomaly) to identify and quantify the determinants of birth weight, small-for-gestational-age (SGA), and LGA in pregnancies complicated by the condition.

The paper was accompanied by extensive supplementary material (**Section 2·5·6**, p97) consisting of an extended description of the statistical analysis, two extended paragraphs of results, an addition table documenting the results of the sensitivity analyses, and two additional figures.

2·5·2 What was known

- LGA was known as the most common obstetric complication in the offspring of women with pre-existing diabetes.
- Although hyperglycaemia was widely recognised as the cause of this excess growth, it was a surprisingly poor predictor of LGA, with the risk being 25-50% even in women with good glycaemic control.
- While hyperglycaemia in late pregnancy was consistently associated with increasing birthweight, the association was less clear before and during early pregnancy.

2·5·3 What this study added

- The relationship between HbA_{1c} and birthweight in women with pre-existing diabetes was found to reverse in direction from pre- to late-pregnancy, with increasing peri-conception HbA_{1c} being associated with reduced birthweight and increasing third-trimester HbA_{1c} being associated with increased birthweight.

- The association between third-trimester HbA_{1c} and birthweight appeared to be non-linear, with the majority of the trend occurring for values up to 53mmol/mol. Thereafter, the risk of LGA was consistently around two-thirds, regardless of HbA_{1c} value.

- Third trimester HbA_{1c} and pre-conception HbA_{1c} were the two strongest modifiable predictors of birthweight in women with pre-existing diabetes, although other well-known factors in the general population, such as maternal BMI and smoking, were also significant.

2·5·4 Contribution of the candidate to this work

I designed and conducted parts of the statistical analysis[xxvi], drafted parts of the methods[xxvii] and parts of the results[xxviii], produced Table 3, Table 5, and Figure 1 and critically-reviewed the draft produced by SVG. A copy of the Newcastle University Co-Authorship form for this publication can be found in **Appendix A(iv)** (p185).

[xxvi] I conducted all analyses relating to birthweight, preliminary LOWESS explorations, the predictive model of LGA, interaction tests, and the sensitivity analyses

[xxvii] Particularly the section entitled, '*Definitions and statistical analysis*'

[xxviii] Particularly those paragraphs relating to the birth weight multivariable model and the sensitivity analyses

2·5·5 Manuscript

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ARTICLE

HbA_{1c} and birthweight in women with pre-conception type 1 and type 2 diabetes: a population-based cohort study

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Abstract
Aims/hypothesis To investigate clinical and sociodemographic predictors of birthweight in singletons born to women with type 1 or type 2 diabetes.
Methods Normally formed singleton live births and intrapartum stillbirths, born to women with pre-conception diabetes during 1996–2008, were identified from the population-based Northern Diabetes in Pregnancy Survey (n=1,505). Associations between potential predictors and birthweight were analysed by multiple regression.
Results Potentially modifiable independent predictors of increase in birthweight were pre-pregnancy care (adjusted regression coefficient [b]=87.1 g; 95% CI 12.9, 161.3), increasing third-trimester HbA_{1c} ≤7% (53 mmol/mol) (b=310.5 g per 1% [11 mmol/mol]; 95% CI 246.3, 374.7) and increasing maternal BMI (b=9.5 g per 1 kg/m^2; 95% CI 3.5, 15.5). Smoking during pregnancy (b=−145.1 g; 95% CI −231.4, −58.8), later gestation at first antenatal visit (b=−15.0 g; 95% CI −26.9, −3.0) and higher peri-conception HbA_{1c} (b=−48.2 g; 95% CI −68.8, −27.6) were independently associated with birthweight reduction. Pre-pregnancy nephropathy (b=−282.7 g; 95% CI −461.8, −103.6) and retinopathy (b=−175.5 g; 95% CI −269.9, −81.0) were independent non-modifiable predictors of reduced birthweight, while greater maternal height was a non-modifiable predictor of increasing birthweight (b=17.8 g; 95% CI 12.3, 23.2). Other predictors of birthweight increase were male sex, multiparity and increasing gestational age at delivery. Type or duration of diabetes, socioeconomic status and ethnicity were not associated with continuous birthweight.
Conclusions/interpretation Poor glycaemic control before and throughout pregnancy is associated with abnormal fetal growth, with increasing peri-conception HbA_{1c} predicting weight reduction and increasing third-trimester HbA_{1c} predicting increased birthweight. Women with microvascular complications of diabetes may require increased surveillance to detect fetal growth restriction.

Keywords Birthweight · HbA_{1c} · Large for gestational age (LGA) · Macrosomia · Pre-conception diabetes · Small for gestational age (SGA)

Abbreviations

IQR	Interquartile range
LGA	Large for gestational age
LMP	Last menstrual period
LOWESS	Locally weighted scatterplot smoothing
NorCAS	Northern Congenital Abnormality Survey
NorDIP	Northern Diabetes in Pregnancy Survey
PMMS	Perinatal Morbidity and Mortality Survey
RMSO	Regional Maternity Survey Office
SGA	Small for gestational age

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Introduction

Women with type 1 and type 2 diabetes have a much higher risk of serious adverse pregnancy outcomes, such as stillbirth, major congenital anomalies, neonatal morbidity and mortality [1–4]. Maternal diabetes is also associated with a higher risk of aberrant fetal growth. About 50% of infants born to mothers with pre-conception diabetes are reported to be macrosomic or large for gestational age (LGA), although there is overlap in the definition of both of these terms (usually defined as birthweight >90th centile for gestational age) [5–8]. Small for gestational age (SGA) is less often associated with maternal diabetes per se, but has been reported in association with severe vascular complications [9, 10] and can result in higher neonatal morbidity and mortality. Both birthweight extremes in offspring of mothers with diabetes are associated with a higher risk of complications during the pregnancy, labour and neonatal period [2, 11] as well as with a potential increase in diseases in childhood and adulthood, including obesity, cardiovascular disease, diabetes and metabolic syndrome [12–15].

The increased risk of an LGA birth in women with diabetes is thought to be associated with poor glycaemic control, usually estimated by concentration of HbA_{1c} before or during pregnancy [5, 11, 16, 17]. However, the evidence and the direction of the association, particularly in relation to pre- and post-conception glycaemic control, is inconsistent. Penney et al, for example, found a negative association between pre-conception HbA_{1c} and standardised birthweight, but no associations at any trimester of pregnancy [16]. In contrast, Evers et al reported a positive association between risk of macrosomia and third-trimester HbA_{1c} [5].

Less is known about the association between gestational glycaemic control and the risk of an SGA birth, and which windows of exposure are most important for increased risk of abnormal birthweight. Moreover, the extent to which other potential determinants of birthweight may modify the effect of glycaemia on fetal growth in women with diabetes has not been extensively investigated in population-based studies.

The aim of this study was to investigate the influence of sociodemographic and clinical factors, including peri-conception and antenatal HbA_{1c}, on birthweight in normally formed singleton infants born to women with type 1 and type 2 diabetes, using the population-based Northern Diabetes in Pregnancy Survey (NorDIP).

Methods

Study population The North of England (UK) is a geographically distinct area with a population of around 3 million and 31,000 births per year. NorDIP collects details of all known pregnancies occurring in the region, irrespective of outcome, in women diagnosed with diabetes at least 6 months before the index pregnancy [18]. All maternity units within the region participate in the survey. Coordinators in each unit notify the survey of relevant pregnancies, and data collection is undertaken by unit clinicians. Pregnancies in women with gestational diabetes (i.e. hyperglycaemia first diagnosed during pregnancy) are not included. Various demographic and clinical variables are collected, including pre-conception and antenatal HbA_{1c} (DCCT aligned since 2000).

This analysis included all normally formed singleton live births and intrapartum stillbirths born in the region between 01 January 1996 and 31 December 2008. Pregnancies resulting in antepartum stillbirth (n=38), identified from the Northern Perinatal Morbidity and Mortality Survey (PMMS) [19], and/or complicated by major congenital anomaly (n=129), identified from the Northern Congenital Abnormality Survey (NorCAS) [20], were excluded due to the known predominance of growth-retarded fetuses in these groups. All three databases are linked into a coordinated database in the Regional Maternity Survey Office (RMSO) (www.rmso.org.uk). The total number of registered singleton live and stillbirths for the North of England was obtained from the UK Office for National Statistics.

Definitions and statistical analysis All NorDIP clinical and sociodemographic variables with a hypothesised influence on birthweight were examined: diabetes type, fetal sex, pre-pregnancy folate supplement usage, pre-pregnancy care, smoking during pregnancy, history of clinically diagnosed pre-pregnancy nephropathy, neuropathy or retinopathy, parity (primiparous vs multiparous) and maternal ethnicity (white vs non-white) were analysed as dichotomous variables. Macrosomia was defined as a birthweight of ≥4,000 g and low birthweight was defined as a birthweight of <2,500 g. Socioeconomic status was estimated from the Index of Multiple Deprivation (a UK area-based measure, derived from a mother's residential postcode at delivery) and analysed in tertiles of rank [21]. Duration of diabetes, maternal age at delivery, maternal BMI at first antenatal visit, maternal height, gestational age at first antenatal visit and at delivery (based on reported estimated date of delivery calculated for the majority of women using ultrasound scan at 10–13 weeks' gestation, or date of the last menstrual period [LMP], if no scan dating was available) and mean maternal HbA_{1c} at three time points (peri-conception, second trimester and third trimester) were analysed as continuous variables. Peri-conception HbA_{1c} was calculated as the closest measurement within 3 months before the date of the LMP (available for 49.5% of pregnancies) or mean first-trimester measurement (up to 14 weeks gestation) (valid 83.3%) for women with no pre-conception measure recorded. Peri-conception HbA_{1c} (valid 86.7%) was chosen as a reasonable surrogate of pre-conception HbA_{1c}, as first-

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trimester HbA$_{1c}$ was highly correlated with pre-conception HbA$_{1c}$ (Spearman correlation coefficient 0.75). The independent effects of pre-conception HbA$_{1c}$ and first-trimester HbA$_{1c}$ were, nevertheless, also examined in a sensitivity analysis on a subsample of participants with both measures.

The association between each variable and birthweight, as a continuous variable, was examined by multiple linear regression. The summary influence of each variable was estimated by constructing a series of simple models that included the variable of interest, alongside sex, parity and gestational age. The independent influence of each variable was estimated in a fully adjusted model, constructed using a backwards stepwise approach. Gestational age (centred to reduce collinearity) was modelled as a three-term polynomial, i.e. b_1(gestational age $-\bar{x}$)+b_2(gestational age $-\bar{x}$)^2+b_3(gestational age $-\bar{x}$)^3 (see electronic supplementary material [ESM] Fig. 1). The shape of the association between each HbA$_{1c}$ variable and birthweight was explored by locally weighted scatterplot smoothing (LOWESS) and fitting fractional polynomials. As a nonlinear association between third-trimester HbA$_{1c}$ and birthweight was observed, it was modelled by piecewise linear regression, with a single knot at 7% (53 mmol/mol) (the choice of location being guided by LOWESS explorations), which divided the regression into two parts, ≤7% (53 mmol/mol) (61.7% of participants) and >7% (53 mmol/mol, 38.3%). The presence of heteroscedasticity was evaluated using the Cook–Weisberg test [22] and, when present, the Huber/White estimator [23] was used (further details in ESM Methods). The proportion of variation directly explained by each variable was estimated from the change in the coefficient of determination (ΔR^2) resulting from removing that variable from the adjusted model.

Separate analyses were performed to examine predictors of LGA and SGA births; LGA (birthweight ≥90th percentile) and SGA (<10th percentile) categories were created based on birthweight standardised for fetal sex, parity and gestational age using Scottish birth population standards [24]. ORs and associated 95% CIs for LGA and SGA were estimated for various predictors using multiple logistic regression; adjusted effects were estimated using a backwards stepwise approach. The probability of LGA for specific values of third-trimester HbA$_{1c}$ was estimated by taking marginal values of the adjusted model; corresponding 95% CIs were obtained using the delta method.

Potential interactions between the HbA$_{1c}$ variables and all other variables in each adjusted model were examined by the inclusion of cross-product terms.

SPSS for Windows 17.0 (IBM Corporation, NY, USA) was used for most of the statistical analyses. Confidence intervals for ΔR^2 were approximated by bootstrapping on 10,000 repeated samples, drawn with replacement, using Stata 11.1 (Statacorp, College Station, TX, USA). $p<0.05$ was considered statistically significant.

Ethics approval and research governance Newcastle Research Ethics Committee originally granted approval for NorDIP in 1993, and data are now obtained and held with informed consent.

Results

Of 389,789 singleton pregnancies resulting in non-malformed stillbirths and live births recorded during 1996–2008, 1,502 were singleton live births and three were intrapartum stillbirths in women with type 1 and type 2 diabetes; 1,495 of these were used for this analysis (10 cases had missing birthweight data).

Descriptive statistics for the study sample are shown in Tables 1 and 2. The median birthweight for offspring of women with diabetes was 3,450 g (interquartile range [IQR]=2,990–3,918), and the median gestational age was 37.0 weeks (IQR=36–38). The proportion of macrosomia was significantly higher in offspring of women with diabetes compared with the North of England background population (22.4% vs 12.1%, RR 1.9, 95% CI 1.7, 2.0) as was the proportion of low birthweight (10.7 vs 5.8%, RR 1.8, 95% CI 1.6, 2.1) (not shown in Tables 1 and 2). There were 50.4% LGA babies born to women with type 1 diabetes compared with 43.7% (p=0.04) to women with type 2 diabetes (22% in our population).

Table 3 shows that increasing peri-conception HbA$_{1c}$ (p<0.0001), later gestation at first antenatal visit (p=0.01), increasing maternal age (p=0.0001), pre-pregnancy retinopathy (p=0.0003), pre-pregnancy nephropathy (p=0.002) and smoking during pregnancy (p=0.001) were all independently associated with lower birthweight. Conversely, increasing third-trimester HbA$_{1c}$ for values ≤7% (53 mmol/mol) (p<0.0001), increasing maternal BMI (p=0.002), pre-pregnancy care (p=0.02), increasing maternal height (p<0.0001), male sex (p=0.0007) and multiparity (p<0.0001) were independently associated with higher birthweight. Type or duration of diabetes, non-white ethnicity, pre-pregnancy neuropathy, second trimester HbA$_{1c}$, third-trimester HbA$_{1c}$ for values >7% (53 mmol/mol), and area-based deprivation were not associated with birthweight after adjustment for other test variables.

The model explained 46.9% (95% CI 40.5, 51.4) of the variation in birthweight. Third-trimester HbA$_{1c}$ explained 5.6% (95% CI 3.7, 7.8) of the variation, six times the contribution of peri-conception HbA$_{1c}$ (ΔR^2=0.9% [95% CI 0.3, 2.0]). The remaining potentially modifiable factors each explained 0.3–0.6% of the variation (Table 3, Fig. 1). The strongest predictor of birthweight was gestational age (as a cubic term), explaining 28.0% (95% CI 23.1, 33.8) of the total variation. Each of other non-modifiable factors (e.g. maternal height and age, parity, pre-pregnancy microvascular complications) explained between 0.2% and 2.4% of the variation in birthweight.

Table 1 Descriptive statistics for singleton, normally formed births in women with pre-conception diabetes delivered in the North of England during 1996–2008 (continuous variables)

Continuous variable	*n*	Median (IQR)	Range
Birthweight (g)	1,495	3,450 (2,990–3,918)	550–5,780
Gestational age at delivery (weeks)	1,495	37 (36–38)	23–42
Maternal height (cm)	1,156	163 (158–168)	127–188
Maternal age (years)	1,495	30 (25–34)	15–46
Duration of diabetes (years)	1,481	9 (4–17)	<1–36
Potentially modifiable variable			
Maternal BMI (kg/m^2)	1,154	26.6 (23.7–31.5)	17.1–63.6
Gestation at first antenatal visit (weeks)	1,490	8 (7–11)	1–34
Peri-conception HbA_{1c} (%)	1,296	7.8 (6.8–9.1)	4.6–16.4
Peri-conception HbA_{1c} (mmol/mol)	1,296	62 (51–76)	27–156
Second trimester HbA_{1c} (%)	1,338	6.6 (5.9–7.3)	3.3–13.1
Second trimester HbA_{1c} (mmol/mol)	1,338	49 (41–56)	13–120
Third-trimester HbA_{1c} (%)	1,315	6.7 (6.1–7.4)	3.8–11.5
Third-trimester HbA_{1c} (mmol/mol)	1,315	50 (43–57)	18–102

Two statistically significant interactions were observed for third-trimester HbA_{1c} in the adjusted model of continuous birthweight. First, the effect of third-trimester HbA_{1c} (for values ≤7% [53 mmol/mol]) decreased with increasing peri-conception HbA_{1c} (p=0.001). Second, the effect of third-trimester HbA_{1c} (≤7% [53 mmol/mol]) increased with increasing BMI (p=0.002) (furher details in ESM Results 1).

For offspring of women with diabetes, 81.8% were at or above the median weight of the reference population (≥50th percentile), 49.0% were LGA and 3.0% were SGA. Table 4 shows that increasing third-trimester HbA_{1c} for values ≤7% (53 mmol/mol) (p<0.0001) and increasing maternal height (p<0.0001) were independently associated with increased odds of LGA, while increasing peri-conception HbA_{1c} (p=0.002), later gestation at first antenatal visit (p=0.005), pre-pregnancy retinopathy (p=0.0004), non-white ethnicity (p=0.03) and smoking during pregnancy (p=0.0001) were associated with reduced odds of LGA. Table 5 shows that with the increase in third-trimester HbA_{1c} from 5.5% (36.6 mmol/mol) to 7.0% (53.0 mmol/mol), the modelled LGA rate increased sharply from 27.1% (95% CI 22.0, 32.2) to 64.1% (95% CI 59.1, 69.0), respectively, with negligible increase thereafter.

Later gestation at first antenatal visit (p=0.01) and pre-pregnancy nephropathy (p=0.003) were associated with higher odds of an SGA birth, while increasing maternal height (p=0.01) and increasing third-trimester HbA_{1c} for values ≤7% (53 mmol/mol) (p=0.03) were associated with lower odds of an SGA birth (Table 4).

A sensitivity analysis found that most of the effect of peri-conception HbA_{1c} on birthweight was attributed to pre-conception HbA_{1c} (ESM Table 1, ESM Results 2).

Discussion

This large population-based cohort study describes the association between clinical and sociodemographic factors and birthweight in normally formed singletons born to women with pre-conception diabetes. The study demonstrates a complex association between glycaemia and birthweight; this relationship changed during pregnancy, such that increasing peri-conception HbA_{1c} was associated with a reduction in birthweight, while increasing third-trimester HbA_{1c} for values ≤7% (53 mmol/mol) was associated with an increase in birthweight. In addition to confirming that known determinants of birthweight in the general population (smoking during pregnancy, maternal height and BMI, parity) also apply to women with diabetes, we identified several additional specific predictors such as HbA_{1c} concentrations and microvascular complications. Among the potentially modifiable predictors of birthweight, peri-conception and third-trimester HbA_{1c} were the most important, while gestational age was the strongest birthweight predictor overall.

This study comprises one of the largest cohorts exploring the association between glycaemia at different stages of pregnancy in women with type 1 or type 2 diabetes and birthweight using data from a population-based survey, NorDIP, and is the only investigation to date to include such a comprehensive range of other clinical and sociodemographic explanatory variables. We also used data from two other linked regional surveys, NorCAS and PMMS, which allowed us to create a complete dataset of normally formed singleton pregnancies in women with diabetes. By excluding pregnancies affected by a major congenital anomaly

Table 2 Descriptive statistics for singleton, normally formed births in women with pre-conception diabetes delivered in the North of England during 1996–2008 (categorical variables)

Categorical variable	*n*	% (total)	% (non-missing)
LGA birthweight[a]			
No	728	48.7	51.0
Yes	700	46.8	49.0
Missing	67	4.5	
SGA birthweight[a]			
No	1,385	92.6	97.0
Yes	43	2.9	3.0
Missing	67	4.5	
Fetal sex			
Female	700	46.8	46.8
Male	795	53.2	53.2
Parity			
Primiparous	585	39.1	40.9
Multiparous (≥1)	844	56.5	59.1
Missing	66	4.4	
Maternal ethnicity			
White	1,396	93.4	93.9
Non-white	90	6.0	6.1
Missing	9	0.6	
Index of multiple deprivation			
Tertile 1 (most deprived)	497	33.2	33.3
Tertile 2	497	33.2	33.3
Tertile 3 (least deprived)	497	33.2	33.3
Missing	4	0.3	
Diabetes type			
Type 1	1,168	78.1	78.1
Type 2	327	21.9	21.9
Pre-pregnancy retinopathy			
No	1,193	79.8	83.1
Yes	242	16.2	16.9
Missing	60	4.0	
Pre-pregnancy neuropathy			
No	1,470	98.3	98.3
Yes	25	1.7	1.7
Pre-pregnancy nephropathy			
No	1,447	96.8	96.8
Yes	48	3.2	3.2
Potentially modifiable variable			
Pre-pregnancy care			
No	870	58.2	58.2
Yes	625	41.8	41.8
Pre-pregnancy folic acid			
No	488	32.6	34.8
Yes	913	61.1	65.2
Missing	94	6.3	
Smoking in pregnancy			
No	1,041	69.6	76.3
Yes	324	21.7	23.7
Missing	130	8.7	

[a] LGA was defined as birthweight ≥90th centile, and SGA as birthweight <10th centile, according to Scottish birthweight standards (by fetal sex, parity and gestational age) [24]

(over 7% in this population [3]) and antepartum stillbirths, known to be associated with low birthweight, we avoided a potential bias of over-representation of SGA fetuses, which other similar studies might not have.

The birthweight distribution of the North of England birth population, both overall and among women with diabetes, is almost identical to the equivalent distribution in England and Wales [8] (ESM Fig. 2). Our results are therefore generalisable to the national population and are likely to be relevant to similar populations in other industrialised countries.

We analysed birthweight as both a continuous measure and the commonly used and clinically meaningful categorical measures LGA and SGA. Analysing LGA and SGA birthweights exclusively may have increased the risk of type II errors, due to reduced statistical power; however, including these alongside the continuous analyses allows for a more complete comparison with previous literature. As some researchers recommend using customised centiles to identify LGA and SGA births, we performed additional analyses using this approach but, because this further reduced the number of available participants and did not materially alter the results, these data are not shown.

Our measure of glycaemia was limited to HbA$_{1c}$; this has excellent validity as an estimate of average blood glucose but does not provide information on glycaemic excursions, which may be an important driver for macrosomia [17, 25, 26]. Moreover, we did not have 100% completeness for peri-conception and trimester-specific HbA$_{1c}$ measurements. We used a composite measure of peri-conception HbA$_{1c}$ as a proxy for pre-conception HbA$_{1c}$, due to the relatively high percentage of participants with missing pre-conception values. This potentially hinders comparisons with previous studies using pre-conception HbA$_{1c}$. However, our sensitivity analysis found that most of the effect of peri-conception HbA$_{1c}$ on birthweight was attributed to pre-conception HbA$_{1c}$, suggesting this was a reasonable surrogate measure in our population-based cohort.

We found that about half of births to women with diabetes were LGA, similar to other studies in women with diabetes reporting LGA rates ranging from 45% to 51% for populations of women with both type 1 and type 2 diabetes [7, 8] and from 47% to 62.5% for women with type 1 diabetes [5, 6, 25, 27].

We found a strong independent association between increasing third-trimester HbA$_{1c}$ for values ≤7% (53 mmol/mol) (about 62% of pregnancies) and higher birthweight (and a three-fold increase in LGA risk per 1% [11 mmol/mol] increase in HbA$_{1c}$), but no significant association with HbA$_{1c}$ >7%. Second-trimester HbA$_{1c}$, although being strongly correlated with third-trimester HbA$_{1c}$, was a much weaker predictor of increase in birthweight and lost its effect after adjustment for third-trimester HbA$_{1c}$. Although earlier studies have not

Table 3 Association between various clinical and demographic factors and birthweight in the offspring of women with pre-conception diabetes born in the North of England during 1996–2008

Variable	Minimally adjusted[a] coefficient (95% CI)	Fully adjusted[b] coefficient (95% CI)	Variance explained, ΔR^2 % (95% CI)
Non-modifiable variable			
Fetal sex			0.7 (0.1, 1.6)
Female	Reference	Reference	
Male	108.1 (45.0, 171.2)	126.8 (53.4, 200.1)	
Parity			2.1 (1.0, 3.7)
Primiparous	Reference	Reference	
Multiparous (≥1)	208.0 (144.8, 271.3)	245.5 (166.8, 324.3)	
Maternal ethnicity			0.2 (<0.1, 0.8)
White	Reference	Reference	
Non-white	−256.4 (−384.9, −127.9)	−153.1 (−324.3, 18.1)	
Index of multiple deprivation			
Tertile 1 (most deprived)	−62.5 (−140.3, 15.4)		
Tertile 2	−5.2 (−80.9, 70.4)		
Tertile 3 (least deprived)	Reference		
Diabetes type			
Type 1	72.4 (−5.9, 150.8)		
Type 2	Reference		
Pre-pregnancy retinopathy			0.7 (0.2, 1.6)
No	Reference	Reference	
Yes	−173.9 (−254.7, −93.0)	−175.5 (−269.9, −81.0)	
Pre-pregnancy neuropathy			
No	Reference		
Yes	−366.2 (−547.6, −184.7)		
Pre-pregnancy nephropathy			0.4 (0.1, 1.1)
No	Reference	Reference	
Yes	−337.8 (−507.5, −168.0)	−282.7 (−461.8, −103.6)	
Gestational age at delivery (weeks)	153.9 (134.1, 173.6)	174.5 (149.3, 199.7)	28.0 (23.1, 33.8)[c]
Gestational age at delivery^2 (weeks^2)	−39.0 (−46.3, −31.7)	−40.7 (−50.4, −30.9)	
Gestational age at delivery^3 (weeks^3)	−2.7 (−3.3, −2.0)	−3.2 (−4.1, −2.4)	
Maternal height (cm)	18.4 (13.0, 23.8)	17.8 (12.3, 23.2)	2.4 (1.2, 4.1)
Maternal age (year)	−11.0 (−16.2, −5.9)	−13.1 (−19.8, −6.4)	0.8 (0.2, 1.9)
Duration of diabetes (years)	−4.9 (−8.8, −1.0)		
Potentially modifiable variable			
Pre-pregnancy care			0.3 (<0.1, 1.0)
No	−33.3 (−96.9, 30.3)	−87.1 (−161.3, −12.9)	
Yes	Reference	Reference	
Pre-pregnancy folic acid			
No	6.1 (−60.3, 72.6)		
Yes	Reference		
Smoking in pregnancy			0.6 (0.1, 1.5)
No	Reference	Reference	
Yes	−146.8 (−222.0, −71.6)	−145.1 (−231.4, −58.8)	
Maternal BMI (kg/m^2)	4.8 (−0.7, 10.2)	9.5 (3.5, 15.5)	0.6 (0.1, 1.6)
Gestation at first antenatal visit (weeks)	−11.8 (−19.4, −4.2)	−15.0 (−26.9, −3.0)	0.5 (<0.1, 1.5)
Peri-conception HbA_{1c} (%)	−9.1 (−28.3, 10.0)	−48.2 (−68.8, −27.6)	0.9 (0.3, 2.0)
Peri-conception HbA_{1c} (mmol/mol)	−0.8 (−2.6, 0.9)	−4.4 (−6.3, −2.5)	0.9 (0.3, 2.0)
Second trimester HbA_{1c} (%)	30.9 (-0.1, 61.9)		

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Table 3 (continued)

Variable	Minimally adjusted[a] coefficient (95% CI)	Fully adjusted[b] coefficient (95% CI)	Variance explained, ΔR^2 % (95% CI)
Second trimester HbA$_{1c}$ (mmol/mol)	2.8 (0.0, 5.7)		
Third-trimester HbA$_{1c}$ (%)			5.6 (3.7, 7.8)[c]
≤7%	231.2 (176.5, 286.0)	310.5 (246.3, 374.7)	
>7%	−43.8 (−107.0, 19.4)	26.7 (−50.4, 103.7)	
Third-trimester HbA$_{1c}$ (mmol/mol)			5.6 (3.7, 7.8)[c]
≤53 mmol/mol	19.5 (15.0, 24.0)	28.4 (22.5, 34.3)	
>53 mmol/mol	4.9 (−0.3, 10.0)	2.4 (−4.6, 9.5)	

[a] Minimally adjusted model included the test variable with sex, parity and gestational age (cubic term)

[b] Fully adjusted model was constructed using backwards stepwise regression. All variables were entered into the model, and then non-significant variables were removed iteratively (according to decreasing p value) until only those with $p<0.1$ remained, details of which are shown. The total number of participants with complete data for all variables with $p<0.1$, and therefore included in the fully adjusted model, was 955

[c] Total variation explained by all constituent terms

explored the linearity of the association between third-trimester HbA$_{1c}$ and birthweight, there is some consistency in the literature reporting the positive association between third-trimester maternal hyperglycaemia and risk of LGA birthweight in women with pre-gestational and gestational diabetes [5, 28–30]. Evers et al found that of the five variables in their final predictive model (third-trimester HbA$_{1c}$, absence of third-trimester severe hypoglycaemia, the use of insulin lispro (B28Lys,B29Pro human insulin), weight gain during pregnancy and non-smoking), third-trimester HbA$_{1c}$ (≤7% [53 mmol/mol] for 84% of women) was the most powerful predictor of LGA birthweight in women with type 1 diabetes, explaining 4.7% of the variance [5]. Third-trimester

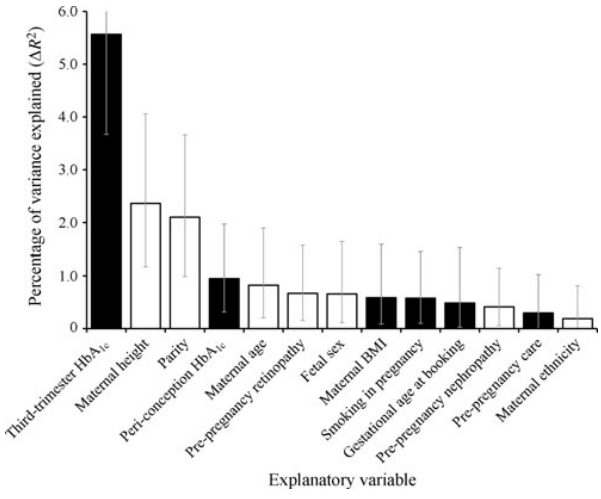

Fig. 1 Percentage of variance (with 95% CIs) directly explained by each significant independent predictor of birthweight in the offspring of women with pre-conception diabetes born in the North of England during 1996–2008. White bars represent non-modifiable variables; black bars represent potentially modifiable variables

HbA$_{1c}$ was reported to be a significant predictor of LGA birthweight in a cohort of women with type 1, type 2 and gestational diabetes after adjustment for a number of confounders [30]. In a study of pregnancies complicated by gestational diabetes or impaired glucose tolerance, maternal fasting glycaemia during 32–35 weeks was the strongest predictor of accelerated growth in the late third trimester, whereas in the late second and early third trimester and at birth the dominant predictors were previous LGA or maternal obesity [29]. The Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study reported that mild antenatal maternal hyperglycaemia in women without known diabetes is also associated with an increased risk of LGA [28]. However, a Scottish study did not find a significant correlation between third-trimester HbA$_{1c}$ and birthweight [16] in women with type 1 diabetes but they did not explore this association in a multivariable model. A Danish study reported a significant association between increased third-trimester HbA$_{1c}$ and risk of LGA birthweight in women with type 1 diabetes for women with higher BMI (>23 kg/m^2) only [27]. Despite a general agreement that maternal late hyperglycaemia causing fetal hyperinsulinaemia is an important determinant of fetal macrosomia, there is some evidence that the contribution of maternal hyperglycaemia to the variance in LGA birthweight is relatively low, and high rates of LGA birthweight are reported despite apparently good glucose control measured by HbA$_{1c}$ [5, 31, 32]. This may be due to the failure of HbA$_{1c}$ to indicate variability in glycaemia and time spent at high glucose levels, which may be critically associated with fetal overgrowth [5, 17, 26, 33]. The lack of association with third-trimester HbA$_{1c}$ >7% (53 mmol/mol) in our study may also reflect the limitations of using HbA$_{1c}$ to measure hyperglycaemia during pregnancy. Measures of glycaemic variation using newer methods, such as continuous glucose monitoring, may contribute to better understanding of the relationship between

Table 4 Association between various clinical and demographic factors and the odds of LGA (≥90th centile) and SGA (<10th centile) birth to women with pre-conception diabetes delivered in the North of England during 1996–2008

Variable	LGA birth[a]		SGA birth[a]	
	Unadjusted OR (95% CI)	Adjusted OR[b] (95% CI)	Unadjusted OR (95% CI)	Adjusted OR[b] (95% CI)
Non-modifiable variable				
Fetal sex				
Female	Reference		Reference	
Male	0.93 (0.75, 1.14)		0.94 (0.51, 1.72)	
Parity				
Primiparous	Reference		Reference	
Multiparous (≥1)	1.19 (0.96, 1.47)		0.87 (0.47, 1.61)	
Maternal ethnicity				
White	Reference	Reference	Reference	
Non-white	0.42 (0.26, 0.68)	0.48 (0.25, 0.93)	1.25 (0.38, 4.14)	
Index of multiple deprivation				
Tertile 1 (most deprived)	0.78 (0.60, 1.01)		1.59 (0.74, 3.43)	
Tertile 2	0.92 (0.71, 1.18)		1.31 (0.64, 3.09)	
Tertile 3 (least deprived)	Reference		Reference	
Diabetes type				
Type 1	1.31 (1.02, 1.70)		0.87 (0.43, 1.79)	
Type 2	Reference		Reference	
Pre-pregnancy retinopathy				
No	Reference	Reference	Reference	
Yes	0.74 (0.56, 0.98)	0.52 (0.37, 0.75)	1.51 (0.74, 3.11)	
Pre-pregnancy neuropathy				
No	Reference		Reference	
Yes	0.32 (0.13, 0.81)		4.65 (1.34, 16.16)	
Pre-pregnancy nephropathy				
No	Reference		Reference	Reference
Yes	0.56 (0.31, 1.02)		4.11 (1.54, 10.95)	5.88 (1.85, 18.67)
Maternal height (cm)	1.06 (1.04, 1.08)	1.06 (1.03, 1.08)	0.95 (0.90, 1.00)	0.94 (0.90, 0.99)
Maternal age (year)	0.99 (0.97, 1.00)		1.04 (0.99, 1.09)	
Duration of diabetes (years)	1.00 (0.99, 1.01)		1.03 (0.99, 1.06)	
Potentially modifiable variable				
Pre-pregnancy care				
Yes	Reference		Reference	
No	0.93 (0.76, 1.15)		0.80 (0.44, 1.47)	
Pre-pregnancy folic acid				
Yes	Reference		Reference	
No	1.01 (0.81, 1.25)		1.24 (0.64, 2.40)	
Smoking in pregnancy				
No	Reference	Reference	Reference	
Yes	0.71 (0.55, 0.92)	0.59 (0.43, 0.82)	1.31 (0.66, 2.58)	
Maternal BMI (kg/m^2)	1.01 (0.99, 1.02)		0.98 (0.92, 1.04)	
Gestation at first antenatal visit (weeks)	0.97 (0.94, 0.99)	0.95 (0.91, 0.98)	1.07 (1.01, 1.13)	1.07 (1.01, 1.13)
Peri-conception HbA_{1c} (%)	1.00 (0.94, 1.06)	0.88 (0.81, 0.95)	0.97 (0.81, 1.16)	
Peri-conception HbA_{1c} (mmol/mol)	1.000 (0.994, 1.005)	0.988 (0.980, 0.996)	0.997 (0.981, 1.014)	
Second trimester HbA_{1c} (%)	1.16 (1.06, 1.28)		0.91 (0.68, 1.20)	
Second trimester HbA_{1c} (mmol/mol)	1.013 (1.004, 1.022)		0.991 (0.958, 1.025)	

Table 4 (continued)

Variable	LGA birth[a]		SGA birth[a]	
	Unadjusted OR (95% CI)	Adjusted OR[b] (95% CI)	Unadjusted OR (95% CI)	Adjusted OR[b] (95% CI)
Third-trimester HbA_{1c} (%)				
≤7%	2.21 (1.79, 2.73)	3.13 (2.38, 4.11)	0.62 (0.39, 0.99)	0.55 (0.33, 0.93)
>7%	0.93 (0.77, 1.13)	1.07 (0.83, 1.39)	0.85 (0.40, 1.83)	0.69 (0.25, 1.88)
Third-trimester HbA_{1c} (mmol/mol)				
≤53 mmol/mol	1.075 (1.055, 1.096)	1.110 (1.082, 1.138)	0.957 (0.918, 0.999)	0.947 (0.904, 0.993)
>53 mmol/mol	0.994 (0.976, 1.011)	1.006 (0.983, 1.030)	0.986 (0.919, 1.057)	0.967 (0.882, 1.059)

[a] LGA was defined as birthweight ≥90th centile, and SGA as birthweight <10th centile, according to Scottish birthweight standards (by fetal sex, parity and gestational age) [24]

[b] Adjusted model was constructed using backwards stepwise regression. All variables with $p<0.5$ in the univariate analysis were entered into the model, and then non-significant variables were removed iteratively (according to decreasing p value) until only those with $p<0.1$ remained, details of which are shown

hyperglycaemia and fetal macrosomia in the future [32]. In a randomised controlled trial, continuous glucose monitoring during pregnancy was associated with improved HbA_{1c} levels at 32–36 weeks and a reduced rate of LGA births [17]. Daily glucose monitored during the second and third trimesters was a good predictor of birthweight in term pregnancies with type 1 diabetes; only infants of women with overall daily glucose values of ≤5.27 mmol/l had birthweight comparable with the control group [34].

The association between pre-conception blood glucose concentration and birthweight has been less studied, in particular with adjustment for covariates, as in our cohort. A Scottish study of 57 pregnancies of women with diabetes reported an increase in pre-conception and early first-trimester total HbA_{1c} in a group with increased median standardised birthweight compared with the control group, while total HbA_{1c} during later periods of pregnancy did not differ significantly between the groups [35]. A larger (203 singletons), more recent, Scottish study of women with type 1 diabetes reported a significant negative association between pre-pregnancy HbA_{1c} and standardised birthweight, consistent with our findings for peri-conception HbA_{1c}, but found no significant association between HbA_{1c} and birthweight for any trimester of pregnancy [16]. Evers et al did not find an association with first-trimester HbA_{1c} in an unadjusted analysis [5], similar to our unadjusted analysis result for peri-conception HbA_{1c}. This may be explained by the direct association (of lower birthweight for increasing HbA_{1c}) being masked by the indirect association (of higher birthweight for increasing HbA_{1c}) acting through correlation with third-trimester HbA_{1c}. The association between pre-conception and maximal maternal HbA_{1c} during pregnancy and birthweight z-score was described as curvilinear in a recent study by Rackham et al [36]. However, that study involved pregnancies resulting in stillbirths or neonatal deaths only, and the number of cases was small. We found an association between increasing peri-conception HbA_{1c} and reduction in birthweight when adjusted for confounders, in particular for ≤7% (≤53 mmol/mol) third-trimester HbA_{1c}. We also identified a significant interaction between peri-conception and third-trimester HbA_{1c} (≤7%) with the effect of increasing third-trimester HbA_{1c} being greater among women with low peri-conception HbA_{1c} than among women with high peri-conception HbA_{1c}. We speculate that high glucose levels in early pregnancy may harm placental development and thus the capacity for fetal growth, such that the effect of hyperglycaemia in later pregnancy is permanently attenuated. The presence of microvascular disease, in particular in combination with first-trimester hyperglycaemia, can inhibit trophoblast proliferation, thereby reducing placental growth and impairing uteroplacental function, which may result in subsequent intrauterine growth restriction [10, 37]. In our study, microvascular complications (pre-pregnancy retinopathy and/or nephropathy) in women with diabetes were associated with lower birthweight. As there

Table 5 Probability of giving birth to an LGA offspring by third-trimester HbA_{1c} in singleton pregnancies of women with pre-conception diabetes delivered in the North of England during 1996–2008

Third-trimester HbA_{1c}, DCCT, % (IFCC, mmol/mol)	Probability of LGA, % (95% CI)
5.5 (36.6)	27.1 (22.0, 32.2)
6.0 (42.1)	38.6 (34.6, 42.6)
6.5 (47.5)	51.5 (47.8, 55.2)
7.0 (53.0)	64.1 (59.1, 69.0)
7.5 (58.5)	64.8 (60.9, 68.7)
8.0 (63.9)	65.5 (60.9, 70.1)
8.5 (69.4)	66.2 (60.0, 72.5)

is some evidence that variation in birthweight may be at least partly determined by fetal growth within the first 12 weeks after conception [38], investigation of the association of peri-conception hyperglycaemia with early fetal growth is crucial for understanding the mechanisms of growth restriction or overgrowth in pregnancies of women with diabetes.

In addition to maternal hyperglycaemia, other factors, such as non-smoking, higher maternal height and BMI, found to be associated with higher birthweight in offspring of women with diabetes by previous studies [27, 30], were also independent significant predictors of increased birthweight in our study.

The apparently contradictory association between peri-conception hyperglycaemia and reduced birthweight and between late-pregnancy hyperglycaemia and increased birthweight may be explained by the effects of multiple factors, including maternal diabetes, on fetal growth mechanism during different periods of pregnancy. While in early pregnancy hyperglycaemia may lead to restricted fetal growth via reduction in trophoblast proliferation, later in pregnancy, fetal hyperglycaemia and hyperinsulinaemia lead to increased placental angiogenesis, increased and altered vascular endothelial-like growth factor and chorionic villous branching, which, in turn, lead to placental vascular dysfunction [39]. As a result, infants of mothers with diabetes may have an unhealthy body composition (increased body fat) even if they have appropriate birthweight for gestational age [40]. If hyperglycaemia-related growth in the third trimester is mostly associated with the deposition of adipose tissue, this might partly explain our finding of an increased association between third-trimester HbA_{1c} and birthweight with increasing maternal BMI.

In conclusion, this study found a varying association between maternal blood glucose concentration and birthweight, with increasing peri-conception HbA_{1c} being associated with lower birthweight and increasing third-trimester HbA_{1c} ≤7% (53 mmol/mol) predicting higher birthweight. Peri-conception and third-trimester HbA_{1c} were the two most important potentially modifiable predictors of birthweight, reinforcing the need for careful glucose control, beginning before conception. While glucose control remains a key focus of pre-conception and antenatal care for women with diabetes, other modifiable risk factors for adverse pregnancy outcome also need to be addressed, such as ensuring that women who smoke are supported to quit. Further, awareness of the potential for poor fetal growth, particularly in women with microvascular disease and sometimes co-existing with apparently normal fetal size, emphasises the need for careful antenatal assessment of fetal well-being. Future studies, using more sensitive measures of both glucose control and fetal growth and body composition, should explore critical windows for the effect of maternal blood glucose concentration on birthweight.

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Contribution statement RB and JR developed the study concept and supervised the research. SVG and PWGT analysed the data, and SVG wrote the first draft of the manuscript. SVG, PWGT, RWB, JR and RB contributed to the interpretation of the results and to the discussion, reviewed the manuscript and approved the final version.

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ESM Methods

Definitions and statistical analysis

All NorDIP clinical and socio-demographic variables with a hypothesised influence on birthweight were examined: diabetes type, fetal sex, pre-pregnancy folate supplement usage, pre-pregnancy care, smoking during pregnancy, history of clinically diagnosed pre-pregnancy nephropathy, neuropathy, or retinopathy, parity (primiparous vs multiparous), and maternal ethnicity (white vs non-white) were analysed as dichotomous variables. Macrosomia was defined as birthweight of ≥4000g, and low birthweight was defined as birthweight of <2500g. Socio-economic status was estimated from the Index of Multiple Deprivation (a UK area-based measure, derived from mothers' residential postcode at delivery), and analysed in tertiles of rank [21]. Duration of diabetes, maternal age at delivery, maternal body mass index (BMI) at first antenatal visit, maternal height, gestational age at first antenatal visit and at delivery (based on reported estimated date of delivery calculated for the majority of women using ultrasound scan at 10-13 weeks' gestation, or date of the last menstrual period [LMP], if no scan dating was available), and mean maternal HbA_{1c} at three time points (peri-conception, second trimester, and third trimester) were analysed as continuous variables. Peri-conception HbA_{1c} was calculated as the closest measurement within three months prior to the LMP date (available for 49.5% of pregnancies) or mean first trimester measurement (up to 14 weeks gestation) (valid 83.3%) for women with no pre-conception measure recorded. Peri-conception HbA_{1c} (valid 86.7%) was chosen as a reasonable surrogate of pre-conception HbA_{1c}, as first trimester HbA_{1c} was highly correlated with pre-conception HbA_{1c} (Spearman correlation coefficient 0.75). The independent effects of pre-conception HbA_{1c} and first trimester HbA_{1c} were, nevertheless, also examined in a sensitivity analysis on a subsample of participants with both measures.

The association between each variable and birthweight, as a continuous variable, was examined by multiple linear regression. The summary influence of each variable was estimated by constructing a series of simple models that included the variable of interest, alongside sex, parity, and gestational age. The independent influence of each variable was estimated in a fully adjusted model, constructed using a backwards stepwise approach (all variables were entered into an adjusted model, and then non-significant variables were removed iteratively, according to decreasing p-value, until only those with $p<0.1$ remained). Gestational age (centred to reduce collinearity) was modelled as a three term polynomial, i.e. b_1(gestational age - $\bar{x}$) + b_2(gestational age - $\bar{x}$)^2 + b_3(gestational age - $\bar{x}$)^3 (ESM Figure 1). The shape of the association between each HbA_{1c} variable and birth weight was explored by Locally Weighted Scatterplot Smoothing (LOWESS) and fitting fractional polynomials. As a non-linear association between third-trimester HbA_{1c} and birthweight was observed, it was modelled by piecewise linear regression, with a single knot at 7% (53mmol/mol) (the choice of location being guided by LOWESS explorations), which divided the regression into two parts, ≤7% (53mmol/mol) (61.7% of participants) and >7% (53mmol/mol) (38.3%). The presence of heteroscedasticity (i.e. where the variance of the model residuals is not constant across the range of fitted values) was evaluated using the Cook-Weisberg test [22] and, when present, the Huber/White estimator [23] (which is robust to heteroscedasticity) was used. The proportion of variation directly explained by each variable was estimated from the change in the coefficient of determination (ΔR^2) resulting from removing that variable from the adjusted model.

Separate analyses were performed to examine predictors of LGA and SGA births specifically; LGA (birthweight ≥90th percentile) and SGA (<10th percentile) categories were created based on birthweight standardised for fetal sex, parity and gestational age using Scottish birth population standards [24]. These standards were considered the most

appropriate for this study because: 1) they were based on births from a neighbouring and demographically similar population, 2) the centile charts were constructed based on 1998-2003 births (part of our study period) by using a method enabling a transformation to obtain normally distributed data. Odds ratios (ORs) and associated 95% confidence intervals (95% CIs) for LGA and SGA were estimated for various predictors using multiple logistic regression, adjusted effects were again estimated using a backwards stepwise approach. The probability of LGA for specific values of third-trimester HbA_{1c} was estimated by taking marginal values of the adjusted model; corresponding 95% CIs were obtained using the delta method.

Potential interactions between the HbA_{1c} variables and all other variables in each adjusted model were examined by the inclusion of cross-product terms.

SPSS for Windows 17.0 (IBM Corporation, NY, USA) was used for most of the statistical analyses. Confidence intervals for ΔR^2 were approximated by bootstrapping on 10,000 repeated samples, drawn with replacement, using Stata 11.1 (Statacorp, TX, USA). $P<0.05$ was considered statistically significant.

ESM Results 1

Two statistically significant interactions were observed in the adjusted model of continuous birthweight, both concerning third trimester HbA_{1c}. Firstly, the effect of third trimester HbA_{1c} (for values ≤7% [53mmol/mol]) decreased with increasing peri-conception HbA_{1c} (p=0.001) such that in women with a peri-conception HbA_{1c} below the median (i.e. under 7.8% [61.7mmol/mol]), each percentage increase in third trimester HbA_{1c} ≤7% (53mmol/mol) was associated with a 385.7g (95% CI: 297.2, 474.1) increase in birthweight, whereas in women with peri-conception HbA_{1c} above the median (i.e. over 7.8% [61.7mmol/mol]) the corresponding increase in birthweight was only 171.5g (95% CI: 59.3, 283.7). Secondly, the effect of third trimester HbA_{1c} (≤7% [53mmol/mol]) increased with increasing BMI (p=0.002) such that each percentage increase in HbA_{1c} was associated with a 216.7g (95% CI 102.6, 330.9), 278.1g (95% CI: 158.6, 397.7), and 395.5g (95% CI: 285.2, 505.7) increase in birthweight among women who were of recommended weight (18.5-24.9kg/m^2), overweight (25-29.9 kg/m^2), and obese (≥30kg/m^2) respectively.

ESM Results 2

A sensitivity analysis examined the separate influences of pre-conception and first trimester HbA_{1c} on continuous birthweight (ESM Table). Some differences were observed between the sensitivity analysis and the main analysis due to sampling fluctuations. Most notably, the effects of pre-pregnancy care and gestation at first antenatal visit were reduced below the nominal significance level, albeit partly due to reduced statistical power. The association between peri-conception HbA_{1c} and birthweight was identical in the subsample (n=549) as in the complete sample (n=955). When split into pre-conception and first trimester HbA_{1c}, most of the effect appeared to be explained by pre-conception HbA_{1c} [adjusted coefficient, b=−39.6g per 1% [11mmol/mol] (95% CI: −73.3, −5.9), p=0.02]. Although a small additional negative association was observed between first trimester HbA_{1c} and birthweight, the effect was not statistically significant [b=−18.8g per 1% [11mmol/mol] (95% CI: −71.6, 33.9), p=0.48].

ESM Table Results of the sensitivity analysis on the comparison between the adjusted regression model results for the continuous birthweight based on the full sample (n=955) and the sub-sample (n=549 with both available pre-conception and first trimester measures) using HbA_{1c} peri-conception measure, and pre-conception and first trimester HbA_{1c} measures.

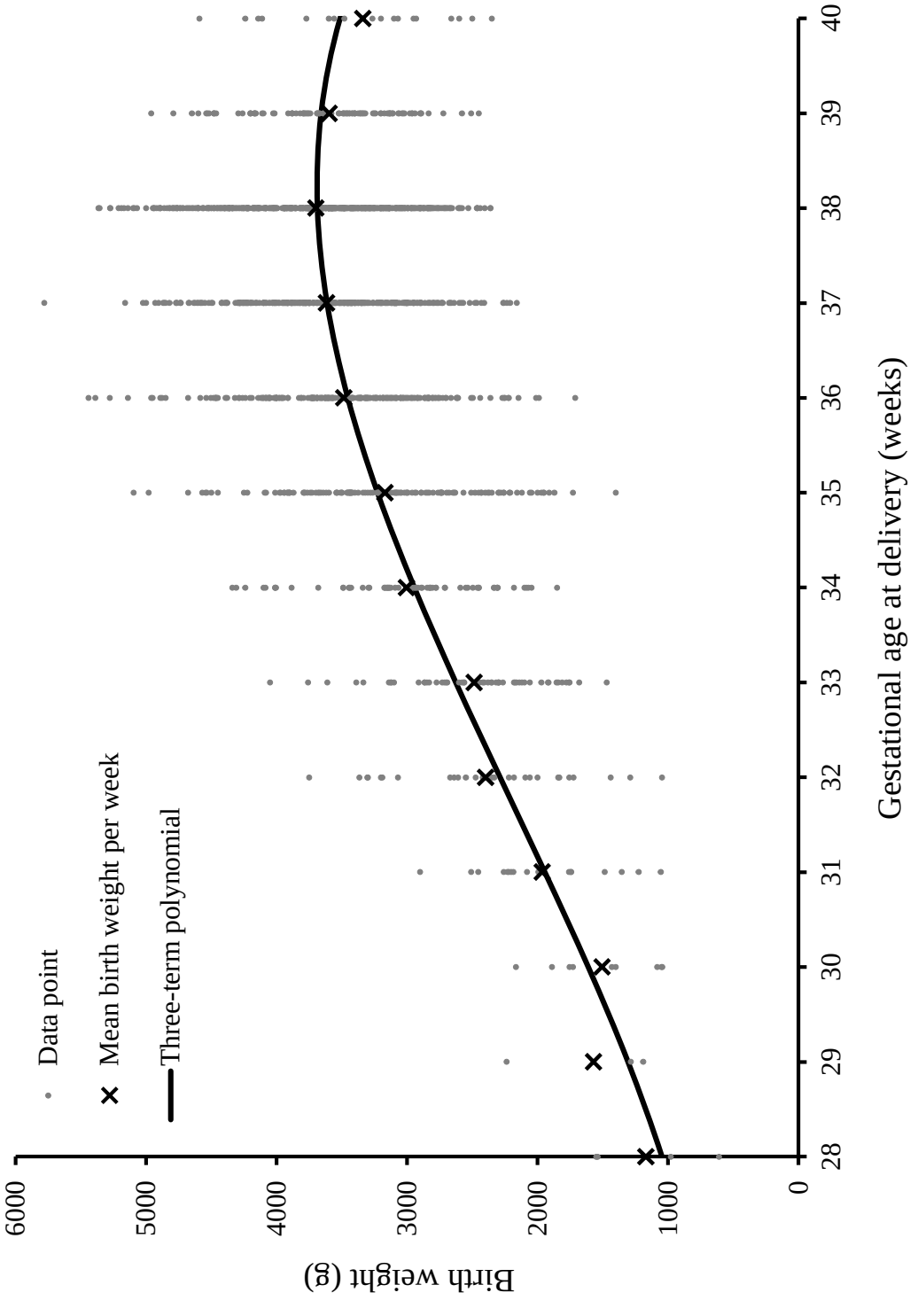
Variable (unit)	Fully adjusted[a] coefficient (95% CI)		
	Peri-conception model (n=955)*	**Peri-conception model (n=549)**	**Pre-conception and first trimester model (n=549)**
Fetal sex			
Female	Reference	Reference	Reference
Male	126.8 (53.4, 200.1)	177.7 (83.3, 272.1)	177.0 (82.6, 271.3)
Parity			
Primiparous	Reference	Reference	Reference
Multiparous (≥1)	245.5 (166.8, 324.3)	278.4 (177.4, 379.4)	281.0 (180.1, 382.0)
Maternal ethnicity			
White	Reference	Reference	Reference
Non-white	-153.1 (-324.3, 18.1)[b]	-109.9 (-346.5, 126.7)[c]	-104.1 (-342.6, 134.3)[c]
Pre-pregnancy retinopathy			
No	Reference	Reference	Reference
Yes	-175.5 (-269.9, -81.0)	-140.5 (-262.2, -18.9)	-137.2 (-258.5, -15.9)
Pre-pregnancy nephropathy			
No	Reference	Reference	Reference
Yes	-282.7 (-461.8, -103.6)	-243.4 (-455.1, -31.7)	-245.0 (-456.5, -33.5)
Gestational age at delivery (weeks)	174.5 (149.3, 199.7)	195.9 (164.3, 227.4)	194.9 (163.5, 226.4)
Gestational age at delivery^2 (weeks^2)	-40.7 (-50.4, -30.9)	-39.2 (-51.2, -27.3)	-39.0 (-51.0, -27.0)
Gestational age at delivery^3 (weeks^3)	-3.2 (-4.1, -2.4)	-3.1 (-4.2, -2.1)	-3.1 (-4.2, -2.0)
Maternal height (cm)	17.8 (12.3, 23.2)	18.0 (11.2, 24.8)	18.1 (11.3, 25.0)
Maternal age (year)	-13.1 (-19.8, -6.4)	-14.4 (-23.3, -5.5)	-14.7 (-23.6, -5.7)
Potentially Modifiable:			
Pre-pregnancy care			
No	-87.1 (-161.3, -12.9)	-63.4 (-158.5, 31.8)[c]	-60.5 (-156.3, -35.3)[c]
Yes	Reference	Reference	Reference
Smoking in pregnancy			
No	Reference	Reference	Reference
Yes	-145.1 (-231.4, -58.8)	-156.2 (-274.6, -37.9)	-156.0 (-274.3, -37.6)
Maternal body mass index (kg/m^2)	9.5 (3.5, 15.5)	12.0 (4.1, 19.9)	11.8 (4.0, 19.6)
Gestation at first antenatal visit (weeks)	-15.0 (-26.9, -3.0)	-12.1 (-28.2, 4.0)[c]	-11.7 (-27.7, -4.4)[c]
Pre-conception HbA_{1c} (DCCT %)	NA	NA	-39.6 (-73.3, -5.9)
First trimester HbA_{1c} (DCCT %)	NA	NA	-18.8 (-71.6, 33.9)[c]
Peri-conception HbA_{1c} (DCCT %)	-48.2 (-68.8, -27.6)	-48.2 (-72.5, -23.9)	NA
Third trimester HbA_{1c} (DCCT %)			
≤7% (53 mmol/mol)	310.5 (246.3, 374.7)	323.4 (238.4, 408.5)	330.7 (242.9, 418.5)
>7% (53 mmol/mol)	26.7 (-50.4, 103.7)[c]	91.1 (-13.8, 196.0)[b]	98.1 (-9.0, 205.2)[b]

[a]Fully adjusted model was constructed to replicate the model detailed in Table 3 (either directly, or with pre-conception HbA_{1c} and first trimester HbA_{1c} instead of peri-conception HbA_{1c}). Similar to Table 3, adjusted model was constructed using backwards stepwise regression. All variables were entered into the model, and then non-significant variables were removed iteratively (according to decreasing p-value) until only those with $p<0.1$ remained, details of which are shown.

*For the purpose of comparison, this column repeats the results of the fully adjusted model shown in column 3 of Table 3.

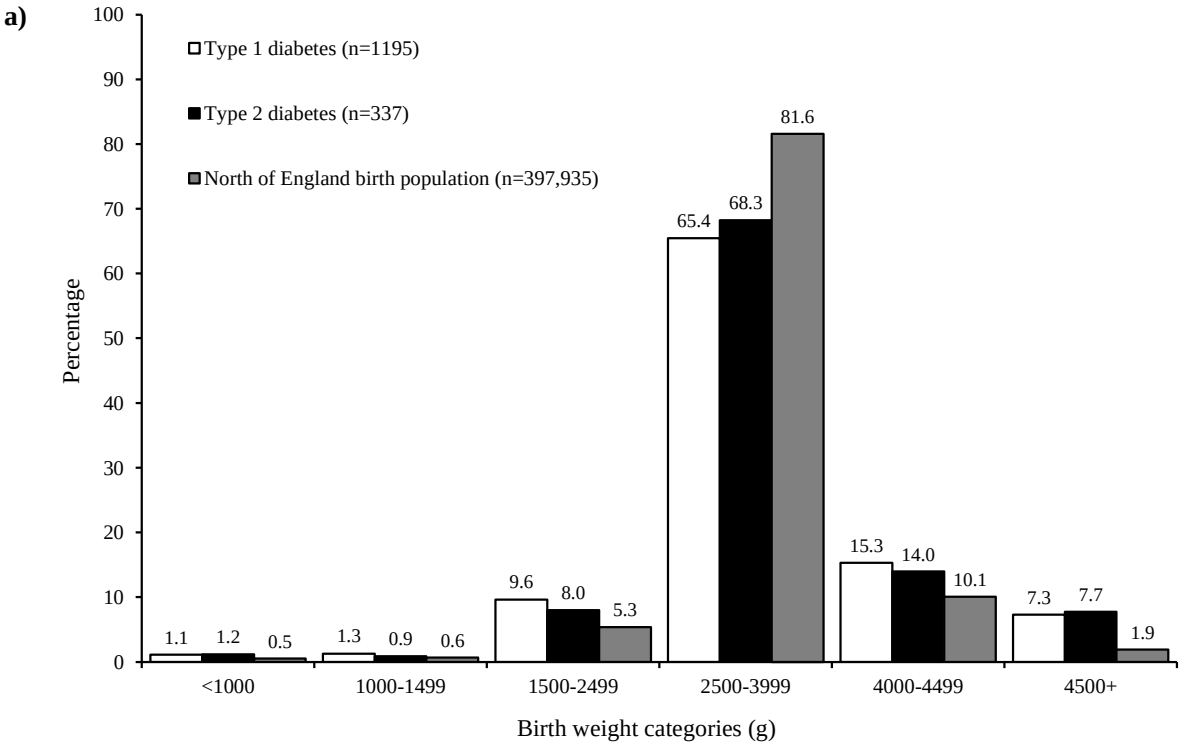
[b]$0.05 \leq p < 0.1$

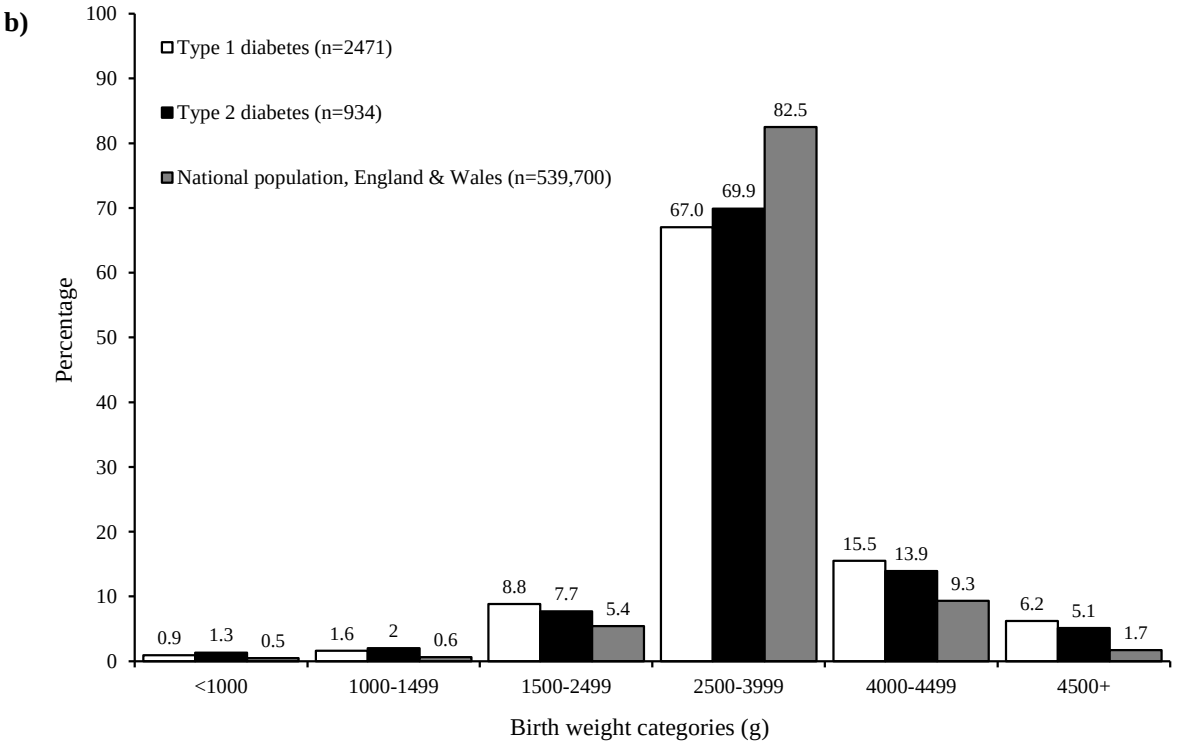
[c]$p > 0.1$



ESM Fig. 1 The association between gestational age from 28 to 40 weeks (the middle 99% of observed values) and birth weight in the offspring of women with pre-conception diabetes born in the North of England during 1996-2008 and a three-term polynomial used to model the association.

ESM Fig. 2 Birth weight distribution of singleton offspring by type of diabetes compared with the general population: a) North of England, 1996-2008, b) England & Wales population, 2002-2003 [8]





Glinianaia *et al* 2012 describes one of the largest cohorts of offspring in women with diabetes, and remains unique in the context of fetal growth for the range and quality of sociodemographic and clinical variables under examination. The downside of such detail is the increased complexity. Alongside some exacting peer review, this led to an unusually large quantity of supplementary material.

The foremost source of this complexity is the outcome. Although birthweight is a common focus of perinatal research, and fetal growth is a core feature of obstetric decision-making in diabetes,[119] it is much more nebulous as an outcome than terminal events like stillbirth.[394] This is partly because of the unusual 'reversed J-shape' relationship with adverse outcome.[394] Examining the extremes of SGA and LGA are a common solution, but can lead to erroneous conclusions without accurate population-norms,[394] in part because no distinction is made between constitutional growth (length) and pathological growth (adiposity).[395] I thus extended Gliniania's initial analysis of SGA and LGA to include a direct examination of birthweight (adjusted internally for sex, parity, and gestational age). As well as avoiding any issues with incorrect standardisation, this provided a large increase in power to examine the determinants of birthweight.

Repeated information on maternal HbA_{1c} enabled the study to resolve what Penny *et al* 2003 had described as the, '*paradoxical inverse relationship between pre-pregnancy glycaemic control and standardized birth weight'* by demonstrating the effect of HbA_{1c} on birthweight reverses through pregnancy.[396] Much of the apparent discordance between previous studies can thus probably be explained either by differences in the timing of exposure and/or low statistical power.[396-404] In fact, Glinianaia *et al* 2012 indicated that the pattern of exposure over pre- and late-pregnancy was also important, such that *low* peri-conceptional HbA_{1c} followed by *high* third-trimester HbA_{1c} conferred the highest risk of LGA. We speculated this reflected two distinct mechanisms. In early pregnancy, hyperglycaemia impairs placental development, leading to reduced blood flow, and a smaller fetus (see **Section 3·4·2·2**, p160). In later pregnancy, maternal hyperglycaemia induces fetal hyperglycaemia, fetal insulinaemia, resulting in the uptake, conversion, and storage of further glucose into fat, and a larger fetus (i.e. the Pedersen hypothesis, see **Section 1·2·3·6**, p19).

Using LOWESS, I identified a non-linear association between third-trimester HbA_{1c} and the risk of LGA, with the prevalence increasing rapidly from around one-quarter in those with HbA_{1c} concentrations of 37mmol/mol to a plateau of nearly two-thirds for concentrations ≥53mmol/mol. An identical pattern was observed in Maresh *et al*'s recent (2015) UK study of 725 women with type 1 diabetes, in which the risk of LGA increased sharply from around

one-third in those with a third-trimester HbA_{1c} of under 42mmol/mol to a peak of around two-thirds for those with values of 48-58mmol/mol.[405] While these values may seem low compared with target pre-conception levels, they do not appear to represent the same relative levels of control. As observed elsewhere,[393] Glinianaia *et al* 2012 found that the average HbA_{1c} declined from an average of 62mmol/mol before pregnancy to 50mmol/mol during the third trimester. Previous observations of high birthweight '*despite good glycaemic control*' thus appear to be artifacts of shifting norms in HbA_{1c} during pregnancy.[399,406,407]

Elsewhere, previous authors have queried the seemingly modest proportion of the variance in birthweight explained by third-trimester HbA_{1c};[407] which is consistently around 5%.[399,408] Glinianaia *et al* 2012 similarly found just 5.6% of the variance in birthweight was explained by third-trimester. Though the proportion of variance is only a weak approximation of importance,[409] this modest contribution may reflect the multidimensional nature of birthweight and the lack of differentiation between adiposity and fat-free mass.[395] Nevertheless, the proportion of variance explained by third-trimester HbA_{1c} was far in excess of other well-known constitutional factors like maternal height and parity, and up to ten-times higher than other potentially-modifiable variables like maternal smoking and BMI

As with Bell *et al* 2012, the analysis was hindered by the absence of pre-conception HbA_{1c} for half the cohort. In order to maintain consistency and comparability with Bell *et al* 2012, the same analytical approach was used, i.e. directly replacing missing pre-conception values with available first-trimester ones. The reversal in the direction of the association between HbA_{1c} and birthweight however, made this even more susceptible to bias. I hence performed an additional sensitivity analysis in the subsample with complete data (details of which are presented in **ESM[xxix] Results 2** and the **ESM Table**). This revealed a stronger inverse effect for pre-conception values than first-trimester ones, showing that the primary (peri-conception) results are likely to underestimate the true effect of pre-conception HbA_{1c}.

[xxix] Electronic Supplementary Material

2·6 TENNANT *et al* 2013 (DIABETES, HbA_{1c}, & FETAL & INFANT DEATH)

Title: Pre-existing diabetes, maternal glycated haemoglobin, and the risks of fetal and infant death: a population-based study

Authors: **Tennant PWG**, Glinianaia SV, Bilous RW, Rankin J, Bell R

Journal: Diabetologia (Volume 57 Issue 2 Pages 285-294)

Publication Date: 29 November 2013

2·6·1 Overview

This article examined the same cohort of pregnant women with pre-existing diabetes described in Bell *et al* 2012 (albeit excluding cases of congenital anomaly) to explore the association between maternal pre-existing diabetes and the risk of fetal and infant death. Outcome data on the occurrence of late miscarriages, stillbirths, and infants deaths were obtained from the PMS.

The paper was accompanied by three supplementary tables, two describing the socio-demographic and physiological features of sample, and one providing full details of the predictors of fetal and infant death (**Section 2·6·6**, p120). A copy of the map of the North of England first used in Rankin *et al* 2010 (**Section 2·2**, p41) was also included.

2·6·2 What was known

- Women with pre-existing diabetes were historically known to experience an increased risk of stillbirth, but it was unclear whether and to what extent this had changed in the last 20 years
- Good glucose control was known to reduce the risk of stillbirth, but it was unclear how much this explained the excess risk of diabetes, and how the contribution of hyperglycaemia changed from pre- to late-pregnancy
- Previous studies had suggested that the increased risk of stillbirth in women with diabetes was confined to term deliveries

2·6·3 What this study added

- The risk of fetal death (3%) was found to be over four times higher in women with pre-existing diabetes than in those without the condition [RR=4.56 ([95% CI: 3.42 to 6.07)], and the risk of infant death (0.7%) was nearly twice as large [RR=1.86 (95% CI: 1.00 to 3.46)].

- There was no evidence that the excess risk of fetal and infant death due to pre-existing diabetes had decreased over the thirteen years between the beginning of 1996 and the end of 2008

- The risk of stillbirth for women with diabetes appeared to be uniformly increased from 24 weeks onwards, with both preterm and term fetal deaths being five-times more common than in women without the condition.

- The odds of stillbirth and infant death appeared to increase linearly by 2-3% for each 1mmol/mol increase in peri-conception HbA_{1c} above 49mmol/mol (6.9%), but even at this optimal level, the odds of fetal death were over twice the proportion observed in the general population.

- Pre-pregnancy retinopathy was also found to be associated with twice the risk of fetal and infant death while pre-pregnancy folic acid was associated with half the risk. There was no apparent difference in the risk of fetal and infant death by diabetes type.

2·6·4 Contribution of the candidate to this work

I designed and conducted the statistical analysis, drafted the introduction, methods, results, tables and discussion, produced the figures, compiled the references, and edited the manuscript following critical-review from SVG, RWB, JR, and RB. A copy of the Newcastle University Co-Authorship form for this publication can be found in **Appendix A(v)** (p187).

2·6·5 Manuscript

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ARTICLE

Pre-existing diabetes, maternal glycated haemoglobin, and the risks of fetal and infant death: a population-based study

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Abstract
Aims/hypothesis Pre-existing diabetes is associated with an increased risk of stillbirth, but few studies have excluded the effect of congenital anomalies. This study used data from a long-standing population-based survey of women with pre-existing diabetes to investigate the risks of fetal and infant death and quantify the contribution of glycaemic control.
Methods All normally formed singleton offspring of women with pre-existing diabetes (1,206 with type 1 diabetes and 342 with type 2 diabetes) in the North of England during 1996–2008 were identified from the Northern Diabetes in Pregnancy Survey. RRs of fetal death (≥20 weeks of gestation) and infant death were estimated by comparison with population data from the Northern Perinatal Morbidity and Mortality Survey. Predictors of fetal and infant death in women with pre-existing diabetes were examined by logistic regression.
Results The prevalence of fetal death in women with diabetes was over four times greater than in those without (RR 4.56 [95% CI 3.42, 6.07], $p<0.0001$), and for infant death it was nearly doubled (RR 1.86 [95% CI 1.00, 3.46], $p=0.046$). There was no difference in the prevalence of fetal death ($p=0.51$) or infant death ($p=0.70$) between women with type 1 diabetes and women with type 2 diabetes. There was no evidence that the RR of fetal and infant death had changed over time ($p=0.95$). Increasing periconception HbA_{1c} concentration above 49 mmol/mol (6.6%) (adjusted odds ratio [aOR] 1.02 [95% CI 1.00, 1.04], $p=0.01$), prepregnancy retinopathy (aOR 2.05 [95% CI 1.04, 4.05], $p=0.04$) and lack of prepregnancy folic acid consumption (aOR 2.52 [95% CI 1.12, 5.65], $p=0.03$) were all independently associated with increased odds of fetal and infant death.
Conclusions/interpretation Pre-existing diabetes is associated with a substantially increased risk of fetal and infant death in normally formed offspring, the effect of which is largely moderated by glycaemic control.

Keywords Diabetes mellitus · HbA_{1c} · Miscarriage · Neonatal death · Pregnancy · Stillbirth

Abbreviations

aOR	Adjusted odds ratio
IQR	Interquartile range
LOWESS	Locally weighted scatterplot smoothing
NICE	National Institute for Health and Care Excellence
NorCAS	Northern Congenital Abnormality Survey
NorDIP	Northern Diabetes in Pregnancy Survey
PMMS	Perinatal Morbidity and Mortality Survey

Introduction

Diabetes is one of the most common pre-existing maternal conditions complicating pregnancy. Affecting 0.5%–2% of

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pregnancies, the prevalence is rising as a consequence of the obesity epidemic and increases in maternal age. This has considerable implications, since pre-existing diabetes (both type 1 and type 2) is associated with a range of pregnancy complications, including increased risks of macrosomia, congenital anomaly and delivery by Caesarean section [1–3]. It has long been observed that pre-existing diabetes is also associated with an increased risk of stillbirth [4], although there is heterogeneity in the estimated RR [5].

Prepregnancy care, particularly focusing on optimising glycaemic control, improves birth outcomes in women with pre-existing diabetes [6]. With intensive support, some women with diabetes can achieve similar outcomes to those without [7], an unmet goal of the St Vincent Declaration [8]. It is uncertain, however, whether such improvements can be achieved in routine clinical care. Observational studies from the last 20 years have not shown any reduction in the RR of fetal death [9–18], despite guidelines advising women with pre-existing diabetes to achieve good glycaemic control before pregnancy [19, 20].

There is a paucity of data on the risks of fetal and infant death independent of congenital anomaly, and the contribution of glucose control and other clinical and sociodemographic factors are poorly described. We used unique data from several long-standing population-based registers in the North of England to investigate the association between pre-existing diabetes and the risks of fetal and infant death in normally formed offspring, and to quantify the contribution of glycaemic control.

Methods

The Northern Diabetes in Pregnancy Survey (NorDIP) The North of England (UK) is a geographically distinct area with a population of three million and approximately 32,000 births per year (see electronic supplementary material [ESM] Fig. 1). The NorDIP records details of all pregnancies in women resident in the region and diagnosed with (type 1 or type 2) diabetes at least 6 months before conception. Pregnancies in women with gestational diabetes (i.e. hyperglycaemia first diagnosed during pregnancy) are not included. Clinicians working in the region's nine units collect and supply information on a range of clinical and sociodemographic variables, including maternal HbA_{1c} concentration before conception, in the first trimester and in the third trimester. For further details, see Glinianaia et al [1].

Study sample This study includes data on all singleton pregnancies in women with pre-existing diabetes delivered at or after 20 completed weeks of gestation between 1 January 1996 and 31 December 2008. Pregnancies complicated by major congenital anomalies, which have previously been shown to be associated with both pre-existing diabetes and the risk of fetal and infant death [2, 21], were identified from the Northern Congenital Abnormality Survey (NorCAS) and excluded. The NorCAS is a long-standing population-based register of congenital anomaly that collects data on all cases of congenital anomaly occurring in all deliveries in the North of England, irrespective of maternal diabetes status (for further details, see Bell et al [2]). The total number of singleton live births and fetal and infant deaths were obtained from the UK Office for National Statistics (www.statistics.gov.uk) and the Northern Perinatal Morbidity and Mortality Survey (PMMS) [22], respectively. The number of normally formed offspring was determined by subtracting the number of NorCAS registrations.

Definitions 'Late miscarriages' are the spontaneous loss of a fetus at 20–23 completed weeks of gestation. 'Stillbirths' are deliveries of a fetus showing no signs of life at 24 or more completed weeks of gestation. 'Late stillbirths' are stillbirths at 28 or more completed weeks of gestation. 'Antepartum stillbirths' are stillbirths where the fetus died before the onset of labour. 'Intrapartum stillbirths' are stillbirths where the fetus died after the onset of labour. 'Fetal deaths' comprise late miscarriages and stillbirths. 'Neonatal deaths' are deaths, after live birth, within the first 28 days of life. 'Postneonatal deaths' are deaths, after live birth, of an infant aged 28 days or more, but less than 1 year. 'Infant deaths' comprise neonatal deaths and postneonatal deaths.

Analysis Prevalence rates were estimated per 1,000 births and late miscarriages for fetal outcomes, and per 1,000 live births for infant outcomes. The Clopper–Pearson (exact) method was used to estimate 95% CIs for prevalences. RRs were calculated by comparing the prevalences in women with pre-existing diabetes with the prevalence in the remaining population. To examine whether the RR for fetal and infant death had changed over time, a cross-product interaction between diabetes status and year of delivery was evaluated in a Poisson regression model. RRs for fetal death at specific gestational ages were estimated using the 'fetuses-at-risk' approach [23]. In each period, the proportion of cases from the total number of ongoing pregnancies (i.e. containing fetuses 'at risk of fetal death') was compared. The number of ongoing pregnancies at each gestational age was estimated from a reference UK population [24].

ORs and 95% CIs for all variables with hypothesised influences on fetal and/or infant death were analysed in relation to fetal death, late stillbirth, infant death, fetal and infant death combined, and late stillbirth and infant death combined within a series of logit-linked generalised estimating equations. Between-mother variation was modelled as a random intercept to account for the non-independence of repeat pregnancies in the same woman. Periconception HbA_{1c} was

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defined as the closest measurement within 3 months before the last menstrual period (available for 48.8% of pregnancies) or mean first-trimester measurement (<14 weeks of gestation) (available for 86.0% of pregnancies) for women with no preconception measurement. Periconception HbA_{1c} concentration was chosen as a reasonable surrogate of preconception HbA_{1c} concentration, as first-trimester HbA_{1c} correlated highly with preconception HbA_{1c} (Spearman's correlation coefficient 0.76). Third-trimester HbA_{1c} was examined only in relation to deliveries at ≥28 weeks of gestation. Adjusted ORs (aORs) were estimated using a backwards stepwise approach; all variables were entered into the model, and non-significant ones were removed iteratively, by descending p value, until only those with $p<0.1$ remained. Cross-product interaction terms were used to explore whether the effect of each variable with a significant independent association on the risk of fetal and infant death varied by diabetes type. The relationships of periconception and third-trimester HbA_{1c} concentration with the risks of fetal and infant death were explored by locally weighted scatterplot smoothing (LOWESS) [25]. LOWESS produces smoothed estimates of the association between two variables without requiring a priori specification. Since J-shaped associations were observed between both variables and the risk of fetal death, all models of fetal death or fetal and infant death combined were modelled by piecewise linear regression with knots at the lowest LOWESS values (49 mmol/mol [6.6%] for periconception HbA_{1c} and 43 mmol/mol [6.1%] for third-trimester HbA_{1c}). LOWESS was also used to estimate the absolute risks of fetal death, stillbirth, late stillbirth and infant death for selected categories of periconception and third-trimester HbA_{1c} by averaging the modelled risk for all values within that category (with CIs being estimated by bootstrapping from 10,000 subsamples). Logit-linked generalised estimating equations were used to estimate the absolute risk of late stillbirth for selected categories of periconception and third-trimester HbA_{1c} simultaneously by evaluating the model at the category-specific means (with CIs being estimated using the delta method [26]). Owing to instability at the LOWESS tails, only categories within the 5th and 95th centile of case values are reported. Participants with missing data were excluded from individual analyses by casewise deletion. Analyses were performed using Stata version 11.1 (Statacorp, College Station, TX, USA). $p<0.05$ was considered statistically significant.

Ethics approval and research governance Newcastle Research Ethics Committee originally granted approval for the NorDIP in 1993. Data are now obtained and held with informed consent.

Role of the funding source The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The views expressed in this manuscript are entirely those of the authors and do not necessarily reflect those of the funders.

Results

Figure 1 shows the derivation of the study sample. Overall, 397,392 singleton live births, stillbirths and late miscarriages uncomplicated by major congenital anomalies were identified during the study period, including 1,548 in women

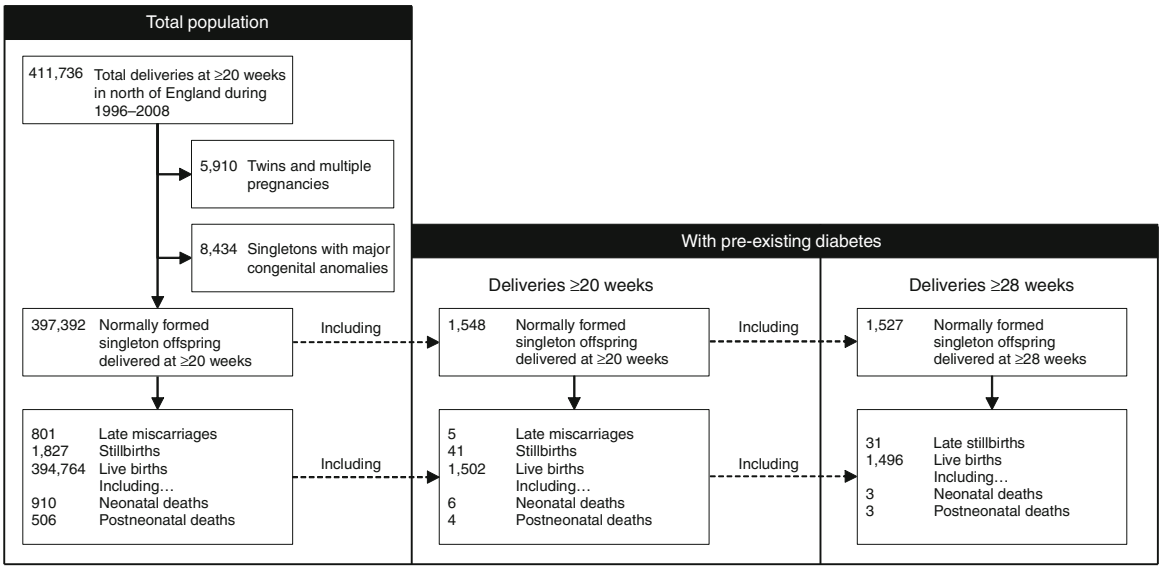

Fig. 1 Derivation of the study sample

with pre-existing diabetes, a prevalence of 3.9 (95% CI 3.7, 4.1) per 1,000 deliveries. Descriptive statistics for pregnancies affected by pre-existing diabetes are shown in ESM Tables 1 and 2. Of these, 53% involved male fetuses, 41% were primiparous, and 94% of the women were white. The median maternal age was 30 years (interquartile range [IQR] 25–34), and the median BMI was 27 kg/m^2 (IQR 24–32). A quarter (24%) of women were recorded as smoking during pregnancy, and 32% as taking folic acid before pregnancy. Type 1 diabetes was recorded in 78% of the women, with the remaining 22% having type 2. The median periconception and third-trimester HbA_{1c} concentrations were 62 mmol/mol (IQR 51–76) (7.8%, IQR=6.8–9.1) and 50 mmol/mol (IQR 43–58) (6.7%, IQR=6.1–7.5), respectively. The median gestational age at delivery was 37 weeks (IQR 36–38), and 38% were delivered preterm (<37 weeks).

Maternal pre-existing diabetes and the risks of fetal and infant death Forty-six fetal deaths (including five late miscarriages, 38 antepartum stillbirths and three intrapartum stillbirths) and ten infant deaths (including six neonatal deaths and four postneonatal deaths) were observed in women with pre-existing diabetes. The prevalence of fetal death in women with pre-existing diabetes was 29.7 (95% CI 21.8, 39.4) per 1,000 deliveries, over four times greater than in those without (RR 4.56 [95% CI 3.42, 6.07], $p<0.0001$) (Table 1). The prevalence of fetal death was not significantly different between women with type 1 diabetes (28.2 [95% CI 19.6, 39.2] per 1,000 deliveries) and women with type 2 diabetes (35.1 [95% CI 18.3, 60.5] per 1,000 deliveries) ($p=0.51$). Significantly increased risks were observed for both antepartum stillbirths (RR 6.10 [95% CI 4.44, 8.38], $p<0.0001$) and intrapartum stillbirths (RR 3.97 [95% CI 1.27, 12.41], $p=0.042$). The estimated RR for a preterm fetal loss (RR 4.95 [95% CI 3.59, 6.82], $p<0.0001$) was almost identical with that for a term stillbirth (RR 5.05 [95% CI 2.62, 9.71], $p<0.0001$), although the RR for a late miscarriage was significantly smaller (RR 1.61 [95% CI 0.67, 3.86], $p=0.25$) (Table 2). The prevalence of infant death in women with

Table 1 RR of a fetal or infant death (in normally formed singleton offspring) associated with maternal pre-existing diabetes in the North of England during 1996–2008

Outcome	Without pre-existing diabetes		With pre-existing diabetes		RR (95% CI)	*p* value
	Cases (n=395,844[a]/393,262[b])	Prevalence (95% CI) per 1,000 deliveries[c]/live births[d]	Cases (n=1,548[a]/1,502[b])	Prevalence (95% CI) per 1,000 deliveries[c]/live births[d]		
Fetal or infant death	3,988	10.1 (9.8, 10.4)	56	36.2 (27.4, 46.7)	3.59 (2.77, 4.65)	<0.0001
Fetal death[e]	2,582	6.5 (6.3, 6.8)	46	29.7 (21.8, 39.4)	4.56 (3.42, 6.07)	<0.0001
Late miscarriage[f]	796	2.0 (1.9, 2.2)	5	3.2 (1.0, 7.5)	1.61 (0.67, 3.86)	0.25[g]
Stillbirth[h]	1,786	4.5 (4.3, 4.7)	41	26.5 (19.1, 35.8)	5.87 (4.32, 7.97)	<0.0001
Antepartum stillbirth[i]	1,593	4.0 (3.8, 4.2)	38	24.5 (17.4, 33.5)	6.10 (4.44, 8.38)	<0.0001
Intrapartum stillbirth[j]	193	0.5 (0.4, 0.6)	3	1.9 (0.4, 5.7)	3.97 (1.27, 12.41)	0.042[g]
Infant death[k]	1,406	3.6 (3.4, 3.8)	10	6.7 (3.2, 12.2)	1.86 (1.00, 3.46)	0.046
Neonatal death[l]	904	2.3 (2.1, 2.5)	6	4.0 (1.5, 8.7)	1.74 (0.78, 3.87)	0.17[g]
Postneonatal death[m]	502	1.3 (1.2, 1.4)	4	2.7 (0.7, 6.8)	2.09 (0.78, 5.57)	0.13[g]

[a] Total singleton live births, stillbirths and late miscarriages

[b] Total singleton live births

[c] The prevalence of fetal or infant death, and fetal death and all subsidiary outcomes of fetal death are presented per 1,000 deliveries

[d] The prevalence of infant death and all subsidiary outcomes are presented per 1,000 live births

[e] Late miscarriages and stillbirths

[f] Spontaneous loss of a fetus at 20–23 completed weeks of gestation

[g] Fisher's exact test

[h] Deliveries of a fetus showing no signs of life at 24 or more completed weeks of gestation

[i] Stillbirths where the fetus died before the onset of labour

[j] Stillbirths where the fetus died after the onset of labour

[k] Neonatal deaths and postneonatal deaths

[l] Death, after live birth, within the first 28 days of life

[m] Death, after live birth, of an infant aged 28 days or more, but less than 1 year

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Table 2 Absolute and relative risks of a fetal death (in normally formed singleton offspring) associated with maternal pre-existing diabetes, by gestational age

Gestational age (weeks)	Fetal deaths		Total deliveries		Ongoing pregnancies		Risk during given gestational age (95% CI)			Compared with RR at term
							Absolute risk (per 1,000 ongoing pregnancies)		RR	
	With	Without	With	Without	With	Without	With	Without		
Preterm (20–36)	37	1,913	585	34,618	1,548	395,844	23.9 (16.9, 32.8)	4.8 (4.6, 5.1)	4.95 (3.59, 6.82)	0.98 (0.47, 2.04)
20–23	5	796	6	796[a]	1,548	395,844	3.2 (1.0, 7.5)	2.0 (1.9, 2.2)	1.61 (0.67, 3.86)	0.32 (0.11, 0.95)
24–27	10	413	15	4,828	1,542	395,048	6.5 (3.1, 11.9)	1.0 (0.9, 1.2)	6.20 (3.32, 11.59)	1.23 (0.50, 3.05)
28–36	22	704	564	28,994	1,527	390,220	14.4 (9.1, 21.7)	1.8 (1.7, 1.9)	7.99 (5.24, 12.17)	1.58 (0.72, 3.46)
Term (37–41)	9	669	963	361,226	963	361,226	9.3 (4.3, 17.7)	1.9 (1.7, 2.0)	5.05 (2.62, 9.71)	1 (reference)
Total	46	2,582	1,548	395,844	1,548	395,844	29.7 (21.8, 39.4)	6.5 (6.3, 6.8)	4.56 (3.42, 6.07)	

Values are shown in women with and without pre-existing diabetes

[a] Bonellie et al [24] provide no estimate of the number of deliveries occurring during 20–23 weeks. This was approximated to be equal to the total number of fetal deaths during the same period

pre-existing diabetes was 6.7 (3.2, 12.2) per 1,000 live births, almost twice that in those without (RR 1.86 [95% CI 1.00, 3.46], $p=0.046$) (Table 1). The prevalence of infant death was not significantly different between women with type 1 diabetes (7.7 [95% CI 3.5, 14.5] per 1,000 live births) and women with type 2 diabetes (3.0 [95% CI 0.8, 16.8] per 1,000 deliveries) ($p=0.70$).

Although the prevalence of fetal and infant death declined from 11.4 (95% CI 10.8, 12.0) per 1,000 deliveries in 1996–1999 to 9.3 (95% CI 8.8, 9.9) per 1,000 deliveries in 2005–2008 ($p<0.0001$), there was no change in the RR associated with diabetes (in 1996–1999: RR 4.5 [95% CI 2.8, 7.0]; in 2005–2008: RR 4.3 [95% CI 2.8, 6.4]) ($p=0.95$).

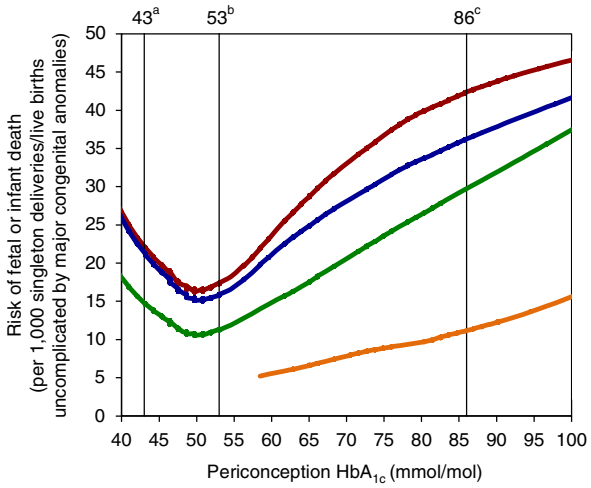
HbA$_{1c}$ and the odds of fetal and infant death Increasing periconception HbA$_{1c}$ concentration above values of 49 mmol/mol (6.6%) (aOR per mmol/mol 1.02 [95% CI 1.00, 1.04], $p=0.01$), prepregnancy retinopathy (aOR 2.05 [95% CI 1.04, 4.05], $p=0.04$) and lack of prepregnancy folic acid consumption (aOR 2.52 [95% CI 1.12, 5.65], $p=0.03$) were all independently associated with increased odds of fetal and infant death (ESM Table 3). Maternal smoking during pregnancy was also crudely associated with the risk of fetal and infant death (OR 1.91 [95% CI 1.08, 3.36], $p=0.03$), but the association was not apparent after adjustment for periconception HbA$_{1c}$ and folic acid consumption (aOR 1.54 [95% CI 0.80, 2.94], $p=0.19$). There was no evidence that the effects of periconception HbA$_{1c}$, prepregnancy retinopathy or lack of prepregnancy folic acid consumption on the risk of fetal and infant death were different in women with type 2 diabetes compared with women with type 1 diabetes ($p=0.85$, $p=0.24$, and $p=0.74$, respectively). In later pregnancy, increasing third-trimester HbA$_{1c}$ concentration above values of 43 mmol/mol (aOR 1.06 [95% CI 1.03, 1.09], $p<0.001$) and lack of prepregnancy folic acid consumption (aOR 3.01 [95% CI 1.03, 8.79], $p=0.04$) were the only variables that were significantly associated with the odds of a late stillbirth or infant death (ESM Table 3).

When fetal and infant death were examined individually, increasing periconception HbA$_{1c}$ concentration above values of 49 mmol/mol was the only variable that was significantly associated with either fetal death (OR 1.02 [95% CI 1.01, 1.04], $p=0.01$) or infant death (OR 1.03 [95% CI 1.00, 1.06], $p=0.01$). The association between periconception HbA$_{1c}$ and the odds of fetal death followed a J-shaped pattern (Fig. 2), although the inverse association for values below 49 mmol/mol was not statistically significant (OR 0.95 [95% CI 0.86, 1.05], $p=0.31$).

The estimated absolute risks of fetal death, stillbirth, late stillbirth and infant death (overall and by periconception and third-trimester HbA$_{1c}$) are reported in Table 3.

Discussion

Principal findings This large population-based study describes the association between pre-existing diabetes and measures of glycaemic control and the risks of fetal and infant death in normally formed singleton offspring. The prevalence of fetal death (3%) was over four times greater in women with pre-existing diabetes, and the prevalence of infant death (0.7%) was nearly doubled. There was no evidence that the RR of fetal and infant death associated with pre-existing diabetes decreased over time, nor that the RR of stillbirth varied by gestational age, although the RR was smaller for late miscarriages.



HbA_{1c}	40–49	50–59	60–69	70–79	80–89	90–99
Pregnancies	236	289	272	183	123	66
Fetal deaths	3	4	8	9	6	2
Infant deaths	0	2	2	1	1	2

Fig. 2 Periconception HbA_{1c} and risk of fetal or infant death in women with pre-existing diabetes. Fetal deaths (red), stillbirths (blue) and late stillbirths (green) are deliveries of a fetus showing no signs of life at ≥20 weeks of gestation, ≥24 weeks of gestation, and ≥28 weeks of gestation, respectively. Infant deaths (orange) are deaths, after live birth, within the first year of life. [a]A prepregnancy HbA_{1c} target of ≤43 mmol/mol is recommended by NICE: 'If it is safely achievable, women with diabetes who are planning to become pregnant should aim to maintain their HbA_{1c} below 6.1% [19]. [b]A prepregnancy HbA_{1c} target of ≤53 mmol/mol is recommended by the ADA: 'A1C levels should be as close to normal as possible (<7%) in an individual patient before conception is attempted.' [20]. [c]NICE advises that women with a prepregnancy HbA_{1c} above 86 mmol/mol should be advised to avoid pregnancy: 'Women with diabetes whose HbA_{1c} is above 10% should be strongly advised to avoid pregnancy.' [19]. To convert values for HbA_{1c} in mmol/mol into %, divide by 10.929 and add 2.15, or use the conversion calculator at www.HbA1c.nu/eng/

Among women with pre-existing diabetes, increasing periconception HbA_{1c} concentration (for values above 49 mmol/mol), history of retinopathy and lack of prepregnancy folic acid consumption were all associated with increased odds of fetal and infant death. Periconception HbA_{1c} concentration was also associated with increased odds of fetal and infant death individually, with each 1 mmol/mol increase (above 49 mmol/mol) conferring a 2% and 3% relative increase, respectively. The association between HbA_{1c} and the odds of fetal death appeared to follow a J-shaped pattern.

There was no difference in the risk of fetal and/or infant death in women with type 1 diabetes compared with those with type 2, nor was there any evidence that the associations with HbA_{1c} concentration, folic acid consumption, or history of retinopathy were different between types.

Strengths and limitations This study, describing one of the largest obstetric cohorts of women with pre-existing diabetes, benefits from the North of England's long history of collaboration between maternity and neonatal services, which created and maintains several complementary population-based registers. Detailed information was collected prospectively on a range of clinical and sociodemographic variables, including multiple measures of HbA_{1c}. All late miscarriages, stillbirths and infant deaths in the region, regardless of whether they occurred in women with diabetes, were obtained from an established register of fetal and infant mortality, minimising the risk of bias from disparities in ascertainment. By excluding all cases of major congenital anomaly derived from an independent and long-standing population-based register (which should again be robust to disparities in ascertainment), this study is novel in describing the associations in normally formed offspring. The results are likely to be generalisable to any predominately white population with similar standards of periconception and perinatal care.

Several limitations result from low statistical power. Only six neonatal deaths, four postneonatal deaths and three intrapartum stillbirths were identified, preventing these events from being analysed with precision. For most analyses, fetal and infant deaths were combined, despite likely differences in aetiology [23]. Owing to instability at the tails of our LOWESS models, we only report absolute risks for the middle 90% of HbA_{1c} concentrations. The primary multivariate analyses had adequate power ($\beta = 0.8$) to detect a 'medium effect' (Cohen's $d \leq 0.5$, equivalent to an OR of ≥2.47) for any variable with a baseline exposure probability of 14–65%. Weaker associations, or associations in exposures outside this range, may therefore have been missed.

Our LOWESS models, unlike our regression models, made no account of the non-independence of repeat pregnancies in the same woman, introducing a potential source of error. For each regression model, however, the addition of the between-mother intercept did not significantly improve the model and only engendered negligible changes in the other coefficients, suggesting that any bias is likely to be trivial.

Preconception HbA_{1c} concentrations were missing for half of the cohort, reflecting low attendance for preconception care. We therefore used a composite measure of periconception HbA_{1c} as a proxy for preconception HbA_{1c}. Although first-trimester values correlate highly with preconception, this may have introduced random error. HbA_{1c} itself is an imperfect measure of glycaemic control, as it provides no information on glycaemic excursions or hypoglycaemic episodes [27], which may be important in the aetiopathology of fetal and/or infant death [28]. Continuous glucose monitoring provides a more complete record of day to day glycaemic control, but is not routinely used in the UK. No information was recorded on pharmacological treatments, so we could not explore their possible contribution. Since the PMMS does not collect information on miscarriages before 20 weeks, we were not able to examine the RR of earlier fetal losses, the risks of which may

Table 3 Absolute risk of a fetal or infant death (in normally formed singleton offspring) in women with pre-existing diabetes, overall and by HbA_{1c} periconception and in the third trimester

Outcome	Risk per 1,000 (95% CI)										
	Overall	By periconception HbA_{1c}[a]									
		40–49 (5.8–6.6)	50–59 (6.7–7.5)	60–69 (7.6–8.5)	70–79 (8.6–9.4)	80–89 (9.5–10.3)	90–99 (10.4–11.2)	≤43[b] (≤6.1)	≤53[c] (≤7)	≥86[d] (≥10)	49[e] (6.6)
Fetal death	29.7 (21.8, 39.4)	19.6 (9.6, 33.6)	19.3 (11.9, 29.0)	28.4 (18.2, 40.6)	36.5 (24.2, 50.8)	41.5 (27.0, 58.3)	44.8 (26.4, 67.3)	31.9 (7.2, 64.8)	22.7 (9.5, 39.4)	46.7 (22.4, 79.41)	16.6 (8.6, 26.8)
Stillbirth	26.6[f] (19.1, 35.9)	18.7 (8.6, 31.6)	17.5 (10.3, 26.6)	24.7 (14.9, 36.0)	30.9 (19.3, 44.2)	35.4 (21.8, 51.1)	39.2 (21.6, 60.9)	30.9 (8.0, 64.7)	21.7 (9.3, 38.1)	42.7 (19.0, 74.2)	15.5 (7.8, 25.1)
Late stillbirth	20.3[f] (13.8, 28.7)	13.0 (4.9, 24.8)	12.4 (6.5, 20.3)	17.5 (9.9, 27.2)	23.4 (14.1, 34.9)	28.7 (16.7, 42.9)	33.9 (17.5, 53.6)	21.8 (3.0, 49.3)	15.2 (0.5, 29.0)	38.9 (16.0, 68.9)	10.7 (4.7, 19.0)
By third trimester HbA_{1c}[g]											
35–44 (5.4–6.2)	10.3 (4.3, 18.9)	7.1 (2.1, 12.0)	6.4 (1.4, 11.4)	8.1 (2.1, 14.1)	10.3 (2.6, 18.1)	12.3 (2.3, 22.3)	14.6 (1.3, 27.9)	8.4 (2.2, 14.5)	8.4 (3.0, 13.9)	19.2 (2.2, 36.2)	5.6 (0.9, 10.4)
45–54 (6.3–7.1)	13.4 (7.0, 21.0)	9.3 (2.6, 15.9)	8.3 (2.4, 14.3)	10.5 (3.8, 17.2)	13.3 (5.0, 21.7)	15.9 (5.1, 26.7)	18.8 (4.2, 33.3)	11.0 (2.2, 19.9)	11.0 (3.7, 18.4)	24.8 (4.2, 45.3)	7.3 (1.5, 13.2)
55–64 (7.2–8.0)	22.5 (13.2, 33.4)	16.1 (4.8, 27.5)	14.5 (4.9, 24.1)	18.3 (8.5, 28.2)	23.3 (12.4, 34.2)	27.8 (14.4, 41.2)	32.7 (14.1, 51.4)	19.1 (3.8, 34.5)	19.2 (7.3, 31.1)	45.5 (15.4, 75.6)	12.8 (3.0, 22.6)
65–74 (8.1–8.9)	39.8 (21.6, 62.2)	29.1 (5.2, 53.0)	26.2 (6.4, 46.1)	33.1 (13.0, 53.2)	42.0 (21.2, 62.8)	49.9 (27.1, 72.8)	58.6 (29.5, 87.7)	34.4 (3.1, 65.6)	34.5 (9.5, 59.5)	76.6 (27.9, 125.3)	23.2 (3.1, 43.3)
75–84 (9.0–9.8)	72.9 (26.4, 123.4)	54.1 (<0.1, 110.2)	49.2 (1.6, 96.7)	61.9 (10.8, 113.0)	78.3 (23.1, 133.6)	92.8 (33.7, 151.9)	108.4 (41.4, 175.4)	63.3 (<0.1, 133.1)	63.8 (3.9, 123.7)	139.7 (36.1, 243.3)	43.6 (<0.1, 90.2)
43[e] (6.1)	8.9 (4.2, 15.4)	6.3 (1.2, 11.3)	5.6 (1.0, 10.3)	7.1 (1.5, 12.7)	9.0 (1.8, 16.2)	10.7 (1.5, 20.0)	12.7 (0.5, 24.8)	7.5 (0.9, 14.1)	7.5 (1.7, 13.3)	16.8 (0.2, 33.3)	5.0 (0.6, 9.3)
Infant death	6.7 (3.2, 12.2)	No cases[h]	4.3 (1.0, 9.2)	6.6 (2.2, 12.5)	8.8 (3.3, 16.0)	10.7 (4.2, 20.4)	13.3 (4.4, 26.0)	No cases[h]	No cases[h]	17.6 (4.0, 39.1)	No cases[h]

Fetal deaths, stillbirths and late stillbirths are deliveries of a fetus showing no signs of life at ≥20 weeks of gestation, ≥24 weeks of gestation and ≥28 weeks of gestation, respectively. Infant deaths are deaths, after live birth, within the first year of life. The absolute risks of fetal death, stillbirth, late stillbirth and infant death, overall and by selected values of periconception and third-trimester HbA_{1c}, were estimated by LOWESS, while the absolute risks of late stillbirth for selected values of periconception and third-trimester HbA_{1c} simultaneously were estimated from logit-linked generalised estimating equations

[a] Defined as the closest measurement within 3 months before the last menstrual period or mean first-trimester measurement (<14 weeks of gestation) for women with no preconception measurement. Values are mmol/mol with DCCT % in parentheses

[b] A prepregnancy HbA_{1c} target of ≤43 mmol/mol is recommended by NICE: 'If it is safely achievable, women with diabetes who are planning to become pregnant should aim to maintain their HbA_{1c} below 6.1%.' [19]

[c] A prepregnancy HbA_{1c} target of ≤53 mmol/mol is recommended by the ADA: 'A1C levels should be as close to normal as possible (<7%) in an individual patient before conception is attempted' [20]

[d] NICE advises that women with a prepregnancy HbA_{1c} above 86 mmol/mol should be advised to avoid pregnancy: 'Women with diabetes whose HbA_{1c} is above 10% should be strongly advised to avoid pregnancy.' [19]

[e] The periconception and third-trimester HbA_{1c} values with the lowest risks of fetal death or late stillbirth were estimated to be 49 mmol/mol (6.6%) and 43 mmol/mol (6.1%), respectively. LOWESS estimates for these values were obtained by averaging each LOWESS curve within ±1 mmol/mol of the target value

[f] Minor discrepancies with Table 1 are due to very slightly different denominators. Table 1 presents the rates per all deliveries after 20 weeks; these values are per deliveries after 24 weeks (stillbirths) and 28 weeks (late stillbirths) specifically

[g] Values are mmol/mol with DCCT % in parentheses

[h] There were no cases of infant death among women with a periconception HbA_{1c} below 53 mmol/mol, thus the estimated risk for these categories are not reported

also be raised in women with diabetes. Finally, although the PMMS records cause of death, over half of all deaths were attributed simply to 'maternal disorder', preventing us from exploring whether diabetes was associated with any particular cause.

Comparison with other studies Flenady et al [5] conducted an abridged meta-analysis, including just four studies, which estimated that the RR of stillbirth was around three times higher in women with diabetes than in those without (OR 2.90 [95% CI 2.05, 4.09]). This is smaller than our estimates for both fetal death (OR 4.56 [95% CI 3.42, 6.07]) and stillbirth (OR 5.87 [95% CI 4.32, 7.97]). The largest study to examine the RR of fetal death is the analysis by Mondestin et al [9] of data from the US natality and mortality surveys during 1995–1997. Describing 271,691 pregnancies complicated by diabetes and excluding births with recorded congenital anomalies, they reported an RR for fetal death of 2.0 (95% CI 1.8, 2.2), less than half our estimate. This may be because they did not distinguish between pre-existing and gestational diabetes or may reflect ascertainment deficiencies inherent in using birth certificate data. Recent data from Ontario describing deliveries from 2005–2006 showed an even smaller RR for stillbirth of 1.53 (95% CI 0.88, 2.63) for pre-existing diabetes, although they also found an implausible protective effect for gestational diabetes (RR 0.33 [95% CI 0.12, 0.71]) [10]. In a large cohort from Australia including 433,379 deliveries from 1998–2002, Mohsin et al [11] reported a similarly small RR of 1.87 (95% CI 1.01, 3.48), although it was not indicated how diabetes was defined or ascertained.

There is more agreement between studies from Northern Europe, which typically report RRs of four to five times for stillbirth and two to four times for neonatal/infant death. In a large study of women with type 1 diabetes from Sweden during 1991–2003, Persson et al reported ORs of 4.04 (95% CI 3.02, 5.40) and 3.08 (95% CI 2.02, 4.70) for late stillbirth and neonatal death, respectively [12], while Jensen et al's study from Denmark during 1993–1999 reported corresponding RRs of 4.72 (95% CI 3.18, 7.01) and 3.40 (95% CI 1.91, 6.07) [13]. Eidem et al's study from Norway during 1985–2004 reported smaller, though not statistically inconsistent, ORs of 3.6 (95% CI 2.5, 5.3) and 1.9 (95% CI 1.1, 3.2), respectively [14]. Four studies from the UK reported strikingly similar results, possibly reflecting the increased homogeneity of care [15–18]. The four RR estimates for stillbirth ranged between 4.39 (95% CI 2.22, 8.64) and 4.7 (95% CI 3.7, 6.0) [15–18], while the two estimates of neonatal death were 2.4 (95% CI 1.4, 4.1) and 2.6 (95% CI 1.7, 3.9) [15, 17].

Eidem et al [14] and dos Santos Silva et al [15] examined whether the RR of stillbirth associated with diabetes varied by gestational age, both reporting that the effect was confined to term deliveries. In contrast, we found the RR of stillbirth was uniformly raised for all gestational ages. This discrepancy is due to different methodological approaches. Eidem et al and dos Santos Silva et al used the traditional method of calculating stillbirth rate per deliveries in that period, an approach that is highly susceptible to confounding by differences in gestational age distribution. The rate of induced preterm birth is considerably higher among women with diabetes than among those without [29]. This shift in the denominator produces an artefactually smaller stillbirth rate during preterm (and a larger one during term). By offsetting against the total population of fetuses at risk of fetal death at a particular gestational age, rather than simply the sample of deliveries at that gestational age, our findings are robust to this problem [23].

Few studies have described the continuous association between HbA_{1c} and the risk of fetal and/or infant death. Using LOWESS, Nielsen et al demonstrated an approximately linear association between increasing first-trimester HbA_{1c} above 53 mmol/mol (7%) and the risk of 'adverse outcome', although this included congenital anomalies and elective terminations [30]. In women with type 1 diabetes, Jensen et al found that the RR of perinatal mortality increased steadily from 2.8 (95% CI 1.3, 6.1) to 7.3 (95% CI 2.5, 19.8) as periconception HbA_{1c} increased from <52 mmol/mol (<6.9%) to >90 mmol/mol (>10.4%), respectively [31]. Neither Nielsen et al nor Jensen et al specifically examined whether low values of HbA_{1c} were potentially harmful, although Nielsen et al's LOWESS curve showed evidence of the same J-shape as observed in our study.

The association between retinopathy, or any microvascular complication, and the risk of fetal or infant death in women with diabetes has not been well described. Contrasting with the current study, Jensen et al found no significant difference ($p = 0.58$) in the rate of 'serious adverse outcome' (perinatal death and/or congenital anomaly) between women with and without retinopathy [13], although the proportion diagnosed with retinopathy was considerably smaller than in our cohort. In a previous study in women with diabetes in the North of England, nephropathy, but not retinopathy, was associated with an increased risk of congenital anomalies [2].

To our knowledge, this is the first study to explore the association between prepregnancy folic acid and the risk of fetal and infant death in women with diabetes. However, in a mixed population from England, during 2009–2011, Gardosi et al also identified a lower risk of stillbirth among women who had taken antenatal folic acid [32].

Implications and conclusions In England, the National Institute for Health and Care Excellence (NICE) recommends that women with pre-existing diabetes aim for a preconception HbA_{1c} below 43 mmol/mol (6.1%) [19]. The ADA suggest 53 mmol/mol (7%) [20]. Our results strongly support the attainment and maintenance of good glycaemic control before and throughout pregnancy. If the average periconception HbA_{1c} had been 53 mmol/mol (the ADA target), rather than

62 mmol/mol (the population median), then our estimates suggest that the prevalence of fetal and infant death would have been 38% lower. However, we found evidence of a J-shaped association between HbA_{1c} concentration and the risk of fetal death. Although it is implausible that euglycaemic levels of HbA_{1c} are harmful, it is possible that hypoglycaemic episodes, which are more common in women with diabetes and low HbA_{1c} [33], may be [28]. At the least, our results show that for fetal deaths, as for congenital anomalies [2], there appears to be no substantive benefit of achieving periconception levels below the ADA target. At the other extreme, NICE discourages pregnancy when the preconception HbA_{1c} is above 86 mmol/mol (10%) [19]. In demonstrating a clear continuum in risk above 53 mmol/mol, our results provide no evidence for this specific threshold.

Even in women with optimal periconception HbA_{1c} concentration (with values of 49 mmol/mol), we estimated the risk of fetal death to be over twice as high as in women without diabetes (16.6 [95% CI 8.6, 26.8] vs 6.5 [95% CI 6.3, 6.8] per 1,000 deliveries). This may reflect the limitations of HbA_{1c} as a marker of glycaemic control, or it may suggest that other risk factors are operating in women with diabetes.

The rate of fetal and infant death was over two times higher among women who did not take prepregnancy folic acid supplements. Women with pre-existing diabetes are advised to take high doses (5 mg/day) of folic acid specifically 'to reduce the risk of having a baby with a neural tube defect' [19]. Our results suggest there may be additional benefits for normally formed offspring, although folic acid use may also simply indicate better preparation for pregnancy.

History of retinopathy was associated with a doubling of the risk of fetal and infant death. It is possible that retinopathy indicates a prolonged history of poor glycaemic control that is not adequately described by HbA_{1c}, or it may signify wider microvascular deficiencies that might impair placental development. These women may warrant additional support when planning their pregnancy.

Over 20 years after the St Vincent Declaration, we found that the excess risk of fetal and infant death in women with diabetes has remained stubbornly persistent. In the North of England, fewer than half of women with pre-existing diabetes attend preconception care, with the proportion declining over time [34]. To achieve any reduction in the RR of stillbirth and infant death in women with pre-existing diabetes, the barriers to uptake of preconception care and adequate preparation for pregnancy must be urgently understood and addressed.

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Contribution statement All authors declare that they read and approved the final version of the manuscript before submission. RB conceived the project and, with JR and SVG, designed the study. PWGT performed the data analysis and drafted the manuscript. RWB was involved in the acquisition of the data. All authors were involved in the interpretation of the data and critically reviewed the manuscript. PWGT had full access to all the data and had final responsibility for the decision to submit for publication.

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2·6·6 Supplementary material

ESM Table 1 Descriptive statistics for 1548 singleton pregnancies uncomplicated by major congenital anomalies in women with pre-existing diabetes delivered in the North of England during 1996-2008 (continuous variables).

Variable	All			Fetal and infant deaths combined			One year survivors		
	N	Median (IQR)	Range	N	Median (IQR)	Range	N	Median (IQR)	Range
Standardised birth weight (Z)[a]	1465	1.2 (0.3-2.2)	-2.8-6.4	48	0.6 (-0.4-2.4)	-2.5-4.9	1417	1.3 (0.3-2.2)	-2.8-6.4
Gestational age at delivery (weeks)[b]	1548	37 (36-38)	20-42	56	33 (27-36)	20-39	1492	37 (36-38)	26-42
Maternal body mass index (kg/m^2)[c]	1190	27 (24-32)	17-64	46	28 (24-32)	19-46	1144	27 (24-32)	17-64
Maternal age (year)	1548	30 (25-34)	15-46	56	30 (24-33)	18-40	1492	30 (25-34)	15-46
Duration of diabetes (years)	1529	9 (4-17)	1-36	55	11 (2-16)	1-27	1474	9 (4-17)	1-36
Gestation at booking (weeks)	1537	8 (7-11)	1-34	54	9 (7-12)	4-24	1483	8 (7-11)	1-34
Peri-conception HbA_{1c} (mmol/mol)[d]	1332	62 (51-76)	27-156	47	75 (60-84)	31-140	1285	62 (51-76)	27-156
Third trimester HbA_{1c} (mmol/mol)	1337	50 (43-57)	18-102	31	57 (50-66)	25-97	1306	50 (43-57)	18-102

[a]Standardised against expected fetal weight for sex, gestational age, and parity. [b]Reported in both continuous and categorical formats to aid comparison. [c]Derived from self-reported height and weight at the first antenatal visit. [d]Defined as the closest measurement within three months prior to the last menstrual period or mean first trimester measurement (<14 weeks' gestation) for women with no pre-conception measurement.

ESM Table 2 Descriptive statistics for 1548 singleton pregnancies uncomplicated by major congenital anomalies in women with pre-existing diabetes delivered in the North of England during 1996-2008 (categorical variables).

Variable	All			Fetal and infant deaths combined			One year survivors		
	N	% (total)	% (non-missing)	N	% (total)	% (not-missing)	N	% (total)	% (non-missing)
Gestational age at delivery[a]									
Preterm (20-36 weeks)	585	37.8	37.8	45	80.4	80.4	540	36.2	36.2
Term (37-41 weeks)	962	62.1	62.1	11	19.6	19.6	951	63.7	63.7
Post-term (≥42 weeks)	1	0.1	0.1	0	0.0	0.0	1	0.1	0.1
Sex									
Male	824	53.2	53.4	30	53.6	54.6	794	53.2	53.2
Female	720	46.5	46.6	25	44.6	45.5	695	46.6	46.7
Missing	4	0.3		1	1.8		3	0.2	
Parity									
Primiparous	605	39.1	41.0	24	42.9	43.6	581	38.9	40.9
Multiparious (≥1)	869	56.1	59.0	31	55.4	56.4	838	56.2	59.1
Missing	74	4.8		1	1.8		73	4.9	
Maternal ethnicity									
White	1443	93.2	94.0	51	91.1	91.1	1392	93.3	94.1
Non-white	93	6.0	6.1	5	8.9	8.9	88	5.9	6.0
Missing	12	0.8		0	0.0		12	0.8	
Index of multiple deprivation[b]									
Tertile 1 (most deprived)	512	33.1	33.2	19	33.9	33.9	493	33.0	33.0
Tertile 2	513	33.1	33.3	23	41.1	41.1	490	32.8	32.8
Tertile 3 (least deprived)	516	33.3	33.5	14	25.0	25.0	502	33.7	33.7
Missing	7	0.5		0	0.0		7	0.5	
Diabetes type									
Type 1	1206	77.9	77.9	43	76.8	76.8	1163	77.8	77.8
Type 2	342	22.1	22.1	13	23.2	23.2	329	22.1	22.1
Pre-pregnancy retinopathy[c]									
No / Not known	1295	83.7	83.7	41	73.2	73.2	1254	84.0	84.0
Yes	253	16.3	16.3	15	26.8	26.8	238	16.0	16.0
Pre-pregnancy neuropathy[c]									
No / Not known	1522	98.3	98.3	54	96.4	96.4	1468	98.4	98.4
Yes	26	1.7	1.7	2	3.6	3.6	24	1.6	1.6
Pre-pregnancy nephropathy[c]									
No / Not known	1499	96.8	96.8	54	96.4	96.4	1445	96.9	96.9
Yes	49	3.2	3.2	2	3.6	3.6	47	3.2	3.2
Pre-pregnancy care									
No	906	58.5	58.5	34	60.7	60.7	872	58.5	58.5
Yes	642	41.5	41.5	22	39.3	39.3	620	41.6	41.6
Pre-pregnancy folic acid[d,e]									
No / Not known	1052	68.0	68.0	48	85.7	85.7	1004	67.3	67.3
Yes	496	32.0	32.0	8	14.3	14.3	488	32.7	32.7
Smoking in pregnancy[d]									
No	1068	69.0	75.9	34	60.7	63	1034	69.3	76.4
Yes	339	21.9	24.1	20	35.7	37	319	21.4	23.6
Missing	141	9.1		2	3.6		139	9.3	

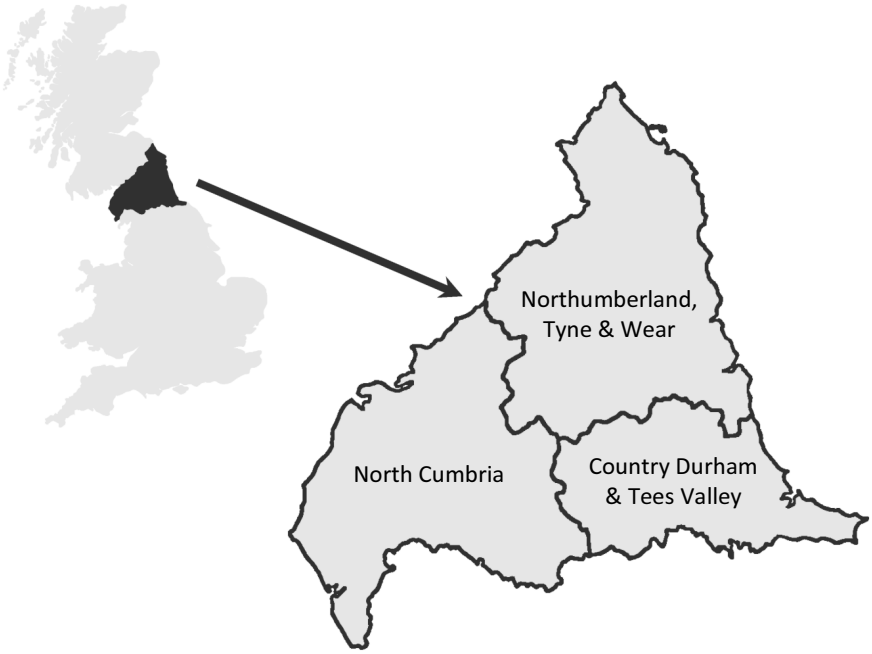
[a]Reported in both continuous and categorical formats to aid comparison. [b]The Index of Multiple Deprivation is an area-based estimate of socio-economic disadvantage derived from the mother's postcode at birth. [c]Clincally-diagnosed pre-pregnancy. [d]Self-reported. [e]Limitations in the recording of dietary supplement usage prevented us from distinguishing between pregnancies where the mother definitely did not consume folic acid pre-pregnancy, and pregnancies where the data was simply not collected or recorded.

ESM Table 3 Predictors of fetal and infant death combined in normally-formed singleton offspring in women with pre-existing diabetes

Variable (unit)	Fetal and infant death		Late stillbirth and infant death	
	Unadjusted odds ratio (95% CI)	Adjusted odds ratio[a] (95% CI)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio[a] (95% CI)
Sex				
Male	Reference		Reference	
Female	0.95 (0.55, 1.63)		0.70 (0.36, 1.37)	
Parity				
Primiparous	Reference		Reference	
Multiparious (≥1)	0.90 (0.52, 1.54)		0.77 (0.40, 1.50)	
Maternal ethnicity				
White	Reference		Reference	
Non-white	1.55 (0.60, 3.98)		0.90 (0.21, 3.81)	
Index of multiple deprivation[b]				
Tertile 1 (most deprived)	0.82 (0.44, 1.53)		1.00 (0.46, 2.17)	
Tertile 2	Reference		Reference	
Tertile 3 (least deprived)	0.59 (0.30, 1.17)		0.83 (0.37, 1.86)	
Diabetes type				
Type 1	Reference		Reference	
Type 2	1.07 (0.57, 2.01)		0.97 (0.44, 2.15)	
Pre-pregnancy retinopathy[c]				
No / Not known	Reference	Reference	Reference	
Yes	1.93 (1.05, 3.54)	2.05 (1.04, 4.05)	1.69 (0.79, 3.63)	
Pre-pregnancy neuropathy[c]				
No / Not known	Reference		Reference	
Yes	2.27 (0.52, 9.83)		No cases	
Pre-pregnancy nephropathy[c]				
No / Not known	Reference		Reference	
Yes	1.14 (0.27, 4.81)		0.87 (0.12, 6.50)	
Pre-pregnancy care				
No	1.10 (0.64, 1.90)		1.05 (0.54, 2.03)	
Yes	Reference		Reference	
Pre-pregnancy folic acid[d]				
No / Not known	2.92 (1.37, 6.21)	2.52 (1.12, 5.65)	4.02 (1.42, 11.41)	3.01 (1.03, 8.79)
Yes	Reference	Reference	Reference	Reference
Smoking in pregnancy[d]				
No	Reference		Reference	
Yes	1.91 (1.08, 3.36)		2.21 (1.14, 4.32)	
Maternal body mass index (kg/m^2)[e]	1.01 (0.96, 1.05)		0.99 (0.93, 1.04)	
Maternal age (year)	0.99 (0.94, 1.03)		0.96 (0.91, 1.02)	
Duration of diabetes (years)	1.00 (0.96, 1.03)		1.00 (0.96, 1.04)	
Gestation at first antenatal visit (weeks)	1.02 (0.96, 1.08)		1.02 (0.95, 1.09)	
Peri-conception HbA_{1c} (mmol/mol)[g]				
< 49mmol/mol (6.6%)	0.97 (0.88, 1.06)	0.96 (0.87, 1.06)	0.95 (0.86, 1.06)	
≥ 49mmol/mol (6.6%)	1.02 (1.00, 1.04)	1.02 (1.00, 1.04)	1.03 (1.01, 1.04)	
Third trimester HbA_{1c} (mmol/mol)				
< 43mmol/mol (6.1%)	NA[h]	NA[h]	0.94 (0.84, 1.05)	0.94 (0.84, 1.04)
≥ 43mmol/mol (6.1%)	NA[h]	NA[h]	1.06 (1.03, 1.09)	1.06 (1.03, 1.09)

[a]Adjusted modes were constructed using a backwards stepwise approach; all variables were entered into the model with non-significant ones being removed iteratively, according to decreasing p-value, until only those with p<0.1 remained (details of which are shown). [b]The Index of Multiple Deprivation is an area-based estimate of socio-economic disadvantage derived from the mother's postcode at birth. [c]Clincally-diagnosed pre-pregnancy. [d]Self-reported [e]Derived from self-reported height and weight at the first antenatal visit. [g]Defined as the closest measurement within three months prior to the last menstrual period or mean first trimester measurement (<14 weeks' gestation) for women with no pre-conception measurement. [h]Not applicable, third-trimester HbA_{1c} was examined only in relation to deliveries at ≥28 weeks' gestation.

ESM Figure 1 The North of England



Next to Mondestin *et al*'s 2002 US study of 271,691 deliveries in women with diabetes,[337] the 1548 included in Tennant *et al* 2013 seems somewhat modest. As with most of the works in this submission however the key strength lies not in the sample size, but in the quality of the available data. While the NorDIP for example includes only those pregnancies which have been clinically-diagnosed with diabetes at least six months before pregnancy,[205] Mondestin *et al* 2002 obtained their information from birth certificates and were hence unable to differentiate between pre-existing and gestational variants.[337] Such ascertainment differences are likely to explain some of the heterogeneity observed in Flenady *et al*'s 2011 meta-analysis,[315] although they may also reflect genuinely variable effects in different healthcare settings. The four previous UK studies for example found remarkably similar ORs to those estimated by Tennant *et al* 2013,[336,340,381,410], although Holman *et al*'s recent (2014) English study – which includes some data from the North of England - report a significantly smaller stillbirth RR of 2.73 (95% CI: 1.90 to 3.92)[xxx]. It is unclear however how they identified their cases, and under-ascertainment would explain the lower RR given the absence of a direct comparison group.[411]

Tennant *et al* 2013 is most innovative for the range and detail of information on the modifiers of risk in women with diabetes. Although Inkster *et al's* systematic review from 2006 had previously sought to quantify the association between 'poor glycated haemoglobin control' and the odds of various adverse outcomes - including congenital anomalies and perinatal death - the analysis was crude, relying on whatever dichotomisation had been made by the constituent study.[412] Jensel *et al*'s (2009) ordinal analysis of the risk of perinatal death for increasing categories of peri-conception HbA_{1c} provided more detail,[413] but Tennant *et al* 2013 improved on this with a superior sample size and modelling approach, as well as having information on HbA_{1c} at multiple time point and other salient variables such as folic acid.

Once again I used LOWESS to provide estimates of the absolute risk of fetal and infant death by peri-conception HbA_{1c}. For late stillbirths however both peri-conception and third-trimester HbA_{1c} contributed separately to the risk, requiring a new approach that could estimate the conditional probabilities. My chosen method - of evaluating marginal values from the regression model – was parametric, which can introduce error if the true relationship diverges from the underlying assumptions. I attempted to minimise any misspecification by

[xxx] In the original article,[411] the 95% confidence intervals are reported as 2.61 to 2.84 – these are incorrect and have been recalculated based on the reported rates. The reported number of stillbirths in the reference population is also incorrect.

using LOWESS to conduct preliminary investigations and by restricting the output to the middle 90% of HbA_{1c} values.

Unlike with birthweight, the direction of the association between HbA_{1c} and the risk of late stillbirth was uniform from peri-conception to third trimester, with the greatest risk occurring in those who had been exposed to high glucose concentrations throughout pregnancy (**Table 3**, p116). Taken with the results of Glinianaia *et al* 2012, this suggests that a fetus with modest initial growth (i.e. reflecting impaired placental development) followed by large late growth (i.e. increasing strain on the placenta) experiences the highest risk of death; even though they may not be the largest in size (for further details see **Section 3·4·2·2**, p160).

In contrast to previous studies of the effect of diabetes on stillbirth by gestational age,[339,343], I used a 'fetuses-at-risk' approach (which is not susceptible to confounding by differences in gestational age distributions)[414] to show that the increased risk of stillbirth in women with diabetes was not restricted to term. The same approach and results were observed in Holman *et al*'s 2014 English study, although errors in the table of results hinder any further comparisons.[411]

Although the largest study of its type, Tennant *et al* 2013 still experienced issues with low statistical power. This most-obviously affected the hypothesis tests for neonatal death and post-neonatal death, for which there were very few cases. Furthermore, the apparent reversal in the risk of fetal death for decreasing values of HbA_{1c} below 49mmol/mol did not reach the formal threshold for statistical significance. Since Nielsen *et al* 2006 had however also observed a J-shaped pattern between HbA_{1c} and risk of adverse outcome,[415] it seemed reasonable to speculate that this was not a chance finding. Regardless, the lack of information on hypoglycaemic episodes – or indeed on glycaemic excursions more generally – is a prominent limitation that applies equally to all the NorDIP studies, and is therefore discussed in more detail in **Section 3·2·5** (p149).

Around half way through the paper's results, readers may note a change in terminology from discussing the risk and RR associated with pre-existing diabetes to discussing the odds and OR for changes in HbA_{1c} (beginning from the subsection entitled, 'HbA_{1c} and the odds of fetal and infant death'). This stems from a shift from simple univariate calculations, to the use of multivariable logistic regression. This uses a logit link function to constrain the model prediction between zero and one, with the outcome equivalent to the log odds.[416] The exponentiated coefficients therefore describe the association between changes in each exposure with changes in the relative odds of the outcome.[416] For rare outcomes, typically defined as those occurring in under 5%-10% of the population, these ORs closely approximate the corresponding RRs. Because this 'rare disease assumption' holds true for

congenital anomalies, stillbirths, and infant deaths, I interpreted most ORs interchangeably with RRs, but I chose to keep the OR label for technical precision. Given the sample was derived from a population-based cohort, the RRs in fact could have been directly estimated by duplicating the cases into the reference group (at the cost of precision),[417] or with an alternative modelling approach, such as Poisson or Cox regression.[417]

2·7 TENNANT *et al* 2015 (RECURRENT ADVERSE OUTCOMES IN DIABETES)

Title: Risk and Recurrence of Serious Adverse Outcomes in the First and Second Pregnancies of Women With Preexisting Diabetes

Authors: **Tennant PWG**, Bilous RW, Prathapan S, Bell R

Journal: Diabetes Care (Volume 38 Issue 4 Pages 610-619)

Date of Publication: 05 January 2015

2·7·1 Overview

This article describes a unique longitudinal study that sought to examine the preparations for, and outcomes of, the first and second pregnancies in a small cohort of women with pre-existing diabetes. Socio-demographic and clinical information for women who delivered two successive singleton pregnancies during 1996-2008 were obtained from the NorDIP and merged with outcome data from the NorCAS and PMS.

The paper was accompanied by two supplementary tables that describe the socio-demographic and physiological features of sample (**Section 2·7·6**, p139), and a modified version of the map of the North of England first used in Rankin *et al* 2010 (**Section 2·2**, p41).

2·7·2 What was known

- Serious adverse pregnancy outcomes (including miscarriages, stillbirths, infant deaths, and congenital anomalies) were known to be substantially more common in women with pre-existing diabetes, but little was known about the absolute risk in specific pregnancies.
- Previous experience of a serious adverse pregnancy outcome was known to be associated with an increased risk of recurrent adverse outcome in the general population, but it was not known how or whether this applied in the high-risk group of women with diabetes
- Optimum preparation for pregnancy was known to be rare for women with diabetes living in the UK, but it was unknown how or whether this changed between pregnancies, particularly following experience of a serious adverse pregnancy outcome.

2·7·3 What this study added

- 39% of women with pre-existing diabetes were found to experience a serious adverse pregnancy outcome in either their first or second pregnancy, with 8% shown to experience serious adverse outcomes in both pregnancies.

- The prevalence of serious adverse pregnancy was found to fall by around half - from 30% to 16% - between the first and second pregnancy respectively, but women with a history of serious adverse outcome in their first pregnancy were found to experience twice the risk [RR=2.59 (95% CI: 1.35 to 4.96)] of adverse outcome in the second pregnancy compared with women with no history of adverse outcome

- Women with diabetes were found to achieve similar levels of preparation for their first and second pregnancies, regardless of whether their first pregnancy was affected by serious adverse pregnancy outcome.

- The odds of serious adverse pregnancy outcome in either pregnancy were found to increase linearly by 1-3% for each 1mmol/mol increase in peri-conception HbA_{1c} above 47mmol/mol (6.5%). Women from minority ethnic groups were found to experience three-times higher odds of serious adverse pregnancy outcome.

- Women's HbA_{1c} values were found to be similar in their first and second pregnancies, but only the values in the current pregnancy were found to be associated with the outcome of that pregnancy

2·7·4 Contribution of the candidate to this work

I designed and conducted the statistical analysis, drafted the introduction, methods, results, tables and discussion, produced the figures, compiled the references, and edited the manuscript following critical-review from RWB, SP, and RB. A copy of the Newcastle University Co-Authorship form for this publication can be found in **Appendix A(vi)** (p189).

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Risk and Recurrence of Serious Adverse Outcomes in the First and Second Pregnancies of Women With Preexisting Diabetes

Peter W.G. Tennant,[1] Rudy W. Bilous,[2,3] Shamini Prathapan,[1] and Ruth Bell[1,4]

Diabetes Care 2015;38:610–619 | DOI: 10.2337/dc14-1888

EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

Women with preexisting (type 1 or type 2) diabetes experience an increased risk of serious adverse pregnancy outcomes. It is not known, however, how these risks change between the first and second pregnancy and whether there is an increased risk of recurrence. This study describes the absolute risks and recurrence of serious adverse pregnancy outcomes in 220 women with preexisting diabetes.

RESEARCH DESIGN AND METHODS

A total of 440 pregnancies occurring in 220 women with preexisting diabetes who delivered successive singleton pregnancies in the North of England during 1996–2008 were identified from the Northern Diabetes in Pregnancy Survey (NorDIP). Predictors of serious adverse outcome were estimated by competing-risks regression.

RESULTS

Sixty-seven first pregnancies (30.5%) ended in serious adverse outcome, including 14 (6.4%) with congenital anomalies and 53 (24.1%) additional fetal or infant deaths. Thirty-seven second pregnancies (16.8%) ended in serious adverse outcome—half the rate among first pregnancies (P = 0.0004)—including 21 (9.5%) with congenital anomalies and 16 (7.3%) additional fetal or infant deaths. Serious adverse outcomes in the second pregnancy occurred twice as frequently in women who experienced a previous adverse outcome than in those who did not (26.9% vs. 12.4%, P = 0.004), but previous adverse outcome was not associated with preparation for the following pregnancy.

CONCLUSIONS

Serious adverse outcomes are less common in the second pregnancies of women with preexisting diabetes, although the risk is comparable in those whose first pregnancy ends in adverse outcome. Reducing the risk of recurrence may require more support in the immediate period after an adverse pregnancy outcome.

Serious adverse pregnancy outcomes, such as miscarriages, stillbirths, and congenital anomalies, are associated with significant psychological distress, and parents who experience such events are often very anxious about their chances of recurrence (1,2). In the general population, the risks of miscarriage, stillbirth, and congenital anomaly in the second pregnancy are approximately two times greater in women who experienced the same event in their first pregnancy (3–5), although the absolute risks remain low in the absence of clear genetic or physiological factors.

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A slide set summarizing this article is available online.

Despite significant improvements in preconception and antenatal care, women with preexisting (type 1 or type 2) diabetes still experience substantially increased risks of serious adverse pregnancy outcomes, including miscarriages (6), congenital anomalies (7), stillbirths (8), and infant deaths (8). Little is known, however, about the absolute risks of these outcomes in first and second pregnancy, specifically, and whether women with diabetes experience the same patterns of recurrence as the general population. Suboptimal glycemic control at the start of pregnancy explains a large proportion of the excess risk of congenital anomalies and fetal and infant death (7,8); however, the extent that interpregnancy changes in glycemic control can modify the risk in subsequent pregnancies has not been demonstrated.

This study used unique data from the U.K.'s longest-running survey of women with preexisting diabetes to estimate: *1*) preparation for and change in preparatory behavior between the first and second pregnancies of 220 women with preexisting diabetes, including the effect of adverse outcome in the first pregnancy, and *2*) risk of, change in risk of, and predictors of serious adverse outcome in each pregnancy, including the effect of adverse outcome in the first pregnancy.

RESEARCH DESIGN AND METHODS

Population and Sample

The North of England is a distinct region of the U.K. with a population of 3 million and ~32,000 births per year (Supplementary Fig. 1). The sample comprises 440 pregnancies occurring in 220 women with preexisting diabetes who completed two successive singleton pregnancies at any gestational age—regardless of outcome—in the North of England during 1996–2008.

Definitions

Miscarriage is the spontaneous loss of a fetus at ≤23 weeks' gestation. *Stillbirth* is the delivery of a fetus showing no signs of life at ≥24 weeks' gestation. *Spontaneous fetal death* comprises miscarriages and stillbirths. *Infant death* is the death of a live-born infant aged ≤1 year. *Congenital anomalies* are any major chromosomal, genetic, or structural abnormality defined by the European Surveillance of Congenital Anomalies (EUROCAT) criteria (9). *Termination of pregnancy* is the induced loss of a fetus for therapeutic or elective reasons. *Serious adverse outcomes* comprise congenital anomalies, spontaneous fetal deaths, and infant deaths.

Data Sources

The Northern Diabetes in Pregnancy Survey (NorDIP) records details of all pregnancies occurring in women resident in the region and diagnosed with diabetes at least 6 months before conception. Clinicians within the region's nine maternity units collect and supply information on a range of clinical and sociodemographic variables (10).

Pregnancies affected by congenital anomaly (regardless of outcome) were identified from the Northern Congenital Abnormality Survey (NorCAS) (11). Stillbirths and infant deaths were identified from the Northern Perinatal Mortality Survey (PMS) (12).

Variables

Available variables with a hypothesized influence on serious adverse pregnancy outcome were obtained for analyses. Maternal ethnicity; diabetes type; prepregnancy history of clinically diagnosed nephropathy, neuropathy, and retinopathy; attendance at preconception care; preconception folic acid supplementation (self-reported); smoking during pregnancy (self-reported); and attendance at the first antenatal appointment before 10 weeks' gestation were all analyzed as dichotomous variables. Socioeconomic circumstances at birth were estimated from the Index of Multiple Deprivation, an area-based measure of disadvantage (13), and analyzed in tertiles of ranks. Year of delivery, maternal age at delivery, duration of diabetes, maternal BMI (derived from height and weight at the first antenatal visit), duration of diabetes, and mean periconception glycated hemoglobin (A1C) concentration were analyzed as continuous variables. Periconception A1C was defined as the closest measurement within 3 months before the last menstrual period (available for 52.9% of pregnancies) or mean first trimester measurement (<14 weeks' gestation) (available for 82.0% of pregnancies) for women with no preconception measurement. Periconception A1C was considered a reasonable proxy for preconception A1C because the first trimester A1C was highly correlated with the preconception A1C (Spearman correlation coefficient 0.73) (14). Gestational age at delivery and the first antenatal appointment were determined during the first ultrasound examination or (rarely) from the date of the last menstrual period. Small for gestational age (SGA; birth weight <10th centile) and large for gestational age (LGA; birth weight >90th centile) were determined from birth weight, standardized for sex, parity, and gestational age against a Scottish reference population (15).

Four variables were selected as markers of pregnancy preparation due to their established associations with outcome (16,17) and integration within care guidelines for women with preexisting diabetes:

1. Periconception A1C <53 mmol/mol (7.0%)—recommended by the American Diabetes Association (based in the U.S.) (18).
2. Self-reported preconception folic acid—the National Institute for Health and Care Excellence (NICE; based in England) recommends that women with diabetes take 5 mg/day folic acid before conception (19).
3. Attendance at the first antenatal visit before 10 weeks' gestation—recommended by NICE (19).
4. Record of attending specialist preconception care services—recommended by NICE to be offered to all women with preexisting diabetes (19). Regional guidelines advise those responsible for routine care to inquire about pregnancy intention, discuss the benefits of preparation, and refer those with plans to specialist services.

Analysis 1: Preparation for Pregnancy

The proportion of women achieving each marker of preparation was calculated per 100 pregnancies. Changes in prevalence and prevalence ratios for repeat behavior were estimated by Poisson regression. The association between an adverse outcome in the first pregnancy and preparation in the second was examined by logistic regression, with adjustment for baseline.

Analysis 2: Prevalence and Predictors of Serious Adverse Outcome

The prevalence of miscarriage, stillbirth, spontaneous fetal death, and congenital anomaly was calculated

per 100 pregnancies. The prevalence of infant death, delivery by Caesarean section, SGA, and LGA was calculated per 100 births. Changes in prevalence and relative risks (RRs) of recurrence were estimated by Poisson regression.

The total probabilities of spontaneous fetal death from 6 weeks, 12 weeks, and 24 weeks were estimated using Kaplan-Meier. Pregnancies were "at risk" between the gestation at the first antenatal appointment and the gestation at delivery. Miscarriages and stillbirths were events, elective terminations of pregnancy were censored, and live births were modeled as surviving throughout.

Predictors of serious adverse outcome in each pregnancy were examined by competing-risks regression (20). Pregnancies were "at risk" between the first antenatal appointment and delivery. The primary event was any serious adverse outcome, and the competing events were live births or terminations without evidence of congenital anomaly. Unadjusted subdistribution hazard ratios (SHRs) were calculated for each variable in relation to serious adverse outcome in each pregnancy separately. Adjusted SHRs (aSHRs) were estimated within multivariable models constructed using a backward stepwise approach. Variables with an unadjusted $P < 0.5$ were entered and removed iteratively (by descending P value) until only those with $P < 0.1$ remained. The shape of association between periconception A1C and a serious adverse pregnancy outcome was explored by locally weighted scatterplot smoothing (21). Because a J shape was observed, periconception A1C was modeled by piecewise linear regression with a knot at the lowest modeled value (47 mmol/mol [6.5%]). Differences in effect by type of diabetes were not explored due to small numbers with type 2 diabetes. The absolute risks of serious adverse outcome in the second pregnancy, stratified by outcome in the first and values of periconception A1C, were estimated by taking marginal values of a simplified logistic regression model (conditioning for first-pregnancy outcome and periconception A1C), with 95% CIs estimated using the delta method (22).

Missing Data

Missing data were more likely in women who experienced adverse pregnancy outcomes. Calculations were hence evaluated across 100 multiply imputed data sets. Missing values were estimated by multivariate imputation by chained equations using the variables described plus second and third trimester A1C. Conditional prevalence proportions were estimated by taking marginal values from Poisson regression models, with 95% CIs predicted using the delta method (22). For complete data, 95% CIs for proportions were estimated by the Clopper-Pearson (exact) method (23). Missing values were not predicted for gestational age when required for competing-risk regression. Analyses were performed using Stata 11.1 software (StataCorp LP, College Station, TX). $P < 0.05$ was considered statistically significant.

Ethics Approval and Research Governance

The Newcastle Research Ethics Committee originally granted approval for the NorDIP in 1993. Data are now obtained and held with informed consent.

RESULTS

Population Characteristics

Of the 220 participating women with preexisting diabetes, 89% had type 1 diabetes and 95% were white. The median interpregnancy interval (the time between the end of the first pregnancy and the start of the second) was 1.8 years (interquartile range [IQR] 0.9–3.0), although this was shorter in women whose first pregnancy ended in serious adverse outcome (1.0 years [IQR 0.4–2.1] vs. 2.0 years [1.2–3.2], $P < 0.0001$). Maternal characteristics during each pregnancy are summarized in Supplementary Tables 1 and 2.

Preparation for Pregnancy

A quarter of women achieved a periconception A1C <53 mmol/mol (7.0%) before their first and second pregnancies (22.6% and 28.9%, respectively), one-half attended preconception care (54.1% and 55.5%, respectively), and two-thirds made their first antenatal visit before 10 weeks (61.6% and 66.2%, respectively) (Table 1). The proportion of women who consumed folic acid supplements before pregnancy increased from 27.1% before the first pregnancy to 43.0% before the second ($P = 0.01$) (Table 1), although this was not significant after adjusting for year of birth ($P = 0.07$). Less than half of the women attended both first antenatal visits before 10 weeks (43.2% [95% CI 36.5–49.8]), a third attended preconception care before both pregnancies (35.0% [95% CI 28.6–41.4]), and less than a fifth achieved a periconception A1C <53 mmol/mol or consumed folic acid supplements before both pregnancies (14.4% [95% CI 9.3–19.4] and 15.9% [10.4–21.5], respectively).

Preparation for pregnancy was correlated between pregnancies. Women who in their first pregnancy achieved a periconception A1C <53 mmol/mol, consumed folic acid supplements, and attended preconception care were, respectively, 3.33 ($P < 0.0001$), 1.57 ($P = 0.04$), and 1.45 ($P = 0.047$) times more likely to do so again in the second (Table 1).

A serious adverse outcome in the first pregnancy was not associated with improved preparation in the second. Achieving a periconception A1C <53 mmol/mol, attending the first antenatal visit before 10 weeks, and attendance of preconception care were, if anything, less likely in the second pregnancy among those who had experienced a previous adverse outcome, although none of the associations were statistically significant (A1C: OR adjusted [aOR] for behavior in the first pregnancy 0.65 [95% CI 0.29–1.42], $P = 0.28$; first appointment before 10 weeks: aOR 0.74 [0.40–1.37], $P = 0.34$; attendance of preconception care: aOR 0.80 [0.44–1.44], $P = 0.45$). There was no association between outcome in the first pregnancy and folic acid consumption in the second (aOR 1.01 [0.54–1.88], $P = 0.98$).

Prevalence of Serious Adverse Outcome in Either Pregnancy

A serious adverse outcome occurred in 39.1% of women (95% CI 32.6–45.9) in at least one pregnancy, and 8.2% (4.9–12.6) experienced serious adverse outcomes in both pregnancies.

Prevalence and Predictors of Serious Adverse Outcome in the First Pregnancy

A serious adverse outcome affected 30.5% of first pregnancies. There was no difference in prevalence by diabetes type (type 1: 30.8% [95% CI 24.4–37.8] vs. type 2: 28.0% [12.1–49.4], $P = 0.78$). A total of 17.3% ended in miscarriage, 5.5% in stillbirth, and 1.4% in infant death, and 6.4% were affected by congenital anomaly (Table 1). Of the 14 first

Table 1—Pregnancy preparation and outcome in first and second pregnancies and prevalence ratios/RRs for repeat behavior/recurrence of adverse outcomes

Variable	Prevalence proportion (95% CI) [*n*/*N*]		Relative change in summary prevalence (95% CI) [*P* value]	Conditional prevalence in second pregnancy (95% CI) [*n*/*N*]		Prevalence ratio/RR (95% CI) [*P* value]
	First pregnancy	Second pregnancy		Also in first pregnancy	Only in second pregnancy	
Preparation for pregnancy						
Periconception A1C <53 mmol/mol (7.0%)	22.6 (16.5–28.6) [50/220]*	28.9 (22.6–35.2) [64/220]*	1.32 (0.89–1.95) [*P* = 0.17]	63.2 (40.4–86.1) [32/50]*	18.8 (11.8–25.8) [32/170]*	3.33 (1.97–5.65) [*P* < 0.0001]*
Preconception folic acid	27.1 (20.4–33.8) [60/220]*	43.0 (36.2–49.9) [95/220]*	1.55 (1.11–2.18) [*P* = 0.01]	58.7 (38.6–78.8) [35/60]*	37.4 (27.5–47.2) [60/160]*	1.57 (1.01–2.43) [*P* = 0.04]*
First antenatal visit <10 weeks	61.6 (55.1–68.2) [136/220]*	66.2 (59.9–72.5) [146/220]*	1.08 (0.85–1.36) [*P* = 0.53]	70.0 (55.9–84.2) [95/136]*	60.1 (43.4–76.7) [50/84]*	1.17 (0.83–1.64) [*P* = 0.38]*
Attended preconception care	54.1 (47.3–60.8) [119/220]	55.5 (48.6–62.1) [122/220]	1.03 (0.80–1.32) [*P* = 0.85]	64.7 (50.3–79.2) [77/119]	44.6 (31.5–57.6) [45/101]	1.45 (1.01–2.10) [*P* = 0.047]
Serious adverse outcome						
Any serious adverse outcome	30.5 (24.4–37.0) [67/220]	16.8 (12.1–22.4) [37/220]	0.55 (0.37–0.83) [*P* = 0.004]	26.9 (16.8–39.1) [18/67]	12.4 (7.6–18.7) [19/153]	2.16 (1.14–4.12) [*P* = 0.02]
Congenital anomaly	6.4 (3.5–10.4) [14/220]	9.5 (6.0–14.2) [21/220]	1.50 (0.76–2.95) [*P* = 0.24]	14.3 (1.8–42.8) [2/14]	9.2 (5.6–14.0) [19/206]	1.55 (0.36–6.65) [*P* = 0.56]
Spontaneous fetal death, infant death, or termination of pregnancy for fetal anomaly	25.5 (19.8–31.7) [56/220]	10.5 (6.7–15.3) [23/220]	0.41 (0.25–0.67) [*P* = 0.0003]	19.6 (10.2–32.4) [11/56]	7.3 (3.8–12.4) [12/164]	2.68 (1.26–5.74) [*P* = 0.009]
Fetal or infant death in normally formed offspring†	24.1 (18.6–30.3) [53/220]	7.3 (4.2–11.5) [16/220]	0.30 (0.17–0.53) [*P* < 0.0001]	13.2 (5.5–25.3) [7/53]	5.4 (2.5–10.0) [9/167]	2.45 (0.91–6.58) [*P* = 0.08]
Spontaneous fetal death†	23.7 (17.4–28.8) [50/220]	6.8 (3.9–11.0) [15/220]	0.30 (0.17–0.53) [*P* < 0.0001]	14.0 (5.8–26.7) [7/50]	4.7 (2.1–9.1) [8/170]	2.98 (1.08–8.20) [*P* = 0.04]
Miscarriage†	17.3 (12.5–22.9) [38/220]	5.5 (2.8–9.3) [12/220]	0.32 (0.17–0.60) [*P* = 0.0005]	5.3 (0.6–17.7) [2/38]	5.3 (2.7–9.9) [10/182]	0.96 (0.21–4.37) [*P* = 0.96]
Stillbirth†	5.5 (2.8–9.3) [12/220]	1.4 (0.3–3.9) [3/220]	0.25 (0.07–0.89) [*P* = 0.03]	0.0 (0.0–26.5) [0/12]	1.4 (0.3–4.2) [3/208]	—
Infant death†	1.4 (0.3–3.9) [3/220]	0.5 (0.1–2.5) [1/220]	0.29 (0.03–2.74) [*P* = 0.28]	0.0 (0.0–70.8) [0/3]	0.5 (0.0–2.5) [1/217]	—
Other outcomes (births only)‡						
Delivery by Caesarean section‡	54.5 (46.9–62.0) [97/178]	60.7 (53.6–67.5) [122/201]	1.05 (0.79–1.41) [*P* = 0.71]	88.6 (80.1–94.4) [78/88]§	31.6 (21.4–43.3) [24/76]§	2.81 (1.78–4.44) [*P* < 0.0001]§
SGA‡	4.5 (2.0–8.7) [8/178]	3.5 (1.4–7.0) [7/201]	0.86 (0.29–2.55) [*P* = 0.78]	14.3 (0.4–57.9) [1/7]§	2.5 (0.7–6.4) [4/157]§	5.61 (0.63–50.17) [*P* = 0.12]§
LGA‡	42.7 (35.3–50.3) [76/178]	58.2 (51.1–65.1) [117/201]	1.04 (0.78–1.39) [*P* = 0.77]	69.5 (59.2–78.5) [66/95]§	44.9 (32.9–57.4) [31/69]§	1.55 (1.01–2.37) [*P* = 0.045]§

*Prevalence proportions were estimated over 100 multiply imputed data sets with CI determined from the analytically derived variance estimator. Counts represent the rounded average across the 100 data sets and should be considered indicative. †Cases exclude offspring with congenital anomalies. ‡Sample restricted to pregnancies resulting in registered births (i.e., live birth or stillbirths) and includes pregnancies complicated by congenital anomaly. §Rates calculated from sample of 164 women with two successive births.

pregnancies affected by congenital anomaly, <5 (<35.7%—the count is censored to conform to U.K. disclosure regulations) ended in termination of pregnancy. The total probability of spontaneous fetal death from 6 weeks' gestation was 33.9% (95% CI 24.7–45.3); from 12 weeks' gestation was 16.1% (11.4–22.4); and from 24 weeks' gestation was 6.3% (3.5–11.0).

A total of 178 first pregnancies (80.9% [95% CI 75.1–85.9]) resulted in a registered birth. Of these, 54.5% were delivered by Caesarean section, 4.5% of offspring were SGA, and 42.7% were LGA (Table 1).

Nonwhite ethnicity (P = 0.02), prepregnancy neuropathy (P < 0.0001), increasing maternal age (P = 0.03), smoking during pregnancy (P = 0.01), and increasing periconception A1C ≥47 mmol/mol (P = 0.003) were all independently associated with an increased risk of a serious adverse outcome in the first pregnancy (Table 2).

Prevalence and Predictors of Serious Adverse Outcome in the Second Pregnancy

A serious adverse outcome affected 16.8% of second pregnancies, 0.55 times (P = 0.004) the rate among first pregnancies (Table 1). There was no difference in prevalence by diabetes type (type 1: 16.9% [95% CI 11.9–22.9] vs. type 2: 16.0% [4.5–36.1], P = 0.91). The proportions of second pregnancies ending in miscarriage (5.5%) and stillbirth (1.4%), respectively, were 0.32 times (P = 0.0005) and 0.25 times (P = 0.03) the rate among first pregnancies (Table 1). The proportions of second pregnancies that ended in infant death (0.5%) or were affected by congenital anomaly (9.5%) were not significantly different from the rates among first pregnancies (P = 0.28 and P = 0.24, respectively) (Table 1). Of the 21 second pregnancies affected by congenital anomaly, <5 (<23.8%) ended in termination of pregnancy. The total probability of spontaneous fetal death from 6 weeks' gestation was 11.9% (95% CI 6.1–22.6), from 12 weeks' gestation

Table 2—Predictors of serious adverse outcome in the first pregnancy

Variable	Unadjusted SHR (95% CI)	*P* value (overall)	aSHR (95% CI)	*P* value (overall)
Nonmodifiable variable				
Type of diabetes			Not entered ($P > 0.5$)	
Type 1	Reference			
Type 2	1.01 (0.45–2.26)	0.98		
Maternal ethnic origin				
White	Reference		Reference	
Nonwhite	3.23 (1.25–8.37)	0.02	3.18 (1.19–8.47)	0.02
Index of deprivation			Not entered ($P > 0.5$)	
Tertile 1 (most deprived)	1.14 (0.63–2.06)	0.67		
Tertile 2	Reference	(0.52)		
Tertile 3 (least deprived)	0.79 (0.42–1.49)	0.47		
Prepregnancy nephropathy			Not entered ($P > 0.5$)	
Yes	1.02 (0.24–4.32)	0.98		
No	Reference			
Prepregnancy neuropathy				
Yes	2.77 (1.83–4.20)	<0.0001	4.65 (2.23–9.68)	<0.0001
No	Reference		Reference	
Prepregnancy retinopathy			Eliminated ($P > 0.1$)	
Yes	0.57 (0.23–1.41)	0.22		
No	Reference			
Year of delivery (year)	0.94 (0.86–1.02)	0.16	0.93 (0.85–1.01)	0.08
Duration of diabetes (years)	0.97 (0.93–1.01)	0.11	Eliminated ($P > 0.1$)	
Maternal age (years)	1.04 (0.98–1.09)	0.20	1.07 (1.01–1.13)	0.03
Potentially modifiable variable				
Smoked during pregnancy				
Yes	1.78 (1.02–3.11)	0.042	2.25 (1.18–4.29)	0.01
No	Reference		Reference	
Preconception folic acid			Eliminated ($P > 0.1$)	
Yes	0.75 (0.35–1.60)	0.45		
No	Reference			
First antenatal visit <10 weeks			Not entered ($P > 0.5$)	
Yes	0.98 (0.53–1.81)	0.94		
No	Reference			
Attended preconception care			Not entered ($P > 0.5$)	
Yes	1.09 (0.66–1.81)	0.73		
No	Reference			
BMI (kg/m^2)	1.02 (0.97–1.06)	0.49	Eliminated ($P > 0.1$)	
Periconception A1C (mmol/mol)		(0.04)		(0.02)
<47 (<6.5%)	1.00 (0.91–1.09)	0.95	1.00 (0.92–1.09)	0.93
≥47 (≥6.5%)	1.01 (1.00–1.02)	0.01	1.02 (1.01–1.03)	0.003

was 2.7% (1.1–6.4), and from 24 weeks' gestation was 1.5% (0.5–4.6).

A total of 201 second pregnancies (91.4% [95% CI 87.6–95.1]) resulted in a registered birth. Of these, 60.7% were delivered by Caesarean section. The proportion of births delivered by Caesarean section in the second pregnancy was 2.81 times greater ($P < 0.0001$) in women whose previous birth was delivered by Caesarean section (88.6%); 11.4% (95% CI 5.6–19.9) delivered by vaginal birth after a Caesarean delivery (Table 1). Of births in the second pregnancy, 3.5% were SGA and 58.2% were LGA (Table 1). The proportion of LGA births in the second pregnancy was 1.55 times greater ($P = 0.045$) in women whose first birth was LGA (69.5%) (Table 1).

Women whose first pregnancy resulted in a serious adverse outcome experienced more than twice the prevalence of a serious adverse outcome in the second (26.9% vs. 12.4%; SHR 2.59 [95% CI 1.35–4.96], $P = 0.004$) (Table 1 and Table 3). Nearly a third of this was explained by other factors. Nonwhite ethnicity ($P = 0.02$), prepregnancy nephropathy ($P = 0.02$), increasing periconception A1C ≥47 mmol/mol ($P = 0.0008$), and earlier year of delivery ($P = 0.002$) were all independently associated with increased risk of serious adverse outcome in the second pregnancy (Table 3). After adjusting for these and other variables with $P < 0.1$, the association between previous adverse outcome and risk in the second pregnancy was not statistically significant (adjusted

Table 3—Predictors of serious adverse outcome in the second pregnancy

Variable	Unadjusted SHR (95% CI)	*P* value (overall)	aSHR (95% CI)	*P* value (overall)
Nonmodifiable variable				
Outcome in the first pregnancy				
Normally formed live birth	Reference		Reference	
Miscarriage, stillbirth, or CA	2.59 (1.35–4.96)	0.004	1.83 (0.96–3.47)	0.07
Type of diabetes			Not entered ($P > 0.5$)	
Type 1	Reference			
Type 2	0.89 (0.31–2.52)	0.83		
Maternal ethnic origin				
White	Reference		Reference	
Nonwhite	2.84 (1.00–8.08)	0.0498	3.38 (1.19–9.61)	0.02
Index of deprivation			Not entered ($P > 0.5$)	
Tertile 1 (most deprived)	1.10 (0.49–2.50)	0.81		
Tertile 2	Reference	(0.96)		
Tertile 3 (least deprived)	1.12 (0.50–2.51)	0.78		
Prepregnancy nephropathy				
Yes	2.76 (1.08–7.10)	0.03	3.37 (1.23–9.26)	0.02
No	Reference		Reference	
Prepregnancy neuropathy				
Yes	1.35 (0.20–9.05)	0.76	Not entered ($P > 0.5$)	
No	Reference			
Prepregnancy retinopathy			Not entered ($P > 0.5$)	
Yes	1.23 (0.55–2.78)	0.62		
No	Reference			
Year of delivery (year)	0.87 (0.78–0.96)	0.007	0.84 (0.76–0.94)	0.002
Duration of diabetes (years)	0.97 (0.93–1.02)	0.28	Eliminated ($P > 0.1$)	
Maternal age (years)	0.98 (0.92–1.03)	0.39	Eliminated ($P > 0.1$)	
Potentially modifiable variable				
Smoked during pregnancy				
Yes	1.24 (0.55–2.76)	0.61	Not entered ($P > 0.5$)	
No	Reference			
Preconception folic acid			Not entered ($P > 0.5$)	
Yes	1.14 (0.56–2.32)	0.72		
No	Reference			
First antenatal visit <10 weeks			Eliminated ($P > 0.1$)	
Yes	0.66 (0.32–1.35)	0.25		
No	Reference			
Attended preconception care				
Yes	1.76 (0.88–3.53)	0.11	1.83 (0.92–3.64)	0.09
No	Reference		Reference	
Interpregnancy interval (years)	0.93 (0.74–1.17)	0.55	Not entered ($P > 0.5$)	
BMI (kg/m^2)	0.95 (0.88–1.03)	0.21	Eliminated ($P > 0.1$)	
Periconception A1C (mmol/mol)		(0.0005)		(0.003)
<47 mmol/mol (<6.5%)	0.94 (0.80–1.11)	0.47	0.94 (0.79–1.11)	0.45
≥47 mmol/mol (≥6.5%)	1.03 (1.01–1.04)	0.0001	1.03 (1.01–1.04)	0.0008

CA, congenital anomaly.

SHR 1.83 [95% CI 0.96–3.47], $P = 0.07$) (Table 3).

To establish the relative importance of contemporaneous compared with historical A1C, additional analyses included periconception A1C in the previous pregnancy. There was no crude association between the first pregnancy A1C and the risk of a serious adverse outcome in the second (A1C <47 mmol/mol: SHR 1.13 [95% CI 0.92–1.40], $P = 0.25$); A1C ≥47mmo/mol: SHR 1.00 [0.99–1.02], $P = 0.46$). After adjusting for other model variables; however, there was some suggestion of a *lower* conditional risk for increasing values of A1C ≥47 mmol/mol, although the effect was outside the nominal significance level (A1C <47 mmol/mol: aSHR 1.15 [95% CI 0.9–1.44], $P = 0.24$; A1C ≥47 mmol/mol: aSHR 0.98 [0.95–1.00], $P = 0.054$).

The absolute risks of a serious adverse outcome in the second pregnancy, stratified by periconception A1C and first pregnancy outcome, are reported in Table 4.

CONCLUSIONS

Principal Findings

This study describes the preparation for and outcome of the first and second pregnancy in women with preexisting diabetes. The overall risk of a serious adverse outcome fell from 30% in the first pregnancy to 17% in the second, predominately due to a fall from 34 to 12% in the probability of spontaneous fetal death.

Women who experienced a serious adverse outcome in their first pregnancy were more than twice as likely to experience another serious adverse outcome in their second. A third of this was explained by persistent risk factors such as ethnicity and periconception A1C.

A greater proportion of women achieved a favorable periconception A1C and consumed folic acid supplements before their second pregnancy than before their first, although both remained minority behaviors. There were no differences in the proportion of women who attended preconception care or their first antenatal visit before 10 weeks. Achieving a periconception A1C <53 mmol/mol, prepregnancy folic acid supplement use, and attendance of preconception care were all more likely in the second pregnancy if they had occurred in the first, but there was no evidence that an adverse outcome in the first pregnancy was associated with preparation for the second.

Strengths and Limitations

This study benefitted from the North of England's unique range of population-based registers. The NorDIP is England's longest-running uninterrupted audit of pregnancies in women with preexisting diabetes and one of few registers that supports the study of repeated pregnancies in the same mother. Detailed information is gathered before and during pregnancy on a range of clinical and sociodemographic variables. Cases of congenital anomaly were identified by the U.K.'s longest-running regional register of congenital anomalies, which receives information, regardless of pregnancy outcome, from multiple sources up to 12 years after birth. The PMS has been collecting information on all stillbirths and infant deaths within the region since 1981 and cross-references with mortality records from the U.K. Office for National Statistics. The results of this study are likely to be generalizable to any predominately white population with similar standards of peripregnancy care.

Several limitations result from low statistical power. Owing to small numbers with each outcome specifically, multivariable analyses was used to examine the composite variable, serious adverse pregnancy outcome, despite possible heterogeneity. Only associations that apply to all constituent outcomes are likely to have been detected. The small numbers with type 2 diabetes ($n = 25$) prohibited examination of effect modification by diabetes type, although previous studies have found negligible evidence of such differences (7,8,16). Several important exposures also had low numbers. Despite significant associations, the sample was too small to stratify the second pregnancy absolute risks by ethnicity or prepregnancy nephropathy. Lack of statistical significance should not be considered evidence of no effect, as demonstrated by the biologically implausible disagreement in the influence of smoking between the first and second pregnancies (Tables 2 and 3). Similarly, the interpregnancy differences in the contributions of neuropathy and nephropathy are consistent with sampling variation. Data were more likely to be missing in women who experienced serious adverse outcomes. Multivariate imputation by chained equations was used to reduce any consequent bias but cannot account for unknown predictors of missingness. Individuals with mild microvascular complications may not have been ascertained because only "clinically diagnosed" cases (regardless of method) were recorded. Other potentially relevant exposures, most notably medication use, were not collected.

It is unlikely that all pregnancies ending in miscarriage were ascertained. Losses before 6 weeks are typically undetected (24), whereas later losses may be recognized but not reported. The earliest miscarriage in a registered pregnancy occurred at 6 weeks, by which

Table 4—Absolute risk of serious adverse outcome in the second pregnancy, stratified by outcome in the first pregnancy and periconception A1C

Outcome in first pregnancy	Periconception A1C		Percentage risk of serious adverse outcome in the second pregnancy (95% CI)
	mmol/mol	DCCT %	
Live birth and infant alive at age 1 year	*Total prevalence →*		*12.4 (7.6–18.7)*
	<53	<7.0	6.5 (2.1–10.9)
	53–63	7.0–7.9	8.3 (3.6–13.0)
	64–74	8.0–8.9	11.1 (5.8–16.4)
	75–85	9.0–9.9	14.9 (8.2–21.6)
	≥86	≥10	25.9 (11.8–40.1)
Spontaneous fetal death, infant death, or congenital anomaly	*Total prevalence →*		*26.9 (16.8–39.1)*
	<53	<7.0	15.2 (5.3–25.0)
	53–63	7.0–7.9	18.9 (8.6–29.2)
	64–74	8.0–8.9	24.3 (13.3–35.2)
	75–85	9.0–9.9	31.1 (18.6–43.6)
	≥86	≥10	47.3 (28.0–66.6)

DCCT, Diabetes Control and Complications Trial.

time a quarter of the women had attended their first antenatal appointment. Kaplan-Meier scales the denominator to account for different entry and exit times (25); thus, this study should provide accurate estimates of the risks of spontaneous intrauterine death from 6 weeks onwards. The total risk of miscarriage from conception, however, may be underestimated.

Approximately half of women in the North of England with preexisting diabetes do not seek preconception care (16). For these women, we used first trimester A1C values to approximate preconception A1C. Although highly correlated, this will have increased variation and biased our estimates toward the null. A1C provides an incomplete profile of overall glycemic control because it provides no information on potentially salient glycemic excursions or hypoglycemic episodes (26). Unfortunately, continuous glucose monitoring is not yet routinely available in the U.K.

Comparison With Other Studies

This study is the first to explore the risk of recurrence of adverse pregnancy outcomes in women with preexisting diabetes and to describe the absolute risks in first and second pregnancies specifically. Nevertheless, there are analogous observations in the general population. The RRs of recurrence for both congenital anomalies (at 1.55 [95% CI 0.40–5.99]) and fetal or infant death (at 2.45 [0.96–6.26]), for example, were highly consistent with the doubling of risk in the general population (3–5). Across both pregnancies, the prevalence of congenital anomaly (8.0% [95% CI 5.4–10.5]), stillbirth (3.4% [1.7–5.1]), and infant death (1.2% (<0.1–2.4]) was consistent with previous observations in larger samples from the same population (7.7% [95% CI 6.5–9.1], 2.7% [1.9–3.6], and 0.7% [0.3–1.2], respectively) (7,8). The proportion of pregnancies ending in miscarriages (11.4% [8.4–14.3]) was consistent with the 5–20% that is typically reported in women with diabetes (27–29).

Comparisons of the change in risk between pregnancies are more problematic, due to large differences in the profiles of primiparous and multiparous women (30). This likely explains the discrepancy between the current study and a previous cross-sectional analysis, where no association was found between parity and risk of stillbirth (8). Even in longitudinal studies, the attributable risk of parity may be masked by changes in other risk factors such as maternal age and BMI (31). Nevertheless, it is broadly recognized that the prevalence of a serious adverse pregnancy is greater among first pregnancies. In the general population, the Flenady et al. (32) meta-analysis estimated the risk of stillbirth as 1.40 (95% CI 1.33–1.42) times higher among primiparous women than multiparous. Though smaller than we observed (RR for primiparity vs. multiparity 4.02 [95% CI 1.15–14.04]), the difference is consistent with sampling variation (P = 0.10). This was similar for miscarriage, with the crude RR for the current study (3.17 [95% CI 1.70–5.90]) being higher, but not significantly (P = 0.07), than in a U.K. sample of women of reproductive age (1.75 [1.42–2.14], comparing first and second pregnancies). We did not find a relationship between pregnancy order and the risk of congenital anomaly, despite it being observed in the general population (33). This may reflect our modest sample size or the aforementioned problems comparing longitudinal and cross-sectional data.

Implications and Conclusions

Women with preexisting diabetes continue to experience very high risks of serious adverse pregnancy outcomes. In the first pregnancy, 30.5% (95% CI 24.4–37.0) were affected. In the second, as in the general population, outcomes were more favorable, especially among those who had not experienced previous adverse outcome (12.4% [7.6–18.7]). This was not explained by changes in the known risk factors and may instead reflect constitutionally lower risks of, for example, preterm delivery, preeclampsia, and intrauterine growth restriction (34–36).

Among those whose first pregnancy was affected by serious adverse outcome, the risk in the second remained very high (26.9% [95% CI 16.8–39.1]). A third of this was explained by persistent and known exposures. Adverse outcomes were more common in both pregnancies among women from minority ethnic groups, consistent with previous observations (37). This may reflect genetic factors or enduring environmental or behavioral influences. Preparation for pregnancy is particularly poor in nonwhite women in the North of England (16), indicating they may require alternative methods of support such as community-based approaches (38).

We observed a familiar J-shaped association between periconception A1C and adverse outcome (39), with the risk increasing by 2–3% per mmol/mol ≥47 mmol/mol. This reiterates the benefits of good, though not overly strict, prepregnancy glycemic control (8). Notably, although periconception A1C levels were correlated across both pregnancies, only current values were associated with outcome, suggesting a causal and reversible association. However, after adjusting for current values, there was suggestion of a protective effect of A1C in the previous pregnancy, indicating the highest risk may occur in women whose glycemic control deteriorates substantially between pregnancies.

Preparation for pregnancy among our sample was poor. Only a quarter managed the preconception A1C target or took folic acid supplements before their first pregnancy, and only just over half attended preconception care or attended their first antenatal appointment before 10 weeks. Although favorable preparation in the first pregnancy was broadly predictive of repeat behavior in the second, this exposes a disheartening converse. Women whose first pregnancy ended in a serious adverse pregnancy outcome did not prepare any differently for their subsequent pregnancy. With an average interpregnancy interval of only 1 year, there is a narrow window for intervention. Because many of the circumstances that inhibited preparation for the first pregnancy likely remain, this motivates a change in approach such as providing intensive postnatal support covering various aspects of care, including control, contraception, and well-being (38). Such interventions, however, would have to be carefully balanced against the distressing consequences of discussing future pregnancies during a period of grief (40). Regardless, because preconception care was equally poor across both pregnancies, changes or greater choice may be needed in style and setting (38). The barriers to improved pregnancy preparation are multifaceted and complex (41), but further progress is urgently needed to reduce the risk of recurrent tragedy.

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Author Contributions. P.W.G.T. performed the primary analysis and drafted the manuscript. P.W.G.T., R.W.B., and R.B. designed the study. R.W.B. acquired the data. R.W.B. and R.B. conceived the project. S.P. prepared the data and performed preliminary analyses. All authors contributed to interpretation of the data, critically reviewed the manuscript, and approved the final version of the manuscript before submission. P.W.G.T. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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2·7·6 Supplementary material

SUPPLEMENTARY DATA

Supplementary Table 1. Descriptive statistics for study participants (continuous variables)

Continuous variable	First pregnancy (N=220)			Second pregnancy (N=220)		
	n	Range	Median (IQR)	n	Range	Median (IQR)
Gestation at first antenatal visit (weeks)	213	1-34	9 (7-11)	219	3-22	8 (6-11)
Gestation at delivery (weeks)	220	4-40	36 (32-38)	220	6-41	37 (35-38)
Duration of diabetes (years)	219	1-27	9 (4-15)	219	2-30	12 (7-18)
Maternal age at delivery (years)	220	15-40	26 (21-30)	220	17-46	29 (24-33)
Maternal body mass index (kg/m^2)	157	17-60	26 (23-29)	172	18-58	26 (23-30)
Peri-conception A1C (mmol/mol)	187	25-187	65 (54-83)	190	29-143	62 (51-77)
Peri-conception A1C (%)	187	4.4-19.3	8.1 (7.1-9.7)	190	4.8-15.2	7.8 (6.8-9.2)
Both pregnancies (N=220)						
Inter-pregnancy interval (years)	220	<0.1-10.1	1.8 (0.9-3.0)			

SUPPLEMENTARY DATA

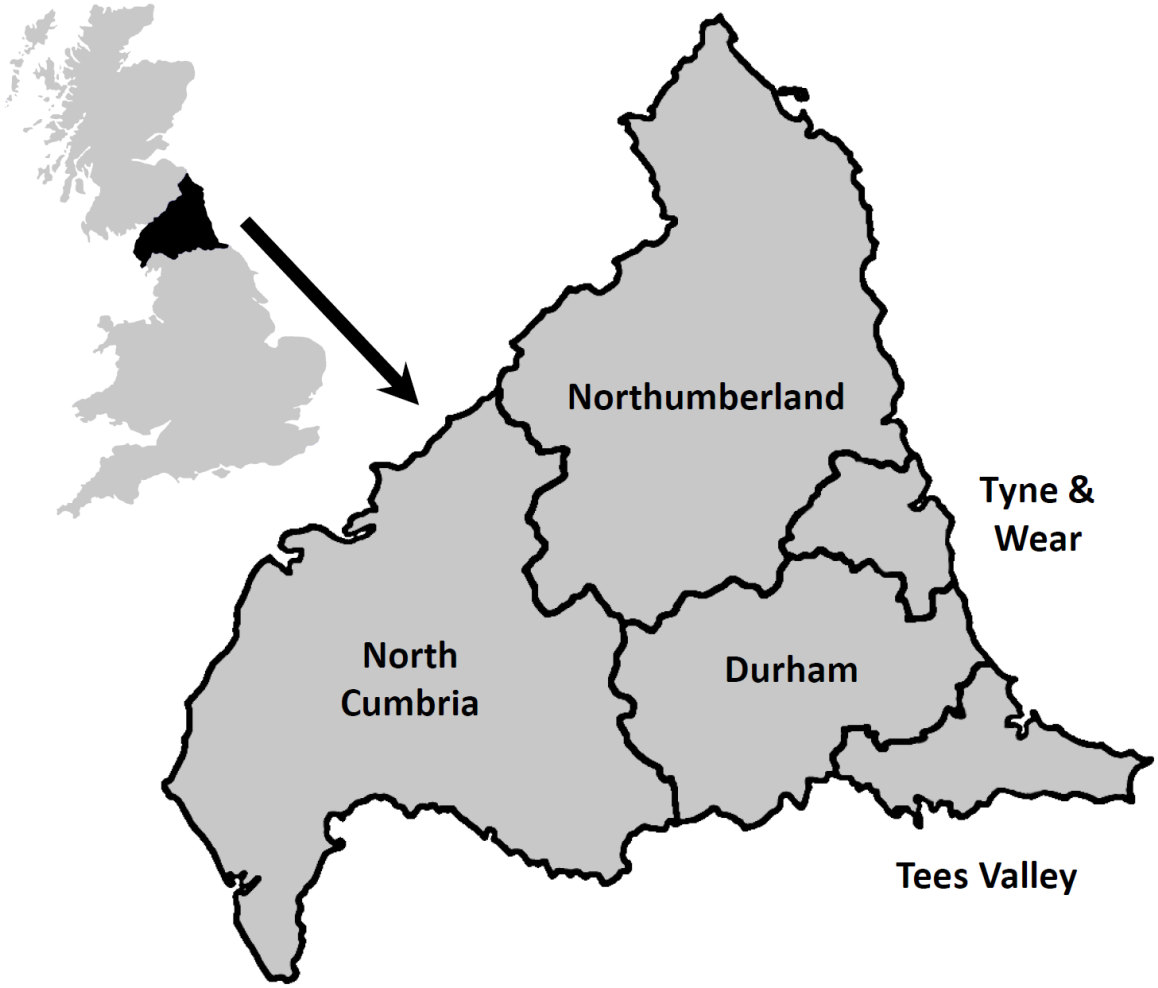
Supplementary Table 2. Descriptive statistics for study participants (categorical variables)

Categorical variable	First pregnancy (N=220)		Second pregnancy (N=220)	
	n	%	n	%
Index of Deprivation				
Tertile 1 (most deprived)	69	31.4	69	31.4
Tertile 2	72	32.7	73	33.2
Tertile 3 (least deprived)	79	35.9	78	35.5
Pre-pregnancy nephropathy				
Yes	7	3.2	10	4.6
No	213	96.8	210	95.5
Pre-pregnancy neuropathy				
Yes	1	0.5	4	1.8
No	219	99.6	216	98.2
Pre-pregnancy retinopathy				
Yes	26	11.8	47	73.6
No	186	84.6	162	21.4
Missing	*8*	*3.6*	*11*	*5.0*
Smoked during pregnancy				
Yes	46	20.9	47	21.4
No	152	69.1	156	70.9
Missing	*22*	*10.0*	*17*	*7.7*
Pre-conception folic acid				
Yes	51	23.2	89	40.5
No	138	62.7	117	53.2
Missing	*31*	*14.1*	*14*	*6.4*
First antenatal visit < 10 weeks				
Yes	131	59.6	145	65.9
No	82	37.3	74	33.6
Missing	*7*	*3.2*	*1*	*0.5*
Attended pre-conception care				
Yes	119	54.1	122	55.5
No	101	45.9	98	44.6
Year of delivery*				
1996-1999	79	35.9	30	13.6
2000-2004	105	47.7	77	35.0
2005-2008	36	16.4	113	51.4
Both pregnancies (N=220)				
Diabetes type				
Type 1	195	88.6		
Type 2	25	11.4		
Ethnicity				
White	209	95.0		
Non-white	11	5.0		

*Year of delivery was analyzed as a continuous variable, but is presented in categories to aid comprehension

SUPPLEMENTARY DATA

Supplementary Figure 1. The North of England, UK



Tennant *et al* 2015 remains the only study of the recurrence of serious adverse pregnancy outcomes in women with pre-existing diabetes and the only to examine the influence - or lack therefore - of previous adverse pregnancy outcome on preparation for pregnancy. This continued novelty can be predominantly attributed to the unique quality and nature of the data collected by the NorDIP. Although the newly-launched National Pregnancy in Diabetes Audit (NPID) will offer a larger sample to those interested in preparatory behaviours and adverse outcomes, it will be several years until similar longitudinal study will be possible.[418] This is important given the stark difference in the apparent influence of parity when examined using a cross-sectional approach - as in Bell *et al* 2012 and Tennant *et al* 2013. Without paired data, the reduction in the risk between the first and second pregnancy is completely obscured by differences in the profile of nulliparous and multiparous women.[3,5]

The study's biggest weakness comes from the reduced sample size, even when compared with previous NorDIP studies. Only a small minority of the total pregnancies notified to the register achieved the necessary criteria of having delivered a first and second successive pregnancy during the study period. Though still sufficient to describe the absolute risks of most summary outcomes – such as congenital anomaly and stillbirth - the numbers were too small for any further subdivision. Regardless, even these were inadequate with respect to the primary outcome, which was not the risk of an adverse outcome *per se*, but of *recurrent* adverse outcome. To maximise the available power, there was no alternative but to create a single composite outcome of 'serious adverse pregnancy outcome' that included miscarriages. This seemed reasonable given the NorDIP collects information for all booked pregnancies in women with diabetes, regardless of gestational age, and given the similarity in risk factors.[419-421]

Unfortunately, observational studies of miscarriages are complicated by the fact that the total denominator – i.e. the total number of conceptions - cannot be known.[244] Since the NorDIP relies on routine data collection, the only recognised miscarriages are thus restricted entirely to those that occur in women who have booked within the region. The consequence is that any marker of early booking will present as a spurious predictor of miscarriage. In a similar manner, any marker of elective termination of pregnancy will appear protective of spontaneous fetal loss by obscuring those pregnancies that would have ended in miscarriage or stillbirth had the termination not occurred. To address this, I used time-to-event methods, which can be used to account for changing windows of observation.[422] Although no formal proof has been provided, my own prior experience indicates that this produces near-identical results to the 'fetuses-at-risk' method.[423,424] Competing-risks regression thus provides an extension of the non-parametric fetuses-at-risk approach to examine predictors of adverse

outcomes in pregnancy, accounting for variable periods under observation. With this method, attending the first antenatal appointment before 10 weeks was not predictive of adverse outcome in the data presented by Tennant *et al* 2015. In fact, early booking was most consistent with a 33% reduction in the prevalence of serious adverse pregnancy outcome in the second pregnancy, although the study was too small to distinguish this from random sampling variation.

Unfortunately, I was not able to generate estimates of the absolute risks from marginal values of the competing-risks model. To derive stratified estimates of serious adverse pregnancy outcome in the second pregnancy I therefore used a simplified logistic regression model. Although the two-variable logistic and competing-risks models produced similar ratios, the former was not technically robust to the aforementioned sampling bias.

The same composite peri-conception HbA_{1c} variable was created and used for Tennant *et al* 2015 as in previous studies. On this occasion however I performed additional imputation because those women with repeat adverse outcomes included a disproportionately high number from the ≈13% who were missing both pre-conception *and* first-trimester data (and had previously hence been excluded from all multivariable analyses). With these cases excluded, peri-conception HbA_{1c} appeared to explain a larger proportion of the variance than when they were included. Although more likely to belong to a minority ethnic group, not attend for preconception care, and book late for their pregnancy, these women experienced an even greater prevalence of recurrent adverse pregnancy outcome than predicted. Given the correlation with other socio-behavioural factors, it seems likely that these may reflect other relevant but unmeasured environmental risk factors, such as diet and alcohol or substance use.[425]

CHAPTER 3: DISCUSSION

3·1 PRINCIPAL FINDINGS

This research examined the impact of maternal pre-pregnancy obesity and maternal pre-existing diabetes on the risks of serious adverse pregnancy outcomes. Obesity and diabetes were both found to be associated with significantly increased risks of congenital anomaly, stillbirth, and infant death. The effects of obesity were generally more modest than diabetes and were not apparent in women with the condition, suggesting that (at least some of) the association may act through diabetes or similar metabolic disturbances. None of maternal age, smoking, ethnicity, or socioeconomic circumstances appeared to explain the effects of obesity on either congenital anomaly or fetal and infant death.

In women with pre-existing diabetes, average peri-conception HbA_{1c} was strongly associated with the risks of congenital anomaly, stillbirth, and infant death, although there was some evidence of non-linearity, with the lowest risks occurring in women with peri-conception HbA_{1c} levels around 45-49mmol/mol (6.3-6.9%). The association between diabetes and the risk of congenital anomaly was consistent across almost all anomaly groups and subtypes, suggesting it may be universally teratogenic. Similarly, the effect of diabetes on the risk of stillbirth and infant death appears to act uniformly throughout pregnancy and is not restricted to late stillbirths.

The effect of HbA_{1c} on birth weight in women with diabetes reverses during pregnancy such that larger size is associated with lower peri-conception HbA_{1c} followed by higher third-trimester HbA_{1c}. Since no such reversal was observed for stillbirth, a pattern of initial growth restriction followed by late overgrowth may confer the highest risk of late pregnancy loss.

The total prevalence of serious adverse pregnancy outcome in women with diabetes is twice as high in first pregnancies than in second pregnancies, although adverse outcome in their first pregnancy is associated with an increased risk in the second. Despite this, experience of a serious adverse pregnancy outcome in a first pregnancy is not associated with any change in preparatory behaviour in those women who subsequently have a second pregnancy.

3·2 STRENGTHS & LIMITATIONS

3·2·1 The Regional Maternity Survey Office

Every article in this submission benefitted from the use of high-quality, population-based data from the North of England. Established by visionary clinical and research staff in the 1980s-1990s, the region's unique confluence of maternal and perinatal registers has long served as an exemplar of public health surveillance in the UK. Housed on a linked database within the Regional Maternity Survey Office (RMSO), registers like the NorCAS, NorDIP, and PMS benefited from the region's long history of clinical collaboration between maternity, neonatal, and paediatric units, and local data ownership. Unfortunately, this regional model of data collection is not favoured by Public Health England (PHE), and the RMSO will cease operating from 1st April 2016. Information on future cases of congenital anomaly and future pregnancies affected by pre-existing diabetes will be notified to the NCARDRS and NPID respectively, while statutory details of stillbirths and infant deaths will be collected by ONS.

The NorCAS went to great lengths to maximise ascertainment. Cases could include any pregnancy ending at or after 20 weeks gestation, or at any gestation for terminations of pregnancy following prenatal diagnosis. Notifications came from a large variety of sources, including antenatal ultrasound, fetal medicine, cytogenetic laboratories, the regional cardiology centre, pathology and paediatric surgery.[426] Postnatal diagnoses were included at any age up to aged 12 years. These approaches ensured that the NorCAS and the other former BINOCAR registers identified around twice the number of cases of congenital anomaly than light-touch surveillance approaches, such as the defunct National Congenital Anomaly System.[427] On the other hand, the NorCAS ensured all cases were clinically-relevant, by routinely excluded all cases defined as minor by the EUROCAT.

The PMS was a collaborative survey that received information from all maternity units in the North of England. Each unit was overseen by a small review team and an elected convenor. Data collection occurred in two phases, with an initial rapid notification on identification of a death; followed by additional information governed by the Centre for Maternal and Child Enquiries (CMACE). When launched in 1981-82, the register received information on 99% of registered deaths in the region. By the years of Tennant *et al* 2011 and Tennant *et al* 2013, cross-linking with ONS records made the ascertainment effectively complete. The PMS categorised the cause of death using an obstetric and a clinicopathological classification system. Like all current schemes for categorising cause of perinatal death, these were relatively uninformative, hence neither Tennant *et al* 2011 nor Tennant *et al* 2013 were able to examine cause of death in any significant detail. The forthcoming International statistical Classification of Diseases and related health problems (ICD) Perinatal Mortality edition (ICD-

PM) is hoped to provide a more meaningful approach to recording the causes of fetal and infant death, but is still under development.[428]

The NorDIP was the UKs longest-running uninterrupted survey of pregnant women with pre-existing diabetes. All women with pre-existing diabetes who presented at any of the region's maternity units were invited to participate. Notification was coordinated within each unit by an elected representative, and each unit received annual feedback. Commenting on the NorDIP's performance during 1996-2004, the steering group stated they were, '*confident that case ascertainment… remained high, and (that) case definition and reporting methods were unchanged throughout the study period*'.[205] Although superseded in size by the NPID, the NorDIP was noteworthy for the quality and detail of the data collected. The downside – as with most registry data - was that only routine data were collected. Hence while several measures of HbA_{1c} were recorded, it did not collect bespoke information such as continuous glucose monitoring. There was also no information on medication use, which may have explained some of the observed effects of retinopathy and nephropathy. Unlike the NorCAS and PMS, the NorDIP also requires consent for inclusion. This may distort the sample towards English-speaking women from more affluent socio-economic circumstances.[429] Since these women typically have lower risk profiles, the summary risks in all the NorDIP studies may be underestimates.

3·2·2 The North of England

The North of England is the commonly-preferred name for the former NHS administrative region once overseen by the Newcastle Hospital Board (1947-1974) and the Northern Regional Health Authority (1974-1996). It is a geographically-defined area that includes the counties of North Cumbria, Northumberland, Tyne and Wear, Durham, Darlington, and Teesside (see **Tennant *et al* 2015 Supplementary Figure 1**, p141)

From an epidemiological perspective, the region benefits from comprising of a mix of urban and rural settings with a large degree of socio-economic variation, although a larger proportion live in deprived areas than in England as a whole.[430] The stability and homogeneity of the population is a significant aid to rare outcome research, as it facilitates pooling data over long time periods. This is especially important given the region's relatively small population (approximately 3 million) and the modest number of births per year (30,000-35,000). Despite many years of data collection, most of the studies therefore experienced issues with low statistical power. Furthermore, pooling data over a long time period is not without consequences. The results of the longer-running NorDIP studies for example may not theoretically be so relevant to current practice. Having said this, when year of birth was

explicitly examined in relation to the association between diabetes and stillbirth, there was no apparent period effect.[5]

Although beneficial from the perspective of minimising confounding, the homogeneity of the population prevented any meaningful examination of the potentially vital role of ethnicity in the pathologies of obesity and diabetes. Tennant *et al* 2015 found a strong effect of ethnicity on the composite serious adverse pregnancy outcome, but no similar effects were found when looking at individual outcomes. Although the lack of ethnic diversity limits the generalisability to similar white populations in Northern Europe and North America, this limitation applies to most studies in this research area.

3·2·3 Congenital anomaly coding

Comparisons between studies of congenital anomalies are complicated by the continued absence of a unified approach to anomaly classification and coding. Although ICD-9 and ICD-10 offer a rudimentary schema for classifying congenital anomalies, neither of these are satisfactory for detailed epidemiological study, due primarily to the inclusion of minor congenital anomalies, a lack of discrimination between subtypes, and an outdating assignment of organ system (ICD-10 for example classifies diaphragmatic hernia to be a musculo-skeletal anomaly).[231] In the USA, this historically led to a long running fragmentation between registers that used the traditional ICD-9 clinical modification (ICD-9-CM) and those that used a version of the ICD-9 modified by the CDC and British Paediatric Association. This may be improved by the recent introduction of the ICD-10-CM,[431] or it may cause further fragmentation if surveillance systems are slow to change to the new criteria. The terminal consequence of such coding inconsistencies is there are rarely two studies, produced by two different research groups around the world, that adopt the same approach to classification and that can therefore be compared directly.

Among studies conducted within Europe, the situation is greatly improved by the widespread use of the EUROCAT guidelines; which informed the reporting of cases in both Rankin *et al* 2010 and Bell *et al* 2012. These guidelines do not however provide a truly uniform framework for comparison, due to the unregulated issue of coding non-isolated anomalies. Though a quarter of cases of congenital anomalies do not occur in isolation, there is no standard approach to classifying these cases. Most studies analyse on a per-anomaly basis, as was the approach used by Rankin *et al* 2010, the downside being that cases are effectively double-counted. Isolated and non-isolated cases may also have different aetiologies; hence some studies often split the analysis into two groups. Although this has appeal in its simplicity, it also erodes the analytic power, and produces groups that are unrepresentative of the true clinical profile of each condition.

In examining survival of children with congenital anomalies, I employed a 'hierarchical' approach, in which diagnoses were assigned iteratively according to the pattern of anomalies.[363] First proposed by Wellesley *et al* 2005,[432] this method maximises the sample size whilst maintaining the homogeneity of each group and subtype. Bell *et al* 2012 used a further-improved algorithm, the primary downside of which was the substantial workload, and the requirement for clinical expertise.

3·2·4 Body mass index

All the studies in this submission relied on BMI to estimate maternal pre-pregnancy adiposity and – in the cases of Rankin *et al* 2010 and Tennant *et al* 2011 – to define the obesity risk group. Though common in Epidemiological endeavour, and ubiquitous in studies using routinely collected data, this presented a number of issues.

Foremost among these is the simple question of whether general adiposity is truly the variable of interest. Since much of the effect of obesity on diabetes and cardiovascular risk appears to act through abdominal adipose,[164,433] then it seems reasonable to suspect that a more centrally-weighted measure might have served as a better predictor of serious adverse pregnancy. Despite its apparent utility, maternal waist circumference has received very limited attention in pregnancy,[434] probably due to the distorting influence of uterine volume in later pregnancy. Though pre-conception measurement might be possible in select populations, it is profoundly impractical for studies in the general population. For a similar reason, although all the studies in this submission were technically interested in pre-pregnancy obesity this could only be approximated from BMI at booking, which may include some instances of self-report.

Even as a measure of general adiposity, BMI has issues. The relationship between BMI and total adiposity for example, is known to vary between different ethnic groups.[58] This is exaggerated by differences in the proportion of abdominal adiposity, and in the degree of metabolic dysfunction for apparently similar distributions.[180] Though less of a problem in the predominantly-white North of England, this clearly limits the generalisability.

Rankin *et al* 2010 and Tennant *et al* 2011 found non-linear associations between BMI and the risks of congenital anomaly and fetal and infant death respectively. Although I selected analytical methods that would not be adversely affected, it suggests competing causal mechanisms may be involved. Observational studies often observe the lowest risk of mortality among overweight participants, most likely due to competing comorbidities in those of lower weight.[435,436] A more precise measure of the underlying trait such as abdominal adiposity might be more robust to such artifacts. Alternatively, further information on the

determinants of adiposity, in particular diet and physical activity, might help delineate the specific mechanisms involved.

3·2·5 Glycated haemoglobin

HbA_{1c} offers a convenient solution to the challenge of estimating glucose concentration. Unlike the hassle of a FPG test or the time demands of an OGTT, an HbA_{1c} test provides a one-stop, cross-sectional proxy of the average blood glucose concentration over the previous three months.[437] Though not strictly a measure of blood glucose concentration itself, the standardised values are so strongly correlated with glycaemic response that it is now widely accepted and permitted as an alternative means to diagnose diabetes.[114,120]

There are however some significant downsides to this convenience. As an average value, HbA_{1c} provides limited information on the degree or extent of short-term variability.[438] An individual with diabetes may hence experience substantial glycaemic excursions, yet have apparently reasonable control when judged on their HbA_{1c} alone.[439] Although Bell *et al* 2012, Glinianaia *et al* 2012, and Tennant *et al* 2013 demonstrate the utility of HbA_{1c} as a proxy exposure of average glucose control, and the importance of this average on pregnancy outcome, the unmeasured patterns of variability have been shown to independently influence fetal growth[440,441] In a similar respect, HbA_{1c} also provides very limited information on the risk of hypoglycaemic episodes,[442] which may explain the J-shaped association between HbA_{1c} and the risk of fetal death observed in Tennant *et al* 2013.

The utility of HbA_{1c} during pregnancy is further complicated by changes in erythocryte volume during gestation.[393] Pre-conception HbA_{1c} values are thus generally higher than first trimester values, which in turn are higher than values in the third trimester.[393] Standardised HbA_{1c} values during pregnancy cannot therefore be interpreted without additional information on the mother's gestational age. In the absence of published norms, it is hence unsurprising that HbA_{1c} is not yet recommended as a means to diagnose gestational diabetes.[114] Despite this, the relative distribution of even third-trimester HbA_{1c} can be potentially highly informative, as demonstrated in Glinianaia *et al* 2012.

3·2·6 Model selection

In addition to exploring HbA_{1c}, the four diabetes publications also examined a range of other clinical and socio-demographic variables that were collected by the NorDIP. This led to some interesting hypothesis-generating results, such as the associations between neuropathy and congenital anomaly and between folic acid and fetal and infant death in normally-formed offspring. The sheer quantity of model variables however also presented an analytical challenge. Simultaneous conditioning for all potentially-relevant variables risked problems of

over-adjustment,[443] as happened in Mohsin *et al* 2006.[341] My remedy was to permit only a subset of variables into the final multivariable model, selected using a backwards elimination approach. Variables with a univariate p-value for association below 0.5 were entered into the model and then removed iteratively (by descending p-value) until all remaining variables had p-values below 0.1. Although strictly data-driven, I was comfortable with the theoretical basis of this approach since all variables had been selected *a priori* according to their biological plausibility. Furthermore, there were no pronounced intermediate variables, lest for the serial measures of HbA_{1c}, which were interpreted accordingly.

Though not uncommon in Epidemiological endeavour, elimination approaches like this are not without problems.[444] Foremost, they are known to produce models that are overly sample-specific and overestimate the true precision of each estimate.[444] More pertinently, the use of p-value criteria, makes the process susceptible to all the problems of hypothesis-testing.[444] Important but rare exposures are therefore unlikely to be detected. In the North of England this includes belonging to a minority ethnic group, which was lost from the multivariable model of fetal and infant death, despite a univariate OR of 1.55 (95% CI: 0.60 to 3.98). For this reason, I selected a less stringent p-value criterion of 0.1, although in hindsight this was still probably too strict, given the rarity of the outcomes under test. A combined p-value and effect size criterion retaining, for example, all variables with a p-value for association below 0.2 or an OR above 2.0 might have been more appropriate.

3·2·7 Missing data

As a consequence of relying on routinely collected information, all six studies in this portfolio experienced issues with missing data. Maternal BMI was missing for almost a quarter of pregnancies in the maternity dataset used for Rankin *et al* 2010 and Tennant *et al* 2011, and pre-conception HbA_{1c} was missing in more than half of pregnancies complicated with pre-existing diabetes. I employed various methods to manage this, ranging from simply excluding all those with missing BMI, to conducting the analysis *de novo* on multivariate imputed data. After long discussion, the research team behind Bell *et al* 2012, Glinianaia *et al* 2012, and Tennant *et al* 2013 favoured simplicity by creating a composite peri-conception HbA_{1c} variable, an approach that - in hindsight - may have caused some error, and still resulted in excluding 13% of the sample with neither a pre-conception nor first-trimester value. In Tennant *et al* 2015, those with missing pre-conception and first-trimester HbA_{1c} data included a disproportionately large percentage with successive adverse pregnancy outcomes, suggesting their exclusion from the earlier studies was not appropriate.

Given the extent of missing data, all six articles would probably have benefitted from the multivariate imputation by chained equations (MICE) approach used in Tennant *et al* 2015,

which makes maximum use of the available data and is generally less susceptible to bias than compete case analyses.[445] Unfortunately, this method was neither widely recognised nor routinely implemented in software during the preparation of most of the papers in this submission. In future, I plan to routinely consider MICE (or similar multivariate approaches) where a considerable proportion of the data are missing (≥10%), following contemporary recommendations to scrutinise the structure and influence of the missing data, and performing post hoc checks on imputation models.[446] Interpretation at individual-level

Each of Bell *et al* 2012, Glinianaia *et al* 2012, Tennant *et al* 2013, and Tennant *et al* 2015 included a table reporting the absolute risk of each adverse outcome by peri-conception and/or third trimester HbA_{1c}. The rational was to provide clear and interpretable information that could help with pre-conception planning and decision-making. In Bell *et al* 2012, for example, **Table 5** (p78) clearly shows that the risk of congenital anomaly is over three-times smaller (1 in 33) at the current NICE pre-conception HbA_{1c} target (48mmol/mol) than at the level beyond which pregnancy is discouraged (86mmol/mol) (1 in 9).

Whether an individual woman can reduce their own corresponding risk with a similar change in HbA_{1c} however is impossible to know. This is not only because of the unproven condition that the association is both causal and reversible, but because of the additional heterogeneity operating between individuals. Epidemiology can provide substantial information about the causes of health and disease at the population-level, but prediction at the individual-level requires a much higher degree of explanatory power.[447] The data should therefore only be used as an aid to what is a complex and individual decision-making process, rather than form the basis of prescriptive criteria.

3·3 CAUSAL CONSIDERATIONS

3·3·1 The challenge

Current practice in medical research asserts that the quality of evidence provided by any individual study can be judged from its position in the 'hierarchy of evidence'.[448] Initially proposed by the Evidence-Based Medicine Working Group,[449] this notion – now firmly rooted into routine quality tools such as the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system - places observational studies above expert opinion and case reports but below randomised controlled trials (RCTs) and meta-analyses.[450,451] In this context, all the studies in this submission would automatically score poorly by virtue of their observational design, as demonstrated in the 2015 NICE guidelines for the management of diabetes in pregnancy, where the authors reportedly used GRADE to judge the quality of Bell *et al* 2012 and Tennant *et al* 2013 as '*very poor*'.

Thankfully, as Rothman explains, the concept of a hierarchy of evidence is a fallacious '*intellectual shortcut*'.[452] While there is no disputing that observational studies are susceptible to multiple biases, the most dangerous of which is systematic residual confounding, this does not make an observational study automatically inferior to an RCT.[450,453] More importantly, it does not make observational data unsuitable for causal inference. Even RCTs are subject to the fundamental problem of causal inference; that we can never know the counterfactual outcome of what would have happened given a different exposure.[454] Where the probability of exposure is random however the comparison group can be shown to approximate the counterfactual, thus permitting causal interpretations for suitably large and well conducted RCTs.[454] Similar results can be achieved with certain observational exposures by examining instrumental variables that are correlated with the exposure but not the outcome, the most common example of which are the genetic alleles used in Mendelian randomisation studies.[455] Alternatively, directed acyclic graph theory asserts that complete randomisation is not itself necessary; as long as the conditional probability of being exposed is random, then the difference between the risk and comparison group – conditioned on all true confounding influences – will again approximate the counterfactual.[456] Except it is impossible to ever know whether all potential confounding factors have been completely conditioned out. This is presumably why some consider observational research incompatible with causal inference.[457]

To demand complete certainty however is not only inconsistent with the scientific process – which is established on repeated testing, retesting, and refinement - but disregards the inherently probabilistic nature of the physical world.[458] Causal inference, as with all inductive reasoning, is thus built not on certainty but on an evolving understanding of likelihood. At

what point we consider that likelihood to be convincing is entirely arbitrary. While 5% may be conventional for an association in clinical medicine,[459] the probability threshold for the acceptance of a novel fundamental particle is a considerably smaller 0.00003%.[460]

Since the probability of confounding, and the effect of such confounding can *never* be completely known, then the process of causal inference is essentially a qualitative judgement that requires, in the words of Bhopal, '*deep scholarship that transcends the disciplines that underpin causal understanding, including biology, pathology, epidemiology, statistics, social science and philosophy*'.[461] Such a task is a considerable undertaking and is therefore beyond the scope of this submission. However, since **Section 3·4** (p158) and **Section 3·5** (p162) are predicated on the assumption of causality, then it would be remiss not to provide at least some examination.

3·3·2 The Bradford-Hill criteria

The following explores the hypotheses that obesity and/or diabetes are causally related to congenital anomalies, stillbirths, and/or infant deaths using the so-called Bradford-Hill criteria.[462] Although each criterion has recognised flaws,[463] the pattern of evidence can nevertheless be a useful aid to evaluating the case for causality.

3·3·2·1 Strength of association

Although Hill was clear that a weak association does not discount causality, he proposed that larger effect sizes are more convincing since they are more difficult to explain by competing factors.[462] For diabetes, the majority of studies have identified either 'large' or 'medium-to-large' effects on congenital anomaly, stillbirth, and infant death.[xxxi] It seems implausible that such effects could be due to several small confounding influences and inconceivable that they might be explained by a single, as yet unrecognised, factor. For obesity, the associations are significantly more modest, with most studies reporting either 'small' or 'medium' effect sizes, so this criterion offers limited information.

3·3·2·2 Consistency

Though not essential, Hill suggested that repeatedly observing the same effect in '*different persons, in different places, circumstances and times*' provides reassurance that an effect is robust to study-specific bias.[462] The effects of obesity and diabetes on congenital anomalies, stillbirth and infant death have all been observed repeatedly in multiple studies. For some –

[xxxi] Qualifying an effect size is a controversial concept, although many adhere to Cohen's descriptions that d values of 0.2, 0.5, and 0.8 are 'small', 'medium', and 'large' respectively. These equate to ORs of around 1.44, 2.47, and 4.25 respectively.[464]

in particular the effects of obesity on congenital anomalies - there is remarkable similarity between individual estimates, despite differences in study design, measurement of BMI, ascertainment and classification of congenital anomaly, and underlying BMI distributions.[7] For diabetes, the results are more heterogeneous, possibly due to differences in the identification and/or definition of the condition. [289]

Hill's criteria for different populations, places, and circumstances have regardless not been strictly satisfied, since the majority of studies for both obesity and diabetes have been performed in either Northern Europe or the USA. As a consequence, Cresswell *et al*'s 2012 study of maternal obesity and the risk of neonatal death in sub-Saharan Africa is perhaps one of the most important in the field.[465] Despite unique socio-environmental influences, the observed OR of 1.46 (95% CI: 1.11 to 1.91) agrees strongly with the 2.07 (95% CI: 1.03 to 4.18) observed by Tennant *et al* 2011.[2,465] More studies of this type in low- or middle-income countries would greatly advance the case for causality, although obtaining accurate numbers for stillbirth and congenital anomalies would be extremely challenging.[294]

3·3·2·3 Specificity

Hill considered specificity to be a strong indicator that an exposure and an outcome were causality related rather than correlated by socio-environmental confounding.[462] If obesity caused an increased risk of congenital anomaly but not normally-formed stillbirth for example then it might imply a specific underlying mechanism. Since both diabetes and obesity are associated with a vast number of different health states, then the verdict of this criterion - in Hill's words – is *'left sitting irresolutely on the fence*'.[462]

3·3·2·4 Temporality

Temporality is arguably the most fundamental of Hill's criteria.[462] By definition, an exposure must occur before an outcome to be causal. For those with diabetes diagnosed before pregnancy – i.e. any of the studies in this submission – this would appear to be achieved. Similarly for obesity, most published studies examined pre-pregnancy BMI, even if only estimated by retrospective recall.

Temporality is however almost impossible to prove from cross-sectional data, particularly for exposures like obesity, which are highly correlated over time. Superior information might be obtained from longitudinal data, especially if the association is reversible. Though not necessary for causality, a reversal of risk following a reduction in dose is nevertheless a provocative observation. Tennant *et al* 2015 found that the risk of serious adverse pregnancy outcome not only changed between serial pregnancies, but was strictly determined by

current peri-conception HbA_{1c} values.[6] Elsewhere, Cnattigius and Villamour's recent (2015) study of the effect of weight change in successive pregnancies on the risks of stillbirths and infant deaths shows that the apparent impact of BMI is modifiable from one pregnancy to the next.[466] Although this still does not definitively implicate obesity – as the effect may act through a confounder such as diet and/or physical activity - it suggests that non-surgical changes in weight are likely to result in changes in risk, regardless of the underlying mechanism.

3·3·2·5 Biological gradient

In Hill's view, evidence of a dose response was more suggestive of a causal relationship than an otherwise inconsistent pattern.[462] Tennant *et al* 2011 and, more recently, Aune *et al* 2014 both demonstrate that the risks of fetal and/or infant death increase linearly with increasing BMI.[2,333] Though more suggestive of causality than traditional categorical analyses; the correlation between parity and the risk of Down Syndrome demonstrates that even confounding variables may demonstrate a strong gradient.[463] Furthermore, Tennant *et al* 2011 found that the relationship was only positive for values above 23kg/m^2. [2] While such U- and J-shaped associations are more challenging to explain, they are not however incompatible with causality. The J-shaped association between HbA_{1c} and stillbirth identified by Tennant *et al* 2013 for example may reflect a homeostatic preference towards euglycaemia.[5] Homeostatic balance may also explain the J-shaped pattern for maternal weight, if underweight reflects a functional deficiency of maternal fat. Alternatively, there may be competing exposures or genuine confounders involved in underweight, such as nutritional deficiencies, comorbid illness, or disordered eating. [467]

3·3·2·6 Plausibility

Hill's suggestion of plausibility is hindered by the fact that almost any observation may be explained with suitable imagination and is therefore omitted from examination.

3·3·2·7 Coherence

For Hill, coherence with current knowledge is another indicator of causality. Although flawed in the same regard that a meta-analysis may draw a precise but inaccurate conclusion,[468] it is still reasonable to expect a correct observation to agree with other robust research findings.

The effects of obesity and diabetes on serious adverse pregnancy outcomes are consistent with the wider implications of both conditions towards adult health (discussed in **Section**

1·2·2·4, p6 and **Section 1·2·3·5**, p17). Similarly, the ecological associations between socio-economic circumstances and the risks of congenital anomalies, stillbirths, and infant deaths are consistent with the known socio-economic patterns of obesity and diabetes. On the other hand, the obesity and diabetes epidemics have not been accompanied by increases in the prevalence proportions of any of the principal outcomes. This may indicate other changes, such as improving antenatal care, but the absence of trend is noteworthy for contradicting what might otherwise be expected.

3·3·2·8 Experiment

Though obviously not opposed to causal inference from observational data, Hill argued that experimental results will always provide the strongest evidence of causality.[462] In the absence of an RCT, this directs us towards laboratory experiments in animal models. Unfortunately, animal models of rare pregnancy outcomes are challenged by the large sample-size requirements. Despite this, there is reasonable evidence concerning the effect of diabetes in pregnancy, with several studies showing the potent and reversible effect of hyperglycaemia on both congenital anomalies,[469] and stillbirth.[470]

There is less experimental evidence concerning the effects of obesity in pregnancy, in part because of the lack of an ideal animal model.[471] Nevertheless, consumption of a high fat diet has been shown to cause increases in the prevalence of stillbirth[472] and congenital anomalies of the central nervous system.[473] Although caution is advised when interpreting the results of animal studies like these, the similarity between these findings and those from observational studies in human populations does support causality.

3·3·2·9 Analogy

Like plausibility, analogy offers little benefit for causal inference since it is determined entirely by the imagination of the interpreter.

3·3·3 Conclusion

There is strong evidence to support the hypothesis that the association between diabetes and serious adverse pregnancy outcomes is causal. A large effect has been observed in a number of studies over a long period of time, there is a clear biological gradient associated with blood glucose control that is coherent with other observations. Changes in blood glucose between pregnancies are associated with a measurable change in risk and laboratory experiments have confirmed and advanced our understanding of the underlying

mechanisms. It is virtually inconceivable that hyperglycaemia, as the fundamental feature of diabetes, is not genuinely teratogenic and harmful to fetal survival.

For obesity, the case for causality is less clear. The average effect sizes are considerably more modest, and although the associations have been demonstrated across multiple studies, there is a lack of evidence in non-white populations and in low- and middle-income settings. Despite large increases in the global prevalence of obesity, the rates of stillbirth and infant death have both declined. On the other hand, the presence of a biological gradient, the evidence of reversibility, and the corroborating findings from animal investigations do suggest that obesity - or a close determinant such as a high-fat diet and/or minimal physical activity – may be directly teratogenic and/or harmful to fetal survival.

3·4 POTENTIAL MECHANISMS

3·4·1 Obesity

3·4·1·1 Congenital anomalies

A number of potential mechanisms have been proposed to explain the association between obesity and congenital anomaly. The most frequently-cited explanation is the presence of undetected diabetes,[474-476] a mechanism that would appear supported by the absence of correlation between BMI and the risk of congenital anomaly in Bell *et al* 2012.[3] It is similarly plausible that moderately raised plasma glucose short of overt diabetes might also be associated with an increased risk of congenital anomalies.[476] The risk of NTDs has been associated with consuming foods with high glycaemic index,[477,478] although the association between gestational diabetes and congenital anomalies is conspicuously small.[479]

Obese women of childbearing age are more likely to experience micronutrient deficiencies.[480] Low levels of folate can impair DNA synthesis in the developing embryo,[481] and has thus been linked to a higher risk of several congenital anomaly groups and subtypes.[261] Obese women who consume folic acid supplements before pregnancy appear to experience an attenuated benefit with respect NTD risk than women of recommended BMI,[482] suggesting a possible combined effect of needing more, yet consuming less. In a recent genetic association study, obese mothers were found to carry a number of gene variants involved in folate metabolism that, either alone or in combination with low folate status, were associated with increased risks of CHD.[483]

Part of the increase in the observed prevalence of congenital anomaly is thought to be due to differences in elective termination rates. Higher BMI has been associated with impaired ultrasound visualisation of the fetus,[484,485] which could have a corresponding impact on the availability of elective termination. In the North of England, Best *et al* 2012 (**Appendix B(ii)**, p206) confirmed that the probability of antenatal diagnosis does decrease with increasing BMI, but found no evidence that this impacted on the proportion of terminations of pregnancy.[8]

3·4·1·2 Stillbirths

The reasons for the association between increasing BMI and the risk of stillbirth are similarly unclear. Across Europe, congenital anomalies are reported to explain between 4% and 53% of stillbirths, depending on the availability of prenatal screening and elective termination of pregnancy.[486] As with congenital anomalies, undiagnosed diabetes or similar metabolic

disturbances consistent with pre-diabetes are also thought to cause stillbirths (discussed in **Section 3·4·2·2**, p160).[487]

Obesity is associated with significantly increased risks of pre-eclampsia and gestational hypertension,[488] both of which are thought to act as intermediates between obesity and at least some episodes of fetal death.[489] Other vascular complications associated with maternal obesity include placental and umbilical dysfunction.[490] An excess of placental dysfunction - which may be indicated by fetal growth restriction, infarction, or abruption – has previously been identified in obese women who delivered stillbirths.[332] These mechanisms were all substantiated in a recent case-cohort study from the USA, in which the burden of excess stillbirth in obese women was almost entirely attributed to maternal conditions (such as diabetes), congenital anomalies, hypertensive disorders, placental disease, and umbilical cord anomalies.[491]

Other proposed mechanisms include an increased risk of hypoxic events due to snoring, which have been associated with pre-eclampsia,[492] although subsequent investigations have not been able to support this hypothesis.[493] Obese women are also thought to be less able to detect decreases in fetal movement, which may alert the mother to fetal distress and encourage investigation.[494]

3·4·1·3 Infant deaths

The association between maternal obesity and the risk of infant death is likely to operate through a number of separate mechanisms. Most prominently, maternal obesity is associated with an increased risk of pre-term birth,[495] which complicates a high minority of infant deaths.[358] Infants born to obese mothers are more likely to experience both bacterial sepsis and pneumonia,[496] which are particularly life-threatening in pre-term offspring. At least some of the excess in infant deaths are likely attributed to congenital anomalies, although Tennant *et al* 2011 and Nohr *et al* 2005 found surprisingly typical associations between obesity and the risk of infant death, despite excluding cases complicated by congenital anomaly.[2,332] Finally, LGA and/or macrosomia are more than twice as common in obese mothers and are themselves associated with increased risks of various birth injuries and neonatal asphyxia.[93,497,498]

3·4·2·1 Congenital anomalies

As the defining feature of diabetes, maternal hyperglycaemia is hypothesised as the primary factor underlying the association between pre-existing diabetes and congenital anomalies.[499] Inkster *et al*'s 2006 meta-analysis estimated that individuals with 'poor' glycaemic control experienced 5.14 (95% CI: 2.94 to 9.01) times the odds of a pregnancy affected by a congenital anomaly compared with those of 'optimum' control, while Bell *et al* 2012 found a linear increase in risk for increasing peri-conceptional HbA_{1c} above 45mmol/mol (6.3%).[3,412]

Several molecular mechanisms have been proposed to specifically explain the association between hyperglycaemia and the risk of congenital anomalies, although the evidence is variable and derived predominantly from animal models. The foremost hypothesis suggests that ROS - produced by the metabolisms described in **Section 1·2·3·5** (p17) - disrupt the expression of certain genes that ultimately impairs organogenesis.[500] Two of the best studied examples include *Pax3 and JNK1/2*, which are both involved in cell-cycle regulation. In the presence of hyperglycaemia, expression of these genes can be impaired by ROS, leading to increases in apoptosis, which – depending on timing – may result in either CHD or NTDs.[501-503]

3·4·2·2 Stillbirths

The mechanisms though which diabetes, or hyperglycaemia more specifically, are thought to cause stillbirth are unclear, although ROS have again been implicated. Normal placentation is a highly-complex process of vascular growth and development, controlled by a fine balance of pro- and anti-angiogenic factors.[504] Oxidative stress in the placenta triggers the activation of a series of transcription factors, including KLF8[xxxii], NFκB[xxxiii] and NFE2L2[xxxiv], which interfere with both angiogenesis and trophoblast invasion.[505] The resulting derangements in vascular structure can lead to impaired blood flow to the fetus.[506] In later pregnancy, this may be exacerbated by increased demand from the fetus due to hyperglycaemia-induced over-growth causing hypoxia and, if sufficiently severe, fetal demise.[507]

[xxxii] Krueppel-like factor 8

[xxxiii] Nuclear factor κB

[xxxiv] Nuclear factor (erythroid-derived 2)-like 2

3·4·2·3 Infant deaths

Chiefly cited among the reasons for the increased risk of infant death is the elevated prevalence of pre-term birth, which occurs in as many as a quarter of pregnancies complicated by pre-existing diabetes.[508] Although some of this is explained by induced pre-term birth, the risk of spontaneous pre-term birth is also significantly elevated.[509] Pre-term birth in diabetes is associated with a range of specific morbidities including respiratory distress syndrome and neonatal hypoglycaemia.[510] Even induced pre-term births are likely to indicate underlying complications with poor prognosis, such as infection or growth restriction.[511] The majority of infants in women with diabetes are LGA,[4] which brings a range of complications.[498] Neonatal asphyxia for example is especially common in the offspring of women with diabetes.[512] Finally, congenital anomalies undoubtedly explain at least some of the excess in infant death. In high-income settings however this may be somewhat offset by higher rates of antenatal diagnosis and hence termination of pregnancy; as demonstrated by Newman *et al* 2013 (**Appendix B(iii)**, p215).[9]

3·5 PUBLIC HEALTH IMPLICATIONS

3·5·1 Obesity

The UK DH recently announced plans to half the proportion of stillbirths and neonatal deaths in England by 2030. This tripling in the current rate of progress[513], [xxxv] is hoped to be achieved by improving care in late pregnancy and during labour, using measures such as, '*appointing maternity safety champions*', buying '*high-tech digital equipment*', and '*developing a new system for staff to review and learn from every stillbirth and neonatal death*'.[514] Although lack of skilled birth-attendants is one of the leading – and most readily modifiable - causes of stillbirth and infant death worldwide, the potential benefits of focussing on obstetric care in high-income settings like England are comparatively small.[315] Instead – as I argued in a letter to the Guardian newspaper with colleagues from the Faculty of Public Health (FPH), Royal College of Obstetricians and Gynaecologists (RCOG), and Royal College of Paediatrics and Child Health (RCPCH) (**Appendix E**, p239) – it would likely prove more effective to address the prevailing social causes of stillbirth and infant death, such as smoking, obesity, and diabetes. Unfortunately, there is a substantial difference between our knowledge of obesity as the cause of adverse health, and our record in countering it.[515] Indeed, the speed and magnitude of the increase in the prevalence of obesity - both within the UK and throughout the world - reflects both our bio-psychosocial inability to resist the causes of obeseogenesis, and a political unwillingness to tackle them.[516]

One of the principal challenges is that, once attained, obesity is extremely difficult to reverse. The probability of an obese individual obtaining a normal weight during a single year through non-surgical means is 1 in 210 for men and 1 in 124 for women.[517] This includes those with unintentional weight loss, which often indicates additional illness.[518] For a more reasonable reduction of 5% in weight, the odds are still only 1 in 12 for men and 1 in 10 for women.[517] Although the global market for weight loss and weight management is thought to be worth in excess of $150 billion,[519] the typical loss from a diet and/or exercise intervention is extremely modest.[520,521] Furthermore, most who lose weight will usually have regained whatever was lost within 2-5 years.[522] The cost/benefit balance of attempting to sustainably reverse obesity through individual lifestyle interventions thus seems somewhat poor, although formal economic evaluations have been relatively rare.[523]

In contrast, bariatric surgical interventions have been shown to facilitate considerable short-term weight-loss in individuals with severe obesity,[524] although there is limited data

[xxxv] During 2000-2015 the prevalence of stillbirth (≥28 weeks) in the UK declined at an average rate of 1.4% per year.[513] Achieving the target reduction of 50% by 2030 will instead require an average decline of $1-(0.5)^{1/15} = 4.5\%$ per year, equivalent to over three times the current rate.

describing the long-term prognosis.[525] A recent study from Israel followed the recipients of laparoscopic sleeve gastrectomy for several years and found the proportion of 'failures' approaching 40% by year five.[526] Given most participants had maintained a weight reduction in excess of 10kg/m^2, the term 'failure' seems somewhat strict.[526] Nevertheless, it demonstrates that even this invasive option is unable to avert some relapsing weight-gain.

Lack of long-term efficacy does not however preclude the potential value of a short-term reduction in weight. In the US Diabetes Prevention Program, no difference was observed after ten years in net weight change between those who received the lifestyle intervention, those who received metformin, and those who received a placebo.[527] The incidence of diabetes however was systematically lower in those who had received the lifestyle intervention with an effect equivalent to a four year delay in the onset of the disease.[527] Though modest, such a window may offer substantial benefits to long-term prognosis. The NICE therefore advise GPs and other health professionals to encourage obese women to reduce their weight before pregnancy, '*using evidence-based behaviour change techniques'*.[528] The American College of Obstetricians and Gynecologists (ACOG), suggest bariatric surgery as a possible means to achieve a healthy pre-pregnancy weight for those with a BMI above 40kg/m^2.[529] There has been limited research regarding the risk and details of pregnancy in women after bariatric surgery,[530] although one study of 298 post-operative deliveries suggest broadly similar outcomes as the general population.[531]

However, nearly half of pregnancies among women living in the UK are not proactively planned,[532] and obese women are less likely to plan than women of recommended BMI.[533] Individual-level interventions thus typically target currently pregnant women as a more pragmatic option, especially given the frequent contact with health professionals. Although such an approach offers little benefit for early outcomes such as congenital anomalies, it is contended that pregnancy represents a '*teachable moment*' in which altered emotions, perceptions of risk, and roles of the self-increase a woman's openness and capacity for behaviour change.[534] This is demonstrated by the 25-50% of cigarette-smoking women who spontaneously quit before the end of their first-trimester.[535]

Regarding obesity specifically, most attempts at behavioural change in pregnancy have focussed on improving diet and/or increasing physical activity levels. Oteng-Ntim *et al*'s 2012 meta-analysis of these typically small studies reported that the average difference in gestational weight gain between controls and those who received lifestyle interventions was 2.2 kg (95% CI: 2.9 to 1.6), equivalent to just 57g (95% CI: 7 to 120) difference in birth weight.[536] More recently, the LIMIT trial of 2212 women from Australia found no effect of a modest lifestyle intervention in the prevalence of LGA.[537] The similarly-sized (n=1555)

UPBEAT[xxxvi] trial tested a more intense intervention that included eight individual sessions with a health trainer, but again found no effect on the risk of LGA.[538] Pharmacological options have fared no better, with a recent trial of metformin use in obese pregnant women showing no effect on birth weight.[539]

The focus on individual-level solutions to what scientists have long recognised as an environmental problem[21,540,541] has been described as '*anachronistic*'.[542] Except, system-level solutions are complicated by the complexity of obesity's causes,[38] and the presence of formidable market forces.[543] Many contend that the solution to the obesity epidemic must therefore be equally complex.[544,545] Schemes such as the INFORMAS [xxxvii] framework propose a package of policy interventions across a broad range of domains.[546] Though varied in detail, these can broadly be summarised as either impeding the consumption of obesogenic produce or facilitating physical activity by moderating the 'Three A's' of affordability, acceptability and accessibility.[547] PHE's recent (2015) report on controlling sugar consumption in England propose a subset of similar solutions, including improving dietary literacy, disrupting marketing, supporting recipe reformulation, and introducing a tax or levy on high-sugar produce.[548] The UK's 2016 budget subsequently proposed a soda-tax consisting of a 18p-24p levy per litre for drinks containing 50-80g of sugar per litre.[549] After Mexico introduced a similar 10% tax on high-sugar drinks, the recorded consumption had fallen by 12% after one year. [550] Considering reformulation, it is estimated that a 40% reduction in the sugar content of sweetened drinks would prevent 800,000 cases of obesity in the UK over the next twenty years.[551] Large-scale interventions like this have a proven history of improving perinatal outcomes, as demonstrated by the fall in stillbirths following the introduction of a ban on smoking in public places.[552] How many policies are enacted will however ultimately depend on political factors. Like all socially-determined health states, reducing the impact of obesity – whether in pregnancy or otherwise - is thus not simply of a matter of accumulating or sharing evidence, but of navigating the economic and ideological challenges of our current 'policy environment'.[553]

3·5·2 Diabetes

In a recent commentary on public health ambitions for 2016, Wareham invoked Rose to advise that even small changes to an individual's risk of diabetes, when '*amassed across large populations…(will have) the greatest impact on the epidemic of diabetes*'.[554] Such changes would conveniently consist of many of the same approaches as for obesity

[xxxvi] UK Pregnancies Better Eating and Activity Trial

[xxxvii] International Network for Food and Obesity / Non-communicable Diseases Research, Monitoring and Action Support

prevention. The aforementioned 40% reduction in the sugar content of sweetened beverages for example would be expected to prevent 250,000 cases of type 2 diabetes over the next two decades.[551]

Having said this, the path between obesity and overt type 2 diabetes is amenable to individual intervention.[555] Indeed, diabetes remission appears to be achievable with bariatric surgery or adherence to an very low-calorie diet.[556,557] The NICE thus recommend a duel approach to diabetes prevention, consisting of both population-level interventions for those at low-risk, and individual-level interventions for those at high-risk.[558,559] The features of individual-level interventions for diabetes are generally similar to obesity interventions, although loss of weight or BMI is not essential. As demonstrated by the US Diabetes Prevention Programme, lifestyle interventions that result in only modest changes in long-term weight can lead to significant delays in the development of the disease. [527] Regardless of weight loss, increasing physical activity and dietary fibre, and decreasing energy from fat and refined carbohydrates seem effective for preventing or delaying diabetes.[560] Such principles underlie the proposed NHS National Diabetes Prevention Programme, which aims to identify individuals at high risk of diabetes and deliver individual-level interventions based around changing diet and increasing physical activity.[561]

Although remission may be possible for some with type 2 diabetes, the mainstay of diabetes management consists of optimising glycaemic control and treating emergent vascular complications. Control of blood glucose primarily involves a close management of diet and exercise and either insulin injections for those with type 1 diabetes or antidiabetic drugs (principally metformin) for those with type 2 diabetes;[562,563] although the boundaries are not exact. Unfortunately, even with recent advances such as the development of insulin analogues, electronic insulin delivery systems, and smartphone applications, sustaining optimal glycaemic control remains a Herculean task that few can achieve without specialist help.[564]

This challenge is greatly exacerbated in pregnancy,[565] where women rightly receive specialist antenatal care.[119,566] As shown however by Bell *et al* 2012, Glinianaia *et al* 2012, Tennant *et al* 2013, and Tennant *et al* 2015, glycaemic control before gestation is also particularly important to the health of the offspring. Pre-conception care services are therefore especially vital to help women with pre-existing diabetes to prepare for pregnancy.[567,568] Unfortunately, as shown by Glinianaia *et al* 2014 (**Appendix B(v)**, p224), the majority of women with diabetes do not attend pre-conception care and the proportion is falling.[11] The consequence is that only a quarter of women with pre-existing diabetes in the UK are currently achieving a pre-conception HbA_{1c} below the new target of 48mmol/mol (6.5%), and less than half are taking any folic acid supplements before pregnancy.[508]

This record of poor preparation for pregnancy presents a compelling opportunity for intervention. Indeed, the 2014 Annual Report of the Chief Medical Officer specifically highlights improved pre-conception care as a means to improve the nation's health.[569] Suggested methods include 1) combining pregnancy prevention and planning services, 2) extending sex-education to include the 'four P's' of prevention, planning, preparation and parenthood, and 3) adopting a multi-agency approach to education provision that stretches beyond the traditional authorities of schools and the NHS. [569] Although such changes may be difficult to implement in the current policy environment, even modest improvements to pre-conception care among women from high-risk groups would likely offer rapid and cost-effective benefits.

3·6 FUTURE RESEARCH

While many hypotheses seek to explain the association between obesity and the risks of serious adverse pregnancy outcome (**Section 3·4·1**, p158), the causes remain speculative (**Section 3·3** p152). Although there is extensive evidence to show the independent effect of obesity, particularly dysfunctional adipose, on adult health outcomes such as diabetes and cardiovascular disease (**Section 1·2·2·4**, p6);[63] the formal division of cause and consequence for pregnancy outcomes like congenital anomalies is yet to be made.[500] Low physical activity, high sedentary behaviour, low intake of micronutrients (such as folic acid), and high calorie consumption for example are all plausible independent causes of adverse pregnancy outcome. Though most obesity interventions would likely target these exposures regardless, knowing the relative contributions might still help to design more cost-effective interventions. Interrupting sedentary behaviour and improving nutritional (particularly folate) status might for example be far less challenging than achieving increases in physical activity and decreases in total calorie intake.

Unfortunately, such information is far in advance of what is routinely collected within clinical records or existing disease registries. Further examination of the interplay between obesity and diet and lifestyle factors therefore demands an alternative approach. Cross-generational cohorts - such as the Avon Longitudinal Study Parents and Children (ALSPAC) and Born in Bradford (BiB) cohort - offer vastly improved information over routine data, but are not statistically powered to examine rare pregnancy outcomes such as stillbirths. These data can nevertheless provide unprecedented insight into the determinants of intermediate pregnancy outcomes, as recently demonstrated in Farrar *et al's* 2015 study of the association between plasma glucose concentration and the risks of LGA.[570] I hope to use similar data to examine the wider influence of maternal plasma glucose concentration on infant health.

For serious adverse pregnancy outcomes, case-control studies, such as the Midland and North of England Stillbirth Study (MiNESS), offer an alternative option.[571] Although retrospective self-reported data is highly susceptible to recall bias, the combination of detailed exposure information and elevated statistical power make these studies highly practical for rare outcome research. I hope to use MiNESS data – linked with maternity records of routine OGTT tests at 24-28 weeks – to examine the potentially-mediating roles of gestational diabetes and plasma glucose concentration on the risk of stillbirth in obese women. Although the case-control design prohibits the calculation of absolute risks, LOWESS could still be used to explore the shape of the relationship between plasma glucose and stillbirth in relative terms.

The utility of retrospective data however has a number of prominent limits. Self-reported physical activity in pregnancy for example shows poor agreement with objectively measured estimates. In particular, data from retrospective recall seems particularly unlikely to delineate complex temporal effects, such as timing and duration of sedentary behaviour. Due to their increased risks of adverse pregnancy outcome, women with diabetes offer a potential route to exploring such factors where prospective data collection is essential. I hope to use prospective data from accelerometers and continuous glucose monitors to investigate the effects of timing and duration of physical activity and sedentary behaviour on glycaemic excursions and the corresponding risks of serious adverse pregnancy outcomes. Bell *et al* 2012 and Tennant *et al* 2013 found that women with optimum concentrations of HbA_{1c} still experienced double the risk of congenital anomaly and stillbirth and the J-shaped pattern of risk indicated a possible effect for hypoglycaemic episodes. Since extreme glycaemic excursions have previously been shown to effect the risk of LGA, it seems plausible that they may explain some of the excess risk of serious adverse pregnancy outcome.[440] If duration of sedentary behaviour is shown to impact glycaemic excursion and in turn on risk of adverse pregnancy outcome, then this offers a potential route to intervention.

3·7 CONCLUSION

This Doctoral Statement described a substantive portfolio of research examining the associations between maternal pre-pregnancy obesity and maternal pre-existing diabetes on the risks of serious adverse pregnancy outcomes.

Pre-pregnancy obesity and pre-existing diabetes were both found to be associated with increased risks of congenital anomaly, stillbirth, and infant death; with smaller effects for obesity than diabetes. Among women with pre-existing diabetes, this was predominantly – but not completely – determined by average peri-conception glucose control. The effect of glucose control on birth weight in women with diabetes was found to reverse during pregnancy, with low peri-conception followed by high third-trimester values associated with the largest size. This suggests that initial growth restriction followed by late overgrowth may confer the highest risk of stillbirth. The risk of serious adverse pregnancy was found to halve between the first and second pregnancy in women with diabetes, except among those who experienced adverse outcome in their first pregnancy. This may reflect recurring preparatory behaviour, with preparation for pregnancy not typically changing between pregnancies.

There is strong evidence that the association between diabetes and serious adverse pregnancy outcomes is causal. A large effect has been observed in a number of previous studies over a long period of time and there is a clear biological gradient with blood glucose control. Although the exact mechanism is unclear, both inflammation and oxidative stress are compellingly implicated. For obesity, the case for causality is less clear. Although the risks of congenital anomaly, stillbirth and infant death all demonstrate a dose-response with increasing BMI, confounding by diet and physical activity has not been discounted. The absence of an effect for BMI among women with pre-existing diabetes however suggests glycaemic disturbance may act as a mediator on the causal pathway.

Reversing obesity and diabetes, whether in pregnancy or otherwise, is extremely challenging. Population-level interventions that aim to prevent obesity and diabetes are therefore likely to offer the most effective means to reduce their impact in pregnancy. On the other hand, the reversible effect of peri-conception glucose control on pregnancy outcome demonstrates the utility of downstream intervention. Improving attendance of pre-conception care among women from high-risk groups for example would likely offer salient benefits.

Future research seeks to explore the mediating effect of plasma glycose concentration on the association between obesity and stillbirth and other aspects of infant health. The interplay between sedentary behaviour and glycaemic excursions on the risks of serious adverse pregnancy outcomes will also be examined as a possible route for intervention.

CHAPTER 4: REFLECTION

Like many epidemiologists, I came to the field by accident. For my undergraduate degree, I followed a unique and disparate programme of Molecular and Cellular Biology with Pure and Applied Mathematics. It left me with a fascination in the causes of disease and a range of theoretical quantitative skills, but an untenable lack of laboratory experience. To address this, I studied for a Master's degree in Biosciences. Alas, although I relished the 'dry' aspects of biological research, difficulties with concentration and coordination meant I was ill-suited to laboratory work.

Epidemiology was suggested as a possible solution during a brief spell researching plagiarism policies in the UK. Instead of the expected qualitative synthesis, I devised a novel Penalty Gradation Score that helped to identify clusters of practice within the higher education sector.[572] This, somewhat unconventional, experience was somehow sufficient to convince Mark Pearce and Judith Rankin in the Institute of Health and Society (IHS) at Newcastle University to risk offering me my first position as an epidemiologist in August 2007. And a risk it was; though acquainted with statistical theory from my undergraduate degree and with p-values and confidence intervals from my Master's degree, I was entirely unfamiliar with the theory and practice of Epidemiology.

This gap in knowledge was all the wider in the context of pregnancy, where the complications of measuring exposure and outcome across two generations - one of which is only partially observable - introduces various specific customs and pitfalls.[244] My first experience of the subject was thus a steep learning curve, and for this reason my input was primarily confined to the statistical analysis. The study in question was **Stothard *et al* 2009** (**Appendix B(i)**, p191); the systematic review of obesity and the risk of congenital anomalies that defined the start of the IHS team's subsequent programme of research into the impact of obesity and diabetes in pregnancy. Beyond the pernickety demands of the target journal, the most challenging aspect of the review for me personally was in handling the sheer number of outcomes. This was not just because of the practical challenge of presenting the results of 30 separate meta-analyses, but because of the bewildering variety of terminology (**Section 1·3·2·1**, p22).

With over 500 citations, Stothard *et al* 2009 now ironically overshadows the study that it was meant to support. **Rankin *et al* 2010** (**Section 2·2**, p38) was planned as the UKs first cohort study of the association between maternal obesity and congenital anomaly. I joined the study team after the data had been supplied by the five participating hospitals following protracted delays. For me, it proved to be a rather stark introduction to routine data. Every variable from

every maternity unit was coded differently, some were described narratively, and there were no apparent attempts at standardisation. Some variables, like parity and folic acid consumption, were so inconsistent or incomplete that they ultimately proved unusable. Cleaning and merging the data was thus a substantial task in itself, and given the workload involved, I was genuinely disappointed that the eventual benefits, in terms of both the final sample size and the usable set of variables, were less than originally hoped. This was exacerbated by the large proportion with missing BMI. Though of limited interest scientifically, this was arguably the most important practical result of the study, and the research team were keen to highlight the need for better recording of maternal BMI wherever possible. The study was also the beginning of my interest in presenting absolute risks. During peer-review for Stothard *et al* 2009, the editors had argued it was, '*very important… (to) include some estimate of the absolute risk*', despite the lack of appropriate data from a cohort study. As one of few such studies, I was therefore keen to include these data when the opportunity arose.

Although the data for Rankin *et al* 2010 had been primarily collected to examine the association between maternal obesity and congenital anomaly, it also provided the research team with an opportunity to explore some of the other implications of obesity in pregnancy. In her PhD submission for example Shakoor used the data to show that obese mothers in the region experienced 1.8 (95% CI: 1. 7 to 2.0) times increased odds of delivery by Caesarean section than those of recommended BMI.[573]

I myself was given the chance to lead a study into the effects of BMI on fetal and infant death, the product of which was **Tennant *et al* 2011** (**Section 2·3**, p53). In conducting the analysis and preparing the manuscript, I primarily followed the approach adopted for Rankin *et al* 2010, albeit with some advances thanks to my new found familiarity with the STROBE [xxxviii] statement.[574] My analysis of BMI however stubbornly adhered to WHO categories. Though I recognised the power benefits of a continuous analysis, I was concerned about non-linearity and was keen to maximise the clinical interpretability. One peer-reviewer disagreed, advising that '*the shape of the relationship should be explored using graphical smoothing methods',* offering the example Kosa *et al* 2011.[575] This remains the most valuable piece of advice I have ever received through peer-review. One look at Kosa *et al*'s V-shaped model of the relationship between continuous BMI and the risk of pre-term birth, and I was keen to do the same. Thus came **Figure 2** (p58), later reproduced in the DH's '*Healthy Lives, Healthy People: A call to action on obesity in England*'.[386]

[xxxviii] STrengthening the Reporting of OBservational Studies in Epidemiology

Having established the impact of obesity on congenital anomalies and fetal and infant death, the research team now moved to explore some of the potential mechanisms. The impacts of obesity and diabetes on the antenatal detection of congenital anomalies were investigated in **Best *et al* 2012** (**Appendix B(ii)**, p206) and **Newman *et al* 2013** (**Appendix B(iii)**, p215). For both, I assumed a more supportive role, advising on analyses and contributing my increasing expertise in the coding of congenital anomalies. Meanwhile, the team had also identified the impact of diabetes in pregnancy on the prevalence of congenital anomaly as ripe for investigation. Whereas studying the role of e.g. folic acid would require novel data collection, the region's unique concurrence of a diabetes in pregnancy survey (NorDIP) and a congenital anomaly register (NorCAS) meant these data were essentially already available. Bell therefore led a funding application to Diabetes UK. My increasing expertise in both the epidemiology of congenital anomalies and in statistical analyses meant I was involved from the outset, although my lack of knowledge of diabetes, and increasing involvement in other areas of enquiry, meant Glinianaia was chosen to lead the research.

Though not apparent from publication, the most time-consuming aspect of preparing **Bell *et al* 2012** (**Section 2·4**, p68) was the hierarchical coding of the congenital anomaly data. While it had not been long since Rankin and I had first developed the approach for Tennant *et al* 2010,[363] my knowledge had grown substantially, and I was aware of considerably more nuance. Diagnosing the region's 9000 cases from 1996-2008 thus tested the viability of the approach to its very limits. During the process, I discovered a cluster of inconsistently-coded cases with persistent cloaca, which ultimately lead to my conducting a national study of its epidemiology and natural history.[576]

Though Glinianaia conducted the routine analysis for Bell *et al* 2012, several issues called for my enhanced involvement. Of most concern was the non-linear relationship between peri-conception HbA_{1c} and the risk of congenital anomaly. While we all agreed that clinical interpretability was paramount, I was not keen on losing the power of the variable by categorisation. I also feared it might reinforce the existing focus of binary pre-conception targets for HbA_{1c}. My solution built on what I had learnt during Tennant *et al* 2011, using LOWESS to inform spline regressions and bootstrapping simulations to estimate the absolute risk of congenital anomaly across the observed values of HbA_{1c}. **Figure 1** (p77) was both computationally and presentationally demanding, but I recognised the value as soon as I conceived the idea. Even so, Hadden's description of the figure as '*a major educational demonstration for diabetic mothers-to-be, as well as all of their advisors*' was extremely satisfying. So too has been the study's subsequent contribution to guidelines for the management of pre-existing diabetes in pregnancy.[119,577]

Though funded specifically to examine the contribution of pre-existing diabetes to congenital anomaly, the linked dataset provided further scope for scrutiny. Due to concerns about statistical power (my *a priori* power calculation had assumed only moderate effect sizes) this would start with an analysis of SGA and LGA as intermediates on the causal pathway to serious adverse pregnancy outcome. Keen to avoid arbitrary cut-offs and maximise analytical power, I also favoured a continuous analysis of birthweight. My initial hope was to take a novel path-analytic approach, but the complexity of the final model proved extremely challenging to present.[578] In fact, finding a robust but clear way to present the results was probably the biggest challenge for **Glinianaia *et al* 2012** (**Section 2·5**, p84). For a start, the clinical realities of diabetes in pregnancy caused some curious anomalies when analysing standardised birthweight[xxxix]. These artefacts only disappeared when I moved to examine crude birthweight with explicit variables for sex, parity, and gestational age. Then were the issues of the reversing effect of HbA_{1c} and the non-linearity in the effect of third-trimester HbA_{1c}. Glinianaia and I worked on many redrafts to attempt to describe the methods and results in sufficient detail without bewildering the reader. The need for an unprecedented quantity of supplementary material suggests we may partly have failed, although it also reflects the multi-dimensionality of birthweight as an outcome.

Regardless, Glinianaia *et al* 2012 is now helping to inform discussions around the clinical utility of HbA_{1c} in pregnancy.[579] For me personally, the intricacies of analysing, interpreting and presenting the results also provided a thorough exposure to the setting of diabetes in pregnancy. Alongside my growing stature as the team's senior methodologist, and my decreasing involvement in other areas of enquiry, I was thus well placed to take a more leading role in the remainder of the research programme.

Having previously led the study of the association between obesity and fetal and infant death, it made sense to start by leading the analogous study in women with diabetes. Sample size limitations meant **Tennant *et al* 2013** (**Section 2·6**, p108) was initially expected to be a short report, but the dramatic effect sizes – for both diabetes and HbA_{1c} – facilitated a more thorough investigation. The analyses lent heavily on the approaches I developed during Bell *et al* 2012 and Glinianaia *et al* 2012, albeit with some notable additions. I was fortunate for example to have sufficient cases to conduct a sensitivity analysis of the risk of stillbirth by gestational age. Adopting the contemporary 'fetuses-at-risk' approach allowed me to demonstrate that the excess risk of stillbirth is not, as previously asserted, simply confined to term (**Table 2**, p114). Because of the joint contributions of peri-conception and third-trimester HbA_{1c}, I also attempted to report the marginal absolute risks of late stillbirth stratified by both

[xxxix] Many offspring at risk of extreme growth were pre-emptively delivered, negating the apparent effect of HbA_{1c} on conventionally standardised birthweight

variables. Since the journal did not allow the shading of rows or columns however the table (**Table 3**, p116) is somewhat difficult to read.

Though Tennant *et al* 2013 is perhaps less innovative than either Bell *et al* 2012 or Glinaiana *et al* 2012, the three papers together form an indispensable triad of information regarding the fetal implications of diabetes in pregnancy. For me, Tennant *et al* 2013 was also a significant personal step forwards. As my first paper as corresponding author, it signified my continuing evolution from competent analyst towards independent researcher.

Shortly after publication, Lewis and Maxwell provided a prompt opportunity to explore that growing confidence by writing to *Diabetologia* (**Appendix D**, p237) Responding directly to Tennant *et al* 2013, they proposed that,

> '*Women with diabetic nephropathy who are considering pregnancy should… not be withdrawn from treatment with angiotensin converting enzyme inhibitor (ACEɪ) and/or angiotensin II receptor blocker (ARB) therapy until their first positive pregnancy test*'.[580]

I did not believe such an assertion was valid from the results we had presented, and thus asked the journal for an opportunity to respond. The result (**Tennant *et al* 2014**) (**Appendix B(iv)**, p222) was my first published contribution to secondary academic discourse. As well as discussing the evidence of the safety of anti-hypertensive medicines in pregnancy, I was particularly keen to reframe the discussion around the results of Tennant *et al* 2013. Thus, though I agreed that women with microvascular complications should receive additional support when planning their pregnancy, I asserted that,

> '*Improving glycaemic control before and during pregnancy is likely to be, by far, the most salient method for improving outcome in women with diabetes*'.

Shortly before starting on the final paper of this submission, I was invited to contribute to another study (**Glinianaia *et al* 2014**) (**Appendix B(v)**, p224), examining the predictors of preparation for pregnancy in women with diabetes. The manuscript had already been submitted, but the peer-review demanded significant changes, including more formally testing for and modelling non-linearity. Although the editor suggested that the authors '*consult a medical statistician for further advice about the data analysis*', my expertise with LOWESS and spline regression meant I was ideally suited. As it happens, Glinianaia *et al* 2014 led seamlessly into **Tennant *et al* 2015** (**Section 2·7**, p127), which also examined the predictors of preparation for pregnancy. The twist, of course, was that Tennant *et al* 2015 also looked at change (and predictors of change) in preparatory behaviour between pregnancies.

Again assuming the role of lead and corresponding author, this study proved much more challenging than Tennant *et al* 2013. Though Prathapan had prepared the data and performed preliminary analyses, it all needed updating. This was partly to provide better continuity and comparison with the previous studies, but - more importantly - there were fundamental flaws with the original approach. Firstly, left-censoring of the data[xl] meant that the existing logistic regression analyses were biased in favour of late booking. Secondly, since HbA_{1c} was far more likely to be missing among cases (especially from minority ethnic groups and more deprived socio-economic circumstances), there was no escaping the need for imputation.

In a certain respect, my evolving handling of missing data symbolises my developing skill and confidence over the course of the PhD. In Rankin *et al* 2010, missing data were managed with limited exploration by listwise deletion. For Tennant *et a*l 2011, this had progressed to include sensitivity analyses using predictive mean matching. By Tennant *et al* 2015, I was conducting the analysis *de novo* on multivariate imputed data.

The challenge with increasing analytical sophistication however is maintaining the readability and interpretability for the non-statistical reader. This was fittingly demonstrated by one of the peer review comments for Tennant *et al* 2015, in which the reviewer worried about '*minor errors'* because the multiple imputation results did not match what could be calculated from the raw counts. This issue was exacerbated by the quantity of material analysed, which combined what could have conceivably formed two separate studies (the first examining preparatory behaviour and the second examining the risk and determinants of adverse outcome). On the other hand, it also elevated the appeal to enable my first publication in *Diabetes Care*. Given the challenge of condensing such a large quantity of material into a single article, I was pleased to receive the following description of the analysis from one of the peer-reviewers:

> *'Complex and sophisticated… performed by experts… taking into consideration any aspect to get clinically relevant data'*

Though no more than the words of a single individual responding to a single aspect of a single paper, this was meaningful for me personally because it captures what has emerged from my PhD as my philosophy as an epidemiologist. Not complexity for the sake of complexity, but to push the boundaries of quality and relevance within applied health research. In fact, it was on this aim that I applied for my first post-doc position in the School

[xl] Left-censoring occurs when outcomes may arise before observation. In pregnancy, this includes all unreported miscarriages.

of Healthcare at the University of Leeds, where I will be taking my first steps towards becoming a fully independent researcher.

AFTERWORD

Like all PhD submissions, this Doctoral Statement tells the story of my research apprenticeship whilst saying very little of the personal trials that – though often central to the lived experience of a PhD - rarely make the page. This is understandable because a PhD is an examination of output, not of effort. There are no awards for those whose who cannot complete, regardless of the personal challenges they may have overcome.

On more than one occasion, I was resigned to accept that I would not complete; as my energy, my confidence, and my health were drained by the torment of mental illness. Many hours of many days of many months were spent staring blankly at one screen or another, either waiting for the spark to return, or paralysed by an unknown fear. In an industry that depends so fundamentally on the abilities to think, focus, concentrate, and communicate, a broken brain is uniquely - and completely - disabling.

Yet, here I am, writing my last words; a day which I never thought would come. I am one of the lucky ones; whose health recovered enough; who had the time, the means, and – most importantly - the support to finish. For these things, I am grateful in ways that cannot be expressed in words.

APPENDICES

A CO-AUTHORSHIP FORMS

Newcastle University

SUBMISSION BY STAFF CANDIDATES FOR THE DEGREE OF PHD BY PUBLISHED WORK

CO-AUTHORSHIP FORM

This form must accompany any submission of a joint authored publication for the degree of Doctor of Philosophy on the basis of published work.

A candidate should submit a separate form for each jointly authored work which is submitted for the degree.

TITLE OF PUBLICATION (article, book, chapter, monograph)

Maternal body mass index and congenital anomaly risk: a cohort study

DATE OF PUBLICATION **06 April 2010**

NAME AND VOLUME OF JOURNAL (where appropriate)

International Journal of Obesity

Volume 34 Issue 9 Pages 1371-1380

PUBLISHER (for book, chapter or monograph) **NA**

EDITORS (chapter only) **NA**

ISBN (where appropriate) **NA**

If the work has not been published but has been accepted for publication *please attach a statement from the Editor or Publisher which confirms the intention to publish the work.*

NAMES OF JOINT AUTHORS	INSTITUTION
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2. **Katherine Stothard**	**University of Manchester**
3. **Mary Bythell**	**N/A**
4. **Carolyn Summerbell**	**Durham University**
5. **Ruth Bell**	**Newcastle University**

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CONTRIBUTION OF THE CANDIDATE TO THIS WORK (%)

Design of investigation	**5%**
Conduct of research	**25%**
Analysis of outcome	**85%**
Preparation for publication	**25%**
(Overall	**35%)**

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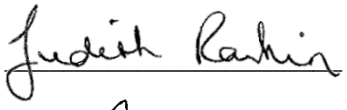
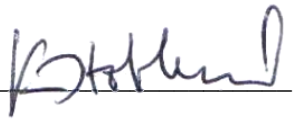
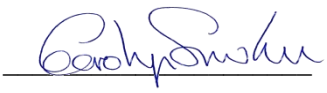
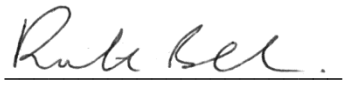
Signature 1  Signature 2 

Signature 3  Signature 4 

Signature 5 

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TITLE OF PUBLICATION (article, book, chapter, monograph)

Maternal body mass index and the risk of fetal and infant death; a cohort study from the North of England

DATE OF PUBLICATION **05 April 2011**

NAME AND VOLUME OF JOURNAL (where appropriate)

Human Reproduction,

Volume 26 Issue 6 Pages 1501-1511

PUBLISHER (for book, chapter or monograph) **NA**

EDITORS (chapter only) **NA**

ISBN (where appropriate) **NA**

If the work has not been published but has been accepted for publication *please attach a statement from the Editor or Publisher which confirms the intention to publish the work.*

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CONTRIBUTION OF THE CANDIDATE TO THIS WORK (%)

Design of investigation	**10%**
Conduct of research	**60%**
Analysis of outcome	**90%**
Preparation for publication	**80%**
(Overall	**60%)**

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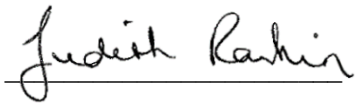
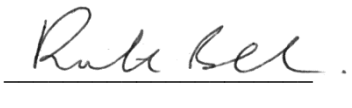
Signature 1  Signature 2 

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TITLE OF PUBLICATION (article, book, chapter, monograph)

Peri-conception hyperglycaemia and nephropathy are associated with risk of congenital anomaly in women with pre-existing diabetes: a population-based cohort study

DATE OF PUBLICATION **08 February 2012**

NAME AND VOLUME OF JOURNAL (where appropriate)

Diabetologia

Volume 55 Issue 4 Pages 936-947

PUBLISHER (for book, chapter or monograph) **NA**

EDITORS (chapter only) **NA**

ISBN (where appropriate) **NA**

If the work has not been published but has been accepted for publication *please attach a statement from the Editor or Publisher which confirms the intention to publish the work.*

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4. **Judith Rankin**	**Newcastle University**

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CONTRIBUTION OF THE CANDIDATE TO THIS WORK (%)

Design of investigation	**20%**
Conduct of research	**30%**
Analysis of outcome	**30%**
Preparation for publication	**20%**
(Overall	**25%)**

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TITLE OF PUBLICATION (article, book, chapter, monograph)

HbA_{1c} and birthweight in women with pre-conception type 1 and type 2 diabetes: a population-based cohort study

DATE OF PUBLICATION **27 September 2012**

NAME AND VOLUME OF JOURNAL (where appropriate)

Diabetologia

Volume 55 Issue 12 Pages 3193-3203

PUBLISHER (for book, chapter or monograph) **NA**

EDITORS (chapter only) **NA**

ISBN (where appropriate) **NA**

If the work has not been published but has been accepted for publication *please attach a statement from the Editor or Publisher which confirms the intention to publish the work.*

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2. **Rudy Bilous**	**Newcastle University**
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4. **Ruth Bell**	**Newcastle University**

cont/d ...

CONTRIBUTION OF THE CANDIDATE TO THIS WORK (%)

Design of investigation	**30%**
Conduct of research	**30%**
Analysis of outcome	**30%**
Preparation for publication	**30%**
(Overall	**30%)**

This statement should be endorsed by all of the co-authors.

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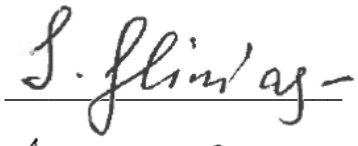
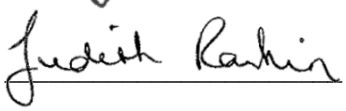
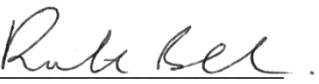
Signature 1  Signature 2 

Signature 3  Signature 4 

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TITLE OF PUBLICATION (article, book, chapter, monograph)

Pre-existing diabetes, maternal glycated haemoglobin, and the risks of fetal and infant death: a population-based study

DATE OF PUBLICATION **29 November 2013**

NAME AND VOLUME OF JOURNAL (where appropriate)

Diabetologia

Volume 57 Issue 2 Pages 285-294

PUBLISHER (for book, chapter or monograph) **NA**

EDITORS (chapter only) **NA**

ISBN (where appropriate) **NA**

If the work has not been published but has been accepted for publication *please attach a statement from the Editor or Publisher which confirms the intention to publish the work.*

NAMES OF JOINT AUTHORS	INSTITUTION
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2. **Rudy Bilous**	**Newcastle University**
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4. **Ruth Bell**	**Newcastle University**

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CONTRIBUTION OF THE CANDIDATE TO THIS WORK (%)

Design of investigation	**30%**
Conduct of research	**40%**
Analysis of outcome	**90%**
Preparation for publication	**60%**
(Overall	**55%)**

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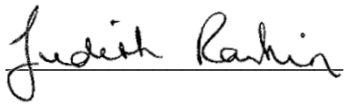
Signature 3  Signature 4 

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A candidate should submit a separate form for each jointly authored work which is submitted for the degree.

TITLE OF PUBLICATION (article, book, chapter, monograph)

Risk and Recurrence of Serious Adverse Outcomes in the First and Second Pregnancies of Women With Preexisting Diabetes

DATE OF PUBLICATION **05 January 2015**

NAME AND VOLUME OF JOURNAL (where appropriate)

Diabetes Care

Volume 38 Issue 4 Pages 610-619

PUBLISHER (for book, chapter or monograph) **NA**

EDITORS (chapter only) **NA**

ISBN (where appropriate) **NA**

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2. **Shamini Prathapan**	**Newcastle University**
3. **Ruth Bell**	**Newcastle University**

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CONTRIBUTION OF THE CANDIDATE TO THIS WORK (%)

Design of investigation	**40%**
Conduct of research	**40%**
Analysis of outcome	**90%**
Preparation for publication	**70%**
(Overall	**60%)**

This statement should be endorsed by all of the co-authors.

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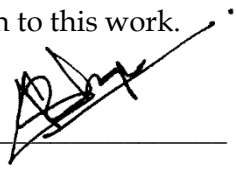
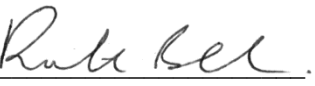
Signature 1  Signature 2 

Signature 3 

REVIEW

Maternal Overweight and Obesity and the Risk of Congenital Anomalies

A Systematic Review and Meta-analysis

Katherine J. Stothard, PhD
Peter W. G. Tennant, MSc
Ruth Bell, MD
Judith Rankin, PhD

Context Evidence suggests an association between maternal obesity and some congenital anomalies.

Objective To assess current evidence of the association between maternal overweight, maternal obesity, and congenital anomaly.

Data Sources MEDLINE, EMBASE, CINAHL, and Scopus (January 1966 through May 2008) were searched for English-language studies using a list of keywords. Reference lists from relevant review articles were also searched.

Study Selection Observational studies with an estimate of prepregnancy or early pregnancy weight or body mass index (BMI) and data on congenital anomalies were considered. Of 1944 potential articles, 39 were included in the systematic review and 18 in the meta-analysis.

Data Extraction and Synthesis Information was extracted on study design, quality, participants, congenital anomaly groups and subtypes, and risk estimates. Pooled odds ratios (ORs) comparing risk among overweight, obese, and recommended-weight mothers (defined by BMI) were determined for congenital anomaly groups and subtypes for which at least 150 cases had been reported in the literature.

Results Pooled ORs for overweight and obesity were calculated for 16 and 15 anomaly groups or subtypes, respectively. Compared with mothers of recommended BMI, obese mothers were at increased odds of pregnancies affected by neural tube defects (OR, 1.87; 95% confidence interval [CI], 1.62-2.15), spina bifida (OR, 2.24; 95% CI, 1.86-2.69), cardiovascular anomalies (OR, 1.30; 95% CI, 1.12-1.51), septal anomalies (OR, 1.20; 95% CI, 1.09-1.31), cleft palate (OR, 1.23; 95% CI, 1.03-1.47), cleft lip and palate (OR, 1.20; 95% CI, 1.03-1.40), anorectal atresia (OR, 1.48; 95% CI, 1.12-1.97), hydrocephaly (OR, 1.68; 95% CI, 1.19-2.36), and limb reduction anomalies (OR, 1.34; 95% CI, 1.03-1.73). The risk of gastroschisis among obese mothers was significantly reduced (OR, 0.17; 95% CI, 0.10-0.30).

Conclusions Maternal obesity is associated with an increased risk of a range of structural anomalies, although the absolute increase is likely to be small. Further studies are needed to confirm whether maternal overweight is also implicated.

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OBESITY IS A MAJOR PUBLIC health and economic concern. Worldwide, an estimated 1.6 billion adults (aged 15 years and older) were overweight (body mass index [BMI] 25-30, calculated as weight in kilograms divided by height in meters squared), and 400 million were obese (BMI>30) in 2005.[1] By 2015, it is expected there will be 2.3 billion overweight and more than 700 million obese adults worldwide. In the United States, a third of women aged 15 years and older were obese in 2004.[2] There are significant health implications of prepregnancy maternal obesity for both mother and child. For the mother, these may include gestational diabetes, hypertensive disorders, thromboembolic disorders, increased cesarean delivery rates, and wound infection.[3-8] Infants of obese mothers are at increased risk of birth difficulties, macrosomia, and perinatal death.[9-12] Maternal obesity may also be associated with the development of congenital anomalies. Congenital anomalies are a leading cause of stillbirth and infant mortality, accounting for 1 in 5 infant deaths in the United States,[13] and are important contributors to preterm birth and childhood morbidity. We conducted a systematic review and meta-analysis of observational studies to assess and quantify the relationship between maternal overweight and obesity and the risk of congenital anomaly in the offspring.

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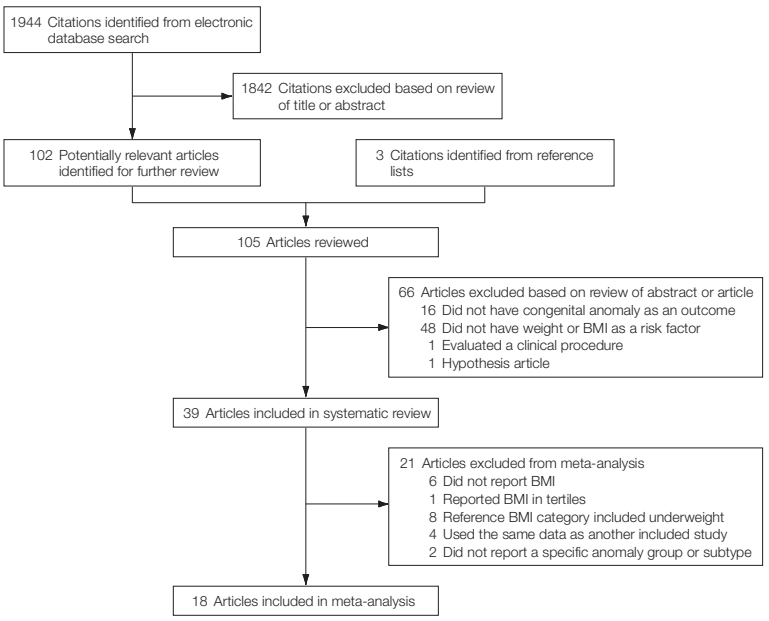
METHODS

Study Selection

We conducted a comprehensive literature search of MEDLINE, EMBASE, CINAHL, and Scopus (January 1966 through May 2008) using terms for mother (eg, *mother**, *matern**, *wom*n*), weight (eg, *weight*, *body mass index*, *BMI*), and congenital anomaly (eg, *anomal**, *malform**, *birth defect*). The full list of terms is available from the authors. Additional articles were identified by reviewing reference lists. Articles were included if the participants were pregnant women, a measure or estimate of prepregnancy or early pregnancy weight was reported, and the outcome was a congenital anomaly. Searches were restricted to English-language articles. Articles were excluded from the meta-analysis if they did not report BMI, report the number of cases with a recommended BMI, or specify a congenital anomaly group or subtype. The database searches elicited 1944 articles. A title and abstract review resulted in 102 original articles and 18 review articles. The abstracts and, where necessary, full articles were reviewed in detail. Reference lists were searched and produced 3 additional studies. Thirty-nine articles were included in the systematic review, and 18 of these articles were included in the meta-analysis (FIGURE 1).

Figure 1. Review and Selection of Articles



BMI indicates body mass index.

Data Extraction

A standardized, piloted data extraction form was used to retrieve information of interest, including study characteristics, participant information, measure for maternal weight estimation, congenital anomaly group or subtype, and analyses conducted. Data extraction was completed by 4 reviewers, each study being independently reviewed by 2 individuals. There were no discrepancies between reviewers in terms of data extracted or choice of articles meriting inclusion.

Meta-analysis

We followed published guidelines for the meta-analysis of observational studies.[14] We calculated odds ratios (ORs) and 95% confidence intervals (CIs) for all articles with sufficient data to compare obese or overweight mothers with maternal recommended BMI (reference category). Recommended and risk BMI categories were selected to best match the World Health Organization guidelines[15] (TABLE 1 and TABLE 2). Where direct calculation was not possible, reported ORs and CIs were used. Where data were duplicated between articles, only the largest or oldest article was included. Few articles presented adjusted ORs, so crude ORs were entered into the primary analysis, although, when reported, adjusted ORs and CIs were obtained for sensitivity analysis.

We calculated pooled ORs as the weighted average of the ORs for all congenital anomaly groups and subtypes where the total number of cases included across the risk and comparison groups, throughout the included articles, was greater than 150. The number of cases was chosen so that inclusion was determined by statistical power (150 cases would provide adequate power [0.81] to detect a medium effect [δ=0.5] in a typical study with a risk group prevalence of ≥10% and control-case ratio of ≥2:1). Weighting was assigned according to the inverse of the variance. Heterogeneity was tested using the Cochrane Q test and quantified with the I^2 statistic.[55] The value of the I^2 statistic was used to select the appropriate pooling method: fixed-effects models were used for I^2 less than 50% and random-effects models for I^2 greater than 50%. The presence of bias was examined using a combination of the Egger regression asymmetry test[56] and the trim and fill method.[57] The trim and fill method simulates studies that may be missing from the literature, for example, due to publication bias, and the trim and fill OR estimates the pooled OR if these "missing" studies were present. Agreement between the standard OR and the trim and fill OR provides confidence that the results are robust to bias.[58] Trim and fill ORs are reported where they

Table 1. Overview of Case-Control Studies Included in the Systematic Review

Study (Location)	Study Period	Risk Factor	Measurement of Maternal Weight	Pregnancy Outcomes Included	Definition of RBMI, Overweight, and Obese[a]	Congenital Anomaly Groups and Subtypes, No. of Cases (No. Used in Meta-analysis)
Richards,[16] 1969 (South Wales, UK)	1964-1966	Weight	Retrospectively self-reported by mother and confirmed in mother's records	"Births"	NA[b]	All nervous system anomalies, 279; neural tube defects, 247; anencephaly, 107; spina bifida, 140; all cardiovascular anomalies, 100; septal anomalies, 21; patent ductus arteriosus, 16; aortic anomalies, 29; all orofacial clefts, 66; pyloric stenosis, 39; limb reduction anomalies, 11; hip dislocation and/or dysplasia, 15; talipes, 92; eye and/or ear anomalies, 16; urinary and/or genital anomalies, 15; skin anomalies, 46[c]
Wald et al,[17] 1981 (Oxford, UK)	1972-1980	Weight	Measured at antenatal visit	NA (performed during pregnancy)	NA[b]	Neural tube defects, 56; anencephaly, 30; spina bifida, 26[c]
Haddow et al,[18] 1982 (US)	NS	Weight	Measured during second trimester	NA (performed during pregnancy)	NA[b]	Anencephaly, 27; spina bifida, 21[c]
Johnson et al,[19] 1990 (US)	NS	Weight	NS	NA (performed during pregnancy)	NA[b]	Spina bifida, 143[c]
Waller et al,[20] 1994 (California, Illinois)	1985-1987	BMI	Retrospectively self-reported by mother	Congenital anomaly diagnosed prenatally or postnatally	Recommended: 19-27; overweight: 28-30; obese: ≥31[d]	Neural tube defects, 499 (408); anencephaly, 156 (156); encephalocele, 39; spina bifida, 199 (199); all cardiovascular anomalies, 81 (81); septal anomalies, 33 (33); all respiratory anomalies, 7; diaphragmatic hernia, 7 (7); pyloric stenosis, 10; upper alimentary anomalies, 13; other intestinal anomalies, 14; all abdominal wall anomalies, 50; renal agenesis, 12; other urinary anomalies, 20; all genital anomalies, 8; limb reduction anomalies, 7; multiple anomalies, 8; other anomalies, 24[e,f,g]
Shaw et al,[21] 1996 (California)	1989-1991	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: 19-27; overweight: 28-30; obese: ≥31[d]	Neural tube defects, 538 (443); anencephaly, 217; spina bifida, 296; other neural tube defects, 25[e]
Watkins et al,[22] 1996 (Georgia)	1968-1980	BMI	Retrospectively self-reported by mother	Stillbirths, livebirths	Recommended: 19.8-26; overweight: >26-29; obese: >29[h]	Neural tube defects, 307 (201)
Werler et al,[23] 1996 (US, Canada)	1988-1994	Weight (1988-1994); BMI (1992-1994)	Retrospectively self-reported by mother	Terminations (from 1990), stillbirths, livebirths	Recommended: 19-23.9; overweight: 24-27.9; obese: ≥28[d]	Neural tube defects, 604 (79)
Lam et al,[24] 1999 (California)	1988-1990	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: 18.1-28.3; overweight: included in recommended and obese categories obese: >28.3[b]	Gastroschisis, 104 (88)[e]
Shaw et al,[25] 2000 (California)	Study A: 1989-1991; study B: 1987-1988	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: ≤29; overweight: included in recommended category; obese: >29[d]	Study 1: neural tube defects, 500; study 2: ; neural tube defects, 247; outflow tract anomalies, 202; cleft lip and cleft palate, 426; cleft palate, 207; all limb anomalies, 156[i]
Hendricks et al,[26] 2001 (Texas)	1995-2000	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: 18.5-24.9; overweight: 25-29.9; obese: ≥30[d]	Neural tube defects, 149 (146)
Shaw et al,[27] 2001 (California)	1989-1991	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: ≤29; overweight: included in recommended category; obese: >29[d]	Neural tube defects, 538[j]
Watkins and Botto,[28] 2001 (Georgia)	1968-1980	BMI	Retrospectively self-reported by mother	Stillbirths, livebirths	Recommended: 19.9-22.7; overweight: 26.1-29; obese: >29 (for all cardiovascular anomalies) or >26 (for named subtypes)[h]	All cardiovascular anomalies, 851 (408); double outlet arteriosus, 5; outflow tract anomalies, 132; septal anomalies, 221 (96); tetralogy of Fallot, 45 (24); transposition of the great arteries, 60 (29); truncus arteriosus, 16[f]
Cedergren et al,[29] 2002 (Sweden)	1982-1996	BMI	Measured at first antenatal visit	"Infants born"	Recommended: 19.8-26.0; overweight: 26.1-28.9; obese: ≥29[b]	Medical records study: all cardiovascular anomalies, 231 (181)
Cedergren et al,[30] 2002 (Sweden)	1973-1990	BMI	Measured at first antenatal visit	"Infants born"	Recommended: <29; overweight: included in recommended category; obese: ≥29[b]	All cardiovascular anomalies, 246[i]
Shaw et al,[31] 2002 (California)	1993-1996	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: ≤29; overweight: included in recommended category; obese: >29[d]	Multiple anomalies, 80[i]

(continued)

Table 1. Overview of Case-Control Studies Included in the Systematic Review (continued)

Study (Location)	Study Period	Risk Factor	Measurement of Maternal Weight	Pregnancy Outcomes Included	Definition of RBMI, Overweight, and Obese[a]	Congenital Anomaly Groups and Subtypes, No. of Cases (No. Used in Meta-analysis)
Cedergren and Källén,[32] 2003 (Sweden)	1992-2001	BMI	Measured at first antenatal visit	Stillbirths, livebirths	Recommended: 19.8-26; overweight: 26.1-29; obese: >29[d]	All cardiovascular anomalies, 7535 (6174); coarctation of the aorta, 117; hypoplastic left heart, 166; septal anomalies, 4220 (3840); tetralogy of Fallot, 223 (195); transposition of the great arteries, 164 (154)[f]
Honein et al,[33] 2003 (Georgia)	1968-1980	BMI	Retrospectively self-reported by mother	Stillbirths, livebirths	Recommended: <25; overweight: 25-29.9; obese: ≥30[h]	All urinary anomalies, 169; hydronephrosis, 91; renal agenesis, 41; renal multicystic dysplasia, 26; renal or ureter duplications, 11; urinary obstruction anomalies, 117[i]
Krauss et al,[34] 2003 (Missouri)	1993-1999	BMI	Birth certificates	Livebirths	Recommended: 19.9-26.0; overweight: 26.1-29.0; obese: ≥29.1[b]	Microcephaly, 360 (276)
Shaw et al,[35] 2003 (California)	1989-1991	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: ≤29; overweight: included in recommended category; obese: >29[d]	Neural tube defects, 454[j]
Waller et al,[36] 2003 (US, Canada)	1993-1997	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: 21.1-25.0; overweight: 25.1-29; obese: >29[b]	Diaphragmatic hernia, 85 (50)
Watkins et al,[37] 2003 (Georgia)	1993-1997	BMI	Retrospectively self-reported by mother	Terminations (≥20 weeks gestation), stillbirths, livebirths	Recommended: 18.5-24.9; overweight: 25-29.9; obese: ≥30[h]	Hydrocephaly, 14 (13); neural tube defects, 43 (40); anencephaly, 12 (11); encephalocele, 9; spina bifida, 22 (20); all cardiovascular anomalies, 195 (175); coarctation of the aorta, 12; hypoplastic left heart, 22; septal anomalies, 55 (49); tetralogy of Fallot, 19 (17); transposition of the great arteries, 25 (21); cleft lip, 26 (23); cleft lip and palate, 34 (33); cleft palate, 30 (29); diaphragmatic hernia, 17 (15); esophageal atresia, 20 (19); large intestinal atresia, 32; small intestinal atresia, 9; gastroschisis, 23 (22); omphalocele, 18; all urinary anomalies, 106; renal agenesis, 20; renal multicystic dysplasia, 30; urinary obstruction anomalies, 67; hypospadias, 21 (19); all limb anomalies, 45; craniosynostosis, 28 (24); multiple anomalies, 96[f,k]
Anderson et al,[38] 2005 (Texas)	1997-2001	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: 18.5-24.9; overweight: 25-29.9; obese: ≥30[h]	Holoprosencephaly, 41; hydrocephaly, 115 (94); neural tube defects, 302 (235); anencephaly, 119 (93); spina bifida, 183 (154)[f]
Martinez-Frias et al,[39] 2005 (Spain)	1995-2001	BMI	Retrospectively self-reported by mother	"Infants delivered"	Recommended: 21-24.9; overweight: 25-29.9; obese: ≥30[h]	Holoprosencephaly, NS; All cardiovascular anomalies, 764 (565); All urinary anomalies, NS; spine/rib defects, NS[l]
Velie et al,[40] 2006 (California)	1989-1991	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: 18.5-24.9; overweight: 25-29.9; obese: ≥30[d]	Neural tube defects, 538 (265)[k]
Carmichael et al,[41] 2007 (US)	1997-2000	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: 19.8-26; overweight: >26-29; obese: >29[b]	Hypospadias, 502[j]
Waller et al,[42] 2007 (US)	1997-2002	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: 18.5-24.9; overweight: 25-29.9; obese: ≥30[h]	Hydrocephaly, 156 (146); neural tube defects, 618 (588); anencephaly, 193 (183); spina bifida, 425 (405); all cardiovascular anomalies, 4128 (3873); cleft lip and palate, 1064 (972); cleft palate, 592 (559); anorectal atresia, 380 (363); diaphragmatic hernia, 286 (271); esophageal atresia, 278 (261); small intestinal atresia, 163; gastroschisis, 400 (359); omphalocele, 177; hypospadias, 793 (750); limb reduction anomalies, 509 (477); craniosynostosis, 422 (400); microtia and anotia, 216 (205)[f]

Abbreviations: NA, not applicable; NS, not specified; RBMI, recommended body mass index; UK, United Kingdom; US, United States.
[a] Calculated as weight in kilograms divided by height in meters squared.
[b] Diabetes status not specified or reported.
[c] Excluded from meta-analysis because BMI not reported.
[d] Included pregestational and/or gestational diabetes.
[e] Included some cases in obese meta-analysis only.
[f] Some cases excluded from meta-analysis because the associated anomaly group had fewer than 150 relevant cases.
[g] Some cases excluded from meta-analysis because there were 0 recorded cases in the risk group.
[h] Excluded pregestational and/or gestational diabetes.
[i] Excluded from meta-analysis because RBMI included underweight.
[j] Excluded from meta-analysis because data set reported elsewhere.
[k] Included some cases in overweight meta-analysis only.
[l] Included cardiovascular anomaly cases without gestational diabetes.

Table 2. Overview of Cohort Studies Included in the Systematic Review

Study (Location)	Study Period	Risk Factor	Measurement of Maternal Weight	Pregnancy Outcomes Included	Definition of RBMI, Overweight, and Obese[a]	Congenital Anomaly Groups and Subtypes, No. of Cases (No. Used in Meta-analysis)
Naeye, [43] 1990 (US)	1959-1966	BMI	Retrospectively self-reported by mother	Livebirths	Recommended: 20-24; overweight: 25-30; obese: >30[b]	"Major congenital malformations," 2504[c]
Berkowitz et al,[44] 1995 (New York)	1987-1990	BMI	NS	Livebirths	Recommended: <27.3; overweight: included in recommended and obese categories; obese: ≥27.3[b]	Cryptorchidism, 63[d]
Källén,[45] 1998 (Sweden)	1983-1989 and 1992-1993	BMI	Retrospectively self-reported by mother and estimated from weight at delivery	Stillbirths, livebirths	Recommended: 19.8-26; overweight: 26.1-29; obese: >29[e]	Neural tube defects, 621 (287); anencephaly, 79; encephalocele, 50; spina bifida, 492 (232)
Feldman et al,[46] 1999 (US)	NS	Weight	Measured "shortly before biochemical screening"	Unclear ("pregnancy outcomes")	NA[e]	Neural tube defects, 79[f]
Moore et al,[47] 2000 (US)	1984-1987	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: <28; overweight: included in recommended and obese categories; obese: ≥28[g]	Hydrocephaly, 12; Neural tube defects, 48; Hypoplastic left heart, 11; Septal anomalies, 20; All orofacial clefts, 16; Lung hypoplasia, 3; Pyloric stenosis, 9; All abdominal wall anomalies, 11; Renal agenesis, 4; All genital anomalies, 30; Lower limb reduction anomalies, 4; Talipes, 14; Polydactyly, 3; Congenital cataracts, 2[d,h]
Shaw et al,[48] 2000 (California)	1989-1991	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: ≤29; overweight: included in recommended category; obese: >29[b]	Spina bifida, 277[d]
Cedergren et al,[29] 2002 (Sweden)	1982-1996	BMI	Measured at first antenatal visit	"Infants born"	Recommended: 19.8-26.0; overweight: 26.1-28.9; obese: ≥29[e]	Register study: all cardiovascular anomalies, 2208; coarctation of the aorta, 95; hypoplastic left heart, 33; septal anomalies, 824; tetralogy of Fallot, 55; transposition of the great arteries, 65
Mikhail et al,[49] 2002 (Illinois)	1982-1994	BMI	NS	"Delivered babies," terminations	Recommended: <27; overweight: included in recommended and obese categories; obese: ≥27[i]	Neural tube defects, 17; all cardiovascular anomalies, 7; all abdominal wall anomalies, 8; renal agenesis, 13; multiple anomalies, 18[d]
García-Patterson et al,[50] 2004 (Spain)	1986-2002	BMI	NS	"Newborn infants"	1st tertile: 15.43-21.91; 2nd tertile: 21.92-24.77; 3rd tertile: 24.78-47.07[j]	All cardiovascular anomalies, 29; all orofacial clefts, 4; all urinary anomalies, 16; hypospadias, 6; skeletal anomalies, 14[k]
Cedergren and Källén,[51] 2005 (Sweden)	1992-2001	BMI	Measured at first antenatal visit	Stillbirths, livebirths	Recommended: 19.8-26; overweight: 26.1-29; obese: >29[e]	Cleft lip, 425 (318); cleft lip and palate, 644 (475); cleft palate, 610 (476)
Ray et al,[52] 2005 (Canada)	1994-2000	Weight	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	NA[b]	Neural tube defects, 292[f]
Callaway et al,[53] 2006 (Australia)	1998-2002	BMI	Prepregnancy weight estimated from measurement at first antenatal visit	"Deliveries"	Recommended: 20.01-25; overweight: 25.01-30; obese: ≥30.01[b]	Group/subtype unspecified: "birth defect(s)," 159[c,l]
Cedergren and Källén,[54] 2006 (Sweden)	1992-2001	BMI	Obtained from antenatal care center document	Stillbirths, livebirths	Recommended: 20-24.9; overweight: 25-29.9; obese: ≥30[i]	All cardiovascular anomalies, 6346[m]

Abbreviations: NA, not applicable; NS, not specified; RBMI, body mass index; UK, United Kingdom; US, United States.
[a] Calculated as weight in kilograms divided by height in meters squared.
[b] Included pregestational and/or gestational diabetes.
[c] Excluded from meta-analysis because no specific anomaly reported.
[d] Excluded from meta-analysis because RBMI included underweight.
[e] Diabetes status not specified or reported.
[f] Excluded from meta-analysis because BMI not reported.
[g] Stratified BMI by diabetes status.
[h] Numbers excluded those with diabetes.
[i] Excluded pregestational and/or gestational diabetes.
[j] Cohort included gestational cases only, no individuals with normal glucose tolerance.
[k] Excluded from meta-analysis because BMI reported in nonstandard format (tertiles).
[l] Estimated from reported percentages.
[m] Excluded from meta-analysis because data set reported elsewhere.

were significantly different from the standard pooled OR or if it changed the significance of the comparison.

A sensitivity analysis was performed to examine the potential effects of varying methodological quality and inclusion criteria. We defined higher-quality articles as those that reported the inclusion of pregnancies ending in termination, excluded mothers with pregestational diabetes, and excluded cases that were chromosomal or syndromic. We also examined the effect of using an objective measure of weight. The pooled ORs for each alternative scenario were compared with the principal ORs using *t* tests performed on the logarithm of the ORs (the logarithm being necessary to equalize the distance of the point estimate from the confidence limits, from which standard errors were derived).

Statistical analyses were performed using Stata 9.2 (StataCorp, College Station, Texas). The metan,[59] metabias,[60] and metatrim[61] macros were used for meta-analytic procedures. *P* values $<.05$ were considered statistically significant.

RESULTS

Thirty-nine articles met our inclusion criteria for the systematic review (Table 1 and Table 2). Of these, 25 were from the United States, 6 were from Sweden, 2 from the United Kingdom, 2 from Spain, 2 from across Canada and the United States, and 1 each from Canada and Australia. Twenty-nine articles reported the results of a case-control study and 12 of a cohort study (1 article reported a case-control and a cohort study[29] and 1 reported 2 case-control studies[25]). Body mass index was the most frequent measure of overweight and obesity (33 articles) while 6 articles reported only maternal weight. Neural tube defects (22 articles) were the most frequently investigated congenital anomaly group followed by cardiovascular anomalies (14).

Articles included in the systematic review varied in the method used to measure weight and in the range of BMI categories (Table 1). Terminations of pregnancy for fetal anomaly were included in 18 articles, stillbirths were included in 24 articles (definitions ranged from >19 weeks to >28 weeks), chromosomal anomalies were excluded in 16 articles, and diabetes status was reported in 27 articles.

Eighteen articles were included in the meta-analysis (TABLE 3). Among the 21 articles excluded, 6 did not report BMI,[16-19,46,52] 1 grouped BMI into tertiles,[50] 8 included maternal underweight in the recommended BMI catagory,[25,30,31,33,44,47-49] 4 reported data from the same population as a larger or earlier study included in the meta-analysis,[27,35,41,54] and 2 did not report a specific congenital anomaly group or subtype.[43,53] Pooled ORs for overweight and obesity were calculated for 16 and 15 anomaly groups or subtypes, respectively. Heterogeneity varied between 0% and 62.9%, with a median of 0.0%.

Neural Tube Defects

Obese mothers were at significantly increased odds of a pregnancy affected by a neural tube defect compared with mothers of recommended BMI (OR, 1.87; 95% CI, 1.62-2.15; $P<.001$) (FIGURE 2). Overweight mothers were also at significantly increased odds of a pregnancy affected by a neural tube defect (OR, 1.20; 95% CI, 1.04-1.38; $P=.01$); however, the trim and fill OR (including 3 simulated studies) was not significant (OR, 1.12; 95% CI, 0.98-1.28; $P=.09$).

Obese mothers were at significantly increased odds of a pregnancy affected by anencephaly compared with mothers of recommended BMI, although the effect size was much smaller than for all neural tube defects (OR, 1.39; 95% CI, 1.03-1.87; $P=.03$). The trim and fill OR (including 2 simulated studies) was not significant (OR, 1.17; 95% CI, 0.90-1.52; $P=.24$). No significant increased risk was found for maternal overweight.

There was a 2-fold increased odds of a pregnancy affected by spina bifida in obese mothers compared with mothers of recommended BMI, with an effect size that was much larger than for all neural tube defects (OR, 2.24; 95% CI, 1.86-2.69; $P<.001$). No significant increased risk was found for maternal overweight.

Nine articles with unique data were excluded from the meta-analysis,[17-19,25,46,47,49,52] of which 3 included more than 150 cases.[25,52] Two of these identified significantly elevated odds among mothers of higher weight or BMI[16,25,52] while the other reported a significant increase for anencephaly but not spina bifida.[16] Of the 6 articles with fewer than 150 cases,[17-19,46,47,49] 5 found no evidence of association[18,19,46,47,49] while 1 reported a significantly lower weight among mothers with a pregnancy affected by anencephaly.[17] In their reanalysis of a previously analyzed data set,[21] Shaw et al[48] reported a higher OR among obese mothers specifically for spina bifida.

Two articles reported the relative odds of a pregnancy affected by encephalocele.[20,37] Neither included more than 50 cases or identified evidence of an association with maternal BMI.

Cardiovascular Anomalies

Obese mothers were at significantly increased odds of a pregnancy affected by a cardiovascular anomaly compared with mothers of recommended BMI (OR, 1.30; 95% CI, 1.12-1.51; $P=.001$) (FIGURE 3). Significantly increased odds were also observed for overweight mothers (OR, 1.17; 95% CI, 1.03-1.34; $P=.02$). In both cases, there was significant evidence of heterogeneity. For the overweight category, there was also evidence of bias ($P=.05$) and the trim and fill OR (including 3 simulated studies) was not significant (OR, 1.08; 95% CI, 0.94-1.25; $P=.27$).

Obese mothers were at significantly increased odds of a pregnancy affected by a septal anomaly compared with mothers of recommended BMI (OR, 1.20; 95% CI, 1.09-1.31; $P<.001$) (Figure 3). No significant evidence of increased risk was found for maternal overweight.

No significant evidence of an association between maternal obesity and

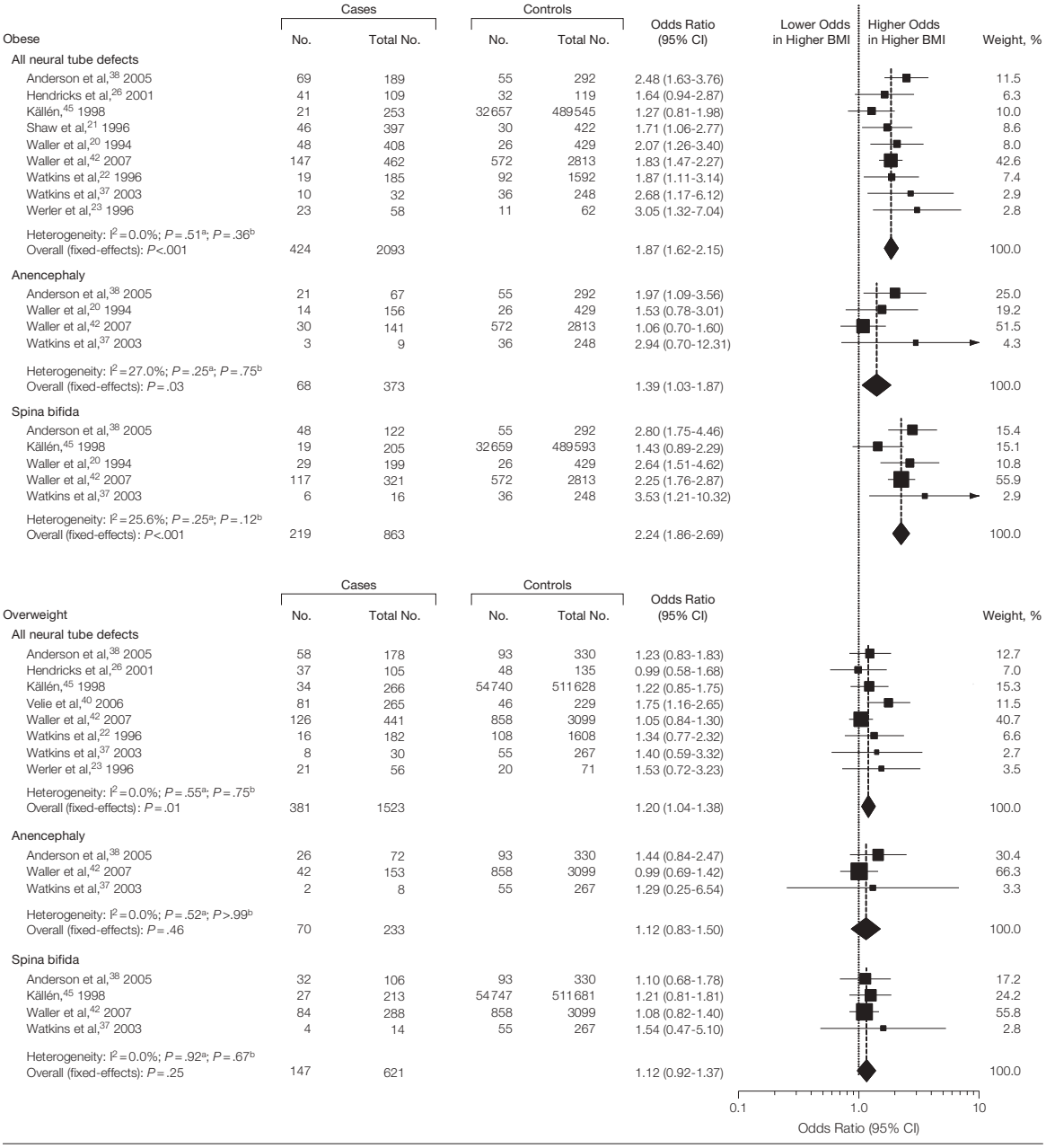
Table 3. Summary Results of the Meta-analysis

Congenital Anomaly Group or Subtype (References)	Studies, No.	Cases, No.	Summary Estimates			Bias Test *P* Value	Trim and Fill Estimates[a]		
			OR (95% CI)	*P* Value	I^2 Heterogeneity Index, % (*P* Value)		Missing Studies, No.	OR (95% CI)	*P* Value
Obese									
Neural tube defects									
All neural tube defects[20-23,26,37,38,42,45]	9	2093	1.87 (1.62-2.15)[b]	<.001	0.0 (.51)	.44	1	1.84 (1.60-2.12)	<.001
Anencephaly[20,37,38,42]	4	373	1.39 (1.03-1.87)[b]	.03	27.0 (.25)	.19	2	1.17 (0.90-1.52)	.24
Spina bifida[20,37,38,42,45]	5	863	2.24 (1.86-2.69)[b]	<.001	25.6 (.25)	.70	2	2.11 (1.68-2.59)	<.001
Cardiovascular anomalies									
All cardiovascular anomalies[20,28,29,32,37,39,42]	7	9349	1.30 (1.12-1.51)[c]	.001	58.1 (.03)	.34	2	1.24 (1.06-1.44)	.006
All septal anomalies[20,28,32,37]	4	3483	1.20 (1.09-1.31)[b]	<.001	9.8 (.34)	.09	2	1.18 (1.08-1.30)	<.001
Tetralogy of Fallot[28,32,37]	3	211	1.10 (0.76-1.61)[b]	.62	0.0 (.63)	.97	1	1.06 (0.74-1.52)	.76
Transposition of the great arteries[28,32,37]	3	182	1.41 (0.97-2.06)[b]	.07	0.0 (.56)	.48	0		
Orofacial clefts									
Cleft lip[37,51]	2	281	1.13 (0.82-1.57)[b]	.45	0.0 (.57)		0		
Cleft lip and palate[37,42,51]	3	1188	1.20 (1.03-1.40)[b]	.02	13.7 (.31)	.91	0		
Cleft palate[37,42,51]	3	865	1.23 (1.03-1.47)[b]	.02	0.0 (.54)	.11	0		
Other congenital anomalies									
Anorectal atresia[42]	1	273	1.48 (1.12-1.97)[d]	.006	NA				
Craniosynostosis[37,42]	2	312	1.18 (0.89-1.56)[b]	.25	0.0 (.59)		0		
Diaphragmatic hernia[20,36,37,42]	4	270	1.28 (0.95-1.71)[b]	.10	0.0 (.66)	.66	0		
Gastroschisis[24,42]	2	379	0.17 (0.10-0.30)[b]	<.001	0.0 (.84)		1	0.17 (0.10-0.28)	<.001
Hydrocephaly[37,38,42]	3	188	1.68 (1.19-2.36)[b]	.003	38.6 (.20)	.88	0		
Hypospadias[37,42]	2	576	1.08 (0.86-1.34)[b]	.52	0.0 (.41)		0		
Limb reduction anomalies[42]	1	354	1.34 (1.03-1.73)[d]	.03	NA				
Microcephaly[34]	1	234	1.10 (0.82-1.48)[d]	.54	NA				
Microtia and anotia[42]	1	159	1.11 (0.75-1.63)[d]	.61	NA				
Esophageal atresia[37,42]	2	222	1.27 (0.60-2.67)[c]	.54	50.6 (.16)		1	0.99 (0.49-2.00)	.97
Overweight									
Neural tube defects									
All neural tube defects[22,23,26,37,38,40,42,45]	8	1523	1.20 (1.04-1.38)[b]	.01	0.0 (.55)	.17	3	1.12 (0.98-1.28)	.09
Anencephaly[37,38,42]	3	233	1.12 (0.83-1.50)[b]	.46	0.0 (.52)	.68	2	0.99 (0.77-1.28)	.93
Spina bifida[37,38,42,45]	4	621	1.12 (0.92-1.37)[b]	.25	0.0 (.92)	.16	1	1.11 (0.91-1.35)	.29
Cardiovascular anomalies									
All cardiovascular anomalies[28,29,32,37,39,42]	6	9630	1.17 (1.03-1.34)[c]	.02	62.9 (.02)	.05	3	1.08 (0.94-1.25)	.27
All septal anomalies[32,37]	2	3355	1.15 (0.71-1.85)[c]	.58	51.9 (.15)		3	0.99 (0.64-1.52)	.96
Tetralogy of Fallot[32,37]	2	183	0.82 (0.53-1.25)[b]	.35	20.0 (.26)		1	0.74 (0.41-1.35)	.33
Orofacial clefts									
Cleft lip[37,51]	2	298	1.29 (0.97-1.71)[b]	.08	0.0 (.90)		0		
Cleft lip and palate[37,42,51]	3	1237	1.00 (0.87-1.15)[b]	>.99	0.0 (.48)	.27	2	0.95 (0.84-1.07)	.41
Cleft palate[37,42,51]	3	890	1.02 (0.86-1.20)[b]	.86	0.0 (.88)	.71	0		
Other congenital anomalies									
Anorectal atresia[42]	1	288	1.19 (0.91-1.54)[d]	.20	NA				
Craniosynostosis[37,42]	2	353	1.24 (0.98-1.58)[b]	.07	0.0 (.43)		1	1.21 (0.96-1.53)	.10
Diaphragmatic hernia[36,37,42]	3	272	0.95 (0.72-1.26)[b]	.72	0.0 (.69)	.50	2	0.89 (0.69-1.15)	.38
Gastroschisis[37,42]	2	369	0.83 (0.39-1.77)[c]	.63	59.5 (.12)		1	0.64 (0.32-1.27)	.20
Hydrocephaly[37,38,42]	3	198	1.28 (0.93-1.75)[b]	.13	0.0 (.50)	.71	2	1.10 (0.84-1.44)	.48
Hypospadias[37,42]	2	646	1.13 (0.94-1.35)[b]	.21	0.0 (.61)		1	1.12 (0.93-1.34)	.24
Limb reduction anomalies[42]	1	387	1.22 (0.97-1.53)[d]	.09	NA				
Microcephaly[34]	1	210	1.21 (0.85-1.73)[d]	.30	NA				
Microtia and anotia[42]	1	170	0.97 (0.69-1.37)[d]	.86	NA				
Esophageal atresia[37,42]	2	234	0.89 (0.66-1.21)[b]	.46	11.1 (.29)		0		

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.
[a] The trim and fill method simulates studies that are likely to be missing from the literature due to publication (or other forms of) bias; the trim and fill OR estimates what the pooled OR would be if these "missing" studies were present in the literature.
[b] Fixed-effects pooling method.
[c] Random-effects pooling method.
[d] No pooling method was used because the data were derived from a single study (with greater than 150 cases across the risk and comparison groups).

tetralogy of Fallot or transposition of the great arteries was found, although the OR for transposition of the great arteries was close to significance (OR, 1.41; 95% CI, 0.97-2.06; $P = .07$) (Figure 3). When overweight mothers were compared with mothers of recommended BMI, there was no significant difference in the occurrence of te-

Figure 2. Forest Plot for Neural Tube Defects



Data markers within each subplot are proportional to the assigned study weight.
[a]Test for heterogeneity between studies. [b]Test for heterogeneity between definitions of obese/overweight.

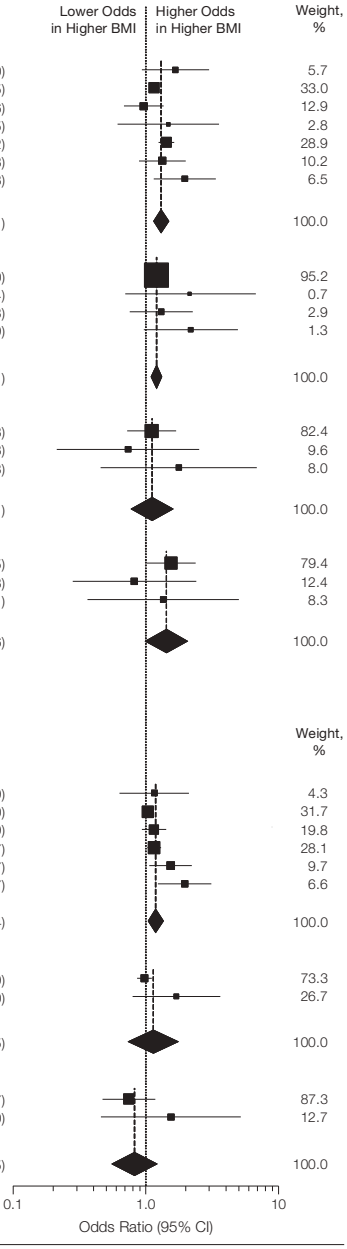
tralogy of Fallot, and there were insufficient cases of transposition of the great arteries for analysis.

Five articles with unique data were excluded from the meta-analysis,[16,30,47,49,50] including 1 with more than 150 cases that found no evidence of an association between maternal obesity and the odds of a pregnancy being af-

Figure 3. Forest Plot for Cardiovascular Anomalies

Obese	Cases No.	Cases Total No.	Controls No.	Controls Total No.	Odds Ratio (95% CI)	Weight, %
All cardiovascular anomalies						
Cedergren et al,[30] 2002	23	162	30	335	1.68 (0.94-3.00)	5.7
Cedergren and Källén,[32] 2003	826	5300	85 207	621 586	1.16 (1.08-1.25)	33.0
Martinez-Frias et al,[39] 2005	43	388	353	3106	0.97 (0.70-1.36)	12.9
Waller et al,[20] 1994	8	81	26	429	1.48 (0.62-3.55)	2.8
Waller et al,[42] 2007	784	2934	572	2813	1.43 (1.26-1.62)	28.9
Watkins and Botto,[28] 2001	38	357	92	1117	1.33 (0.89-1.98)	10.2
Watkins et al,[37] 2003	32	127	36	248	1.98 (1.16-3.38)	6.5
Heterogeneity: I^2 = 58.1%; P = .03[a]; P = .05[b]						
Overall (random-effects): P = .001	1754	9349			1.30 (1.12-1.51)	100.0
All septal anomalies						
Cedergren and Källén,[32] 2003	524	3317	85 509	623 569	1.18 (1.08-1.30)	95.2
Waller et al,[20] 1994	4	33	26	429	2.14 (0.70-6.54)	0.7
Watkins and Botto,[28] 2001	25	96	200	1225	1.30 (0.76-2.23)	2.9
Watkins et al,[37] 2003	10	37	36	248	2.18 (0.97-4.89)	1.3
Heterogeneity: I^2 = 9.8%; P = .34[a]; P = .34[b]						
Overall (fixed-effects): P<.001	563	3483			1.20 (1.09-1.31)	100.0
Tetralogy of Fallot						
Cedergren and Källén,[32] 2003	26	174	86 007	626 712	1.10 (0.73-1.68)	82.4
Watkins and Botto,[28] 2001	3	24	200	1225	0.73 (0.22-2.48)	9.6
Watkins et al,[37] 2003	3	13	36	248	1.77 (0.46-6.73)	8.0
Heterogeneity: I^2 = 0.0%; P = .63[a]; P = .63[b]						
Overall (fixed-effects): P = .62	32	211			1.10 (0.76-1.61)	100.0
Transposition of the great arteries						
Cedergren and Källén,[32] 2003	27	137	86 006	626 749	1.54 (1.01-2.35)	79.4
Watkins and Botto,[28] 2001	4	29	200	1225	0.82 (0.28-2.38)	12.4
Watkins et al,[37] 2003	3	16	36	248	1.36 (0.37-5.01)	8.3
Heterogeneity: I^2 = 0.0%; P = .56[a]; P = .56[b]						
Overall (fixed-effects): P = .07	34	182			1.41 (0.97-2.06)	100.0

Overweight	Cases No.	Cases Total No.	Controls No.	Controls Total No.	Odds Ratio (95% CI)	Weight, %
All cardiovascular anomalies						
Cedergren et al,[30] 2002	19	158	36	341	1.16 (0.64-2.09)	4.3
Cedergren and Källén,[32] 2003	874	5348	102 504	638 883	1.02 (0.95-1.10)	31.7
Martinez-Frias et al,[39] 2005	177	522	1236	3989	1.14 (0.94-1.39)	19.8
Waller et al,[42] 2007	939	3089	858	3099	1.14 (1.02-1.27)	28.1
Watkins and Botto,[28] 2001	51	370	108	1113	1.52 (1.06-2.17)	9.7
Watkins et al,[37] 2003	48	143	55	267	1.95 (1.23-3.07)	6.6
Heterogeneity: I^2 = 62.9%; P = .02[a]; P = .02[b]						
Overall (random-effects): P = .02	2108	9630			1.17 (1.03-1.34)	100.0
All septal anomalies						
Cedergren and Källén,[32] 2003	523	3316	102 855	640 915	0.99 (0.90-1.09)	73.3
Watkins et al,[37] 2003	12	39	55	267	1.71 (0.82-3.60)	26.7
Heterogeneity: I^2 = 51.9%; P = .15[a]; P = .15[b]						
Overall (random-effects): P = .58	535	3355			1.15 (0.71-1.85)	100.0
Tetralogy of Fallot						
Cedergren and Källén,[32] 2003	21	169	103 857	644 062	0.74 (0.47-1.17)	87.3
Watkins et al,[37] 2003	4	14	55	267	1.54 (0.47-5.10)	12.7
Heterogeneity: I^2 = 20.0%; P = .26[a]; P = .26[b]						
Overall (fixed-effects): P = .35	25	183			0.82 (0.53-1.25)	100.0



Data markers within each subplot are proportional to the assigned study weight.
[a]Test for heterogeneity between studies.
[b]Test for heterogeneity between definitions of obese/overweight.

fected by a cardiovascular anomaly.[30] Of the 4 articles with fewer than 150 cases, 3 found no evidence of association[16,47,50] while 1 reported significantly higher odds among obese mothers.[49] Additional data provided in Cedergren et al[29] also identified increased odds of cardiovascular anomalies associated with maternal obesity.

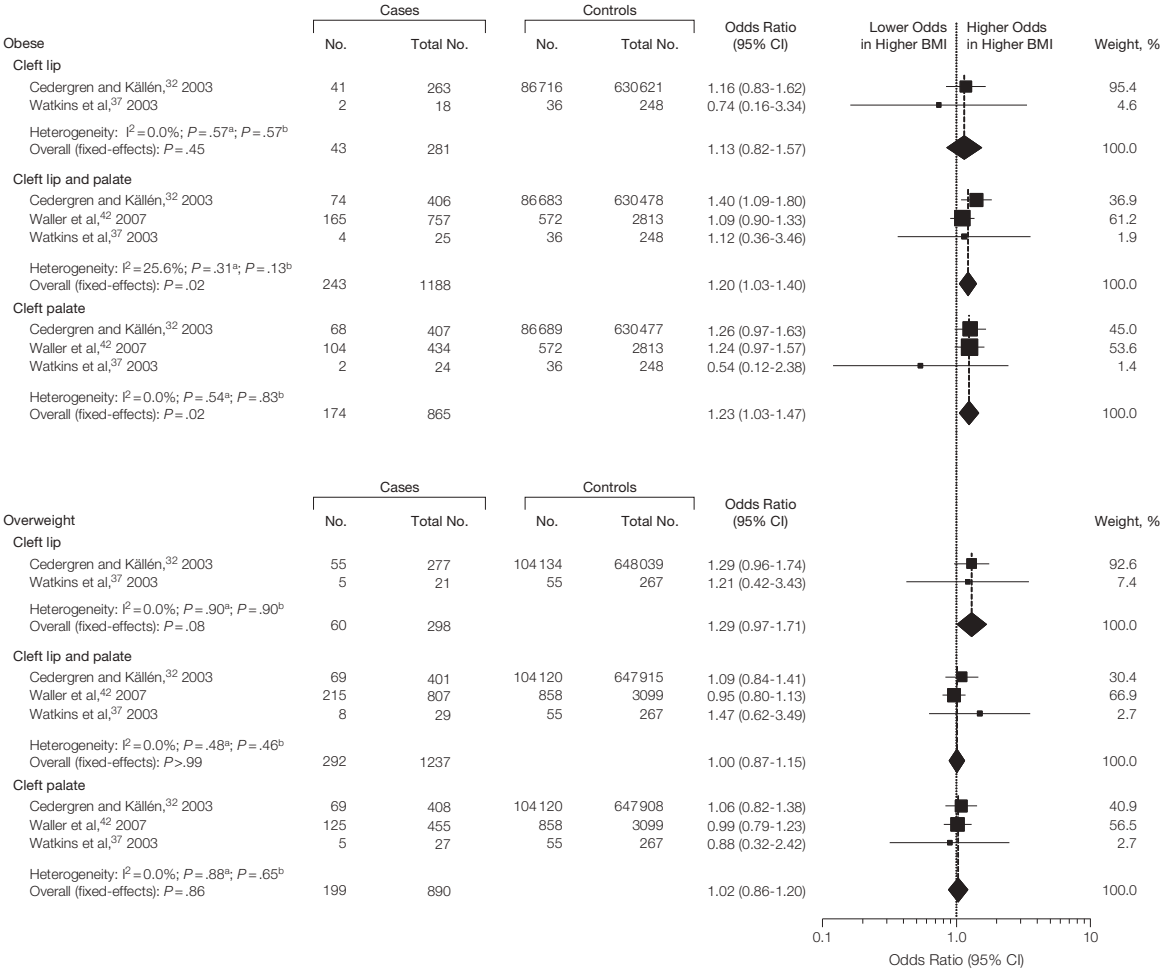
Two additional articles reported the relative odds of a pregnancy affected by an outflow tract anomaly,[25,28] including 1 with more than 150 cases.[25] Neither identified a significant association with maternal obesity. Body mass index or weight data were also reported in relation to hypoplastic left heart,[32,37,47] coarctation of the aorta,[32,37] patent ductus arteriosus,[16] and aortic anomalies.[16] No significant evidence of an association was identified in any of these articles.

Orofacial Clefts

Obese mothers were at significantly increased odds of a pregnancy affected by either cleft palate (OR, 1.23; 95% CI, 1.03-1.47; $P=.02$) or cleft lip and palate (OR, 1.20; 95% CI, 1.03-1.40; $P=.02$) compared with mothers of recommended BMI (FIGURE 4) but not for cleft lip alone. Cleft lip, cleft palate, or cleft lip and palate did not occur more frequently in mothers who were overweight, although, for cleft lip, the OR was close to significance (OR, 1.29; 95% CI, 0.97-1.71; $P=.08$).

Three articles with unique data were excluded from the meta-analysis,[16,25,47] including 1 with more than

Figure 4. Forest Plot for Orofacial Clefts



Data markers within each subplot are proportional to the assigned study weight.
[a]Test for heterogeneity between studies. [b]Test for heterogeneity between definitions of obese/overweight.

150 cases that found no evidence of an association between maternal obesity and the risk of a pregnancy affected by an orofacial cleft.[25] Of the 2 others, one included evidence of an increased risk associated with maternal obesity[47] while the other found no evidence of an association.[16]

Other Congenital Anomalies

Obese mothers were at significantly increased odds of a pregnancy affected by anorectal atresia compared with mothers of recommended BMI (OR, 1.48; 95% CI, 1.12-1.97; $P=.006$). There was no evidence of an association with maternal overweight.

Obese mothers were at significantly increased odds of a pregnancy affected by hydrocephaly compared with mothers of recommended BMI (OR, 1.68; 95% CI, 1.19-2.36; $P=.003$). No significant increased risk was found for maternal overweight.

There was an increased risk of a pregnancy affected by a limb reduction anomaly (OR, 1.34; 95% CI, 1.03-1.73; $P=.03$) among obese mothers compared with mothers of recommended BMI. There was no association with maternal overweight, although the OR was close to significance (OR, 1.22; 95% CI, 0.97-1.53; $P=.09$).

The prevalence of gastroschisis was significantly lower among mothers who were obese compared with mothers of recommended BMI (OR, 0.17; 95% CI, 0.10-0.30; $P<.001$). There was no association with maternal overweight.

There was no association between either maternal overweight or obesity and the risk of a pregnancy affected by diaphragmatic hernia, esophageal atresia, hypospadias, microcephaly, or microtia/anotia. The OR for a pregnancy affected by craniosynostosis was close to significance (OR, 1.24; 95% CI, 0.98-1.58; $P=.07$) among overweight mothers, but no evidence of an association was observed for maternal obesity.

Two additional articles that were not included in the meta-analysis reported maternal BMI data in relation to hydrocephaly[47] and limb reduction anomalies.[16] Neither included more than 150 cases nor found evidence of an association with maternal obesity.

Several additional congenital anomaly subtypes were reported that could not be included in the meta-analysis. Of 6 articles involving urinary anomalies[20,33,37,50] and/or renal agenesis specifically,[20,37,47,49] only 1 had more than 150 cases.[33] Neither this article nor 4 of the others[20,37,47,49] found an association with maternal obesity.

Three articles considered abdominal wall anomalies;[20,47,49] 2 specifically considered omphalocele,[37,42] 1 of which had more than 150 cases.[42] These articles identified a significantly increased risk of an omphalocele among obese mothers. One article reported a significantly elevated risk of an abdominal wall defect among obese mothers[20] while the others did not.[47,49]

Four articles investigated the relative odds of multiple anomalies.[20,31,37,49] Two articles reported significantly increased odds among obese mothers[31,37] while 2 found no association.[20,49]

Body mass index or weight data were reported for holoprosencephaly,[38] lung hypoplasia,[47] upper alimentary anomalies,[20] pyloric stenosis,[16,20,47] small intestinal atresia,[37,42] large intestinal atresia,[37] renal multicystic dysplasia,[37] urinary obstruction,[37] all genital anomalies,[20,47] cryptorchidism,[44] limb anomalies,[37] talipes,[16,47] hip dislocation or dysplasia,[16] skeletal anomalies,[50] skin anomalies,[16] eye or ear anomalies,[16] and urinary or genital anomalies.[16] Only 2 articles reported an association with maternal weight or BMI; 1 reported increased odds of cryptorchidism, although the association with preterm birth was not analyzed,[44] and the other reported increased odds of talipes among obese mothers.[16]

Sensitivity Analysis

Changing the pooling model or any of the methodological inclusion or exclusion criteria did not significantly modify the pooled ORs for either neural tube defects or cardiovascular anomalies (FIGURE 5). Omitting articles with fewer than 150 cases did not significantly alter any of the pooled ORs, although larger effect sizes were reported, consistent with a publication bias effect.

COMMENT

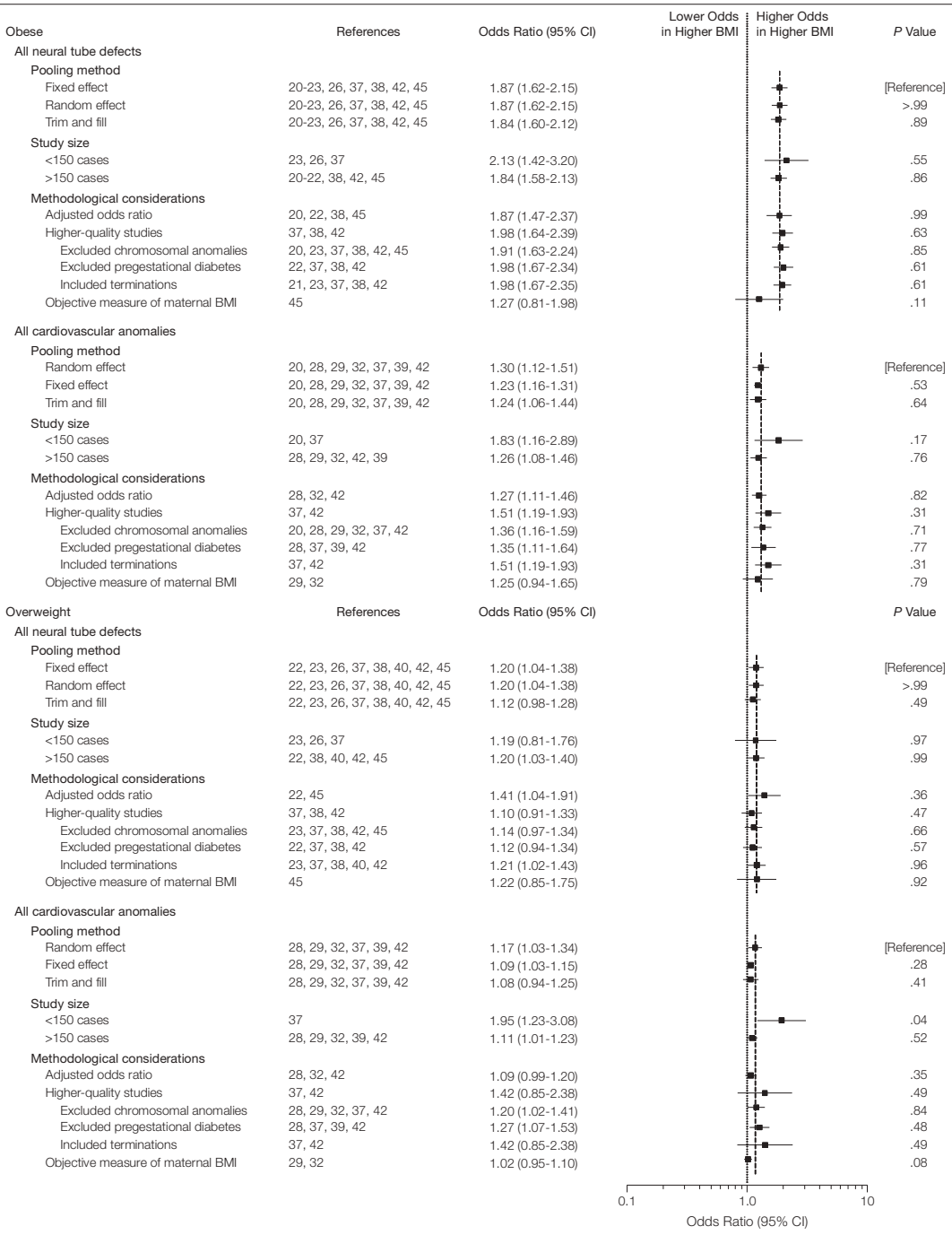
This systematic review investigated the effect of greater-than-recommended maternal weight, either prepregnancy or early pregnancy, on congenital anomaly risk. In women who were obese at the start of pregnancy, the meta-analysis demonstrated a significantly increased risk of a pregnancy affected by a neural tube defect, including spina bifida; cardiovascular anomaly, including a septal anomaly; cleft palate and cleft lip and palate; anorectal atresia; hydrocephaly; and a limb reduction anomaly. The risks of anencephaly among obese mothers, and for neural tube defects and cardiovascular anomalies among overweight mothers, were also significantly elevated, but these results were not robust to potential bias. The risk of gastroschisis among obese mothers was significantly reduced.

Articles included in the systematic review but not included in the meta-analysis generally had low power to find an effect, and thus, the majority found no evidence of association between increased maternal BMI or weight and the risk of congenital anomaly. Of the congenital anomaly subgroups not analyzed in the meta-analysis, it is noteworthy that the risks of omphalocele and multiple congenital anomalies were both found to be significantly higher among obese mothers.

We report results for neural tube defects similar to those reached in a recent meta-analysis,[62] which reported pooled ORs of 1.70 (95% CI, 1.34-2.15) and 1.22 (95% CI, 0.99-1.49) for obese and overweight mothers, respectively. The range of articles included in that analysis differed from those presented here. Notably, we were able to include a large, recently published article.[42] Rasmussen et al[62] also included weight alongside BMI in their meta-analysis and employed Bayesian pooling methods.

Our study, thus, extends the findings of this previous analysis. First, our

Figure 5. Sensitivity Analysis



Obese	References	Odds Ratio (95% CI)	*P* Value
All neural tube defects			
Pooling method			
Fixed effect	20-23, 26, 37, 38, 42, 45	1.87 (1.62-2.15)	[Reference]
Random effect	20-23, 26, 37, 38, 42, 45	1.87 (1.62-2.15)	>.99
Trim and fill	20-23, 26, 37, 38, 42, 45	1.84 (1.60-2.12)	.89
Study size			
<150 cases	23, 26, 37	2.13 (1.42-3.20)	.55
>150 cases	20-22, 38, 42, 45	1.84 (1.58-2.13)	.86
Methodological considerations			
Adjusted odds ratio	20, 22, 38, 45	1.87 (1.47-2.37)	.99
Higher-quality studies	37, 38, 42	1.98 (1.64-2.39)	.63
Excluded chromosomal anomalies	20, 23, 37, 38, 42, 45	1.91 (1.63-2.24)	.85
Excluded pregestational diabetes	22, 37, 38, 42	1.98 (1.67-2.34)	.61
Included terminations	21, 23, 37, 38, 42	1.98 (1.67-2.35)	.61
Objective measure of maternal BMI	45	1.27 (0.81-1.98)	.11
All cardiovascular anomalies			
Pooling method			
Random effect	20, 28, 29, 32, 37, 39, 42	1.30 (1.12-1.51)	[Reference]
Fixed effect	20, 28, 29, 32, 37, 39, 42	1.23 (1.16-1.31)	.53
Trim and fill	20, 28, 29, 32, 37, 39, 42	1.24 (1.06-1.44)	.64
Study size			
<150 cases	20, 37	1.83 (1.16-2.89)	.17
>150 cases	28, 29, 32, 42, 39	1.26 (1.08-1.46)	.76
Methodological considerations			
Adjusted odds ratio	28, 32, 42	1.27 (1.11-1.46)	.82
Higher-quality studies	37, 42	1.51 (1.19-1.93)	.31
Excluded chromosomal anomalies	20, 28, 29, 32, 37, 42	1.36 (1.16-1.59)	.71
Excluded pregestational diabetes	28, 37, 39, 42	1.35 (1.11-1.64)	.77
Included terminations	37, 42	1.51 (1.19-1.93)	.31
Objective measure of maternal BMI	29, 32	1.25 (0.94-1.65)	.79
Overweight	**References**	**Odds Ratio (95% CI)**	***P* Value**
All neural tube defects			
Pooling method			
Fixed effect	22, 23, 26, 37, 38, 40, 42, 45	1.20 (1.04-1.38)	[Reference]
Random effect	22, 23, 26, 37, 38, 40, 42, 45	1.20 (1.04-1.38)	>.99
Trim and fill	22, 23, 26, 37, 38, 40, 42, 45	1.12 (0.98-1.28)	.49
Study size			
<150 cases	23, 26, 37	1.19 (0.81-1.76)	.97
>150 cases	22, 38, 40, 42, 45	1.20 (1.03-1.40)	.99
Methodological considerations			
Adjusted odds ratio	22, 45	1.41 (1.04-1.91)	.36
Higher-quality studies	37, 38, 42	1.10 (0.91-1.33)	.47
Excluded chromosomal anomalies	23, 37, 38, 42, 45	1.14 (0.97-1.34)	.66
Excluded pregestational diabetes	22, 37, 38, 42	1.12 (0.94-1.34)	.57
Included terminations	23, 37, 38, 40, 42	1.21 (1.02-1.43)	.96
Objective measure of maternal BMI	45	1.22 (0.85-1.75)	.92
All cardiovascular anomalies			
Pooling method			
Random effect	28, 29, 32, 37, 39, 42	1.17 (1.03-1.34)	[Reference]
Fixed effect	28, 29, 32, 37, 39, 42	1.09 (1.03-1.15)	.28
Trim and fill	28, 29, 32, 37, 39, 42	1.08 (0.94-1.25)	.41
Study size			
<150 cases	37	1.95 (1.23-3.08)	.04
>150 cases	28, 29, 32, 39, 42	1.11 (1.01-1.23)	.52
Methodological considerations			
Adjusted odds ratio	28, 32, 42	1.09 (0.99-1.20)	.35
Higher-quality studies	37, 42	1.42 (0.85-2.38)	.49
Excluded chromosomal anomalies	28, 29, 32, 37, 42	1.20 (1.02-1.41)	.84
Excluded pregestational diabetes	28, 37, 39, 42	1.27 (1.07-1.53)	.48
Included terminations	37, 42	1.42 (0.85-2.38)	.49
Objective measure of maternal BMI	29, 32	1.02 (0.95-1.10)	.08

Dashed lines indicate the value of the odds ratio for the default model in each subcategory (reference). *P* values are for difference from reference odds ratio. Adjusted odds ratios were adjusted for maternal age, cigarette smoking status, and vitamin supplementation. BMI indicates body mass index; CI, confidence interval.

extensive examination of publication bias helps confirm that the effect of obesity on neural tube defects is unlikely to be the result of differential publication. Second, by analyzing spina bifida and anencephaly separately, we are able to confirm previous observations[20,21,63] that the effect of obesity is distinct between anencephaly and spina bifida. Finally, our study investigates numerous other congenital anomaly groups and subtypes.

Study Strengths and Limitations

The use of exhaustive search techniques and validated systematic review methods, following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines,[14] strengthens our conclusions. Our approach enabled the subdivision of several congenital anomaly groups, reducing the problem of combining anomalies with potentially heterogenic etiologies. We also examined the possible impact of maternal overweight on congenital anomaly risk. In the meta-analysis, robust statistical procedures were used to estimate the presence of bias, and we further employed the trim and fill method to estimate the impact of bias as has been recommended.[58]

There are several methodological limitations. The exclusion of non-English publications means that potentially relevant articles may have been missed. For example, our literature search identified 1 non–English language article in which statistically significant associations were found between maternal obesity and encephalocele, common truncus arteriosus, orofacial clefts, eye anomalies, Potter syndrome, and anomalies of the urogenital system.[64]

Inherent in a systematic review is the risk of publication bias, and indeed smaller studies consistently reported larger effect sizes. We did not attempt to access "gray literature," which may contain smaller null-result studies that were not accepted for publication.

In the meta-analysis, articles were pooled regardless of their internal definitions of overweight and obesity. Weight categories were therefore not identical across the studies; recommended BMI ranged from 18.1 to 28.3, overweight from 22.8 to 30, and obese from less than 26 to greater than 30. However, many articles used predefined BMI categories (such as the World Health Organization[15] and Institute of Medicine[65] classifications); thus, broadly similar definitions were used. Furthermore, for the majority of congenital anomaly subtypes, no significant heterogeneity was found between articles adopting different definitions of obesity (Figures 2, 3, and 4). However, it is possible that the pooling of data based on these different definitions will have introduced some random error.

As with all meta-analyses, the validity of the results is limited by the conduct and reporting of the studies from which the data were extracted and pooled. One issue was the ascertainment of maternal weight. In most studies, prepregnancy or early pregnancy maternal weight was based on self-report. Since weight is usually differentially underreported by heavier individuals,[66,67] the pooled ORs in this meta-analysis are likely to be overestimates. This appears to be supported by the reduced (albeit nonsignificantly) ORs for cardiovascular anomalies taken from the 2 articles that had an objective measure of maternal BMI.

False negatives are possible where only a limited number of cases were available for a particular congenital anomaly group or subtype. For this reason, any congenital anomaly with fewer than 150 total cases was not included in the meta-analysis. However, for subtypes with a small numbers of cases, a null result should not be taken as evidence of no effect. For some congenital anomalies, the published data were insufficient to draw firm conclusions. For others, no evidence is available.

We performed a sensitivity analysis to examine how alternative inclusion criteria may have altered the results of our meta-analysis. The observation that none of the ORs from the more selective, alternative models were significantly different from the reference ORs, and that none would have altered the conclusions of significance (except for the small models that only included articles with objective measures of BMI), supports the primary conclusions and suggests that our results are robust to confounding influences.

Only articles that reported maternal BMI and included a recommended BMI reference category were included in the meta-analysis. Although some potentially relevant studies may therefore have been excluded, the reported risk estimates are independent of height, and are less likely to be biased by the inclusion of underweight or (in most instances) overweight mothers in the reference category.

Potential Mechanisms

A number of potential explanations for an association between maternal overweight and obesity and congenital anomaly have been posited. Obesity and diabetes share similar metabolic abnormalities, including insulin resistance and hyperglycemia,[68-70] and obesity is a strong risk factor for type 2 diabetes. Maternal diabetes is an established risk factor for congenital anomaly, especially central nervous system and cardiovascular anomalies.[71,72] Thus, undiagnosed diabetes and hyperglycemia in obese pregnant women is one potential explanation for the increased risk of congenital anomalies.

Maternal obesity has also been associated with nutritional deficiencies, specifically reduced folate levels,[73,74] and the protective effect of folic acid in reducing the risk of a neural tube defect may not be observed in obese women.[23] It is notable that many of the congenital anomalies implicated in this review have similar developmental timing and responsiveness to folic acid, suggesting a common underlying etiology. Deficiencies in other nutrients may underlie the association with other congenital anomalies.

Ultrasound scanning is more difficult in obese women,[75] potentially

resulting in fewer terminations of pregnancy for fetal anomaly and therefore increased prevalence at birth. This would explain the discordant effect sizes of anencephaly and spina bifida, as prenatal detection of spina bifida is less sensitive than anencephaly,[76] providing a greater opportunity for differentially missed cases. However, the sensitivity analysis found no evidence of a smaller OR when considering only articles that included terminations of pregnancy.

The observation that the risk of gastroschisis was reduced among obese mothers is most likely due to correlation with maternal age, since low maternal age is an established risk factor for gastroschisis[77] and BMI is itself associated with age.[78]

Implications

Our review confirms that maternal obesity raises the risk of a range of congenital anomalies, including neural tube defects, cardiovascular anomalies, cleft palate, hydrocephaly, and limb reduction anomalies. Further research should be powered to investigate the complete range of BMI to investigate the possible pattern of dose response, which may contribute to understanding the etiology of these congenital anomalies.

Furthermore, large, high-quality, population-based studies are needed to confirm or refute associations for several other congenital anomaly groups or subtypes that have currently only been investigated in very small numbers, such as renal anomalies and genital anomalies, or have not been investigated at all, such as respiratory anomalies.

The sensitivity analyses suggested that inclusion of affected pregnancies ending in termination, inclusion of women with diabetes, exclusion of chromosomal anomalies, and adjustment for other factors (such as smoking and parity) had limited impact on the effect estimates because the summary ORs were not significantly different between the default model and any of the models with more complete inclusion criteria. That we did not identify a detectable confounding influence by maternal diabetes corresponds with several of the constituent articles, which individually found no evidence of confounding after mothers with diabetes were excluded.* However, it was difficult to evaluate the impact of retrospective self-reporting of prepregnancy or early pregnancy weight because of its widespread use. Nevertheless, future studies are encouraged to consider these, and other, factors as possible confounders because the sensitivity analysis may not have had sufficient power to rule out subtle potential confounding influences.

An estimated 3% of all livebirths in the United States are affected by a structural anomaly[79] with 0.68 per 1000 births being affected by a neural tube defect and 2.25 per 1000 births being affected by a serious heart anomaly. Given the findings of this review, and the BMI profile of the female population during the period when these estimates were generated,[80] we calculate that the absolute risk of a pregnancy affected by a neural tube defect or a serious heart anomaly is respectively 0.47 per 1000 births and 0.61 per 1000 births greater in an obese woman than a woman of recommended BMI in prepregnancy or early pregnancy. This has health implications, particularly given the continued rise in the prevalence of obesity in many countries.

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Study concept and design: Rankin, Bell.
Acquisition of data: Stothard.
Analysis and interpretation of data: Stothard, Tennant, Bell, Rankin.
Drafting of the manuscript: Stothard, Tennant.
Critical revision of the manuscript for important intellectual content: Stothard, Tennant, Bell, Rankin.
Statistical analysis: Tennant.
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Epidemiology

Impact of maternal body mass index on the antenatal detection of congenital anomalies

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Objective To investigate the association between maternal body mass index (BMI) and antenatal ultrasound detection of congenital anomalies.

Design Population-based register study.

Setting North of England (UK).

Population All pregnancies (n = 3096) associated with a congenital anomaly notified to the Northern Congenital Abnormality Survey (NorCAS) during 2006–2009. Cases with chromosomal and teratogenic anomalies (n = 611) or without information on antenatal scanning (n = 4) were excluded.

Methods Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for antenatal detection according to maternal BMI categories were estimated using logistic regression.

Main outcome measures For all anomalies combined, cases were defined as 'detected' if any congenital anomaly was suspected antenatally. Organ system-specific anomalies were defined as detected if an anomaly of the correct system was suspected.

Results Antenatal detection of any anomaly occurred in 1146 of 2483 (46.2%) cases with normal karyotype. The odds of detection were significantly decreased in obese (BMI ≥ 30 kg/m^2) women compared with women of recommended BMI (18.5–24.9 kg/m^2; aOR, 0.77; 95% CI, 0.60–0.99; P = 0.046). Cardiovascular system anomalies were suspected antenatally in 109 of 945 (11.5%) cases. The odds of detecting a cardiovascular anomaly were significantly greater in underweight women (BMI < 18.5 kg/m^2) than in women of recommended BMI (aOR, 2.95; 95% CI, 1.13–7.70; P = 0.027). There was no association between BMI and detection in any other organ system or between BMI and termination of pregnancy for fetal anomaly.

Conclusions Antenatal ultrasound detection of a congenital anomaly is decreased in obese pregnant women. This has implications for the scanning and counselling of obese women.

Keywords Body weight, congenital abnormalities, congenital heart disease, prenatal diagnosis, ultrasonography.

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Introduction

The proportion of overweight and obese women of childbearing age is increasing, with first-trimester obesity [body mass index (BMI) ≥ 30 kg/m^2] more than doubling from 7.6% in 1989 to 15.6% in 2007 in England.[1] This has implications for the prevalence of congenital anomalies, some of which occur more frequently in overweight (BMI = 25–29.9 kg/m^2) and obese pregnant women.[2,3]

Antenatal detection of congenital anomalies gives the opportunity to prepare parents for the birth of a child with a congenital anomaly, to plan postnatal management or to consider termination of pregnancy. However, between 2005 and 2009, antenatal diagnosis occurred in only 47% of nonchromosomal cases notified to UK congenital anomaly registers.[4]

Evidence suggests that the sensitivity of antenatal ultrasound detection of congenital anomalies is further reduced with increasing BMI.[5,6] Dashe et al.[6] found a decreasing trend in ultrasound detection rates for congenital anomaly as BMI at the first antenatal visit increased. Similarly, Tabor et al.[5] found that women with a BMI > 25 kg/m^2 had a significantly lower detection rate than women with a BMI ≤ 25 kg/m^2. Although both were large cohort studies, they only included 181 and 100 cases of congenital anomaly respectively, and neither investigated trends in specific anomaly groups.

Several studies have found associations between increased maternal BMI and suboptimal visualisation of the fetus.[7–12] Visualisation of cardiac structures[12,13] and soft tissues[12] has been shown to be particularly impaired with increasing BMI. This association may partly explain the increased prevalence of congenital anomalies at birth in overweight and obese women,[2] if a lower proportion are detected antenatally and, subsequently, fewer cases result in the termination of pregnancy, but this hypothesis has not been investigated.

This study investigated the association between maternal BMI and the antenatal ultrasound detection of congenital anomalies and between maternal BMI and pregnancy outcome in a population-based case series from the north of England.

Methods

Study population

The Northern Congenital Abnormality Survey (NorCAS) is a population-based register of congenital anomalies established in 1985. NorCAS prospectively collects data on congenital anomalies in mothers residing in the north of England (the North East and North Cumbria). This is a stable population with approximately 32 000 births per year. Data are collected on cases that occur in late miscarriages (20–23 weeks of gestation), terminations of pregnancy following antenatal diagnosis of a fetal anomaly (at any gestation), stillbirths (≥24 weeks of gestation) or live births. All anomalies are coded using the World Health Organization (WHO) *International Classification of Diseases*, Version Ten (ICD-10) and categorised according to the European Surveillance of Congenital Anomalies (EUROCAT) guidelines.[14] NorCAS allows up to six anomaly subtypes to be recorded for each case. Minor anomalies, such as syndactyly (between toes two and three) or tongue tie, were excluded from all analyses. Further information on minor anomalies and coding is available in the EUROCAT guidelines (www.eurocat-network.eu/content/EUROCAT-Guide-1.3.pdf). To ensure a high case ascertainment, congenital anomalies are notified to the register from a variety of sources, including antenatal ultrasound departments, fetal medicine records, cytogenetic laboratories, the regional cardiology centre, pathology departments and paediatric surgery departments. Cardiovascular anomalies are confirmed by surgery, echocardiography, cardiac catheterisation or autopsy. Anomalies suspected antenatally are followed up after delivery and, if an anomaly is confirmed, both antenatal and final diagnoses are recorded.

All cases with a confirmed congenital anomaly notified to NorCAS, delivered between 1 January 2006 and 31 December 2009, were included in this study. Isolated cases (defined as occurring alone, or if all coexisting anomalies are commonly associated with the main anomaly) were assigned to groups depending on the organ system with which they were associated. Cases with two or more major anomalies from different organ systems were categorised as multiple anomalies.

Pregnancies associated with chromosomal anomalies and teratogenic syndromes were excluded as they are not primarily detected using the routine second-trimester ultrasound scan (generally offered between 18 and 21 weeks of gestation in the UK). Information regarding antenatal suspicion of a congenital anomaly was recorded from the routine second-trimester ultrasound scan, the subsequent anomaly scan or occasionally, the initial dating scan (carried out at around 10 to 12 weeks of gestation). Data may have come from any of these scans, but NorCAS only records gestational age at final antenatal diagnosis, which does not always correspond to the gestational age at first antenatal suspicion.

At the first antenatal visit, self-reported or measured maternal height and weight were documented in the mother's medical records. These were then reported on the NorCAS notification form and BMI was derived as weight (kg)/[height $(m)^2$]. Denominator data for total births (live and stillbirths) and live births for the same years, used to calculate prevalence, were obtained from the Office for National Statistics.

Information on maternal pre-gestational diabetes status was derived from the Northern Survey of Diabetes in Pregnancy (NorDIP),[15] a collaborative survey of all pregnancies in women with diabetes at least six months before pregnancy.

Information on multiple pregnancies was derived from the Northern Survey of Twin and Multiple Pregnancy (NorSTAMP),[16] a register of all multiple pregnancies occurring in the region.

Statistical analyses

Maternal BMI (kg/m^2) was categorised as underweight (<18.5 kg/m^2), recommended BMI (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2) and obese (≥30 kg/m^2) according to the WHO guidelines. Maternal age at delivery (years), gestational age at final antenatal diagnosis (weeks) and gestational age at first antenatal visit (weeks) were examined as continuous variables. The Index of Multiple Deprivation (IMD) 2007, determined from the maternal residential postcode at delivery, was used as a proxy measure of individual deprivation. The IMD is an area-level measure of deprivation compiled from data across seven domains: income, employment, health deprivation and disability, education skills and training, barriers to housing and services, crime and living environment, and is the UK government's preferred area-based measure of deprivation.[17] IMD scores were ranked and divided into tertiles

and treated as a categorical variable, where the lowest tertile represents the least deprived women and the highest tertile the most deprived women.

For all anomalies combined, cases were defined as 'detected' if any EUROCAT-classified congenital anomaly was suspected antenatally. Organ system-specific anomalies were categorised as detected if any anomaly of the correct system was suspected. The Cuzick's test for trend was used to test for a trend in detection rates across increasing BMI categories. Crude and adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for antenatal detection of congenital anomaly were estimated via maximum likelihood logistic regression. Models representing the adjusted odds of antenatal detection included maternal age, IMD, diabetes, multiple pregnancy and BMI. Gestational age at the first antenatal visit and gestational age at the final antenatal diagnosis were compared across BMI groups using Kruskal–Wallis tests. As approximately 30% of BMI data were missing, these cases were excluded from the regression analysis. Cases with missing data for one or more of the covariates were listwise excluded from the regression analysis. A test of proportions was performed to assess whether there was a difference in detection rates between women with missing and recorded BMI.

Interactions between maternal BMI and diabetes and maternal BMI and multiple pregnancies were investigated through the addition of cross-product terms. Interactions between maternal BMI and other statistically significant variables were also examined. Using termination of pregnancy for fetal anomaly as a binary outcome variable (categorised as Yes/No), a test for trend across BMI categories was performed and aORs were calculated, with adjustment for maternal age, IMD, diabetes, multiple pregnancy and BMI. Statistical analysis was performed using Stata 12 (StataCorp, College Station, TX, USA) and $P < 0.05$ was considered to be statistically significant.

Results

There were 3096 cases of congenital anomaly confirmed postnatally among 132 885 pregnancies during the four-year study period, giving a total prevalence of 23.3 (95% CI: 22.5–24.1) per 1000 live and stillbirths. There were 597 (19.3%) cases associated with chromosomal anomalies and 14 (0.5%) associated with a teratogenic syndrome excluded from further analysis. Two cases that were not antenatally scanned and two with missing information on whether or not they were antenatally scanned were also excluded.

Of the remaining 2483 cases, 40 (1.6%) occurred in women with pre-gestational diabetes, 128 (5.2%) in twin pregnancies and three in separate triplet pregnancies. Other summary statistics are shown in Table 1.

Cardiovascular anomalies were the most common congenital anomaly group notified to NorCAS (945 cases; 38.1%; Table S1), but were the least commonly suspected antenatally (11.5%; Table S1). Urinary anomalies, nervous system anomalies, orofacial clefts and digestive system anomalies were specifically suspected antenatally in 88.4, 84.7, 44.4 and 35.1% of cases, respectively (Table S1).

Excluding women with missing maternal BMI, 67 (4.0%) anomalies occurred in women who were underweight, 793 (47.0%) in women who were of recommended BMI, 468 (27.8%) in women who were overweight and 358 (21.2%) in women who were obese (Table 1). An anomaly of any system was detected antenatally in 40 (59.7%), 417 (52.6%), 225 (48.1%) and 164 (45.8%) cases in women who were underweight, of recommended BMI, overweight and obese, respectively (Figure 1). Detection rates decreased significantly with increasing BMI category (test for trend: $P = 0.007$). Cases in women with missing BMI were significantly less likely to have been detected antenatally (300/797 = 37.6%) than those in women with a recorded BMI (846/1686 = 50.2%; test of proportions: $P < 0.001$). There was no evidence of a difference in the distribution of gestational age at final antenatal detection of anomaly or gestational age at first antenatal visit across BMI categories (Kruskal–Wallis test: $P = 0.688$ and $P = 0.430$, respectively).

The odds of detection of an anomaly (in any system) were significantly lower in obese women than in women of recommended BMI (aOR = 0.77; 95% CI: 0.60–0.99; $P = 0.046$; Table 2). There were no significant differences in the odds of detection in underweight ($P = 0.414$) or overweight ($P = 0.157$) women compared with women of recommended BMI. Increasing maternal age was significantly associated with decreasing odds of antenatal detection (aOR = 0.97; 95% CI: 0.96–0.99; $P < 0.001$). The odds of detection were also increased in women with multiple pregnancies (aOR = 1.55; 95% CI: 1.06–2.26; $P = 0.024$). There were no significant associations with IMD ($P = 0.889$ and $P = 0.698$ for least and most deprived, respectively) or pre-gestational diabetes ($P = 0.766$).

There was no evidence that the influence of BMI on the odds of antenatal detection was significantly different in multiple relative to singleton pregnancies or in women with pre-gestational diabetes relative to those without. One significant interaction was observed between overweight BMI and maternal age ($P = 0.017$). In women aged 35 years or more, the odds of an anomaly being detected antenatally was significantly lower in overweight women (aOR = 0.46; 95% CI: 0.25–0.84; $P = 0.012$) than in women of recommended BMI. No such effect was observed in women under the age of 35 years (overweight versus recommended BMI: aOR = 0.95; 95% CI: 0.74–1.22; $P = 0.663$).

Table 1. Demographic statistics by antenatally suspected and unsuspected congenital anomalies*

Variable	All cases, *n* (%)	Undetected cases, *n* (%)	Detected cases, *n* (%)	*P*
BMI (kg/m^2)				
Underweight (<18.5)	67 (2.7)	27 (40.3)	40 (59.7)	0.007$^{\mu}$****
Recommended weight (18.5–24.9)	793 (31.9)	376 (47.4)	417 (52.6)	
Overweight (25–29.9)	468 (18.9)	243 (51.9)	225 (48.1)	
Obese (≥30)	358 (14.4)	194 (54.2)	164 (45.8)	
Missing	797 (32.1)	497 (61.4)	300 (37.6)	
Maternal age at delivery (years)				
<20	267 (10.8)	125 (46.8)	142 (53.2)	<0.001****
20–34	1820 (73.3)	956 (52.5)	864 (47.5)	
≥35	383 (15.4)	244 (63.7)	139 (36.3)	
Missing	13 (0.5)	12 (92.3)	1 (7.69)	
Index of Multiple Deprivation				
Least deprived	773 (31.1)	435 (56.3)	338 (43.7)	0.078****
Moderate	844 (34.0)	461 (54.6)	383 (45.34)	
Most deprived	863 (34.8)	439 (50.9)	424 (49.1)	
Missing	1 (0.1)	2 (66.7)	1 (33.3)	
Pre-gestational diabetes***				
Yes	40 (1.6)	20 (50.0)	20 (50.0)	0.623
No	2443 (98.4)	1317 (53.9)	1126 (46.1)	
Multiple pregnancy***				
Yes	131 (5.3)	53 (40.5)	78 (59.5)	0.002
No	2352 (94.7)	1284 (54.6)	1068 (45.3)	
Birth outcomes***				
Late miscarriage	30 (1.2)	14 (46.7)	16 (53.3)	<0.001
Termination of pregnancy	361 (14.5)	0	360 (100.0)	
Antepartum stillbirth	35 (1.4)	9 (25.7)	26 (74.3)	
Intrapartum stillbirth	2 (0.1)	0 (0)	2 (100.0)	
Early neonatal death	47 (1.9)	11 (23.4)	36 (76.6)	
Late neonatal death	26 (1.1)	14 (53.9)	12 (46.2)	
Post-neonatal death	38 (1.5)	19 (50.0)	19 (50.0)	
Live birth	1940 (78.1)	1270 (65.5)	670 (34.5)	
Missing	4 (0.1)	0	4 (100.0)	
Sex***				
Male	1304	705 (54.1)	599 (45.9)	0.470
Female	1131	628 (55.5)	503 (44.5)	
Unknown	48	4 (8.3)	44 (91.7)	
Year of delivery				
2006	648 (26.1)	358 (55.3)	290 (44.8)	0.718****
2007	620 (25.0)	337 (54.4)	283 (45.7)	
2008	650 (26.2)	350 (53.5)	301 (46.5)	
2009	565 (22.8)	297 (52.0)	271 (48.0)	
Gestational age at delivery,***** (weeks)**	38 (35–40)	39 (37–40)	36 (21–39)	<0.001
Gestation at booking,***** (weeks)**	9 (8–12)	9 (7–12)	10 (8–12)	0.201
Gestation at diagnosis of anomaly,***** (weeks)**	20 (18–22)	N/A	20 (18–22)	N/A

*Chromosomal and teratogenic syndromes and women who did not have a scan were excluded. Missing categories were not included in any of the statistical tests.
**Median (interquartile range) and Mann–Whitney *U*-test.
***χ^2 test of association (Fisher's exact test where column frequency <5).
****Cuzick's test for trend.
*****Gestational age at delivery: 1% missing. Gestational age at booking: 45.7% missing. Gestation at diagnosis of anomaly: 54.3% missing.

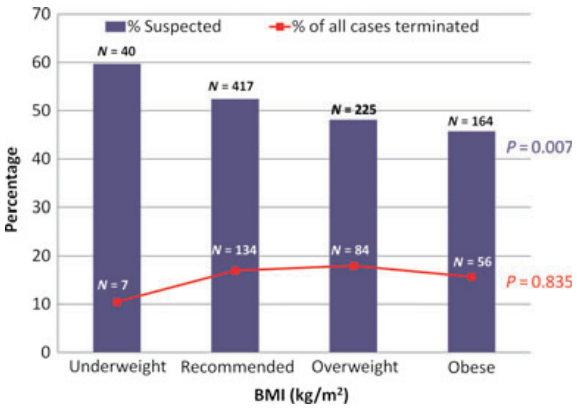

Figure 1. Trends in the percentage of suspected cases and the percentage of cases ending in termination of pregnancy across body mass index (BMI) categories (chromosomal and teratogenic syndromes were excluded). *P* values calculated using Cuzick's test for trend.

Of the cases that were confirmed postnatally as having isolated cardiovascular anomalies, there was an approximate three-fold increased odds of detecting a cardiovascular anomaly in underweight women than in women of recommended BMI (aOR = 2.95; 95% CI: 1.13–7.70; $P = 0.027$; Table 2). There were no significant differences in the antenatal detection of cardiovascular anomalies in overweight and obese women compared with women of recommended BMI (Table 2).

There were no significant associations between BMI (of any category) and antenatal detection of congenital anomalies in any other organ system (the most commonly affected organ systems are shown in Table 2).

Overall, 361 (14.5%) of all cases ended in termination of pregnancy, with seven (10.5%), 134 (17.0%), 84 (18.0%) and 56 (15.7%) cases occurring in underweight, recommended BMI, overweight and obese women, respectively (Figure 1). There was no trend in termination of pregnancy rates over increasing BMI categories (test for trend: $P = 0.835$). Of those cases that were suspected antenatally, 17.5, 32.4, 37.3 and 34.4% ended in a termination of pregnancy in underweight, recommended BMI, overweight and obese women, respectively (test for trend: $P = 0.112$). After adjusting for maternal age, IMD, diabetes and multiple pregnancies, there was no significant association between termination and BMI (logistic regression: $P = 0.075$, $P = 0.182$ and $P = 0.431$ in underweight, overweight and obese women, respectively). There was no association with IMD ($P = 0.335$ and $P = 0.081$ for least and most deprived, respectively) or diabetes ($P = 0.408$), but there was some evidence that the odds of termination decreased with increasing maternal age (aOR = 0.98; 95% CI: 0.96–1.00; $P = 0.051$) and in multiple relative to singleton pregnancies (aOR = 0.43; 95% CI: 0.23–0.80; $P = 0.008$).

Termination of pregnancy occurred in 28 (3.0%) confirmed cases of cardiovascular anomaly. There was no association between BMI categories and termination of pregnancy among cardiovascular cases ($P = 0.876$ and $P = 0.201$ for overweight and obese women, respectively).

Discussion

This study found a significant decreasing trend in the antenatal ultrasound detection of congenital anomalies across all BMI categories. In addition, there was a significantly increased odds of detecting an anomaly of the cardiovascular system in underweight women relative to women of recommended BMI. There was no significant association between BMI and antenatal detection of congenital anomalies in any other organ system, or between BMI and termination of pregnancy for fetal anomaly.

This study is the largest to examine the effect of maternal BMI on the antenatal detection of congenital anomalies. The primary strength of the study is that information on cases was extracted from a high-quality, population-based congenital anomaly register. Consistent methods of identifying and notifying cases are used to ensure a high case ascertainment. In addition, NorCAS is an active register that follows cases to age 12 years to maximise ascertainment of anomalies, such as those of the cardiovascular system, which may not be diagnosed until well into childhood. NorCAS records data on up to six congenital anomalies per case; thus, we were able to classify each case as isolated, associated or chromosomal, and to examine antenatal detection rates by organ system, which has not been performed previously.

NorCAS is held within the same database as two other high-quality population-based registers (NorDIP and NorSTAMP). As records are linked as cases are notified, we were able to accurately identify cases occurring in women with pre-gestational diabetes or multiple pregnancies. Therefore, we could adjust for these potentially confounding factors, which are both associated with an increased risk of congenital anomaly[18,19] and increased antenatal surveillance.[20,21]

The study has some limitations. The maternal BMI data recorded at the first antenatal visit were mostly derived from self-reported height and weight. It has been suggested that around 20% of women underreport their weight at first attendance for antenatal care, leading to an underestimation of their BMI.[2] Moreover, almost one-third of the BMI data were missing. Despite our best efforts to obtain these data, they were not recorded in the study years. Cases in women with missing BMI data were less likely to have been detected antenatally than those in women who had a BMI recorded. If overweight or obese women account for a higher proportion of the missing data, the strength of our association may be an underestimate.

Table 2. Association between maternal body mass index (BMI) and the odds of antenatal detection of congenital anomaly (overall and in most common anomaly groups*), as estimated by logistic regression

Postnatal diagnosis	BMI category**	Total, *n* (%)	Detected antenatally***, *n* (% in BMI category)	Unadjusted		Adjusted****	
				OR (95% CI)	*P*	aOR (95% CI)	*P*
Any congenital anomaly	Underweight	67 (2.7)	40 (59.7)	1.34 (0.80–2.22)	0.264	1.24 (0.74–2.06)	0.414
	Recommended	793 (31.9)	417 (52.6)	1 (Reference)	–	1 (Reference)	
	Overweight	468 (18.9)	225 (48.1)	0.83 (0.66–1.05)	0.122	0.85 (0.67–1.07)	0.157
	Obese	358 (14.4)	164 (45.8)	0.76 (0.59–0.98)	0.034	0.77 (0.60–0.99)	0.046
	Missing	797 (32.1)	300 (37.6)				
Cardiovascular anomaly	Underweight	25 (2.7)	7 (28.0)	2.56 (1.00–6.56)	0.050	2.95 (1.13–7.70)	0.027
	Recommended	273 (28.9)	36 (13.2)	1 (Reference)	–	1 (Reference)	
	Overweight	177 (18.7)	27 (15.3)	1.19 (0.69. 2.03)	0.537	1.18 (0.68–2.04)	0.557
	Obese	144 (15.2)	18 (12.5)	0.94 (0.51–1.72)	0.843	0.84 (0.45–1.56)	0.575
	Missing	326 (34.5)	21 (6.4)				
Urinary system anomaly	Underweight	7 (2.3)	7 (100.0)	–	–	–	
	Recommended	112 (37.1)	103 (92.0)	1 (Reference)	–	1 (Reference)	
	Overweight	61 (20.2)	52 (85.3)	0.57 (0.22–1.48)	0.246	0.58 (0.22–1.56)	0.284
	Obese	37 (12.3)	34 (91.9)	0.81 (0.24–2.75)	0.734	0.84 (0.24–2.96)	0.815
	Missing	84 (28.2)	73 (85.9)				
Nervous system anomaly	Underweight	8 (3.1)	8 (100.0)	–	–	–	
	Recommended	93 (35.5)	85 (91.4)	1 (Reference)	–	1 (Reference)	
	Overweight	51 (19.5)	45 (88.2)	1.01 (0.35–2.90)	0.991	1.06 (0.36–3.14)	0.914
	Obese	41 (15.7)	38 (92.7)	1.24 (0.37–4.15)	0.726	1.47 (0.43–5.07)	0.540
	Missing	69 (26.3)	51 (73.9)				
Orofacial cleft	Underweight	3 (2.1)	0 (0.0)	–	–	–	
	Recommended	58 (40.9)	30 (51.7)	1 (Reference)	–	1 (Reference)	
	Overweight	32 (22.5)	15 (46.9)	0.88 (0.37–2.09)	0.777	0.92 (0.38–2.20)	0.846
	Obese	17 (12.0)	9 (52.9)	0.89 (0.30–2.62)	0.831	0.68 (0.21–2.16)	0.508
	Missing	32 (22.5)	11 (34.4)				
Digestive system anomaly	Underweight	5 (4.5)	3 (60.0)	1.62 (0.23–11.26)	0.628	1.95 (0.26–14.86)	0.519
	Recommended	27 (28.8)	13 (48.2)	1 (Reference)	–	1 (Reference)	
	Overweight	13 (11.7)	4 (30.8)	0.48 (0.12–1.94)	0.302	0.59 (0.13–2.74)	0.503
	Obese	17 (15.3)	7 (41.2)	0.75 (0.22–2.57)	0.651	0.67 (0.17–2.61)	0.564
	Missing	49 (44.1)	13 (26.5)				

CI, confidence interval; OR, odds ratio; –, insufficient data to produce an OR.
*Groups are categorised according to the European Surveillance of Congenital Anomalies (EUROCAT) guidelines.[14]
**The missing categories were not included in the regression analysis.
***Ultrasound detection of any EUROCAT congenital anomaly within the same anomaly group as the final diagnosis. For the summary analysis of 'any congenital anomaly', the number is for any antenatally detected anomaly.
****Adjusted for Index of Multiple Deprivation (IMD) tertiles, maternal age at delivery, pre-gestational diabetes, multiple pregnancy.

Although we were able to account for pregnancies associated with pre-gestational diabetes, we could not account for those associated with gestational diabetes. Mothers with gestational diabetes are more likely to be overweight or obese[22] and, because of the higher risks associated with their pregnancy, may receive additional antenatal scans. Thus, we may have underreported the size of the true association between antenatal detection and obesity.

The second-trimester ultrasound may have been too early to detect certain nervous system anomalies, such as posterior fossa or agenesis of the corpus callosum, which are not usually detectable until a later gestational age. However, a large proportion of nervous system anomalies were suspected antenatally (84.7%), and so this would not have had a major impact on the results.

As the purpose of the study was to investigate the sensitivity of routine antenatal ultrasound scanning to detect congenital anomalies, we excluded chromosomal anomalies. We could not distinguish between those anomalies identified via ultrasound examination and those detected by other means (e.g. genetic testing). Therefore, this study cannot describe the association between BMI and the odds of antenatal detection in this group of anomalies.

In addition, we could not adjust the logistic regression models for gestational age at scanning. Although gestational age at final antenatal diagnosis is recorded, this may correspond to a scan subsequent to that which caused the initial suspicion. Furthermore, this variable has a high proportion of missing values. Evidence suggests that scans occurring at later gestational ages may lead to better visualisation of the fetus,[7,13] although not all studies support this finding.[5,8] Nevertheless, we examined gestational age at final antenatal diagnosis, and at first antenatal visit, and found no significant difference across BMI categories, which suggests that the association between BMI and the odds of detection is not related to differences in gestational age at the time of the scan.

Considering all congenital anomalies, we found similar antenatal detection rates to those described by EUROCAT in the UK.[4] However, we identified significantly lower detection rates of cardiovascular anomalies than did Boyd et al.[23] in 2005–2006 in England and Wales. However, the study by Boyd et al.[23] only included serious cardiac anomalies (defined as common arterial trunk, discordant ventriculoarterial connection, transposition of the great vessels, tetralogy of Fallot, Ebstein's anomaly or coarctation of the aorta) that were amenable to detection, whereas we investigated all EUROCAT-defined major anomalies of the cardiovascular system.[14] Garne et al.[24] reported cardiovascular detection rates of 25% in Europe and 35% in England, which are slightly more consistent with ours, but this was an older study and detection rates may have since improved.

Apart from the cardiovascular system, there were a limited number of anomalies from other individual organ systems. As a result, this study may have been underpowered to detect associations between maternal BMI and the antenatal detection of anomalies within other organ systems. Nonsignificant associations should therefore not be interpreted as evidence of no effect. Further studies are needed with larger sample sizes.

Few studies have investigated the association between maternal BMI and the detection of congenital anomalies, but those that have, show consistent findings to those reported here. In low-risk pregnancies, Dashe et al.[6] identified a negative trend in the rates of detection as BMI increased, with rates of 66 and 48% in normal (BMI < 25 kg/m^2) and class 1 obese (BMI = 30–34.9 kg/m^2) women, respectively. These detection rates are higher than ours, possibly because the authors excluded cases associated with atrial septal defect, a cardiovascular anomaly which is difficult to detect antenatally [e.g. in our study, 2.9% (1/35) of isolated atrial septal defects were suspected antenatally]. In addition, Dashe et al.[6] only recorded cases if they were diagnosed before hospital discharge or if they occurred in neonatal deaths, whereas NorCAS can receive notification of a case up to age 12 years. Similarly, Tabor et al.[5] identified a difference in detection rates between women with BMI ≤ 25 kg/m^2 and BMI > 25 kg/m^2 (76.4 and 53.3%, respectively). These detection rates may also appear to be higher than in our study because of a more modest BMI categorisation and because the length of follow-up was shorter than ours (median of 22 months). Neither of these studies performed regression analyses, and so we cannot compare the adjusted odds of detection.[5,6] A number of other studies showing greater suboptimal visualisation for increasing BMI[7–10,12,25] also complement our findings.

In our study, obese BMI was not significantly associated with antenatal detection of cardiovascular anomalies. This contrasts with the studies by Hendler et al.[7] and Khoury et al.,[12] who both identified greater suboptimal visualisation of the fetal heart in obese women than in women of recommended BMI. This discrepancy may have occurred because of low study power. Although we found an overall effect in obese women, and cardiovascular anomalies were the largest congenital anomaly group, they also had the lowest rate of detection (11.5%), and therefore very few antenatally detected cases (n = 88). Hence, although our study had sufficient power to detect a large effect size for cardiovascular anomalies (as observed with underweight women), it may not have had sufficient power for a moderate effect, which potentially exists for obese women. To our knowledge, this is the first study to investigate the effect of maternal underweight on the ultrasound detection of congenital anomalies. We found an increased rate of antenatal detection in underweight women, which suggests

that ultrasound visibility decreases continuously over all BMI categories.

Although obese women were less likely to have an anomaly suspected antenatally, they were not significantly less likely to have a termination of pregnancy, compared with women of recommended BMI. Termination of pregnancy was a relatively rare outcome and the effect of obesity on antenatal detection was moderate, and so it is possible that we did not have the power to identify a small effect. However, a recent systematic review found no evidence to support this, as the association between congenital anomaly and maternal obesity was similar irrespective of whether terminations of pregnancy for fetal anomaly were included.[3] Thus, antenatal scanning for congenital anomalies is less effective as BMI increases, resulting in fewer cases detected antenatally, but this study provides no evidence that this has an impact on termination of pregnancy for fetal anomaly.

We found that cases occurring in a multiple pregnancy were more likely to be detected than cases occurring in a singleton pregnancy. Congenital anomalies may be more frequently suspected in multiple pregnancies because more scans are offered to these women or, potentially, more experienced sonographers might scan these women.[21] Further research is required to investigate this association. There was no evidence that the effect of BMI on antenatal detection was different among multiple relative to singleton pregnancies, and so it was feasible to incorporate and adjust for multiple pregnancies in our analysis.

As the amount of abdominal adipose tissue increases, the depth travelled by the ultrasound waves during the mid-trimester scan becomes greater.[25] Therefore, more waves are absorbed into the surrounding tissue, which causes the signal to weaken and, as a result, visualisation of the fetus and therefore any congenital anomalies diminishes.[25] If BMI is considered as a marker for abdominal adipose tissue, this would explain why detection decreases over all BMI categories, and is not impaired in obese women alone. Furthermore, this might explain why we identified an interaction between overweight BMI and maternal age, if the older overweight mothers had more abdominal adipose tissue than their younger counterparts with the same BMI, as has been reported previously.[26,27]

The National Institute for Health and Clinical Excellence (NICE) suggests that pregnant women should be informed that antenatal detection rates may vary by maternal BMI.[28] Recommendations should be directed to improving ultrasound sensitivity, for example by advising enhanced scanning for overweight and obese women. Paladini[25] has described several methods to boost ultrasound image quality and therefore enhance visualisation of the fetal heart, which should be further evaluated in women of increased BMI.

Conclusions

Congenital anomalies, particularly within the cardiovascular system, are difficult to detect antenatally. Our study shows that this is further challenged as maternal BMI increases. However, we found that this had no measurable impact on the proportion of pregnancies resulting in a termination of pregnancy. Women should be informed of the limitations of ultrasound for the detection of congenital anomalies. To maximise visualisation of the fetal heart, recommendations to improve ultrasound scanning sensitivity in women with increased BMI should be evaluated further.

Disclosure of interests

All authors report no conflict of interest.

Contribution to authorship

KEB undertook the analysis and interpretation of the data and drafted the manuscript. JR conceived the project and, with RB and PWGT, participated in the interpretation of the data and the critical review of the manuscript. All authors read and approved the final version of the manuscript before submission.

Details of ethics approval

As part of the British Isles Network of Congenital Anomaly Registers (BINOCAR), NorCAS has exemption from the National Information Governance Board for Health and Social Care from a requirement for consent for inclusion on the register and has ethical approval (09/H0405/48) to undertake studies involving the use of the data. This study was given a favourable ethical opinion from the Northumberland Research Ethics Committee (07/Q0902/2) and Research and Development approval from each of the participating hospitals.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Number and percentage of cases by congenital anomaly group.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting information

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Improved antenatal detection of congenital anomalies in women with pre-gestational diabetes: population-based cohort study

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Abstract

Aims To compare antenatal detection of congenital anomaly in women with and without pre-gestational diabetes and their pregnancy outcomes in a regional cohort study.

Methods Data from a total of 7148 singleton pregnancies with a congenital anomaly delivered between 1 January 1996 and 31 December 2008 were extracted from the Northern Diabetes in Pregnancy and Northern Congenital Abnormality Surveys. Antenatal ultrasound detection rates of congenital anomaly in pregnancies complicated by major non-chromosomal congenital anomaly and resulting in live birth, stillbirth, late miscarriage (20–23 weeks of gestation) or termination of pregnancy for a congenital anomaly, were compared between women with and without diabetes (120 and 7028, respectively).

Results A significantly higher rate of antenatal detection of congenital anomalies was observed in women with diabetes compared with women without diabetes (50.8 vs. 38.6%, respectively; relative risk 1.32; 95% CI 1.10–1.57; $P = 0.003$). Cardiovascular anomalies were the only group with a significantly higher antenatal detection rate in women with diabetes (31.8 vs. 10.4%; relative risk 3.05; 95% CI 1.95–4.76; $P < 0.00001$). This difference remained after excluding cases of ventricular septal defect (52.2 vs. 16.3%; relative risk 3.20; 95% CI 2.13–4.80; $P < 0.0001$). Among women with diabetes, male fetal sex was the only factor associated with a higher antenatal detection rate. There were no differences in the rates of termination of pregnancy, late miscarriage, stillbirth or infant death between groups.

Conclusions Antenatal detection of cardiovascular anomalies was higher in women with diabetes, suggesting that recommendations for enhanced cardiovascular scanning may improve detection. Greater awareness of the increased risk of anomalies in other organ systems is needed.

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Introduction

Maternal pre-gestational diabetes is the most common chronic condition complicating pregnancy, affecting around 1 in 200 births in the UK [1,2]. The number of pregnancies affected is increasing because of the obesity epidemic and consequent increase in Type 2 diabetes in younger women [3,4]. Women with existing diabetes have an approximately fourfold increased risk of pregnancy affected by major structural congenital anomaly [5,6]. Congenital anomalies are a leading cause of perinatal mortality and a substantial proportion end in termination of pregnancy [2,7]. Cardiovascular anomalies are the most common group observed, accounting for approximately 30–40% of all anomalies [2,5,8,9], but the risk is increased across all common anomaly groups [5].

In the UK, pregnant women are offered a second trimester ultrasound scan between 18 and 20 completed weeks' gestation to identify any structural anomalies in the fetus and, in recent years, targets for detection of specific anomalies have been set [10]. This information allows women to make informed decisions whether to terminate the pregnancy if an anomaly is detected and helps guide both antenatal and post-natal management. Nevertheless,

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What's new?

- Higher rates of antenatal ultrasound detection of a fetal anomaly (specifically cardiovascular anomalies) were observed in women with pre-existing diabetes compared with women without diabetes, using a large cohort of pregnancies in women with diabetes with a comprehensive data set of socio-demographic and clinical variables.
- These findings provide support for recommendations that women with diabetes receive enhanced antenatal screening for fetal anomaly.
- This is the first study to report higher rates of antenatal detection of congenital anomaly in women with diabetes, irrespective of BMI.

only approximately half of all major congenital anomalies are reported to be diagnosed antenatally in the UK [11,12]. Both the National Institute of Health and Clinical Excellence (NICE) [13] and the Confidential Enquiry into Maternal and Child Health (CEMACH) [14] recommend that women with diabetes should be offered antenatal visualization of the four-chamber view of the fetal heart and outflow tracts as part of second trimester fetal anomaly screening. Antenatal detection rates in women with diabetes, who are at an increased risk of a congenital anomaly [5,6], have not been investigated in the UK. Hence, it is not known whether the more intensive screening recommended is effective in improving detection rates in these women [13,14].

This study compares antenatal ultrasound detection rates of congenital anomalies in pregnant women with and without diabetes, using data from established population-based registers, and investigates factors associated with antenatal detection in women with diabetes.

Subjects and methods

Study population

The study area was the North of England (North East and North Cumbria) with a population of approximately 3 million and approximately 31 000 deliveries per year [15]. This study included all singleton pregnancies complicated by a congenital anomaly to women resident in the region and resulting in live birth, stillbirth (≥ 24 weeks' gestation), late miscarriage (20–23 weeks' gestation) or termination of pregnancy following antenatal diagnosis of a fetal anomaly (any gestation) during 1996–2008 (n = 9484). Cases of chromosomal anomalies (n = 9 and n = 1747 for women with and without diabetes, respectively) were excluded from the analysis as antenatal screening tests other than ultrasound were used for their detection.

Pregnancies in women with and without pre-gestational diabetes

The Northern Diabetes in Pregnancy Survey (NorDIP) records demographic and clinical details of all known pregnancies, irrespective of outcome, in resident women diagnosed with diabetes at least 6 months before conception [1]. The NorDIP audits performance against regional standards of care for women with diabetes, which include a recommendation for a 'detailed fetal cardiovascular scan' in the second trimester. Data on congenital anomalies in women without diabetes were obtained from the Northern Congenital Abnormality Survey (NorCAS), which collects information on cases of congenital anomaly (with up to six anomalies recorded for each case) diagnosed to age 12 years, including those arising in miscarriage or termination of pregnancy for fetal anomaly. This population-based register uses multiple sources of ascertainment, including fetal medicine records, cytogenetic laboratories, pathology departments and antenatal ultrasound departments [16]. Cardiovascular anomalies are confirmed by autopsy, surgery, echocardiography or cardiovascular catheterization. Anomalies suspected antenatally are followed up after delivery and, if an anomaly is confirmed, both antenatal and final diagnoses are recorded. The NorDIP and NorCAS are held on a single linked database at the Regional Maternity Survey Office (RMSO), Newcastle upon Tyne.

Classification of congenital anomalies

All major congenital anomalies were coded according to the World Health Organization (WHO) International Classification of Disease 10th revision (ICD-10) and categorized according to European Surveillance of Congenital Anomalies (EUROCAT) criteria (www.eurocat@ulster.ac.uk) [8]. Cases with an isolated anomaly (defined as occurring alone, or if all coexisting anomalies are commonly associated with the main anomaly) were assigned to groups depending on the organ system with which they were associated. Cases were classified as multiple anomalies if they had two or more unrelated anomalies across separate organ systems. Recognized syndromes, sequences and associations were classified separately.

Data detailing antenatal detection were recorded from the routine second trimester ultrasound scan, subsequent anomaly scans and, occasionally, first trimester scans. Cases were classified as 'antenatally suspected' if any antenatal diagnosis was recorded, irrespective of whether this differed from the final post-natal diagnosis. The NorDIP database also collects information as to whether 'a detailed cardiovascular scan' (not further defined) was performed in addition to a routine anomaly scan.

Statistical analyses

Relative risks, with 95% confidence intervals (estimated using exact methods), were calculated to compare the proportion of cases in women with and without diabetes where an anomaly was suspected antenatally, and for each anomaly group in which five or more cases were reported in women with diabetes. Where less than five cases were reported, these anomaly groups were combined as 'other' anomalies. Only anomaly groups with cases occurring in women with diabetes were analysed, resulting in 7028 cases without diabetes for comparison.

Odds ratios and associated 95% confidence intervals for antenatal detection of a non-chromosomal congenital anomaly among women with diabetes were estimated for various socio-demographic and clinical variables using logistic regression. Independent effects were estimated from an adjusted model, constructed using backwards stepwise regression. All variables with an unadjusted *P*-value below 0.5 were entered into the model and variables were iteratively removed until all remaining had $P < 0.1$.

The index of multiple deprivation, an area-based measure of socio-economic status, was determined from maternal residential postcode at first antenatal visit and grouped into tertiles of rank [17]. Statistical analyses were performed using SPSS for Windows version 17.0 (IBM Corporation, Somers, NY, USA). $P < 0.05$ was considered statistically significant.

Ethics approval and research governance

NorCAS, as part of the British Isles Network of Congenital Anomaly Registers, has been granted exemption from the UK National Information and Governance Board (PIAG 2-08(e)/2012) from a requirement for individual consent and has ethics approval (09/H0405/48) to undertake studies using the data. NorDIP data are collected and held with the consent of the mother.

Results

Study population and pregnancy outcome

During the 13 years, 7148 singleton live births, stillbirths, late miscarriages and terminations of pregnancy with at least one major non-chromosomal congenital anomaly were recorded. Of these, 120 had diabetes (1.6%); with 100 (83.3%) having Type 1 diabetes and 20 (16.7%) having Type 2 diabetes. There was no difference between those pregnancies with and without diabetes in the proportion ending in termination [22 (18.3%) vs. 1036 (13.6%), respectively; relative risk 1.35; 95% CI 0.92–1.97; $P = 0.13$], late miscarriage or stillbirth [3 (2.5%) vs. 219 (2.9%); relative risk 0.87; 95% CI 0.28–2.68; $P = 0.81$] or infant death [9 (7.5%) vs. 395 (5.2%); relative risk 1.44; 95% CI 0.77–2.73; $P = 0.26$].

Antenatal detection of a congenital anomaly

There was a significantly higher rate of antenatal detection of a congenital anomaly in women with diabetes compared with women without diabetes (50.8 vs. 38.6%, respectively; relative risk 1.32; 95% CI 1.10–1.57; $P = 0.003$) (Table 1). Cardiovascular anomalies were the most frequent anomalies, accounting for 36.6% in women with diabetes (44/120) and 38.3% in women without diabetes (2916/7028). When individual groups were examined, cardiovascular anomalies were the only anomaly group with a significantly higher antenatal detection rate in women with diabetes (31.8 vs. 10.4%, respectively; relative risk 3.05; 95% CI 1.95–4.76; $P < 0.00001$) (Table 1). When cases of ventricular septal defect were excluded, as these are not usually detected antenatally, the antenatal detection rate of major heart anomalies was increased to 52% in women with diabetes. There remained a significantly higher rate of detection of cardiovascular anomalies in comparison with women without diabetes (12/23 vs. 267/1636; 52.2 vs. 16.3%; relative risk 3.20; 95% CI 2.13–4.80; $P < 0.0001$). There was no significant difference in antenatal detection rates when all non-cardiovascular cases were combined ($P = 0.56$).

Of the 120 cases with diabetes, 90 (75%) were recorded on NorCAS as having a detailed cardiovascular scan. Of these 90 cases, 13 of 39 cardiovascular anomalies were detected antenatally (33.3%).

Predictors of antenatal detection in women with diabetes

In univariate analysis, neither diabetes type, maternal ethnicity, index of multiple deprivation, early pregnancy BMI (when entered either as continuous or categorical variable) nor gestation at first antenatal visit were associated with antenatal detection of an anomaly in women with diabetes (Table 2). Conversely, fetal sex was significantly associated with antenatal diagnosis of an anomaly, with anomalies in male fetuses more likely to be suspected antenatally (odds ratio 2.31; 95% CI 1.10–4.87; $P = 0.03$). In multivariate analysis, infant sex remained the only significant factor associated with antenatal diagnosis of a congenital anomaly (adjusted odds ratio 2.31; 95% CI 1.10–4.87; $P = 0.03$) (Table 2), with female fetuses being significantly less likely to have a cardiovascular anomaly detected than males (relative risk 0.55; 95% CI 0.34–0.88; $P = 0.01$). The number of participants was too small to perform a comparison of detection rates by fetal sex for any other congenital anomaly group.

Discussion

This study found a higher rate of antenatal ultrasound detection of congenital anomalies in women with diabetes compared with women without diabetes. Anomaly group-specific analyses showed that the difference was

Table 1 Relative risk of antenatal suspicion of a major non-chromosomal congenital anomaly in women with and without pre-gestational diabetes according to anomaly group

Group	Pregnancies with diabetes (n = 120)		Pregnancies without diabetes (n = 7028)		
	Antenatal suspicion of anomaly n (%)	Total with anomaly n	Antenatal suspicion of anomaly n (%)	Total with anomaly n	Relative risk (95% CI)
Nervous system	14 (87.5)	16	605 (79.0)	766	1.11 (0.92–1.34)
Cardiovascular	14 (31.8)	44	304 (10.4)	2916	3.05 (1.95–4.76)†
Digestive system	3 (33.3)	10	153 (36.3)	421	0.83 (0.32–2.15)
Urinary	9 (75.0)	12	848 (87.1)	974	0.86 (0.62–1.20)
Syndrome	6 (54.5)	11	161 (36.8)	438	1.48 (0.85–2.58)
Sequence	6 (85.7)	7	94 (67.6)	139	1.27 (0.92–1.75)
Multiple	6 (66.7)	9	286 (65.0)	440	1.03 (0.64–1.64)
Other anomalies*	3 (27.3)	11	263 (28.2)	934	0.97 (0.37–2.56)
Non-cardiac anomalies	47 (61.8)	76	2410 (58.6)	4112	1.06 (0.88–1.26)
Total non-chromosomal	61 (50.8)	120	2714 (38.6)	7028	1.32 (1.10–1.57)‡

*Pre-gestational diabetes: 0/2 eye; 0/1 orofacial clefts; 1/2 genital; 0/2 limb; 1/3 musculo-skeletal; 1/1 association. Without pre-gestational diabetes: 3/98 eye; 135/437 orofacial clefts; 21/76 genital; 55/234 limb; 24/55 musculo-skeletal; 25/34 association.
†$P < 0.00001$.
‡$P = 0.003$.

attributed to a threefold increase in detection rates of cardiovascular anomalies in pregnancies with diabetes compared with pregnancies without diabetes. Among women with diabetes, higher rates of detection were observed in male foetuses, but no other clinical or socio-demographic variables showed a significant association. There was no significant difference in pregnancy outcomes, including rates of termination of pregnancy for fetal anomaly, between women with and without diabetes.

The study has a number of strengths; it is one of the largest cohorts of pregnancies of women with diabetes with a comprehensive data set of socio-demographic and clinical variables. Congenital anomalies in pregnancies of women with and without diabetes are recorded prospectively in NorCAS, irrespective of maternal diabetes status, thus reducing potential detection bias. Ascertainment and coding of anomalies has been standardized according to international guidelines [18].

The study was limited by a relatively low number of cases in women with diabetes, which reduced study power to explore groups other than the cardiovascular anomalies, and prevented analyses of less common groups that had no cases in women with diabetes. The study could also have been insufficiently powered to assess the impact of each clinical and socio-demographic variable on chance of detection, most notably type of diabetes. During the 13-year study period, changes in clinical practice and technological advances may have influenced detection rates. This may include changes at the gestational age at which anomaly scans and more detailed cardiovascular scans were performed. Unfortunately, the NorCAS register does not record the gestational age at which scans were performed, nor the date at which an anomaly was first suspected. With regards to pregnancy outcomes, no significant differences between women with and without diabetes were observed, but the relative risk of anomaly detection in pregnancies of women with diabetes (relative risk 1.32) was comparable with that of pregnancies ending in termination (relative risk 1.35). Similarly, low power prevented full comparison of those with and without a detailed cardiovascular scan in women with diabetes.

Few previous studies have examined the antenatal detection of anomalies in women with diabetes in comparison with a cohort of women without diabetes. Dashe and colleagues [19] found, irrespective of BMI, detection of fetal anomaly was significantly lower for women with diabetes (n = 261) compared with women who received targeted screening for other indications (n = 762) in a sample from the USA (38 vs. 88%; $P < 0.001$), although the number with anomalies was very small. Similarly, Wong *et al.* [20] found a significantly lower rate of detection following routine ultrasound screening in 130 women with diabetes (85 Type 1 and 45 Type 2) compared with a low-risk population in an Australian sample (n = 12 169) (30 vs. 73%, respectively) ($P < 0.001$), but again the absolute number of anomaly cases was small. Furthermore, Wong *et al.*'s sample of women with diabetes had a higher BMI than the control group, which may have confounded the comparison, as increasing BMI is associated with a reduced probability of antenatal detection [21]. In our cohort, BMI was not associated with antenatal detection in women with diabetes when analysed as either a continuous or categorical variable. This was an unexpected finding and may indicate that the heightened awareness of congenital anomaly risk and more detailed surveillance in women with diabetes counteracts any effect of BMI in reducing detection rates. Thus, our study is the first to report higher rates of antenatal detection of congenital anomaly in women with diabetes, but irrespective of BMI.

Table 2 Association between maternal demographic and clinical variables and antenatal detection of a major non-chromosomal congenital anomaly in offspring of women with pre-gestational diabetes (n = 120) (results of univariate and multivariate logistic regression with corresponding odds ratios and 95% confidence intervals)

Factor		Total pregnancies	Antenatal suspicion							
			Yes (n = 61)	No (n = 59)				Adjusted*		
Categorical variable		n	n (%)	n (%)	Odds ratio	95% CI	P-value	odds ratio	95% CI	P-value
Diabetes type	Type 1	100	52 (52)	48 (48)	1					
	Type 2	20	9 (45.0)	11 (55.0)	0.76	0.29–1.98	0.57			
Ethnicity	White British	112	57 (50.9)	55 (49.1)	1					
	Other	8	4 (50.0)	4 (50.0)	0.97	0.23–4.05	0.97			
Sex	Female	59	23 (39.0)	36 (61.0)	1					
	Male	57	34 (59.6)	23 (40.4)	2.31	1.10–4.87	0.03*	2.31	1.10–4.87	0.03*
	Missing	4	4 (100)	0 (0)						
Parity	Primara (0)	43	23 (53.4)	20 (46.6)	1					
	Multipara (≥ 1)	76	37 (48.7)	39 (51.3)	1.21	0.57–2.56	0.62			
	Missing	1	0 (0)	1 (100)						
Index of multiple deprivation	Tertile 1 (most deprived)	52	27 (51.9)	25 (48.1)	1.94	0.76–5.00	0.17			
	Tertile 2	40	24 (60.0)	16 (40.0)	2.70	0.99–7.33	0.05			
	Tertile 3 (least deprived)	28	10 (35.7)	18 (64.3)	1					
BMI category	18.5–24.9 kg/m^2	38	19 (50)	19 (50)	1					
	25–29.9 kg/m^2	26	13 (50)	13 (50)	1.00	0.37–2.71	1.00			
	≥ 30 kg/m^2	31	16 (52)	15 (48)	1.07	0.41–2.76	0.89			
	Missing	25	13 (52)	12 (48)						
Continuous variable	n		Median (interquartile range)	Median (interquartile range)						
Maternal age (years)		120	27 (23–33)	30 (25–34)	0.95	0.89–1.01	0.09			
BMI		95	27.7 (23.8–30.8)	25.5 (23.1–32.8)	0.99	0.94–1.05	0.76			
Gestation at first antenatal visit (weeks)		120	9 (7–13)	9 (8–14)	0.98	0.89–1.08	0.68			

*P < 0.05. Adjusted model was constructed using backwards stepwise regression. All variables with an unadjusted P-value below 0.5 were entered into the model (maternal age, index of multiple deprivation tertile and fetal sex) and variables were iteratively removed until all remaining had P < 0.1 (fetal sex only).

The reported sensitivity of ultrasound detection rates for non-chromosomal anomaly groups has varied between 30 and 72% for women with diabetes [20,22–24]. The overall detection rate of antenatal congenital anomaly in the current study for women with diabetes (50.8%) was comparable with published estimates and to reported rates from the national Fetal Anomaly Screening Programme [10]. In relation to cardiovascular anomalies specifically, the detection rate was lower for both women with and without diabetes (31.8 and 10.4%, respectively) than reported for the Fetal Anomaly Screening Programme. While the Fetal Anomaly Screening Programme standards recommend a 50% detection rate for 'serious' cardiac anomalies, these are not further defined [10], making comparison with our study difficult. When cases of ventricular septal defect were excluded from our analysis, the significant difference remained between groups, and the rate of detection in the women with diabetes was in line with Fetal Anomaly Screening Programme standards (52%). The rate of detection in women without diabetes remained low (16%); however, a recent study reported the antenatal detection rate for non-chromosomal-related congenital heart disease as 25.6% (irrespective of diabetes diagnosis) [25], with post-natal follow-up limited to 1 year post-partum. It is likely that the relatively low detection rate in our study was attributable in part to the greater post-natal ascertainment of cases in NorCAS (up to 12 years), as many cardiovascular anomalies are diagnosed after the neonatal period, and studies restricting follow-up to the neonatal period will overestimate antenatal detection rates [26].

We report a higher rate of antenatal detection in male fetuses of women with diabetes. There is no obvious explanation for this finding, and previous studies have not examined or reported this comparison. While some congenital anomalies are more prevalent in male fetuses, others are more prevalent in female fetuses [27]. Theoretically, this may influence detection rates as those anomalies more characteristic of male fetuses may be more easily identifiable antenatally, but the small numbers preclude fuller investigation.

The Confidential Enquiry into Maternal and Child Health report on standards of care for women with diabetes in the UK in 2002–2003 [28] highlighted the inefficient use of ultrasound scanning in pregnancies of women with diabetes. More detailed scanning was not always performed, but, in the current study, three quarters of pregnancies affected by maternal diabetes were reported to have specific cardiovascular scanning performed in accordance with the regional consensus standards of care. This policy may have contributed to the higher detection rate of cardiovascular anomalies compared with those without diabetes. The number of women with diabetes who did not have the additional scan was too few to examine its effect on the rate of detection.

Our findings suggest that recommending specific fetal cardiovascular scanning in women with diabetes may have increased the detection rate compared with those without diabetes. Nevertheless, even in women with diabetes, only a minority of cardiovascular anomalies were detected before delivery (31.8%), indicating potential for improvement. Blyth *et al.* [29] suggest that changing national policy to include routine examination of the cardiac outflow tracts would bring UK guidelines in line with those produced by the International Society of Ultrasound in Obstetrics and Gynaecology [30]. This would require additional training for sonographers and increase time taken for routine scans, but could improve detection rates. It is also notable that antenatal detection rates were not significantly higher in women with diabetes for non-cardiovascular anomalies. Diabetes is associated with an increased risk of anomalies across all major groups, and not just cardiovascular anomalies [5]; although, as many of these anomaly groups are relatively uncommon, there may be less awareness of this risk among sonographers. The emphasis on cardiovascular anomalies in national and regional guidance may have improved detection rates of these anomalies, but sonographers need to have a high degree of suspicion for any type of anomaly in women with diabetes. More accurate identification ultimately enables the antenatal care team to appropriately manage the pregnancy, facilitate liaison with genetic counselling services, allow women to make informed choices about their pregnancy and ultimately help prepare for birth.

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Competing interests

None declared.

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LETTER

Should women with diabetic nephropathy considering pregnancy continue ACE inhibitor or angiotensin II receptor blocker therapy until pregnancy is confirmed? Reply to Lewis G and Maxwell AP [letter]

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Keywords ACE inhibitors · Angiotensin II receptor antagonists · HbA_{1c} · Hypertension · Nephropathy · Pregnancy

Abbreviations
ACEI ACE inhibitor
ARB Angiotensin II receptor blocker

To the Editor: We were pleased to read the letter by Lewis and Maxwell [1], which highlights the need for extra vigilance when caring for and counselling women with diabetes with a history of microvascular disease. Our own observational research shows that, in addition to the consequence of typically poor glycaemic control, women with pre-pregnancy retinopathy or nephropathy experience additional increases in their risks of perinatal death and congenital anomaly [2, 3].

For this reason, we have suggested that all women with diabetes and a history of retinopathy or nephropathy receive additional support when planning their pregnancy [3]. In their letter, Lewis and Maxwell recommend a more specific pharmacological solution by proposing that 'women with diabetic nephropathy who are considering pregnancy should, after appropriate counselling, be encouraged to consider continuing their ACEI [ACE inhibitor] or ARB [angiotensin II receptor blocker] therapy up until the first positive pregnancy test in the first trimester' [1].

Although we agree with the need to minimise the risk of serious maternal complications, such as pre-eclampsia, we are less persuaded by Lewis and Maxwell's assertion that administering ACEI and ARB medication before pregnancy and until pregnancy is confirmed, 'offers the best chance of safe delivery of a healthy child for these women' [1].

As the authors discuss, the fetal consequences of ACEI and ARB therapy use in pregnancy remain unclear. While it is well established that these drugs cause fetal and neonatal complications when used during the second and third trimesters of pregnancy [4], the impact during the first-trimester—the most sensitive period for severe teratogenicity—is unclear.

The work by Cooper et al [5] remains the only epidemiological study to demonstrate an increased risk associated with ACEI and ARB use compared with other anti-hypertensive medications specifically. However, with the exception of Li et al [6], all studies that have performed similar investigations—i.e, comparing first-trimester exposure between groups of women with hypertension—have had modest sample sizes. Even the meta-analysis by Walfisch et al was hindered by imprecision [7]. Although the conclusion seems unambiguous (that exposure ACEIs and ARBs during the first trimester is not associated with an elevated risk of major malformations compared with other antihypertensive medications), the uncertainty around the point estimate, itself not insignificant (RR 1.41, 95% CI 0.66, 3.04), is insufficient to exclude a medium-to-large teratogenic effect [7]. Of more concern, however, are the frequent methodological issues. Li et al [6],

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for example, failed to include cases ending in termination of pregnancy for fetal anomaly—something that we believe is vital when performing studies examining the epidemiology of congenital anomalies [8].

Until a large randomised controlled trial or, at least, a large prospective observational study with detailed information on the most pertinent potential confounders (such as diabetes, obesity and maternal age), can provide a more precise estimate of the association of ACEI and ARB medications with the risk of congenital anomalies, we urge caution. In the meantime, we recommend that healthcare professionals focus on what we do know: that improving glycaemic control before and during pregnancy is likely to be, by far, the most salient method for improving outcome in women with diabetes. Hypertension, or ACEI and ARB use, may yet be proven to be important risk factors for congenital anomalies and/or perinatal death, but, regardless, our results suggest any effect will likely be considerably smaller (for women with diabetes at least) than the influence of glycaemic control.

Duality of interest All authors declare that they have no duality of interest.

Contribution statement PWGT drafted the letter and SVG, RWB, JR and RB critically revised the draft. All authors declare that they read and approved the final version of the letter before submission.

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Research: Care Delivery

Fifteen-year trends and predictors of preparation for pregnancy in women with pre-conception Type 1 and Type 2 diabetes: a population-based cohort study

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Abstract

Aims To investigate trends in indicators of preparation for pregnancy in women with Type 1 and Type 2 diabetes and explore their predictors.

Methods Data on 2293 pregnancies delivered during 1996–2010 by women with Type 1 (n = 1753) and Type 2 (n = 540) diabetes were obtained from the Northern Diabetes in Pregnancy Survey. Multiple logistic regression was used to analyse the relationship between potential predictors and three indicators of inadequate pregnancy preparation: non-attendance for pre-conception care; no pre-conception folate consumption; and peri-conception $HbA_{1c} \geq 53$ mmol/mol (≥ 7%).

Results Overall, 40.3% of women with diabetes attended pre-conception care, 37.4% reported pre-conception folate consumption, and 28.2% had adequate peri-conception HbA_{1c}. For all patients, pre-conception folate consumption improved over time, while peri-conception glucose control did not. Attendance for pre-conception care for women with Type 1 diabetes significantly declined. Residence in deprived areas, smoking and younger maternal age (for women aged < 35 years) were independently associated with all three indicators of inadequate preparation for pregnancy. Additional predictors of inadequate peri-conception HbA_{1c} were: Type 1 diabetes (adjusted odds ratio 5.51, 95% CI 2.71–11.22), longer diabetes history (adjusted odds ratio 1.16, 95% CI 1.09–1.23 per year increase for those with < 15 years' diabetes duration), non-white ethnicity (adjusted odds ratio 3.13, 95% CI 1.23–7.97) and higher BMI (adjusted odds ratio 1.05, 95% CI 1.01–1.09 per 1-kg/m^2 increase). Non-attendance for pre-conception care was additionally associated with Type 2 diabetes (P = 0.003) and multiparity (P < 0.0001).

Conclusions There are socio-demographic inequalities in preparation for pregnancy among women with diabetes. Women with Type 2 diabetes were less likely to attend pre-conception care. Pre-conception services need to be designed to maximize uptake in all groups.

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Introduction

Women with Type 1 or Type 2 diabetes are at high risk of adverse pregnancy outcomes, including stillbirth, neonatal mortality, major congenital anomalies and macrosomia [1–5]. There is robust evidence of an association between glycaemic control before and during pregnancy, estimated by concentration of HbA_{1c}, and pregnancy outcomes [6]. For example, the risk of major congenital anomalies is strongly associated with increasing pre-conception or early pregnancy HbA_{1c} [1]. Careful planning and preparation prior to pregnancy, particularly focused on ensuring safe and attainable pre-conception glucose control, but also including high-dose folic acid, review of medications, diabetic complications and other modifiable risk factors, are therefore recommended [7,8]. Although randomized trials have not been undertaken, a meta-analysis of 14 cohort studies reported a threefold reduction in the risk of major congenital anomalies among pre-conception care recipients, together with a reduction in first trimester HbA_{1c} [9]. This finding was confirmed by a more recent meta-analysis, which also found the attendance at pre-conception care was associated with a reduction in preterm delivery [10]. An evaluation of a regional pre-pregnancy care programme in England showed

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What's new?

- This study reports 15 years of data on preparation for pregnancy from a regional population-based register of pregnancies in women with diabetes.
- Attendance for pre-conception care declined and peri-conception glucose control did not improve, while pre-conception folate consumption improved.
- Residence in deprived areas, maternal smoking and younger maternal age (for women aged < 35 years) were associated with inadequate preparation for pregnancy. Women with Type 2 diabetes were less likely to attend for pre-conception care or take folate, but had better peri-conception glucose control.
- Pregnancy was more likely to result in adverse outcome if the woman was not adequately prepared for pregnancy.

that attendees at pre-pregnancy care were more likely to take high-dose folic acid and had improved pregnancy outcomes independent of improvements in glycaemic control [11].

Despite the likely benefits, uptake of pre-conception care remains low, many pregnancies are unplanned and there is evidence of inequality in preparation for pregnancy [11–13].

The aim of this study was to describe trends and investigate factors associated with selected indicators of preparation for pregnancy in women with Type 1 or Type 2 diabetes over 15 years using data from the population-based Northern Diabetes in Pregnancy Survey (NorDIP).

Methods

Study population

The North of England (UK) is a geographically distinct area with a population of approximately 3 million and 31 000 deliveries per year. NorDIP collects details of all known pregnancies occurring in the region, irrespective of outcome, in women diagnosed with diabetes at least 6 months before the index pregnancy [14]. Pregnancies in women with gestational diabetes (i.e. hyperglycaemia first diagnosed during pregnancy) are not included. All maternity units within the region participate in the survey. Coordinators in each unit notify the survey of relevant pregnancies and data collection is undertaken by unit clinicians. Demographic and clinical variables are collected, including pre-conception and antenatal HbA_{1c} [Diabetes Control and Complications Trial (DCCT)-aligned since 2000]. Regional standards agreed a target pre-conception HbA_{1c} of < 53 mmol/mol (< 7%), superseded in 2008 by the national target of 43 mmol/mol (6.1%) [8].

This analysis included all pregnancies (including miscarriages, terminations of pregnancy, stillbirths and live births) in women with Type 1 or Type 2 diabetes who were resident in the region and delivered between 1 January 1996 and 31 December 2010. NorDIP data records are maintained and held at the Regional Maternity Survey Office (RMSO), on a single database linked through the mother's details to regional surveys of pregnancy outcome, including the Perinatal Morbidity and Mortality Survey (PMMS) [15] and the Northern Congenital Abnormality Survey (NorCAS) [16].

Definitions and statistical analysis

Three indicators of preparation for pregnancy were defined: pre-conception folate supplementation at any dose ('yes'/'no'), documented attendance for pre-conception care ('yes'/'no') and adequate glycaemic control, indicated by peri-conception HbA_{1c} [< 53 mmol/mol (< 7%) vs. ≥ 53mmol/mol (≥ 7%)]. We also defined 'good' preparation for pregnancy as having both pre-conception folate supplementation and peri-conception HbA_{1c} < 53 mmol/mol (< 7%) [13].

All clinical and socio-demographic variables available in NorDIP, which were hypothesized to be important predictors or markers of preparation for pregnancy, were examined. Diabetes type (Type 2 vs. Type 1), maternal smoking during pregnancy (no vs. yes) and maternal ethnicity (white vs. non-white) were analysed as dichotomous variables, as was parity [primiparous vs. multiparous (defined as parity ≥ 1)], which was collapsed since the variable was considered ordinal. Socio-economic status was estimated from the Index of Multiple Deprivation (a UK area-based measure, derived from mothers' residential postcode at delivery) and analysed in tertiles of rank [17]. Information on contraception or pregnancy planning was not available in NorDIP. Duration of diabetes, maternal age at delivery, maternal BMI at first antenatal visit, gestational age at first antenatal visit and year of delivery were analysed as continuous variables. The assumption of linearity was examined by locally weighted scatterplot smoothing (LOWESS), which models the shape of the association between variables without requiring a priori specification. Duration of diabetes and maternal age at delivery appeared curvilinear in relation to at least one outcome. Both variables were hence analysed by piecewise regression, with knots at the apparent turning points (35 years for maternal age and 15 years for duration of diabetes). Peri-conception HbA_{1c} was calculated as the closest measurement within 3 months prior to the last menstrual period (available for 47.6% of pregnancies) or mean first trimester measurement (up to 14 weeks' gestation) (available for 77.9%) for women with no pre-conception measure recorded. Peri-conception HbA_{1c} (complete for 81.2%) proved to be a reasonable surrogate of pre-conception HbA_{1c} in our recent analysis [3].

The independent influence of each variable on the three indicators of preparation for pregnancy, presented as adjusted odds ratios with 95% confidence intervals, were estimated within a series of logit-linked generalized estimat-

ing equations. Between-mother variation was modelled as a random intercept to account for the non-independence of repeat pregnancies in the same woman. Models were constructed to balance the explanatory power with parsimony using a backwards stepwise approach; all variables were entered into the model and then removed iteratively, by descending *P*-value, until only those with $P < 0.1$ remained. All three adjusted models passed the Hosmer–Lemeshow test. The variation explained by each model was estimated from the (McFadden) pseudo-R^2-value. Participants with missing data were excluded from individual logistic regression analyses by performing complete-case analyses. To explore any possible bias from data not missing completely at random, all generalized estimating equations were recalculated over 100 multiply imputed data sets, created using multivariate imputation by chained equations (MICE) and assuming an arbitrary missing-data pattern. Cross-product interaction terms were used to explore whether there were any differences in the independent effect of each significant variable on each outcome by diabetes type.

Relative risks with 95% confidence intervals (estimated using exact methods) were calculated to compare the proportion of adverse outcomes of singleton pregnancies in women with adequate preparation for pregnancy (based on each of the three indicators) with that in women with inadequate preparation for pregnancy. All pregnancies resulting in a miscarriage, termination of pregnancy, stillbirth, infant death or those complicated by a major congenital anomaly were included in the group of combined adverse outcomes. All major congenital anomalies were categorized using European surveillance of congenital anomalies (EUROCAT) criteria (www.eurocat@ulster.ac.uk) and coded according to the International Classification of Diseases 10th revision (ICD-10; www.who.int/classifications/icd/en/).

SPSS for Windows version 17.0 (IBM Corporation, Armonk, NY, USA) and Stata 11.2 (StataCorp, College Station, TX, USA) were used for the statistical analyses. $P < 0.05$ was considered statistically significant.

Ethics approval and research governance

Newcastle Research Ethics Committee originally granted approval for the NorDIP in 1993 and data are now obtained and held with informed consent.

Results

Study population

There were 2298 pregnancies (2264 singleton and 34 multiple pregnancies: 32 twin and two triplet pregnancies) delivered between 1996 and 2010 in the North of England. Overall, the median (interquartile range) maternal age at delivery was 30 (25–34) years; 904 (39.4%) women were primiparous and the median (interquartile range) peri-conception HbA_{1c} was 63 mmol/mol (51–77 mmol/mol) (7.9%) (6.8–9.2%).

Preparation for pregnancy in Type 1 and Type 2 diabetes

A total of 1753 (76.5%) women had Type 1 diabetes and 540 (23.5%) had Type 2 diabetes (Table 1). On average, women with Type 1 diabetes were younger, had lower BMI and had a longer history of diabetes, while women with Type 2 diabetes were more likely to be multiparous, of non-white ethnicity and from more deprived areas.

Table 1 shows that the proportion of women who attended pre-conception care was significantly higher in women with Type 1 than Type 2 diabetes, with no significant difference in pre-conception folate consumption. However, from women with recorded peri-conception HbA_{1c}, only 21.9% of women with Type 1 diabetes had HbA_{1c} < 53 mmol/mol (< 7%), compared with 48.2% of women with Type 2 diabetes. Only 15.0% of women overall had 'good' preparation for pregnancy based on folate and HbA_{1c} (13.0% for Type 1 diabetes vs. 21.6% for Type 2 diabetes, $P < 0.001$) (Table 1).

Time trends

The number of reported pregnancies in women with diabetes increased from 381 in 1996–1998 to 558 in 2008–2010. The proportion with Type 2 diabetes increased fivefold, from 7% in 1996–1998 to 36% in 2008–2010 ($P < 0.0001$, χ^2 for trend). The proportion attending pre-conception care declined from 47.0% in 1996–1998 to 34.5% in 2008–2010 for Type 1 diabetes ($P < 0.0001$, χ^2 for trend) and from 38.5% in 1996–1998 to 31.5% in 2008–2010 for Type 2 diabetes ($P = 0.5$, χ^2 for trend) (Table 2), although the absolute numbers attending substantially increased for Type 2 diabetes. There was a significant improvement in the proportion taking folate pre-conception, rising to 55.0% and 45.4% in 2008–2010 in women with Type 1 and Type 2 diabetes, respectively ($P < 0.0001$ for both, χ^2 for trend). Peri-conception glucose control did not improve over time for Type 1 diabetes ($P = 0.74$) or Type 2 diabetes ($P = 0.13$, χ^2 for trend, Table 2).

Preparation for pregnancy and outcome

Among the 2264 singleton pregnancies, 484 (21.4%) resulted in an adverse outcome: 254 miscarriages (247 before 20 weeks of gestation), 48 terminations of pregnancy (31 for a congenital anomaly), 47 antepartum and three intrapartum stillbirths, 14 neonatal deaths, nine post-neonatal deaths and 109 infant survivors born with a major congenital anomaly. The proportion of singleton pregnancies resulting in adverse outcome was significantly higher among women who had inadequate preparation for pregnancy, as measured by any of the three indicators. In women who did

Table 1 Characteristics of mothers with Type 1 and Type 2 diabetes*

Continuous variable	Type 1 (n = 1753) n	Median (interquartile range)	Range	Type 2 (n = 540) n	Median (interquartile range)	Range	P-value†
Maternal age (years)	1753	29 (24–33)	15–46	540	34 (29–37)	17–46	< 0.001
Duration of diabetes (years)	1736	12 (6–18)	0.9–36	524	2.5 (1–5)	0.9–19	< 0.001
Maternal BMI (kg/m^2)	1302	25.7 (23–29)	17–54	439	34.8 (29–40)	19–64	< 0.001
Gestation at first antenatal visit (weeks)	1694	8 (7–11)	1–34	531	9 (7–11)	2–34	0.074
Peri-conception HbA_{1c} (IFCC mmol/mol)	1400	65 (54–79)	25–187	440	53 (44–66)	27–144	< 0.001
Peri-conception HbA_{1c} (DCCT%)	1400	8.1 (7.1–9.4)	4.4–19.3	440	7.0 (6.2–8.2)	4.6–15.3	< 0.001
Year of delivery	1753	2003 (1999–2007)	1996–2010	540	2006 (2003–2008)	1996–2010	< 0.001

Categorical variable	Type 1 (n = 1753) n	%	Type 2 (n = 540) n	%	P-value†
Pre-conception folic acid					
Yes	576	32.9	166	30.7	0.41
No	947	54.0	299	55.4	
Missing	230	13.1	75	13.9	
Pre-pregnancy care					
Yes	755	43.1	168	31.1	< 0.001
No	998	56.9	372	68.9	
Missing	0	0.0	0	0.0	
Peri-conception HbA_{1c}					
< 53 mmol/mol (< 7%)	307	17.5	212	39.3	< 0.001
≥ 53mmol/mol (≥ 7%)	1093	62.4	228	42.2	
Missing	353	20.1	100	18.5	
Good preparation for pregnancy‡					
Yes	172	9.8	88	16.3	< 0.001
No	1151	65.7	319	59.1	
Missing	430	24.5	133	24.6	
Smoking during pregnancy					
Yes	385	22.0	125	23.1	0.91
No	1164	66.4	373	69.1	
Missing	204	11.6	42	7.8	
Parity					
Primipara (parity = 0)	768	43.8	136	25.2	< 0.001
Multipara (≥ 1)	937	53.5	376	69.6	
Missing	48	2.7	28	5.2	
Ethnicity					
White	1687	96.2	429	79.4	< 0.001
Non-white	40	2.3	94	17.4	
Missing	26	1.5	17	3.1	
Index of Multiple Deprivation (tertiles)					
1 (most deprived)	530	30.2	231	42.8	< 0.001
2 (middle)	587	33.5	178	33.0	
3 (least deprived)	633	36.1	130	24.1	
Missing	3	0.2	1	0.2	

*The type of diabetes was missing in five cases.
†Mann–Whitney test was used for testing differences in continuous variables between Type 1 and Type 2 diabetes; the χ^2-test was used for testing differences in categorical variables between Type 1 and Type 2 diabetes.
‡Good preparation for pregnancy has been defined as having both pre-conception folate supplementation and peri-conception HbA_{1c} < 53 mmol/mol (< 7%).
DCCT, Diabetes Control and Complications Trial; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine.

not attend for pre-conception care, 23.5% of pregnancies resulted in adverse outcome vs. 18.1% in those who did (relative risk 1.30, 95% CI 1.10–1.53, P = 0.002). The risk of an adverse outcome was also higher for women who did not take pre-conception folate (18.2%) compared with those who did (11.8%): relative risk 1.54, 95% CI 1.22–1.94, P < 0.001. In women with peri-conception HbA_{1c} ≥ 53 mmol/mol (≥ 7%), 19.2% of pregnancies had an adverse outcome vs. 10.4% in those with peri-conception HbA_{1c} < 53 mmol/mol (< 7%): relative risk 1.85, 95% CI 1.40–2.44, P < 0.0001. Similarly, a higher percentage of pregnancies (15.5%) resulted in an adverse outcome in

Table 2 Trends in indicators of preparation for pregnancy for mothers with Type 1 and Type 2 diabetes, 1996–2010

	n (%)					
	Type 1 (*n* = 1753)			Type 2 (*n* = 540)		
Time period of delivery	Attendance for pre-conception care	Pre-conception folate*	Peri-conception HbA_{1c}* < 53 mmol/mol (< 7%)	Attendance for pre-conception care	Pre-conception folate*	Peri-conception HbA_{1c}* < 53 mmol/mol (< 7%)
1996–1998	167 (47.0)	62 (20.2)	44 (18.7)	10 (38.5)	1 (4.3)	8 (38.1)
1999–2001	184 (53.0)	81 (26.0)	62 (22.5)	15 (35.7)	4 (10.5)	10 (35.7)
2002–2004	145 (42.2)	140 (44.9)	77 (24.4)	38 (30.2)	38 (34.2)	50 (45.0)
2005–2007	137 (38.8)	138 (44.4)	68 (22.7)	42 (28.8)	49 (37.7)	64 (54.7)
2008–2010	122 (34.5)	155 (55.0)	56 (20.4)	63 (31.5)	74 (45.4)	80 (49.1)
P (χ^2 for trend)	< 0.0001	< 0.0001	0.74	0.50	< 0.0001	0.13

*Number with valid data for pre-conception folate is *n* = 1523 for Type 1 diabetes and *n* = 465 for Type 2 diabetes; for peri-conception HbA_{1c}, *n* = 1400 for Type 1 diabetes and *n* = 440 for Type 2 diabetes; the proportions of women for each outcome are calculated from those with valid data.

women who were poorly prepared for pregnancy (based on both folate and HbA_{1c}) vs. those with 'good' preparation (9.1%): relative risk 1.72, 95% CI 1.14–2.58, *P* = 0.007.

Predictors of inadequate preparation for pregnancy

Tables 3–5 show predictors of each indicator of inadequate preparation for pregnancy. In multivariate analyses, younger maternal age (for women under 35 years), residence in more deprived areas and maternal smoking were independently associated with all three indicators. Not attending pre-conception care was additionally associated with Type 2 diabetes, multiparity, later year of delivery, older maternal age (for women ≥ 35 years) and longer duration of diabetes (in those with ≥ 15 years' duration) (Table 3). Lack of folate consumption was additionally associated with Type 2

Table 3 Association of maternal factors with non-attendance for pre-conception care for women with pre-conception diabetes (results of univariate and multivariate logistic regression)

	Type 1 and Type 2 diabetes (*n* = 2293)			
Variable	Unadjusted odds ratio (95% CI)	*P*-value	Adjusted odds ratio* (95% CI)	*P*-value
Year of delivery†	1.07 (1.04–1.09)	< 0.0001	1.06 (1.04–1.09)	< 0.0001
BMI at first antenatal visit (kg/m^2)†	1.01 (0.99–1.03)	0.25	‡	
Duration of diabetes (years)†				
< 15 years	0.97 (0.95–1.00)	0.02	0.99 (0.96–1.01)	0.36
≥ 15 years	1.01 (0.98–1.04)	0.73	1.04 (1.01–1.08)	0.01
Maternal age at delivery (years)†				
< 35 years	0.95 (0.93–0.96)	< 0.0001	0.92 (0.90–0.95)	< 0.0001
≥ 35 years	1.10 (1.04–1.18)	0.003	1.07 (1.00–1.15)	0.04
Type of diabetes				
Type 1	0.56 (0.44–0.71)	< 0.0001	0.63 (0.46–0.85)	0.003
Type 2	Reference		Reference	
Ethnicity				
White	Reference		Reference	
Non-white	1.75 (1.13–2.70)	0.01	‡	
Parity				
Primara (0)	Reference		Reference	
Multipara (≥ 1)	1.47 (1.21–1.78)	0.0001	1.65 (1.33–2.05)	< 0.0001
Index of Multiple Deprivation (tertiles)				
1 (most deprived)	2.32 (1.84–2.93)	< 0.0001	1.84 (1.43–2.37)	< 0.0001
2 (middle)	1.99 (1.58–2.50)	< 0.0001	1.61 (1.26–2.06)	0.0001
3 (least deprived)	Reference		Reference	
Smoking during pregnancy				
No	Reference		Reference	
Yes	2.04 (1.60–2.60)	<0.0001	1.59 (1.25–2.02)	0.0002

*Adjusted model was constructed using backwards stepwise regression. All variables were entered into the model. Variables were then iteratively removed until all remaining had $P < 0.1$.
†Continuous variable.
‡Not retained in adjusted model as $P < 0.1$.
Those with missing data on type of diabetes were excluded (*n* = 5).

diabetes, multiparity, non-white ethnicity, older maternal age (for women ≥ 35 years) and earlier year of delivery (Table 4). Finally, inadequate peri-conception glucose control was additionally associated with Type 1 diabetes, higher maternal BMI, non-white ethnicity and longer duration of diabetes (up to 15 years) (Table 5). There was a steady increase between duration of diabetes and risk of inadequate peri-conception HbA_{1c} [≥ 53 mmol/mol (≥ 7%)] until reaching a plateau at 15 years. The final models explained 6.3%, 12.7% and 9.1% of the variation in non-attendance for pre-conception care, lack of pre-conception folate consumption and inadequate peri-conception HbA_{1c}, respectively.

Two statistically significant interactions were observed with diabetes type. The association between smoking and non-attendance of pre-conception care was stronger in women with Type 2 diabetes (adjusted odds ratio 3.13, 95% CI 1.83–5.34, $P < 0.0001$) compared with Type 1 diabetes (adjusted odds ratio 1.36, 95% CI 1.04–1.79, $P = 0.03$). The inverse association between increasing maternal age (for women under 35 years) and lack of pre-conception folate supplementation was stronger in women with Type 1 diabetes (adjusted odds ratio 0.86, 95% CI 0.82–0.89 per 1-year increase in women aged < 35 years, $P < 0.0001$) compared with Type 2 diabetes (adjusted odds ratio 0.95, 95% CI 0.89–1.02, $P = 0.14$). Given there were 24 possible interactions, however, these two occurrences provide insufficient evidence that the predictors of pregnancy were consistently different between women with Type 1 and those with Type 2 diabetes ($P = 0.34$). Tables S1–3 of the Supporting Information show the associations between each predictor and all three preparation for pregnancy outcomes separately for Type 1 and Type 2 diabetes.

When the adjusted models were recalculated on multiply imputed data, none of the *P*-values were materially altered and only two of the 29 odds ratios differed by more than 0.2 units. These were both in the model of inadequate peri-conception HbA_{1c}, where the effects of ethnicity (adjusted odds ratio for non-white ethnicity 2.66, 95% CI 1.29–5.46, $P < 0.0001$) and diabetes type (adjusted odds ratio for Type 1 diabetes 4.10, 95% CI 2.49–6.74, $P = 0.008$) were approximately one fifth smaller than in the complete-case analyses.

Discussion

Main findings

Our study reports trends over 15 years in preparation for pregnancy in women with Type 1 and Type 2 diabetes, from a regional population-based register. Attendance for pre-conception care and peri-conception glycaemic control did not

Table 4 Association of maternal factors with no pre-conception folate supplementation for women with pre-conception diabetes (results of univariate and multivariate logistic regression)

	Type 1 and Type 2 diabetes ($n = 1988$)			
Variable	Unadjusted odds ratio (95% CI)	*P*-value	Adjusted odds ratio* (95% CI)	*P*-value
Year of delivery†	0.84 (0.81–0.87)	< 0.0001	0.85 (0.82–0.89)	< 0.0001
BMI at first antenatal visit (kg/m^2)†	1.00 (0.97–1.02)	0.61	‡	
Duration of diabetes (years)†				
< 15 years	0.97 (0.94–1.00)	0.04	‡	
≥ 15 years	0.95 (0.91–0.99)	0.02	‡	
Maternal age at delivery (years)†				
< 35 years	0.87 (0.84–0.90)	< 0.0001	0.87 (0.84–0.90)	< 0.0001
≥ 35 years	1.21 (1.10–1.32)	0.0001	1.18 (1.08–1.29)	0.0002
Type of diabetes				
Type 1	0.84 (0.61–1.16)	0.29	0.55 (0.40–0.77)	0.0004
Type 2	Reference		Reference	
Ethnicity				
White	Reference		Reference	
Non-white	2.32 (1.22–4.40)	0.01	2.48 (1.37–4.48)	0.003
Parity				
Primara (0)	Reference		Reference	
Multipara (≥ 1)	1.22 (1.95–1.55)	0.12	1.69 (1.30–2.19)	0.0001
Index of Multiple Deprivation (tertiles)				
1 (most deprived)	3.05 (2.22–4.19)	< 0.0001	1.79 (1.31–2.44)	0.0002
2 (middle)	2.12 (1.57–2.87)	< 0.0001	1.54 (1.14–2.07)	0.005
3 (least deprived)	Reference		Reference	
Smoking during pregnancy				
No	Reference		Reference	
Yes	3.26 (2.35–4.52)	< 0.0001	2.52 (1.83–3.46)	< 0.0001

*Adjusted model was constructed using backwards stepwise regression. All variables were entered into the model. Variables were then iteratively removed until all remaining had $P < 0.1$.
†Continuous variable.
‡Not retained in adjusted model as $P < 0.1$.

Table 5 Association of maternal factors with inadequate peri-conception blood glucose control [peri-conception $HbA_{1c} \geq 53$ mmol/mol (≥ 7%)] for women with pre-conception diabetes (results of univariate and multivariate logistic regression)

	Type 1 and Type 2 diabetes (n = 1840)			
Variable	Unadjusted odds ratio (95% CI)	P-value	Adjusted odds ratio* (95% CI)	P-value
Year of delivery†	0.94 (0.90–0.98)	0.0003	‡	
BMI at first antenatal visit (kg/m^2)†	0.95 (0.92–0.98)	0.001	1.05 (1.01–1.09)	0.01
Duration of diabetes (years)†				
< 15 years	1.21 (1.16–1.27)	< 0.0001	1.16 (1.09–1.23)	< 0.0001
≥ 15 years	0.91 (0.86–0.97)	0.003	0.94 (0.87–1.01)	0.09
Maternal age at delivery (years)†				
< 35 years	0.89 (0.85–0.93)	< 0.0001	0.91 (0.86–0.95)	0.0002
≥ 35 years	1.00 (0.90–1.12)	0.98	1.09 (0.96–1.24)	0.19
Type of diabetes				
Type 1	7.02 (4.35–11.32)	< 0.0001	5.51 (2.71–11.22)	< 0.0001
Type 2	Reference		Reference	
Ethnicity				
White	Reference		Reference	
Non-white	0.65 (0.29–1.48)	0.30	3.13 (1.23–7.97)	0.02
Parity				
Primara (0)	Reference		Reference	
Multipara (≥ 1)	0.73 (0.52–1.02)	0.07	‡	
Index of Multiple Deprivation (tertiles)				
1 (most deprived)	2.10 (1.31–3.36)	0.002	1.82 (1.05–3.14)	0.03
2 (middle)	1.50 (0.95–2.35)	0.08	1.27 (0.76–2.13)	0.37
3 (least deprived)	Reference		Reference	
Smoking during pregnancy				
No	Reference		Reference	
Yes	2.04 (1.31–3.17)	0.002	1.97 (1.18–3.29)	0.01

*Adjusted model was constructed using backwards stepwise regression. All variables were entered into the model. Variables were then iteratively removed until all remaining had $P < 0.1$.
†Continuous variable.
‡Not retained in adjusted model as $P < 0.1$.

improve over this time. The proportion of women taking pre-conception folate increased over time, but remained disappointing, reaching 52% by 2008–2010. Deprivation, smoking and younger maternal age (for women aged < 35 years) were independently associated with inadequate preparation for pregnancy. Women with Type 2 diabetes were less likely to attend for pre-conception care or to take folate, but had generally better peri-conception glucose control. There was limited evidence that the predictors of preparation for pregnancy were different in women with Type 1 diabetes and those with Type 2 diabetes. Pregnancy was more likely to result in an adverse outcome if the woman was not adequately prepared for pregnancy.

Strengths and limitations of the study

This study used regional population-based data collected consistently over a 15-year period and linked to regional surveys of pregnancy outcome (the Perinatal Morbidity and Mortality Survey and the Northern Congenital Abnormality Survey), and included women with Type 1 and those with Type 2 diabetes. High case ascertainment is maintained through well-established links with local clinicians, and by cross-validation with the Office for National Statistics for mortality outcomes. Ascertainment of congenital anomalies was consistent throughout the study period and independent of diabetes status. By using generalized estimating equations, we were able to account for the potential bias of analysing repeat pregnancies in the same woman.

Availability of detailed clinical information over a 15-year time period enabled exploration of the temporal trends in uptake of pre-conception care and the analysis of the independent effects of a wide range of clinical and socio-demographic risk factors on broader indicators of pregnancy preparation.

We used a composite measure of peri-conception HbA_{1c} as a proxy for pre-conception HbA_{1c} as the latter had a high percentage of missing values. However, peri-conception HbA_{1c} proved to be a reasonable surrogate of pre-conception HbA_{1c} in our recent analysis of the NorDIP data [3]. Data collection was also reliant on the completeness and accuracy of the medical records. Missing data were primarily managed by performing complete-case analysis, which may introduce bias if data are not missing completely at random. However, our results were negligibly modified when the analyses were re-performed on multiply imputed data.

Despite a large number of statistically significant associations, even our most explanatory model (the model of pre-conception folate supplement usage) only explained 13% of the variance. Although low in absolute terms, this is quite typical of epidemiological studies, particularly those concerning dichotomous outcomes. The NorDIP does not collect

information on various other factors, including pertinent behavioural factors (e.g. maternal and paternal educational levels, whether or not the pregnancy was planned, and previous pregnancy experience) that might have explained more of the variation in non-attendance for pre-conception care. Inadequate peri-conception glucose control is likely affected by a complex range of biological, genetic, social and behavioural factors that are not be captured by our survey.

Comparison with other studies

The rapid rise in both the prevalence of pregnancies complicated by existing diabetes, and the proportion with Type 2 diabetes, is consistent with trends reported elsewhere in the UK and internationally [18,19]. In our population, with a relatively low proportion of women of high-risk ethnicity, this is largely attributable to increasing BMI and obesity rates among younger women; regions with more ethnic diversity report higher rates of pregnancy in women with Type 2 diabetes [12]. Type 2 diabetes is associated with similar or even worse pregnancy outcomes compared with Type 1 diabetes [19,20]. We found, as did Murphy and co-workers in East Anglia, that women with Type 2 diabetes were significantly less likely to attend pre-conception care, but had better pre-conception glycaemic control [11]. This may suggest that current models of provision of pre-conception care in England, largely delivered by hospital-based specialists, may be less accessible for women with Type 2 diabetes.

Despite the acknowledged importance of pre-conception care for women with diabetes [9–12,21], uptake remains universally low [11–13,22]. According to the Confidential Enquiry into Maternal and Child Health (CEMACH) report, women with diabetes were poorly prepared for pregnancy: only 39% of women took folic acid pre-conception, 35% had documented pre-pregnancy counselling and 37% had some documentation of glycaemic control measurement before pregnancy [12]. In our study, only approximately one third of women in the most recent time period had documented evidence of pre-conception advice, similar to Murphy *et al*. [11]. Even more disappointingly, this had declined from 47% in 1996–1998. However, the absolute numbers of women receiving pre-conception advice remained relatively constant in the face of rising numbers of pregnancies. This suggests that service capacity may be one issue contributing to poor access, based on anecdotal reports from local diabetes obstetric teams.

In addition to lower uptake of pre-conception care in women with Type 2 diabetes, our study also found marked socio-demographic inequalities in uptake and in the adequacy of preparation for pregnancy. Women resident in deprived areas, smokers and younger women were less likely to attend for care or to take folic acid pre-conception, and also had higher peri-conception HbA_{1c}. Murphy *et al*. found an association between social disadvantage and pre-pregnancy care attendance only for women with Type 2 diabetes, but not for women with Type 1 diabetes [11]. An analysis of our data separated by type of diabetes confirmed that social deprivation was a significant predictor for non-attendance for pre-conception care and no pre-conception folate consumption for both women with Type 1 and Type 2 diabetes (Supporting Information, Tables S1–3). Murphy *et al*. found that Asian women were less likely to attend pre-conception care than white women [11]; in our study, non-white ethnicity was independently associated with pre-conception folate consumption and higher peri-conception HbA_{1c}, but only approximately 6% of women overall were of non-white ethnicity.

A number of qualitative studies and surveys have explored potential reasons for poor attendance for pre-conception care [8,23–25]. Some studies report that women with diabetes do not realize the importance of pre-conception care for pregnancy outcome [24,26] or have limited knowledge of specific risks related to diabetes [24]. However, another study suggested that, although the majority of women (90%) were aware of the risks of pregnancy with diabetes, neither this knowledge nor past pre-conception counselling (38%) encouraged women to attend pre-pregnancy care [25]. Surprisingly, even personal experience of previous poor pregnancy outcome may not encourage women to attend pre-pregnancy care [25,27]. Commonly, negative messages from health professionals about pregnancy discourage women from attendance for pre-conception care, but good relationships with health professionals, who are aware of personal circumstances and goals of individual women, are highly valued [24,25,28]. Furthermore, as more than half of women with diabetes have an unplanned pregnancy [29], information and advice about pregnancy and diabetes needs to be integrated into routine diabetes care in both primary and secondary care settings, to ensure all women of reproductive age have the knowledge and understanding they need to access pre-conception care well before they plan a pregnancy. Recording information on responsibility for diabetes care (primary or secondary care) may be helpful in elucidating one of the origins of poor uptake of pre-conception care.

Our study found that women who attended pre-conception care were more likely to experience a good pregnancy outcome. Thus, it adds to a large body of observational evidence [9,10], including other prospective multi-centre cohort studies [11,12,21], which report benefits of pre-conception care and good pregnancy preparation in women with diabetes. However, there remains an absence of evidence from randomized trials and, given the evident bias in uptake of pre-conception care, causal attribution and extrapolation of anticipated benefits must be made with caution. Nevertheless, it is clear that there is considerable room for improvement in helping women to prepare for pregnancy and to minimize risks of adverse outcome.

Clinical implications

The rising prevalence of pregnancy complicated by diabetes, and a changing population profile, including increased proportion of women with Type 2 diabetes and with co-morbidities including high rates of obesity, provide further challenges to ensuring that women with diabetes are adequately prepared for pregnancy and have the best chance of a successful pregnancy outcome. Inequalities in uptake of pre-conception care and in successful preparation for pregnancy also need to be addressed. Specialist-based service models may need to be revisited and new models of care developed or redesigned, building on existing routine care for diabetes in primary and community settings. Both women with diabetes and health professionals must be educated of the need for and benefits of pre-conception care [30]. This may be particularly important for women with Type 2 diabetes, where greater awareness of the possibility of pregnancy is required from diagnosis. Incorporating pregnancy preparation and counselling within chronic disease management frameworks such as the Quality Outcome Framework in England may also raise awareness. Importantly, innovative methods of service provision should be rigorously evaluated to determine whether the anticipated benefits and cost-effectiveness can be achieved.

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Competing interests

None declared.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Association of maternal factors with non-attendance for pre-conception care for women with pre-conception diabetes (results of univariate and multivariate logistic regression) by type of diabetes.
Table S2. Association of maternal factors with no pre-conception folate supplementation for women with pre-conception diabetes (results of univariate and multivariate logistic regression) by type of diabetes.
Table S3. Association of maternal factors with inadequate peri-conception blood glucose control for women with pre-conception diabetes (results of univariate and multivariate logistic regression) by type of diabetes.

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COMMENTARY

Congenital anomalies in diabetic pregnancy: an important confirmation

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Keywords Congenital anomalies · Diabetic pregnancy · HbA_{1c} · Prepregnancy counselling

Abbreviations
NorCAS Northern congenital abnormality survey
NorDIP Northern diabetes in pregnancy survey

> *The study of things caused must precede the study of the causes of things*
> J.H. Biggart [1]

The birth of a baby with a severe congenital anomaly is a family tragedy. Feelings are often suppressed, and this is perhaps even more likely if there has been a therapeutic termination. Much obstetric effort is now focused on prevention of these tragedies, but with regard to diabetes the underlying suspicion is that excess glucose is the teratogen, and that if the mother's blood glucose level had been entirely normal in the very early days of the conception the developmental anomaly would have been less likely to occur. Not totally prevented, just reduced to the background risk in the non-diabetic population. So it is the responsibility of the diabetes care team, as much as the mother herself, to try and achieve this perhaps unattainable goal—a totally normal maternal blood glucose level at a time when she will not know for sure whether she is pregnant or not.

I remember a baby born with a badly twisted foot—a subset or 'sequence' of the caudal dysplasia syndrome that we all learnt about as a diabetes-related congenital fetal anomaly. After much orthopaedic effort the foot eventually had to be amputated. The young man must now be in his mid-30s, but his mother will still have her sense of guilt—the record of the pregnancy and the evidence of the early hyperglycaemia were all in her hospital record, and there was even a photograph of the twisted foot, until she could no longer stand the questions and well-meant interest from the next junior doctor who happened to open her chart, and she defaulted from the diabetic clinic for some time. Removing the offending part of the record to a separate folder helped, but the guilt should not have been hers, but ours, for not having a better system of diabetes management, or a better sort of insulin, or even being able to prevent her diabetes altogether.

The paper in this issue of *Diabetologia* by Bell et al. is important [2]. It is the first time that epidemiologists with particular knowledge of congenital fetal anomalies, and of diabetes management before and during pregnancy, have come together to observe—albeit retrospectively—all of the actual outcomes of pregnancy in a defined region. The authors, from the Institute of Health and Society in Newcastle upon Tyne, with its related Northern Congenital Abnormality Survey (NorCAS) and Northern Diabetes in Pregnancy Survey (NorDIP) are the first combined group to have properly tackled this observational task.

Although many of the problems associated with pregnancy in a diabetic woman have been recognised since the very first reported case, by Heinrich Bennewitz at the Charité Hospital, Berlin, in 1824 [3, 4], and might have been thought to have been overcome by the use of insulin following the first successful diabetic pregnancy managed with insulin by George Graham at St Bartholomew's Hospital, London, 100 years later [5], it is perhaps strange that the increased risk of fetal congenital anomalies was not

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suspected until much later. A report by the UK Medical Research Council in 1955 carefully documented a number of congenital anomalies in several centres during a randomised clinical trial [6], but as the report was focused on disproving the alleged benefit of oestrogen therapy in diabetic pregnancy, this perhaps more important observation was overlooked. The larger series from the Rigshospitalet in Copenhagen in 1964, by Lars Mølsted-Pedersen and coworkers [7], established the problem. A number of experimental models of hyperglycaemic pregnancy in rats by Ulf Eriksson in Uppsala, Sweden, subsequently established the teratogenic role of excess glucose in the very early stages of gestation, and threw some light on possible aetiological mechanisms [8]. Norbert Freinkel's stimulating Banting Lecture on 'fuel-mediated teratogenesis' led to much research on this aspect of diabetic pregnancy [9].

It was, however, the prospective randomised clinical trials of folic acid supplementation in non-diabetic pregnancy that have provided the evidence base for current guidelines on nutritional supplementation in diabetic pregnancy. The worthy aim of the St Vincent Declaration of a pregnancy outcome for a diabetic woman not different from that of a non-diabetic mother [10] has still not in general been achieved, and the persistence of fetal congenital anomalies, associated with undoubted early pregnancy hyperglycaemia, is one of the main reasons for this ongoing problem. The UK Confidential Enquiry on Maternal and Child Health (CEMACH) report on diabetes and pregnancy [11] confirmed the practical difficulty in achieving normoglycaemia in very early pregnancy—effective universal prepregnancy counselling may be an impossible goal.

Nevertheless, there has always been a degree of doubt concerning the actual relationship between maternal hyperglycaemia and congenital anomalies. These same anomalies all occur in non-diabetic pregnancies. A distinguished paediatrician from Cincinnati, Harold Kalter, who had a background in teratology, was brave enough to challenge the long-accepted belief in a detailed monograph [12] suggesting that errors might have arisen from misclassification of anomalies and from overenthusiastic reporting of uncontrolled series of diabetic pregnancies. Previous cohort studies have included only cases diagnosed antenatally, or apparent shortly after birth, which is a major methodological limitation. This paper from Newcastle upon Tyne is a final answer to Dr Kalter, and sets the record straight in a large population-based epidemiological study.

The north of England has a population of around three million, and there are about 30,000 pregnancies per year. Specific results for all of these pregnancies are presented for the years 1996–2008, including all births after 20 weeks' gestation and terminations following prenatal diagnosis of a fetal anomaly. We might ask 'Has this sort of analysis or audit not been done before?' The answer is no, not at this degree of sophistication. The unique juxtaposition of regionally funded surveys to record the outcomes of all pregnancies in diabetic women, and separately to record and classify all congenital anomalies in the region (NorDIP and NorCAS) has resulted in an answer to Dr Kalter's question. With some appropriate statistical analyses, including bootstrapping and locally weighted scatter plot smoothing (LOWESS) graphics, the answer is very clear.

In the 12 year period there were 401,149 singleton live births, spontaneous fetal losses and terminations. Of these, 1,677 occurred in mothers who had type 1 or type 2 diabetes (those with 'gestational diabetes' or 'hyperglycaemia in pregnancy' were excluded, wisely in view of ongoing differences in definition). Using the very detailed European Surveillance of Congenital Anomalies (EUROCAT) classification, the risk of any major congenital anomaly, excluding chromosomal anomalies, in the diabetic pregnancies was nearly four times that in the non-diabetic background population. In regard to early pregnancy glycaemia, for each 1% increase in HbA_{1c} above 6.3% (or rise of 11 mmol/mol above 45 mmol/mol), the odds of a pregnancy being affected by a congenital anomaly increased by 30%. Overall, one in 13 (7.7%) singleton deliveries to women with pre-existing diabetes was affected, and the relative risk of an anomaly was nearly four times that in the general population. These data are visually presented in a graph that will certainly become a major educational demonstration for diabetic mothers-to-be, as well as all of their advisors.

As in all studies there are some imponderables. Why should maternal diabetic nephropathy (not fully defined) also be a risk factor? Not so long ago, severe nephropathy was considered one of the few absolute contraindications to pregnancy in a diabetic woman, because of the risk to the woman herself. Could ACE inhibitors be at fault? Is maternal obesity a separate risk or is it compounded in type 2 diabetes? These points are discussed and possible explanations offered. Those of us who have been along this road for many years will be grateful to the collaborative teams in Newcastle upon Tyne for producing this definitive epidemiological assessment of an important diabetes-related pregnancy problem. The clinical cause of the problem is already clear. Now that any lingering doubt is removed about the additive effect of maternal hyperglycaemia superimposed on a background population risk, we can all try to facilitate normoglycaemia in very early gestation.

Contribution statement The author conceived, drafted and approved this commentary.

Duality of interest The author declares that there is no duality of interest associated with this manuscript.

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LETTER

Should women with diabetic nephropathy considering pregnancy continue ACE inhibitor or angiotensin II receptor blocker therapy until pregnancy is confirmed?

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Keywords ACE inhibitor · Angiotensin II receptor blocker · Clinical diabetes · Hypertension · Nephropathy · Pregnancy

Abbreviations
ACEI ACE inhibitor
ARB Angiotensin II receptor blocker

To the Editor: We read with interest the article by Tennant et al [1], which highlights the increased risk of fetal and infant death in women with pre-existing diabetes. The magnitude of these risks increases with HbA_{1c} concentrations above 49 mmol/mol, and women with diabetes and a history of retinopathy have twice the incidence of fetal or infant death. The findings of Tennant et al support the need for not only good glycaemic control but also more intensive pre-pregnancy counselling for the women in higher risk categories. Women who have diabetic nephropathy (persistent albuminuria and/or estimated glomerular filtration rate <60 ml min^{-1} 1.73 m^{-2}) are in one of the highest risk groups for adverse maternal and fetal events. In order to improve outcomes, we suggest that ACE inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) should be more widely prescribed for women with diabetic nephropathy who are considering pregnancy, to optimise blood pressure control and reduce proteinuria.

The risks of fetal malformation and death when ACEIs or ARBs are taken throughout pregnancy or in the second or third trimester are well established [2]. There is, however, more controversy regarding the risks associated with ACEI or ARB exposure when restricted to the first trimester only. A study by Cooper et al assessed the risks of exposure during the first trimester alone to an ACEI or any other antihypertensive agent compared with no antihypertensive drug exposure [3]. A relative risk of 2.71 was derived for congenital malformations in those exposed to ACEI vs the control group, with no differences in outcome between the control group and those exposed to any other antihypertensive treatment. These results suggested that use of an ACEI in the first trimester could not be considered safe. However, there were several important confounding factors in this retrospective study that could not be controlled for. These included diabetes (not requiring drug treatment), obesity, hypertension and maternal age (women who had taken an ACEI were on average 6 years older than the control group). The teratogenic effects of these confounders have been explored in subsequent studies, with systematic reviews and a meta-analysis that incorporate prospective data finding no increased risk of major congenital malformations following ACEI or ARB exposure in the first trimester [4]. Associations with malformations in many of these studies have been attributed by their authors to diabetes or hypertension rather than the direct effects of antihypertensive drugs. It is interesting to note that in the Diabetic Retinopathy Candesartan Trials, among normotensive women with diabetes, there was no difference in fetal outcomes between those exposed to candesartan up to week 8 of gestation vs those who were not exposed to ARBs during pregnancy [5]. Furthermore, there were fewer cardiovascular malformations than expected; an observation attributed to the absence of hypertension in the study participants, reinforcing the view that hypertension itself confers a significant malformation risk.

In women with diabetic nephropathy, adverse outcomes, including pre-term delivery, preeclampsia, a small-for-gestational-age baby and progression of renal failure, are

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substantially increased when blood pressure, glycaemic control or proteinuria are uncontrolled. Rates of preeclampsia in women with diabetic nephropathy can exceed 60% with attendant risks to both mother and baby [6].

Conversely, tight control of blood pressure and proteinuria are associated with better outcomes. Nielsen et al reported similar pregnancy outcomes in 117 pregnant women with type 1 diabetes and microalbuminuria (vs normoalbuminuric controls) when these women maintained rigorous glycaemic and blood pressure control (<135/85 mmHg) and urinary albumin excretion was reduced to <300 mg/24 h [7]. In those with established diabetic nephropathy Bar et al employed a strategy of intensive blood pressure control with captopril for 6 months prior to conception in 24 women [8]. Captopril was discontinued once pregnancy was confirmed. Eighteen women delivered healthy infants at term and four delivered healthy children, but pre-term. There was one late intrauterine death and one baby born with severe malformation but these were comparable to background population rates. These reports suggest that using ACEIs to reduce blood pressure and proteinuria is both safe and effective, with beneficial effects on pregnancy outcome and preservation of maternal renal function in these high-risk groups.

Given the emerging evidence base, are we doing more harm than good by denying those women with diabetic nephropathy who are considering pregnancy a substantial preconception period of optimal treatment for renal disease because of concerns about later ACEI or ARB exposure during the first trimester? By so doing are we exposing both mother and fetus to the much greater morbidity and mortality risks of preeclampsia and accelerated progression of nephropathy? We propose that women with diabetic nephropathy who are considering pregnancy should, after appropriate counselling, be encouraged to consider continuing their ACEI or ARB therapy up until the first positive pregnancy test in the first trimester. These agents should be stopped when pregnancy is confirmed and alternative antihypertensive treatment employed. This approach offers the best chance of safe delivery of a healthy child for these women at highest risk of major complications.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement Both authors conceived and wrote the article, revised it and have approved the final version for publication.

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theguardian

Public health the key to cutting stillbirths

Letters

Wednesday 25 November 2015 19.34 GMT

Last week's perinatal mortality report is a stark reminder of the tragically avoidable burden of stillbirth for families living in the UK (Report, 19 November). Among the world's 35 richest nations, the UK's stillbirth rate is the third highest. Of the nine British families who each day must face the devastating loss of their baby, three would instead be celebrating a healthy live-born child if they'd been living in Denmark, Norway or Finland. We welcomed Jeremy Hunt's recently announced ambition to halve England's rate of stillbirth by 2030, but his proposed "maternity safety champions" and the provision of "high-tech digital equipment" offer no solution for the majority of stillbirths, which occur before labour.

Most preventable stillbirths in the UK are attributable to social factors that are shaped by poverty, deprivation, and income inequality: cigarette smoking, obesity, diabetes, alcohol use - with stillbirths being twice as common among mothers living in England's poorest 10% of regions than the richest 10%. Resolving such a disparity is undeniably challenging; but even small improvements to population health far outweigh any "one-by-one" approach. The English ban on smoking in public spaces, for example, has been linked to an 8% decrease in stillbirth; an improvement that's patently beyond what could be achieved by spending on maternity care alone. Instead, if the UK government wants any real hope of halving the stillbirth rate by 2030, it would do better to reverse the proposed cuts to public health funding - which provides vital services, such as stop-smoking programmes - and increase efforts to address the social factors that cause ill-health from the very start of life.

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Kate Pickett *Professor of epidemiology, University of York*
Linda McGowan *Professor of applied health research, University of Leeds*
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