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Gestational diabetes and the risk of late stillbirth: a case-control study from England, UK

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Abstract

Objective - To explore the separate effects of being at risk of gestational diabetes mellitus (GDM) and screening for GDM, and of raised fasting plasma glucose (FPG) and clinical diagnosis of GDM, on the risk of late stillbirth.

Design - Prospective case-control study.

Setting – 41 maternity units in the United Kingdom.

Population - Women who had a stillbirth ≥28 weeks' gestation (n=291) and women with an ongoing pregnancy at the time of interview (n=733).

Methods - Causal mediation analysis explored the joint effects of 1) 'at risk' of GDM and screening for GDM and 2) raised FPG (≥5·6mmol/L) and clinical diagnosis of GDM on the risks of late stillbirth. Adjusted odds ratios (aOR) were estimated by logistic regression adjusted for confounders identified by directed acyclic graphs.

Main outcome measures – Screening for GDM and FPG levels

Results -Women 'at risk' of GDM, but not screened, experienced 44% greater risk of late stillbirth than those not at risk (aOR=1·44 95%CI=1·01-2·06). Women 'at risk' of GDM who were screened experienced no such increase (aOR=0·98, 95%CI=0·70-1·36). Women with raised FPG not diagnosed with GDM experienced four-fold greater risk of late stillbirth than women with normal FPG (aOR=4·22, 95%CI=1·04-17·02). Women with raised FPG who were diagnosed with GDM experienced no such increase (aOR=1·10 95%CI=0·31-3·91).

Conclusions - Optimal screening and diagnosis of GDM mitigates higher risks of late stillbirth in women at risk of GDM and/or with raised FPG. Failure to diagnose GDM leaves women with raised FPG exposed to avoidable risk of late stillbirth.

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Tweetable abstract: Risk of #stillbirth in gestational diabetes is mitigated by effective screening and diagnosis.

Keywords: Stillbirth, gestational diabetes mellitus, pregnancy

Abbreviations:

FPG	Fasting plasma glucose
GDM	Gestational diabetes mellitus
IADPSG	International Association of Diabetes and Pregnancy Study Groups
OGTT	Oral glucose tolerance test
OR	Odds ratio
WHO	World Health Organisation

Introduction

The prevalence of stillbirth in the United Kingdom (UK) is above the European average, affecting almost one in three hundred pregnancies after 28 weeks of pregnancy.[1] Though likely influenced by a higher burden of population risk factors, such as obesity and cigarette smoking, a recent Confidential Enquiry concluded that up to 60% of antepartum stillbirths could have been prevented with improved antenatal care.[2] Of particular concern was a lack of consistent adherence to the National Institute for Health and Care Excellence (NICE) guidelines for the screening and diagnosis of gestational diabetes (GDM) [3]. Early identification and appropriate management of GDM has been considered an important factor in reducing the burden of adverse perinatal outcome.[4, 5] Hence, the Confidential Enquiry recommended an increased focus on the detection and management of GDM.[2]

Pre-existing diabetes in pregnancy is associated with a four-to-six-fold increase in the risk of stillbirth.[6] The relationship between GDM and stillbirth is more complex; with no consensus in the relationship between GDM and risk of stillbirth.[4, 7-8] These studies employed a range of diagnostic criteria for GDM and there is inconsistency as to whether or not they included women who were diagnosed with GDM or who, retrospectively, met the criteria for GDM diagnosis.

There is variation in recommendations regarding which women should be screened for GDM as well as differences in the criteria used for the diagnosis of GDM.[9, 10] In the UK, the 2015 NICE guidelines advise selected screening for GDM and the criteria recommended for GDM diagnosis are FPG≥5·6mmol/L or 2-hour glucose on the OGTT≥7·8mmol/L, which differs from the World Health Organisation (WHO) recommendations (≥5·1 mmol/L and ≥8·5mmol/L) [3, 10].The rationale for this was to balance the benefits of increased detection of women with a higher risk of adverse outcomes with the health economics relating to the cost and capacity limits of antenatal care provision.[11] To date there has been no assessment of the impact of the thresholds recommended by NICE, nor on the impact of screening practice in the UK on the prevalence of late stillbirth. We aimed to investigate the joint and separate effects of 1) being at risk of GDM and receiving blood glucose screening for GDM

and 2) hyperglycaemia and diagnosis of GDM (as a proxy for receiving specialised diabetes care) on the risk of late stillbirth in a large case-control study from across England.

Methods

Population and sample

The Midlands and North of England Stillbirth Study (MiNESS) is a case-control study of singleton non-anomalous late stillbirths (≥28 weeks' gestation) and controls with ongoing pregnancies which ended in live births that were recruited in 41 maternity units in the UK between April 2014 and March 2016. It was principally established to explore the association between modifiable factors including maternal going-to-sleep position and the risk of late stillbirth.[12] The study was registered on www.clinicaltrials.gov (NCT02025530) and the protocol was published before data collection was complete.[13] Ethical and research approvals were obtained (Ref 13/NW/0874) on 20/01/14, with all participants providing written consent to take part in the study. MiNESS arose from the parent-led Stillbirth Summit in Minneapolis in 2011 [14] and a Priority Setting Partnership which included input from over 550 parents and members of the public. However, there was no active patient involvement in data analyses or interpretation of this secondary analysis.

Inclusion and exclusion criteria

Full details of the study are available elsewhere.[12] Briefly, cases were stillbirths occurring in singleton pregnancies ≥28 complete weeks' of gestation. Prior to their discharge from the maternity unit eligible women were given information about the study and asked whether a researcher (who was also either a midwife or a nurse) could contact them to discuss the study. If the woman agreed, the researcher contacted her separately and, if consent was given to participate, an appointment for an interview was made. Participants were interviewed by research midwives or nurses at each site. Controls were women with an ongoing pregnancy at a similar gestational age to the cases. Controls were randomly selected (using a computer-generated sequence of random numbers) from the

booking lists of each participating maternity unit based (on a 2:1 ratio) on the number and gestation of late stillbirths in the previous four years in that hospital. Controls were introduced to the study by their community midwife or a research midwife and a similar consent process to the cases was carried out. Multiple pregnancies or pregnancies complicated by congenital anomaly were not eligible for recruitment, neither were pregnancies where the mother was aged under 16 years or could not give informed consent.[13] Pregnancies where the mother had pre-existing (type 1 or type 2) diabetes were also excluded from the current sample.

Analyses

The separate effects of being 'at risk' of GDM and receiving blood glucose screening for GDM (and all consequences thereof) on the risk of stillbirth were examined by causal mediation analysis in the total study sample (N=1012).[15] This approach, rooted in the potential outcome framework, involves examining how the occurrence of an outcome (Y) varies with more than one exposure, such as an exposure ($Y|_{X=x} = Y_x$) and mediator ($Y|_{X=x,\ M=m} = Y_xM_m$). This enables the distinct and joint effects of the exposure and mediator to be estimated.

A composite exposure variable denoting 'at risk' of GDM was constructed from four of the five NICE recommended criteria for blood glucose screening for GDM, with 'at risk' defined as any of South Asian or Black Caribbean ethnicity, BMI ≥30kg/m^2, or previous pregnancy effected by GDM or macrosomic (≥4·5kg) birth.[3] Data were not available on the fifth criterion, family history of GDM. The effects of both the exposure and mediator on the relative risk ratio of late stillbirth were estimated from odds ratios (ORs) calculated by logistic regression. 'At risk' of GDM was the principal exposure and receipt of screening for GDM was the principal mediator. Interactions terms were omitted due to negligible evidence of effect (p-for-interaction=0.932). Confounding variables were identified by specifying directed acyclic graphs (DAGs) (**Figure S1**)**.** No variables were considered appropriate for adjustment as all partial confounding variables were concurrent partial mediators.

The separate effects of hyperglycaemia and diagnosis of GDM (as a proxy for receiving specialist diabetes care) on the risk of stillbirth were also examined by causal mediation analysis in all women who were screened for GDM (N=371). FPG was chosen as the measure of underlying glycaemic control, because 31.3% (n=5/16) of screened participants with an FPG≥5·6mmol/L were *not* clinically diagnosed with GDM during pregnancy, compared with just 5.9% (n=2/34) of those with a 2-hour OGTT≥7·8mmol/L). This variation in practice allows the distinct effects of the underlying glycaemic control and subsequent clinical diagnosis with GDM to be explored; as different combinations of both the exposure and mediator can be observed. FPG concentration was the principal exposure and clinical diagnosis of GDM was the principal mediator. Two models were evaluated; to explore FPG as a binary variable and continuous variable. Binary FPG concentration was defined using the 2015 NICE criteria for GDM diagnosis into 'normal' (FPG<5·6mmol/L) and 'raised' (FPG≥5·6mmol/L). Prior to 2015, the NICE criteria for the diagnosis of GDM by FPG was ≥7·0mmol/L. The shape of the association between continuous FPG concentration and risk of late stillbirth was examined by locally-weighted scatterplot smoothing (LOWESS) (**Figure 2**). Interactions terms were again omitted due to negligible evidence of effect (p-for-interaction=0.772 for binary FPG, p=0.501 for continuous FPG). Our DAG (**Figure S1**) implied the following confounding variables required adjustment: maternal ethnicity, socio-economic circumstances, family history of GDM, height, weight, age, parity, previous histories of GDM and macrosomia, and smoking. Family history of GDM was however not known and is therefore a potential source of unobserved confounding.

Adjusted odds ratios (aORs) for the following causal effects were estimated by combining marginal values within each multivariable logistic regression model (further descriptions of each are available in the glossary): 1) the **natural effect** ($Y_1M_{m|y=1}$-$Y_0M_{m|y=0}$), 2) the **total effect** (Y_1M_1-Y_0M_0), 3) the **controlled direct effect** (Y_1M_0-Y_0M_0), 4) the **total indirect effect** (Y_1M_1-Y_1M_0), and 5) the **natural indirect effect** ([$Y_1M_{m|y=1}$-$Y_0M_{m|y=0}$]-[Y_1M_0-Y_0M_0]). Causal effect estimates for mediators 'screening for GDM' and 'diagnosis with GDM' comprise all the consequences thereof. They should not therefore be

interpreted as the isolated effect of e.g. 'diagnosis', but as everything that 'diagnosis' typically effects (i.e. receipt of enhanced care and management).

95% confidence intervals (95% CIs) were derived using the delta method. We do not report total causal effects decomposed into direct and indirect effects, since our exposures (harmful) and mediators (beneficial) act in opposite directions.

Our primary results are derived from complete case analyses as data were available for 96·6% of total participants (N=978/1012) and 91·9% (N=341/371) of those screened for GDM**.** Sensitivity analyses were however conducted in multiply imputed data and negligible differences were observed (see **Tables S1-4**). For these sensitivity analyses; 50 datasets were generated via multivariate imputation by chained equations comprising case/control status, maternal age, height, weight, parity, education, ranked index of multiple deprivation (an area-based measure of socio-economic deprivation derived from the mother's residential postcode), ethnicity, country of birth, first language, FPG, 2-hour OGTT, and glycated haemoglobin concentrations, smoking and marital status, and previous histories of GDM and macrosomia. Point estimates and standard errors were summarised using Rubin's rule.

Analyses were conducted using Stata 14·2 (Statacorp, College Station, TX, USA). Exact p-values are presented to indicate compatibility with null distributions but no null-hypothesis significance tests were performed.[16] The 'significance' of each estimate was instead evaluated by considering the clinical implications of each point estimate judged against the overall uncertainty. This corresponds with guidance from the American Statistical Association [17] and current practice in leading Epidemiology journals. E-values for the point estimate (E) and least extreme confidence limit (ELL) were also determined for the controlled direct effect and total indirect effect to indicate the average required effect for an unobserved confounder to explain the observed associations with the outcome.[18]

A core outcomes set was not used in this analysis.*Role of the funding source*

The Midland and North of England Stillbirth Study was funded by grant GN2156 from Action Medical

Research, Cure Kids and Sands. The funding sources had no role in: 1) the design or conduct of the study, 2) the collection, analysis, or interpretation of the data, or 3) the preparation of the manuscript and decision to submit for publication.

Results

Figure 1 shows the derivation of the study and analytical samples. 1024 women were recruited, including 291 cases and 733 controls. 2·8% (n=8/291) of cases and 0·6% (n=4/733) of controls had pre-existing diabetes and were excluded from this analysis.

Table 1 describes the profile of the study population. Of the 1012 total participants (283 cases and 729 controls), 94 cases and 277 controls were screened for GDM and 8 cases and 30 controls were clinically diagnosed with GDM. 35·9% (n=99/276) of the cases and 32·6% (n=231/709) of the controls had at least one of the four known NICE risk factors for GDM. 69·7% (n=69/99) of these 'at risk' cases and 76·6% (n=177/231) of these 'at risk' controls received screening for GDM (**Figure 1**). The proportion of 'at risk' women who received GDM screening varied between maternity units (median=85%, IQR=60-100, range=20-100, p<0·0001). Of those without a known NICE risk factor for GDM, 13·6% (n=24/177) of the cases and 19·3% (n=92/478) of the controls were screened for GDM for other unspecified reasons (likely family history of GDM). 74·3% (n=156/210) of obese women were screened for GDM, 74·7% (n=106/142) of those self-reporting as South Asian or Black Caribbean, 71·4% (n=5/7) with previous history of GDM, and 90·0% (n=9/10) with previous history of GDM.

'At risk' of GDM, screening for GDM, and risk of late stillbirth

Women known to be 'at risk' of GDM overall experienced only modestly increased risk of late stillbirth (aOR=1·17 95%CI=0·87-1·57) (**Table 2**). This separated into a harmful direct effect of being 'at risk' of GDM and a protective indirect effect of receiving screening for GDM. Women 'at risk' of GDM who did *not* receive blood glucose screening experienced nearly 50% higher risks of stillbirth than women

without a known risk factor (aOR=1·44 95%CI=1·01-2·06, E=2.24, ELL=1.11) (**Table 2**). In contrast, women 'at risk' of GDM who *did* receive blood glucose screening had similar risks to women without a known risk factor (aOR=0·98, 95%CI=0·70-1·36) (**Table 2**). The risk of late stillbirth was thus around one-third lower for those 'at risk' of GDM who received blood glucose screening compared with those 'at risk' of GDM who were not screened (aOR=0·68, 95%CI=0·47-0·98, E=2.30, ELL=1.21) (**Table 2**).

FPG concentration, clinical diagnosis of GDM, and risk of late stillbirth

Overall, the risk of late stillbirth in women with a raised FPG was almost twice as high as in women with normal FPG (aOR=1·97, 95%CI=0·61-6·32,) (**Table 3**). This separated into a harmful direct effect of raised FPG, and a protective indirect effect of being clinically diagnosed with GDM and receiving specialised antenatal care. Women with a raised FPG who were *not* diagnosed with GDM and therefore did *not* receive specialist care experienced four-times higher risks of stillbirth than (undiagnosed) women with normal FPG (aOR=4·22, 95%CI=1·04-17·02, E=7.91, ELL=1.24) (**Table 3**). In contrast, women with a raised FPG who *were* diagnosed with GDM and *did* receive specialist care had similar risks to women with normal FPG (aOR=1·10 95%CI=0·31-3·91,) (**Table 3**). The risk of late stillbirth was thus around four-times lower for those with raised FPG who were clinically diagnosed with GDM, then those with raised FPG who were not clinically- diagnosed (aOR=0.26, 95%CI=0.07-0.93, E=7.15, ELL=1.36) (**Table 3**).

The effect of FPG concentration on the risk of late stillbirth was approximately linear (**Figure 2**). Without GDM diagnosis, each 1mmol/L increase in FPG was associated with 61% greater risk of late stillbirth (aOR=1·63, 95%CI=1·01-2·64). The OR of late stillbirth for a range of FPG values (relative to women with FPG<4·1mmol/L, not diagnosed with GDM) with and without diagnosis and treatment for GDM are shown in **Table 4**.

Discussion

Main findings

This large, multi-centre case-control study reveals the separate and competing effects of 'risk' of GDM and screening, and of hyperglycaemia and clinical diagnosis of GDM, on the risk of late stillbirth. Using causal mediation analysis, we show how the harmful effects of being 'at risk' of GDM and of raised FPG are mitigated by GDM screening and diagnosis respectively.

Without screening, women 'at risk' of GDM (as per NICE criteria) experienced 47% greater risk of late stillbirth. For those who were screened, this excess was essentially eliminated. Similarly, without GDM diagnosis, women with raised FPG experienced a four-fold greater risk of late stillbirth. For those who were diagnosed this excess was no longer apparent. Since a third of women with an FPG≥5·6mmol/L did not receive a GDM diagnosis - partly due to the change in NICE guidance in 2015 - the overall risk of late stillbirth was still over two-times greater in women with a raised FPG.

Strengths and limitations

This is the first study to explore the separate and contrasting effects of underlying hyperglycaemia and diagnosis of GDM (with the presumed consequent enhanced care) on risk of late stillbirth. Information was collected on a large range of confounding variables which were identified using DAGs. Data were relatively complete, 96·6% for ethnicity, BMI, previous histories of GDM and macrosomia; and 91·9% for FPG among those screened. The results were also not materially different in sensitivity analyses that used multiple imputation, increasing confidence in the observed associations.

All participants received routine care, thus less than a third were screened for GDM. It was therefore not possible to jointly examine the effects of screening, FPG concentration, and diagnosis in the full sample (n=1012). The results from our subsample (n=371) are therefore only representative of women with indications for screening and should not be generalised to all pregnant women. Unfortunately, we did not have complete information on the NICE criteria for screening, as family history of diabetes was not collected. Nor do we know the reasons why the quarter of women 'at risk' of GDM were not screened. Unrecorded differences in risk profile, or in the participant's engagement with health

services, may introduce bias. However, the observed differences in screening levels between maternity units suggest these may reflect true variations in UK clinical practice.

Our analyses and interpretations focussed on effect estimates, not null-hypothesis significance tests, as the latter are strongly discouraged within observational studies [16]. There are hence no formal risks of type I or type II errors. For some subgroups, particularly women with diagnosed GDM, our sample included very small numbers, leading to substantial uncertainty that should be appreciated when interpreting absolute effect sizes.

Causal mediation analysis makes several assumptions, including that the exposure(s) and mediator(s) have a causal effect on the outcome. We believe these are plausible, and our assumptions are clearly outlined in our DAGs (**Figure S1**). Nevertheless, for both GDM screening and diagnosis, the hypothesised effects depend on presumed enhanced clinical response to diagnosis, without which we would not expect to see a benefit.

Unbiased estimates of causal effects require no unobserved confounding. Family history of GDM may therefore bias the estimated causal effects of FPG and diagnosis of GDM on risk of stillbirth. Mediation analyses are also highly susceptible to intermediate confounding from unobserved causes of both mediator(s) and outcome(s),[19] although we could not identify any such variables for the relationships examined. Our E-values suggest that considerable confounding would be necessary to explain the observed point estimates; although modest confounding could explain the conservative estimates from our lower confidence limits.

Interpretation

Few previous studies have explored the separate and contrasting effects of raised blood glucose, as a harmful exposure, and the receipt of specialised care, as a mitigating factor; making it difficult to meaningfully compare results. Our findings do however support previous studies which have suggested that a *diagnosis* of GDM leads to improved perinatal outcomes in women with raised blood glucose [5, 20]. Few studies have been large enough to explore a relationship with stillbirth specifically,

Aberg et al. (1997) found very little difference in the risk of stillbirth between women with and without diagnosed GDM (OR=1·33, 95%CI=0·64-2·77), but identified much higher risks of intrauterine death in the previous pregnancy of women subsequently diagnosed with GDM (OR=1.56, 95%CI=1.12-2.19) [21]. Similarly Kodoma at al. (2013) found that when new, more stringent GDM criteria, were retrospectively applied to a cohort of 318 stillbirths, the prevalence of GDM increased from 2.4% to 13.5% in women who had unexplained stillbirths.[22] These studies support our observations that untreated hyperglycaemia confers a greater risk of stillbirth, which is greatly reduced by a clinical diagnosis with GDM.

There continues to be debate about the merit of universal versus targeted screening [23] and the ideal threshold for the diagnosis of GDM. In our sample, 2·8% of cases and 5·1% of controls were diagnosed with GDM. Although prevalence proportions vary greatly between populations, proportions of ≥5% are usual,[24] suggesting potential under-diagnosis. This would correspond with findings from the 2015 UK Confidential Enquiry into Term Antepartum Stillbirths [2]. The NICE criteria for the diagnosis of GDM however changed in 2015, during the conduct of this study, from FPG ≥7·0mmol/L to ≥5·6mmol/L,[3,25] which may explain a lower prevalence. The NICE reportedly selected their new FPG criterion to reflect increases in perinatal morbidity, specifically large-for-gestational-age at lower levels of FPG, [11] although it remains higher than the FPG ≥5·1mmol/L threshold recommended by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) [26].

For those 'at risk' of GDM, we found a linear effect of increasing FPG on the risk of late stillbirth, which is in line with the findings of a continuous relationship between blood glucose levels and adverse pregnancy in the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study.[27] Our data do not therefore support the biological justification of one threshold over another, instead suggesting that it may be best determined by a pragmatic balance of resources required for the increased antenatal workloads and health costs with more stringent GDM diagnostic criteria against the reduced costs of improved perinatal outcome.[28] Our results suggest that universal adherence to NICE guidelines for the screening and diagnosis of GDM would greatly reduce the excess risk of stillbirth due to raised FPG

in the population. To lower this risk further - especially in individuals on the border of diagnosis - it may also be worth considering a graded approach to the care and management of blood glucose control in pregnant women, rather than relying on a single diagnostic threshold.

Conclusion

Women 'at risk' of GDM and/or with raised FPG experience higher risk of late stillbirth. With appropriate screening, diagnosis, and the presumed management and care practices that result, these risks can be largely mitigated. However, variation in practice leaves many women with borderline hyperglycaemia exposed to avoidably elevated risk. If the UK is to improve its record for preventable stillbirth, and have a hope of achieving ambitious government targets [29] then all women 'at risk' of GDM and/or with raised FPG must receive the care recommended by NICE. Further research needs to address the economic and practical implications of implementing different thresholds of FPG to diagnose GDM.

Disclosure of interests

All authors declare that they have no competing interests

Contribution to authorship

AH, TS, BM, DR, EM, and LM contributed to all aspects of the study design and obtained funding. JB coordinated the running of the study. PWGT performed the data analysis with input from TS, ML and JT. TS drafted the manuscript. All authors were involved in interpreting the data and critically reviewing manuscript drafts. All authors gave approval for the final version of the manuscript.

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Ethics committee Approval

This study was reviewed by NRES Committee North West - Greater Manchester Central Reference (13/NW/0874) approval granted 2013, with all participants providing written consent to take part in the study.

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References

[1] Flenady V, Wojcieszek AM, Middleton P, Ellwood D, Erwich JJ, Coory M et al (2016) Stillbirths: recall to action in high-income countries. Lancet 387: 691-702

[2] Draper E, Kurinczuk J, Kenyon S, on behalf of MBRRACE-UK. MBRRACE-UK Perinatal Confidential Enquiry (2015) MBRRACE-UK 2015 Perinatal Confidential Enquiry Term, singleton, normally-formed, antepartum stillbirth. Leicester

[3] NICE National Institute for Health and Care Excellence (2015) Diabetes in pregnancy: management from preconception to the postnatal period (NG3).

[4] Lapolla A, Dalfrà MG, Bonomo M, Parretti E, Mannimo D, Mello G et al. (2009) Gestational diabetes mellitus in Italy: A multicenter study. Eur J Obstet Gynecol Reprod Biol 145: 149-153

[5] Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS (2005) Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med 352: 2477-2486

[6] Tennant PWG, Glinianaia SV, Bilous RW, Rankin J, Bell R (2014) Pre-existing diabetes, maternal glycated haemoglobin, and the risks of fetal and infant death: a population-based study. Diabetologia 57: 285-294

[7] Schmidt MI, Duncan BB, Reichelt AJ, Branchtein L, Matos MC, Costa e Forti A et al. (2001) Gestational Diabetes Mellitus Diagnosed With a 2-h 75-g Oral Glucose Tolerance Test and Adverse Pregnancy Outcomes. Diabetes Care 24: 1151-1155

[8] Peticca P, Keely EJ, Walker MC, Yang Q, Bottomley J (2009) Pregnancy Outcomes in Diabetes Subtypes: How Do They Compare? A Province-based Study of Ontario, 2005–2006. J Obstet Gynaecol Canada 31: 487-496

[9] Metzger BE, Buchanan TA, Coustan DR, de Leiva A, Dunger DB, Hadden DR et al. (2007) Summary and recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. Diabetes Care 30: S251 - 260

[10] Coustan DR, Lowe LP, Metzger BE, Dyer AR, International Association of Diabetes and Pregnancy Study G (2010) The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: paving the way for new diagnostic criteria for gestational diabetes mellitus. Am J Obstet Gynecol 202: 654.e651-656

[11] NCC-WCH (National Collaborating Centre for Women's and Children's Health) (2015) Diabetes in pregnancy: Management of diabetes and its complications from preconception to the postnatal period, NICE

[12] Heazell AEP, Li M, Budd J,Thompson JMD, Stacey T, Cronin R et al (2018) Association between maternal sleep practices and late stillbirth – findings from a stillbirth case-control study. BJOG 125: 254-262

[13] Platts J, Mitchell EA, Stacey T, Martin B, Roberts R, McCowan L et al. (2014) The Midland and North of England Stillbirth Study (MiNESS). BMC Pregnancy Childbirth 14: 171

[14] Mitchell, E. A. (2015). Proceedings of 2011 Stillbirth Summit. BMC Pregnancy and Childbirth **15**(Suppl 1): A2-A2.

[15] VanderWeele TJ (2016) Mediation Analysis: A Practitioner's Guide. Annu Rev Public Health 37: 17-32

[16] Greenland S, Senn S, Rothman K, Carlin JB, Poole C, Goodman SN et al. (2016) Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations. Eur J Epidemiol 31: 337-350

[17] Wasserstein RL, Lazar NA (2016) The ASA's Statement on p-Values: Context, Process, and Purpose. The American Statistician 70: 129-133

[18] VanderWeele, T. J. and P. Ding (2017). Sensitivity Analysis in Observational Research: Introducing the E-Value. Ann Intern Med 167(4): 268-274.

[19] Langer O, Yogev Y, Most O, Xenakis EMJ (2005) Gestational diabetes: The consequences of not treating. Am J Obstet Gynecol 192: 989-997

403 [20] Richiardi L, Bellocco R, Zugna D (2013) Mediation analysis in epidemiology: methods,
404 interpretation and bias. Int J Epidemiol, 42: 1511-9
405 [21] Aberg A, Rydhstrom H, Kallen B, Kallen K (1997) Impaired glucose tolerance during pregnancy
406 is associated with increased fetal mortality in preceding sibs. Acta Obstet Gynecol Scand 76: 212-217
407 [22] Kodama Y, Sameshima H, Ohashi M, Ikenoue T (2013) Impact of new gestational diabetes
408 mellitus criteria on stillbirth: a regional population-based study in Japan. J Obstet Gynaecol Res 39:
409 1242-1245
410 [23] Farrar D, Fairley L, Wright J, Tuffnell D, Whitelaw D, Lawlor DA (2014) Evaluation of the impact
411 of universal testing for gestational diabetes mellitus on maternal and neonatal health outcomes: a
412 retrospective analysis. BMC Pregnancy Childbirth 14: 317
413 [24] Farrar D, Duley L, Medley N, Lawlor DA (2015) Different strategies for diagnosing gestational
414 diabetes to improve maternal and infant health. Cochrane Database Syst Rev 1: CD007122
415 [25] NICE National Institute for Health and Clinical Excellence (2008) Diabetes in pregnancy:
416 management from preconception to the postnatal period (CG63).
417 [26] International Association of Diabetes and Pregnancy Study Groups Consensus Panel (2010)
418 International association of diabetes and pregnancy study groups recommendations on the diagnosis
419 and classification of hyperglycemia in pregnancy. Diabetes Care*;* **33***:* 676–682.
420 [27] The HAPO Study Cooperative Research Group (2008) Hyperglycemia and Adverse Pregnancy
421 Outcomes. N Engl J Med 358: 1991-2002
422 [28] Duran A, Sáenz S, Torrejón MJ, Bordiu E, del Valle L, Galindo M et al(2014) Introduction of IADPSG
423 Criteria for the Screening and Diagnosis of Gestational Diabetes Mellitus Results in Improved
424 Pregnancy Outcomes at a Lower Cost in a Large Cohort of Pregnant Women: The St. Carlos Gestational
425 Diabetes Study. Diabetes Care 37: 2442-2450
426 [29] Hunt J (2015) New ambition to halve rate of stillbirths and infant deaths. Available from
427 https://www.gov.uk/government/news/new-ambition-to-halve-rate-of-stillbirths-and-infant-deaths,
428 accessed 5/3/18

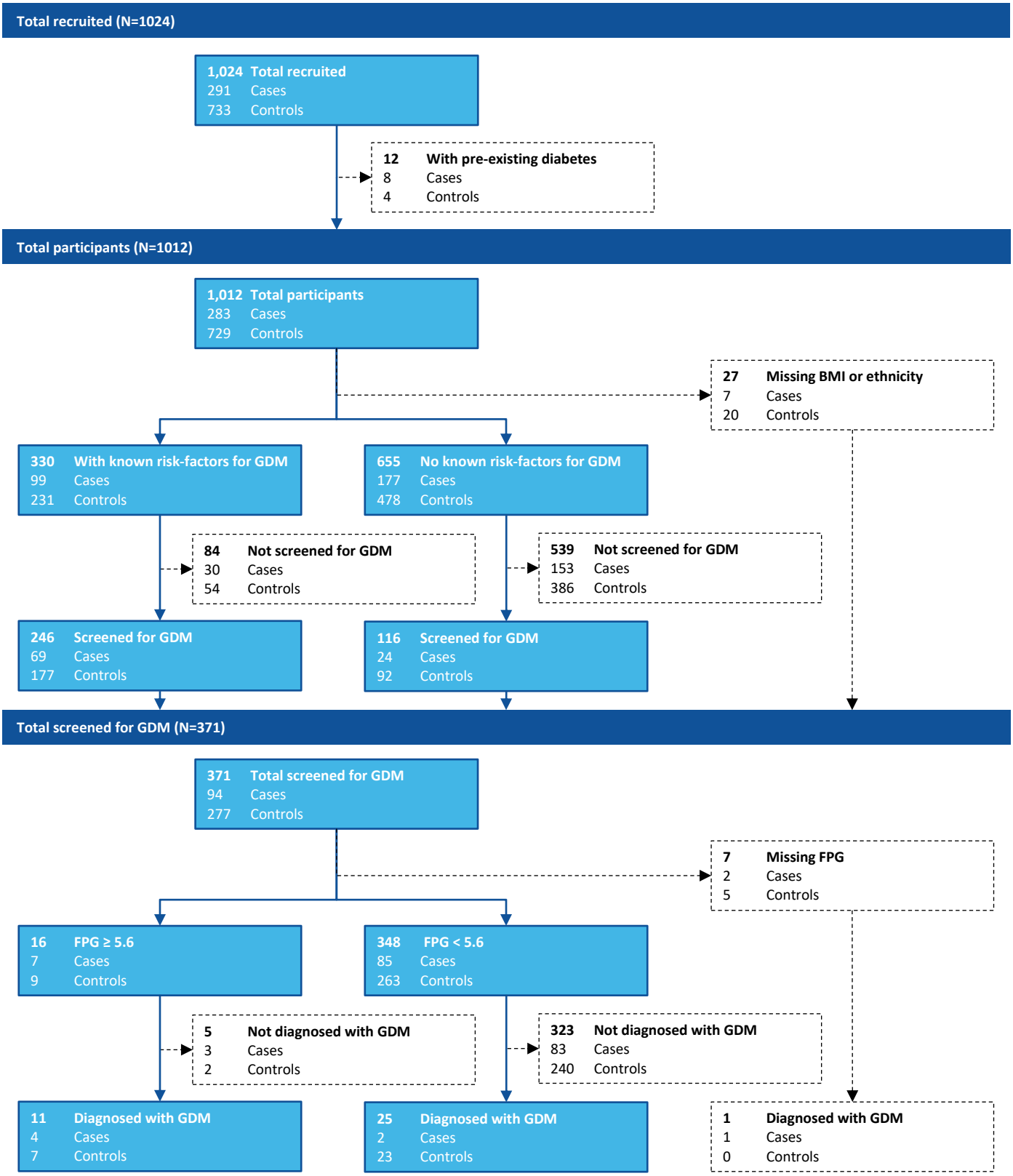

Figure 1 Derivation of the study and analytic sample(s).

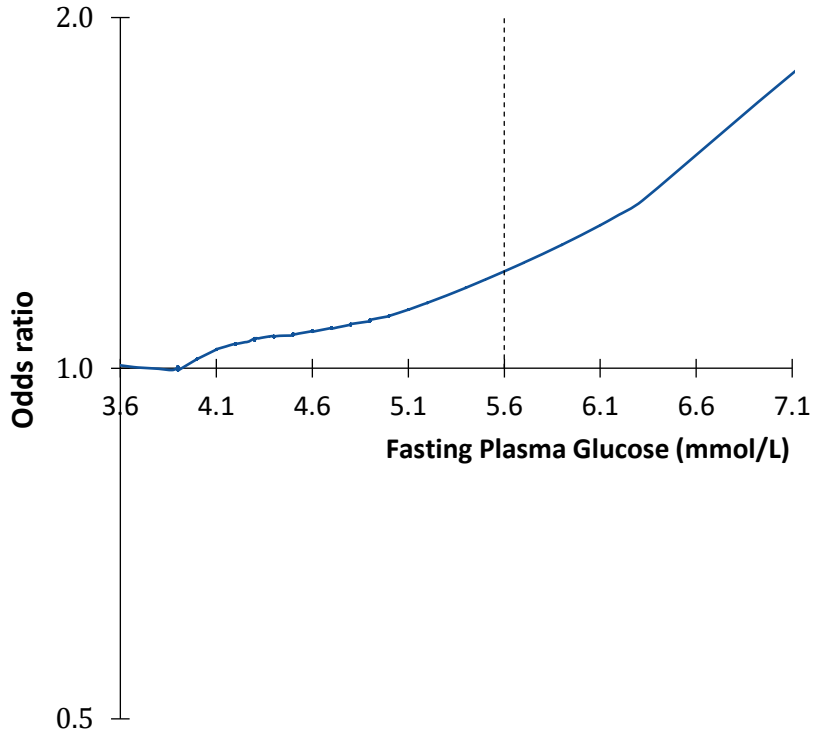

Figure 2: Unconditional odds ratio for late stillbirth across typical values of fasting plasma glucose (FPG), relative to women with FPG<4.1mmol/L.

Dotted line indicates current FPG threshold recommended by NICE.[3]

Table 1. Risk factors, screening and FPG concentration

	Total participants (N=1012) N(%)			Screened for GDM (N=371) N(%)		
	Cases (N=283)	Controls (N=729)	All (N=1012)	Cases (N=94)	Controls (N=277)	All (N=371)
NICE GDM risk variables						
Ethnicity						
White	227 (81.4)	590 (82.8)	817 (82.4)	60 (64.5)	182 (67.7)	242 (66.9)
South Asian	40 (14.3)	93 (13.0)	133 (13.4)	27 (29.0)	71 (26.4)	98 (27.1)
Black Caribbean	1 (0.4)	8 (1.1)	9 (0.9)	1 (1.1)	7 (3.4)	8 (2.2)
Other	11 (3.9)	22 (3.1)	33 (3.3)	5 (5.4)	9 (2.6)	14 (3.8)
Missing	*4*	*16*	*20*	*1*	*8*	*9*
BMI (kg/m^2)						
<18.5 (underweight)	9 (3.2)	23 (3.2)	32 (3.2)	3 (3.2)	8 (2.9)	11 (3.0)
18.5-24.9 (recommended)	111 (39.9)	342 (47.5)	453 (45.4)	19 (20.2)	90 (33.0)	109 (29.7)
25-29.9 (overweight)	88 (31.7)	215 (29.9)	303 (30.4)	22 (23.4)	69 (25.3)	91 (24.8)
≥30 (obese)	70 (25.2)	140 (19.4)	210 (21.0)	50 (53.2)	106 (38.8)	156 (42.5)
Missing	*5*	*9*	*14*	*0*	*4*	*4*
Previous GDM						
No	282 (99.6)	723 (99.2)	1005 (99.3)	93 (98.9)	273 (98.6)	366 (98.7)
Yes	1 (0.4)	6 (0.8)	7 (0.7)	1 (1.1)	4 (1.4)	5 (1.4)
Previous macrosomic infant						
No	282 (99.7)	720 (98.8)	1002 (99.0)	94 (100.0)	268 (96.8)	362 (97.6)
Yes	1 (0.4)	9 (1.2)	10 (1.0)	0 (0.0)	9 (3.3)	9 (2.4)
'At risk' of GDM[a]						
No	177 (64.1)	478 (67.4)	655 (66.5)	24 (25.8)	92 (34.2)	116 (32.0)
Yes	99 (35.9)	231 (32.6)	330 (33.5)	69 (74.2)	177 (65.8)	246 (68.0)
Missing	*7*	*20*	*27*	*1*	*8*	*9*
FPG concentration (mmol/L)						
<4.10				17 (18.5)	51 (18.8)	68 (18.7)
4.10-4.59				44 (47.8)	129 (47.4)	173 (47.5)
4.60-5.09				21 (22.8)	62 (22.8)	83 (22.8)
5.10-5.59				3 (3.3)	21 (7.7)	24 (6.6)
5.60-6.09				3 (3.3)	5 (1.8)	8 (2.2)
≥6.10				4 (4.4)	4 (1.5)	8 (2.2)
Missing				*2*	*5*	*7*
GDM diagnosed						
No				87 (92.6)	247 (89.2)	334 (90.0)
Yes				7 (7.5)	30 (10.8)	37 (10.0)

[a]Women known to be 'at risk' of GDM and who are indicated for screening comprise those who reported their ethnic origin as South Asian, black Caribbean, had body mass index≥30Kg/m^2, or who had a previous pregnancy affected by gestational diabetes or macrosomic birth (>4·5kg).

448 **Table 2** Estimated effects of 'at risk' of GDM[a] and screening for GDM on risk of late stillbirth

Effect estimated	Exposure regime	Reference regime	aOR[b]	(95% CI)	E-value (lower CI)
Total effect	'At risk' of GDM + screened for GDM	Not 'at risk' + + not screened	0·98	(0·70-1·36)	
Natural effect	'At risk' of GDM + 'natural' chance of screening	Not 'at risk' + + not screened	1·17	(0·87-1·57)	
Controlled direct effect	'At risk' of GDM + not screened for GDM	Not 'at risk' + + not screened	1·44	(1·01-2·06)	2.24 (1.11)
Total indirect effect	'At risk' of GDM + screened for GDM	'At risk' of GDM + + not screened	0·68	(0·47-0·97)	2.30 (1.21)
Natural indirect effect	'At risk' of GDM + 'natural' chance of screening	'At risk' of GDM + + not screened	0·81	(0·67-0·98)	

449 [a]Known risk factors for GDM (indicated by NICE for blood glucose screening) comprise South Asian or black Caribbean
450 ethnicity, body mass index≥30Kg/m^2, and previous pregnancy affected by gestational diabetes or macrosomic birth (>4·5kg).

451 [b]Models included the exposure ('at risk' of GDM) and mediator (screened for GDM) only, as all partial confounding variables
452 were also partial mediators.
453

454 **Table 3** Estimated effects of FPG concentration and clinical diagnosis of GDM on risk of late stillbirth

Effect estimated	Exposure regime	Reference regime	aOR[a]	(95% CI)	E-value (lower CI)
Total effect	≥5·6mmol/L[b] + diagnosed with GDM	<5·6mmol/L + Not diagnosed	1·10	(0·31-3·91)	
Natural effect	≥5·6mmol/L[b] + 'natural' chance of diagnosis	<5·6mmol/L + Not diagnosed	1·97	(0·61-6·32)	
Controlled direct effect	≥5·6mmol/L[b] + not diagnosed with GDM	<5·6mmol/L + Not diagnosed	4·22	(1·04-17·02)	7.91 (1.24)
Total indirect effect	≥5·6mmol/L[b] + diagnosed with GDM	≥5·6mmol/L[b] + Not diagnosed	0·26	(0·07-0·93)	7.15 (1.36)
Natural indirect effect	≥5·6mmol/L[b] + 'natural' chance of diagnosis	≥5·6mmol/L[b] + Not diagnosed	0·47	(0·23-0·96)	

455 [a]Models included the exposure (binary FPG concentration), mediator (clinical diagnosis of GDM), and all observed variables
456 in the minimum sufficient adjustment set (maternal ethnicity, socio-economic circumstances, family history of GDM, height,
457 weight, age, parity, previous histories of GDM and macrosomia, and smoking).

458 [b]NICE criteria for diagnosis of GDM
459

460

Table 4 Estimated odds ratio for late stillbirth for different levels of FPG - with and without diagnosis and treatment for GDM - relative to (undiagnosed) women with FPG<4.1mmol/L

FPG	No diagnosis & treatment aOR[a] (95% CI)	Diagnosed & treated aOR[a] (95% CI)
4·1	1·15 (1·01-1·30)	
4·6	1·46 (1·01-2·10)	
5·1	1·87 (1·02-3·42)	
5·6	2·39 (1·03-5·55)	0·61 (0·21-1·72)
6·1	3·05 (1·03-9·02)	0·78 (0·26-2·34)
6·6	3·89 (1·03-14·65)	1·00 (0·30-3·33)
7·1	4·97 (1·04-23·80)	1·27 (0·33-4·90)
7·6	6·34 (1·04-38·67)	1·62 (0·35-7·40)

[a]Models included the exposure (continuous FPG concentration), mediator (clinical diagnosis of GDM), and all observed variables in the minimum sufficient adjustment set (maternal ethnicity, socio-economic circumstances, family history of GDM, height, weight, age, parity, previous histories of GDM and macrosomia, and smoking).