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

DOI:

[10.1111/1471-0528.15659](https://doi.org/10.1111/1471-0528.15659)

Document Version

Accepted author manuscript

[Link to publication record in Manchester Research Explorer](#)

Citation for published version (APA):

Stacey, T., Tennant, P., McCowan, L. M. E., Mitchell, E. A., Budd, J., Li, M., Thompson, J. M. D., Martin, B., Roberts, D., & Heazell, A. (2019). Gestational diabetes and the risk of late stillbirth: a case-control study from England, UK. *British Journal of Obstetrics and Gynaecology*. <https://doi.org/10.1111/1471-0528.15659>

Published in:

British Journal of Obstetrics and Gynaecology

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1 **Title page**

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

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28 **Running title: Gestational diabetes and the risk of late stillbirth**

29 |

30 **Abstract**

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

34 *Design* - Prospective case-control study.

35 *Setting* – 41 maternity units in the United Kingdom.

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

38 *Methods* - Causal mediation analysis explored the joint effects of 1) 'at risk' of GDM and screening
39 for GDM and 2) raised FPG (≥ 5.6 mmol/L) and clinical diagnosis of GDM on the risks of late stillbirth.
40 Adjusted odds ratios (aOR) were estimated by logistic regression adjusted for confounders identified
41 by directed acyclic graphs.

42 *Main outcome measures* – Screening for GDM and FPG levels

43 *Results* -Women 'at risk' of GDM, but not screened, experienced 44% greater risk of late stillbirth
44 than those not at risk (aOR=1.44 95%CI=1.01-2.06). Women 'at risk' of GDM who were screened
45 experienced no such increase (aOR=0.98, 95%CI=0.70-1.36). Women with raised FPG not diagnosed
46 with GDM experienced four-fold greater risk of late stillbirth than women with normal FPG
47 (aOR=4.22, 95%CI=1.04-17.02). Women with raised FPG who were diagnosed with GDM experienced
48 no such increase (aOR=1.10 95%CI=0.31-3.91).

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

52 *Funding* – The Midland and North of England Stillbirth Study was funded by grant GN2156 from
53 Action Medical Research, Cure Kids and Sands.

54 |

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

57 |

58 **Keywords:** Stillbirth, gestational diabetes mellitus, pregnancy

59

60 **Abbreviations:**

61 FPG Fasting plasma glucose

62 GDM Gestational diabetes mellitus

63 IADPSG International Association of Diabetes and Pregnancy Study Groups

64 OGTT Oral glucose tolerance test

65 OR Odds ratio

66 WHO World Health Organisation

67 |

68

69 Introduction

70 The prevalence of stillbirth in the United Kingdom (UK) is above the European average, affecting
71 almost one in three hundred pregnancies after 28 weeks of pregnancy.[1] Though likely influenced
72 by a higher burden of population risk factors, such as obesity and cigarette smoking ~~compared to~~
73 ~~some countries with lower rates of late stillbirth~~, a recent Confidential Enquiry concluded that up to
74 60% of antepartum stillbirths could have been prevented with improved antenatal care.[2] Of
75 particular concern was a lack of consistent adherence to the National Institute for Health and Care
76 Excellence (NICE) guidelines for the screening and diagnosis of gestational diabetes (GDM) [3], ~~which~~
77 ~~recommends that all women with one or more risk factor for GDM (South Asian or Black Caribbean~~
78 ~~ethnicity, body mass index (BMI) $\geq 30 \text{ kg/m}^2$, previous pregnancy affected by GDM or macrosomic~~
79 ~~birth, and family history of diabetes) have a 75g 2-hour Oral Glucose Tolerance Test (OGTT) at 24-26~~
80 ~~weeks of pregnancy.[3]~~ Early identification and appropriate management of GDM has been
81 considered an important factor in reducing the burden of adverse perinatal outcome.[4, 5] Hence,
82 the Confidential Enquiry recommended an increased focus on the detection and management of
83 GDM.[2]

84 Pre-existing ~~(Type 1 or type 2)~~ diabetes in pregnancy is associated with a four-to-six-fold increase in
85 the risk of stillbirth.[46] ~~However,~~ the relationship between GDM and risk of stillbirth is more
86 complex; with no consensus in the relationship between GDM and risk of stillbirth. ~~[4, 7-8] studies~~
87 ~~have either suggested that GDM is associated with an increased risk[5] or found no difference in the~~
88 ~~risk of stillbirth,[6] with one study even finding a protective association between diagnosis of~~
89 ~~gestational diabetes and stillbirth.[7]~~ These studies employed a range of diagnostic criteria for GDM
90 and there is inconsistency as to whether or not they ~~have~~ included women who were diagnosed with
91 GDM ~~(and therefore received enhanced care)~~ or who, retrospectively, met the criteria for GDM
92 diagnosis. ~~Early identification and appropriate management of GDM has been considered an~~
93 ~~important factor in reducing the burden of adverse perinatal outcome in those women at risk of~~
94 ~~developing GDM.[6, 8]~~

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. ~~with recent changes to the internationally recommended criteria for diagnosis of GDM.~~ [9, 10] Following extensive research, [11] the International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommended that GDM be diagnosed for fasting plasma glucose (FPG) concentrations ≥ 5.1 mmol/L, ≥ 10 mmol/L 1-hour or ≥ 8.5 mmol/L 2-hours after 75g oral glucose tolerance test (OGTT). [10] These diagnostic criteria have since been adopted by the World Health Organisation (WHO). [12] In the UK, the 2015 NICE guidelines ~~instead advised~~ adapted selected screening for GDM and the criteria recommended for GDM diagnosis ~~of a~~ are FPG ≥ 5.6 mmol/L or 2-hour glucose on the OGTT ≥ 7.8 mmol/L, which differs from the World Health Organisation (WHO) recommendations (≥ 5.1 mmol/L and ≥ 8.5 mmol/L) [3, 10]. [3]. 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. [13] ~~It is noted that the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study found a continuous relationship between all glucose levels in the OGTT and adverse pregnancy outcome.~~ [14] 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.^[15,13] 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 the analyses or interpretation of this secondary analysis.

Inclusion and exclusion criteria

Full details of the study are available elsewhere.^[16,12] 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.^[15,3] 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).^[1715] This approach, rooted in the potential outcome framework, involves ~~evaluating~~ [examining how](#) the occurrence of ~~the an~~ outcome (Y) ~~across-varies with more than one exposure, various theoretical (counterfactual) levels of the~~ [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 e.g. 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 $\geq 30\text{kg/m}^2$, or previous pregnancy effected by GDM or macrosomic ($\geq 4.5\text{kg}$) birth.^[3] Data were not available on the fifth criterion, family history of GDM.

The effects of ~~each exposure~~ [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, ~~not 2-hour OGTT~~, was chosen as the measure of underlying glycaemic control, because ~~of much lower concordance with 31.3% (n=5/16) of screened participants with an FPG $\geq 5.6\text{mmol/L}$ were not~~ clinically ~~diagnosis-diagnosed of with~~ GDM ~~during pregnancy, compared with just 94.15.9% (n=322/34) of those with a 2-hour OGTT $\geq 7.8\text{mmol/L}$~~

received a clinical diagnosis of GDM compared with 69.4% (n=11/16) with an FPG $\geq$ 5.6mmol/L. This discordance 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 $\geq$ 5.6mmol/L). Prior to 2015, the NICE criteria for the diagnosis of GDM by FPG was $\geq$ 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** ($[Y_1M_{m|y=1}-Y_0M_{m|y=407/1}]-[Y_1M_0-Y_0M_0]$). 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-complete~~ case analyses ~~were performed~~ 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.^[1816] 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 ^[1917] 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 1a 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. ~~Table 1b describes the profile of the sample who received blood glucose screening.~~

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

~~The joint and distinct effects of being 'at risk' of GDM and receiving blood glucose screening for GDM on the risk of late stillbirth were examined by causal mediation analysis.~~ Women known to be 'at risk' of GDM overall ~~did not have experienced only modestly an~~ increased risk of late stillbirth (aOR=1.17 95%CI=0.87-1.57, ~~p=0.289~~) (**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, p=0.043)

(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, $p=0.896$) (Table 2). ~~In women without a known risk factor for GDM, the~~ 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 ~~did not were not screened~~ (aOR=0.68, 95%CI=0.47-0.98, $E=2.30$, $ELL=1.21$, $p=0.032$) (Table 2).

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

~~The joint and distinct effects of hyperglycaemia and receiving a clinical diagnosis of GDM (as a proxy for specialised antenatal care) on the risk of late stillbirth were also examined by causal mediation analysis.~~ 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, $p=0.255$) (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, $E=7.91$, $ELL=1.24$, $p=0.043$) (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, $p=0.883$) (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, $p=0.047$). The ~~odds ratio~~OR of late stillbirth for a range of FPG

270 values (relative to women with FPG<4.1mmol/L, not diagnosed with GDM) with and without
271 diagnosis and treatment for GDM are shown in **Table 4**.

272

273 |

274 Discussion

275 Main findings

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

280 Without screening, women 'at risk' of GDM (as per NICE criteria) experienced 47% greater risk of late
281 stillbirth. For those who were screened, this excess was essentially eliminated. ~~A similar pattern—~~
282 ~~albeit with a more dramatic effect—is observed for a raised FPG. Similarly, Without~~ without GDM
283 diagnosis, women with raised FPG experienced a four-fold greater risk of late stillbirth. For those
284 who were diagnosed ~~and therefore are presumed to have received additional specialised care in~~
285 ~~accordance with NICE guidance~~, this excess was no longer apparent. Since a third of women with an
286 FPG $\geq$ 5.6mmol/L did not ~~however~~ receive a GDM diagnosis - partly due to the change in NICE
287 guidance in 2015 - the overall risk of late stillbirth was still over two-times greater in women with a
288 raised FPG.

289 Strengths and limitations

290 This is the first study to explore the separate and contrasting effects of ~~the~~ underlying
291 hyperglycaemia and ~~the diagnosis of GDM (with the presumed~~ consequent ~~enhanced management~~
292 ~~and care] of GDM~~ on risk of late stillbirth. Information was collected on a large range of ~~contextual~~
293 ~~confounding~~ variables, ~~and confounders requiring adjustment~~ which were identified using ~~directed~~
294 ~~acyclic graphs~~ DAGs. Data were relatively complete, ~~with~~ 96.6% ~~completeness across for~~ ethnicity,
295 BMI, ~~and~~ previous histories of GDM and macrosomia; and 91.9% for FPG among those screened. The
296 results were also not materially different in sensitivity analyses that used multiple imputation,
297 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 this 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 [1816]. There are hence no formal risks of type I or type II errors. For some subgroups ~~however~~, particularly women with diagnosed GDM, [our sample included very small numbers, led to imprecise estimates 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 (~~Supplementary 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), [2419] 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 [85, 2020]. 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) [2221]. Similarly Kodoma et al. (2013) found that when new, more stringent GDM criteria, were retrospectively applied to a cohort of 318 stillbirths, the prevalence of GDM increased ~~5-7 times (from 2.4% to 13.5%)~~ in women who had unexplained stillbirths.[2322] These studies support our observations that untreated hyperglycaemia confers a greater risk of stillbirth, ~~but this which~~ is greatly reduced by a clinical diagnosis with GDM. ~~It is unclear which aspect has the greatest impact on outcome following diagnosis of GDM, from the additional antenatal care, help stabilising blood sugar levels, or timing of birth delivery. Our study is unfortunately too small and does not have the relevant data to further investigate these effects.~~

There continues to be debate about the merit of universal versus targeted screening [2423] 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 $\geq 5\%$ are usual,[2524] 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 ≥ 7.0 mmol/L to ≥ 5.6 mmol/L, [3, ~~26~~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, [1211] although it remains higher than the FPG ≥ 5.1 mmol/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, ~~suggesting that all women with an increased risk of GDM may benefit from optimising their glucose control, regardless of whether they meet the threshold for diagnosis, 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 available resource. It has been suggested that~~ the increased antenatal workloads and health costs ~~required for with~~ more stringent GDM diagnostic criteria ~~are offset by against~~ the reduced costs of improved perinatal outcome. [2728]. ~~Different resource pressures almost certainly explain the variations in screening and diagnostic practices that we observed between maternity units, despite uniform governance from NICE guidelines.~~ 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 ~~exploring a more~~ considering a graded stepped approach to the care and management of blood glucose control in pregnant women, rather than relying on a single diagnostic threshold ~~consistent with current notions on stratified medicine~~ [28].

Conclusion

372 Women 'at risk' of GDM and/or with raised FPG experience higher risk of late stillbirth. With
373 appropriate screening, diagnosis, ~~management~~and the presumed management and care practices
374 that result, and care practices these risks can be largely mitigated. However, variation in practice
375 leaves many women with borderline hyperglycaemia exposed to avoidably elevated risk. If the UK is
376 to improve its record for preventable stillbirth, and have a hope of achieving ambitious government
377 targets [29] then all women 'at risk' of GDM and/or with raised FPG must receive the care
378 recommended by NICE. Further research needs to address the economic and practical implications
379 of implementing different thresholds of FPG to diagnose GDM. ~~in particular consider the number of~~
380 ~~women needed to be screened to prevent one stillbirth if the threshold of 5.1 mmol/L were to be~~
381 ~~implemented.~~

382 *Disclosure of interests*

383 All authors declare that they have no competing interests

384

385 *Contribution to authorship*

386 AH, TS, BM, DR, EM, and LM contributed to all aspects of the study design and obtained funding. JB

387 coordinated the running of the study. PWGT performed the data analysis with input from TS, ML and

388 JT. TS drafted the manuscript. All authors were involved in interpreting the data and critically

389 reviewing manuscript drafts. All authors gave approval for the final version of the manuscript.

390 The authors thank all the participants who participated in interviews in order to help us better

391 understand stillbirth.

392

393 *Ethics committee Approval*

394 This study was reviewed by NRES Committee North West - Greater Manchester Central Reference

395 (13/NW/0874) approval granted 2013, with all participants providing written consent to take part in

396 the study.

397

398 *Funding*

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

400 Research, Cure Kids and Sands. AH receives salary support from Tommy's and the National Institute

401 of Health Research (Clinician Scientist Award CS-13-009). EM and JT were supported by Cure Kids. [PWGT](#)

402 [is supported by The Alan Turing Institute \[EP/N510129/1\]](#). The funders had no role in the study

403 design, data collection and analysis, decision to publish, or preparation of the manuscript. The views

404 expressed in this manuscript are entirely those of the authors and do not necessarily reflect those of

405 the funders.

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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)			Screened for GDM (N=371)		
	N(%)			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)

^aWomen 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 $\geq 30 \text{ kg/m}^2$, or who had a previous pregnancy affected by gestational diabetes or macrosomic birth ($>4.5 \text{ kg}$).

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)	

^aKnown risk factors for GDM (indicated by NICE for blood glucose screening) comprise South Asian or black Caribbean ethnicity, body mass index $\geq 30 \text{ Kg/m}^2$, and previous pregnancy affected by gestational diabetes or macrosomic birth ($>4.5 \text{ kg}$).

^bModels included the exposure ('at risk' of GDM) and mediator (screened for GDM) only, as all partial confounding variables were also partial mediators.

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)	

^aModels included the exposure (binary 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).

^bNICE criteria for diagnosis of GDM

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)

^aModels 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).