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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

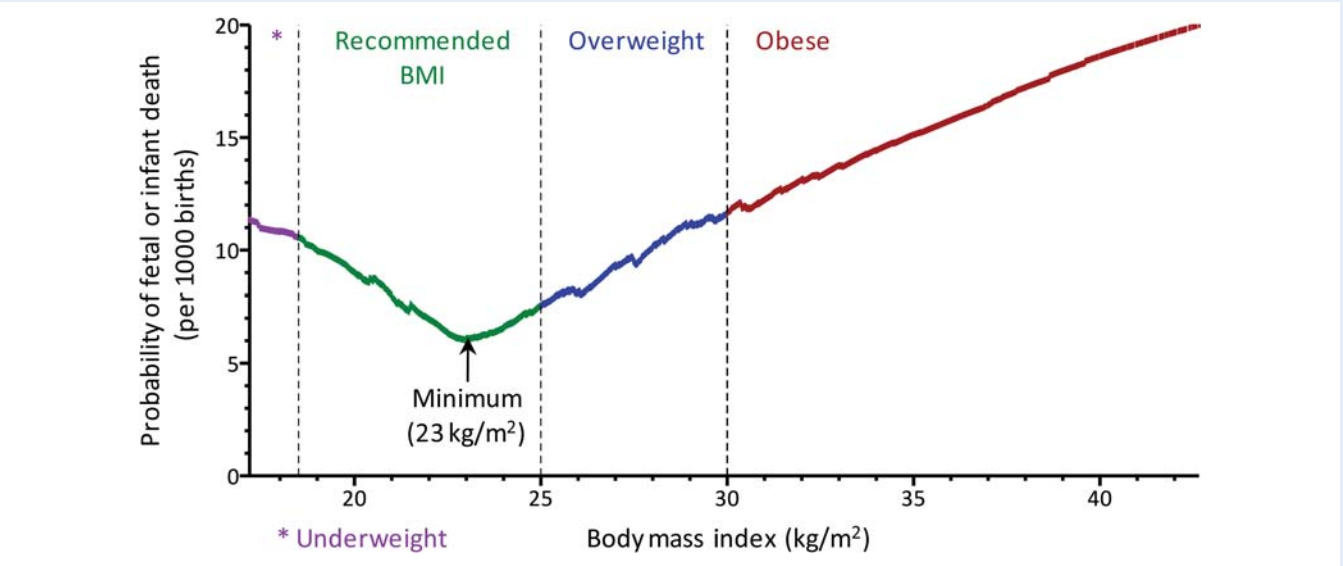

Figure 1 The association between maternal body mass index and the risk of a fetal or infant death, as estimated by locally weighted scatter plot regression.

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

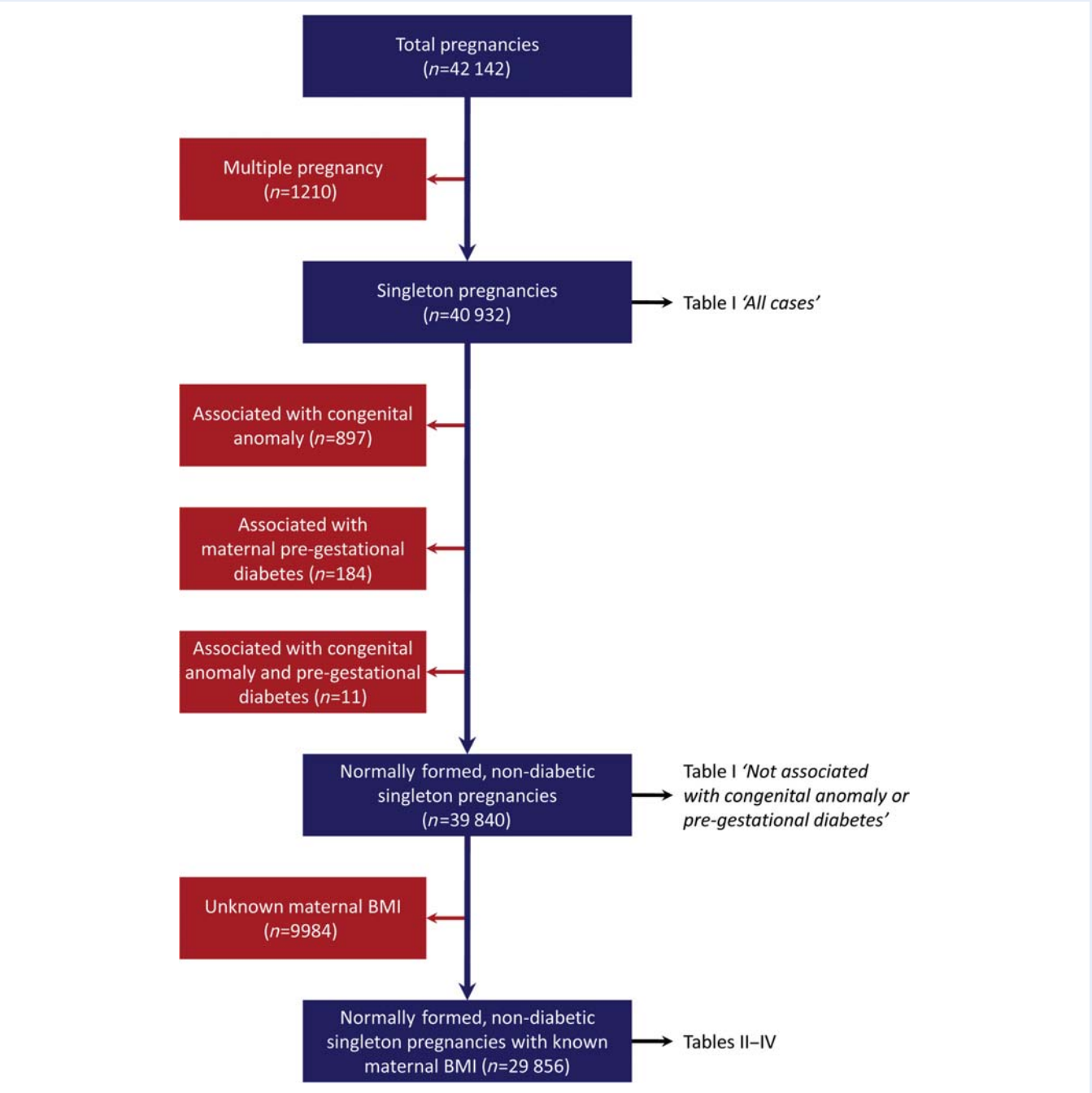

Figure 2 The flow of cases through the study.

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 I 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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