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ORIGINAL ARTICLE

Second-trimester maternal distress increases the risk of small for gestational age

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Background. The effect of prenatal distress on the risk of a small for gestational age (SGA) infant is uncertain. We have addressed the influences of prenatal stress, anxiety and depression on the risk of SGA. We also examined the effects of infant sex and timing of distress during pregnancy on any observed associations.

Method. The study population comprised 5606 healthy nulliparous pregnant women who participated in the international prospective Screening for Obstetric and Pregnancy Endpoints (SCOPE) study. Women completed the Perceived Stress Scale (PSS), the short form of the Spielberger State–Trait Anxiety Inventory (STAI) and the Edinburgh Postnatal Depression Scale (EPDS) at 15±1 and 20±1 weeks' gestation. SGA was defined as birthweight below the 10th customized percentile. Logistic regression was used for data analysis, adjusting for several potential confounders such as maternal age, body mass index (BMI), smoking, socio-economic status and physical exercise.

Results. The risk of SGA was increased in relation to mild [adjusted odds ratio (aOR) 1.35, 95% confidence interval (CI) 1.07–1.71], moderate (aOR 1.26, 95% CI 1.06–1.49), high (aOR 1.45, 95% CI 1.08–1.95) and very high stress scores (aOR 1.56, 95% CI 1.03–2.37); very high anxiety score (aOR 1.45, 95% CI 1.13–1.86); and very high depression score (aOR 1.14, 95% CI 1.05–1.24) at 20±1 weeks' gestation. Sensitivity analyses showed that very high anxiety and very high depression increases the risk of SGA in males but not in females whereas stress increases the risk of SGA in both males and females.

Conclusions. These findings suggest that prenatal stress, anxiety and depression measured at 20 weeks' gestation increase the risk of SGA. The effects of maternal anxiety and depression on SGA were strongest in male infants.

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Key words: Estimated fetal weight, prenatal anxiety, prenatal depression, prenatal stress, small for gestational age.

Introduction

Small for gestational age (SGA) is a serious complication in pregnancy that is associated with increased risk of perinatal mortality, birth hypoxia, neonatal complications, impaired neurodevelopment, diabetes and hypertension (Barker, 1995; McIntire *et al*. 1999; Gardosi *et al*. 2005; Barker *et al*. 2007). Furthermore, it has been reported that the effect of being SGA on long-term health outcomes may be dependent on the timing of the adverse intrauterine environment that caused SGA (Godfrey & Barker, 2000).

Maternal psychological stress exposures, such as perceived stress, anxiety and depression, have been variably linked to reduced birthweight and SGA (Nordentoft *et al*. 1996; Rondo *et al*. 2003; Khashan *et al*. 2008; Class *et al*. 2011). In a systematic review by Grote *et al*. (2010), only two out of the 12 studies eligible for inclusion in the review reported a significant association between maternal depression and the risk of SGA. The pooled estimate showed that antenatal depression was not significantly associated with SGA, with a relative risk (RR) of 1.03. Another systematic review found very few studies on maternal anxiety and the risk of SGA or birthweight, and emphasized that the larger and methodologically more robust studies that controlled for confounding factors found no association between maternal anxiety and adverse pregnancy outcome, including SGA (Littleton *et al*. 2007).

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Conversely, we, and others, have reported that maternal exposure to bereavement is associated with a negative effect on birthweight. Furthermore, the effect of psychological exposures on the risk of SGA may be trimester dependent (Khashan *et al*. 2008; Class *et al*. 2011), which is consistent with animal research suggesting that the timing of the prenatal stress exposure has a significant effect on the nature of the outcome (Kapoor *et al*. 2006; Weinstock, 2011). However, the literature is inconsistent concerning the crucial trimester or month of pregnancy when prenatal stress would have the most impact on the risk of SGA and/or birthweight (Khashan *et al*. 2008; Zhu *et al*. 2010; Class *et al*. 2011). For example, Khashan *et al*. (2008) reported an association, using Danish population-based data, between prenatal severe stress and risk of SGA that was not trimester specific. Class *et al*. (2011) performed a similar study using Swedish population-based data and found that prenatal severe stress during months 5 and/or 6 increased the risk SGA. By contrast, Zhu *et al*. (2010) reported reduced birthweight in relation to perceived stressful life events in the first trimester but not in the second or third.

Exploring the effect of the timing of the psychological exposure in early to mid-pregnancy may help to clarify vulnerable periods of development and eventually lead to improved understanding of the aetiological mechanisms of SGA. It has been hypothesized that prenatal stress, through fetal programming (Welberg & Seckl, 2001; Seckl & Holmes, 2007; Seckl, 2008), where high levels of maternal glucocorticoids are conveyed to the fetus, may lead to adverse pregnancy outcome, adverse neurodevelopment and disease in adolescence or adult life. For example, prenatal stress exposure in early to mid-pregnancy may influence mid-pregnancy estimated fetal weight and the risk of SGA by altering the hypothalamic–pituitary–adrenal (HPA) axis or impacting the maternal immune system, which may, in turn, influence the offspring's rapidly developing brain and nervous system (Diego *et al*. 2006). Furthermore, evidence from animal and human research suggests that the effect of prenatal stress on childhood and adulthood health outcomes may be dependent on infant sex (Kapoor *et al*. 2006; Weinstock, 2011). It seems that prenatal stress may increase the risk of some outcomes in males and other outcomes in females (Kapoor *et al*. 2006; Glover & Hill 2012). We, and others, have used population-based cohorts from Denmark and Sweden and reported that maternal exposure to bereavement in early to mid-pregnancy increased the risk of infant death, attention deficit hyperactivity disorder (ADHD) and affective disorders in male offspring but not in females (Li *et al*. 2010; Khashan *et al*. 2011; Class *et al*. 2013). However, we found no evidence that the impact of bereavement on the risk of SGA was sex specific (Khashan *et al*. 2008).

There is very limited research on the effect of psychological stress on the estimated fetal weight (EFW) measured by ultrasound in mid-pregnancy. Such data would be important to gain an understanding of whether the effect of stress on fetal growth starts at an early stage. Henrichs *et al*. (2010) reported an association between anxiety reported at 20 weeks' gestation and EFW in late pregnancy but there was no evidence for such as association in mid-pregnancy. There was also little evidence for such an association in relation to depressive symptoms or family stress.

The aims of the current study were to use a prospective multicentre international birth cohort and examine: (1) the effect of prenatal psychosocial stress, anxiety and depression reported at 15±1 and 20±1 weeks' gestation on the risk of SGA (although the 15 weeks' assessments were conducted in the second trimester, they would relate more to the period preceding the 15 weeks' gestation, that is the first trimester); (2) whether any observed associations were dependent on infant sex; and (3) whether the psychological exposures had an effect on the estimated fetal size as assessed by ultrasound in the mid-trimester. We hypothesized that prenatal exposure to high levels of stress, anxiety or depression would increase the risk of SGA and that the association would be dependent on infant sex and timing of exposure.

Method

The study cohort

The study cohort consisted of all women who participated in the Screening for Obstetric and Pregnancy Endpoints (SCOPE) study. Nulliparous healthy women with singleton pregnancies were recruited to the SCOPE study in six centres: Auckland, New Zealand; Adelaide, Australia; Manchester, London and Leeds in the UK; and Cork, Ireland. Enrolment into the study took place between November 2004 and January 2011, and the last SCOPE baby was delivered in Cork in August 2011. The aim of the SCOPE study was to develop early pregnancy screening tests to predict pre-eclampsia, SGA infants and spontaneous preterm birth.

Pregnant women attending antenatal care settings such as maternity units, general practitioners, and outreach clinics and early pregnancy ultrasound appointments were invited to participate in the SCOPE study. Women who agreed to take part were interviewed and examined by a SCOPE research midwife at 15±1 (visit 1) and 20±1 (visit 2) weeks' gestation. Detailed clinical and demographic data were collected at the

first visit, including maternal characteristics such as age, body mass index (BMI), education level, ethnic origin, marital status, family income, previous pregnancy loss, participant birthweight and family history of obstetric complications and medical conditions. Women were excluded if they were at high risk of SGA, pre-eclampsia or spontaneous preterm birth because of underlying medical conditions. The data were entered into an internet-accessed central database with a complete audit trail (MedSciNet AB, Sweden). More details are reported in recent SCOPE publications (McCowan *et al*. 2010; North *et al*. 2011).

Participating women completed validated lifestyle questionnaires at the first and second visits, which included information on smoking, alcohol, recreational drugs, exercise and outdoor activities. They also completed the Perceived Stress Scale (PSS), which assessed perceived stress levels in the past month (Cohen *et al*. 1983), the short form of the Spielberger State–Trait Anxiety Inventory (STAI), which assessed current anxiety symptoms (Marteau & Bekker, 1992), and the Edinburgh Postnatal Depression Scale (EPDS), which assessed depressive symptoms in the past week (Cox *et al*. 1996). These measures are traditionally used as continuous variables, which makes interpreting the odds ratios (ORs) difficult. Therefore, for the purposes of the present study, we also categorized the variables. The depression variable was converted using three standardized cut-offs to indicate unlikely to have depression (EPDS score<5), increased risk of depression in the next 6–12 months (EPDS score 5–9) and very likely depressed (EPDS score>9) (Peindl *et al*. 2004). As there are no published cut-offs for the stress and anxiety variables, they were converted into five categories to indicate low (<25th percentile), mild (25th to<50th percentile), moderate (50th to <75th percentile), high (75th to <90th percentile) and very high ($\geqslant$ 90th percentile) scores. This enabled a comparison of the impact of low and high and very high scores on the risk of SGA. The effects of stress, anxiety and depression were examined as continuous and categorical variables.

At the second visit at 20±1 weeks' gestation, a fetal ultrasound examination was performed. Fetal weight was estimated using the following Hadlock formula, which is recommended when the fetus is expected to be very small (Hadlock *et al*. 1985; Kaaij *et al*. 1999):

$$\begin{aligned}\log_{10}(\mathrm{EFW}) = {} & 1.3596 - 0.00386(\mathrm{AC} \times \mathrm{FL}) \\ & + 0.0064(\mathrm{HC}) + 0.00061(\mathrm{BPD} \times \mathrm{AC}) \\ & + 0.0425(\mathrm{AC}) + 0.174(\mathrm{FL}),\end{aligned}$$

where EFW is the estimated fetal weight (g), AC the abdominal circumference (cm), FL the femur length (cm), HC the head circumference (cm), and BPD the biparietal diameter (cm).

Because the scans were performed between 18 and 22 weeks' gestation and fetal weight is strongly dependent on gestational age, *Z* scores were calculated so that the EFW was independent of the gestational age at which the scan was performed. All ultrasound scans were performed by trained sonographers. The estimated date of delivery (DoD) was calculated based on a particular last menstrual period (LMP) date, and dates from the dating scan were used for women with an uncertain LMP date. The estimated DoD was corrected only if: (1) the difference between the LMP DoD and the scan DoD was $\geqslant$7 days and the ultrasound scan was performed before 16 weeks; or (2) the difference was $\geqslant$20 days and the ultrasound scan was performed at around 20 weeks.

Outcome measures

The primary outcome measure was SGA, which was defined as a birthweight below the 10th customized percentile. The secondary outcome was small EFW, defined as the weight below the 10th percentile of the EFW *Z* score distribution in accordance with Chang *et al*. (1992).

Potential confounders

Based on previous psychosocial stress and pregnancy outcome studies and risk factors for SGA, the following variables were assessed for their potential confounding effect on the association between the exposure variables and the outcome measures: maternal age, BMI, smoking, alcohol, binge drinking, drug use, gravidity, marital status, family income, education level, ethnic origin, vigorous exercise during pregnancy, recreational walking, blood pressure at 15±1 weeks' gestation, history of depression, family history of coronary heart disease, maternal birthweight, >12 months to conceive and proteinuria.

Statistical analysis

Logistic regression models were used to estimate the ORs of the association between maternal perceived stress, anxiety and depression scores at the first and second SCOPE visits and the risk of SGA and small EFW. The logistic models were adjusted *a priori* for maternal age, BMI, ethnic origin, smoking, family income and education level. In addition, the confounding effects of the variables listed under 'potential confounders' were assessed in all the models. However, none of these variables seemed to have a significant confounding effect and were therefore not included in the final models. To avoid overadjustment,

the exposure variables were not included in the same models. Furthermore, exposures from the first and second visits were assessed in separate models. However, *post-hoc* analyses were performed to examine whether any observed associations between the exposure variables measured at 20 weeks' gestation and SGA were related to the first visit exposure measures. Separate models were performed for continuous and categorical exposure measures. As women were recruited from six centres in four countries, all logistic models were adjusted for a potential clustering effect by recruiting centre using the 'cluster' option in Stata (Stata Corporation, USA).

Sensitivity analyses

Sensitivity analyses were performed to examine whether any observed associations were sex specific by adding a statistical interaction term between the exposure variable and infant sex. Another sensitivity analysis was performed excluding infants who were below the 10th percentile of mid-pregnancy EFW. We also performed sensitivity analyses by excluding pregnancies with pre-eclampsia or spontaneous preterm birth. Davis *et al*. (2009) reported that prenatal treatment with glucocorticoids reduces birthweight. Therefore, we performed a sensitivity analysis excluding pregnancies where prenatal treatment with steroids was administered to rule out the possibility that any observed associations were mediated by this treatment.

The sensitivity analyses were only performed if there was an overall significant association between the exposure and the risk of SGA. All statistical analyses were performed using Stata release 10.0.

Ethical approval

Ethical approval was obtained from local ethics committees [New Zealand AKX/02/00/364, Australia REC 1712/5/2008, London and Manchester 06/MRE01/98 and Cork ECM5(10)05/02/08] and all women provided written informed consent.

Results

During the study period between November 2004 and February 2011, 8531 women were invited to participate in the SCOPE study; 2542 declined to participate and the final study cohort consisted of 5628 infants, of whom 5606 had SGA data (see Fig. 1 for details). There were 633 SGA infants (11.3% of the SCOPE cohort) and 548 of the cohort (10%) had small EFW at 20 weeks' gestation. SCOPE mothers who had SGA infants were slightly more likely to be Indian and have a higher BMI, much more likely to be smokers, slightly more likely to drink alcohol and more likely to have lower income. Maternal characteristics in relation to SGA status are summarized in Table 1. More than 99% of SCOPE women completed the 15 weeks' gestation distress questionnaires and at the 20 weeks' gestation visit, more that 97% completed the questionnaires. Women with missing distress data were excluded from the relevant analyses. The numbers of SGA and non-SGA babies in each of the stress, anxiety and depression scores categories are presented in Tables 2, 3 and 4 respectively.

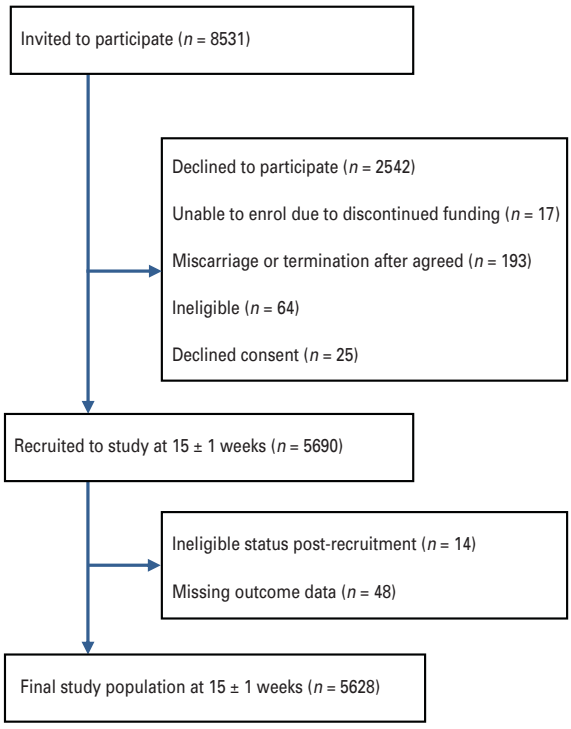

Fig. 1. Flowchart of recruited participants.

Perceived stress

Table 2 presents the results of the association between the perceived stress score at the first (at 15 weeks) and second (at 20 weeks) visits and the outcome measures. There was very little evidence that higher perceived stress scores at the first visit affected the risk of SGA or small EFW. However, increased stress scores at the second visit seemed to be associated with increased risk of SGA. For example, very high perceived stress at the second visit was associated with more than 50% increase in the risk of SGA [adjusted OR (aOR) 1.56, 95% confidence interval (CI) 1.03–2.37]. There was a significant association between the continuous stress score variable at the second visit and risk of SGA (aOR 1.01, 95% CI 1.01–1.02). The results did not support an association between stress score at the second visit and small EFW at 20 weeks' gestation.

Table 1. *Maternal and fetal characteristics in relation to small for gestational age (SGA)*

	Non-SGA *n*=4973 (88.7%)	SGA *n*=633 (11.3%)
Maternal characteristics		
Maternal age (years), mean (S.D.)	28.7 (5.5)	28.6 (5.8)
Ethnic origin, *n* (%)		
White	4481 (90.1)	564 (89.1)
Indian	115 (2.3)	19 (3.0)
Other	377 (7.6)	50 (7.9)
BMI (kg/m^2), mean (S.D.)	25.2 (4.8)	25.9 (5.5)
Smoking status at 15 weeks, *n* (%)		
Non-smoker	3821 (76.8)	428 (67.6)
Ceased smoking before 15 weeks	669 (13.4)	84 (13.3)
Current smoker	483 (9.7)	121 (19.1)
Alcohol status at 15 weeks, *n* (%)		
Non-drinker	1946 (39.1)	233 (36.8)
Stopped drinking	2531 (50.9)	326 (51.5)
Current drinker	496 (10.0)	74 (11.7)
Education, *n* (%)		
>13 years	3407 (68.5)	414 (65.4)
12–13 years	718 (14.4)	116 (18.3)
<12 years	848 (17.1)	103 (16.3)
Vigorous exercise, *n* (%)		
Never	3208 (64.5)	395 (62.4)
1–3 times a week	1602 (32.2)	205 (32.4)
⩾4 times a week	144 (2.9)	28 (4.4)
Missing	19 (0.4)	5 (0.8)
Primigravid, *n* (%)	3853 (77.5)	466 (73.6)
Income in 1000 AUD		
>124	568 (11.4)	69 (10.9)
75–124	1824 (36.7)	205 (32.4)
25–74	1631 (32.8)	214 (33.8)
<25	465 (9.3)	82 (13.0)
Unknown	485 (9.7)	63 (9.9)
Fetal characteristics		
Infant sex, *n* (%)		
Female	2438 (49)	320 (49.5)
Male	2535 (51)	313 (50.5)
EFW at 20 weeks (g), mean (S.D.)	369.3 (58)	349 (54)
Small EFW at 20 weeks, *n* (%)	424 (8.8)	122 (20.0)

BMI, Body mass index; EFW, estimated fetal weight; S.D., standard deviation.

Anxiety

The estimates of the association between the anxiety score and SGA and small EFW are presented in Table 3. The results suggest that the risk of SGA was increased in women who reported mild anxiety scores at the first visit (aOR 1.20, 95% CI 1.13–1.29), but not in those who reported higher anxiety scores. The risk of SGA was increased by 32% in women who reported a very high anxiety score, but not significantly. Women who reported a mild, high or very high anxiety score at the first visit seemed to be at a lower risk of having a small EFW at 20 weeks' (e.g. very high anxiety aOR 0.60, 95% CI 0.42–0.85). Women who reported a very high anxiety score at the second visit had a higher risk of SGA (aOR 1.45, 95% CI 1.13–1.86).

Depression

There was no evidence to suggest that the depression score, categorical or continuous measures, measured

Table 2. *Odds ratios (ORs) of the association between perceived stress scores at 15 and 20 weeks' gestation and risk of SGA and small EFW*

	SGA			Small EFW		
Variable	*n/N*	Crude OR (95% CI)	aOR (95% CI)	*n/N*	Crude OR (95% CI)	aOR (95% CI)
Perceived stress score, first visit						
Low	130/1187	Reference	Reference	132/1191	Reference	Reference
Mild	155/1141	1.24 (0.90–1.71)	1.24 (0.88–1.74)	115/1182	0.88 (0.69–1.11)	0.85 (0.67–1.08)
Moderate	170/1346	1.15 (0.93–1.43)	1.11 (0.90–1.37)	154/1367	1.02 (0.85–1.22)	0.93 (0.76–1.15)
High	107/838	1.17 (0.99–1.38)	1.04 (0.84–1.30)	99/852	1.05 (0.84–1.31)	0.92 (0.73–1.16)
Very high	63/437	**1.32 (1.04–1.67)**	1.09 (0.84–1.42)	45/458	0.89 (0.60–1.30)	0.75 (0.51–1.10)
Continuous score	625/4949	**1.01 (1.00–1.02)**	1.00 (0.99–1.02)	545/5050	1.00 (0.99–1.01)	0.99 (0.98–1.00)
Perceived stress score, second visit						
Low	127/1266	Reference	Reference	122/1271	Reference	Reference
Mild	148/1106	**1.34 (1.05–1.69)**	**1.35 (1.07–1.71)**	128/1126	**1.18 (1.04–1.35)**	**1.16 (1.05–1.29)**
Moderate	166/1332	**1.24 (1.11–1.39)**	**1.26 (1.06–1.49)**	142/1356	1.09 (0.97–1.23)	1.00 (0.87–1.15)
High	105/733	**1.43 (1.13–1.81)**	**1.45 (1.08–1.95)**	93/746	1.30 (0.97–1.74)	1.15 (0.90–1.47)
Very high	65/403	**1.61 (1.25–2.06)**	**1.56 (1.03–2.37)**	50/418	1.25 (0.91–1.71)	1.06 (0.74–1.52)
Continuous score	611/4840	**1.02 (1.01–1.03)**	**1.01 (1.01–1.02)**	535/4917	**1.01 (1.01–1.02)**	1.00 (0.99–1.01)

SGA, Small for gestational age; EFW, estimated fetal weight; *n*, number of infants SGA (or with small EFW); *N*, number of infants non-SGA (or not small EFW); aOR, adjusted odds ratio; CI, confidence interval.

Adjusted for body mass index (BMI), age, smoking, family income, maternal education and ethnic origin.

Bold values indicate statistically significant associations.

Table 3. *Odds ratios (ORs) of the association between anxiety scores at 15 and 20 weeks' gestation and risk of SGA and small EFW*

	SGA			Small EFW		
Variable	*n/N*	Crude OR (95% CI)	aOR (95% CI)	*n/N*	Crude OR (95% CI)	aOR (95% CI)
Anxiety score, first visit						
Low	157/1365	Reference	Reference	162/1364	Reference	Reference
Mild	155/1101	**1.22 (1.15–1.31)**	**1.20 (1.13–1.29)**	116/1143	**0.85 (0.78–0.94)**	**0.84 (0.76–0.93)**
Moderate	165/1395	1.03 (0.88–1.20)	1.00 (0.86–1.16)	157/1407	0.94 (0.79–1.12)	0.92 (0.80–1.05)
High	82/710	1.00 (0.85–1.18)	0.93 (0.79–1.11)	79/719	0.92 (0.80–1.06)	**0.83 (0.76–0.90)**
Very high	68/379	**1.56 (1.15–2.11)**	1.32 (0.93–1.87)	33/418	**0.66 (0.48–0.91)**	**0.60 (0.42–0.85)**
Continuous score	627/4950	**1.01 (1.00–1.01)**	1.00 (0.99–1.01)	547/5051	0.99 (0.99–1.00)	0.99 (0.99–1.00)
Anxiety score, second visit						
Low	184/1652	Reference	Reference	181/1655	Reference	Reference
Mild	141/1064	1.19 (0.96–1.47)	1.19 (0.98–1.43)	107/1099	0.89 (0.76–1.05)	0.86 (0.71–1.04)
Moderate	156/1245	1.12 (0.82–1.54)	1.15 (0.85–1.56)	141/1260	1.02 (0.77–1.36)	0.90 (0.77–1.28)
High	50/429	1.15 (0.69–1.93)	1.16 (0.63–2.13)	52/427	1.01 (0.77–1.32)	0.91 (0.75–1.11)
Very high	80/451	**1.59 (1.21–2.09)**	**1.45 (1.13–1.86)**	54/477	1.03 (0.82–1.31)	0.93 (0.77–1.14)
Continuous score	611/4841	**1.01 (1.00–1.02)**	1.01 (1.00–1.01)	535/4918	1.00 (1.00–1.01)	1.00 (0.99–1.01)

SGA, Small for gestational age; EFW, estimated fetal weight; *n*, number of infants SGA (or with small EFW); *N*, number of infants non-SGA (or not small EFW); aOR, adjusted odds ratio; CI, confidence interval.

Adjusted for body mass index (BMI), age, smoking, family income, maternal education and ethnic origin.

Bold values indicate statistically significant associations.

at the first SCOPE visit increased the risk of SGA or small EFW, with all ORs close to 1 and not significant (Table 4). However, women with high depression scores (very likely depressed) at the second SCOPE visit were at a significantly increased risk of SGA (OR 1.14, 95% CI 1.05–1.24). There was a significant association between the continuous depression score variable and the risk of SGA (aOR 1.01, 95% CI

Table 4. *Odds ratios (ORs) of the association between depression scores at 15 and 20 weeks' gestation and risk of SGA and small EFW*

	SGA			Small EFW		
Variable	*n/N*	Crude OR (95% CI)	aOR (95% CI)	*n/N*	Crude OR (95% CI)	aOR (95% CI)
Depression score, first visit						
Unlikely to have depression	215/1844	Reference	Reference	194/1872	Reference	Reference
Increased risk of depression in the next year	233/1819	1.10 (0.95–1.28)	1.07 (0.93–1.22)	209/1848	1.09 (0.97–1.23)	1.05 (0.92–1.19)
Very likely depressed	180/1292	1.19 (1.04–1.37)	1.04 (0.90–1.21)	144/1337	1.04 (1.00–1.08)	0.92 (0.88–0.96)
Continuous score	628/4955	**1.02 (1.01–1.03)**	1.01 (0.99–1.02)	547/5057	1.01 (0.99–1.02)	1.00 (0.98–1.01)
Depression score, second visit						
Unlikely to have depression	261/2222	Reference	Reference	234/2249	Reference	Reference
Increased risk of depression in the next year	203/1627	1.06 (1.00–1.13)	1.03 (0.94–1.12)	183/1648	1.07 (0.94–1.21)	1.03 (0.94–1.14)
Very likely depressed	149/994	**1.28 (1.14–1.42)**	**1.14 (1.05–1.24)**	119/1024	1.12 (0.95–1.31)	0.98 (0.87–1.11)
Continuous score	613/4843	**1.02 (1.01–1.03)**	**1.01 (1.00–1.02)**	536/4921	**1.01 (1.00–1.02)**	1.00 (0.99–1.01)

SGA, Small for gestational age; EFW, estimated fetal weight; *n*, number of infants SGA (or with small EFW); *N*, number of infants non-SGA (or not small EFW); aOR, adjusted odds ratio; CI, confidence interval.

Adjusted for body mass index (BMI), age, smoking, family income, maternal education and ethnic origin. Bold values indicate statistically significant associations.

1.00–1.02). There was no evidence that small EFW at 20 weeks' gestation was associated with the depression score at the second SCOPE visit.

Sensitivity analyses

The association between the stress score and SGA seemed to be similar in male and female infants. For example, the OR of SGA was increased by about 40% in women with mildly elevated stress scores and by about 46% in women with very high stress scores in both male and female infants. However, the effect of a very high anxiety score (OR 1.82, 95% CI 1.36–2.44 in males and OR 1.15, 95% CI 0.86–1.53 in females; p for interaction=0.015) and very likely depressed state (OR 1.36, 95% CI 1.13–1.63 in males and OR 0.99, 95% CI 0.79–1.24 in females; p for interaction=0.09) on the risk of SGA was limited to male infants (Table 5). Excluding infants who had small EFW in mid-pregnancies from the models did not affect the results of stress, anxiety or depression at 20 weeks' gestation and risk of SGA. Finally, excluding pregnancies with pre-eclampsia, preterm birth or treated with steroids did not change the results materially.

Discussion

In this study we investigated the association between maternal stress, anxiety and depression at 15 and 20 weeks' gestation and the risk of small EFW and SGA. The effects of anxiety and depression seemed to be restricted to risk of SGA in male infants whereas the effect of stress was associated with the risk of SGA in both male and female infants. Our findings show that the effect of maternal distress on the risk of SGA is dependent on the timing of the exposure during pregnancy, infant sex and the type of psychological exposure. We found that stress, anxiety and depression measured at 20 weeks' gestation were associated with an increased risk of SGA but not small EFW in mid-pregnancy. The effects of the exposures on SGA were not apparent in mid-pregnancy, suggesting that maternal distress increased the risk of SGA in infants who were well grown at 20 weeks' gestation. This hypothesis was supported by the sensitivity analyses that excluded infants who had small EFW in mid-pregnancy. Of note, increased anxiety levels at 15 weeks' gestation seemed to reduce the risk of small EFW in mid-pregnancy.

Previous research

Previous research on the effect of maternal distress on the risk of SGA and low birthweight (LBW) has reported inconsistent results. Grote *et al.* (2010) conducted a systematic review on the association between

Table 5. *The association between PSS, STAI and EPDS scores at the second SCOPE study visit and SGA stratified by infant sex*

Exposure variable	All males	All females
Stress score (PSS)		
Low	Reference	
Mild	1.39 (1.15–1.68)	1.40 (0.99–1.96)
Moderate	1.15 (0.88–1.50)	1.29 (1.05–1.59)
High	1.53 (1.14–2.04)	1.24 (0.78–1.96)
Very high	1.44 (0.99–2.09)	1.46 (1.01–2.14)
Anxiety score (STAI)		
Low	Reference	Reference
Mild	1.37 (1.21–1.54)	1.11 (0.84–1.47)
Moderate	1.02 (0.76–1.37)	1.15 (0.63–2.07)
High	0.95 (0.54–1.68)	1.12 (0.62–2.01)
Very high	1.82 (1.36–2.44)	1.15 (0.86–1.53)
Depression score (EPDS)		
Unlikely to have depression	Reference	Reference
Increased risk of depression in the next year	0.99 (0.73–1.33)	1.07 (0.75–1.54)
Very likely depressed	1.36 (1.13–1.63)	0.99 (0.79–1.24)

PSS, Perceived Stress Scale; STAI, State–Trait Anxiety Inventory; EPDS, Edinburgh Postnatal Depression Scale; SCOPE, Screening for Obstetric and Pregnancy Endpoints; SGA, small for gestational age.

Adjusted for body mass index (BMI), age, smoking, family income, maternal education and ethnic origin.

maternal depression and SGA and LBW. Out of 12 eligible studies, only two reported significant associations with SGA and five with LBW, and the association was dependent on whether depression was analysed as a continuous or categorical measure. Significant heterogeneity was noted across studies. The authors highlighted the lack of adjustment for several potential confounders, such as socio-economic status, ethnic origin and other stressful or anxious events, that may have been present when depression was assessed. However, the pooled estimate of the association was in line with the present findings. In another systematic review, Littleton *et al*. (2007) found no evidence of an association between general anxiety symptoms and perinatal outcomes including birthweight, although they did not include SGA in their review. They found that poor quality studies that were based on a small number of participants and those based on less frequently used measures to assess anxiety were more likely to report a significant association between general anxiety and perinatal outcomes. Many studies have investigated the impact of prenatal stress on adverse pregnancy outcome, such as birthweight and SGA, using different instruments to assess stress, such as stressful life events inventory, bereavement and national disasters. Our results on SGA are consistent with two large population-based studies from Sweden and Denmark, which found the greatest risk of SGA following maternal exposure to bereavement in the second trimester (Khashan *et al*. 2008) and in months 5 and 6 (Class *et al*. 2011). However, prenatal stress in those two studies was defined as bereavement due to the death of a close relative of the pregnant woman. Loss of a child, spouse or parent is an objective measure of stress and may be the most severe type of stress (Stroebe *et al*. 2007) whereas the present study used perceived, and subjective, measures of stress, anxiety and depression. Zhu *et al*. (2010) reported a significant reduction in birthweight among women who were exposed to stressful life events in the first trimester but not in the second or third, which is inconsistent with the present second-trimester findings. Rondo *et al*. (2003) found a twofold increased risk of LBW in relation to maternal exposure to distress [measured using the General Health Questionnaire (GHQ) and the STAI] during the second trimester. However, contrary to the present study they reported no evidence for an association between PSS score or distress and the risk of SGA. Hedegaard *et al*. (1996) reported no significant association between maternal distress, measured using the GHQ at the 16th and 30th weeks' gestation, and birthweight or SGA.

Very recently, Witt *et al*. (2014) used population-based survey data from the USA and reported an association between maternal pre-pregnancy stressful life events and the risk of low and very low birthweight. However, contrary to our findings, there was no association between maternal stressful life events during pregnancy and the risk of LBW. Other studies reported an association between maternal exposure to population level stressful events and reduced birthweight (Lederman *et al*. 2004; Tan *et al*. 2009). However, it is difficult to compare the findings from these studies with the present findings because of the obvious difference in the nature of the events. Events such as earthquakes and the World Trade Center attack may involve other factors in addition to stress, such as air pollution and infections, and therefore the observed associations in these studies could be related to factors other than stress.

The present finding on maternal distress and EFW is in line with the recent study from the Generation R cohort, which found no association between maternal distress and EFW in mid-pregnancy (Henrichs *et al*. 2010). However, the finding that increased anxiety levels at 15 weeks' gestation may reduce the risk of small EFW in mid-pregnancy may need further research to be confirmed. The finding that the effect of anxiety and depression on SGA was evident in male infants only is in line with recent epidemiological studies that found significant associations between prenatal bereavement and increased risk of infant mortality, affective disorders and ADHD in the offspring (Li *et al*. 2010; Khashan *et al*. 2011; Class *et al*. 2013). The mechanistic link between the experience of maternal psychosocial stress and fetal outcome is still unclear; however, at the maternal–fetal interface and if the observed associations are causal, the placenta is an intriguing candidate. Glucocorticoids are the biological mediators through which maternal stress influences fetal development (Reynolds, 2013). Although glucocorticoids are essential for the normal fetal organogenesis, excessive fetal glucocorticoid exposure results in LBW and abnormalities in fetal tissues (Reynolds, 2013). The amount of fetal exposure to maternal glucocorticoids depends on placental expression of the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD-2) (Reynolds, 2013). This acts as a placental shield to protect the fetus from excessive glucocorticoid exposure by converting active maternal glucocorticoids into their inactive metabolites.

It has been suggested that the impact of maternal stress on the risk of fetal growth restriction may be sex specific. Lingas & Matthews (2001) reported that restriction of maternal nutrient intake for 48 h resulted in a 50% decrease in fetal plasma glucose concentrations and fetal growth restriction in the guinea pig. Furthermore, young adult male guinea pigs exposed to maternal nutrient restriction had reduced basal and stress-induced HPA activity whereas females from the same litters had elevated basal and activated HPA function. The acute response of placental autoregulation of 11β-HSD-2 to exogenous glucocorticoid exposure in females only suggests an intrinsic difference in the placenta of the male and female fetus (Stark *et al*. 2009). Placental tissue is largely sex specific because of the substantially greater fetal contribution compared with the maternal contribution (Rossant & Cross, 2001), suggesting that the 'male placenta' may be more vulnerable to the effects of prenatal stress. Contrary to previous assumptions that, in females (XX), most genes on one X chromosome are silenced as a result of X-chromosome inactivation, it has been shown that up to 15% of X-linked genes escape inactivation to some degree, suggesting that they can be expressed from both XX chromosomes, which would lead to higher placental expression in females (XX) than in males (XY) (Carrel & Willard, 2005; Rawn & Cross, 2008).

Moreover, prenatal stress in mice has been shown to upregulate the expression of insulin-like growth factor-binding protein (IGFBP)-1 in the placenta of male offspring but not female offspring (Mueller & Bale, 2008). This protein binds insulin-like growth factor (IGF)-1, which is essential for normal fetal and postnatal growth (Randhawa, 2008). Furthermore, significantly higher levels of placental IGFBP-1 and lower levels of placental IGF-1 are present in infants with SGA (Akram *et al*. 2011). Collectively, these data suggest that the placenta of the fetal male may be particularly vulnerable to the effects of prenatal stress, which negatively impacts the placental molecular mechanisms that regulates fetal glucocorticoid exposure and the signal for normal growth. Therefore, it could be hypothesized that similar mechanisms may explain our sex-specific findings, although the fact that we found sex-specific associations in relation to maternal anxiety and depression but not stress makes such generalization difficult without further replication.

In the present study, the effect of prenatal stress, anxiety and depression on the risk of SGA was specific to 20 weeks' gestation; at this crucial time, fetal growth and organ development are associated with an increase in the maternal blood supply to the fetus and placenta, consequent on invasion of the maternal spiral arteries by placental trophoblast cells (Galligan & Parkman, 2007). The finding that maternal distress measured at 20 weeks' gestation, but not at 15 weeks', was associated with SGA may be surprising as the measures are very close in time. However, animal studies have shown the importance of the timing of prenatal stress (Kapoor *et al*. 2006). In normal

pregnancies, 11β-HSD-2 protects the fetus from high levels of cortisol and corticosterone by converting them to relatively inactive products. Although 11β-HSD-2 is found in the placenta and the central nervous system, its expression is significantly reduced between 19 and 26 weeks' gestation in humans (Stewart *et al*. 1994) and in mid-pregnancy in rats (Diaz *et al*. 1998). The reduced expression of 11β-HSD-2 in addition to maternal distress may increase the vulnerability of the fetal brain to excessive levels of glucocorticoids, which could result in increased risk of SGA. However, considering that maternal distress was assessed twice in the second trimester but not in the first or third trimester, we cannot rule out that prenatal stress, anxiety and depression in the first and/or third trimesters may have a significant effect of the risk of SGA. On the contrary, we could argue that the 15 weeks' assessment would relate more to the period preceding the 15 weeks' gestation, that is the first trimester. Finally, we cannot rule out the possibility that the association could also be related to unmeasured confounding due to genetic factors.

Strengths and limitations

The present study has several strengths. First, this is a prospective cohort with excellent follow-up (98.7%) and real-time data monitoring procedures that helped to ensure the quality of the data. Therefore, the study avoids the problem of recall bias in retrospective studies. Second, three psychological states (stress, anxiety and depression) were assessed at two time points during pregnancy. Third, the study was conducted in six centres in four developed countries with different sociodemographic backgrounds, which make the results more generalizable. Fourth, we had mid-pregnancy scan data, which are important in assessing the potential mechanisms of the association between the psychological state and SGA. Fifth, we were able to adjust for several potential confounders. Sixth, the PSS and STAI questionnaires used for the psychological assessments are validated questionnaires for use in pregnancy. Although the EPDS questionnaire is designed to assess postnatal depression, it has been heavily used to assess depressive symptoms during pregnancy. The main study limitation is that the psychological assessment questionnaires were completed twice in the second trimester, with no assessments in the first or third trimester. However, this showed that the effect of maternal psychological exposures on SGA might depend on the month of pregnancy and not just on the trimester. Another limitation is that stress was measured with a subjective rating of stress only, and including an objective rating of stress may have yielded additional data. The ability to differentiate objective stressors might have allowed us to explore why the effects of stress are across genders whereas those of anxiety and depression are sex specific.

In conclusion, maternal distress including perceived stress, anxiety and depression may have a serious effect on the risk of SGA. This effect seems to be time dependent, where high stress, anxiety or depression levels in mid-pregnancy, in particular, increase the risk of SGA. The effects of anxiety and depression were limited to male infants and independent of small EFW in mid-pregnancy. The findings highlight the public health risk of SGA posed by maternal distress. Prenatal care planners seeking to reduce the risk of SGA should consider reducing maternal distress when designing intervention programmes.

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Declaration of Interest

None.

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