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Risk factors for first trimester miscarriage—results from a UK-population-based case–control study

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Objective The aim of this study was to examine the association between biological, behavioural and lifestyle risk factors and risk of miscarriage.

Design Population-based case–control study.

Setting Case–control study nested within a population-based, two-stage postal survey of reproductive histories of women randomly sampled from the UK electoral register.

Population Six hundred and three women aged 18–55 years whose most recent pregnancy had ended in first trimester miscarriage (<13 weeks of gestation; cases) and 6116 women aged 18–55 years whose most recent pregnancy had progressed beyond 12 weeks (controls).

Methods Women were questioned about socio-demographic, behavioural and other factors in their most recent pregnancy.

Main outcome measure First trimester miscarriage.

Results After adjustment for confounding, the following were independently associated with increased risk: high maternal age; previous miscarriage, termination and infertility; assisted conception; low pre-pregnancy body mass index; regular or high alcohol consumption; feeling stressed (including trend with number of stressful or traumatic events); high paternal age and changing partner. Previous live birth, nausea, vitamin supplementation and eating fresh fruits and vegetables daily were associated with reduced risk, as were feeling well enough to fly or to have sex. After adjustment for nausea, we did not confirm an association with caffeine consumption, smoking or moderate or occasional alcohol consumption; nor did we find an association with educational level, socio-economic circumstances or working during pregnancy.

Conclusions The results confirm that advice to encourage a healthy diet, reduce stress and promote emotional wellbeing might help women in early pregnancy (or planning a pregnancy) reduce their risk of miscarriage. Findings of increased risk associated with previous termination, stress, change of partner and low pre-pregnancy weight are noteworthy, and we recommend further work to confirm these findings in other study populations.

Keywords Diet, miscarriage, paternal factors, pregnancy history, stress, termination, UK population.

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Introduction

Most studies report that around one in five clinical pregnancies will end in miscarriage (fetal death before 24 weeks),[1,2] while prospective studies on conception and early pregnancy have reported fetal loss rates approaching one-third.[3–5] Some women will experience recurrent (three or more consecutive) miscarriages, but these are estimated to be a small proportion (<10%) of all women experiencing miscarriage. Specific clinical factors have been shown to increase a woman's risk of recurrent miscarriage, including thrombophilias and parental cytogenetic abnormalities, but the determinants of the majority of miscarriages that occur are not wholly understood, and many putative risk factors remain controversial or unconfirmed.

Well-established risk factors for miscarriage include increased maternal age,[6,7] history of miscarriage[8] and infertility,[9–11] although the interaction between age, parity, infertility and previous pregnancy loss is complex and still not entirely understood. Several behavioural and social risk factors have been reported as increasing the risk of miscarriage, but most remain controversial or unconfirmed. Alcohol consumption,[12–15] smoking[14–18] and caffeine intake[14,15,19–22] are the main examples, and controversy remains because few studies

have examined these associations in the context of nausea, known to reduce the risk of miscarriage,[22–24] and other potential confounding factors. Evidence for an effect of vitamin supplementation, particularly folic acid, on risk of miscarriage is also conflicting, but the few studies that have adjusted for confounding support a protective effect.[25]

There is also increasing interest in the role that stress and emotional wellbeing play in pregnancy. Recent emotional trauma and major life events during pregnancy, as well as stressful employment, have been linked to increased risk of miscarriage,[26–29] but these findings require confirmation, particularly with respect to potential confounding. Evidence to link the classic occupational exposures of lifting, standing, noise and cold to miscarriage is not strong.[30–32] Finally, although the evidence relating to paternal age is reasonably well established,[7,33,34] current evidence relating the effect of other paternal factors, including paternal occupation, and alcohol drinking and smoking prior to conception, to risk of miscarriage is limited[35–37] and warrants further investigation.

There is a clear need for more evidence on avoidable risk for this common and distressing outcome. Sources of good scientific data on which to base epidemiological investigations are, however, hard to find, and few large-scale population-based studies have been conducted, particularly in the UK. As an epidemiological outcome, miscarriage is hard to measure: many miscarriages are managed at home and some not even reported to a clinician. In the UK, there are no registers of miscarriage and few, if any, routine data collection systems that can both cover the full range of miscarriage (including early losses) and link to individual-based data that relate to exposures during early pregnancy or prior to conception. Different clinical sources rarely see the full range of cases, and clinical-based studies are often subject to selection bias by excluding early fetal losses. Such studies may also be limited in their ability to consider past reproductive outcomes, including infertility. Large prospective cohort studies are theoretically the ideal design but take time and tend to be prohibitively expensive.[2]

An alternative and practical approach to these problems is a population-based survey in which the women themselves are asked their full reproductive history, including all fetal losses at all gestations and periods of infertility. The National Women's Health Study, which we report here, was such a study, where women participating were not identified from medical records of any kind but from the UK electoral register, and there was no outcome restriction because every woman participating was asked about her whole reproductive experience, including periods of infertility and each pregnancy.

Participants and methods

Full details of the study design are reported elsewhere.[38] In brief, the study comprised a two-stage postal survey of reproductive histories of adult women living in the UK in 2001, sampled from the electronic electoral roll. Stage 1 was a short 'screening' questionnaire sent to more than 60 000 randomly selected women to identify those aged younger than 55 years (to minimise recall bias), who had ever been pregnant or ever attempted to achieve a pregnancy, from whom a brief reproductive history was requested. The response rate was 46% for the first stage, with 26 050 questionnaires being returned. Comparison of key reproductive indicators (stillbirth and multiple birth rates and maternal age at first birth) with national statistics showed that the data were remarkably similar to those of the general population.[38] Furthermore, miscarriage rates were also in line with expectation: for example, 15.5% (n = 1322) of the 8523 pregnancies ending in 1995 onwards were reported as miscarriages. It was therefore concluded that selection bias in relation to reproduction was unlikely.

Eighty-eight percent of eligible women responding to the first stage, who reported ever attempting to have children (successfully or unsuccessfully), agreed to participate in the second stage of the study. Stage 2 involved a more lengthy questionnaire sent to 10 828 women who reported ever having been pregnant or tried to conceive and who agreed to be re-contacted. The response rate for this more targeted stage was 71% (7702 women, of whom 7508 had ever been pregnant). The stage 2 questionnaire requested more general detail about the women (including height, age at menarche, educational level, marital status and details of any periods of infertility) plus detailed information on all pregnancies. Participants were asked to consider each pregnancy in turn, pregnancy outcomes being chosen from a list. Gestation at pregnancy end was requested in weeks (+days, if known), preferably as told by the medical staff, otherwise calculated according to instructions given. Other information included paternal date of birth and whether paternity had changed from the previous pregnancy, whether the pregnancy was planned and whether it had resulted from infertility treatment. Finally, socio-demographic and behavioural details relating to the most recent pregnancy were requested in relation to two time periods, the 3 months prior to conception and the first 12 weeks of pregnancy. Questions included details of pre-pregnancy weight, nausea, smoking, alcohol and caffeine (tea, coffee, caffeinated drinks) consumption, diet, vitamin supplementation, ill health, air travel, sexual intercourse, education, occupation and stress levels. The last (most recent) pregnancy was selected to minimise biases related to recall, and as it could be at the start, middle or end of the respondents' reproductive careers, potential biases relating to ending reproductive careers on a 'success' were not expected to be large.

These most recent pregnancies were predominantly (80%) second-order and higher order pregnancies (where miscarriage risk is lower); so to increase the number of cases for

the risk factor analysis, women whose last pregnancy was not a miscarriage but who had recently (since 1995) experienced a miscarriage at any gestation were sent a third (stage 3) questionnaire. This was a shortened version of the stage 2 questionnaire, containing only the questions relating to biological, socio-demographic and behavioural details of the last pregnancy but now requesting these details in relation to the most recent miscarriage.

Ethical permission

The study received approval from the Trent Multi-Centre Research Ethics Committee and the Ethics Committee of the London School of Hygiene & Tropical Medicine.

Definition of cases and controls

Figure 1 summarises the selection of cases and controls for the risk factor analysis. Cases were all women whose most recent pregnancy resulted in a first trimester miscarriage (<13 completed weeks) or, if the most recent pregnancy did not result in miscarriage, who had had a miscarriage since 1995. Controls were all women whose most recent pregnancy (including pregnancies current at the time of survey) went beyond 13 weeks of gestation. The (case or control) pregnancy on which information was collected is referred to as the 'index pregnancy'.

Controls whose index pregnancy was an ectopic or a molar pregnancy, or a termination for any reason, were excluded from all the analyses, as were all women (cases and controls) whose index pregnancy was a multiple, where one or more fetus was lost at <13 weeks and the other(s) progressed beyond this point. Women whose last pregnancy was conceived before 1 January 1980 were also excluded to avoid recall bias.

Women who took part in both second and third stages of the survey were included as both a case and a control if they fulfilled the criteria for cases and controls mentioned above; analyses were adjusted accordingly.

After exclusions, 6442 women were included in the case–control study, of whom, 277 had two records in the analysis. There were a total of 603 cases whose index pregnancy had ended in early miscarriage and 6116 controls, 5792 (95%) of whom had index pregnancies ending in live birth.

Statistical methods

All the analyses in this study were performed using Stata statistical software.[39] All *P* values quoted are two sided, and values less than 0.05 were taken to indicate statistical significance. The association between miscarriage and each risk factor was explored using logistic regression analysis, effects on risk being estimated by odds ratios with 95% confidence intervals. As some women had two records in the analysis (Figure 1), a robust method based on the 'sandwich estimate'[40] was used to compute standard errors, with Wald tests to test statistical significance of parameters.[41] All the analyses were adjusted for year of conception to allow for the oversampling of miscarriages occurring from 1995 onwards. Confounding was investigated in all models by the addition of variables that were plausibly associated with both the exposure under consideration and the risk of early miscarriage. We adjusted for year of conception, maternal age at conception, pregnancy order, history of miscarriage and history of live birth in all models, and additionally for nausea, fertility treatment and relationship status where stated.

Statistical power

This study was well powered. Sample size calculations were based on achieving at least 80% power for key risk factors in the case–control analysis and cost. With the number of participants achieved, we had more than 80% power to detect an odds ratio of 1.4 or more for exposures present in controls at prevalence of 10% or more, and for exposure prevalence in controls at 50%, we had power to detect an odds ratio as low as 1.3.

Results

Three hundred and sixty-two women reported that their most recent pregnancy had ended in a first trimester miscarriage, with a further 241 reporting a first trimester miscarriage since 1995 but not their last pregnancy. As expected from the design, the majority (83%) of case pregnancies were conceived after 1995, although about equal numbers of control pregnancies were before (51%) and after (49%) 1995.

As expected, maternal age at conception, history of miscarriage and history of live birth were all strong predictors of miscarriage, and all odds ratios were adjusted for these factors.

Maternal age

Mean maternal age at conception of the index pregnancy was 31.9 years for cases and 30.0 years for controls (Table 1). There was no difference in odds of miscarriage below the age of 35 years ($P = 0.73$), but the odds rose sharply thereafter, with a 75% increase for mothers aged 35–39 years and a five-fold increase where the mother was aged 40 and above (relative to mothers aged 25–29 years) (Table 1). The effect was independent of pregnancy history.

Socio-demographic factors

The odds of miscarriage were significantly increased if the woman was not married or living with a partner. There was no evidence of an effect of social class, when measured by either the husband/partner's ($P = 0.10$) or the woman's own ($P = 0.29$) occupation, although there was a suggestion that unemployment might be associated with (nonstatistically significant) increased odds of miscarriage (adjusted odds ratio when both parents were unemployed was 1.46 [95% CI 0.87–2.42]),

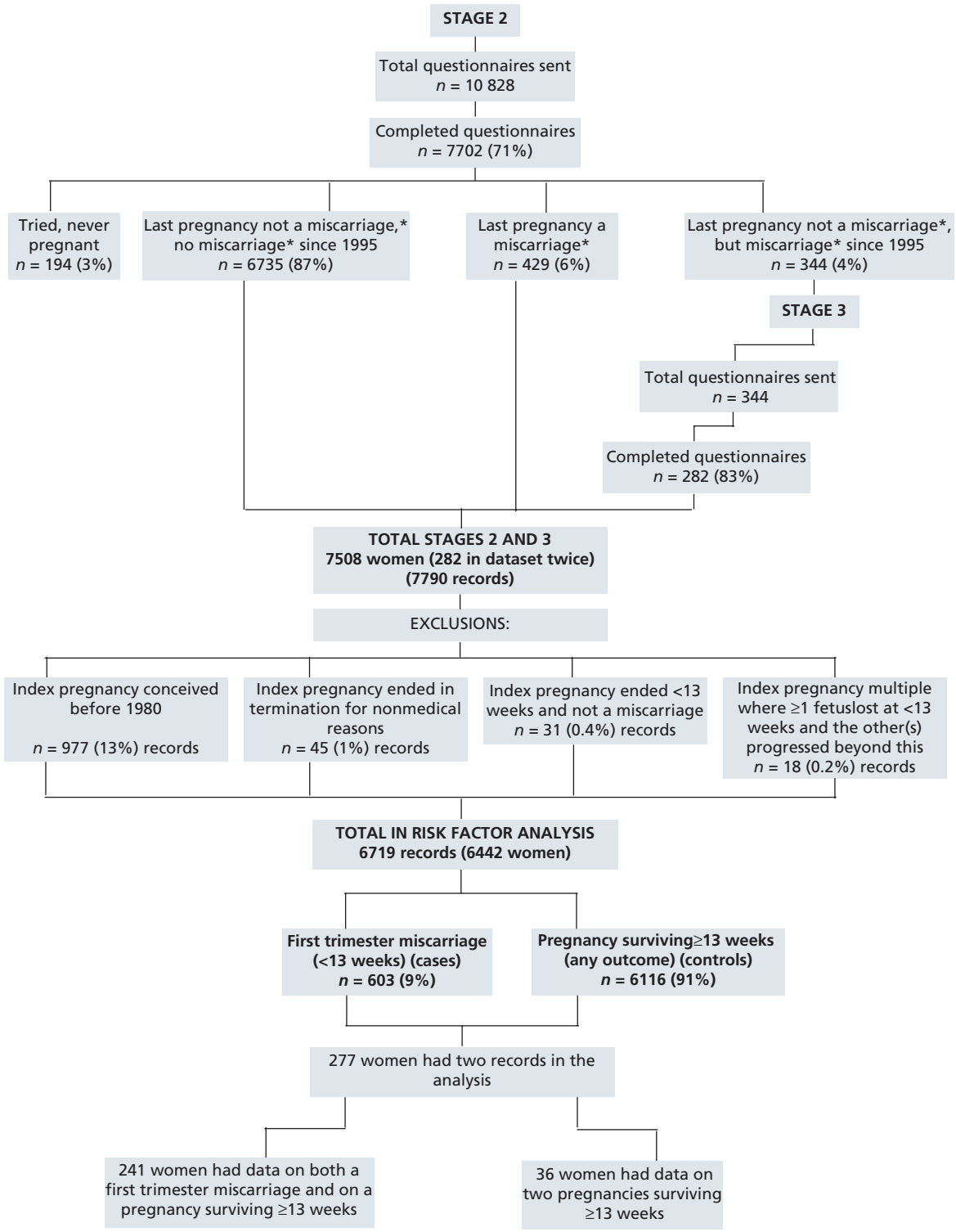

Figure 1. The National Women's Health Study: construction of the data set for analysis of risk factors for first trimester miscarriage.

*Miscarriage at any gestation.

Table 1. Risk factors for first trimester miscarriage (<13 weeks): socio-demographic factors

	Cases, *n* (%)*	Controls, *n* (%)*	Adjusted** OR (95% CI)
Total	603 (100)	6116 (100)	
Year of conception			
1980–84	23 (4)	913 (15)	N/A***
1985–89	35 (6)	998 (16)	N/A***
1990–94	48 (8)	1242 (20)	N/A***
1995–99	293 (49)	1953 (32)	N/A***
2000–02	204 (34)	1010 (17)	N/A***
Pregnancy order			
1	156 (26)	1238 (20)	1.00 (—)
2	174 (29)	2539 (42)	0.99 (0.70–1.41)
3	135 (22)	1402 (23)	1.24 (0.81–1.90)
4	69 (11)	659 (11)	1.13 (0.69–1.86)
≥5	69 (11)	278 (5)	1.58 (0.86–2.90)
Maternal age at conception (years)			
<25	71 (12)	875 (14)	1.09 (0.81–1.45)
25–29	161 (27)	2175 (36)	1.00 (—)
30–34	180 (30)	2156 (35)	1.06 (0.85–1.31)
35–39	132 (22)	804 (13)	1.75 (1.37–2.22)
≥40	59 (10)	106 (2)	5.16 (3.54–7.52)
Mean (SD) of maternal age	*31.9 (6.0)*	*30.0 (4.8)*	
Relationship status			
Married or living together	539 (91)	5751 (95)	1.00 (—)
Other	56 (9)	308 (5)	1.73 (1.25–2.38)
Missing	*8 (1)*	*57 (1)*	
Educational level			
No formal qualifications	27 (5)	442 (7)	0.84 (0.55–1.27)
CSE, 'O' level, GCSE or similar	191 (32)	2222 (37)	1.00 (—)
'A' level, City and Guilds or similar	136 (23)	1354 (23)	1.08 (0.86–1.34)
University degree, RGN or similar	244 (41)	1995 (33)	1.17 (0.96–1.42)
Missing	*5 (1)*	*103 (2)*	
Social class (based on paternal occupation)**			
I and II	284 (50)	2690 (45)	1.00 (—)
IIINM	55 (9)	543 (9)	1.00 (0.74–1.34)
IIIM	147 (25)	1630 (27)	1.08 (0.88–1.33)
IV and V	65 (11)	896 (15)	0.80 (0.60–1.05)
Unemployed or student	29 (5)	236 (4)	1.52 (0.98–2.34)
Missing	*23 (4)*	*121 (2)*	
Social class (based on maternal occupation)			
I and II	219 (37)	1850 (30)	1.00 (—)
IIINM	124 (21)	1203 (20)	1.03 (0.82–1.29)
IIIM	22 (4)	155 (3)	1.43 (0.90–2.27)
IV and V	61 (10)	507 (8)	1.29 (0.95–1.74)
Looking after family/home	141 (24)	2125 (35)	1.02 (0.80–1.30)
Unemployed/student	29 (5)	236 (4)	1.34 (0.87–2.06)
Missing	*7 (1)*	*40 (1)*	
Pre-pregnancy BMI (weight/height^2)			
<18.5 (underweight)	31 (6)	202 (4)	1.72 (1.17–2.53)
18.5–24.9 (normal)	351 (66)	3647 (70)	1.00 (—)
25.0–29.9 (overweight)	106 (20)	1017 (20)	0.95 (0.76–1.19)
≥30.0 (obese)	41 (8)	349 (7)	0.92 (0.65–1.31)
Missing	*74 (12)*	*901 (15)*	

NM, nonmanual; M, manual.

*Denominators for percentages are total nonmissing values; missing values (which include 'Don't remember', 'Don't know' and unanswered questions) calculated as percentage of total number of cases and controls.

**Adjusted for year of conception, maternal age, previous miscarriage and previous live birth.

***Study design oversampled miscarriages conceived since 1995, so analysis by year of conception not meaningful.

****Based on maternal occupation if father looks after home and children and mother works.

and there was weak evidence of a shallow increasing trend in odds with increasing educational attainment ($P = 0.04$) (Table 1). There was a little change in any of these estimates after adjustment for general or work-related stress.

Weight

Overall, pre-pregnancy weight (as measured by body mass index [BMI]) was significantly associated with odds of miscarriage ($P = 0.03$). This was wholly due to a 72% increase in odds associated with being underweight (BMI < 18.5): there was no evidence of an effect of being overweight or obese (Table 1).

Pregnancy history

Among gravid women, there was a strong association with history of miscarriage, the odds increasing with each additional miscarriage. By contrast, having a live birth reduced the odds of miscarriage in subsequent pregnancies by around 40%, but there was no trend with increasing number of live births ($P = 0.71$) (Table 2).

Unadjusted, pregnancy order had a J-shaped relationship with miscarriage, the odds reducing by about 30% between the first and the second pregnancies but subsequently rising with each further pregnancy ($P < 0.0001$). Adjusting for previous miscarriage (with maternal age and year of conception) removed the increasing trend in odds with increasing pregnancy order, leaving a 30–40% reduction for all second- and higher order pregnancies, with no heterogeneity with increasing pregnancy order ($P = 0.73$). On further examination, however, this 'gravidity effect' proved to be wholly explained by having ever had a live birth.

Fifteen percent of cases and 8% of controls reported a previous nonclinically indicated termination. This appeared to increase the odds of subsequent miscarriage by more than 60% (Table 2). There was no apparent difference in effect according to whether the termination was in the immediately preceding pregnancy (OR 1.18, 95% CI 0.63–2.21; 51 cases and 256 controls) or not (OR 1.83, 95% CI 1.32–2.54; 18 cases and 128 controls).

Previous pre-eclampsia was not associated with the odds of subsequent miscarriage ($P = 0.80$) and there was no evidence to suggest that interpregnancy interval was associated with increased odds, those being conceived a very short period of time after the previous pregnancy had ended (e.g. <6 months) being just as likely to succeed as those being conceived after longer periods of time ($P = 0.17$) (Table 2).

Fertility history

Women who described their index pregnancy as 'planned' had 40% reduced odds of miscarriage, the effect remaining after additional adjustment for relationship status (Table 2). After further adjustment for markers of a healthy lifestyle and behaviour (consumption of vitamins, caffeine and alcohol plus smoking), the effect remained, although slightly reduced (OR 0.73, 95% CI 0.59–0.90).

Among those who had consciously tried to conceive, there was a strong trend of increasing odds of miscarriage with increasing length of time to conception ($P < 0.0001$), reaching a doubling in odds for those who took more than a year to conceive relative to those conceiving within 3 months. This effect appeared independent of any effect of fertility treatment (Table 2).

Nineteen percent of cases and 10% of controls reported a fertility problem diagnosed before conceiving the index pregnancy. This was associated with 41% increased odds of miscarriage, which reduced to around 24% after further adjustment for fertility treatment. There was a suggestion that this effect was strongest among those diagnosed with tubal problems, the odds of miscarriage being more than doubled in this group, even after adjustment for fertility treatment (Table 2).

The odds of miscarriage were increased if the pregnancy had resulted from infertility treatment. All types of assisted reproduction technique were associated with increased odds, but the estimated odds ratio was highest and statistically significant among pregnancies resulting from intrauterine insemination or artificial insemination.

Nausea

Women who suffered from nausea and sickness in the first 12 weeks of pregnancy were almost 70% less likely to miscarry, with a marked increasing trend of reducing odds with increasing severity of nausea (Table 3). All the analyses of diet and behaviour were additionally adjusted for nausea, owing to its strong influence on these variables.

Diet and behaviour

All factors given in Table 3 were further explored for confounding by consumption of fresh fruit and vegetables, vitamins, caffeine and alcohol, and by smoking, with very similar results.

Sixty-two percent of women in both groups took vitamins in the first 12 weeks of pregnancy, although this varied greatly with the year of conception: prior to 1995, only 44% controls took vitamins, but this rose to 76% in 1995–99 and 89% thereafter. Most commonly taken was folic acid, where the change in prevalence of consumption over time was even more marked (21% prior to 1995, 66% in 1995–99 and 72% thereafter, among the controls). In general, taking vitamins reduced the odds of miscarriage by around 50%. All the vitamins appeared to confer reduced odds, but the effect was most marked among those taking folic acid or iron or multivitamins (including pregnancy preparations) which contain these (Table 3).

Eating fresh fruit and vegetables daily or most days was associated with a halving in the odds of miscarriage (Table 3). Consumption of dairy products (milk, yoghurt, cheese) and

Table 2. Risk factors for first trimester miscarriage (<13 weeks): reproductive history

Risk factor	Cases, *n* (%)[a]	Controls, *n* (%)[a]	Adjusted[b] OR (95% CI)	Further adjusted[c] OR (95% CI)
Pregnancy history—second-order and higher order pregnancies only				
Total	447 (100)	4878 (100)		
Previous miscarriage				
Never	244 (55)	3754 (77)	1.00 (—)	—
Ever	203 (45)	1124 (23)	1.84 (1.47–2.31)	
1	*136 (23)*	*892 (15)*	*1.65 (1.27–2.13)*	
2	*37 (6)*	*180 (3)*	*2.00 (1.31–3.06)*	
≥3	*30 (5)*	*52 (1)*	*3.87 (2.29–6.54)*	
Previous live birth				
Never	77 (17)	342 (7)	1.00 (—)	—
Ever	370 (83)	4536 (93)	0.63 (0.48–0.84)	
1	*225 (50)*	*3020 (62)*	*0.62 (0.46–0.83)*	
≥2	*145 (32)*	*1516 (31)*	*0.66 (0.48–0.90)*	
Termination of pregnancy[d]				
Never	378 (85)	4494 (92)	1.00 (—)	—
Ever	69 (15)	384 (8)	1.63 (1.21–2.19)	
1	*64 (14)*	*351 (7)*	*1.72 (1.27–2.31)*	
≥2	*5 (1)*	*33 (1)*	*0.85 (0.25–2.83)*	
Previous pre-eclampsia				
Never	439 (98)	4766 (98)	1.00 (—)	—
Ever	8 (2)	112 (2)	0.78 (0.39–1.57)	
Interpregnancy interval (months)				
<6	76 (17)	462 (9)	1.03 (0.71–1.48)	1.05[e] (0.73–1.51)
6–11	67 (15)	623 (13)	0.99 (0.70–1.41)	1.01[e] (0.71–1.43)
12–17	47 (11)	765 (16)	0.82 (0.57–1.18)	0.82[e] (0.57–1.18)
18–35	118 (20)	1657 (27)	1.00 (—)	1.00[e] (—)
36–59	59 (10)	738 (12)	1.06 (0.76–1.49)	1.07[e] (0.76–1.49)
≥60	80 (18)	633 (13)	1.37 (0.98–1.91)	1.36[e] (0.91–1.75)
Fertility history—all pregnancies				
Total	603 (100)	6116 (100)		
Pregnancy				
Unplanned	208 (36)	1549 (26)	1.00 (—)	1.00[f] (—)
Planned	364 (64)	4351 (74)	0.58 (0.48–0.69)	0.60[f] (0.50–0.73)
Missing	*31 (5)*	*216 (4)*		
Time taken to conceive (months)				
Unplanned pregnancy	208 (39)	1549 (29)	2.21 (0.98–1.77)	2.23[e] (1.78–2.80)
<3	139 (26)	2286 (42)	1.00 (—)	1.00[e] (—)
3–6	74 (14)	807 (15)	1.32 (1.01–2.13)	1.31[e] (0.98–1.76)
7–12	39 (7)	358 (7)	1.46 (1.76–3.23)	1.44[e] (0.99–2.10)
>12	80 (15)	427 (8)	2.39 (1.76–3.23)	2.01[e] (1.42–2.84)
Missing	*63 (10)*	*689 (11)*		
Fertility problems diagnosed				
No fertility problems	489 (82)	5470 (90)	1.00 (—)	1.00[e] (—)
≥1 fertility problem	111 (19)	591 (10)	1.41 (1.12–1.78)	1.24[e] (0.96–1.62)
Missing	*3 (0.5)*	*55 (1)*		
Fertility diagnosis (women may appear more than once below; odds ratios relative to not having that specific problem)				
Ovulation problems[g]	31 (5)	194 (3)	1.27 (0.85–1.90)	1.01[e] (0.65–1.56)
Tubal problems[g]	17 (3)	63 (1)	2.67 (1.45–4.90)	2.28[e] (1.24–4.20)
Endometriosis[g]	10 (2)	64 (1)	1.22 (0.63–2.39)	0.98[e] (0.49–1.94)
Other female diagnosis[g]	36 (6)	129 (2)	1.72 (1.16–2.56)	1.47[e] (0.98–2.23)
Poor sperm quality[h]	30 (5)	149 (2)	1.38 (0.88–2.14)	1.19[e] (0.75–1.89)
Other male diagnosis[h]	13 (2)	44 (1)	1.97 (1.00–3.90)	1.74[e] (0.87–3.47)
'Unexplained'[i]	18 (3)	125 (2)	0.98 (0.62–1.56)	0.84[e] (0.51–1.36)
Missing	*See footnotes*			

(*continued*)

Table 2. (*Continued*)

Risk factor	Cases, *n* (%)[a]	Controls, *n* (%)[a]	Adjusted[b] OR (95% CI)	Further adjusted[c] OR (95% CI)
Pregnancy conceived through fertility treatments				
No	562 (93)	5962 (97)	1.00 (—)	—
Yes	41 (7)	154 (3)	1.82 (1.24–2.67)	
Drugs only	*16 (3)*	*86 (1)*	*1.52 (0.85–2.72)*	
IVF/GIFT/ICSI	*16 (3)*	*49 (1)*	*1.76 (0.93–3.31)*	
IUI/AIH/AID	*9 (1)*	*19 (0.3)*	*3.13 (1.33–7.40)*	

AID, artificial insemination by donor; AIH, artificial insemination by husband or partner; GIFT, gamete intrafallopian transfer; ICSI, intracytoplasmic sperm injection; IUI, in-uterine insemination; IVF, *in vitro* fertilisation.
[a]Denominators for percentages are total nonmissing values; missing values (which include Don't remember, Don't know and unanswered questions) calculated as percentage of total cases and controls.
[b]Adjusted for year of conception, maternal age, previous miscarriage and previous live birth.
[c]See relevant footnotes e or f.
[d]For nonclinical reasons.
[e]Additionally adjusted for fertility treatment.
[f]Additionally adjusted for relationship status.
[g]Thirty-one (5%) cases and 118 (2%) controls have missing information on ovulation problems, tubal problems, endometriosis and other female diagnoses.
[h]Four (1%) cases and 60 (1%) controls have missing information on semen quality and other male diagnoses.
[i]Twenty-eight (5%) cases and 63 (1%) controls have missing information on unexplained infertility.

chocolate was also associated with decreased odds, and there was a suggestion that eating fish or white meat twice weekly or more reduced the odds, although this was not statistically significant. Regularly eating foods like red meat or eggs had no effect on the odds ($P = 0.82$ and 0.80, respectively). We found no association with (known) frequent consumption of soya and soya products or sugar substitutes (including diet drinks) ($P = 0.82$ and 0.43, respectively).

When adjusted for maternal age, year of conception, previous miscarriage and previous live birth, there was a strong trend of increasing odds of miscarriage with increasing daily caffeine consumption ($P = 0.0003$ for trend). However, the effect of caffeine was almost entirely due to the effect of nausea (women who felt sick did not tend to drink coffee, the main source of caffeine), and after adjusting for nausea, the effect of caffeine disappeared ($P = 0.67$).

Both increasing frequency and increasing average weekly amount of alcohol consumption were associated with statistically significant increasing trends in the odds of miscarriage ($P = 0.001$ and $P = 0.03$, respectively), although the effect appeared to be concentrated among those who drank regularly (at least once a week to daily) and possibly among those who drank more than 14 units of alcohol a week. Nausea accounted for some of the apparent effect of alcohol consumption ($P = 0.10$ for frequency and $P = 0.11$ for amount after additional adjustment for nausea), but the odds ratios remained high for women drinking regularly and for women drinking more than 14 units per week (Table 3).

There was no evidence of an association between early miscarriage and smoking in the first 12 weeks of pregnancy ($P = 0.73$) nor was there evidence of an effect of strenuous exercise ($P = 0.21$).

Twelve percent of cases and 10% of controls travelled by air in the first 12 weeks of pregnancy. This was associated with an apparent almost halving in the odds of miscarriage, with a striking decreasing trend in odds with increasing numbers of hours flown ($P = 0.001$).

Sexual intercourse was also associated with reduced odds of miscarriage, unless there was bleeding during intercourse, in which case, the odds of miscarriage almost doubled.

Work

Overall, there was no evidence that working full time had a worse effect on odds of miscarriage than working part time or staying at home ($P = 0.41$) (Table 3). However, those reporting that their job was generally stressful and/or demanding had significantly higher odds of miscarriage than those who did not (OR 1.30, 95% CI 1.01–1.68) (Table 4). Among women who were in paid employment, there was no evidence of an effect of sitting or standing for more than 6 hours/day or of lifting heavy objects or people on the risk of first trimester miscarriage (Table 3).

Emotional wellbeing

The majority (61%, $n = 3658$) of controls and 40% ($n = 233$) of cases reported feeling 'happy', 'relaxed' and 'in control'

Table 3. Risk factors for first trimester miscarriage (<13 weeks): lifestyle and behaviour in the first 12 weeks of pregnancy (or until miscarriage)

Risk factor	Cases, *n* (%)*	Controls, *n* (%)*	Adjusted** OR (95% CI)	Further adjusted for nausea, OR (95% CI)
Total	603 (100)	6116 (100)		
Nausea in the first 12 weeks* **				
No	355 (59)	1925 (32)	1.00 (—)	
Yes	246 (41)	4163 (68)	0.27 (0.22–0.32)	
Mild or moderate nausea***	235 (39)	3542 (58)	0.30 (0.25–0.36)	
Severe nausea***	11 (2)	621 (10)	0.07 (0.04–0.14)	
Missing	*2 (0.3)*	*28 (0.5)*		
Food and drink				
Vitamin supplementation				
No vitamin supplements	222 (38)	2248 (38)	1.00 (—)	1.00 (—)
Vitamin supplements	362 (62)	3695 (62)	0.46 (0.38–0.55)	0.53 (0.43–0.65)
(women may appear more than once below; odds ratios relative to no vitamins)				
Folic acid	293 (50)	2641 (44)	0.46 (0.37–0.56)	0.53 (0.43–0.66)
Iron	27 (5)	1046 (18)	0.25 (0.16–0.37)	0.30 (0.19–0.45)
Zinc	5 (2)	14 (1)	0.50 (0.20–1.23)	0.53 (0.21–1.33)
Vitamin C	13 (2)	102 (2)	0.55 (0.30–1.01)	0.57 (0.29–1.11)
Pregnancy preparation	65 (11)	383 (6)	0.53 (0.39–0.73)	0.64 (0.45–0.89)
Other multivitamin tablets	32 (5)	279 (5)	0.59 (0.39–0.88)	0.65 (0.43–1.00)
Other vitamins	17 (3)	114 (2)	0.52 (0.27–0.97)	0.57 (0.31–1.04)
Missing	*19 (3)*	*173 (3)*		
Red meat twice weekly or more				
No	262 (47)	2324 (40)	1.00 (—)	1.00 (—)
Yes	299 (53)	3435 (60)	1.03 (0.86–1.23)	0.98 (0.81–1.18)
Missing	*42 (7)*	*357 (6)*		
White meat twice weekly or more				
No	125 (22)	1030 (18)	1.00 (—)	1.00 (—)
Yes	436 (78)	4729 (82)	0.86 (0.69–1.06)	0.82 (0.65–1.02)
Missing	*42 (7)*	*357 (6)*		
Fish twice weekly or more				
No	372 (66)	3552 (62)	1.00 (—)	1.00 (—)
Yes	189 (34)	2207 (38)	0.83 (0.69–1.00)	0.86 (0.71–1.03)
Missing	*42 (7)*	*357 (6)*		
Eggs twice weekly or more				
No	323 (58)	2888 (50)	1.00 (—)	1.00 (—)
Yes	238 (42)	2871 (50)	1.04 (0.87–1.24)	1.02 (0.85–1.24)
Missing	*42 (7)*	*357 (6)*		
Fresh fruit and vegetables daily or most days				
No	69 (12)	402 (7)	1.00 (—)	1.00 (—)
Yes	517 (88)	5563 (93)	0.54 (0.41–0.72)	0.49 (0.36–0.66)
Missing	*17 (3)*	*151 (2)*		
Dairy products daily or most days				
No	58 (10)	439 (7)	1.00 (—)	1.00 (—)
Yes	528 (90)	5522 (93)	0.75 (0.56–1.01)	0.67 (0.49–0.91)
Missing	*17 (3)*	*155 (3)*		
Soya products daily or most days				
No	566 (97)	5783 (97)	1.00 (—)	1.00 (—)
Yes	20 (3)	175 (3)	0.99 (0.61–1.59)	1.06 (0.66–1.70)
Missing	*17 (3)*	*158 (3)*		
Sugar substitutes daily or most days				

(*continued*)

Table 3. (*Continued*)

Risk factor	Cases, *n* (%)*	Controls, *n* (%)*	Adjusted** OR (95% CI)	Further adjusted for nausea, OR (95% CI)
No	482 (82)	5002 (84)	1.00 (—)	1.00 (—)
Yes	104 (18)	956 (16)	1.12 (0.90–1.41)	1.10 (0.87–1.40)
Missing	*17 (3)*	*158 (3)*		
Chocolate daily or most days				
No	299 (51)	2666 (45)	1.00 (—)	1.00 (—)
Yes	287 (49)	3297 (55)	0.85 (0.71–1.01)	0.81 (0.68–0.97)
Missing	*17 (3)*	*153 (3)*		
Caffeine consumption (mg/day)				
None	49 (9)	607 (11)	1.00 (—)	1.00 (—)
<151	114 (21)	1106 (20)	1.18 (0.82–1.69)	1.03 (0.71–1.49)
151–300	134 (25)	1433 (25)	1.23 (0.87–1.76)	0.93 (0.64–1.33)
301–500	124 (23)	1207 (21)	1.51 (1.06–2.17)	1.04 (0.72–1.50)
>500	125 (23)	1268 (23)	1.70 (1.19–2.43)	1.14 (0.79–1.66)
Missing	*57 (9)*	*495 (8)*		
Frequency of alcohol consumption				
Did not drink alcohol	215 (36)	2455 (40)	1.00 (—)	1.00 (—)
Stopped when found pregnant	108 (18)	1016 (17)	1.08 (0.84–1.38)	1.04 (0.80–1.34)
Less than once a week	130 (22)	1478 (24)	1.14 (0.91–1.44)	1.03 (0.81–1.30)
At least once a week	135 (23)	1105 (18)	1.46 (1.16–1.85)	1.28 (1.01–1.63)
Every day	6 (1)	19 (0.3)	3.80 (1.28–11.30)	3.19 (0.96–10.58)
Missing	*9 (1)*	*43 (1)*		
Average amount of alcohol consumed per week (standard UK units)				
Did not drink alcohol	215 (38)	2455 (42)	1.00 (—)	1.00 (—)
<1	105 (18)	1277 (22)	0.99 (0.77–1.26)	0.94 (0.73–1.21)
1–7	174 (31)	1600 (27)	1.29 (1.05–1.60)	1.23 (0.98–1.53)
>7–14	44 (8)	376 (6)	1.23 (0.86–1.77)	1.20 (0.83–1.74)
>14	31 (5)	181 (3)	1.64 (1.09–2.47)	1.44 (0.92–2.26)
Missing	*34 (6)*	*227 (4)*		
Other behavioural factors				
Average smoking per day (no. of cigarettes) in the first 12 weeks				
Did not smoke	455 (77)	4615 (76)	1.00 (—)	1.00 (—)
Smoked	136 (23)	1448 (24)	1.06 (0.86–1.29)	0.96 (0.78–1.19)
Stopped when found pregnant	28 (5)	354 (6)	0.82 (0.55–1.23)	0.83 (0.54–1.26)
<5/day	36 (6)	379 (6)	0.97 (0.69–1.36)	0.87 (0.61–1.24)
5–10/day	28 (5)	343 (6)	0.91 (0.60–1.37)	0.81 (0.52–1.24)
11–20/day	38 (5)	305 (5)	1.68 (1.16–2.42)	1.41 (0.97–2.06)
21–30/day	6 (1)	67 (1)	1.29 (0.56–2.99)	1.25 (0.55–2.86)
Missing	*12 (2)*	*53 (1)*		
Strenuous exercise				
Rarely or never	365 (65)	3968 (68)	1.00 (—)	1.00 (—)
Once a week	100 (18)	890 (15)	1.23 (0.97–1.57)	1.18 (0.92–1.51)
2–3 times a week	68 (12)	670 (12)	1.13 (0.85–1.48)	1.00 (0.75–1.34)
>4 times a week	30 (5)	279 (5)	1.32 (0.88–1.99)	1.31 (0.86–2.00)
Missing	*40 (7)*	*309 (5)*		
Air travel in the first 12 weeks				
No	528 (90)	5278 (88)	1.00 (—)	1.00 (—)
Yes	60 (10)	741 (12)	0.55 (0.42–0.73)	0.54 (0.40–0.71)
Missing	*15 (2)*	*97 (2)*		
No. of hours flown in the first 12 weeks				
No air travel	528 (90)	5278 (89)	1.00 (—)	1.00 (—)
<5	25 (4)	200 (3)	0.80 (0.52–1.21)	0.74 (0.49–1.12)

(*continued*)

Table 3. (*Continued*)

Risk factor	Cases, *n* (%)*	Controls, *n* (%)*	Adjusted** OR (95% CI)	Further adjusted for nausea, OR (95% CI)
5–9	23 (4)	322 (5)	0.52 (0.34–0.81)	0.52 (0.33–0.82)
10–20	5 (1)	79 (1)	0.44 (0.18–1.07)	0.40 (0.16–1.02)
>20	5 (1)	68 (1)	0.42 (0.17–1.04)	0.39 (0.16–0.97)
Missing	*17 (3)*	*169 (3)*		
Sexual intercourse				
No sexual intercourse	124 (23)	895 (15)	1.00 (—)	1.00 (—)
Sexual intercourse	417 (77)	4936 (85)	0.88 (0.71–1.10)	0.78 (0.62–0.98)
Never bled during intercourse	340 (66)	4665 (81)	0.76 (0.61–0.95)	0.67 (0.52–0.84)
Ever bled during intercourse	47 (9)	168 (3)	2.14 (1.46–3.13)	1.96 (1.31–2.92)
Missing	*62 (10)*	*285 (5)*		
Occupation				
Paid employment				
Not in paid employment (looking after family/home)	141 (24)	2125 (35)	1.00 (—)	—
Full time	273 (45)	2063 (34)	1.10 (0.85–1.43)	
Part time	153 (26)	1653 (27)	1.00 (0.79–1.27)	
Unemployed or student	29 (5)	236 (4)	1.34 (0.86–2.11)	
Missing	*7 (1)*	*39 (1)*		
Occupational exposure (women in paid employment only)				
Total	426 (100)	3716 (100)		
Sitting for >6 hours/day				
No	274 (65)	2586 (70)	1.00 (—)	—
Yes	146 (35)	1093 (30)	1.04 (0.85–1.28)	
Missing	*6 (1)*	*37 (1)*		
Standing for >6 hours/day				
No	388 (80)	2865 (78)	1.00 (—)	—
Yes	82 (20)	816 (22)	0.89 (0.69–1.14)	
Missing	*6 (1)*	*35 (1)*		
Lifting heavy objects or people				
No	326 (78)	2891 (79)	1.00 (—)	—
Yes	93 (22)	790 (21)	1.08 (0.85–1.38)	
Missing	*7 (2)*	*35 (1)*		

*Denominators for percentages are total nonmissing values; missing values (which include Don't remember, Don't know and unanswered questions) calculated as percentage of total cases and controls.

**Adjusted for year of conception, maternal age, previous miscarriage and previous live birth.

***Nausea was defined as mild, feeling sick only; moderate, feeling sick and sometimes vomiting; and severe, frequent vomiting, could not retain meals. Reported nausea relates here only to that experienced in the first 12 weeks of pregnancy.

throughout the first 12 weeks of their last pregnancy. Being happy, relaxed or in control was associated with a 60% reduction in odds compared with all other women (adjusted [including nausea] OR: 0.41 [95% CI 0.34–0.49]). Conversely, women who reported feeling 'stressed', 'anxious', 'depressed', 'out of control' or 'overwhelmed' in the first 12 weeks of pregnancy had much higher odds of miscarriage than those who described themselves as happy, relaxed or in control. This effect increased to a tripling in odds after adjusting for confounding by nausea (Table 4). Women who reported feeling 'other' emotions (which tended to be negative, including guilt and fear) also had increased odds of miscarriage.

There was a strong trend in increasing odds of miscarriage with increasing number of stressful or traumatic events ($P < 0.0001$ for trend) (Table 4). The most common event was having a stressful or demanding job.

The father

Although overall paternal age did not significantly influence the odds of miscarriage ($P = 0.21$), there was some indication that the odds might be increased when the father was aged older than 45 years, over and above any effect of late maternal age (Table 5).

Women who conceived after a change in partner also had increased odds of miscarriage—more than 60% higher than

Table 4. Risk factors for first trimester miscarriage (<13 weeks): emotions and adverse life events in the first 12 weeks of pregnancy (or until miscarriage)

Risk factor	Cases, *n* (%)*	Controls, *n* (%)*	Adjusted** OR (95% CI)	Further adjusted for nausea, OR (95% CI)
Total	603 (100)	6116 (100)		
Emotions and adverse life events				
General feelings in the first 12 weeks				
Happy, relaxed or in control	233 (40)	3658 (61)	1.00 (—)	1.00 (—)
Stressed, anxious, depressed, out of control or overwhelmed	230 (39)	1151 (19)	2.47 (2.02–3.02)	3.04 (2.46–3.76)
Periods of feeling both happy and relaxed and stressed and anxious	53 (9)	451 (8)	1.13 (0.82–1.56)	1.22 (0.88–1.70)
Other	73 (12)	751 (12)	1.37 (1.03–1.81)	1.70 (1.26–2.29)
Missing	*14 (2)*	*105 (2)*		
No. of stressful or traumatic events* **				
None	345 (58)	4181 (69)	1.00 (—)	1.00 (—)
1	193 (33)	1497 (25)	1.37 (1.13–1.67)	1.47 (1.19–1.80)
2	41 (7)	298 (5)	1.60 (1.08–2.36)	1.72 (1.15–2.58)
≥3	11 (2)	62 (1)	2.36 (1.05–5.32)	3.27 (1.39–7.68)
Missing	*13 (2)*	*78 (1)*		
Stressful or traumatic events *(women may appear more than once below; odds ratios relative to not having that specific problem)*				
Job generally demanding or stressful	96 (16)	583 (10)	1.23 (0.97–1.57)	1.30 (1.01–1.68)
Loss of job or job insecurity	14 (2)	113 (2)	0.87 (0.46–1.64)	0.87 (0.45–1.67)
Husband or partner lost the job or had job insecurity	12 (2)	88 (1)	1.36 (0.71–2.59)	1.61 (0.85–3.06)
Separation or divorce	16 (3)	125 (2)	1.46 (0.83–2.58)	1.64 (0.90–3.01)
Serious financial problems	19 (3)	143 (2)	1.36 (0.82–2.25)	1.60 (0.92–2.78)
Accident	7 (1)	40 (1)	2.00 (0.82–4.91)	2.33 (0.94–5.80)
Serious illness	6 (1)	21 (0.4)	2.04 (0.69–5.99)	2.18 (0.62–7.68)
Serious illness of someone close	16 (3)	145 (2)	1.03 (0.61–1.77)	1.08 (0.62–1.90)
Death of someone close	13 (2)	154 (3)	0.80 (0.43–1.48)	0.75 (0.37–1.49)
Other stressful or traumatic event	88 (15)	517 (9)	1.82 (1.40–2.36)	1.99 (1.52–2.61)
Missing	*13 (2)*	*78 (1)*		

*Denominators for percentages are total nonmissing values; missing values (which include Don't remember, Don't know and unanswered questions) calculated as percentage of total cases and controls.

**Adjusted for year of conception, maternal age, previous miscarriage and previous live birth.

***The following options were given (women ticked all that applied): job generally demanding or stressful, loss of job or had job insecurity, husband or partner lost the job or had job insecurity, separation or divorce, serious financial problems, accident, serious illness, serious illness of someone close, death of someone close, other stressful or traumatic event.

women whose index pregnancy was fathered by the same man as that in the previous pregnancy.

There was no evidence to suggest an effect of pre-conceptual paternal alcohol consumption ($P = 0.24$) or paternal smoking either in the 3 months prior to conception ($P = 0.66$) or in the first 12 weeks of pregnancy (in the presence of the mother) ($P = 0.17$) on the risk of miscarriage (Table 5).

All the analyses were repeated twice more: (a) restricted to pregnancies conceived since 1995 and (b) restricted to stage 2 pregnancies only (i.e. excluding the miscarriages of stage 3 participants, whose most recent pregnancy had ended in a live birth but who had experienced a miscarriage since 1995). The results were broadly similar.

Discussion

This study has assembled a large UK-population-based data set that appears unbiased compared with the general UK population. It is unique in allowing a truly population-based investigation of the association between biological, lifestyle and behavioural factors and risk of early miscarriage, a hard-to-measure outcome often not routinely captured through medical records. The case–control design also enabled examination of numerous, often coexisting and inter-related, risk factors.

The main findings are summarised in Table 6. In this study, we have confirmed some well-established risk factors, including increased maternal age and history of miscarriage

Table 5. Risk factors for first trimester miscarriage (<13 weeks): paternal factors

Risk factor	Cases, *n* (%)*	Controls, *n* (%)*	Adjusted** OR (95% CI)
Total	603 (100)	6116 (100)	
Paternal factors			
Paternal age at conception (years)			
<25	39 (7)	448 (7)	1.18 (0.80–1.73)
25	116 (20)	1609 (27)	1.00 (—)
30	188 (32)	2282 (38)	1.05 (0.83–1.33)
35	150 (25)	1185 (20)	1.22 (0.94–1.59)
40	50 (8)	356 (6)	1.04 (0.71–1.53)
≥45	46 (8)	189 (3)	1.63 (1.08–2.47)
Missing	*14 (2)*	*47 (1)*	
Mean (SD) paternal age	34.3 (6.8)	32.5 (5.8)	
Change of father			
First pregnancy	156 (26)	1267 (21)	1.25 (0.87–1.81)
Same father as that in previous pregnancy	370 (62)	4425 (73)	1.00 (—)
Different father from that in previous pregnancy	73 (12)	411 (7)	1.66 (1.22–2.26)
Missing	*4 (1)*	*13 (0.2)*	
Average amount of alcohol consumed per week (standard UK units) in 3 months prior to conception			
Did not drink alcohol	33 (7)	271 (5)	1.00 (—)
<1	44 (9)	547 (11)	0.77 (0.48–1.26)
1–10	176 (35)	2085 (40)	0.73 (0.49–1.07)
>10–21	147 (30)	1395 (27)	0.87 (0.58–1.29)
>21–35	60 (12)	516 (10)	0.95 (0.61–1.50)
>35	37 (7)	354 (7)	0.84 (0.51–1.40)
Missing	*106 (18)*	*948 (16)*	
Average smoking (no. of cigarettes per day) in 3 months prior to conception			
Did not smoke	398 (69)	4021 (67)	1.00 (—)
Smoked	180 (31)	1963 (33)	1.04 (0.87–1.25)
<5/day	22 (4)	276 (5)	0.68 (0.43–1.07)
5–10/day	32 (6)	339 (6)	1.03 (0.71–1.50)
11–20/day	83 (14)	867 (14)	1.13 (0.88–1.44)
>20/day	43 (7)	481 (8)	1.19 (0.86–1.66)
Missing	*25 (4)*	*132 (2)*	
Smoking in the first 12 weeks of pregnancy			
Did not smoke in the presence of mother	406 (70)	4154 (69)	1.00 (—)
Smoked in the presence of mother	174 (30)	1836 (31)	1.14 (0.95–1.37)
Missing	*23 (4)*	*126 (2)*	

*Denominators for percentages are total nonmissing values; missing values (which include Don't remember, Don't know and unanswered questions) calculated as percentage of total cases and controls.
**Adjusted for year of conception, maternal age, previous miscarriage and previous live birth.

and infertility, and also the reduced risk associated with nausea. We confirmed the complex relationship with pregnancy order and found that having a live birth is more predictive of 'success' in a future pregnancy than pregnancy order itself. This study found no evidence for the commonly held beliefs that risk of early miscarriage varies by social class, employment status or strenuous exercise. Neither did it confirm that caffeine intake was independently linked to risk of miscarriage nor that exposure to physical stress at work increased the risk. We have also added evidence to the debate surrounding smoking in pregnancy and risk of miscarriage[14–18] by finding no association.

This was an exploratory study, involving multiple statistical tests; so some of the associations may have arisen by chance. Interpretation of individual findings must be therefore made with caution. Nevertheless, several themes emerged, which we would like to highlight. First, diet. Eating fresh fruit and vegetables daily was apparently protective. Consuming these with or without meat probably indicates a nutritious and well-balanced diet. Vitamin supplementation was also associated with reduced risk. As all these data are self-reported, it is difficult to know how far diet and vitamins are causally related to reduced risk of miscarriage. But at the very least, the findings provide opportunities for encouraging a healthy diet during pregnancy.

Table 6. Summary of main findings

Factors associated with increased risk of first trimester miscarriage	Factors associated with decreased risk of first trimester miscarriage	No evidence of association with risk of first trimester miscarriage
Socio-demographic factors	**Obstetric factors**	**Socio-demographic factors**
Maternal age more than 35 years	Previous live birth	Social class
Not living with the father of the baby	Nausea	Education
Pre-pregnancy BMI	**Vitamins and diet**	**Obstetric factors**
Being underweight	Taking vitamins (in particular folic acid, iron and multivitamins)	Pregnancy order (after accounting for previous pregnancy outcome)
Obstetric factors	Eating fresh fruits and vegetables daily	Short pregnancy interval
Previous miscarriage	Eating dairy products daily	Pre-eclampsia in previous pregnancies
Previous termination of pregnancy	Eating chocolate daily	**Work**
Longer time to conception	Possibly eating white meat and fish twice weekly or more	Full-time work
Infertility problems, particularly tubal infertility	**Indicators of wellbeing**	Sitting or standing for 6 hours or more per day at work
Assisted conception	Feeling happy and relaxed	Lifting heavy objects or people at work
Indicators of stress	Planned pregnancy	**Diet**
Being stressed or anxious	Air travel	Eating red meat, eggs, soya products and sugar substitutes
Experiencing one or more stressful or traumatic event	Sexual intercourse (no bleeding)	Caffeine consumption (after accounting for nausea)
Having a stressful job		**Smoking and alcohol**
Alcohol		Smoking
Regularly drinking alcohol		Moderate and occasional alcohol consumption (after accounting for nausea)
High alcohol consumption		**Exercise**
Paternal factors		Strenuous exercise
Changing partners		**Paternal smoking and alcohol**
Paternal age more than 45 years		Paternal preconceptual alcohol
Other factors		Paternal preconceptual smoking (and during the first 12 weeks)
Bleeding during sexual intercourse		

Low BMI before pregnancy, which we found was linked to increased risk of miscarriage, may be a marker for poor diet and low vitamin intake around the time of conception.

The second set of findings relate to emotional wellbeing in pregnancy. Stress and traumatic events appear to increase risk; feeling relaxed and happy appears to decrease the risk. The first question that springs to mind is whether recall bias could play a part in driving these associations. It is possible that women who experienced miscarriage were likely to recall the stress and the anxiety associated with this event rather than report how they felt prior to miscarriage. However, we also included a more objective measure relating to stressful or traumatic events experienced in the first 12 weeks of pregnancy and found a very strong trend of increasing odds with increasing number of traumatic events. Furthermore, previous studies on exposures relating to reproductive events have found that maternal recall has acceptably high reliability and is little affected by time from event.[42–44] This is consistent with our finding that when analyses were restricted to the most recent pregnancies (conceived since 1995), the results were virtually identical. We conclude that at the very least, the data relating to stress indicate an interesting phenomenon. There are increasing numbers of publications reporting a relationship between stress and adverse reproductive outcomes,[26–29] and clearly, this is an area deserving further attention. It is uncertain how our finding of increased risk of miscarriage following termination for nonclinical reasons fits into the general picture, but feelings of guilt and fear in any subsequent pregnancy may play a part as they may when there has been a previous miscarriage. Findings in the literature relating to the effect of induced abortion on subsequent risk of miscarriage in general are conflicting: a prospective study based in China[45] found an increased risk of first trimester miscarriage, although a large-scale Danish[46] study found increased miscarriage risks only for women who

conceived within 3 months of the induced abortion. Other studies have found no increase in risk.[47,48] It is possible that some of these conflicting results are due to inadequate adjustment for confounding.

Third, men. Having a father older than 45 years, with or without an older mother, increased the odds of early fetal death. This has been reported in a few previous studies.[7,33,34] In addition, if the father was not the same father as that in the previous pregnancy, the risk was the same as that for a first pregnancy. This observation is novel. It parallels with the findings in the literature for pre-eclampsia, which suggest that the protective effect of a previous live birth is lost when the subsequent pregnancy is conceived with a new partner[49–52] and with the recent finding that women who change partner between their first two births have increased risk of delivering a preterm, low birthweight baby with an increased risk of infant mortality.[53] As the authors of the latter article point out, most studies relating to change of partner have focused on risk of recurrence of an adverse outcome,[52,54,55] hypothesised mechanisms relating to paternal antigens and genes, but the biological interpretation for 'sporadic' outcomes is less clear. Further investigation of this finding is warranted.

A potential limitation of this study is selection bias, given the relatively low response to the first (screening) stage of the study. In terms of the key reproductive indicators of stillbirth and multiple birth, the data do, however, look remarkably similar to those of the general population,[38] and reported miscarriage rates were also as expected. We therefore feel confident that response was unlikely to be related to adverse reproductive outcome. Furthermore, the average age of around 40 years at survey, coupled with average ages at first birth and all births that are exactly as would be expected from general population data,[38] could be seen to indicate that nonresponders to the survey tended to concentrate among younger women who had not yet tested their fertility. Response to the more targeted stage 2 was good, and the characteristics of the women responding were almost identical to those of the women in stage 1, indicating that stage 2 responders were an apparently unbiased subset of those responding to stage 1.[38] We therefore feel confident that the data can be considered unbiased with respect to reproduction and representative of patterns among all women in the UK population who have ever tried to have children.

As with all case–control studies, the study relies on maternal recall and this could also be a source of bias. As mentioned above, studies on self-reported reproductive history and exposures relating to reproductive events have, however, found maternal recall to have acceptably high reliability and to be little affected by time from event.[42–44] Results for well-established factors are also entirely consistent with the literature, further indicating a lack of bias.

Finally, a limitation of this study design is that we could not distinguish chromosomally normal from abnormal miscarriages. This requires a prospective cohort study with tissue sampling, an approach that is logistically difficult and expensive. We could not distinguish the so-called sporadic from recurrent miscarriages in our study as the women were at various stages of their reproductive lives and some who did not report recurrent miscarriage may yet go on to miscarry repeatedly. Recurrent miscarriage is, however, rare: for example, among the 6408 women aged ≥40 years in stage 1 of this study, only 0.8% (n = 49) reported two and 0.3% (n = 21) reported three or more consecutive miscarriages in their reproductive lifetime—so we would expect this issue to have had little impact on our overall findings.

Notwithstanding these limitations, our data are as complete as it is possible to be with regard to reporting miscarriage because we asked randomly selected women from the general population to report their pregnancy histories themselves, and we have identified factors associated with risk of miscarriage, some of which are modifiable and could be used to advise women either pre-pregnancy or in the early stages of pregnancy.

Conclusions and recommendations

Reduced risks associated with taking vitamins, consumption of fresh fruit and vegetables and feeling happy and relaxed during pregnancy are perhaps not surprising, but further work is needed to establish causal pathways. Nevertheless, it is likely that advice to encourage a healthy diet and to try and reduce stress and promote emotional wellbeing might help women in early pregnancy (or those planning a pregnancy) reduce their risk of miscarriage.

Our findings of increased risk associated with previous termination, stress and traumatic events in pregnancy, change of partner and low pre-pregnancy weight are noteworthy. We suggest further work be initiated to confirm these findings in other study populations.

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References

1 Garcia-Enguidanos A, Calle ME, Valero J, Luna S, Dominguez-Rojas V. Risk factors in miscarriage: a review. *Eur J Obstet Gynecol Reprod Biol* 2002;102:111–19.

2 Savitz DA, Hertz-Picciotto I, Poole C, Olshan AF. Epidemiologic measures of the course and outcome of pregnancy. *Epidemiol Rev* 2002; 24:91–101.

3 Zinaman MJ, Clegg ED, Brown CC, O'Connor J, Selevan SG. Estimates of human fertility and pregnancy loss. *Fertil Steril* 1996;65:503–9.

4 Ellish NJ, Saboda K, O'Connor J, Nasca PC, Stanek EJ, Boyle C. A prospective study of early pregnancy loss. *Hum Reprod* 1996;11: 406–12.

5 Wilcox A, Weinberg C, O'Connor J, Baird DD, Schlatterer JP, Canfield RE, *et al*. Incidence of early loss of pregnancy. *N Engl J Med* 1988;319: 189–94.

6 Nybo Andersen A-M, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. *BMJ* 2000;320:1708–12.

7 De la Rochebrochard E, Thonneau P. Paternal age and maternal age are risk factors for miscarriage; results of a multicentre European study. *Hum Reprod* 2002;17:1649–56.

8 Regan L, Braude PR, Trembath PL. Influence of past reproductive performance on risk of spontaneous abortion. *BMJ* 1989;299:541–5.

9 Hakim RB, Gray RH, Zacur H. Infertility and early pregnancy loss. *Am J Obstet Gynecol* 1995;172:1510–17.

10 Gray RH, Wu LY. Subfertility and risk of spontaneous abortion. *Am J Public Health* 2000;90:1452–4.

11 Axmon A, Hagmar L. Time to pregnancy and pregnancy outcome. *Fertil Steril* 2005;84:966–74.

12 Abel EL. Maternal alcohol consumption and spontaneous abortion. *Alcohol* 1997;32:211–19.

13 Windham GC, Von Behren J, Fenster L, Schaefer C, Swan SH. Moderate maternal alcohol consumption and risk of spontaneous abortion. *Epidemiology* 1997;8:509–14.

14 Rasch V. Cigarette, alcohol and caffeine consumption: risk factors for spontaneous abortion. *Acta Obstet Gynecol Scand* 2003;82: 182–8.

15 Armstrong BG, McDonald AD, Sloan M. Cigarette, alcohol, and coffee consumption and spontaneous abortion. *Am J Public Health* 1992; 82:85–7.

16 Windham GC, Swan SH, Fenster L. Parental cigarette smoking and the risk of spontaneous abortion. *Epidemiology* 1992;135:1394–403.

17 Kline J, Levin B, Kinney A, Stein Z, Susser M, Warburton D. Cigarette smoking and spontaneous abortion of known karyotype. Precise data but uncertain inferences. *Am J Epidemiol* 1995;141:417–27.

18 Wisborg K, Kesmodel U, Henriksen TB, Hedegaard M, Secher NJ. A prospective study of maternal smoking and spontaneous abortion. *Acta Obstet Gynecol Scand* 2003;82:936–41.

19 Bech BH, Nohr EA, Vaeth M, Henriksen TB, Olsen J. Coffee and fetal death: a cohort study with prospective data. *Am J Epidemiol* 2005;162: 983–90.

20 Signorello LB, McLaughlin JK. Maternal caffeine consumption and spontaneous abortion: a review of the epidemiologic evidence. *Epidemiology* 2004;15:229–39.

21 Fenster L, Hubbard AE, Swan SH, Windham GC, Waller K, Hiatt RA, *et al*. Caffeinated beverages, decaffeinated coffee and spontaneous abortion. *Epidemiology* 1997;8:515–23.

22 Wen W, Shu XO, Jacobs DR, Brown JE. The associations of maternal caffeine consumption and nausea with spontaneous abortion. *Epidemiology* 2001;12:38–42.

23 Brandes JM. First trimester nausea and vomiting as related to outcome of pregnancy. *Obstet Gynaecol* 1967;30:427–31.

24 Jarnfelt-Samsioe A, Samsioe G, Velinder GM. Nausea and vomiting in pregnancy: a contribution to its epidemiology. *Gynaecol Obstet Invest* 1983;16:221–9.

25 Bailey LB, Berry RJ. Folic acid supplementation and the occurrence of congenital heart defects, orofacial clefts, multiple births, and miscarriage. *Am J Clin Nutr* 2005;81:1213–17S.

26 Arck PC. Stress and pregnancy loss: role of immune mediators, hormones and neurotransmitters. *Am J Reprod Immunol* 2001;46:117–23.

27 O'Hare T, Creed F. Life events and miscarriage. *Br J Psychiatry* 1995;167:799–805.

28 Neugebauer R, Kline J, Stein Z, Shrout P, Warburton D, Susser M. Association of stressful life events with chromosomally normal spontaneous abortion. *Am J Epidemiol* 1996;143:588–96.

29 Schenker MB, Eaton M, Green R, Samuels S. Self-reported stress and reproductive health of female lawyers. *J Occup Environ Med* 1997;39: 556–68.

30 McDonald AD, Armstrong B, Cherry NM, Delorme C, Diodati-Nolin A, McDonald JC, Robert D. Spontaneous abortion and occupation. *J Occup Med* 1986;28:1232–38.

31 Fenster L, Hubbard AE, Windham GC, Waller KO, Swan SH. A prospective study of work-related physical exertion and spontaneous abortion. *Epidemiology* 1997;8:66–74.

32 Ahlborg G Jr. Physical work load and pregnancy outcome. *J Occup Environ Med* 1995;37:941–4.

33 Slama R, Bouyer J, Windham G, Fenster L, Werwatz A, Swan SH. Influence of paternal age on the risk of spontaneous abortion. *Am J Epidemiol* 2005;161:816–23.

34 Nybo Andersen AM, Handen KD, Andersen PK, Davey Smith G. Advanced paternal age and risk of fetal death: a cohort study. *Am J Epidemiol* 2004;160:1214–22.

35 Lindbohm ML, Hemminki K, Bonhomme MG, Anttila A, Rantala K, Heikkila P, *et al*. Effects of paternal occupational exposure on spontaneous abortions. *Am J Public Health* 1991;81:1029–33.

36 Halmesmaki E, Valimaki M, Roine R, Ylikahri R, Ylikorkala O. Maternal and paternal alcohol consumption and miscarriage. *Br J Obstet Gynaecol* 1989;96:188–91.

37 Chatenoud L, Parazzini F, di Cintio E, Zanconato G, Benzi G, Bortolus R, *et al*. Paternal and maternal smoking habits before conception and during the first trimester: relation to spontaneous abortion. *Ann Epidemiol* 1998;8:520–6.

38 Maconochie N, Doyle P, Prior S. The National Women's Health Study: assembly and description of a population-based reproductive cohort. *BMC Public Health* 2004;4:35.

39 Statacorp. *Stata Statistical Software: Release 8.0*. College Station, TX: Stata Corporation, 2003.

40 Huber PJ. The behaviour of maximum likelihood estimates under nonstandard conditions. In: *Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability*. Berkley, CA: University of California Press; 1967.

41 Korn EL, Graubard BI. Simultaneous testing of regression coefficients with complex data: use of Bonferoni t statistics. *Am Stat* 1990;44:270–6.

42 Olson JE, Shu XO, Ross JA, Pendergrass T, Robison LL. Medical record validation of maternally reported birth characteristics and pregnancy-related events: a report from the Children's Cancer Group. *Am J Epidemiol* 1997;145:58–67.

43 Farrow A, Farrow SC, Little R, Golding J. The repeatability of self-reported exposure after miscarriage. ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. *Int J Epidemiol* 1996;25:797–806.

44 Yawn BP, Suman VJ, Jacobsen SJ. Maternal recall of distant pregnancy events. *J Clin Epidemiol* 1998;51:399–405.

45 Sun Y, Che Y, Gao E, Olsen J, Zhou W. Induced abortion and risk of subsequent miscarriage. *Int J Epidemiol* 2003;32:449–54.

46 Zhou W, Olsen J, Nielsen GL, Sabroe S. Risk of spontaneous abortion following induced abortion is only increased with short interpregnancy interval. *J Obstet Gynaecol* 2000;20:49–54.

47 Infante-Rivard C, Gauthier R. Induced abortion as a risk factor for subsequent fetal loss. *Epidemiology* 1996;7:540–2.

48 Levin AA, Schoenbaum SC, Monson RR, Stubblefield PG, Ryan KJ. Association of induced abortion with subsequent pregnancy loss. *JAMA* 1980;243:2495–9.

49 Saftlas AF, Levine RJ, Klebanoff MA, Martz KL, Ewell MG, Morris CD, *et al*. Abortion, changed paternity, and risk of preeclampsia in nulliparous women. *Am J Epidemiol* 2003;157:1108–14.

50 Trupin LS, Simon LP, Eskenazi B. Change in paternity: a risk factor for preeclampsia in multiparas. *Epidemiology* 1997;7:240–4.
51 Li DK, Wi S. Changing paternity and the risk of preeclampsia/eclampsia in the subsequent pregnancy. *Am J Epidemiol* 2000;151:57–62.
52 Lie RT, Rasmussen S, Brunborg H, Gjessing HK, Lie-Nielsen E, Irgens LM. Fetal and maternal contributions to risk of pre-eclampsia: population based study. *BMJ* 1998;316:1343–7.
53 Vatten LJ, Skjaerven R. Effects on pregnancy outcome of changing partner between first two births: prospective population study. *BMJ* 2003;327:1138.
54 Basso O, Olsen J, Christensen K. Recurrence risk of congenital anomalies—the impact of paternal, social and environmental factors: a population-based study in Denmark. *Am J Epidemiol* 1999;150:598–604.
55 Li DK. Changing paternity and the risk of preterm delivery in the subsequent pregnancy. *Epidemiology* 1999;10:148–52.

