

Adverse childhood experiences are associated with increased risk of miscarriage in a national population-based cohort study in England

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STUDY QUESTION: Is there an association between adverse childhood experiences (ACE) and the risk of miscarriage in the general population?

SUMMARY ANSWER: Specific ACE as well as the summary ACE score were associated with an increased risk of single and recurrent miscarriages.

WHAT IS KNOWN ALREADY: There is scarce evidence on the association between ACE and miscarriage risk.

STUDY DESIGN, SIZE, DURATION: We conducted a retrospective national cohort study. The sample consisted of 2795 women aged 55–89 years from the English Longitudinal Study of Ageing (ELSA).

PARTICIPANTS/MATERIALS, SETTING, METHODS: Our study was population-based and included women who participated in the ELSA Life History Interview in 2007. We estimated multinomial logistic regression models of the associations of the summary ACE score and eight individual ACE variables (pertaining to physical and sexual abuse, family dysfunction and experiences of living in residential care or with foster parents) with self-reported miscarriage (0, 1, ≥ 2 miscarriages).

MAIN RESULTS AND THE ROLE OF CHANCE: Five hundred and fifty-three women (19.8% of our sample) had experienced at least one miscarriage in their lifetime. Compared with women with no ACE, women with ≥ 3 ACE were two times more likely to experience a single miscarriage in their lifetime (relative risk ratio 2.00, 95% CI 1.25–3.22) and more than three times more likely to experience recurrent miscarriages (≥ 2 miscarriages) (relative risk ratio 3.10, 95% CI 1.63, 5.89) after adjustment for birth cohort, age at menarche and childhood socioeconomic position. Childhood experiences of physical and sexual abuse were individually associated with increased risk of miscarriage.

LIMITATIONS, REASONS FOR CAUTION: Given the magnitude of the observed associations, their biological plausibility, temporal order and consistency with evidence suggesting a positive association between ACE and adverse reproductive outcomes, it is unlikely that our findings are spurious. Nevertheless, the observed associations should not be interpreted as causal as our study was observational and potentially susceptible to bias arising from unaccounted confounders. Non-response and ensuing selection bias may have also biased our findings. Retrospectively measured ACE are known to be susceptible to underreporting. Our study may have misclassified cases of ACE and possibly underestimated the magnitude of the association between ACE and the risk of miscarriage.

WIDER IMPLICATIONS OF THE FINDINGS: Our study highlights experiences of psychosocial adversity in childhood as a potential risk factor for single and recurrent miscarriages. Our findings contribute to a better understanding of the role of childhood trauma in miscarriage and add an important life course dimension to the study of miscarriage.

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Introduction

Miscarriage, the loss of clinically established pregnancy at gestational age ≤ 24 weeks (Tur-Torres et al., 2017; ESHRE Guideline Group on RPL et al., 2018), is the commonest complication in pregnancy (Feodor Nilsson et al., 2014; Smith et al., 2019). In UK, it is estimated that miscarriage occurs in one in five pregnancies (National Institute for Health and Care Excellence, 2019). Miscarriages, especially recurrent ones (ESHRE Guideline Group on RPL et al., 2018), pose a challenging clinical problem because in many cases their aetiology cannot be determined and are characterized as unexplained (Saravelos and Li, 2012; Tur-Torres et al., 2017). Chromosomal abnormalities and genetic disorders are responsible for 50–70% of pregnancy losses at gestational age < 10 weeks, but only explain a small proportion of miscarriages that occur at gestational age ≥ 12 weeks (Tur-Torres et al., 2017) or miscarriages in younger women (Christiansen et al., 2008). The burden of miscarriage combined with the unexplained aetiology of many cases underlines the need to improve our understanding of the implicated risk factors. Improved knowledge of the pathogenic processes and pathways could lead to better identification of prevention and therapeutic targets, and potentially help to reduce the number of incident cases of miscarriage.

Aside from karyotype abnormalities, genetic disorders and high-risk genetic variants, there are numerous maternal risk factors that contribute to the majority of single and recurrent miscarriages (Christiansen et al., 2008; Feodor Nilsson et al., 2014; ESHRE Guideline Group on RPL et al., 2018). Paternal contribution to miscarriage has been studied less. This can be sperm-related (Tur-Torres et al., 2017; Jayasena et al., 2019) but also behavioural, social and psychological and related to maternal stress levels and well-being (Maconochie et al., 2007; Leeners et al., 2013, 2014). The numerous maternal factors that have been implicated in miscarriage range from downstream factors such as uterine immune imbalances to more upstream factors such as obesity, unhealthy behaviours and advanced maternal age (Christiansen et al., 2008; Feodor Nilsson et al., 2014; ESHRE Guideline Group on RPL et al., 2018). Stress is a recognized contributing factor to miscarriage but is not currently considered to be a direct cause of recurrent miscarriage (ESHRE Guideline Group on RPL et al., 2018).

Adverse childhood experiences (ACE), a term that typically describes childhood experiences of abuse and a dysfunctional family or lacking a family, are known to exert a negative effect on multiple health domains (Hughes et al., 2017). Recent literature suggests that ACE and other psychosocial adversity in childhood are systematically associated with reproduction-related outcomes such as pubertal maturation and age at menarche (Li et al., 2014; Yermachenko and Dvornyk, 2014; Magnus et al., 2018; Demakakos et al., 2019), adolescent pregnancy (Madigan et al., 2014), younger age at menopause (Magnus et al., 2018; Demakakos et al., 2019) and increased risk of

pre-menopause bilateral oophorectomy (Gazzuola Rocca et al., 2017). Despite inconsistent results (Wosu et al., 2015), evidence also indicates that ACE are associated with preterm delivery (Wosu et al., 2015; Selk et al., 2016; Smith et al., 2016; Liu et al., 2018; Cammack et al., 2019) and pregnancy complications (Leeners et al., 2010). The association between ACE and miscarriage has not been studied adequately (Hillis et al., 2004; Abajobir et al., 2018; Li et al., 2018). A US study found a graded association between the ACE score and risk of miscarriage or stillbirth (Hillis et al., 2004), whereas another US study found a positive association between own or family substance abuse problems in childhood and risk of miscarriage (Li et al., 2018). A prospective study of young Australian women also reported associations between neglect and emotional and physical abuse and increased risk of miscarriage (Abajobir et al., 2018).

Based on the biological plausibility of the association of ACE, a major childhood stressor, with miscarriage, the clinical and social relevance of this association and the paucity of evidence about it, we studied whether individual ACE and a summary ACE score were associated with the lifetime risk of single and recurrent miscarriage in a national sample of older English women. Our main aim was to add to the limited evidence on this association and improve our understanding of it. Our objective was to contribute to the discussion about the role of psychosocial factors in miscarriage and bring to the forefront lesser known risk factors such as childhood adversity.

Materials and methods

Study population

Our sample was from the English Longitudinal Study of Aging (ELSA) (www.elsa-project.ac.uk). ELSA is a panel study of English adults aged ≥ 50 years that is designed to be nationally representative. The ELSA baseline interview (wave 1) was in 2002–2003 and included a core sample of 11 391 individuals (6205 women). After the baseline interview, participants were re-interviewed at regular intervals every 2 years and had a health examination every 4 years. The childhood adversity and miscarriage data were collected during the 2007 ELSA Life History Interview. This was a one-off survey that followed the 2006–2007 ELSA follow-up interview (wave 3) and collected retrospective information about the lives of the respondents before joining ELSA.

Of the 7535 individuals, who had participated in ELSA wave 3, 6199 participated in the ELSA Life History Interview, of which 3441 were women. The analytical sample included 2795 women who were aged ≥ 55 years in 2007 after the exclusion of 59 women aged ≥ 90 years, 497 women who did not complete the childhood experiences questionnaire, 38 with missing information on age at menarche (including 2 with age at menarche > 20 years), 1 with missing miscarriage data and

51 with missing values in education and total net household wealth. ELSA has been approved by the London Multi-Centre Research Ethics Committee (MREC/01/2/91) and informed consent has been obtained by the respondents.

Measurement of childhood adversity

All childhood adversity variables were retrospectively measured. We generated a summary ACE score by adding up the following eight binary ACE variables: (i) having lived most of childhood in a single natural mother family, (ii) ever lived in institutions providing residential care for children (such as children's home) or with foster parents, (iii) separation from mother for ≥ 6 months at age ≤ 16 years, (iv) victim of serious physical attack/assault at age ≤ 16 years, (v) victim of sexual assault (including rape or harassment) at age ≤ 16 years, (vi) physically abusive parents at age < 16 years, (vii) parents with substance abuse or mental health problems at age < 16 years and (viii) parents argued or fought very often at age < 16 years. For the purposes of our analyses, we categorized the summary ACE score as follows: 0, 1, 2, ≥ 3 ACE.

The eight ACE variables in our study covered domains that the original ACE study had examined, such as abuse (physical and sexual abuse), household dysfunction (living with parents with substance abuse or mental health problems) and parental separation (separation from mother for ≥ 6 months) (Felitti *et al.*, 1998; Dietz *et al.*, 1999). We also measured experiences of residential and foster care in childhood (ever lived in institutions providing residential care for children or with foster parents), which is an adversity domain that has been included in later ACE measures (Cronholm *et al.*, 2015). Finally, we included two variables (parents fought very often and participants lived most of their childhood in a single mother family) that expand the family relationships/household dysfunction dimension of the original ACE measure (Wade *et al.*, 2014).

Measurement of miscarriage

Information on reproductive history was self-reported and retrospectively collected. After a detailed assessment of pregnancies that ended in live births, respondents were asked to remember all pregnancies that did not result in live birth including any experience of miscarriage. We counted the number of miscarriages experienced by the respondents. Based on the ESHRE guidelines about recurrent miscarriages (ESHRE Guideline Group on RPL *et al.*, 2018), we categorized the miscarriage count into a variable with the following three categories: no miscarriage, one/single miscarriage and recurrent (≥ 2) miscarriages.

Covariates

To account for potential generational differences, we used generation/birth cohort categories (born between 1917 and 1926, 1927 and 1936, 1937 and 1946 and 1947 and 1952) instead of continuous age. We measured the following childhood covariates: age at menarche (that is the age at first menstrual period: ≤ 10 , 11, 12, 13, 14, 15 and ≥ 16 years) and childhood socioeconomic position (SEP) (three variables: experience of severe financial crisis at age ≥ 16 years, paternal or main carer's occupational class at age 14 years and number of books in the household at age 10 years). On the understanding that adult SEP and unhealthy behaviours can be pathways linking ACE with

miscarriage, we measured the following adulthood covariates: education (1, post-secondary education including college and university; 2, completed secondary education or equivalent; 3, no educational qualifications including not having completed secondary education or lower), tertiles of total net household wealth in 2006, smoking history (never, ever or current smoker) and BMI (< 25 , 25 to < 30 and ≥ 30 kg/m^2) and waist circumference (< 80 , 80–87 and ≥ 88 cm) in 2004. We also measured parity (0, 1, 2, ≥ 3 children).

Statistical analyses

Our study was based on secondary analysis of the ELSA data. We examined the bivariate associations between the summary ACE score and each of the covariates (Table I). We also estimated multinomial logistic regression models of the association between the summary ACE score and the risk of miscarriage (0, 1, ≥ 2 miscarriages) (Table II). In terms of modelling, we estimated the unadjusted associations, which we first adjusted for birth cohort and potential childhood confounders: age at menarche and childhood SEP, and then for potential adult pathways including adult SEP, obesity and smoking. In addition, we estimated multinomial logistic regression models of the associations between each of the eight individual ACE variables and the risk of miscarriage (Table III). These were adjusted for birth cohort, age at menarche and childhood SEP. The bivariate associations between each of the eight individual ACE variables and miscarriage categories are presented in the online supplement (Supplementary Table SI).

Results

Women with multiple ACE were more likely to be younger, of lower SEP both in childhood and adulthood, and either childless or with ≥ 3 biological children. They were also more likely to have a history of smoking and early (≤ 10 years) or late menarche (≥ 16 years) (Table I).

The summary ACE score was positively associated with the risk of miscarriage. Compared with women with no ACE, those with ≥ 3 ACE were two times more likely to experience a single miscarriage in their lifetime and more than three times more likely to experience recurrent miscarriages (Table II). Adjustment for childhood confounders explained a relatively small part of the association. Further adjustment for adult SEP also explained a small part of the association, but adjustment for unhealthy behaviours did not affect it. Regarding individual ACE variables, it was experiences of physical and sexual abuse that were associated with increased risk of miscarriage (Table III). Long-term separation from mother was also associated with increased risk of recurrent miscarriages, but this association did not reach statistical significance.

Discussion

Principal findings

In a national sample of English postmenopausal women, we found significant associations between experiences of psychosocial adversity in childhood and the risk of miscarriage. Women with ≥ 3 ACE and

Table I Sample characteristics by summary adverse childhood experience (ACE) score categories^a (N = 2795).

	No ACE (N = 1695)	1 ACE (N = 741)	2 ACE (N = 247)	≥3 ACE (N = 112)	P-value
Age, mean (SD)	68.6 (9.0)	68.8 (8.9)	67.6 (8.2)	65.4 (7.4)	<0.001
Generation/birth cohort (born between), N (%)					0.009
1917–1926	235 (13.8)	86 (11.6)	22 (8.9)	3 (2.7)	
1927–1936	468 (27.6)	252 (34.0)	78 (31.6)	27 (24.1)	
1937–1946	620 (36.6)	243 (32.8)	94 (38.1)	51 (45.5)	
1947–1952	372 (22.0)	160 (21.6)	53 (21.4)	31 (27.7)	
Paternal or main carer's occupation at age 14 years, N (%)					0.009
Managerial, professional, business owner, administration	584 (34.5)	229 (30.9)	77 (31.2)	25 (22.3)	
Sales, trade and care professions	529 (31.2)	211 (28.5)	71 (28.7)	27 (24.1)	
Plant worker, casual jobs, unemployed	521 (30.7)	265 (35.7)	88 (35.6)	48 (42.9)	
Other incl. pensioners, armed forces and missing ^b	61 (3.6)	36 (4.9)	11 (4.5)	12 (10.7)	
Number of books in the household at age 10 years, N (%)					<0.001
Enough to fill ≥two bookcases (>100)	333 (19.6)	138 (18.6)	38 (15.4)	18 (16.1)	
Enough to fill one bookcase (26–100)	530 (31.3)	198 (26.7)	56 (22.7)	20 (17.9)	
Enough to fill one shelf (11–25)	423 (25.0)	164 (22.1)	58 (23.5)	22 (19.6)	
None or very few	357 (21.0)	202 (27.3)	75 (30.3)	36 (32.1)	
Missing/other ^b	52 (3.1)	39 (5.3)	20 (8.1)	16 (14.3)	
Ever experienced severe financial hardship at age ≤16 years, N (%)					<0.001
No	1586 (93.6)	652 (88.0)	209 (84.6)	90 (80.4)	
Yes	32 (1.9)	31 (4.2)	11 (4.5)	7 (6.2)	
Yes (but at an unknown age)	53 (3.1)	45 (6.1)	23 (9.3)	11 (9.8)	
Missing ^b	24 (1.4)	13 (1.7)	4 (1.6)	4 (3.6)	
Education, N (%)					0.20
Post-secondary, including college and university	458 (27.0)	187 (25.2)	58 (23.5)	39 (34.8)	
Secondary	579 (34.2)	248 (33.5)	80 (32.4)	29 (25.9)	
Did not complete secondary education/no educational qualifications	658 (38.8)	306 (41.3)	109 (44.1)	44 (39.3)	
Tertiles of total net non-pension household wealth, N (%)					0.014
Wealthiest tertile (>£295 000) ^c	580 (34.2)	242 (32.7)	78 (31.6)	31 (27.7)	
Intermediate tertile (≤£295 000–>£152 100)	576 (34.0)	237 (32.0)	91 (36.8)	27 (24.1)	
Poorest tertile (≤£152 100)	539 (31.8)	262 (35.3)	78 (31.6)	54 (48.2)	
Smoking history, N (%)					<0.001
Never a smoker	831 (49.0)	318 (42.9)	94 (38.1)	38 (33.9)	
Ex-smoker	625 (36.9)	305 (41.2)	105 (42.5)	42 (37.5)	
Current smoker	239 (14.1)	118 (15.9)	48 (19.4)	32 (27.6)	
BMI, N (%)					0.23
<25 kg/m ² (normal weight) ^d	454 (26.8)	181 (24.4)	58 (23.5)	27 (24.1)	
25 to ≥30 kg/m ² (overweight)	561 (33.1)	265 (35.8)	74 (30.0)	36 (32.1)	
≥30 kg/m ² (obese)	452 (26.7)	198 (26.7)	82 (33.2)	35 (31.3)	
Missing ^b	228 (13.4)	97 (13.1)	33 (13.4)	14 (12.5)	
Waist circumference, N (%)					0.30
<80 cm	306 (18.1)	129 (17.4)	36 (14.6)	19 (17.0)	
80–87 cm	353 (20.8)	148 (20.0)	41 (16.6)	18 (16.1)	
≥88 cm	842 (49.7)	385 (51.9)	141 (57.1)	62 (55.3)	
Missing ^b	194 (11.4)	79 (10.7)	29 (11.7)	13 (11.6)	
Age at menarche (in years of age), N (%)					0.020
≤10	75 (4.4)	35 (4.7)	18 (7.3)	11 (9.8)	
11	275 (16.2)	126 (17.0)	57 (23.2)	15 (13.4)	
12	263 (15.5)	117 (15.8)	31 (12.6)	18 (16.1)	

(continued)

Table I Continued

	No ACE (N = 1695)	1 ACE (N = 741)	2 ACE (N = 247)	≥3 ACE (N = 112)	P-value
13	400 (23.6)	154 (20.8)	49 (19.8)	22 (19.6)	
14	356 (21.0)	171 (23.1)	50 (20.2)	19 (17.0)	
15	208 (12.3)	83 (11.2)	28 (11.3)	11 (9.8)	
≥16	118 (7.0)	55 (7.4)	14 (5.7)	16 (14.3)	
Parity (number of biological children), N (%)					0.009
0	199 (11.7)	96 (13.0)	37 (15.0)	17 (15.2)	
1	222 (13.1)	94 (12.7)	25 (10.1)	8 (7.1)	
2	717 (42.3)	265 (35.8)	92 (37.2)	38 (33.9)	
≥3	557 (32.9)	286 (38.6)	93 (37.7)	49 (43.8)	
Miscarriages					<0.001
0	1362 (80.4)	606 (81.8)	204 (82.6)	70 (62.5)	
1	248 (14.6)	99 (13.4)	31 (12.5)	28 (25.0)	
≥2	85 (5.0)	36 (4.8)	12 (4.9)	14 (12.5)	

^aThe summary ACE score is a composite measure consisting of the following eight ACE variables: (i) having lived most of childhood in a single natural mother family, (ii) ever lived in institutions providing residential care for children or with foster parents), (iii) separation from mother for ≥6 months at age ≤16 years, (iv) victim of serious physical attack/assault at age ≤16 years, (v) victim of sexual assault at age ≤16 years, (vi) physically abusive parents at age <16 years, (vii) parents with substance abuse or mental health problems at age <16 years and (viii) parents argued or fought very often at age <16 years.

^bOther/missing category has not been used in the calculation of the P-value.

^cOn 1 January 2007, the Euro (€) to British Pound (£) exchange rate was: 1.48, and the US Dollar (\$) to British Pound (£) exchange rate was: 1.96.

^dThis category included 15 underweight women: BMI < 18.5 kg/m².

those physically abused in childhood had considerably increased risk for single and recurrent miscarriage, whereas the risk for recurrent miscarriage was also increased for those who were sexually abused in childhood.

Previous evidence

Only a few previous studies examined the association between ACE and miscarriages (Hillis *et al.*, 2004; Abajobir *et al.*, 2018; Li *et al.*, 2018). A study of 2106 US women in mid-pregnancy (16th–27th weeks) reported inconsistent findings (Li *et al.*, 2018). They found a positive association between own or family substance abuse in childhood and the risk of miscarriage but failed to find an association between a cumulative (childhood and adulthood) adversity score and miscarriage. They also did not find any association between childhood abuse and loss of someone close including parental loss and miscarriage. Another US study found a positive association between the ACE score and the risk of foetal death (miscarriage or stillbirth) in 9159 women aged >18 years (mean age: 56 years) who attended a primary care clinic in California (Hillis *et al.*, 2004). Finally, a study of 1980 Australian young women (mean age: 20.6 years) also reported positive associations between neglect and physical, sexual and emotional abuse and the risk of miscarriage (Abajobir *et al.*, 2018). The discrepancy between the findings reported by Li *et al.* (2018) and those from other studies including ours is likely to be related to methodological differences. Li *et al.* (2018) used a selected sample of women in mid-pregnancy that was recruited from multiple clinics over a long period of time. They also examined childhood and adult adversities in combination.

Strengths and limitations

Our study covered an important gap in the literature. Previous studies analysed regional samples in USA and Australia, and there is an absence of evidence on the association between ACE and the risk of miscarriage in UK. The use of ELSA, which is a well-characterized nationally representative study, added strength to our study making our findings more generalizable to the general population of women. The excellent characterization of childhood and adult SEP helped us disentangle the effect of psychosocial adversity on the risk of miscarriage from that of material disadvantage. The use of a standard set of ACE items facilitated the replication of our work by future research.

A weakness of our study is the use of retrospectively measured ACE and miscarriage data. Retrospectively measured ACEs are known to be susceptible to measurement bias (Hardt and Rutter, 2004). Nevertheless, two of our ACE measures (parental separation and having lived in institutional care) have been compared with prospectively collected data and found to have good validity (Jivraj *et al.*, 2017). On the understanding that our study may have misclassified cases of ACE, it is possible that our findings underestimate the magnitude of the association between ACE and miscarriage and are a conservative account of it. In addition, we measured sexual and physical abuse using two victimization questions (ever been a victim of sexual or physical assault) that were not well-defined and thus potentially susceptible to reporting bias. The same applies to the measure of physical abuse by parents; it was not based on a clear definition of physical abuse.

In relation to miscarriage measurement, we did not have access to medical records that might be used to ascertain reports of pregnancy and miscarriage. Nevertheless, our miscarriage data appear to be relatively valid as they are directly comparable to the UK national estimate

Table II The associations between summary adverse childhood experience (ACE) score categories^a and miscarriage risk^b (N = 2795).

	No miscarriage (reference category)	1 miscarriage	≥2 miscarriages
Model A			
No ACE (reference category)	1.00	1.00	1.00
One ACE	1.00	0.90 (0.70–1.15)	0.95 (0.64–1.42)
Two ACEs	1.00	0.84 (0.56–1.25)	0.94 (0.51–1.76)
≥3 ACEs	1.00	2.20 (1.39–3.48) ^c	3.21 (1.73–5.92) ^c
Model B			
No ACE (reference category)	1.00	1.00	1.00
One ACE	1.00	0.88 (0.68–1.13)	0.95 (0.63–1.42)
Two ACEs	1.00	0.79 (0.53–1.19)	0.94 (0.50–1.78)
≥3 ACEs	1.00	2.00 (1.25–3.22) ^d	3.10 (1.63–5.89) ^c
Model C			
No ACE (reference category)	1.00	1.00	1.00
One ACE	1.00	0.86 (0.67–1.12)	0.91 (0.60–1.38)
Two ACEs	1.00	0.79 (0.52–1.19)	0.93 (0.49–1.76)
≥3 ACEs	1.00	1.96 (1.20–3.20) ^d	2.95 (1.52–5.74) ^c

Model A is the unadjusted association.

Model B is adjusted for generation/cohort category (10-year age cohort groups), age at menarche ($\leq 10, 11, 12, 13, 14, 15, \geq 16$ years) and childhood socioeconomic position (experience of severe financial crisis at age ≤ 16 years, paternal or main carer's occupational class at age 14 years, number of books in the household at age 10 years).

Model C is further adjusted for parity (0, 1, 2, ≥ 3 biological children), adult socioeconomic position (education and total net household wealth), smoking history (never a smoker, ex-smoker, current smoker), BMI ($<25, 25$ to <30 and $\geq 30 \text{ kg/m}^2$) and waist circumference ($<80, 80$ – 87 and ≥ 88 cm).

^aThe summary ACE score is a composite measure consisting of the following eight ACE variables: (i) having lived most of childhood in a single natural mother family, (ii) ever lived in institutions providing residential care for children or with foster parents, (iii) separation from mother for ≥ 6 months at age ≤ 16 years, (iv) victim of serious physical attack/assault at age ≤ 16 years, (v) victim of sexual assault at age ≤ 16 years, (vi) physically abusive parents at age <16 years, (vii) parents with substance abuse or mental health problems at age <16 years and (viii) parents argued or fought very often at age <16 years.

^bThe estimates are relative risk ratios (95% CI) and denote the probability of miscarriage in different ACE categories compared with women who reported no ACE (reference category).

^cP ≤ 0.001 .

^dP ≤ 0.05 .

of miscarriages occurring in one in five pregnancies (National Institute for Health and Care Excellence, 2019).

Another potential limitation of our work is the use of data from a sample of older women that were no longer able to reproduce. This might have affected the applicability of our findings to younger generations of women. However, we strongly believe that the biological plausibility and strength of the observed association make this generational mismatch a minor disadvantage of our work.

The decrease in reported ACE with age is not surprising. Older people tend to assess their autobiographical memories more positively. This phenomenon is known as the age-related positivity effect (Reed and Carstensen, 2012). Additional analyses, where we excluded women born before 1927 (aged > 80 years), confirmed that the positivity effect did not bias our findings (see Supplementary Table SII).

As with most observational studies, it was impossible to account for all potential confounders and eliminate the possibility of spurious associations. Nevertheless, we were able to confirm that potentially confounding factors such as childhood SEP and age at menarche did not explain our findings. In the same vein, we did not have data to explore important pathways such as prenatal care and pregnancy-related social and psychological factors (Leeners et al., 2013, 2014). We also lacked biological and physiological data necessary to explore stress-related neuroendocrine and immunological pathways.

Non-response is potentially another source of bias. The overall individual response rate in ELSA wave 3 (after excluding people who died, became institutionalized or migrated) was 73%, with no noticeable gender differences. Eighty-four per cent of responders in ELSA wave 3 participated in the ELSA Life History in 2007 (Scholes et al., 2009), but not all participants completed the childhood adversity questionnaire.

Possible mechanisms for the findings

Evidence highlights the role of advanced maternal age (≥ 40 years) as a major risk factor for miscarriage (Feodor Nilsson et al., 2014; Magnus et al., 2019). It is unlikely though that advanced maternal age can explain our findings as most cases (89.8%) in our study experienced their first miscarriage at age ≤ 35 years.

Childhood socioeconomic disadvantage, in the form of severe financial hardship in childhood, was the only childhood factor that explained a part of the association. The lack of a major confounding role of childhood SEP in the association likely signifies that this association was to a large extent psychosocial in nature and not directly related to one's socioeconomic situation in childhood. This conclusion is corroborated by findings indicating that adult SEP also explained a small part of the association.

Unhealthy behaviours before and during pregnancy are good candidate pathways for explaining the observed associations (Boots and

Table III The associations between individual adverse childhood experience (ACE) variables and miscarriage risk^a (N = 2795).

	No miscarriage (reference category)	1 miscarriage	≥2 miscarriages
Sexual assault at age ≤16 years			
No/missing (reference category)	1.00	1.00	1.00
Yes	1.00	1.31 (0.79–2.18)	2.10 (1.10–4.03) ^b
Physical attack/assault at age ≤16 years			
No/missing (reference category)	1.00	1.00	1.00
Yes	1.00	3.35 (1.36–8.23) ^b	8.22 (3.12–21.65) ^c
Physically abusive parents at age <16 years			
No/missing (reference category)	1.00	1.00	1.00
Yes	1.00	1.34 (0.77–2.33)	2.59 (1.31–5.11) ^b
Spent most of childhood in a single natural mother family			
No/missing (reference category)	1.00	1.00	1.00
Yes	1.00	1.09 (0.70–1.70)	0.97 (0.46–2.06)
Ever lived in institutions providing residential care for children or with foster parents			
No/missing (reference category)	1.00	1.00	1.00
Yes	1.00	0.66 (0.32–1.35)	1.35 (0.56–3.23)
Separation from mother for ≥6 months at age ≤16 years			
No/missing (reference category)	1.00	1.00	1.00
Yes	1.00	1.15 (0.86–1.54)	1.39 (0.88–2.19)
Parental mental health or substance abuse problems at age <16 years			
No/missing (reference category)	1.00	1.00	1.00
Yes	1.00	1.17 (0.76–1.79)	1.06 (0.54–2.11)
Parents argue/fight very often when respondent aged <16 years			
No/missing (reference category)	1.00	1.00	1.00
Yes	1.00	1.08 (0.83–1.41)	1.23 (0.82–1.84)

All models are adjusted for generation/cohort category (10-year age cohort groups), age at menarche (≤10, 11, 12, 13, 14, 15, ≥16 years) and childhood socioeconomic position (experience of severe financial crisis at age ≤16 years, paternal or main carer's occupational class at age 14 years and number of books in the household at age 10 years).

^aThe estimates are relative risk ratios (95% CI) and denote the probability of miscarriage in women in different ACE categories compared with women who reported no ACE (reference category).

^bP ≤ 0.05.

^cP ≤ 0.001.

Stephenson, 2011; Feodor Nilsson *et al.*, 2014; Pineles *et al.*, 2014; Cavalcante *et al.*, 2019). We lacked lifetime information on obesity and alcohol and thus could not assess their mediating effect on the examined associations. Assuming that adult obesity is likely to be related to obesity at earlier stages of the life course, we included in our models current BMI and waist circumference, but neither of these measures affected the associations. The same applied to smoking history; it did not explain any part of the association.

Given the potency of childhood psychosocial adversity as a stressor, the systematic effect of chronic childhood stress on the developing brain (Gunnar and Quevedo, 2007; Lupien *et al.*, 2009) and subsequent dysregulation of the neuroendocrine and immune systems (Hunter *et al.*, 2011; Slopen *et al.*, 2012; Chiang *et al.*, 2015; Elwenspoek *et al.*, 2017; Khoury *et al.*, 2019), we also hypothesized that ACE could be directly related with miscarriage risk via biological pathways. The existence of a direct biological effect is all the more plausible given the association of ACE and childhood experiences of

poor-quality parenting with reproduction-related outcomes including age at menarche (Li *et al.*, 2014; Yermachenko and Dvornyk, 2014; Magnus *et al.*, 2018; Demakakos *et al.*, 2019) and a shorter reproductive lifespan and premature/early menopause (Demakakos *et al.*, 2019). Based on this evidence and evidence highlighting the importance of hormonal and immune factors for reproduction and a healthy pregnancy, we hypothesized that endocrine and inflammation pathways likely mediate the observed association.

Regarding inflammation, an uncomplicated pregnancy is considered to be a state of low-grade inflammation and intravascular coagulation (Cotechini and Graham, 2015). Systematic and local inflammation imbalances can affect key pregnancy processes such as embryo implantation, spiral artery remodelling, uteroplacental perfusion, as well as the immunological tolerance of the pregnancy, and increase the risk of adverse pregnancy outcomes including miscarriage (Christiansen *et al.*, 2008; Cotechini and Graham, 2015). Systematically increased levels of pro-inflammatory cytokines such as the tumour necrosis factor and

some of the interleukins such as interleukin 6 appear to play a key role in pathogenic processes leading to placental insufficiency and increased risk of miscarriage (Calleja-Agius et al., 2009; Prins et al., 2012; Cotechini and Graham, 2015). Childhood adversity is known to be associated with increased levels of pro-inflammatory cytokines in adulthood, especially tumour necrosis factor- α (Baumeister et al., 2015). Another potentially relevant immunological parameter are autoimmune diseases, which are known to be associated with both increased risk of miscarriage (Christiansen et al., 2008) and ACE (Dube et al., 2009).

Experiences of psychosocial adversity in childhood and subsequent dysregulation of the stress response can also affect the endocrine milieu of early pregnancy (Moog et al., 2016; Thomas et al., 2018). Elevated levels of cortisol likely alter the decidual and placental metabolism and threaten the immunological tolerance of the pregnancy (Parker and Douglas, 2010). Moreover, chronic stress and the activation of HPA exert an inhibitory effect on the hypothalamic–pituitary–ovaries axis, which will result in a suppression of the luteinizing hormone (Valsamakis et al., 2019), and subsequently in the suppression of progesterone production by corpus luteum (Parker and Douglas, 2010). Chronic stress might also affect the dopamine–prolactin system and alter prolactin levels (Qu et al., 2017). Lower levels of prolactin are associated with an increased risk of miscarriage (Li et al., 2013). Hypothyroidism, and its common cause, thyroid autoimmunity are known to be related to increased risk of miscarriage (Thangaratinam et al., 2011; Seungdamrong, 2016). Experiences of childhood maltreatment are associated with altered thyroid function in adolescents (Machado et al., 2015) and subclinical hypothyroidism in pregnant women (Moog et al., 2017).

Conclusions

Miscarriage, especially when recurrent, is likely multifactorial. Our findings link unfavourable childhood circumstances and childhood psychosocial adversity with increased risk of single and recurrent miscarriages. They contribute to a better understanding of the pathogenic processes leading to miscarriage over the life course but should be used with caution as our study was observational and the observed associations are not necessarily causal. Given the potency of ACE, as a chronic stressor, and its effect on human development, we postulate that experiences of psychosocial adversity qualify to be a factor that increases the risk of miscarriage via a number of pathways including biological and behavioural ones. Our findings can be used to inform prevention strategies and potentially improve clinical practice through a better identification of women at increased risk for recurrent miscarriages. Awareness of the importance of childhood trauma and a trauma-informed care approach may contribute to the provision of more effective health services to pregnant women and those undergoing fertility treatment. More researches on the association between ACEs and miscarriage risk are needed.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Authors' roles

P.D. conceived and designed the study, had substantial contributions to the analysis and interpretation of the data, drafted the article and approved of the final version to be published. E.L.D. and G.D.M. had substantial contributions to the analysis and interpretation of the data, revised the article critically for important intellectual content article and approved of the final version to be published.

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Conflict of interest

None declared.

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