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Research paper

The association between threatened miscarriage in early pregnancy and depression or anxiety in offspring in late adolescence

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ABSTRACT

Background: Adolescent mental health is a known determinant of health across the lifespan underscoring the importance of identifying determining factors. Threatened miscarriage is a common pregnancy complication, yet its influence on child mental health outcomes is unclear. Here we examined the association between pregnancies complicated by threatened miscarriage and the risk of offspring depression or anxiety in late adolescence using the representative longitudinal UK Millennium Cohort Study.

Methods: Maternal reported data on threatened miscarriage and potential confounders were collected at 9-months postpartum. Data on depression and anxiety were collected as one variable when children were aged 17 years using self-reported doctor diagnosis. Multivariable logistic regression adjusted for several maternal and sociodemographic factors. We examined separate interaction effects for threatened miscarriage and hypertensive disorders of pregnancy, small for gestational age (SGA) and preterm birth.

Results: $N = 9521$ mother-child dyads were included in the analyses, with $n = 574$ (6 %) women experiencing a threatened miscarriage, and 978 (10.3 %) children reported depression or anxiety diagnosis. Adjusted results suggested that threatened miscarriage was associated with a 34 % increase in the odds of depression or anxiety (OR: 1.34, 95 % CI 1.03, 1.73). An interaction effect was observed for threatened miscarriage and SGA (OR: 2.09, 95 % CI: 1.01, 4.36) and threatened miscarriage and preterm birth (OR:2.23, 95 % CI: 1.26, 3.95).

Conclusion: Threatened miscarriage was associated with an increased odds of depression or anxiety in offspring by age 17 years, albeit residual and unmeasured confounding cannot be ruled out. Future research should examine the potential biological mechanisms mediating this association.

1. Introduction

Threatened miscarriage is one of the most prevalent early pregnancy complications affecting up to one-fifth of all pregnancies (Sharma et al., 2020). Threatened miscarriage is characterised by vaginal bleeding before 20 weeks' gestation, with a closed cervix on examination, and no foetal loss (Saraswat et al., 2010; Sharma et al., 2020). There are numerous causes of bleeding in pregnancy with bleeding from the chorionic membrane to the uterine wall being the most prevalent in early pregnancy (van Oppenraaij et al., 2009). Threatened miscarriage is associated with an increase in adverse pregnancy and perinatal outcomes, including preterm delivery, hypertensive disorders of pregnancy (HDP), antepartum haemorrhage, placental abruption, perinatal death and small for gestational age (SGA) infants (Mulik et al., 2004; van Oppenraaij et al., 2009).

Early pregnancy threatened miscarriage occurs during a sensitive period of embryonic development, particularly for early brain development. Moreover, the time at which threatened miscarriage typically occurs is a critical period for neuronal migration in the developing fetal brain. This is necessary for the correct establishment of cortical architecture underlying later higher-order cognitive function (Gressens, 2000). Given the known impacts of adverse prenatal exposures with uteroplacental involvement on neurodevelopmental outcomes in the offspring (Maher et al., 2018, 2020), it is therefore possible that

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threatened miscarriage may alter neurodevelopmental trajectories to increase the risk of adverse mental health outcomes in exposed offspring. In this context, depression and anxiety are the most common mental health disorders globally and are the largest contributors to the health burden experienced by children and adolescents (Erskine et al., 2015). While there is an array of contributing factors to their origins (Wahid et al., 2021), here we examine the hypothesis that prenatal exposure to threatened miscarriage increases the risk of depression and anxiety in affected offspring in late adolescence. This is important as depression and anxiety in childhood and adolescence is known to increase the risk or depression and anxiety and a range of other adverse outcomes in adulthood (Morales-Muñoz et al., 2023).

There is emerging evidence to support this hypothesis. Buckley and colleagues demonstrated using the Millennium Cohort Study that there is an increased odds of neurodevelopmental disorders (in particular autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD)) in offspring at age 14 years that were exposed to threatened miscarriage in utero (Buckley et al., 2024). Moreover, using Danish national registry data, Dudukina and colleagues demonstrated that children exposed to threatened abortion had an increased likelihood of epilepsy and ADHD by age 16 years (Dudukina et al., 2021). To our knowledge, there is limited evidence for any association between maternal threatened miscarriage and the risk of depression or anxiety in adolescence specifically, which is important given their global disease burden. Furthermore, given the known associations between threatened miscarriage and adverse pregnancy and perinatal outcomes (Mulik et al., 2004; van Oppenraaij et al., 2009), it is also important to consider the role that these factors may play when examining a threatened miscarriage-depression/anxiety relationship.

Therefore, the aim of this study was to firstly examine the association between pregnancies complicated by threatened miscarriage and depression or anxiety in the offspring in adolescence (by age 17 years). Secondly, we aimed to examine potential interaction effects of threatened miscarriage and common pregnancy complications including HDP, SGA and preterm birth and examined their associations with depression or anxiety. Thirdly, if any interaction effects were observed for threatened miscarriage and HDP, SGA or preterm birth, we aimed to examine the potential mediating role of these factors.

2. Methods

2.1. Study population

The UK Millennium Cohort Study (MCS) is a nationally representative sample of children born in the UK between September 2000 and January 2002. It used a cluster sample design stratified by UK area (Scotland, England, Wales, and Northern Ireland), electoral ward, ethnic group, and social deprivation (Connelly and Platt, 2014). Sweep one of data collection took place when children were around 9-months old, and follow-ups have currently been conducted at ages 3 years, 5 years, 7 years, 11 years, 14 years and 17 years. The total population at baseline (age 9-months) was 18,552 families (18,827 children). This reduced to 15,590 families at age 3 years, 15,246 at age 5 years, 13,857 at age 7 years, 13,287 at age 11 years, 11,726 at age 14 years, and 10,625 at age 17 years (Centre for Longitudinal Studies, 2019). See Fig. S1 for flow chart of study participants.

2.2. Exposure

When the children were 9-months of age, data on threatened miscarriage during pregnancy was collected via a face-to-face computer-assisted interview. Mothers were asked if they had experienced "any illnesses or problems during their pregnancy requiring medical attention and treatment". If they answered "yes", they were prompted to select all applicable illnesses/problems from a pre-defined list. The list contained, "bleeding or threatened miscarriage in early pregnancy". If this was selected, then threatened miscarriage was assumed.

2.3. Outcome

The outcome of interest was an adolescent diagnosis of depression or anxiety measured at age 17 years collected from the adolescents via self-completion questionnaires. The adolescent was asked "Has a doctor ever told you that you suffer from depression or serious anxiety?", if the response was "yes", then depression or anxiety was assumed diagnosed by a clinical doctor. The MCS used question testing, piloting and dress rehearsals to ensure cohort members understood the questions, were willing to answer them, and provided accurate and valid answers (Fitzsimons et al., 2020).

2.4. Confounding variables

In our primary analysis, we included variables potentially associated with the exposure and outcome of interest and excluded variables that could be potential mediators of the association (See Supplementary Fig. S2 for directed acyclic graph). We considered the following potential confounders, all of which were measured at baseline (when children were aged 9-months):

Maternal age was measured in years and refers to the mother's age at the time of birth. Maternal education refers to the highest level of academic achievement, including diplomas, A-levels, O-levels, and below. Household income was categorised using the Organisation for Economic Co-operation and Development (OECD) income weighted quintiles. A history of maternal depression or anxiety, in which mothers were asked if they ever suffered from depression or anxiety, with a "yes/no" response. Parity was determined by the number of siblings in the home and classified as either primiparous or multiparous. Maternal smoking status, in which mothers were asked about their daily cigarette consumption prior to pregnancy, as well as any changes to their smoking habits throughout pregnancy. This information was recategorized as non-smoker, quit during pregnancy, or smoked throughout pregnancy. Maternal alcohol consumption during pregnancy was categorised as "yes/no". Pre-pregnancy body mass index (BMI) was calculated using self-reported maternal weight and height prior to pregnancy. The variable was re-categorised as underweight, normal weight, overweight, obese, and unknown. Infant sex was categorised as "male/female".

2.5. Interaction terms and mediator variables

Hypertensive disorders of pregnancy (HDP): HDP was categorised as "yes/no". During the survey, participants were asked, "Did you have any illnesses or other problems during your pregnancy that required medical attention or treatment?" If they answered "yes", they were given a list to select from. The list mentioned "Raised blood pressure, eclampsia/pre-eclampsia, or toxaemia." If "yes" was checked, HDP were assumed. *SGA:* SGA was categorised as "yes/no" and was based on maternal reported birthweight less than the 10th percentile for the child's gestational age and sex. *Preterm birth*: Preterm birth was determined based on maternal reporting of the child's gestational age in days. This was translated to weeks and reclassified as <37 weeks' gestation and $\geq$ 37 weeks' gestation.

2.6. Statistical analyses

2.6.1. Primary analyses

Multivariable logistic regression was used to examine the association between threatened miscarriage and depressive or anxiety disorder in offspring at age 17 years and reported unadjusted and adjusted odds ratios (OR) and 95 % confidence intervals (95 % CI). Four models were performed: Model 1 was the unadjusted model. Model 2 controlled for sociodemographic factors including maternal age, maternal education, and household income. Model 3 controlled for maternal and lifestyle

factors including maternal history of depression/anxiety, parity, maternal smoking status, maternal alcohol consumption, pre-pregnancy BMI and infant sex. Model 4 was the fully adjusted analysis, which adjusted for the sociodemographic factors in Model 2 and maternal and lifestyle factors in Model 3. Data were analysed using Stata 18.0.

2.6.2. Subgroup analyses

As depression and anxiety are more prevalent in females than males, we repeated models 1–4 stratified by infant sex (categorised as male or female).

2.6.3. Interaction terms

We conducted three separate analyses and fitted interaction terms for threatened miscarriage and 1) HDP; 2 SGA; and 3) preterm birth and examined their associations with depression or anxiety. For each interaction term, three exposures of interest were included. For example, for the threatened miscarriage and HDP interaction term, the exposure groups were as follows: 1) those exposed to threatened miscarriage only (i.e., excluding those exposed to HDP), 2) those exposed to HDP only (i.e., excluding those exposed to threatened miscarriage), and 3) those exposed to both threatened miscarriage and HDP. The same approach was used for SGA and preterm birth.

2.6.4. Mediation analyses

As a significant interaction was observed between threatened miscarriage and SGA and threatened miscarriage and preterm birth, we conducted mediation analyses using the Stata command **mediate** (potential-outcomes framework), to investigate the mediating role of these factors on the association between threatened miscarriage and depression or anxiety.

2.6.5. Sensitivity analyses

We compared the baseline characteristics of the cohort with the characteristics of those remaining in the study at age 17 years according to exposure to threatened miscarriage. We repeated the models 1–4 among participants with complete-case data on exposure, outcome and confounders to examine the impact of loss to follow-up.

2.6.6. Post-hoc analysis

First, we examined the association between threatened miscarriage and the Kessler Psychological Distress scale (K6) at age 17 years to examine if an association persists when using psychopathology symptoms as our outcome of interest. A binary variable was created defining the K6 cut-off for serious mental illness as a score of ≥13. (Kessler et al., 2010; Palma et al., 2024). Similarly, we also examined the association between threatened miscarriage and the parent-reported and child-reported Strengths and Difficulties Questionnaire (SDQ) at age 17 years. A binary variable was created defining behavioural difficulties as a total SDQ cut-off of ≥17 (Goodman, 1997). A description of the K6 and the SDQ can be found in Methods S1 in the Supplement. Finally, we repeated models 3 and 4 of our primary analysis, using the Rutter Malaise Inventory (RMI-9) to adjust for maternal psychological distress. The RMI-9 was measured at baseline and is a 9-item scale. The participants answered yes or no about how they are feeling generally with regards to being tired, miserable/depressed, worried, rage, scared, upset/irritated, jittery, little things getting on their nerves and whether their heart often races, with a score of ≥4 (out of 9) indicating psychological distress (Schoon et al., 2005; Noonan et al., 2018).

3. Results

After exclusion of multiple births, there were 18,294 singleton mother-child pairs with data on threatened miscarriage included at baseline. A total of 10,331 singleton mother-child pairs remained in the study for the most recent data survey sweep of 17-year-olds, of which 9521 answered the survey question on depression or anxiety and were included in the current analysis. Of these, 574 (6.0 %) experienced threatened miscarriage during pregnancy. There were 978 (10.3 %) offspring with diagnosis of depression or anxiety disorder at age 17 years, of which 303 were male and 675 were female (Table 1).

3.1. Primary analyses

In the unadjusted analysis, (Model 1), the OR for the association between threatened miscarriage and depression or anxiety in offspring by age 17 years was 1.38 [95 % CI 1.08 to 1.78]. This association did not change significantly after adjusting for confounders in Model 4, (adjusted odds ratio (aOR): 1.34 [95 % CI 1.03 to 1.73]) (Table 2).

Table 1
Maternal and child characteristics at age 17 years among Millennium Cohort Study participants (n = 9521).

Characteristics	No threatened miscarriage n = 8947	Threatened miscarriage n = 574
	n (%)	n (%)
Depression/anxiety at age 17 in the offspring		
No	8046 (89.9 %)	497 (86.6 %)
Yes	901 (10.1 %)	77 (13.4 %)
Infant sex		
Male	4351 (48.6)	294 (51.2)
Female	4596 (51.4)	280 (48.8)
Parity		
Nulliparous	3798 (42.5)	257 (44.8)
Multiparous	5149 (57.6)	317 (55.2)
Maternal age, years		
14–19	570 (6.4)	34 (5.9)
20–29	3953 (44.3)	239 (41.7)
30–39	4200 (47.0)	283 (49.3)
≥40	209 (2.3)	18 (3.1)
Maternal education, completed		
Less than O-level	1384 (15.5)	69 (12)
O-Level	3651 (40.8)	256 (44.6)
A-level	911 (10.2)	64 (11.2)
Diploma or above	2713 (30.3)	175 (30.5)
Unknown/missing	288 (3.2)	10 (1.7)
Maternal smoking status		
Non-smoker	6214 (69.5)	405 (70.6)
Quit during pregnancy	1036 (11.6)	79 (13.7)
Smoked during pregnancy	1690 (18.9)	90 (15.7)
Maternal alcohol consumption during pregnancy		
No	6202 (69.4)	383 (66.7)
Yes	2731 (30.6)	191 (33.3)
Maternal pre-pregnancy BMI		
Underweight (<18.5 kg/m^2)	429 (4.8)	22 (3.8)
Normal weight (18.5–24.9 kg/m^2)	5341 (59.7)	356 (62.1)
Overweight (25–29.9 kg/m^2)	1649 (18.4)	117 (20.4)
Obese (30–39 kg/m^2)	728 (8.2)	49 (8.5)
Unknown/missing	800 (8.9)	30 (5.2)
Household income		
Lowest quintile	1792 (20.1)	88 (15.3)
2nd quintile	1872 (20.9)	110 (19.2)
3rd quintile	1700 (19.0)	117 (20.5)
4th quintile	1768 (19.8)	143 (24.9)
Highest quintile	1791 (20.1)	115 (20.1)
Maternal history of depression/serious anxiety (ever)		
No	6931 (77.5)	393 (68.5)
Yes	2009 (22.5)	181 (31.5)
Hypertensive disorder of pregnancy		
No	8327 (93.1)	492 (85.7)
Yes	616 (6.9)	82 (14.3)
Small for gestational age (SGA)		
No	8009 (90.7)	523 (91.6)
Yes	823 (9.3)	48 (8.4)
Preterm birth		
No	8285 (93.7)	492 (86.2)
Yes	555 (6.2)	79 (13.8)

If missing data >3 %, number (%) of missing data reported.

Table 2
Logistic regression examining the association between threatened miscarriage and offspring depression or anxiety by age 17 years among Millennium Cohort Study participants=.

Depression or anxiety	No. of exposed cases	Model 1 OR (95 % CI)[a]	Model 2 OR (95 % CI)[b]	Model 3 OR (95 % CI)[c]	Model 4 OR (95 % CI)[d]
Threatened miscarriage	77	1.38 (1.08 to 1.78)	1.39 (1.09 to 1.79)	1.34 (1.03 to 1.73)	1.34 (1.03 to 1.73)
Subgroup by infant sex					
Threatened miscarriage (males)	27	1.49 (0.99 to 2.26)	1.49 (0.98 to 2.26)	1.47 (0.97 to 2.25)	1.46 (0.97 to 2.24)
Threatened miscarriage (females)	50	1.38 (1.01 to 1.90)	1.39 (1.01 to 1.91)	1.28 (0.92 to 1.76)	1.27 (0.92 to 1.76)

Abbreviations: OR, odds ratio; CI, confidence interval.
Model 1[a]: crude analysis.
Model 2[b]: adjusted for maternal age, maternal education and household income.
Model 3[c]: adjusted for history of maternal depression or anxiety, parity, maternal smoking status, maternal alcohol consumption, pre-pregnancy BMI and infant sex.
Model 4[d]: adjusted for both Model 2[b] and Model 3[c] combined.

3.1.1. Subgroup analysis

Among male offspring, the aOR for the association between threatened miscarriage and depression or anxiety by age 17 years was 1.46 [95 % CI 0.97 to 2.24]. Among female offspring, the association attenuated slightly (aOR 1.27 [95 % 0.92 to 1.76]) (Table 2).

3.2. Interaction terms for HDP, SGA and preterm birth

The aOR among those exposed to threatened miscarriage only (i.e., excluding those exposed to HDP) was 1.41 [95 % CI 1.07 to 1.86] compared to those not exposed to threatened miscarriage or HDP. This reduced to 1.13 [95 % CI 0.57 to 2.24] among those exposed to both threatened miscarriage and HDP (p for interaction: 0.72).

Results of the analysis examining exposure to threatened miscarriage only (i.e., excluding those born SGA) were consistent with our main findings (aOR: 1.28 [0.97 to 1.68)]), while exposure to both threatened miscarriage and SGA resulted in an aOR of 2.09 [95 % CI 1.01 to 4.36] compared to those not exposed to threatened miscarriage or SGA (p for interaction: 0.04).

Finally, when preterm birth was excluded, the aOR for the association between threatened miscarriage and depression or anxiety was 1.22 [95 % CI 0.92 to 1.62]. This increased to 2.23 among those exposed to both threatened miscarriage and born preterm compared to those not exposed to threatened miscarriage and not born preterm (aOR 2.23 [95 % CI 1.26 to 3.95]) (p for interaction: 0.006). (Table 3).

Table 3
Interaction terms examining the association between threatened miscarriage and offspring depression or anxiety by age 17 years among Millennium Cohort Study participants.

	No. of exposed cases	OR (95 % CI)[a]	Adjusted OR (95 % CI)[b]	P for interaction
Interaction term by HDP[c]				
Threatened miscarriage only	67	1.44 (1.10 to 1.88)	1.41 (1.07 to 1.86)	
HDP only	78	1.32 (1.03 to 1.69)	1.28 (0.99 to 1.66)	
Both	10	1.27 (0.65 to 2.46)	1.13 (0.57 to 2.24)	0.72
Interaction term by SGA[d]				
Threatened miscarriage only	67	1.32 (1.01 to 1.72)	1.28 (0.97 to 1.68)	
SGA only	92	1.13 (0.90 to 1.42)	1.05 (0.83 to 1.34)	
Both	10	2.36 (1.17 to 4.76)	2.09 (1.01 to 4.36)	0.04
Interaction term by preterm birth[e]				
Threatened miscarriage only	61	1.27 (0.96 to 1.68)	1.22 (0.92 to 1.62)	
Preterm birth only	64	1.17 (0.89 to 1.53)	1.07 (0.81 to 1.41)	
Both	16	2.28 (1.31 to 3.96)	2.23 (1.26 to 3.95)	0.006

Abbreviations: OR, odds ratio; CI, confidence interval; HDP, hypertensive disorders of pregnancy; SGA, small for gestational age.
[a] Crude analysis.
[b] Adjusted for maternal age, maternal education, household income, history of maternal depression or anxiety, parity, maternal smoking status, maternal alcohol consumption, pre-pregnancy BMI and infant sex.
[c] Reference = not exposed to threatened miscarriage and not exposed to HDP.
[d] Reference = not exposed to threatened miscarriage and not born SGA.
[e] Reference = not exposed to threatened miscarriage and not born preterm.

3.3. Mediation analyses

3.3.1. SGA

The adjusted natural indirect effect (NIE) was 0.99 [95 % CI: 0.98 to 1.01] and estimated the effect of threatened miscarriage on depression or anxiety through being born SGA. The adjusted natural direct effect (NDE) of 1.33 [95 % CI: 1.03 to 1.71] estimated the effect of threatened miscarriage on depression or anxiety through alternative mechanisms to SGA.

3.3.2. Preterm birth

The adjusted NIE of 1.05 [95 % CI: 0.99 to 1.12] estimated the effect of threatened miscarriage on depression or anxiety through preterm birth. The adjusted NDE of 1.26 [95 % CI: 0.97 to 1.63] estimated the effect of threatened miscarriage on depression or anxiety through alternative mechanisms to preterm birth. (Table 4).

3.4. Sensitivity and post-hoc analyses

Supplementary Table S1 compares the baseline characteristics of the cohort to those remaining in the study at age 17 years according to exposure to threatened miscarriage. While characteristics were broadly similar, mothers who remained in the study had higher levels of educational attainment, and higher levels of income. Results of the complete-case analysis (Supplementary Table S2) were not materially different to the main findings (aOR: 1.28 [95 % CI: 0.98 to 1.67]). There were 1538 (16.1 %) offspring categorised as meeting the K6 cut-off for serious mental illness of ≥13, while the aOR examining the association between threatened miscarriage and the K6 was 1.20 [95 % CI: 0.96 to 1.51] (Supplementary Table S3). A total of 893 (10.1 %) and 1628 (17.5 %) offspring were categorised as meeting the total SDQ behavioural difficulties cut-off of ≥17 according to the parent-reported and child-reported SDQ respectively. The aOR examining the association between threatened miscarriage and the parent-reported SDQ was 1.29 [95 % CI: 0.98 to 1.70], while the aOR for threatened miscarriage and the child-reported SDQ was 1.34 [95 % CI: 1.08 to 1.66] (Supplementary

Table 4
Pathway decomposition for small for gestational age (SGA) and preterm birth as a mediator in the relationship between threatened miscarriage and offspring depression or anxiety by age 17 years among Millennium Cohort Study participants.

Mediator	Unadjusted Indirect	Unadjusted Direct		Adjusted Indirect	Adjusted Direct	
	OR (95 % CI)	OR (95 % CI)	% M	OR (95 % CI)	OR (95 % CI)	% M
SGA ($n = 871$)	0.99 (0.98 to 1.01)	1.39 (1.08 to 1.79)	0.01	0.99 (0.98 to 1.01)	1.33 (1.03 to 1.71)	<0.001
Preterm birth ($n = 634$)	1.05 (0.99 to 1.12)	1.31 (1.02 to 1.70)	0.01	1.05 (0.99 to 1.12)	1.26 (0.97 to 1.63)	<0.001

Abbreviations: OR, Odds Ratio; CI, Confidence Intervals; % M, Percentage of mediation.
Adjusted for maternal age, maternal education, household income, history of maternal depression or anxiety, parity, maternal smoking status, maternal alcohol consumption, pre-pregnancy BMI and infant sex.

Table S3). Finally, adjusting for maternal psychological distress using the RMI-9 (Supplementary Table S4) did not materially change results (aOR: 1.41 [95 % CI: 1.09 to 1.82]).

4. Discussion

4.1. Main findings

This study investigated the association between threatened miscarriage and depression or anxiety disorder in adolescent offspring by age 17 years and yielded three principal findings. First, threatened miscarriage was associated with a 34 % increase in the likelihood of depression or anxiety in adolescent offspring by age 17 years. This association remained significant after controlling for several sociodemographic, maternal and lifestyle factors. Second, results suggested an interaction between threatened miscarriage and SGA, as well as threatened miscarriage and preterm birth. Infants exposed to threatened miscarriage and born SGA were over twice as likely to have a diagnosis of depression or anxiety, compared to those not exposed to threatened miscarriage and not born SGA. This result supports findings of previous research that those born SGA have greater mental health problems than non-SGA controls in later life (Grissom and Reyes, 2013; Lahti et al., 2014). Similarly, offspring exposed to threatened miscarriage and preterm birth were over twice as likely to have depression or anxiety in the current study than those unexposed to threatened miscarriage and born at term, which is in line with previous research suggesting that those born preterm display 1.5–2.9 times greater odds of developing depression (Nosarti et al., 2012; Shaw et al., 2023). Third, results of our mediation analysis suggested that the association observed between threatened miscarriage and depression or anxiety were not mediated through SGA or preterm birth.

These findings raise questions of how and why threatened miscarriage would increase the risk of depression or anxiety in the offspring. Firstly, maternal stress may play a role in the observed association. Threatened miscarriage may increase the risk of maternal distress and anxiety, which are associated with later offspring mental health outcomes potentially due to the effects of stress on placental blood flow and maternal glucocorticoid effects on foetal brain development (Welberg and Seckl, 2001; O'Connor et al., 2003; Rice et al., 2010; Harris and Seckl, 2011). Secondly, it is worth considering human brain development as a variable in relation to gestational stage at which the exposure occurs. Threatened miscarriage refers to vaginal bleeding and uterine cramping in an otherwise viable pregnancy before 20 weeks of gestation (Sotiriadis et al., 2004). This is the timeframe of peak neurogenesis of the developing human brain (Semple et al., 2013). Pre-clinical models of uteroplacental insufficiency have been shown to affect neurodevelopmental processes occurring at the time the exposure occurs (Mallard et al., 1998; Liu et al., 2022), which may have structural and functional implications for long-term outcomes. It is important to stress however that these are pre-clinical models with different neurodevelopmental programmes when compared to the human brain, but conceptually it suggests a model whereby threatened miscarriage, may lead to subtle changes in neurodevelopment as a result of placental insufficiency, leading to an increased risk of long-term adverse outcomes in affected offspring. Studying this question in human populations is by its nature very difficult, but structural and functional brain imaging in a prospective cohort of offspring exposure to threatened miscarriage may be informative.

4.2. Strengths and limitations

This study had several strengths. First, we used data from a large, nationally representative cohort of children born in the UK from 2000 to 2002. Second, this cohort contains information on economic, sociodemographic, and perinatal characteristics that prior studies have not consistently accounted for when examining associations between threatened miscarriage and maternal and child outcomes (Saraswat et al., 2010; Wang et al., 2017). This facilitated adjustment of potential confounders, including maternal age, maternal education, household income, a history of maternal depression or anxiety, parity, maternal smoking status, maternal alcohol consumption during pregnancy, pre-pregnancy BMI and infant sex. Third, the combined prevalence of depression or anxiety observed in the current study (10.3 %) is similar to that reported by a large European study assessing over 12,000 adolescents from 11 countries which estimated the prevalence of depression and anxiety disorder to be 10.5 % and 5.8 % respectively (Balázs et al., 2013). Finally, the data allowed us to conduct several sensitivity analyses and to examine interaction terms and potential mediating roles of SGA and preterm birth.

There were also several limitations that should be noted. First, the sample size was reduced from 18,294 mother-child pairs at baseline to 9521 pairs at 17 years, which may introduce bias. However, when the baseline characteristics of the paired cohort were compared to those remaining in the study at age 17 years, the rate of exposure (threatened miscarriage) was consistent with those remaining in the study and those lost to follow-up (Supplementary table S1). In addition, the characteristics of both cohorts were broadly similar, with the exception that the mothers who remained in the study were more educated and had a higher level of income than those who were lost to follow-up. Furthermore, results of the complete-case analysis were also similar to the main findings suggesting that bias due to loss to follow-up may not be major issue in the current study. Second, data on associated confounders were self-reported at 9-months postpartum, which may lead to recall bias. However, there is considerable agreement between self-reported lifestyle factors (e.g. smoking) and prenatal records 4–9 years after delivery (Rice et al., 2007; Skulstad et al., 2017). Moreover, this study's data on potential confounders were obtained 9-months after delivery, which would likely be more accurate than data collected 4–9 years postpartum. Third, the exposure of early pregnancy threatened miscarriage was potentially subject to recall bias, as exposure data were not collected until 9-months postpartum. However, as mothers were asked if their illness or problem during pregnancy required medical attention or treatment, this may improve recall of threatened miscarriage as the encounter may be more memorable to the participant. Additionally, while the rate of exposure observed in the current study (6 %) may be underestimated compared to previously reported estimates of up to 20 % (Sharma et al., 2020), our rate of 6 % is more comparable to the rate of 3.2 % reported in a Danish registry-based cohort which used ICD-coding

to classify threatened miscarriage (Dudukina et al., 2021). Fourth, measurement of depression or anxiety was based on doctor diagnosed self-reported data, collected as one variable. Therefore, we were unable to differentiate between distinct types of depression or anxiety. Fifth, there is an issue with the timing of diagnosis of depression or anxiety in our study. Individuals were asked if they had ever been told by a doctor that they suffer from depression or serious anxiety, therefore this diagnosis may have occurred at any time point between 5 and 17 years. In addition to this, while results of our post-hoc analyses were similar to our main findings and the K6 and SDQ are validated and reliable questionnaires that can be used to identify psychopathology symptoms and aid onward referring, these do not confirm a diagnosis of depression or anxiety. Therefore, future research should examine threatened miscarriage and the trajectory of psychopathology up to 17 years. Lastly, a diagnosis of depression or anxiety are prone to social desirability bias. However, interviewers advised cohort members to complete sensitive questions in a private location away from other household members to ensure confidentiality (Fitzsimons et al., 2020).

5. Conclusion

Pregnancies complicated by threatened miscarriage were associated with an increased likelihood of depression or anxiety in the offspring by late adolescence. While we controlled for a wide range of potential confounding factors, it is not possible to rule out the presence of unmeasured or residual confounding. Future research should examine the potential biological mechanisms observed in this study. This multidisciplinary approach would increase opportunities for establishing causal associations between threatened miscarriage and adverse mental health in offspring, which in turn would allow for more targeted interventions to improve outcomes.

CRediT authorship contribution statement

Ciara Kidd: Writing – original draft, Formal analysis. **David O'Driscoll:** Writing – review & editing, Methodology. **Laura J. O'Byrne:** Writing – review & editing. **Gerard W. O'Keeffe:** Writing – review & editing. **Ali S. Khashan:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Gillian M. Maher:** Writing – original draft, Supervision, Methodology, Formal analysis, Data curation, Conceptualization.

Author statement

Authors CK and GM undertook the statistical analysis. CK and GM drafted the manuscript with support from all authors. All authors edited and provided critical input to improve the manuscript, and all authors approved the submitted version.

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Declaration of competing interest

No conflicts of interest, including financial interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2025.04.060.

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