


Maternal migraine and the risk of psychiatric disorders in offspring: a population-based cohort study

H. Wang^{1,2,*}, H. He^{3,*}, M. Miao⁴, Y. Yu⁵, H. Liu⁶, J. Zhang¹, F. Li^{3,†} and J. Li^{1,2,†} 

Original Article

*These two authors contributed equally to the manuscript and considered as co-first authors.

†These two authors are considered as co-corresponding authors.

Cite this article: Wang H, He H, Miao M, Yu Y, Liu H, Zhang J, Li F, Li J (2021). Maternal migraine and the risk of psychiatric disorders in offspring: a population-based cohort study. *Epidemiology and Psychiatric Sciences* **30**, e55, 1–8. <https://doi.org/10.1017/S2045796021000421>

Received: 28 February 2021

Revised: 10 June 2021

Accepted: 10 June 2021

Keywords:

cohort study; migraine; psychiatric disorders; register-based research

Author for correspondence:

Jiong Li, E-mail: jl@clin.au.dk

¹MOE-Shanghai Key Laboratory of Children's Environmental Health, Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China; ²Department of Clinical Medicine-Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; ³Department of Developmental and Behavioral Pediatric & Child Primary Care, Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China; ⁴NHC Key Lab. of Reproduction Regulation (Shanghai Institute of Planned Parenthood Research), Fudan University, Shanghai, China; ⁵Department of Biostatistics, School of Public Health, and The Key Laboratory of Public Health Safety of Ministry of Education, Fudan University, Shanghai, China and ⁶School of Public Health/Medical Informatics Center, Peking University, Beijing, China

Abstract

Aims. Maternal migraine may contribute to mental health problems in offspring but empirical evidence has been available only for bipolar disorders. Our objective was to examine the association between maternal migraine and the risk of any and specific psychiatric disorders in offspring.

Methods. This population-based cohort study used individual-level linked Danish national health registers. Participants were all live-born singletons in Denmark during 1978–2012 ($n = 2\,069\,785$). Follow-up began at birth and continued until the onset of a psychiatric disorder, death, emigration or 31 December 2016, whichever came first. Cox proportional hazards model was employed to calculate the hazard ratios (HRs) of psychiatric disorders.

Results. Maternal migraine was associated with a 26% increased risk of any psychiatric disorders in offspring [HR, 1.26; 95% confidence interval (CI), 1.22–1.30]. Increased rates of psychiatric disorders were seen in all age groups from childhood to early adulthood. Increased rates were also observed for most of the specific psychiatric disorders, in particular, mood disorders (HR, 1.53; 95% CI, 1.39–1.67), neurotic, stress-related and somatoform disorders (HR, 1.44; 95% CI, 1.37–1.52) and specific personality disorders (HR, 1.47; 95% CI, 1.27–1.70), but not for intellectual disability (HR, 0.84; 95% CI, 0.71–1.00) or eating disorders (HR, 1.10; 95% CI, 0.93–1.29). The highest risk was seen in the offspring of mothers with migraine and comorbid psychiatric disorders (HR, 2.13; 95% CI, 1.99–2.28).

Conclusions. Maternal migraine was associated with increased risks of a broad spectrum of psychiatric disorders in offspring. Given the high prevalence of migraine, our findings highlight the importance of better management of maternal migraine at childbearing ages for early prevention of psychiatric disorders in offspring.

Introduction

Psychiatric disorders affect one in five people (Charlson *et al.*, 2019). The aetiology of psychiatric disorders involves interaction of genetic, environment and lifestyle behaviours (Kraemer *et al.*, 2001). Even though genetic components might be significant contributors to many psychiatric disease, increasing empirical evidence have shown that adverse early-life environment, starting in utero or even before, may increase the lifetime risk of mental health problems (Tegethoff *et al.*, 2011). Research on prenatal origins of those diseases would provide important knowledge for developing more effective prevention strategies, which may open a new era of disease control for mental health problems (O'Donnell and Meaney, 2017).

Migraine is the most common chronic neurovascular disorder, ranking the second leading cause of years of life with disability (Vos *et al.*, 2017; Dodick, 2018). Women are three times more likely to experience migraine than men, and are predominantly affected during their childbearing years (Burch *et al.*, 2018). There is growing concern of the long-term mental health problems in the children born to mothers with migraine (Evans *et al.*, 2005; Kaasbøll *et al.*, 2012; Güngen *et al.*, 2017). Children of mothers with migraine had more psychological and behavioural problems that were assessed through questionnaires in several previous studies (Evans *et al.*, 2005; Kaasbøll *et al.*, 2012; Güngen *et al.*, 2017). It was suggested that maternal migraine may affect offspring psychiatric disorders via altered intrauterine environment in the central nervous system (Burch, 2020). If this hypothesis holds true, we should expect that maternal migraine would be associated with a higher risk of psychiatric disorders in offspring. Only one study examined maternal migraine and bipolar disorder in offspring

© The Author(s), 2021. Published by Cambridge University Press. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted re-use, distribution and reproduction, provided the original article is properly cited.

(Sucksdorff *et al.*, 2016). To our knowledge, no research has provided a comprehensive evaluation of the mental health outcomes of these children exposed to maternal migraine.

We hypothesised that maternal migraine could affect the fetal brain development and consequently mental health in offspring throughout the lifespan (Gandal *et al.*, 2018). The aim of this study was to investigate the association of maternal migraine with any or specific psychiatric disorders in offspring, taking into account the timing of maternal migraine diagnosis and a number of other factors that may affect the association (McLaughlin *et al.*, 2012; Skajaa *et al.*, 2019).

Methods

Study population

We conducted a nationwide cohort study using data from the Danish national registers (Lyng *et al.*, 2011; Mors *et al.*, 2011; Wallach Kildemoes *et al.*, 2011; Schmidt *et al.*, 2015; Bliddal *et al.*, 2018). In Denmark, all live births have a unique personal identification number that permits an accurate linkage of individual-level data. We identified all singleton live births from 1 January 1978 to 31 December 2012 ($n = 2\,105\,712$) from the Danish Medical Birth Registry (Bliddal *et al.*, 2018) and excluded 461 children who had missing or extreme gestational age (<154 days or >315 days), 86 children without information on sex, 28 611 children with chromosomal abnormalities and 6769 children without links to their fathers. The final analysis included 2 069 785 children. We followed them from birth until the date of the first diagnoses of any psychiatric disorders, emigration, death or end of follow-up (31 December 2016), whichever came first. The Danish Data Protection Agency and the Danish Health Data Authority approved this study.

Exposure

Information on maternal migraine before childbirth was obtained from the Danish National Patient Register (DNPR) and the Danish National Prescription Registry (Lyng *et al.*, 2011; Wallach Kildemoes *et al.*, 2011). The DNPR contains data on hospital admissions since 1977 and visits to outpatient clinics since 1995. Diagnoses for migraine are defined according to the *International Classification of Diseases, Eighth Revision (ICD-8)* (1973 to 1993) code: 346 and the *International Classification of Diseases, Tenth Revision (ICD-10)* (1994 and onwards) code: G43 (Schmidt *et al.*, 2015; Adelborg *et al.*, 2018). A migraine case was also defined when the individual had at least two redeemed prescriptions for migraine-specific treatment (Anatomical Therapeutic Chemical (ATC) codes: N02CC (triptans) and N02CA (ergotamine)) (Skajaa *et al.*, 2019). The index date of exposure was the date of the first diagnosis of migraine or the first date of the redeemed prescription, whichever came first.

The outcome of interest

Information on psychiatric disorders was obtained from the DNPR and the Danish Psychiatric Central Research Register (Mors *et al.*, 2011; Schmidt *et al.*, 2015). Our primary outcome was the first diagnosis of a psychiatric disorder using ICD codes (ICD-8 codes from 1977 to 1993: 290–315; ICD-10 codes from 1994: F00–F99), which was further categorised into the following specific diagnostic groups: (1) schizophrenia and related disorders; (2)

mood disorders; (3) neurotic, stress-related and somatoform disorders; (4) eating disorders; (5) specific personality disorders; (6) intellectual disability; (7) pervasive developmental disorders; (8) behavioural and emotional disorders with onset usually occurring in childhood and adolescence (online Supplementary Table 1). When investigating the specific psychiatric disorders, we defined the date of onset as the first day of each specific psychiatric disorder diagnosis, irrespective of other previous psychiatric disorder diagnoses, if existed (Köhler-Forsberg *et al.*, 2019).

Covariates

Based on previous research (McGrath *et al.*, 2014; Nilsson *et al.*, 2017), the following variables were considered as potential confounders: sex of the child (male, female), calendar period of birth (a 5-year interval during 1978–2012), parity (1, 2, or ≥ 3), maternal age at birth (≤ 25 , 26–30, 31–35, ≥ 36 years), paternal age at birth (≤ 25 , 26–30, 31–35, ≥ 36 years), maternal country of origin (Denmark, other countries), maternal education level (0–9, 10–14, ≥ 15 years), maternal cohabitation status (yes, no), maternal psychiatric disorder history (yes, no), paternal psychiatric disorder history (yes, no) and maternal cardiovascular disease (ICD-8 codes: 390–459; ICD-10 codes: I00–I78) (yes, no). The information for maternal education and origin of country was obtained from the Danish Integrated Database for Longitudinal Labor Market Research (Petersson *et al.*, 2011).

Statistical analysis

We used Cox proportional hazards regression model to estimate the hazard ratio (HR) with 95% confidence interval (CI) for the association of maternal migraine with the risk of any or specific psychiatric disorders in offspring. Treating deaths from causes other than psychiatric disorders as competing events, we performed competing risk analysis to estimate cumulative incidences in exposed and unexposed offspring.

In model 1, we adjusted for sex and calendar year of birth. In model 2, we additionally adjusted for parity, parental age at birth, maternal education level, maternal income, maternal origin, maternal cohabitation, paternal migraine, parental psychiatric disorders before the childbirth and maternal cardiovascular disease. In addition, we tested whether the association between maternal migraine and the risk of psychiatric disorders in offspring varied by the sex of the child. We also separated the analyses according to offspring's attained age of psychiatric disorders. Age groups were set using cut-off points that captured potentially relevant development periods: 0–9 years (childhood), 10–18 years (adolescence) and ≥ 19 years (early adulthood) (Svahn *et al.*, 2015).

As migraine is a chronic disease and there might be a lag in time for diagnosis (Weatherall, 2015), we took into consideration the timing of diagnosis (diagnosis before the childbirth, ≤ 2 years after the childbirth, 2–5 years after the childbirth, 5–10 years after the childbirth and >10 years after the childbirth) in separate analyses. We explored whether the risk for psychiatric disorders was different among children born to mothers with the following a priori defined mutually exclusive categories: no migraine and psychiatric disorders (referent), migraine, psychiatric disorders and migraine with psychiatric disorders (the joint effect).

We did several sensitivity analyses. First, in order to examine potential mediating effects of neonatal complications (Higgins *et al.*, 2015), we performed the analyses after excluding children with preterm birth (<37 gestation weeks), low birth weight

(<2500 g) and low Apgar score at 5 min (<7), to see whether the associations would be changed significantly, compared to those overall estimates. Second, due to the change on ICD codes (ICD-10 was adopted since 1994 in Denmark) and the migraine identification strategy (both outpatient diagnosis and prescription registry were available since 1995), we restricted the analysis to offspring born after 1996. Third, owing to the availability of data on maternal smoking (since 1991) and maternal pregnancy body mass index (since 2004), we restricted subanalyses to offspring born after 1991 and 2004, respectively. Fourth, to deal with the problems of missing values on covariates (i.e. maternal education level and cohabitation status), we consequently applied multiple imputation procedure by chained equations to impute ten replications to handle missing values of the confounders. Fifth, to capture the effect of migraine episodes during pregnancy, we additionally performed the analyses by further dividing exposure time window into two periods: prior to index pregnancy and during index pregnancy. Lastly, to better evaluate the mediation effect, we conducted a mediation analysis to determine the proportion of the association between maternal migraine and psychiatric disorders in offspring that was mediated by the potential mediators (preterm birth, low birth weight and low Apgar score at 5 min). The mediators were assessed through multivariable logistic regression models of the outcome and the mediators; these results were then combined to estimate direct and indirect effects (via the mediators), adjusted for all the covariates as in model 2 (VanderWeele, 2016; Kim and VanderWeele, 2019). This mediation method assume that the covariates adjusted could adequately control exposure-outcome, mediator-outcome and exposure-mediator confounding (VanderWeele, 2016). The proportion mediated was calculated as $\log(\text{natural indirect relationship})/\log(\text{total relationship})$. The mediation analyses were conducted using the PARAMED package in STATA. All statistical analyses were performed using STATA, version 15.1 (StataCorp).

Results

Among 2 069 785 participants, 51 717 (2.5%) were born to mothers with migraine. The proportion of offspring born to mothers diagnosed with migraine increased over time (online Supplementary Fig. S1). Table 1 shows the baseline characteristics of children in the exposed and unexposed groups. Compared with unexposed offspring, exposed offspring were more likely to be born preterm, had low birth weight and older parents. Mothers of exposed offspring tended to have a higher level of education, a higher prevalence of comorbid psychiatric disorders or cardiovascular diseases.

The median follow-up time was 19 years (interquartile range: 11–27 years). 277 063 (13.4%) were diagnosed as having any psychiatric disorders. The cumulative incidence of psychiatric disorders was 38.4% (95% CI, 34.4–43.4) for the exposed offspring and 26.2% (95% CI, 26.0–26.4) for the unexposed offspring (Fig. 1). The crude incidence rates of any psychiatric disorders were 8.40 and 6.88 per 1000 person-years among offspring of mothers with migraine and without migraine, respectively. Compared with the unexposed offspring, exposed offspring had a 26% increased risk of any psychiatric disorders (HR, 1.26; 95% CI, 1.22–1.30). There was a tendency that HRs increased with age, with the highest HR (1.34; 95% CI, 1.23–1.46) observed in the early adulthood (Table 2). Stratification by sex of the offspring did not indicate any significant differences (online Supplementary Table 2).

Maternal migraine was associated with most of the specific psychiatric disorders in offspring, for example mood disorders

(HR, 1.53; 95% CI, 1.39–1.67), neurotic, stress-related and somatoform disorders (HR, 1.44; 95% CI, 1.37–1.52) and specific personality disorders (HR, 1.47; 95% CI, 1.27–1.70). Maternal migraine was also associated with an increased risk of behavioural and emotional disorders with onset usually during childhood and adolescence (HR, 1.23; 95% CI, 1.17–1.28). Maternal migraine was not associated with intellectual disability (HR, 0.84; 95% CI, 0.71–1.00) or eating disorders (HR, 1.10; 95% CI, 0.93–1.29) in offspring (Table 3).

We also observed associations between maternal migraine diagnosed after the childbirth and psychiatric disorders in offspring (HR, 1.15; 95% CI, 1.14–1.17). The overall HR is 1.24 (95% CI, 1.18–1.30) when the mother was diagnosed with migraine within 2 years after the childbirth, which is similar to the HR for prenatal exposure. But the HRs decreased over time in offspring of mothers diagnosed migraine within 2–5 years after the childbirth (HR, 1.21; 95% CI, 1.17–1.25), 5–10 years after the childbirth (HR, 1.19; 95% CI, 1.16–1.21) and more than 10 years after the childbirth (HR, 1.13; 95% CI, 1.11–1.14) (Fig. 2).

The highest overall risk of psychiatric disorders was observed in offspring of mothers with both migraine and comorbid psychiatric disorders (HR, 2.13; 95% CI, 1.99–2.28), comparing to offspring of mothers with migraine only (HR, 1.28; 95% CI, 1.24–1.32) (Table 4).

When excluding offspring with adverse birth outcomes such as preterm birth, low birth weight and low Apgar score, the estimates remained unchanged (online Supplementary Table 3). Similar associations were observed in the analyses restricted to offspring born after 1991, 1996 or 2004, respectively, and when we use the multiple imputation for missing values of the covariates (online Supplementary Tables 4–7). We observed that the associations between maternal migraine and psychiatric disorders in offspring were similar for maternal migraine diagnosed prior to the index pregnancy and diagnosed during the index pregnancy (online Supplementary Table 8). Adverse birth outcomes probably accounted for only a very small proportion (0.10–1.95%) of the association between maternal migraine and risk of psychiatric disorders (online Supplementary Table 9).

Discussion

In this large population-based cohort study, we found that maternal migraine was associated with an increased risk of any psychiatric disorders in offspring from childhood to early adulthood. Prenatal exposure to maternal migraine was associated with most specific psychiatric disorders, in particular, mood disorders, neurotic, stress-related and somatoform disorders and personality disorders. The highest risk of psychiatric disorders was observed in offspring of mothers with migraine and comorbid psychiatric disorders before childbirth.

Interpretation of results and comparison with other studies

To our knowledge, the association between maternal migraine and risk of psychiatric disorders in offspring has only been investigated in a Finnish Prenatal study of Bipolar disorders (FIPS-B), in which a 1.5-fold risk of bipolar disorders in offspring was reported (Sucksdorff *et al.*, 2016). Consistently, we observed a similar magnitude of association between maternal migraine and mood disorders (including bipolar disorder) in offspring. However, in the Finnish study the information on psychiatric disorders was only available on bipolar disorders (Sucksdorff *et al.*,

Table 1. Characteristics of the study population born between 1978 and 2012 at birth according to maternal migraine status

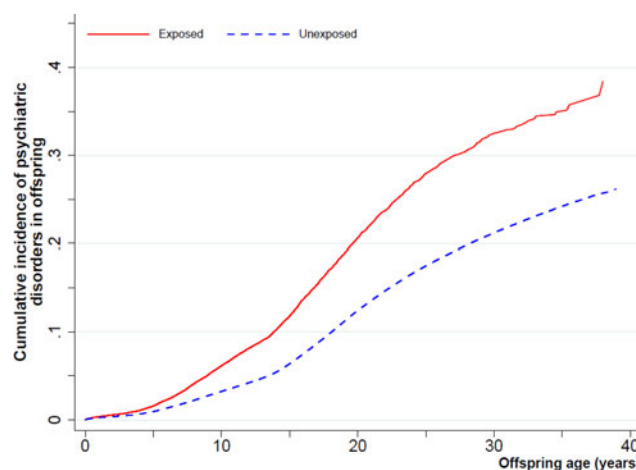
Characteristics	Maternal migraine status	
	Migraine <i>n</i> = 51 717	No migraine <i>n</i> = 1 800 517
Sex		
Boys	26 388 (51.0)	923 760 (51.3)
Girls	25 329 (49.0)	876 757 (48.7)
Preterm		
No	47 987 (92.8)	1 651 645 (91.7)
Yes	2974 (5.7)	81 886 (4.6)
Missing	756 (1.5)	66 991 (3.7)
Low birth weight		
No	48 816 (94.4)	1 705 162 (94.7)
Yes	2043 (3.9)	68 594 (3.8)
Missing	858 (1.7)	26 761 (1.5)
Apgar score at 5 minutes		
10	47 073 (91.0)	1 647 627 (91.5)
7–9	3442 (6.6)	108 597 (6.0)
0–6	386 (0.8)	15 063 (0.9)
Missing	816 (1.6)	29 230 (1.6)
Maternal age (years)		
≤ 25	7383 (14.3)	484 928 (26.9)
26–30	18 421 (35.6)	684 346 (38.0)
31–35	17 723 (34.3)	463 094 (25.7)
> 36	8190 (15.8)	168 149 (9.4)
Paternal age (years)		
≤ 25	3966 (7.7)	248 106 (13.8)
26–30	14 158 (27.3)	570 602 (31.7)
31–35	18 075 (35.0)	540 076 (30.0)
> 36	14 799 (28.6)	364 472 (20.2)
Missing	719 (1.4)	77 261 (4.3)
Maternal education level		
0–9	9817 (20.0)	490 319 (27.2)
10–14	24 153 (46.7)	786 075 (43.7)
≥ 15	17 444 (33.7)	493 488 (27.4)
Missing	303 (0.6)	30 635 (1.7)
Maternal psychiatric disorders		
No	46 818 (90.5)	1 731 179 (96.1)
Yes	4899 (9.5)	69 338 (3.9)
Paternal psychiatric disorders		
No	49 017 (94.8)	1 738 192 (96.5)
Yes	2700 (5.2)	62 325 (3.5)
Maternal original		
Born in Denmark	47 603 (92.0)	1 603 856 (89.1)

(Continued)

Table 1. (Continued.)

Characteristics	Maternal migraine status	
	Migraine <i>n</i> = 51 717	No migraine <i>n</i> = 1 800 517
Not born in Denmark	4103 (7.9)	192 006 (10.7)
Missing	11 (0.1)	4655 (0.2)
Maternal cohabitation status		
Yes	27 873 (53.9)	1 005 508 (55.8)
No	23 843 (46.1)	793 348 (44.1)
Missing	NA	1661 (0.1)
Maternal cardiovascular disease		
No	48 630 (94.0)	1 761 410 (97.8)
Yes	3087 (6.0)	39 107 (2.2)

Expresses as frequency (percentage); NA indicates less than three.

**Fig. 1.** Cumulative incidence of overall psychiatric disorders among offspring exposed versus unexposed to maternal migraine.

2016). To our knowledge, our study provided the novel evidence that offspring of mothers with migraine tended to be at an increased risk of any psychiatric disorders, persisting from childhood into early adulthood. Maternal migraine may lead to hypothalamic–pituitary–adrenal dysfunction (Galletti *et al.*, 2009), fluctuating hormone and oxidative stress (Bernecker *et al.*, 2011; Aggarwal *et al.*, 2012; Neri *et al.*, 2015), which can result in sub-optimal intrauterine environment. Changes in the intrauterine environment could have a long-lasting effect on fetal brain development and, thus, increase the susceptibility to psychiatric disorders over the lifespan (Weinstock, 2005; O'Donnell and Meaney, 2017). Our study showed that maternal migraine diagnosed after the childbirth, especially diagnosed with migraine within 2 years after the childbirth, was associated with overall increased risk of psychiatric disorders in offspring. This is plausible because migraine may already be present for a period of time before the diagnosis (Wessman *et al.*, 2007). As expected, the effect sizes associated postnatal exposure to maternal migraine decreased over time, supporting the programming effect of intrauterine environment on psychiatric disorders. On the other hand, we

Table 2. Incidence rate and HRs of all psychiatric disorders in offspring according to maternal migraine status

	No. of offspring with psychiatric disorders	Rate per 1000 person-years	HR (95% CI)	HR (95% CI)
			Model 1	Model 2
Offspring psychiatric disorders				
Attained ages 0–39 years				
No maternal migraine	271 843	6.88	1 (Reference)	1 (Reference)
Maternal migraine	5099	8.40	1.32 (1.28–1.36)	1.26 (1.22–1.30)
Attained ages 0–9 years				
No maternal migraine	52 112	3.05	1 (Reference)	1 (Reference)
Maternal migraine	2216	5.41	1.26 (1.21–1.32)	1.22 (1.17–1.27)
Attained ages 10–18 years				
No maternal migraine	118 147	8.81	1 (Reference)	1 (Reference)
Maternal migraine	2309	13.97	1.32 (1.27–1.38)	1.26 (1.21–1.31)
Attained ages 19–39 years				
No maternal migraine	101 584	11.21	1 (Reference)	1 (Reference)
Maternal migraine	574	17.73	1.44 (1.32–1.56)	1.34 (1.23–1.46)

Model 1 adjusted for sex, birth year; Model 2 additionally adjusted for parity, maternal characteristic (age, education level, origin, cohabitation, cardiovascular diseases), paternal age, paternal migraine and parental psychiatric disorders before the childbirth.

Table 3. Incidence rate and HR of specific psychiatric disorders in offspring according to maternal migraine status

	No of offspring with psychiatric disorders	Rate per 1000 person-years	HR (95% CI)	HR (95% CI)
			Model 1	Model 2
Schizophrenia and related disorders				
No maternal migraine	19 251	0.84	1 (Reference)	1 (Reference)
Maternal migraine	166	0.89	1.30 (1.11–1.51)	1.21 (1.03–1.42)
Mood disorders				
No maternal migraine	45 608	2.02	1 (Reference)	1 (Reference)
Maternal migraine	485	2.61	1.61 (1.47–1.76)	1.53 (1.39–1.67)
Neurotic, stress-related and somatoform disorders				
No maternal migraine	98 606	3.16	1 (Reference)	1 (Reference)
Maternal migraine	1455	3.90	1.52 (1.44–1.60)	1.44 (1.37–1.52)
Eating disorders				
No maternal migraine	14 458	0.63	1 (Reference)	1 (Reference)
Maternal migraine	153	0.82	1.13 (0.96–1.33)	1.10 (0.93–1.29)
Specific personality disorders				
No maternal migraine	24 076	1.58	1 (Reference)	1 (Reference)
Maternal migraine	200	2.52	1.58 (1.38–1.82)	1.47 (1.27–1.70)
Intellectual disability				
No maternal migraine	9258	0.22	1 (Reference)	1 (Reference)
Maternal migraine	144	0.23	0.86 (0.73–1.02)	0.84 (0.71–1.00)
Pervasive developmental disorders				
No maternal migraine	25 375	0.61	1 (Reference)	1 (Reference)
Maternal migraine	865	1.37	1.15 (1.07–1.23)	1.10 (1.03–1.18)
Behavioural and emotional disorders ^a				
No maternal migraine	61 887	1.77	1 (Reference)	1 (Reference)
Maternal migraine	2193	2.44	1.28 (1.22–1.33)	1.23 (1.17–1.28)

^aBehavioural and emotional disorders with onset usually occurring in childhood and adolescence; Model 1 adjusted for sex, birth year; Model 2 additionally adjusted for parity, maternal characteristic (age, education level, origin, cohabitation, cardiovascular diseases), paternal age, parental psychiatric disorders before the childbirth.

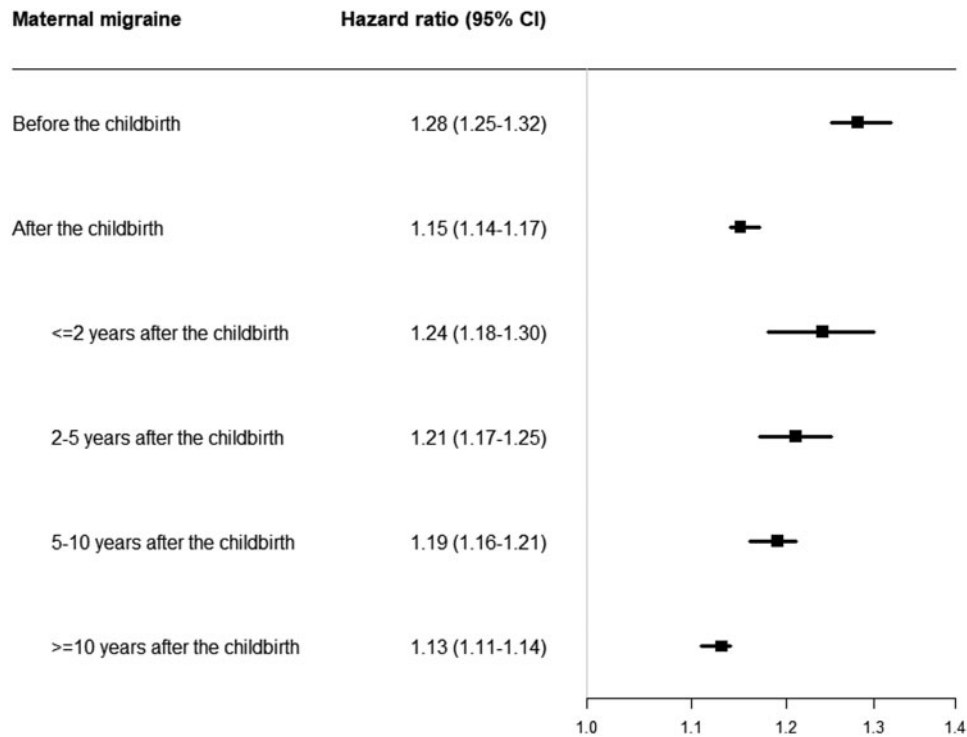


Fig. 2. Hazard ratio and 95% CI for overall psychiatric disorders according to the timing of maternal migraine diagnosed.

Table 4. Joint effect of maternal migraine and maternal psychiatric disorders before the childbirth on psychiatric disorders in offspring

Exposure	No. of offspring with psychiatric disorders	Rate per 1000 person-years	HR (95% CI)	
			Model 1	Model 2
No maternal migraine and psychiatric disorders	253 699	6.65	1 (Reference)	1 (Reference)
Maternal migraine only	4239	7.79	1.29 (1.25–1.33)	1.28 (1.24–1.32)
Maternal psychiatric disorders only	18 144	12.99	2.13 (2.10–2.16)	1.81 (1.78–1.84)
Joint effect of maternal migraine and psychiatric disorder	860	13.57	2.46 (2.30–2.63)	2.13 (1.99–2.28)

Model 1 adjusted for sex, birth year; Model 2 additionally adjusted for parity, maternal characteristic (age, education level, origin, cohabitation, cardiovascular diseases), paternal age, paternal psychiatric disorders before the childbirth.

could not rule out the possibility that the observed association could be partly explained by the shared environmental risk factors (Sucksdorff *et al.*, 2016).

Furthermore, we also observed that maternal migraine was associated with increased risks of most subtypes of psychiatric disorders in offspring, for example, mood disorders, neurotic, stress-related and somatoform disorders. Different types of psychiatric disorders may share common pathogenic mechanisms (Insel and Wang, 2010). For example, similar high level of transcriptomic overlap has been observed among mood disorders, personality disorders and pervasive developmental disorders (Gandal *et al.*, 2018). Genome-wide analysis studies have also revealed substantial genetic overlap among different psychiatric disorders (Anttila *et al.*, 2018; Martin *et al.*, 2018). Moreover, shared neurocognitive endophenotypes, such as deficits in executive function, processing speed and working memory, have been described in most psychiatric disorders (McTeague *et al.*, 2016).

We observed a two-fold increased risk of psychiatric disorders in offspring of mothers with both migraine and comorbid

psychiatric disorders before the childbirth. The FIPS-B study also reported that the greatest risk was observed in offspring of parents with comorbid migraine and bipolar disorders (Sucksdorff *et al.*, 2016). Even if the biological mechanism of coexisting maternal migraine and psychiatric disorders during pregnancy is unknown, genetic component can contribute to the highest incidence rate of psychiatric disorders in offspring (Wessman *et al.*, 2007). Another possible explanation could be that mothers with co-morbid migraine and psychiatric disorders have a higher level of psychological stress (Minen *et al.*, 2016). As a result, offspring may be exposed to more severe psychological stress *in utero*, which is associated with an increased risk of psychiatric disorders (Tegethoff *et al.*, 2011; MacKinnon *et al.*, 2018). Additionally, if the women diagnosed with migraine before the childbirth, she may exhibit increased circulating concentrations of inflammatory markers and could be aggravated by psychiatric disorders (Vanmolkot and De Hoon, 2007; Saunders *et al.*, 2014); maternal inflammation has been proposed to play a role in the development of psychiatric disorders in offspring (Estes and McAllister, 2016). Further studies to elucidate the underlying biological pathways are warranted.

Strengths and limitations of this study

Our study has several strengths. First, the present study is the first to examine the association of maternal migraine and psychiatric disorders in offspring using the entire population in a country (Denmark). The nature of register data minimises the possibility of recall and selection bias. Second, we had detailed information on parental psychiatric disorders, family socioeconomic status and maternal cardiovascular diseases. Adjustment for these potential confounders could allow us to disentangle the effect of maternal migraine on psychiatric disorders in offspring from the effects of these potential confounders. Third, we had a long follow-up with a maximum of age 39 years. Thus, we can investigate not only psychiatric disorders manifested in childhood or adolescence, but also psychiatric disorders such as schizophrenia spectrum disorders, mood disorders and adult personality disorders that are often diagnosed in adulthood (Kessler *et al.*, 2007).

Our findings should be interpreted with caution due to several limitations. First, as in other observational studies there may still be potential residual confounding that could not be entirely eliminated (Fewell *et al.*, 2007). For example, maternal pre-pregnancy body mass index, a risk factor for offspring psychiatric disorders (Mackay *et al.*, 2017), might confound the observed association. However, additionally adjusting for pre-pregnancy BMI in women with available data did not change our results (shown in online Supplementary Table 6). Second, migraine was identified using a combination of hospitalisation registers and national prescription system, and the prevalence of migraine in our study is similar to another Danish population study (Le *et al.*, 2012). However, the information on outpatient contact and medicine prescription were not available until 1995. This would lead to under diagnosis of maternal migraine before 1995, and some of them could be identified as postnatal migraine after 1995, which may underestimate the effect of prenatal exposure to migraine. Third, we could not rule out possible detection bias (Delgado-Rodriguez and Llorca, 2004). Children whose mothers with migraine are more likely to be in close contact with medical care than the unexposed children because of increased medical awareness, which might increase the opportunities to be diagnosed with psychiatric disorders. However, when investigating the specific psychiatric disorders with onset at different ages, varied risk estimates were observed. Thus, detection bias is unlikely to explain the association of maternal migraine with psychiatric disorders in offspring. Fourth, we chose not to adjust for perinatal factors such as preterm birth and low birth weight, as it has been shown that such adjustment may introduce bias (Hernández-Díaz *et al.*, 2006). Furthermore, these neonatal characteristics could be potential mediators in the pathway from maternal migraine and psychiatric disorders in offspring (Mathewson *et al.*, 2017; Skajaa *et al.*, 2019). Nevertheless, our findings showed that the elevated risk of psychiatric disorders in offspring was not attenuated after excluding children of preterm birth, low birth weight or low Apgar score, as shown in the sensitivity analysis.

Conclusion and policy implications

This study provides important information about offspring's mental well-being affected by maternal migraine using data from the Danish national registers. Given the high prevalence of migraine, especially among women at reproductive ages, our finding stands as strong evidence for concrete actions to be better management of women with migraine at reproductive ages and to screen mental health problems in their children.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S2045796021000421>.

Data. All data are stored at the secure platform of Denmark Statistics, which is the central authority on Danish Statistics with the mission to collect, compile and publish statistics on the Danish society. Due to restrictions related to Danish law and protecting patient privacy, the combined set of data as used in this study can only be made available through a trusted third party, Statistics Denmark (<http://www.dst.dk/en/kontakt>).

Acknowledgements. None.

Author contributions. H.W. and H.H.: performed the literature review, conducted data analysis, interpreted findings and drafted the manuscript. F.L. and J.L.: conceptualised ideas, designed and directed analytic strategy, interpreted findings, revised drafts of the manuscript and supervised the study from conception to completion. All other authors: interpreted of data and revised of the manuscript for important intellectual content. All authors approved the final version.

Financial support. This work was supported by grants from the National Natural Science Foundation of China (No. 81703237, No. 81530086, No. 82073570 and No. 81761128035), the Novo Nordisk Foundation (NNF18OC0052029), the Danish Council for Independent Research (DFR-6110-00019B, DFR-9039-00010B and DFR-1030-00012B), the Nordic Cancer Union (R275-A15770), Karen Elise Jensens Fond (2016), Collaborative Innovation Program of Shanghai Municipal Health Commission (2020CXJQ01) and Xinhua Hospital of Shanghai Jiao Tong University School of Medicine (2018YJRC03).

Conflict of interest. None declared.

Ethical standards. The study was approved by the Danish Data Protection Agency (No 2013-41-2569). According to Danish legislation, no informed consent is required for a registry-based study using anonymised data.

Patient and public involvement. No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study patients or the relevant patient community.

References

- Adelborg K, Szépligeti SK, Holland-Bill L, Ehrenstein V, Horváth-Puhó E, Henderson VW and Sørensen HT (2018) Migraine and risk of cardiovascular diseases: Danish population based matched cohort study. *BMJ (Clinical Research Ed.)* **360**, k96.
- Aggarwal M, Puri V and Puri S (2012) Serotonin and CGRP in migraine. *Annals of Neurosciences* **19**, 88.
- Anttila V, Bulik-Sullivan B, Finucane HK, Walters RK, Bras J, Duncan L, Escott-Price V, Falcone GJ, Gormley P and Malik R (2018) Analysis of shared heritability in common disorders of the brain. *Science (New York, N.Y.)* **360**, eaap8757.
- Bernecker C, Ragginer C, Fauler G, Horejsi R, Möller R, Zelzer S, Lechner A, Wallner-Blazek M, Weiss S and Fazekas F (2011) Oxidative stress is associated with migraine and migraine-related metabolic risk in females. *European Journal of Neurology* **18**, 1233–1239.
- Bliddal M, Broe A, Pottegard A, Olsen J and Langhoff-Roos J (2018) The Danish medical birth register. *European Journal of Epidemiology* **33**, 27–36.
- Burch R (2020) Epidemiology and treatment of menstrual migraine and migraine during pregnancy and lactation: a narrative review. *Headache: The Journal of Head and Face Pain* **60**, 200–216.
- Burch R, Rizzoli P and Loder E (2018) The prevalence and impact of migraine and severe headache in the United States: figures and trends from government health studies. *Headache* **58**, 496–505.
- Charlson F, van Ommeren M, Flaxman A, Cornett J, Whiteford H and Saxena S (2019) New WHO prevalence estimates of mental disorders in

- conflict settings: a systematic review and meta-analysis. *The Lancet* **394**, 240–248.
- Delgado-Rodriguez M and Llorca J** (2004) Bias. *Journal of Epidemiology & Community Health* **58**, 635–641.
- Dodick DW** (2018) Migraine. *Lancet (London, England)* **391**, 1315–1330.
- Estes ML and McAllister AK** (2016) Maternal immune activation: implications for neuropsychiatric disorders. *Science (New York, N.Y.)* **353**, 772–777.
- Evans S, Shipton EA and Keenan TR** (2005) Psychosocial functioning of mothers with chronic pain: a comparison to pain-free controls. *European Journal of Pain* **9**, 683–690.
- Fewell Z, Davey Smith G and Sterne JA** (2007) The impact of residual and unmeasured confounding in epidemiologic studies: a simulation study. *American Journal of Epidemiology* **166**, 646–655.
- Galletti F, Cupini LM, Corbelli I, Calabresi P and Sarchielli P** (2009) Pathophysiological basis of migraine prophylaxis. *Progress in Neurobiology* **89**, 176–192.
- Gandal MJ, Haney JR, Parikshak NN, Leppa V, Ramaswami G, Hartl C, Schork AJ, Appadurai V, Buil A and Werge TM** (2018) Shared molecular neuropathology across major psychiatric disorders parallels polygenic overlap. *Science (New York, N.Y.)* **359**, 693–697.
- Güngen BD, Aras YG, Gül SS, Acar T, Ayaz AB, Alagöz AN and Acar BA** (2017) The effect of maternal migraine headache on their children's quality of life. *Acta Neurologica Belgica* **117**, 687–694.
- Hernández-Díaz S, Schisterman EF and Hernán MA** (2006) The birth weight “paradox” uncovered? *American Journal of Epidemiology* **164**, 1115–1120.
- Higgins KS, Birnie KA, Chambers CT, Wilson AC, Caes L, Clark AJ, Lynch M, Stinson J and Campbell-Yeo M** (2015) Offspring of parents with chronic pain: a systematic review and meta-analysis of pain, health, psychological, and family outcomes. *Pain* **156**, 2256.
- Insel TR and Wang PS** (2010) Rethinking mental illness. *Jama* **303**, 1970–1971.
- Kaasbøll J, Lydersen S and Indredavik MS** (2012) Psychological symptoms in children of parents with chronic pain—the HUNT study. *PAIN®* **153**, 1054–1062.
- Kessler RC, Amminger GP, Aguilar-Gaxiola S, Alonso J, Lee S and Ustun TB** (2007) Age of onset of mental disorders: a review of recent literature. *Current Opinion in Psychiatry* **20**, 359.
- Kim ES and VanderWeele TJ** (2019) Mediators of the association between religious service attendance and mortality. *American Journal of Epidemiology* **188**, 96–101.
- Köhler-Forsberg O, Petersen L, Gasse C, Mortensen PB, Dalsgaard S, Yolken RH, Mors O and Benros ME** (2019) A nationwide study in Denmark of the association between treated infections and the subsequent risk of treated mental disorders in children and adolescents. *JAMA Psychiatry* **76**, 271–279.
- Kraemer HC, Stice E, Kazdin A, Offord D and Kupfer D** (2001) How do risk factors work together? Mediators, moderators, and independent, overlapping, and proxy risk factors. *American Journal of Psychiatry* **158**, 848–856.
- Le H, Tfelt-Hansen P, Skytthe A, Kyvik KO and Olesen J** (2012) Increase in self-reported migraine prevalence in the Danish adult population: a prospective longitudinal population-based study. *BMJ Open* **2**, e000962.
- Lyng E, Sandegaard JL and Rebolj M** (2011) The Danish national patient register. *Scandinavian Journal of Public Health* **39**, 30–33.
- Mackay E, Dalman C, Karlsson H and Gardner RM** (2017) Association of gestational weight gain and maternal body mass index in early pregnancy with risk for nonaffective psychosis in offspring. *JAMA Psychiatry* **74**, 339–349.
- MacKinnon N, Kingsbury M, Mahedy L, Evans J and Colman I** (2018) The association between prenatal stress and externalizing symptoms in childhood: evidence from the avon longitudinal study of parents and children. *Biological Psychiatry* **83**, 100–108.
- Martin J, Taylor MJ and Lichtenstein P** (2018) Assessing the evidence for shared genetic risks across psychiatric disorders and traits. *Psychological Medicine* **48**, 1759–1774.
- Mathewson KJ, Chow CH, Dobson KG, Pope EI, Schmidt LA and Van Lieshout RJ** (2017) Mental health of extremely low birth weight survivors: a systematic review and meta-analysis. *Psychological Bulletin* **143**, 347.
- McGrath JJ, Petersen L, Agerbo E, Mors O, Mortensen PB and Pedersen CB** (2014) A comprehensive assessment of parental age and psychiatric disorders. *JAMA Psychiatry* **71**, 301–309.
- McLaughlin KA, Gadermann AM, Hwang I, Sampson NA, Al-Hamzawi A, Andrade LH, Angermeyer MC, Benjet C, Bromet EJ and Bruffaerts R** (2012) Parent psychopathology and offspring mental disorders: results from the WHO World Mental Health Surveys. *The British Journal of Psychiatry* **200**, 290–299.
- McTeague LM, Goodkind MS and Etkin A** (2016) Transdiagnostic impairment of cognitive control in mental illness. *Journal of Psychiatric Research* **83**, 37–46.
- Minen MT, De Dhaem OB, Van Diest AK, Powers S, Schwedt TJ, Lipton R and Silbersweig D** (2016) Migraine and its psychiatric comorbidities. *Journal of Neurology Neurosurgery & Psychiatry* **87**, 741–749.
- Mors O, Perto GP and Mortensen PB** (2011) The Danish psychiatric central research register. *Scandinavian Journal of Public Health* **39**, 54–57.
- Neri M, Frustaci A, Milic M, Valdiglesias V, Fini M, Bonassi S and Barbanti P** (2015) A meta-analysis of biomarkers related to oxidative stress and nitric oxide pathway in migraine. *Cephalalgia* **35**, 931–937.
- Nilsson SF, Laursen TM, Hjorthøj C, Thorup A and Nordentoft M** (2017) Risk of psychiatric disorders in offspring of parents with a history of homelessness during childhood and adolescence in Denmark: a nationwide, register-based, cohort study. *The Lancet Public Health* **2**, e541–e550.
- O'Donnell KJ and Meaney MJ** (2017) Fetal origins of mental health: the developmental origins of health and disease hypothesis. *American Journal of Psychiatry* **174**, 319–328.
- Petersson F, Baadsgaard M and Thygesen LC** (2011) Danish registers on personal labour market affiliation. *Scandinavian Journal of Public Health* **39**, 95–98.
- Saunders EF, Nazir R, Kamali M, Ryan KA, Evans S, Langenecker S, Gelenberg AJ and McInnis MG** (2014) Gender differences, clinical correlates and longitudinal outcome of bipolar disorder with co-morbid migraine. *The Journal of Clinical Psychiatry* **75**, 512.
- Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L and Sørensen HT** (2015) The Danish National Patient Registry: a review of content, data quality, and research potential. *Clinical Epidemiology* **7**, 449.
- Skajaa N, Szepliget SK, Xue F, Sorensen HT, Ehrenstein V, Eisele O and Adelborg K** (2019) Pregnancy, birth, neonatal, and postnatal neurological outcomes after pregnancy with migraine. *Headache* **59**, 869–879.
- Sucksdorff D, Brown AS, Chudal R, Heinimaa M, Suominen A and Sourander A** (2016) Parental and comorbid migraine in individuals with bipolar disorder: a nationwide register study. *Journal of Affective Disorders* **206**, 109–114.
- Swahn M, Hargreave M, Nielsen T, Plessen KJ, Jensen SM, Kjaer S and Jensen A** (2015) Mental disorders in childhood and young adulthood among children born to women with fertility problems. *Human Reproduction* **30**, 2129–2137.
- Tegethoff M, Greene N, Olsen J, Schaffner E and Meinschmidt G** (2011) Stress during pregnancy and offspring pediatric disease: a national cohort study. *Environmental Health Perspectives* **119**, 1647–1652.
- VanderWeele TJ** (2016) Mediation analysis: a practitioner's guide. *Annual Review of Public Health* **37**, 17–32.
- Vanmolkot F and De Hoon J** (2007) Increased C-reactive protein in young adult patients with migraine. *Cephalalgia* **27**, 843–846.
- Vos T, Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, Abdulkader RS, Abdulle AM, Abebo TA and Abera SF** (2017) Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet* **390**, 1211–1259.
- Wallach Kildemoes H, Toft Sørensen H and Hallas J** (2011) The Danish national prescription registry. *Scandinavian Journal of Public Health* **39**, 38–41.
- Weatherall MW** (2015) The diagnosis and treatment of chronic migraine. *Therapeutic Advances in Chronic Disease* **6**, 115–123.
- Weinstock M** (2005) The potential influence of maternal stress hormones on development and mental health of the offspring. *Brain, Behavior, and Immunity* **19**, 296–308.
- Wessman M, Terwindt GM, Kaunisto MA, Palotie A and Ophoff RA** (2007) Migraine: a complex genetic disorder. *The Lancet Neurology* **6**, 521–532.