Epidemiology and Psychiatric Sciences

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

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

H. Wang1,2,*, H. He3,*, M. Miao4, Y. Yu5, H. Liu6, J. Zhang1, F. Li3† and J. Li1,2†

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; 4National 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
(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 (Lynge 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 diagnosis 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 (Lynge 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, Ninth Revision (ICD-9) (1974 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: 290–301; 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: 100–178) (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, paternal 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 (natural indirect relationship)/log (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 used 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., 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 suboptimal 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 1. Characteristics of the study population born between 1978 and 2012 at birth according to maternal migraine status

| Characteristics                                      | Maternal migraine status | Migraine n = 51 717 | No migraine n = 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                                    |                          | 47 603 (92.0)        | 1 603 856 (89.1)          |

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

Table 1. (Continued.)

| Characteristics                                      | Maternal migraine status | Migraine n = 51 717 | No migraine n = 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                      |                          |                      |                           |
| Yes                                                  |                          | 48 630 (94.0)        | 1 761 410 (97.8)          |
| No                                                   |                          | 3087 (6.0)           | 39 107 (2.2)              |

Fig. 1. Cumulative incidence of overall psychiatric disorders among offspring exposed versus unexposed to maternal migraine.
| Offspring psychiatric disorders | Rate per 1000 person-years | HR (95% CI) Model 1 | HR (95% CI) Model 2 |
|-------------------------------|----------------------------|---------------------|---------------------|
| **Attained ages 0–39 years**  |                            |                     |                     |
| No maternal migraine          | 271 843                    | 6.88                | 1 (Reference)       |
| Maternal migraine             | 5099                       | 8.40                | 1.32 (1.28–1.36)    |
| **Attained ages 0–9 years**   |                            |                     |                     |
| No maternal migraine          | 52 112                     | 3.05                | 1 (Reference)       |
| Maternal migraine             | 2216                       | 5.41                | 1.26 (1.22–1.30)    |
| **Attained ages 10–18 years** |                            |                     |                     |
| No maternal migraine          | 118 147                    | 8.81                | 1 (Reference)       |
| Maternal migraine             | 2309                       | 13.97               | 1.32 (1.27–1.38)    |
| **Attained ages 19–39 years** |                            |                     |                     |
| No maternal migraine          | 101 584                    | 11.21               | 1 (Reference)       |
| Maternal migraine             | 574                        | 17.73               | 1.44 (1.32–1.56)    |

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.

| Specific personality disorders | Rate per 1000 person-years | HR (95% CI) Model 1 | HR (95% CI) Model 2 |
|-------------------------------|----------------------------|---------------------|---------------------|
| No maternal migraine          | 24 076                     | 1.58                | 1 (Reference)       |
| Maternal migraine             | 200                        | 2.52                | 1.58 (1.38–1.82)    |

| Intellectual disability       | Rate per 1000 person-years | HR (95% CI) Model 1 | HR (95% CI) Model 2 |
|-------------------------------|----------------------------|---------------------|---------------------|
| No maternal migraine          | 9258                       | 0.22                | 1 (Reference)       |
| Maternal migraine             | 144                        | 0.23                | 0.86 (0.73–1.02)    |

| Pervasive developmental disorders | Rate per 1000 person-years | HR (95% CI) Model 1 | HR (95% CI) Model 2 |
|----------------------------------|----------------------------|---------------------|---------------------|
| No maternal migraine             | 25 375                     | 0.61                | 1 (Reference)       |
| Maternal migraine                | 865                        | 1.37                | 1.15 (1.07–1.23)    |

| Behavioural and emotional disorders* | Rate per 1000 person-years | HR (95% CI) Model 1 | HR (95% CI) Model 2 |
|--------------------------------------|----------------------------|---------------------|---------------------|
| No maternal migraine                 | 61 887                     | 1.77                | 1 (Reference)       |
| Maternal migraine                    | 2193                       | 2.44                | 1.28 (1.22–1.33)    |
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). 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 in offspring (Wessman et al., 2007). 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.

### 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 | HR (95% CI) Model 2 |
|-----------------------------------------|--------------------------------------------|-----------------------------|---------------------|---------------------|
| No maternal migraine and psychiatric disorders | 25369                                      | 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     | 18144                                      | 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.

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

H. Wang et al.
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; Skaja 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.
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, Capunio LM, Corbelli I, Calabresi P and Sarchielli P (2009) Pathophysiological basis of migraine prophylaxis. Progress in Neurobiology 89, 176–192.

Gandal MJ, Haney JR, Parikhshak NN, Leppa V, Ramaswami G, Hartl C, Schork AJ, Appadurai V, Bull 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-Diaz 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.

Kaesboll 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 Kuper 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, Tielt-Hansen P, Skytte A, Kyriv 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.

Lyne E, Sandegaard JL and Rebol 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 register research. 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 Nordenfelt 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.

Petersen OF, 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 Mcninnes 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 Sorensen HT (2015) The Danish National Patient Registry: a review of content, data quality, and research potential. Clinical Epidemiology 7, 449.

Skaja N, Szepligeti 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, Heimimaa M, Suominen A and Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L and Johnsen TB (2016) Increase in self-reported migraine prevalence in the Danish adult population: a prospective longitudinal population-based study. BMJ Open 2, e000962.

Thompson RJ, Ford I, Mann J, Everitt B, Smith C and Williams J (2011) The birth weight paradox uncovered? American Journal of Epidemiology 164, 1115–1120.

Tilbrook H, Greenland S and Longnecker M (2011) 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.

VanderWeele TJ (2016) Mediation analysis: a practitioner’s guide. Annual Review of Public Health 37, 17–32.

Vanmolkot F and De Hoorn J (2007) Increased C-reactive protein in young adult patients with migraine. Cephalalgia 27, 843–846.

Vos T, Abajobir AA, Abate KH, Abbafati C, Abbasi KM, Abd-Allah F, Abdulkader RS, Abdulle AM, Adebayo TA and Abhara 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 register. 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 Immunology 19, 296–308.

Wessa M, Tervindt GM, Kaunisto MA, Palotie A and Ophoff RA (2007) Migraine: a complex genetic disorder. The Lancet Neurology 6, 521–532.