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ORIGINAL CONTRIBUTION

Associations of parental mental disorders and age with childhood mental disorders: a population-based cohort study with four million offspring

Chih-Sung Liang[1,2] · Ya-Mei Bai[3,4] · Ju-Wei Hsu[3,4] · Kai-Lin Huang[3,4] · Nai-Ying Ko[5] · Ta-Chuan Yeh[6] · Hsuan-Te Chu[1] · Shih-Jen Tsai[3,4] · Tzeng-Ji Chen[7,8] · Mu-Hong Chen[3,4]

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Abstract

This Taiwan study examined the associations of parental age and mental disorders with the offspring risks of attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), major depressive disorder (MDD), and bipolar disorder (BD). Children born between January 1991 and December 2004 in Taiwan were enrolled as the birth cohort ($n = 4{,}138{,}151$) and followed up until December 2011. A logistic regression analysis was performed to identify the odds ratio (OR). The advanced age effects were significant in ADHD (range of OR: 1.04 to 1.49) and ASD (range of OR: 1.35 to 2.27). Teenage mothers, teenage fathers, and fathers ≥ 50 years had higher offspring risks of MDD (range of OR: 1.24 to 1.46); and teenage mothers and fathers ≥ 50 years had increased offspring risks of BD (range of OR: 1.23 to 1.87). Both paternal and maternal mental disorders were associated with higher risks of within-disorder transmission for ADHD, ASD, MDD, and BD (range of OR: 2.64 to 30.41). Besides, parents with one of these four mental disorders (ADHD, ASD, MDD, and BD) might have higher risk of cross-disorder transmission to at least one of the other three mental disorders in the offspring (range of OR: 1.35 to 7.15). Parental age and mental disorders had complex and nuanced patterns in association with offspring mental disorders.

Keywords Parental age · Mental disorder · Offspring · Transmission · Genetics

✉ Ju-Wei Hsu
jwhsu@vghtpe.gov.tw

✉ Mu-Hong Chen
kremer7119@gmail.com

1 Department of Psychiatry, Beitou Branch, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

2 Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei, Taiwan

3 Department of Psychiatry, Taipei Veterans General Hospital, No. 201, Shih-Pai Road, Sec. 2, 11217 Taipei, Taiwan

4 Department of Psychiatry, College of Medicine, National Yang-Ming University, Taipei, Taiwan

5 Department of Nursing, College of Medicine, National Cheng Kung University and Hospital, Tainan, Taiwan

6 Department of Psychiatry, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

7 Department of Family Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

8 Institute of Hospital and Health Care Administration, National Yang-Ming University, Taipei, Taiwan

Introduction

More than half of mental disorders start during childhood or adolescence, and mental disorders are the major contributors to health-related disability in children and adolescence worldwide [1, 2]. According to the Global Burden of Disease Study 2010 report, major depressive disorder (MDD) is the leading cause of the disability-adjusted life years (DALYs) in people younger than age 24 years, while autism spectrum disorder (ASD) is the leading cause in children younger than age five years. The global burden of attention-deficit/hyperactivity disorder (ADHD) is also significant, and ADHD is estimated to contribute to 491,500 DALYs in 2010 [2, 3]. Besides, suicide is one of the leading causes of youth mortality [2], and bipolar disorder (BD) is the second cause of first onset of lifetime suicide attempt among adolescents based on a national study in United States [4] and a meta-analysis addressing juvenile bipolar disorder and suicidality [5].

Among the risk factors for child and adolescent mental disorder, parental age and parental mental disorder

have been suggested [6–10]. For example, epidemiological studies have suggested that offspring of older fathers (age ≥ 45 years) had increased risks of ADHD [6, 7], MDD [7], and BD [6, 7]; besides, offspring of older mothers (age ≥ 35 or > 40 vs age 25–29) had an increased risks of ASD [8], but not of ADHD, mood disorder, and psychotic disorder [9, 10]. A nationwide study in Danish reported that offspring of teenage parents had increased risks of several mental disorders, including MDD and BD [10].

On the other hand, the transgenerational transmission of mental disorder to offspring can be either in concordant association (within-disorder transmission, that is, developing the same disorder as their parent) or through broad-spectrum effects (cross-disorder transmission, that is, developing another mental disorder), although there is a strong tendency for within-disorder transmission [11, 12]. For example, offspring of parents with MDD [11], BD [11], ADHD [12], and ASD [13] had higher risk for the same psychiatric disorder than controls {MDD, range of odds ratio [OR]: 1.91–42.13; BD, range of OR: 1.24–9.98; ADHD, hazard ratio = 45.12, 95% confidence interval (CI) [38.57, 52.78]; ASD, hazard ratio = 64.47, 95% CI [15.33, 271.15]}. For cross-disorder transmission, a systematic review published in 2015 (including 76 studies) reported that children of parents with MDD had a 4.35-fold risk of developing BD (range of OR: 2.96–5.40), a 4.35-fold risk of developing conduct disorder/ADHD (range of OR: 1.59–10.78), and a 4.61-fold risk of developing non-specified mental disorders (range of OR: 2.05–9.75) [11]. Moreover, children of parents with BD had a 4.44-fold risk of developing MDD (range of OR: 1.24–9.98), a 6.10-fold risk of developing conduct disorder/ADHD (range of OR: 0.29–17.00), and a 5.04-fold risk of developing non-specified mental disorders (range of OR: 2.54–11.39). There are also studies examining cross-transmission on ADHD [12] and ASD [13], suggesting shared etiology for certain psychiatric disorders.

To date, no study has simultaneously explored the effects of parental age and parental mental disorder on the risk of major psychiatric disorders in the offspring. We focused on two major neurodevelopmental disorders (ASD and ADHD) and two major mood disorders (MDD and BD) in childhood and adolescence. We examined the relative influence of (maternal and paternal) older vs younger age with the four major mental disorders by using an Asian population-based database (four million offspring). We also investigated the risk of these four mental disorders in the offspring of parents with these four mental disorders. We hypothesized that paternal and maternal ages have different effects on these four mental disorders, and that these four mental disorders have different within- and cross-disorder transmissions. We believe our study findings may help make policy decisions regarding allocation of limited resources for the prevention and treatment of psychopathology in childhood and adolescence.

Methods

Data source

The Taiwan's National Health Insurance, a mandatory universal health insurance program, offers comprehensive medical care coverage to all Taiwanese residents (more than 23 million people). The National Health Research Institute manages the National Health Insurance Research Database (NHIRD). The NHIRD consists of healthcare data from > 99% of the entire population of Taiwan. The National Health Research Institute audits and releases the NHIRD for scientific and study purposes. Individual medical records are anonymous to protect patient privacy and are linked based on each resident's unique ciphered personal identification number. Comprehensive information of insured individuals is included in the database, such as demographic data, dates of clinical visits, diagnoses, and medical interventions. The registry for beneficiaries dataset included the demographic data (i.e., birthdate, sex, residence) of entire Taiwanese population. A specialized dataset of mental disorders including all psychiatric medical records of insured individuals between 2001 and 2011 was used to identify individuals with mental disorders, including ADHD, ASD, BD, and MDD. Following the method of Chen et al. and Cheng et al., family kinships in the NHIRD were used for genealogy reconstruction [13, 14]. Diagnostic codes used were based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The NHIRD has been used extensively in several epidemiologic studies [15–17]. This study was approved by the Taipei Veterans General Hospital institutional review board (2018-07-016AC).

Enrollment of children and their parents

In this study, we enrolled children born between January 1991 and December 2004 as the birth cohort and followed up until December 2011. The supplementary eTable 1 provides the percentage of the recruited children to the entire study population between 1991 and 2004. Fathers and mothers of the enrolled children were identified for their age at childbirth with the subsequent risks of offspring mental disorders. We included both inpatients and outpatients and focused on four major mental disorders, including ADHD (ICD-9-CM code: 314), ASD (ICD-9-CM code: 299), BD (ICD-9-CM codes: 296 except 296.2, 296.3, 296.82 and 296.9), and MDD (ICD-9-CM codes: 296.2 and 296.3). The diagnoses were made by board-certified psychiatrists. For the improvement of the diagnosis validity, the participants

were required to visit the outpatient department at least thrice within one year. The level of urbanization (from level one, most urbanized region, to level five, least urbanized region) was also assessed for each participant in this study.

A total of 4,138,151 live births in Taiwan between 1991 and 2004 were enrolled and followed up until 2011. Table 1 shows the paternal, maternal, and offspring demographics and characteristics.

Statistical analysis

The F test was used for continuous variables and Pearson's χ^2 test for nominal variables, where appropriate, for between-group comparisons. Logistic regression models were performed to examine the associations of parental age with the offspring mental disorders, with children whose parents were 25 to 29 years of age at the time of childbearing as the reference category [10]. Odds ratio (OR) with 95% CI was calculated from the logistic regression models, with adjustment of paternal age when considering the maternal age effects and vice versa. Besides, the model was adjusted for demographic data (children age, sex of children, income, and residence) and parental mental disorders (all ICD-9-CM classifications of mental disorders), because evidence suggested that sex, low socioeconomic status, and urbanicity were associated with the likelihoods of ASD and ADHD [18–20]. We also examined with the risk of mental disorders (ADHD, ASD, MDD, and BD) in offspring of parents with mental disorders compared with controls of parents without mental disorder, after adjustment for demographic data (parental age at childbirth, sex of children, income, and residence). Continuous variables were presented with

Table 1 Demographic characteristics and parental age of childbearing between 1991 and 2004

		Offspring ($n=4,138,151$)
Sex (n, %)		
Male		2,160,904 (52.2)
Female		1,977,247 (47.8)
Incidence of mental disorders		
ASD (n, %)		23,866 (0.6)
Age at diagnosis (years, SD)		7.37 (3.91)
ADHD (n, %)		170,130 (4.1)
Age at diagnosis (years, SD)		8.38 (2.95)
Major depressive disorder (n, %)		8,341 (0.2)
Age at diagnosis (years, SD)		15.54 (3.14)
Bipolar disorder (n, %)		4,460 (0.1)
Age at diagnosis (years, SD)		14.73 (3.59)
	Fathers ($n=3,336,800$)	Mothers ($n=3,026,526$)
Age at childbirth (years, SD, n, %)	31.29 (5.43)	28.13 (4.83)
Prevalence of mental disorders (n, %)		
ASD	123 (0.0)	169 (0.0)
ADHD	1347 (0.0)	4670 (0.1)
Major depressive disorder	50,808 (1.2)	94,089 (2.3)
Bipolar disorder	16,638 (0.4)	22,640 (0.5)
		Demographic data of family
Level of urbanization (n, %)		
1 (most urbanized)		568,549 (13.7)
2		1,201,829 (29.0)
3		40,8122 (9.9)
4		400,754 (9.7)
5 (most rural)		1,558,916 (37.7)
Family economic state (n, %)		
< 19,100 NTD/month		831,665 (20.1)
19,100–42,000 NTD/month		2,150,287 (52.0)
> 42,000 NTD/month		1,156,218 (27.9)

ASD autism spectrum disorder, *ADHD* attention-deficit hyperactivity disorder, *NTD* new Taiwan dollar, *SD* standard deviation

mean ± standard deviation. A two-tailed p value of less than 0.05 was considered statistically significant. All data processing and statistical analyses were performed with the Statistical Package for Social Science (SPSS) software version 17 (SPSS Inc, Chicago, IL, USA) and Statistical Analysis Software (SAS) version 9.1 (SAS Institute Inc, Cary, NC).

Results

We found a positive linear relationship between increasing parental age (paternal and maternal) and the risk of offspring ADHD (Table 2). Compared with parents aged 25–29 years, younger fathers (aged < 20 years) and younger mothers (aged < 20, aged 20–24) had lower risks of offspring ADHD; in contrast, the ORs gradually increased in the offspring of both fathers and mothers older than 30 years compared with parents aged 25–29 years.

Positive linear relationships were also observed for paternal and maternal ages and the risk of offspring ASD. Compared with parents aged 25–29 years, younger fathers (aged < 20 and aged 20–24) and young mothers (aged < 20 and aged 20–24) had lower risks of offspring ASD; in contrast, the ORs gradually increased in the offspring of both fathers and mothers older than 30 years compared with parents aged 25–29 years. The supplementary eTable 2 and eTable 3 provided the detailed statistics of the results of the logistic regression models. In brief, paternal and maternal ages showed positive linear relationships with both ADHD and ASD in offspring.

We observed different relationships between age and the risk of mood disorders for MDD and BD (Table 3). Compared with the offspring of parents aged 25–29 years, paternal age showed a U-shaped relationship, with the offspring of teenage fathers (OR = 1.36, 95% CI [1.12, 1.66]) and fathers ≥ 50 years (OR = 1.46, 95% CI [1.11, 1.93]) having a higher risk of MDD. The offspring risks of MDD were lower for fathers aged 30–34 years (OR = 0.88, 95% CI [0.83, 0.93]), aged 35–39 years (OR = 0.79, 95% CI [0.73, 0.85]), and aged 40–44 years (OR = 0.80, 95% CI [0.71, 0.92]) compared with that of fathers aged 25–29 years. Teenage mothers had a higher offspring risk of MDD (OR = 1.24, 95% CI [1.10, 1.39]) compared with the 25–29 age category. The offspring risk of MDD was decreased in mothers ≥ 30 years of age; however, only the category of mothers aged 30–34 years had a statistically significant lower offspring risk of MDD (OR = 0.92, 95% CI [0.86, 0.98]).

On the other hand, both paternal and maternal ages showed U-shaped relationships for the risk of BD; however, the increased risks were observed only in fathers ≥ 50 years (OR = 1.87, 95% CI [1.33, 2.64]) and teenage mothers (OR = 1.23, 95% CI [1.04, 1.45]). In brief, younger parents

Table 2 Parental age and risk of offspring ADHD and ASD*

	Attention-deficit/hyperactivity disorder			Autism spectrum disorder		
	Event (*n*, %)	OR, 95% CI	*p* value	Event (*n*, %)	OR, 95% CI	*p* value
Paternal age at childbirth						
< 20 years (*n* = 34,494)	1126 (3.3)	**0.87 (0.82–0.93)**	< 0.001	75 (0.2)	**0.54 (0.43–0.68)**	< 0.001
20–24 years (*n* = 297,921)	11,321 (3.8)	1.01 (0.99–1.04)	0.240	850 (0.3)	**0.69 (0.64–0.74)**	< 0.001
25–29 years (*n* = 1,097,434)	42,294 (3.9)	1 (reference)		4802 (0.4)	1 (reference)	
30–34 years (*n* = 1,189,887)	48,744 (4.1)	**1.04 (1.03–1.05)**	< 0.001	7539 (0.6)	**1.38 (1.33–1.43)**	< 0.001
35–39 years (*n* = 529,502)	23,295 (4.4)	**1.11 (1.09–1.13)**	< 0.001	4178 (0.8)	**1.71 (1.64–1.78)**	< 0.001
40–44 years (*n* = 140,628)	6646 (4.7)	**1.21 (1.18–1.25)**	< 0.001	1254 (0.9)	**1.99 (1.87–2.12)**	< 0.001
45–49 years (*n* = 31,056)	1581 (5.1)	**1.34 (1.27–1.41)**	< 0.001	307 (1.0)	**2.27 (2.02–2.54)**	< 0.001
≥ 50 years (*n* = 15,878)	827 (5.2)	**1.39 (1.30–1.49)**	< 0.001	154 (1.0)	**2.27 (1.93–2.67)**	< 0.001
Maternal age at childbirth						
< 20 years (*n* = 117,903)	4280 (3.6)	**0.91 (0.88–0.94)**	< 0.001	310 (0.3)	**0.54 (0.48–0.61)**	< 0.001
20–24 years (*n* = 666,068)	25,755 (3.9)	**0.96 (0.95–0.98)**	< 0.001	2262 (0.3)	**0.68 (0.65–0.72)**	< 0.001
25–29 years (*n* = 1,236,240)	50,817 (4.1)	1 (reference)		6497 (0.5)	1 (reference)	
30–34 years (*n* = 774,096)	34,668 (4.5)	**1.07 (1.05–1.09)**	< 0.001	5723 (0.7)	**1.35 (1.30–1.40)**	< 0.001
35–39 years (*n* = 200,226)	10,271 (5.1)	**1.22 (1.19–1.25)**	< 0.001	1856 (0.9)	**1.68 (1.60–1.77)**	< 0.001
≥ 40 years (*n* = 31,993)	1958 (6.1)	**1.49 (1.42–1.57)**	< 0.001	342 (1.1)	**1.99 (1.79–2.22)**	< 0.001

CI confidence interval, *OR* odds ratio

Bold type indicates statistical significance ($p < 0.05$)

*Adjusted for demographic data (children age, sex of children, income, and residence) and parental mental disorders (all ICD-9-CM classifications of mental disorders)

*Adjusted for paternal age when considering the maternal age effects and vice versa

Table 3 Parental age and risk of offspring major depressive disorder and bipolar disorder*

	Major depressive disorder			Bipolar disorder		
	Event (*n*,‰)	OR, 95% CI	*p* value	Event (*n*,‰)	OR, 95% CI	*p* value
Paternal age at childbirth						
< 20 years (*n* = 34,494)	104 (3.0)	**1.36 (1.12–1.66)**	0.002	45 (1.3)	1.13 (0.84–1.52)	0.425
20–24 years (*n* = 297,921)	668 (2.2)	1.04 (0.95–1.13)	0.439	327 (1.1)	0.97 (0.86–1.10)	0.662
25–29 years (*n* = 1,097,434)	2363 (2.2)	1 (reference)		1223 (1.1)	1 (reference)	
30–34 years (*n* = 1,189,887)	2265 (1.9)	**0.88 (0.83–0.93)**	< 0.001	1259 (1.1)	0.95 (0.88–1.03)	0.214
35–39 years (*n* = 529,502)	904 (1.7)	**0.79 (0.73–0.85)**	< 0.001	541 (1.0)	0.91 (0.83–1.01)	0.080
40–44 years (*n* = 140,628)	245 (1.7)	**0.80 (0.71–0.92)**	0.001	157 (1.1)	0.99 (0.84–1.17)	0.940
45–49 years (*n* = 31,056)	54 (1.7)	0.79 (0.60–1.03)	0.083	36 (1.2)	1.03 (0.74–1.44)	0.863
≥ 50 years (*n* = 15,878)	52 (3.3)	**1.46 (1.11–1.93)**	0.007	34 (2.1)	**1.87 (1.33–2.64)**	< .001
Maternal age at childbirth						
< 20 years (*n* = 117,903)	329 (2.8)	**1.24 (1.10–1.39)**	< 0.001	161 (1.4)	**1.23 (1.04–1.45)**	0.015
20–24 years (*n* = 666,068)	1464 (2.2)	1.02 (0.96–1.09)	0.483	754 (1.1)	1.06 (0.97–1.16)	0.192
25–29 years (*n* = 1,236,240)	2588 (2.1)	1 (reference)		1290 (1.0)	1 (reference)	
30–34 years (*n* = 774,096)	1491 (1.9)	**0.92 (0.86–0.98)**	0.009	820 (1.1)	1.01 (0.93–1.11)	0.763
35–39 years (*n* = 200,226)	392 (2.0)	0.92 (0.83–1.03)	0.145	221 (1.1)	1.05 (0.91–1.21)	0.537
≥ 40 years (*n* = 31,993)	65 (2.0)	0.95 (0.74–1.21)	0.670	41 (1.3)	1.21 (0.88–1.65)	0.242

CI confidence interval, *OR* odds ratio

Bold type indicates statistical significance ($p < 0.05$)

*Adjusted for demographic data (parental age at childbirth, sex of children, income, and residence)

and fathers ≥ 50 years had higher offspring risks of MDD, while teenage mothers and fathers ≥ 50 years had increased offspring risks of BD.

Both paternal and maternal mental disorders were associated with a higher risk of within-disorder transmission than the controls of parents without mental disorders, including ADHD, ASD, MDD, and BD (Table 4). For cross-disorder transmission in fathers, the paternal ADHD was associated with a higher offspring risk for ASD, MDD, and BD than the controls. The paternal ASD was associated with a higher

Table 4 Parental mental disorders and risk of offspring ADHD, ASD, major depressive disorder, and bipolar disorder

	Offspring ADHD (OR, 95% CI)	Offspring ASD (OR, 95% CI)	Offspring MDD (OR, 95% CI)	Offspring BD (OR, 95% CI)
Paternal mental disorders (Presence vs. Absence)				
ADHD	**19.02 (16.98–21.31)**	**7.15 (5.59–9.16)**	**2.76 (1.52–5.02)**	1.65 (0.61–4.43)
ASD	**5.19 (3.27–8.23)**	**16.45 (9.12–30.76)**	2.51 (0.35–18.02)	3.90 (0.54–28.67)
MDD	**1.44 (1.38–1.50)**	**1.44 (1.30–1.59)**	**2.64 (2.33–2.99)**	**1.52 (1.25–1.86)**
BD	**1.35 (1.26–1.44)**	1.17 (0.97–1.40)	**2.02 (1.65–2.48)**	**5.50 (4.46–6.77)**
Maternal mental disorders (Presence vs. Absence)				
ADHD	**29.38 (27.63–31.25)**	**6.36 (5.54–7.30)**	**2.73 (1.94–3.85)**	**2.76 (1.75–4.37)**
ASD	**4.34 (2.89–6.51)**	**30.41 (19.98–46.27)**	2.48 (0.61–10.19)	**6.79 (2.09–22.00)**
MDD	**1.97 (1.92–2.03)**	**1.75 (1.63–1.88)**	**3.95 (3.64–4.28)**	**2.06 (1.79–2.36)**
BD	**1.44 (1.37–1.52)**	**1.41 (1.23–1.62)**	**1.86 (1.52–2.12)**	**4.94 (4.14–5.88)**

Adjusted for data (parental age at childbirth, sex of children, income, and residence)

ADHD attention-deficit/hyperactivity disorder, *ASD* autism spectrum disorder, *BD* bipolar disorder, *CI* confidence interval, *MDD* major depressive disorder, *OR* odds ratio

Bold type indicates statistical significance ($p < 0.05$)

offspring risk for ADHD and MDD than the controls. The paternal MDD was associated with a higher offspring risk for ADHD and BD than the controls. The paternal BD was associated with a higher offspring risk for MDD than the controls. For cross-disorder transmission in mothers, the maternal ADHD was associated with a higher offspring risk for ASD, MDD, and BD. The maternal ASD was associated with a higher offspring risk for ADHD, MDD, and BD. The maternal MDD was associated with a higher offspring risk for ADHD and BD. The maternal BD was associated with a higher risk for ADHD, ASD, and MDD. In brief, among ADHD, ASD, MDD, and BD, parents with one of these four mental disorders might have cross-disorder transmission to one of the other three mental disorders in the offspring.

Discussion

This is the largest population-based study examining the impact of parental age and mental disorders on the offspring risks of mental disorder. The principal findings were as follows: (1) paternal and maternal ages showed positive linear relationships with both ADHD and ASD in offspring; (2) parents < 20 years and fathers ≥ 50 years had higher offspring risks of MDD; (3) fathers ≥ 50 years and teenage mothers had increased offspring risks of BD; (4) both paternal (ADHD, ASD, MDD, and BD) and maternal (ADHD, ASD, MDD, and BD) mental disorders were associated with higher risks of within-disorder transmission for ADHD, ASD, MDD, and BD; and (5) offspring of parents with one of these four mental disorders (ADHD, ASD, MDD, and BD) had a higher risk of cross-disorder transmission to at least one of the other three mental disorders.

Meta-analyses of epidemiological studies have provided strong evidence regarding the association of advanced paternal [21] and maternal [8] ages at childbearing with increased offspring risk of ASD, which is consistent our study findings. However, there are inconsistent results regarding the association of parental age with ADHD in offspring. Most population-based studies reported younger paternal [10, 22, 23] or maternal [10, 22–25] ages being associated with increased offspring risk of ADHD, although some reported an increased offspring risk in older fathers [6, 10] or a lack of association between paternal age and ADHD in offspring [7]. In this study, both younger fathers (< 20 years) and mothers (≤ 24 years) at childbearing were associated with a decreased offspring risk of ADHD, while older fathers and mothers at childbearing were associated with an increased offspring risk of ADHD. The decreased risk in younger parents and the increased risk in older mothers have not been reported in previous studies, most of which were conducted in the Western countries. A meta-analysis reported that the prevalence of ADHD varies worldwide, which is associated with diagnostic criteria, source of information, requirement of impairment for diagnosis, and geographic origin [26]. In addition, in Taiwanese population, ADHD has been found to highly co-aggregate with ASD [12], which showed a positive linear relationship between parental age and offspring risk of ASD. Therefore, in Taiwanese population, there could be a monotonic positive linear relationship between parental age and offspring risk of ADHD.

Population-based studies regarding the association between parental age and offspring mood disorders are limited. There was one study reporting an increased offspring risk of MDD in younger parents and older fathers [10], which was consistent with our findings. The relationship between parental age and offspring BD is inconclusive. Our study found that teenage mothers and older fathers had increased offspring risks of BD, while the other age categories had nonsignificant offspring risk of BD. Although our findings were completely consistent with a Danish population-based study [10], previous studies have reported various associations, such as a decreased risk in teenage parents, no association, a U-shaped relationship, a monotonic increase, and an increased risk in advanced parental age category [7]. The inconsistent findings may be related to challenges in differential diagnosis of BD [27, 28]. For example, the core symptom irritability of pediatric BD may also occur in ASD, MDD, ADHD, conduct disorder, and oppositional defiant disorder [28]. Besides, it is suggested that diagnostic criteria of BD were not systematically applied in some clinical settings, leading to discrepancies between increasing billing diagnoses and a stable epidemiological prevalence of BD [28]. In brief, we suggested that younger parents and older fathers had higher offspring risks of MDD, while teenage mothers and older fathers had increased offspring risks of BD.

We found that parent age effect on offspring risk of mental disorder might be different from that of parental mental disorder effect. The ORs of age effect on offspring risk of mental disorder range from 1.04 (95% CI [1.03, 1.05]) to 2.27 (95% CI [1.93, 2.67]), with the largest OR of developing ASD in children of older fathers (age 45–49 years and age ≥ 50 years). Besides, we found a lower risk of ADHD and ASD in offspring of teenage parents, and a lower risk of MDD in fathers aged between 30 and 44 years. However, the ORs of parental mental disorder effect on within-disorder transmission range from 2.64 (95% CI [2.33, 2.99]) to 30.41 (95% CI [19.98, 46.27]), with the largest OR for offspring of mothers with ASD in developing ASD. The ORs of parental mental disorder effect on cross-disorder transmission range from 1.35 (95% CI [1.26, 1.44]) to 7.15 (95% CI [5.59, 9.16]), with the largest OR for offspring of fathers with ADHD in developing ASD. A stronger tendency for within-disorder transmission than cross-disorder transmissions was similar to that of other studies [11–13]. A large-scale

cross-disorder genome-wide meta-analysis investigated genomic relationships, novel loci, and pleiotropic mechanisms across 8 psychiatric disorders (including MDD, BD, ADHD, ASD) [29]. This study found that 109 loci at least affected 2 or more psychiatric disorders, and 23 loci had pleiotropic effects on 4 or more psychiatric disorders [29]. The authors concluded that these results highlight disparities between our clinically defined classification of psychiatric disorders and underlying biology. Integrating our findings and those of other studies suggested a complex within- and cross-disorder transgenerational transmission and different age effects on offspring risk of mental disorder, which require future comprehensive and extensive investigation.

The finding of cross-disorder transmission suggests that cross-disorder approaches may be useful for studies exploring shared biological underpinnings between these mental disorders. However, early prevention programs are necessary for parents and their offspring in preventing offspring mental disorders and supporting them when their children developed mental disorders. Targeting common pathophysiological and pathogenetic mechanisms may reduce the familiar risk of extending across different mental disorders. Besides, treatment can focus on alleviating the common predisposing factors for the development of various mental disorders, such as child abuse, physical maltreatment, lack of social support, interpersonal conflict, and chronic economic disability. Future studies could examine the association of treatment of parental mental disorder and the common predisposing factors with the offspring risk of mental disorder.

A strength of the current study is the sample size (four million participants). We used a nationwide population-based study and recruited all children born between January 1991 and December 2004 as a birth cohort. We might avoid selection bias by using this representative sample. Therefore, our study findings may be generalizable to other non-Western populations. The second strength is that the Taiwan's National Health Insurance is low-cost and easily accessible. Therefore, most of the cases with clinical mental problems could be included. The third strength of this study is the validity of the diagnosis. All the diagnoses of mental disorders were made by board-certified psychiatrists and required these patients to visit the outpatient department at least thrice within one year. Fourth, our study is the first study to examine both parental age and parental mental disorder effects on the risk of mental disorders in offspring. Importantly, in addition to age and mental disorder of parents, several factors may also contribute to the development of mental disorder in offspring, such as maternal obesity [30], obstetric complications [31], personality disorder [32] or alcohol abuse [32]. Face-to-face interview would be necessary to further assess the complexity of risk factors for mental disorder in offspring.

This study has several limitations. First, the prevalence of ADHD, ASD, MDD, and BD may have been underestimated. Only patients who sought medical consultation and treatment at least thrice within one year were included in this study. Second, the risk of MDD and BD may be underestimated because MDD and BD may develop during adulthood. In this study, the total follow-up duration was 21 years, and individuals with adult-onset MDD and BD may not have been diagnosed in our study sample. Third, several important psychosocial factors were not available in the NHIRD. For example, a study reported that the number of household members positively correlated with scores on good mental health [33]. Therefore, the interaction effects between parental age, parental mental disorders, and psychosocial factors on the offspring risk of mental disorders require further investigation. Fourth, the differences in diagnostic criteria between ICD and Diagnostic and Statistical Manual of Mental Disorders (DSM) might be another source of bias. For example, a study reported that only 56% of patients met DSM-5 criteria of ASD in 150 patients with ASD diagnosed by the criteria of ICD-10 [34]. Five, we only examined four mental disorders. Maybe there are other distributions for parental and maternal risks when considering other mental disorders, which warrant future investigation. Sixth, the interactions between parental ages and parental mental disorders were not assessed in the regression models because so many interactions would be too complicated to be fairly interpreted. Whether the interactions between parental ages and parental mental disorders may need further investigation. Finally, some information, such as level of education and immigrant status, was not available in the NHIRD and could, thus, not be controlled for.

Conclusion

This is the first Asian population-based study to examine the complex effects of parental age and mental disorders on the offspring risks of ADHD, ASD, MDD, and BD using a sample of four million people from Taiwan. Our study suggest that psychiatrists should consider the risk of both within-disorder and cross-disorder familial transmission of major mental disorders, and the age of childbearing and the significant base rates of mental disorders in the general population. Psychiatrists should take these findings under consideration and offer information, social support, and prevention strategies no matter if the child was already born or if the parents want to have children. Parents with these mental disorders and their children need to get the opportunity for prevention programs to prevent offspring mental disorders or to support them when their children developed mental disorders. Prevention strategies and social support

for parents and children with mental disorders need to be implemented with a low threshold.

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Declarations

Conflict of interest None of the authors had any conflicts of interest related to this study.

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