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ORIGINAL ARTICLE ***Infertility***

Mental disorders in childhood and young adulthood among children born to women with fertility problems

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STUDY QUESTION: Is the risk of hospital admission or outpatient contact for mental disorders increased in children born to women with fertility problems compared with children born to women without fertility problems?

SUMMARY ANSWER: We found an increased risk of hospital admission or outpatient contact for mental disorders in children born to women with fertility problems.

WHAT IS KNOWN ALREADY: Few studies have investigated the risk of mental disorders in children born after fertility treatment and although some studies have pointed to an increased risk, others found no association. The inconsistent results may be due to methodological constraints in many previous studies, including small sample size and short follow-up, resulting in imprecise risk estimates and lack of information on risk patterns of mental disorders in adulthood.

STUDY DESIGN, SIZE, DURATION: This nationwide retrospective register-based cohort study included all 2 412 721 children born in Denmark between 1969 and 2006. All children were followed from date of birth until date of hospital contact for a mental disorder, date of emigration, date of death or 31 December 2009, whichever occurred first.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Information concerning maternal fertility status for all children in the cohort was obtained by linkage to the Danish Infertility Cohort, which contains data on nearly all women with fertility problems in Denmark since 1963. A total of 124 269 (5%) children were born to women with fertility problems and 2 288 452 (95%) to women without fertility problems. To identify children hospitalized for a mental disorder, the cohort was linked to the Danish Psychiatric Central Research Registry. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between maternal fertility status and the risk of hospital admission or outpatient contact for various groups of mental disorders, including any mental disorder and all 11 main discharge diagnostic groups, classified according to the International Classification of Diseases, version 10.

MAIN RESULTS AND THE ROLE OF CHANCE: During a mean follow-up period of 21 years (range, 0–40 years), 168 686 (7%) children were admitted to hospital or had an outpatient contact for a mental disorder. Children born to women with fertility problems had a significantly higher risk of any mental disorder (HR 1.23; 95% CI 1.20–1.26) and for most of the 11 main discharge groups, including schizophrenia (HR 1.16; 95% CI 1.07–1.27), mood (affective) disorders (HR 1.21; 95% CI 1.15–1.28) and disorders of psychological development (HR 1.15; 95% CI 1.09–1.21) as well as the subgroup of attention-deficit/hyperactivity disorders (HR 1.36; 95% CI 1.29–1.45) compared with children born to women without fertility problems. The risk estimates did not change markedly when analyses were performed separately for mental disorders diagnosed during childhood (0–19 years) and in young adulthood (20–40 years).

LIMITATIONS, REASON FOR CAUTION: The true risk of mental disorders may be somewhat underestimated, as only severe disorders requiring hospital admission or outpatient contact were considered as events. Furthermore, we could not determine whether the increased risks observed were due to factors related to the underlying infertility or to fertility treatment procedures.

WIDER IMPLICATIONS OF THE FINDINGS: This is the first report on mental disorders in adulthood among children born to women with fertility problems. Furthermore, we have assessed the risk of several severe mental disorders not previously studied (e.g. neurotic, stress-related and somatoform disorders and disorders of adult personality and behaviour). These important findings should be investigated further in large epidemiological studies designed to differentiate between factors related to fertility treatment and to the underlying infertility.

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Key words: infertility / children / mental disorders / population-based cohort study / epidemiology

Introduction

Infertility, defined as waiting time to pregnancy longer than 12 months, affects 10–15% of couples worldwide (Evers, 2002; Bonde and Olsen, 2008). In Denmark, ~4% of the birth cohort in 2013 was conceived with assisted reproduction technology (ART), and ~8% were conceived after any type of fertility treatment (Danish Fertility Association, 2013). In other European countries, ART accounts for an estimated 0.6–4.5% of all births (Ferraretti *et al.*, 2013). Since the birth of the first child born after *in vitro* fertilization (IVF) in 1978 (Steptoe and Edwards, 1978), over 5 million children have been born after ART worldwide (European Society of Human Reproduction and Embryology, 2012).

Although fertility treatment is generally considered to be safe, recent research has shown that the children born after such treatment may be at increased risk of several adverse short-term health consequences, such as low birthweight (McDonnald *et al.*, 2009; Pandey *et al.*, 2012), preterm birth (McDonnald et al., 2009, 2010; Pandey *et al.*, 2012) and birth defects (Hansen *et al.*, 2013). Few large-scale epidemiological studies have been conducted to investigate the risk of long-term health consequences, such as mental disorders.

Concern that fertility treatment may affect the risk of mental disorders in children arises mainly from studies that found increased risks of autism spectrum disorders (ASD) (Zachor and Ben Itzchak, 2011; Lyall *et al.*, 2012; Shimada *et al.*, 2012; Bay *et al.*, 2013; Grether *et al.*, 2013; Mamidala *et al.*, 2013; Kissin *et al.*, 2015), but increased risk of mental retardation (Sandin *et al.*, 2013), hyperkinetic disorders (Källén *et al.*, 2011), tic disorders, behavioural and emotional disorders with early onset and attention-deficit/hyperactivity disorders (ADHD) (Bay *et al.*, 2013) have also been found. Still other studies failed to find an association between fertility treatment and mental disorders (Strömberg *et al.*, 2002; Pinborg *et al.*, 2004, 2010; Stein *et al.*, 2006; Hvidtjorn et al., 2011; Lethi *et al.*, 2013; Lyall *et al.*, 2013), or even suggested a decreased risk (Maimburg and Vaeth, 2007). Hence, the results have been inconsistent, which may be due to methodological limitations, including small study size, short or incomplete follow-up, lack of adjustment for potential confounders and variation in the definition of fertility treatment. Also, even if effects of fertility treatment on mental health are found, they may be related to the underlying infertility rather than the treatment.

By using register data for all children born in Denmark between 1969 and 2006, our aim was to determine whether children born to women with fertility problems are at higher risk of being hospitalized or attending outpatient clinics at psychiatric hospitals for mental disorders (hereafter referred to as severe mental disorders) compared with children born to women without fertility problems. This retrospective, register-based cohort study will be the most well-powered study to date and the first with an adequately long follow-up period for assessing risk patterns from infancy to young adulthood.

Materials and Methods

Study population

Since 2 April 1968, all residents of Denmark have been recorded in the computerized Civil Registration System by a unique personal identification number (PIN) (Pedersen, 2011). The PIN, which contains information about date of birth and sex, is included in all Danish health registries and ensures accurate linkage of information among registries. The Civil Registration System also contains information on vital status (date of migration, date of death or date of loss to follow-up) and linkage between legal parents and live born children if both were alive on April 1968 and the child was born after 1953. We used this registry to obtain the PIN, maternal PIN, paternal PIN, birth order and vital status of all 2 412 721 children born in Denmark between 1 April 1969 and 31 December 2006.

Follow-up for severe mental disorders

The study population was followed for the occurrence of severe mental disorders by linkage to the nationwide Danish Psychiatric Central Research Registry using the PIN. This registry contains records of all hospital admissions for mental disorders in Denmark since 1 April 1969 (Mors *et al.*, 2011). Since 1995, the Registry has also included information on all outpatient contacts at psychiatric hospitals and is considered virtually complete for diagnoses of severe mental disorders, as there were no private psychiatric hospitals in Denmark in the study period (Mors *et al.*, 2011). Before 1995, all psychiatric diagnoses were reported according to the classification system of the International Classification of Diseases, 8th revision (ICD-8), whereas, after 1994, they were reported according to the 10th revision (ICD-10) (Mors *et al.*, 2011). On the basis of the ICD-10 and ICD-8 codes, we separated the psychiatric diagnoses into 1 main group 'any mental disorder' and 11 main discharge diagnostic groups (Table I). Furthermore, two discharge subgroups of interest were defined: autism spectrum disorders (ASD) and attention deficit/hyperactivity disorders (ADHD). A standardized conversion table of ICD-8 and ICD-10 codes from the Danish National Centre for Register-based Research was used for the categorization, and the diagnoses were further verified by a specialist in child and adolescent psychiatry (K.J.P.). For all analyses, we used the first registered main discharge diagnosis for the child or the adult in question. Thus, individuals who were hospitalized for different main discharge diagnoses could be included in analyses of more than one main discharge group of mental disorders.

All analyses were performed separately for: (i) severe mental disorders occurring at any age, (ii) severe mental disorders occurring in childhood (0–19 years) and (iii) severe mental disorders occurring in young adulthood (20–40

Table I Discharge diagnoses of mental disorders according to ICD-8 and ICD-10 codes.

Discharge diagnosis	ICD-8	ICD-10
Any mental disorder	290–315	F00–99
Organic, including symptomatic, mental disorders	290.xx, 292.xx–294.xx, 299.04, 309.xx, 342.xx	F00.x–09.x
Mental disorders due to psychoactive substance use	291.xx, 294.3x, 303.xx–304.xx	F10.x–19.x
Schizophrenia	295.xx, 297.xx, 298.2x–298.9x, 299.00–299.03, 299.05, 299.09	F20.x–29.x
Mood (affective) disorders	296.xx, 298.09, 298.19, 300.49, 301.19	F30.x–39.x
Neurotic, stress-related and somatoform disorders	300.xx, 305.xx, 306.8x–306.9x, 307.xx	F40.x–49.x
Behavioural syndromes associated with physiological and physical factors	305.6x, 306.4x–306.5x, 309.9x, 677.9x+294.4x, 677.9x+298.0x	F50.x–59.x
Disorders of adult personality and behaviour	301.xx–302.xx	F60.x–69.x
Mental retardation	310.xx–315.xx	F70.x–79.x
Disorders of psychological development	306.0x–306.1x, 306.3x, 308.0x	F80.x–89.x
Autism spectrum disorders	299.0x, 299.01–299.03	F84.0–84.1, F84.5, F84.8–84.9
Behavioural and emotional disorders with early onset	306.0x, 306.2x–306.3x, 306.5x–306.7x, 306.9x	F90.x–98.x
Attention-deficit hyperactivity disorders	308.3x	F90.x, F98.9
Unspecified mental disorders	NA	F99.x

ICD-8 codes were used for registration of mental disorders in the Psychiatric Central Research Registry until 1994 and ICD-10 codes from 1995 onwards.
ICD, International Classification of Diseases; NA, not applicable.

years). For the main analyses of severe mental disorders occurring at any age, the study population was followed from the date of birth until the event of interest or censoring. Censoring was performed on the date of loss to follow-up, date of death, date of migration or 31 December 2009, whichever occurred first. For the analyses of severe mental disorders occurring in childhood, censoring was additionally performed on the date of the 20th birthday. For the analyses of severe mental disorders occurring in young adulthood, all children who had reached the age of 20 years during the study period without a diagnosis of a severe mental disorder or censoring were included and followed from their 20th birthday until the event of interest or censoring (i.e. date of loss to follow-up, date of death, date of migration or 31 December 2009).

Ascertainment of maternal fertility status

We identified the exposure status of the children (i.e. maternal fertility status) by linkage to the Danish Infertility Cohort, using the maternal PIN. This cohort was established in 1997 and has been described in detail elsewhere (Jensen *et al.*, 2009). In brief, the cohort consists of all women referred to private fertility clinics or public gynaecological hospitals in the period 1963–1998, all women with a diagnosis of infertility (codes 628 and N97, ICD-8 and ICD-10, respectively) recorded in the National Patient Registry in the period 1977–2009 and all women in the Danish IVF registry in the period 1994–2005. The total Danish Infertility Cohort consists of 109 009 women with fertility problems in the period 1 September 1963 and 31 December 2009. In all the analyses reported here, mothers in the Danish Infertility Cohort were considered to have fertility problems and mothers not in the Cohort were considered to be fertile.

Statistical analysis

Cox proportional hazards models were used to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for associations between maternal fertility status and severe mental disorders in their children. Age was used as the underlying timescale, and all analyses were further adjusted for the following potential confounders, chosen *a priori*: year of birth, sex, birth order (1, 2, ≥3), maternal age of birth (≤25, 26–28, 29–32, ≥33), paternal age at birth (≤26, 27–30, 31–34, ≥35) and parental history of mental disorder (yes/no). Information on year of birth, birth order, singleton or multiple births as well as maternal and paternal age of birth was obtained from the Civil Registration System, whereas information on parental history of mental disorder was obtained from the Danish Psychiatric Central Research Registry. All analyses were performed for: (i) all births and (ii) singleton births only. A frailty model was used to take into account the potential correlations between outcomes of children from the same mother. However, as this sensitivity analysis did not markedly change the risk estimates (results not shown), we chose to report risk estimates without the frailty model. Tests were conducted as Wald tests, and *P*-values below 5% were considered statistically significant. All analyses were performed in R version 3.0.1.

Research ethics and data protection

The study protocol was approved by the Danish Scientific Ethical Committee and the Danish Data Protection Agency.

Results

Of the 2 412 721 children born between 1 April 1969 and 31 December 2006 and followed for the occurrence of severe mental disorders, we excluded 25 614 children for whom information on one or more potential confounders was missing, leaving 2 387 107 children for analyses. Of these, 124 269 (5%) were born to women with fertility problems. The overall mean follow-up time was 21.4 years (range, 0–40.8 years; median, 20.8 years) resulting in a total of 50 306 814 person-years of observation. For children born to women with fertility problems, mean follow-up time was 14.4 years (range, 0–40.8 years; median, 12.4 years), whereas the mean follow-up time for children born to women without fertility problems was 21.2 years (range, 0–40.8 years; median, 20.5 years). A severe mental

disorder was diagnosed in 168 686 children during the follow-up period and of these, 7843 children (5%) were born to women with fertility problems (Fig. 1). The mean age at diagnosis was 19.1 years (standard deviation, 8.6 years; range, 0–40.5 years).

The distribution of selected birth characteristics according to maternal fertility status is shown in Table II. Children born to women with fertility problems differed slightly from those born to fertile women: more were born after 1996, of male sex and the first-born child; furthermore, the maternal and paternal age at birth was generally higher for children born to women with fertility problems.

Figure 2 shows the relative risks of severe mental disorders according to maternal fertility status among all births. Children born to women with fertility problems had a modest increase in risk of any severe mental disorder (HR 1.23; 95% CI 1.20–1.26) and increased risks of all the main discharge diagnostic groups of severe mental disorders examined (risk estimates, 1.06–1.45). The highest risk was found for severe mental disorders due to psychoactive substance use (HR 1.45; 95% CI 1.35–1.56), and notably increased risks were observed for schizophrenia (HR 1.16; 95% CI 1.07–1.27), mood (affective) disorders (HR 1.21; 95% CI 1.15–1.28) and mental retardation (HR 1.20; 95% CI 1.09–1.31). Increased risk was also observed for one of the two specific subgroups examined, ADHD (HR 1.36; 95% CI 1.29–1.45).

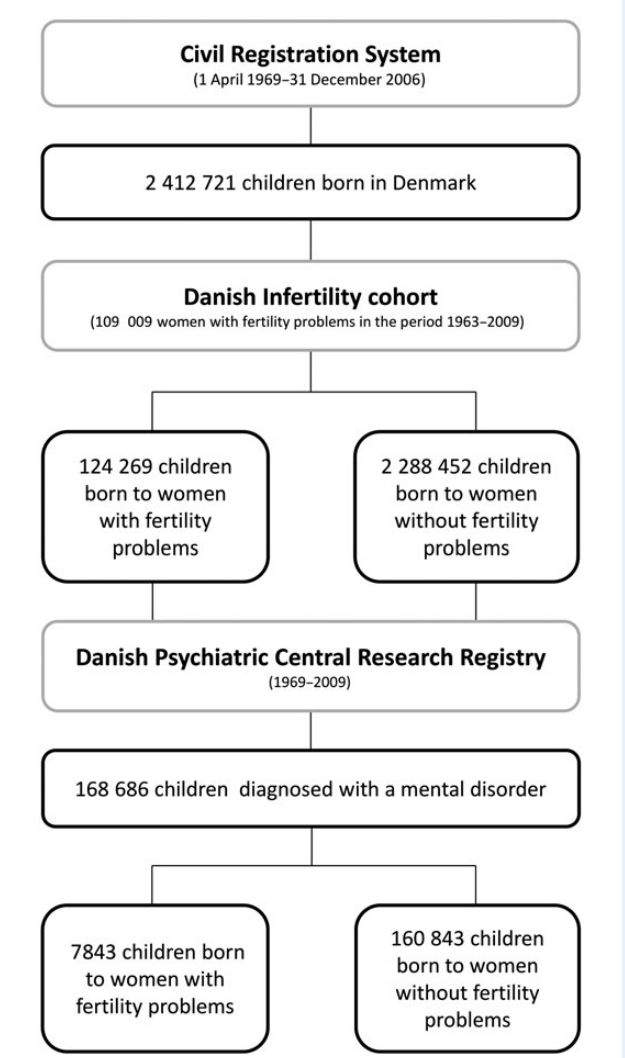

Figure 1 Identification of children born to women with and without fertility problems and number of children diagnosed with severe mental disorders.

Of the 124 269 children born to women with fertility problems, 108 707 (87%) children were singletons, whereas 2 234 433 (98%) out of all 2 288 452 children born to women without fertility problems were singletons. When the risk of mental disorder in singletons only was addressed, the risk estimates did not change notably (Supplementary Figure S1).

Separate analyses for severe mental disorders diagnosed in childhood (0–19 years) and in young adulthood (20–40 years) are shown in Table III. The risks of any severe mental disorder and of all but one (Organic, including symptomatic, mental disorder diagnosed in childhood) discharge diagnostic groups assessed were increased in children born to women with fertility problems, both in childhood and in young adulthood. For any severe mental disorder and for the vast majority of the main discharge diagnostic groups, no statistically significant difference was observed in childhood and in adulthood. The only exceptions were disorders of adult personality and behaviour, behavioural and emotional disorders with early onset including ADHD, and unspecified mental disorders, for which the risk estimates in young adulthood were statistically significantly higher than those in childhood. For example, the risk for ADHD was increased by 1.73 in young adulthood (95% CI 1.43–2.09) but only by 1.33 (95% CI 1.26–1.42) during childhood (P for difference =0.01).

Discussion

In the largest nationwide register-based cohort study to date, consisting of all Danish children born between 1969 and 2006, we found a 23% increased risk for any severe mental disorder in children born to women with fertility problems. Increased risks of 6–45% were observed for all the main discharge diagnostic groups of severe mental disorders examined, including schizophrenia, mood (affective) disorders, mental retardation, disorders of psychological development (including ASD) and behavioural and emotional disorder with early onset (including ADHD). The risks were also increased after stratification by age at diagnosis, indicating that the increased risk for a mental disorder persists into adulthood.

The strengths of our study include the high statistical precision of the risk estimates, because of the large sample size of almost 2 400 000 children born from 1969 to 2006 and the large number of children with a severe mental disorder (n = 168 686) during a follow-up period of up to 40 years. Due to the long follow-up period (median = 21 years), this is the first study that has been able to assess the risk of mental disorders in young adulthood (20–40 years). Furthermore, from our comprehensive data on all the main discharge diagnoses after hospital admission or outpatient contact at psychiatric hospitals for mental disorders, we were able to estimate the risks of several mental disorders that have not previously been studied (i.e. organic, including symptomatic, mental disorders, mental disorders due to psychoactive substance use, neurotic, stress-related and somatoform disorders, behavioural syndromes associated with physiological and physical factors and disorders of adult personality and behaviour). Other strengths include the nationwide population-based design, which allows generalization of the results, no loss to follow-up (as relocations within the country, emigration and

Table II Distribution of selected birth characteristics according to maternal fertility status.

Characteristic	Children born to women with fertility problems No. (%)	Children born to women without fertility problems No. (%)
Total	124 269 (100.0)	2 288 452 (100.0)
Sex		
Male	64 063 (51.6)	1 174 616 (51.3)
Female	60 206 (48.4)	1 113 836 (48.7)
Period of birth		
1969–1976	6 551 (5.3)	548 004 (23.9)
1977–1986	19 690 (15.8)	537 466 (23.5)
1987–1996	36 302 (29.2)	611 546 (26.7)
1997–2006	61 726 (49.7)	591 436 (25.8)
Birth order		
1	72 735 (58.5)	994 764 (43.5)
2	37 695 (30.3)	854 993 (37.4)
≥3	13 839 (11.1)	435 766 (19.1)
Maternal age at birth (years)		
≤25	20 382 (16.4)	646 217 (28.3)
26–28	17 084 (13.7)	535 069 (23.4)
29–32	34 147 (27.5)	623 308 (27.3)
≥33	52 656 (42.4)	480 939 (21.0)
Paternal age at birth (years)		
≤26	18 396 (15.0)	591 390 (26.1)
27–30	25 149 (20.4)	666 407 (29.4)
31–34	33 327 (27.1)	526 793 (23.3)
≥35	46 114 (37.5)	480 334 (21.2)
Parental history of mental disorder		
No	109 365 (88.0)	2 093 270 (91.5)
Yes	14 904 (12.0)	195 182 (8.5)

death are recorded in Danish registries) and no recall bias, as the study is entirely register-based.

Few studies have been published on the association between infertility, its treatment and the risk of mental disorders in children, and the results have been inconsistent. In line with our results, another recent Danish study (Bay *et al.*, 2013) showed a ~20% increased risk of any mental disorder in children born after fertility treatment as compared with spontaneously conceived children. The study by Bay *et al.* (2013) is also based on data from the Danish national health registers but differed from our study in the definition of the exposure variables as the study by Bay *et al.* (2013) analysed the association between fertility treatment and risk of mental disorders whereas the present study analysed the association between fertility problems and risk of mental disorders. Further, the studies differed in the number of study subjects included. Bay *et al.* (2013) included 555 828 children born from 1995 to 2003 (maximal attained age at the end of follow-up: 17 years), whereas the present study included 2 412 721 children born from 1969 to 2006 (maximal attained age at end of follow-up: 40 years). Furthermore the studies differ in the mean length of the follow-up period (12.7 years in the study by Bay *et al.* (2013) versus 21.4 years in the present study).

The main part of studies in this research field has focused on risks for specific mental disorders and in particular ASD, a subgroup of disorders of psychological development (ICD-10 codes F80–89.9). The results of most studies indicated increased risks of both disorders of psychological development (Bay *et al.*, 2013) and ASD (Funderburk *et al.*, 1983; Hvidtjorn *et al.*, 2011; Zachor and Ben Itzchak, 2011; Lyall *et al.*, 2012; Shimada *et al.*, 2012; Bay *et al.*, 2013; Grether *et al.*, 2013; Mamidala *et al.*, 2013; Kissin *et al.*, 2015). Still other studies found no association (Pinborg *et al.*, 2004; Stein *et al.*, 2006; Lethi *et al.*, 2013; Sandin *et al.*, 2013) or a decreased risk of infantile autism (Maimburg and Vaeth, 2007). A limited number of studies focused on groups of mental disorders other than ASD. In accordance with our results, some of these studies found increased risks of behavioural and emotional disorders with early onset (Bay *et al.*, 2013), ADHD (Källén *et al.*, 2011; Bay *et al.*, 2013), mental retardation (Sandin *et al.*, 2013), mood (affective) disorders (Wagenaar *et al.*, 2009; Beydoun *et al.*, 2010) and schizophrenia (Funderburk *et al.*, 1983). Others found no association with mental retardation (Strömberg *et al.*, 2002; Pinborg *et al.*, 2004, 2010), severe mental development disturbances (Pinborg *et al.*, 2004) or Tourette syndrome (Shimada *et al.*, 2012). An explanation for the divergent results may be due to heterogeneity of the previous studies as they vary by source of exposure information (questionnaires filled out by parents, hospital records, and national registers), diagnostic inclusion criteria, differences in the definition of fertility treatment/infertility and adjustment for different potential confounders. Furthermore several studies are limited by other methodological problems including a small sample size and a limited follow-up period.

Despite the increased interest in the field of mental disorders during the past few decades, their aetiology is still largely unknown, although there is strong evidence of environmental (Landrigan, 2010; Atladottir *et al.*, 2012), genetic (Betancur, 2011; O'Roak et al., 2012) and epigenetic (Flashner *et al.*, 2013; Millan, 2013) influences for certain types, such as ASD. A possible mechanism linking infertility, fertility treatment and mental disorders in children is epigenetic changes. Experimental studies on animals have shown altered expression of imprinted genes in sheep and mice born after fertility treatment (Young *et al.*, 2001; Fortiere et al., 2008). Similarly, in humans, fertility drugs (Brannian *et al.*, 2010), oocyte manipulation and *in vitro* culture (Leese *et al.*, 1998) have been linked to altered cell physiology leading to changes in early embryo gene expression patterns. In support of the accumulating evidence that fertility treatment affects epigenetic mechanisms in humans, children born after fertility treatment have been found to be at increased risk of extremely rare imprinting disorders that are due to abnormal genomic imprinting (Horsthemke and Ludwig, 2005), indicating widespread epigenetic disruption in these children. It is still unclear, however, whether any epigenetic effects seen after fertility treatment are due to the treatment or to the infertility. It has been suggested that women with fertility problems are more likely to generate gametes with epigenetic modifications (Paoloni-Giacobino and Chaillet, 2004) and that some subfertile couples have a genetic predisposition to epigenetic instability (Dada *et al.*, 2012). Furthermore, steroid hormone imbalance, which is central to certain types of infertility (Lyall *et al.*, 2013), may affect the risk of mental disorders by affecting epigenetic fetal programming (Jessen and Auger, 2011; Nugent and McCarthy, 2011; Morgan and

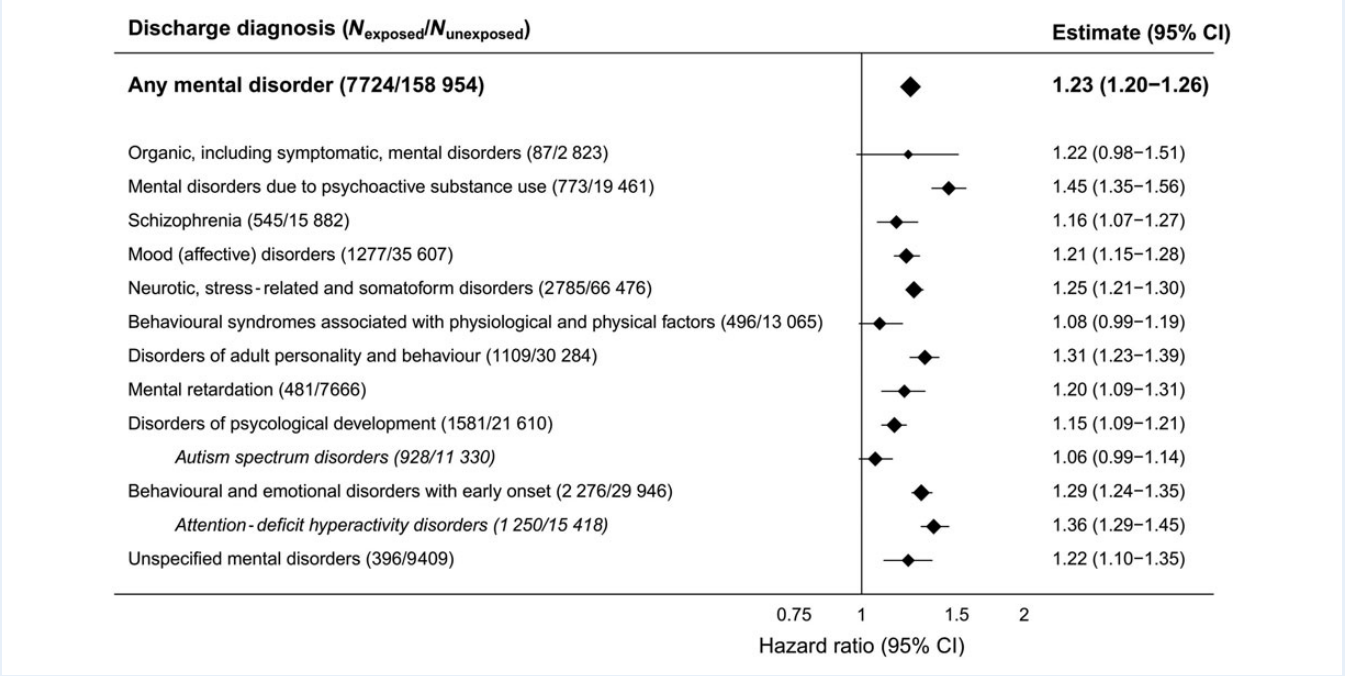

Figure 2 Hazard ratios (HRs) and 95% confidence intervals (CIs) for severe mental disorders at any age in children born to women with fertility problems in comparison with children born to women without fertility problems. All HRs are adjusted for year of birth, birth order (1, 2, ≥3), sex, maternal age at birth (≤25, 26–28, 29–32, ≥33 years), paternal age at birth (≤26, 27–30, 31–34, ≥35 years) and parental history of mental disorder (yes/no). The sizes of the diamonds are proportional to the number of events in each group.

Table III Hazard ratios (HRs) and 95% confidence intervals (CIs) for severe mental disorders in childhood (0–19 years) and in young adulthood (20–40 years) for children born to women with fertility problems compared with children born to women without fertility problems.

Discharge diagnosis	Childhood			Young adulthood			
	$N_{exposed}/N_{unexposed}$	HR	(95% CI)	$N_{exposed}/N_{unexposed}$	HR	(95% CI)	*P*, difference
Any mental disorder	5715/85 611	1.22	(1.19–1.25)	2 128/75 232	1.27	(1.22–1.33)	0.10
Organic, including symptomatic, mental disorder	34/1017	0.97	(0.69–1.37)	54/1846	1.45	(1.10–1.91)	0.07
Mental disorders due to psychoactive substance use	272/4813	1.38	(1.22–1.57)	523/14 936	1.48	(1.36–1.62)	0.38
Schizophrenia	269/5302	1.21	(1.06–1.37)	290/10 798	1.13	(1.00–1.27)	0.46
Mood (affective) disorders	545/9085	1.26	(1.16–1.38)	747/26 844	1.18	(1.10–1.27)	0.25
Neurotic, stress-related and somatoform disorders	1637/26 003	1.25	(1.19–1.31)	1202/41 210	1.26	(1.19–1.34)	0.77
Behavioural syndromes associated with physiological and physical factors	299/6050	1.03	(0.92–1.16)	203/7122	1.17	(1.01–1.34)	0.19
Disorders of adult personality and behaviour	418/8702	1.21	(1.09–1.33)	713/21 963	1.37	(1.27–1.48)	0.04
Mental retardation	444/6001	1.22	(1.10–1.34)	41/1792	1.03	(0.75–1.41)	0.33
Disorders of psychological development	1560/20 938	1.14	(1.09–1.21)	35/997	1.29	(0.92–1.82)	0.48
Autism spectrum disorder	910/10 740	1.06	(0.99–1.13)	28/753	1.39	(0.95–2.03)	0.17
Behavioural and emotional disorder with early onset	2181/27 836	1.27	(1.22–1.33)	130/2574	1.72	(1.44–2.06)	<0.001
Attention-deficit hyperactivity disorder	1152/13 482	1.33	(1.26–1.42)	117/2165	1.73	(1.43–2.09)	0.01
Unspecified mental disorder	196/3324	1.09	(0.94–1.27)	213/6220	1.35	(1.18–1.56)	0.04

HRs adjusted for year of birth, birth order (1, 2, ≥3), sex, maternal age at birth (≤25, 26–28, 29–32, ≥33 years), paternal age at birth (≤26, 27–30, 31–34, ≥35 years) and parental history of mental disorder (yes/no).

Bale, 2012). This suggestion is supported by recent findings of increased fetal testosterone in the amniotic fluid of children who later received a diagnosis of ASD (Baron-Cohen *et al.*, 2015). However, in the present study design we did not include information on fertility treatment and were therefore unable to distinguish between the effects of infertility and fertility treatment.

Some limitations of our study should be noted. We only had information on mental disorders so severe that they warranted hospitalization or outpatient care at hospitals. Therefore, the present study was not designed to analyse the association between fertility status and less severe mental disorders. Maternal fertility status (i.e. exposure status) was identified using information from all public gynaecological departments and private fertility clinics in Denmark supplemented with information from the Danish National Patient Registry and the Danish IVF Registry; consequently most women evaluated for fertility problems in the study period were identified. However, some women have undiagnosed fertility problems and some may have been referred to private gynaecologists or midwifes; wherefore the obtained risk estimates may be slightly underestimated. Also, although we controlled for several important potential confounders, including age, sex, birth year, birth order, maternal age at birth, paternal age at birth and parental history of mental disorder; however, we cannot rule out the possibility that there could be other confounders that we were unable to control for. In contrast to other studies (Pinborg *et al.*, 2004; Maimburg and Vaeth, 2007; Bay *et al.*, 2013; Grether *et al.*, 2013; Lethi *et al.*, 2013), we chose not to adjust for perinatal factors such as gestational age, preterm birth, multiple gestations and low birthweight, as it has been shown that such adjustment may introduce bias (Peterson *et al.*, 2006). Furthermore, perinatal factors may be considered intermediary factors rather than potential confounders and should therefore not be adjusted for when examining the effect of the primary exposure (i.e. maternal fertility problems) on the outcome (i.e. mental disorders), unless examining mediating variables. Adjustment for socioeconomic status could be argued for as ASD is more likely to be identified in children whose parents have long education (Baird *et al.*, 2006), and women with higher socioeconomic status may be more likely to use fertility treatment (Lethi *et al.*, 2013). In Denmark, however, all visits to general practitioners are free of charge and fertility treatment is heavily subsidized, for what reason the proportion of women in different socioeconomic groups who use fertility treatment may be more homogenous than in other Western countries. However, as socioeconomic status is also associated with differences in various lifestyle factors, we cannot rule out that our risk estimates may be slightly affected by unmeasured confounding of socioeconomic status. Finally, during the study period, the classification codes for mental disorders changed from the ICD-8 (1969–1994) to ICD-10 (1995–2009), which might have affected the results of the study; however, sensitivity analyses restricted to the period in which only ICD-10 codes were used (children born after 1994) gave results that were virtually unchanged (data not shown).

In conclusion, our results show that children born to women with fertility problems are at increased risk for severe mental disorders in both childhood and young adulthood. Further large studies with differentiation between factors related to fertility treatment and to the underlying infertility are needed to elucidate the mechanisms. Irrespective of whether the increased risk is related to the treatment or the underlying infertility, this study shows that children born to women with fertility problems are at a modestly increased risk of severe, long-term mental health consequences. It is therefore important to focus on the long-term health of these children.

Supplementary data

Supplementary data are available at http://humrep.oxfordjournals.org/.

Authors' roles

S.K.K., M.H. and A.J. contributed to the conception and design of the study. S.K.K., A.J. and M.H. acquired data. M.H., A.J., T.S.S.N., M.F.S., S.M.J., K.J.P. and S.K.K. analysed and interpreted the data. M.F.S. wrote the first draft of the manuscript, which was critically revised by M.H., A.J., K.J.P., T.S.S.N., S.M.J. and S.K.K. All authors had full access to all data and take full responsibility for its integrity and the accuracy of the analysis. All the authors approved the final version of the manuscript.

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Conflict of interest

None declared.

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