Neurocognitive Development and Mental Health

Parental age and attention-deficit/hyperactivity disorder (ADHD)

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Abstract

Background: Previous studies have suggested that young mothers more often have children with ADHD. We used sibling comparisons to examine the nature of this association and to investigate if this association is explained by early environment or genetic and socioeconomic factors.

Methods: A large population-based cohort including all singletons born in Denmark from 1 January 1991 through 31 December 2005 was followed from birth until 30 April 2011. Data were available for 94% (N = 943,785) of the population. Offspring ADHD was identified by an ICD-10 diagnosis of Hyperkinetic Disorder (HKD). We used sibling-matched Cox regression to control for genetic and socioeconomic factors.

Results: In the population cohort we found that children born by parents aged 20 years or younger had more than twice the risk of being diagnosed with ADHD compared with children with parents between 26 and 30 years of age. When comparing full siblings the associations were attenuated, but we found a trend of increased risk of ADHD with decreasing maternal age, which was not seen for paternal age.

Conclusions: Sibling comparisons suggested that the associations between both maternal and paternal age and ADHD are partly explained by common genetic and socioeconomic factors. The trend of increased risk of ADHD with decreasing maternal age, but not with paternal age, may be linked to pregnancy or early-life environmental factors. Even though only a smaller part of the association can be attributed to environmental factors, there is a public health interest to support young parents through their first years of parenthood.

Key words: Maternal age, paternal age, parental age, hyperkinetic disorder, attention-deficit/hyperactivity disorder, sibling design
Attention-deficit/hyperactivity disorder (ADHD) is one of the most common psychiatric disorders in childhood. During recent decades a trend towards an increase in ADHD diagnosis has been observed, with a current estimated prevalence of 3–7% among children and adolescents. This trend may to some extent be related to changes in diagnostic criteria, earlier age at diagnosis, increased clinical awareness and media attention.

There is robust evidence from a wide range of study designs that the development of ADHD has a strong genetic component. First-degree relatives of those with ADHD are two to eight times more likely than relatives of unaffected individuals to also show ADHD symptoms. Twin studies have found higher concordance rates for ADHD among monozygotic twin than dizygotic twin pairs, with a heritability estimate around 80%. However, heritability estimates include not only genetic influences, but also the effects of gene-environment interaction. Genetic predisposition in parents may lead to inherited predisposition in children with expression triggered by environmental factors.

ADHD constitutes a major social and economic challenge, and identification of potentially preventable environmental factors is of major public health interest. Environmental exposures in utero as well as in early life have been shown to be important for lifetime health, but to date only few plausible environmental causes have been identified for the development of ADHD, leaving limited room for prevention.

There is an increasing focus on potential perinatal factors related to mental health in offspring. A systematic review of pre- and perinatal risk factors for ADHD implicated exposure to tobacco smoke in utero as a suspected risk factor although recent research questions this conclusion. Also, exposure to other substances during pregnancy has been linked to ADHD. Moderate maternal alcohol use during pregnancy and exposure to illicit substances have been associated with increased risk of ADHD in some, but not all, studies. The probably most robust associations so far are the links between intrauterine growth retardation and prematurity and subsequent ADHD in the offspring. Another consistently found association is that children with ADHD have younger parents compared with children without ADHD, but surprisingly few studies have aimed to explore the nature of this association by including both parents in their analyses.

Although the association has not been studied in depth, a number of biological hypotheses have been suggested. An imbalance between the competing nutritional needs of the mother and child may play a role; and, further, children of young mothers are exposed to different amounts of sex-related hormones compared with children of older mothers. A likely alternative explanation is that the association simply reflects genetic and socioeconomic factors accompanying young parenthood. A recent Swedish study using sibling and cousin comparisons to partly control for unmeasured genetic and environmental confounding, supported that the association is mainly explained by genetic factors contributing to both young maternal age at childbirth and ADHD in the offspring. If this is the case, a mother may confer risk to her children regardless of whether she gives birth as a teenager or later in life, which has been supported by studies finding that maternal age at first birth was more predictive of later-born children’s psychiatric problems than maternal age at the child’s own birth. Maternal age at her first birth could be seen as a marker of genetic and social factors related to ADHD in young mothers.

The crucial question is whether this higher risk in offspring of younger mothers constitutes a potential for prevention by delaying fertility, or whether focus should be on supportive interventions in young parents to improve the upbringing environment and thereby reduce symptoms in offspring with a genetic predisposition.

If the association between young maternal age and offspring ADHD is caused by familial factors, a similar

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**Key messages**

- Children diagnosed with ADHD were more likely to have younger parents than children without ADHD.
- The highest risk of ADHD was found when both parents were very young.
- Sibling comparisons suggested that the association between both young maternal and paternal ages and ADHD mainly can be accounted for by genetic and socioeconomic factors.
- In the area of public health, focus on delaying fertility without ameliorating the background risks experienced by young parents and their children may not be fully effective in reducing offspring ADHD. Public policy initiatives should be targeted at attention to young parents and individual support of at-risk parents and their children.
association is to be expected between young paternal age and ADHD and, further, an additional risk is to be expected when both parents are very young. Few studies have reported on associations between paternal age and ADHD, and results have been conflicting.23,27,39,40 A study from Sweden reported advanced paternal age to be associated with an increased risk of ADHD.40 In contrast, another study from Israel found that the paternal age distribution among children with ADHD was similar to what we see in the general population.39

We studied offspring ADHD according to maternal as well as paternal age, and combined parental age in a large population-based cohort. We did comparisons of risk between full and half siblings to control for unmeasured genetic and socioeconomic factors and other shared family characteristics.

Methods

Setting

All citizens in Denmark are given a unique civil registration number at birth or immigration, by the Danish Central Population Registry (DCPR). This registry includes information on date of birth and biological relationships for all citizens in Denmark since 1968. Using the civil registration number we linked data from the Danish Medical Birth Registry (DMBR) and the Danish Psychiatric Central Research Register (DPCR) with psychiatric outcome.

We defined a cohort study with follow-up of singletons born in Denmark from 1 January 1991 to 31 December 2005. All births by women with permanent residence in Denmark (N=999 713) were identified in the Danish Medical Birth Registry, DMBR. We excluded multiple births (n=37 406) and, after linkage with the DPCR, we excluded additionally 18 522 children with insufficient or missing data for the biological father; this left 943 785 children in the cohort (Figure 1). The study was approved by the Danish Health Authority and the Danish Data Protection Agency.

Maternal and paternal ages at birth were calculated based on the civil registration numbers of mothers, fathers and children, and was then divided into five age groups ranging from 20 years or younger to older than 35 years, in 5-year intervals.

Outcome definition

We defined offspring ADHD as children with an ICD-10 diagnosis of Hyperkinetic Disorder (F90x) after the age of 5 years, identified in the DPCR. The ICD-10 classification system has been used since 1994. The DPCR provides individual-level data on clinical diagnoses and admission dates for all inpatient psychiatric hospital admissions since 1969.

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Figure 1. Flowchart.
and outpatient visits at psychiatric hospitals and clinics since 1995.

Statistical analyses

Maternal and paternal ages were studied separately. We used maternal or paternal age between 26 and 30 years as the reference group. In a subanalysis, maternal and paternal ages were further divided into three age groups—< 26, 26–30, > 30 years—to study parental age combining both maternal and paternal age. We used maternal and paternal ages > 30 years as the reference group. Finally, to examine the full childbearing age range, maternal and paternal ages were studied as continuous variables using cubic splines.41 Measured covariates included: gender (girls, boys); parity (1, > 1); maternal smoking during pregnancy (yes, no); and birth-year groups (1-year intervals).

We examined the relative risk (RR) of being diagnosed with ADHD associated with the exposure variable of interest, using Cox regression. Cox regression estimates hazard rate ratios comparing the different exposure groups, assuming the hazard ratio remains constant over time. We evaluated the proportional hazard assumption by graphical assessment of log-log plots, and the assumption was acceptable. Results are reported as hazard ratios (HR) with 95% confidence intervals (CIs). The Cox regression allowed us to control for entry at different time points, varying length of follow-up and changing rates of ADHD over time. Since ADHD is a rare outcome resulting in low hazard rates, the relative HR will approximate RR and hazard ratios can be interpreted in terms of additional cumulative risk. Each child contributed with risk time beginning at the age of 5 years old and ending at diagnosis, immigration, death or end of follow-up on 30 April 2011, whichever came first. To control for the lack of independence of children within the same family, we used robust variance estimation in the population cohort analyses. We did regular cohort analyses and then compared results with both full and half sibling-matched analyses. All statistical analyses were performed with Stata/SE 12.

Population cohort analyses

To adjust for changing diagnostic criteria, differences in assessment methods over time, changing age at first childbirth and the changing prevalence of ADHD during the study period, we adjusted for calendar time by including separate baseline diagnostic rates (strata) for each birth year.1,10,42

We estimated crude and adjusted HR within the population cohort. Maternal and paternal age were studied categorically and as continuous variables expressed as cubic splines with five knots, which are the default knot values based on Harrell’s recommended percentiles.41 The adjusted HR was in addition adjusted for parity, maternal smoking during pregnancy and gender. As maternal and paternal ages are highly correlated, we adjusted for the other parent’s age by including the age difference between parents in the model; this covered both the parental age difference and the age of the other parent as a confounder.43

Gestational age and birthweight are assumed to be potential intermediate factors and were therefore not adjusted for in the final models,46 but in subanalyses we examined if the association between maternal age and ADHD was modified by gestational age or birthweight. Further, we examined whether associations of interest were modified by parity, gender or birth year.

Sibling-matched analyses

Two sibling subcohorts were identified as children born in the time period 1 January 1991 to 31 December 2005. One included full siblings; the other included half siblings with the same biological mother. Full sibling comparisons provide stronger adjustment for shared genetic and time-stable environmental factors compared with half sibling comparisons. Only families with at least two siblings, of which at least one child was diagnosed with ADHD, were included, corresponding to 6436 families in the full sibling cohort and 1795 families in the half sibling cohort.

The sibling-matched design extends the Cox regression model by stratifying on the set of either full or half siblings. In the stratified Cox regression model, each family has its own baseline rate function reflecting the family’s shared genetic and environmental factors and thus adjustment for all factors that are shared within each sibling set. Additionally, the sibling comparisons allow us to control for the age difference between parents among full siblings and maternal age at birth of first child among both full and half siblings. Only families with at least two siblings discordant for parental age group contributed with information on the association between parental age and ADHD. The adjusted sibling-matched analyses were controlled for the same covariates as in the population cohort and, in addition, adjustment for the increasing prevalence of ADHD was achieved by including calendar time in a cubic spline with five knots.41

Results

Population cohort

In the population cohort, 1.30% of the children had a hospital diagnosis of ADHD (1.99% boys and 0.58% girls,
respectively) (Table 1). We found that both decreasing maternal and paternal ages were associated with higher risk of being diagnosed with ADHD; the associations were marginally attenuated after adjustment for the measured covariates. Children with mothers or fathers 20 years of age or younger had more than twice the risk of ADHD (HR = 2.24, 95% CI 2.07–2.42 and HR = 2.28, 95% CI 2.03–2.57, respectively) (Table 2) compared with children with parents between 26 and 30 years of age. The associations between the categorized maternal as well as paternal age and ADHD followed a ‘dose-response’ relation with increasing risk of ADHD with decreasing parental age (test for trend P-value < 0.001).

Additionally, we found almost similar associations when maternal and paternal ages were studied as continuous variables expressed as cubic splines. Compared with children with mothers aged 29 years or fathers aged 32 years, a higher risk of ADHD was found with decreasing maternal or paternal age (Figures 2 and 3). For children with an older father (> 30 years), the younger the mother the higher risk of ADHD. The risk increased by 25% (HR = 1.25, 95% CI 1.18–1.33) among children born to mothers aged 26–30 years and by 98% (HR = 1.98, 95% CI 1.81–2.15) among children born to mothers aged below 26 years (Table 3). Among children born to mothers older than 30 years, the risk of ADHD was also affected by paternal age (Table 3). The combination of both a young mother and a young father resulted in the highest risk for ADHD (HR = 2.31, 95% CI 2.16–2.46). In the population cohort, we did not find interaction by gestational age, birthweight, gender, parity or birth year.

Table 1. Descriptive statistics of the population cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>All births No. (%)</th>
<th>ADHD-diagnose No. (%)</th>
<th>Maternal age, mean (95% CI)</th>
<th>Paternal age, mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. (%)</td>
<td>943 785 (100)</td>
<td>12 294 (1.30)</td>
<td>29.43 (29.42–29.44)</td>
<td>32.32 (32.31–32.34)</td>
</tr>
<tr>
<td>Gender no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>458 749 (48.61)</td>
<td>2647 (0.58)</td>
<td>29.63 (29.61–29.64)</td>
<td>32.32 (32.30–32.34)</td>
</tr>
<tr>
<td>Male</td>
<td>485 036 (51.39)</td>
<td>9647 (1.99)</td>
<td>29.64 (29.62–29.65)</td>
<td>32.33 (32.31–32.34)</td>
</tr>
<tr>
<td>Birthweight, no. (%), grams</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 2000</td>
<td>13 224 (1.40)</td>
<td>281 (2.12)</td>
<td>29.74 (29.65–29.83)</td>
<td>32.50 (32.39–32.61)</td>
</tr>
<tr>
<td>2001–2500</td>
<td>23 953 (2.54)</td>
<td>467 (1.95)</td>
<td>29.36 (29.29–29.42)</td>
<td>32.03 (31.95–32.11)</td>
</tr>
<tr>
<td>2501–3000</td>
<td>111 746 (11.84)</td>
<td>1723 (1.54)</td>
<td>29.09 (29.06–29.12)</td>
<td>31.91 (31.87–31.94)</td>
</tr>
<tr>
<td>3001–3300</td>
<td>307 588 (32.59)</td>
<td>3827 (1.24)</td>
<td>29.35 (29.33–29.37)</td>
<td>32.10 (32.08–32.12)</td>
</tr>
<tr>
<td>3501–4000</td>
<td>318 112 (33.71)</td>
<td>3845 (1.21)</td>
<td>29.78 (29.76–29.80)</td>
<td>32.43 (32.41–32.45)</td>
</tr>
<tr>
<td>&gt; 4000</td>
<td>158 909 (16.84)</td>
<td>2013 (1.27)</td>
<td>30.27 (30.25–30.29)</td>
<td>32.81 (32.78–32.83)</td>
</tr>
<tr>
<td>Missing</td>
<td>10 253 (1.09)</td>
<td>138 (1.35)</td>
<td>30.08 (29.99–30.17)</td>
<td>32.99 (32.87–33.10)</td>
</tr>
<tr>
<td>Gestational age, no. (%), full weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 32</td>
<td>6581 (0.70)</td>
<td>144 (2.19)</td>
<td>29.86 (29.74–29.99)</td>
<td>32.58 (32.43–32.73)</td>
</tr>
<tr>
<td>32–36</td>
<td>38 441 (4.07)</td>
<td>708 (1.84)</td>
<td>29.52 (29.47–29.57)</td>
<td>32.18 (32.12–32.24)</td>
</tr>
<tr>
<td>37–40</td>
<td>634 759 (67.26)</td>
<td>8218 (1.29)</td>
<td>29.66 (29.65–29.67)</td>
<td>32.35 (32.34–32.37)</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>250 395 (26.53)</td>
<td>3015 (1.20)</td>
<td>29.59 (29.57–29.60)</td>
<td>32.27 (32.25–32.29)</td>
</tr>
<tr>
<td>Missing</td>
<td>13 609 (1.44)</td>
<td>209 (1.54)</td>
<td>29.27 (29.19–29.35)</td>
<td>32.22 (32.11–32.32)</td>
</tr>
<tr>
<td>Apgarscore 5 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 9</td>
<td>67 232 (7.12)</td>
<td>1070 (1.59)</td>
<td>29.59 (29.56–29.63)</td>
<td>32.16 (32.12–32.21)</td>
</tr>
<tr>
<td>10</td>
<td>86 3277 (91.47)</td>
<td>11 031 (1.28)</td>
<td>29.63 (29.62–29.64)</td>
<td>32.33 (32.32–32.34)</td>
</tr>
<tr>
<td>Missing</td>
<td>13 276 (1.41)</td>
<td>193 (1.45)</td>
<td>29.70 (29.61–29.78)</td>
<td>32.69 (32.59–32.80)</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>406 476 (43.07)</td>
<td>5565 (1.37)</td>
<td>27.76 (27.75–27.78)</td>
<td>30.54 (30.53–30.56)</td>
</tr>
<tr>
<td>2</td>
<td>342 850 (36.33)</td>
<td>4245 (1.24)</td>
<td>30.22 (30.21–30.23)</td>
<td>32.85 (32.84–32.87)</td>
</tr>
<tr>
<td>&gt; 2</td>
<td>177 717 (18.83)</td>
<td>2255 (1.27)</td>
<td>32.82 (32.80–32.84)</td>
<td>35.40 (35.38–35.43)</td>
</tr>
<tr>
<td>Missing</td>
<td>16 742 (1.77)</td>
<td>229 (1.37)</td>
<td>29.10 (29.03–29.18)</td>
<td>32.02 (31.93–32.11)</td>
</tr>
<tr>
<td>Smoking during pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non smoker</td>
<td>676 117 (71.64)</td>
<td>6661 (0.99)</td>
<td>29.89 (29.88–29.90)</td>
<td>32.56 (32.55–32.57)</td>
</tr>
<tr>
<td>Missing</td>
<td>47 792 (5.06)</td>
<td>676 (1.41)</td>
<td>29.54 (29.50–29.58)</td>
<td>32.37 (32.32–32.42)</td>
</tr>
<tr>
<td>Birthyear</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1991–95</td>
<td>318 085 (33.70)</td>
<td>4839 (1.52)</td>
<td>28.87 (28.86–28.89)</td>
<td>31.63 (31.61–31.65)</td>
</tr>
<tr>
<td>1996–2000</td>
<td>318 521 (33.75)</td>
<td>5025 (1.58)</td>
<td>29.67 (29.65–29.68)</td>
<td>32.36 (32.34–32.38)</td>
</tr>
<tr>
<td>2001–2005</td>
<td>307 179 (32.55)</td>
<td>2430 (0.79)</td>
<td>30.38 (30.37–30.40)</td>
<td>33.01 (32.99–33.03)</td>
</tr>
</tbody>
</table>
Sibling cohort
In the full sibling cohort we found a weaker ‘dose-response’ relation with higher risk of ADHD with decreasing maternal age (P-value < 0.05). Compared with children born to mothers aged between 26 and 30 years, the risk of ADHD was increased by 28% (HR = 1.28, 95% CI 0.94–1.73) among children born to mothers aged 20 years or younger (Table 4). Maternal age above 30 years remained associated with lower risk of ADHD in the offspring (Table 4). In the half sibling cohort, the same tendency of a ‘dose-response’ relation was seen (P-value 0.30). We found no indication of a ‘dose-response’ relation between paternal age and ADHD either in the full sibling or in the half sibling cohort (P-value 0.21 and 0.56, respectively).

Further, results from the full sibling cohort suggested that a sibling born when both parents were < 26 years old had 61% (HR = 1.61, 95% CI 1.13–2.30) higher risk of ADHD compared with a later-born sibling with both parents being older than 30 years old. Compared with a sibling with both parents above 30 years, a sibling born earlier in the parents’ lifespan with only a father above 30 years had a 32% (HR = 1.32, 95% CI 1.12–1.56) and a 70% (HR = 1.70, 95% CI 1.26–2.29) higher risk of ADHD if the mother was 26–30 years old or younger than 26 years, respectively (Table 5). Conversely, in full siblings,
born to mothers aged above 30 years, decreasing paternal age was no longer associated with an additional risk for ADHD. (Table 5).

**Discussion**

In the population-based cohort we found that young maternal age as well as young paternal age were associated with offspring ADHD, with the highest risk found when both parents were younger than 26 years old. In the sibling comparison, the association between maternal age and ADHD was weaker, with the weakest association observed in full siblings. We found no association between parental age and ADHD in full or half siblings. The results including comparisons between children with different degrees of genetic similarity support the hypothesis that part of the population-wide association between young maternal age as well as young paternal age and offspring ADHD may be explained by family-related factors. The association may partly be caused by genetic risk factors, as we observed the weakest association in the full sibling comparison, which provides a stronger adjustment for shared genetics than the half sibling comparison. Initiating parenting at a young age may be a proxy for behavioural genetic risk factors shared among members of the same family and transmitted from parents to their offspring, contributing to young parental age as well as offspring ADHD.

**Table 3.** Population cohort; crude and adjusted combined effect of parental age on risk of ADHD

<table>
<thead>
<tr>
<th>Maternal age, years</th>
<th>Paternal age, years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude HR*1 No.: 943 785</td>
</tr>
<tr>
<td>&lt; 26</td>
<td>2.40 (2.27–2.54)</td>
</tr>
<tr>
<td>26–30</td>
<td>1.69 (1.51–1.89)</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>2.02 (1.59–2.57)</td>
</tr>
<tr>
<td></td>
<td>1.83 (1.72–1.95)</td>
</tr>
<tr>
<td></td>
<td>1.23 (1.17–1.30)</td>
</tr>
<tr>
<td></td>
<td>1.00 (ref.)</td>
</tr>
</tbody>
</table>

*1Crude estimate stratified by birth year.
*2Adjusted estimate (parity 1/> 1; smoking no/yes; gender), stratified by birth year.
*3Test for trend.
Young parents represent a selected group of young people, and many of their characteristics may increase the risk of ADHD in offspring. Compared with those who become parents at an older age, young parents more often have a history of hyperactivity problems and they may transmit the genetic susceptibility to ADHD in the offspring even though the severity of their own symptoms would not reach the diagnostic threshold. This hypothesis is also

**Table 5. Sibling cohorts; crude and adjusted combined effects of parental age on risk of ADHD**

Risk of ADHD; HR (95% CI)

<table>
<thead>
<tr>
<th>Maternal age, years</th>
<th>Full sibling cohort</th>
<th>Paternal age, years</th>
<th>Full sibling cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude HR*1 No.: 12,769</td>
<td>&lt; 26</td>
<td>26–30</td>
</tr>
<tr>
<td></td>
<td>&lt; 26</td>
<td>1.30 (0.96–1.77)</td>
<td>1.33 (1.04–1.70)</td>
</tr>
<tr>
<td></td>
<td>26–30</td>
<td>1.08 (0.78–1.50)</td>
<td>1.32 (1.10–1.58)</td>
</tr>
<tr>
<td></td>
<td>&gt; 30</td>
<td>0.95 (0.40–2.27)</td>
<td>1.05 (0.83–1.33)</td>
</tr>
<tr>
<td></td>
<td>Adjusted HR*2 No.: 11,967</td>
<td>&lt; 26</td>
<td>1.61 (1.13–2.30)</td>
</tr>
<tr>
<td></td>
<td>26–30</td>
<td>1.35 (0.93–1.96)</td>
<td>1.45 (1.18–1.79)</td>
</tr>
<tr>
<td></td>
<td>&gt; 30</td>
<td>0.79 (0.29–2.13)</td>
<td>1.09 (0.84–1.42)</td>
</tr>
<tr>
<td>Half sibling cohort</td>
<td>Crude HR*1 No.: 3730</td>
<td>&lt; 26</td>
<td>1.96 (1.00–3.94)</td>
</tr>
<tr>
<td></td>
<td>26–30</td>
<td>1.28 (0.70–2.33)</td>
<td>1.32 (1.10–1.58)</td>
</tr>
<tr>
<td></td>
<td>&gt; 30</td>
<td>1.06 (0.40–2.82)</td>
<td>1.05 (0.83–1.33)</td>
</tr>
<tr>
<td></td>
<td>Adjusted HR*2 No.: 3683</td>
<td>&lt; 26</td>
<td>1.80 (0.86–3.80)</td>
</tr>
<tr>
<td></td>
<td>26–30</td>
<td>1.18 (0.60–2.29)</td>
<td>1.43 (0.86–2.37)</td>
</tr>
<tr>
<td></td>
<td>&gt; 30</td>
<td>1.50 (0.51–4.38)</td>
<td>0.82 (0.43–1.56)</td>
</tr>
</tbody>
</table>

*1Crude estimate (adjusting for birth date by cubic spline).
*2Adjusted estimate (birth date by cubic spline; parity 1/0; smoking no/yes; gender; other parent’s age).
*3Test for trend.
supported by research reporting that young people with ADHD behaviour are found to have earlier sexual debut and have more risky sexual behaviour with more sexual partners, and thus a higher probability of becoming parents at an earlier age.\textsuperscript{2,32,34,45–49}

If the association between young maternal age and ADHD is explained by a genetic predisposition, the timing of the birth in the mother's life may not be the critical factor in determining offspring ADHD.\textsuperscript{35,36,50–52} If such a maternal disposition to initiate childbearing at a younger age explained the observed association in the population-based cohort, we would not have expected to find an association in the sibling comparisons, as the risk will be the same among siblings. The early childbearing phenotype of the mother will be the same for all siblings, and the attenuation in the association between maternal age and ADHD found in the sibling comparison may reflect that this phenotype is central in the association found in the population cohort. Although young maternal age was not associated with ADHD in full siblings, we did find a trend of increasing risk of ADHD with decreasing maternal age. Additionally, when studying the combined effect of parental ages in full siblings, we observed a tendency to maternal age affecting the association between paternal age and ADHD; the younger the mother, the higher the risk. Paternal age did not modify the association between maternal age and ADHD.

A study found that young mothers showed more negative responsiveness and were more restrictive in controlling their children, less supportive, more inadequate in guiding their children and generally less responsive compared with older mothers.\textsuperscript{34,35} Further, children of young mothers were found likely to experience higher levels of maternal depression, marital conflict and family disruption compared with children of older mothers,\textsuperscript{54} which has been associated with ADHD.\textsuperscript{34–36} This trend observed with maternal age may be due to improved maternal parenting skills and maturity resulting in a more accepting attitude towards a second or third child’s behaviour, potentially causing fewer symptoms and/or decreased impairment among later-born siblings. Also, the first child’s behaviour could have made the mother more robust and competent in handling later-born children with similar behaviour.

Mother-child attachment will differ among siblings but, explaining part of the increased risk of ADHD with decreased maternal age, we would also have expected an association between low paternal age and ADHD as a result of paternal immaturity. However, the finding of a trend with only maternal age may reflect less paternal involvement in early parenting. Even though there have been cultural changes towards more gender equality, pregnancy and breastfeeding keep mothers in closer contact with the child especially in the first years, which may explain this finding.

This study supports that the association between young maternal age and offspring ADHD is due to risk factors at a family level, mainly accounted for by genetic factors, but environmental factors or gene-environment interactions might also play a role in the aetiology of ADHD. It has been suggested that children with some genetic vulnerability to develop ADHD can be more susceptible to environmental risk factors, for example adversities in the perinatal environment, exposure to alcohol and cannabis, and adverse obstetric and postnatal events. Maternal lifestyle during pregnancy might explain the trend of increasing risk of ADHD with decreasing maternal age, observed in full siblings, as young mothers more often tend to engage in risky behaviours during pregnancy that have been associated with mental problems in the offspring\textsuperscript{24,34} Young mothers are more likely to smoke during pregnancy, which affects the developing fetus.\textsuperscript{57} However, it is also possible that they are involved with other kinds of risky behaviours such as poor nutrition, alcohol and cannabis use. Prenatal exposure to alcohol has been shown to be associated with increased risk of ADHD, independently of the effects of prenatal smoking exposure.\textsuperscript{57} Maternal lifestyle and risky behaviour during pregnancy may explain why the trend of increased risk of ADHD with decreased age only is observed regarding maternal age. In addition, studies of the relationship between maternal age and low birthweight found that children born to very young mothers had a higher risk of low birthweight,\textsuperscript{58} and low birthweight has been found to be associated with ADHD. We also conducted subanalyses stratified by gestational age and birthweight, but the estimates did not change significantly either in the population-based cohort or in the sibling cohorts.

If different amounts of sex-related hormones\textsuperscript{29} or gynaecological immaturity explained the association between young maternal age and ADHD, we would have expected almost similar associations in the sibling cohorts as in the population cohort and, further, we would not have expected an additional risk also when the father was very young.

The present study has a number of strengths. It is based on a complete 20-year follow-up using established diagnostic data obtained from highly reliable nationwide registers, based on standardized diagnostic reporting procedures. In addition, data on both inpatient and outpatient visits were available for the whole study population. Furthermore, our study was able to examine the associations in both a full and a half sibling cohort, corresponding to 6436 and 1795 families, respectively. Finally, as an important
methodological strength, we controlled for time trends including the increase in ADHD diagnosis during the study period.

Although the Danish register contains complete information for inpatient as well as outpatient contacts since 1995 in the public health system, some children are unrecognized and thus untreated or treated without contact with the hospital system. Accordingly, ADHD is undiagnosed in the hospital system and we have false-negatives, especially for the oldest children in the cohort. Among siblings, false-negatives might therefore be more likely among the oldest siblings, which might have biased the estimates towards the null. We controlled for time trends and do not expect them to influence our estimates significantly. In contrast, as the literature also reports ADHD being over-diagnosed typically referring to false-positives, we cannot exclude non-differential misclassification.10,59,60 If we expect increased focus on families with young parents, the likelihood of getting in contact with the paediatric psychiatry system and of being diagnosed may differ between parental age groups, resulting in diagnostic parental age bias. In this case, an overestimation of the association between young parental age and ADHD cannot be rejected.

Only 1.30% of the children had an ICD-10 diagnosis of Hyperkinetic Disorder (F90x), which is lower than suggested in other studies. In this study, the ICD-10 diagnosis of Hyperkinetic Disorder mainly represents the more severe cases of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) definition of attention-deficit/hyperactivity disorder (ADHD) with some of the less severe cases being missing.

We excluded less than 2% off the children on the basis of missing data on paternal age. As an association between lonely parenthood and offspring ADHD has been observed, we might have excluded a group of children with higher prevalence of ADHD.54 Compared with the total study population, we found that children with missing data on paternal age had 0.1% higher prevalence of ADHD, but including these children in the analysis did not change the crude associations between maternal age and offspring ADHD either in the population cohort or in the half sibling cohort.

Although the sibling design can be a powerful tool for accounting for confounding because of both measured and unmeasured stable within-family factors,28,40,61–63 the sibling comparisons face a limitation, as they cannot account for uncontrolled confounding by unmeasured sibling-varying within-family factors as carry-over effects from one sibling to another. We should therefore carefully consider factors that may affect the exposure and outcome differently between siblings. A sibling being diagnosed with ADHD could affect parental behaviour in relation to the other siblings within the family. Parental perceptions, experience and behaviour may impact on the associations of interest at the level of an individual child or family, but these factors may be difficult or impossible to measure and control for. Also, birth order might play an important role when comparing the risk of ADHD among siblings. It is possible that a diagnosis given to a child will make it more likely that an undiagnosed sibling with the disorder will be diagnosed and probably also lower the threshold for diagnosing another. In the sibling design, this would generate fewer discordant sibling pairs attenuating the estimates.

Our results are much in line with the study from Sweden, using sibling- and cousin-comparisons, indicating that the association between maternal age and ADHD mainly could be explained by genetic confounding,37 as we found the weakest association among full siblings. Another Swedish study reported that siblings with fathers aged 45 years or older had a highly increased risk of ADHD (HR = 13.13, 95% CI 6.85-25.16) compared with their siblings born when the father was 20 to 24 years old,40 which they suggest is consistent with the hypothesis that new genetic mutations that occur during spermatogenesis are causally related to offspring ADHD. In contrast, we did not find any associations between either young or advantaged paternal age and ADHD. A potential explanation could be failure to control for the trend of increase in ADHD diagnosis as well as increase in parental childbearing age over time in the Swedish study.64 In addition, inconsistencies between studies may be due to variation in the demographics of the study participants, sample size and availability of data on potential confounders. Further, in the present study we were able to include data on clinical diagnoses and admission dates for all inpatient psychiatric hospital admissions since 1969 and outpatient visits at psychiatric hospitals and clinics since 1995, comparing 1973 and 2001 in Sweden, respectively.

Conclusion

We found that children diagnosed with ADHD more often had younger parents compared with children without a diagnosis of ADHD. The risk of ADHD was highest if both parents were very young. However, the risk attenuated in the sibling-comparisons, suggesting that the population-wide association between young parental age and offspring ADHD is due to risk factors at a family level, mainly accounted for by genetic factors, or that sibling comparisons are too conservative. As we found a trend of increased risk of ADHD with decreasing maternal age, which was not found according to paternal age, we cannot exclude the early-life environment or maternal behaviour related to young maternal age playing a role in the aetiology of ADHD.
Our results suggest that young parenthood could be a marker of genetic traits and, if so, delaying fertility will not be fully effective in reducing offspring ADHD. Public policy initiatives should still be targeted at attention to young parents to support parenting as well as guidance on healthy lifestyle during pregnancy among young mothers.

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