Original Investigation

# A Comprehensive Assessment of Parental Age and Psychiatric Disorders

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**IMPORTANCE** There has been recent interest in the findings that the offspring of older fathers have an increased risk of both de novo mutations and neuropsychiatric disorders. However, the offspring of younger parents are also at risk for some adverse mental health outcomes.

**OBJECTIVE** To determine the association between maternal and paternal age and a comprehensive range of mental health disorders.

**DESIGN, SETTING, AND PARTICIPANTS** A comprehensive, population-based record linkage study using the Danish Psychiatric Central Research Register from January 1, 1995, through December 31, 2011. A total of 2 894 688 persons born in Denmark from January 1, 1955, through December 31, 2006, were followed up during the study period.

**EXPOSURES** Maternal and paternal age at the time of offspring's birth.

**MAIN OUTCOMES AND MEASURES** We examined a broad range of *International Classification of Diseases*–defined mental disorders, including substance use; schizophrenia and related disorders; mood disorders; neurotic, stress-related, and somatoform disorders; eating disorders; specific personality disorders; and a range of developmental and childhood disorders. The incidence rate ratios for each mental disorder outcome were estimated by log linear Poisson regression with adjustments for the calendar period, age, sex, and age of the other parent.

**RESULTS** The cohort was observed for 42.7 million person-years, during which 218 441 members of the cohort had their first psychiatric contact for any psychiatric disorder. Based on the overall risk of psychiatric disorders, the offspring of younger and older parents were at increased risk compared with those of parents aged 25 to 29 years. When the offspring were examined for particular disorders, the nature of the relationship changed. For example, the offspring of older fathers were at an increased risk of schizophrenia and related disorders, mental retardation, and autism spectrum disorders. In contrast, the offspring of young mothers (and to a lesser extent young fathers) were at an increased risk for substance use disorders, hyperkinetic disorders, and mental retardation.

**CONCLUSIONS AND RELEVANCE** The offspring of younger mothers and older fathers are at risk for different mental health disorders. These differences can provide clues to the complex risk architecture underpinning the association between parental age and the mental health of offspring.

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Systematic reviews and meta-analyses have provided strong evidence indicating that the offspring of older fathers have an increased risk for schizophrenia[1] and autism.[2] Malaspina and colleagues[3] proposed that age-related de novo mutations in the male germline may contribute to an increased risk for neurodevelopmental disorders. In recent years, a growing body of data from genetic studies[4-7] has lent weight to this hypothesis. Apart from schizophrenia and autism, evidence suggests that the offspring of older fathers have an increased risk for bipolar disorder.[8] Age-related mutagenesis in the male germline may also contribute to an increased risk for schizophrenia and autism in grandchildren,[9,10] suggesting that some mutations may be silent (ie, with lower penetrance) in the first-generation offspring but still contribute to disease risk in subsequent generations.

With the recent interest in the mental health of the children of older fathers, the sizeable literature describing adverse mental health outcomes in the offspring of younger parents has been somewhat overshadowed. Although the effect is not as prominent as for older fathers, a small but significantly increased risk for schizophrenia occurs in the offspring of fathers younger than 25 years vs fathers aged 25 to 29 years.[1] A robust literature[11-13] has linked adverse behavioral outcomes in the offspring of young parents, especially with respect to teenaged mothers. For example, compared with the offspring of mothers older than 30 years, the offspring of teenaged mothers have an increased risk for educational underachievement, juvenile crime, substance misuse, and mental health problems.[11] Other studies[12,13] have confirmed that the offspring of younger parents have poorer outcomes on a broad range of socioeconomic, educational, and health outcomes. The mechanisms underpinning these associations are generally thought to involve a broad range of psychosocially and culturally mediated factors. For example, younger mothers and fathers are often associated with a less supportive and less stable home environment[11] and impaired socioeconomic and educational status of the parents.[14] Risk factors that are associated with teenaged parenthood and suboptimal outcomes in the offspring are often highly intercorrelated and socially patterned.[15-17]

Regardless of the precise nature of the mechanisms linking parental age and the risk for mental disorders in the offspring, an informed public health debate on these matters requires a solid empirical foundation. For example, the literature exploring the effect of parental age on mental health has tended to examine a single disease at a time. In addition, studies based on cohorts have generally used modest sample sizes and/or younger cohorts (ie, that have not passed through their risk period for many mental disorders). Using Danish linked nationwide registers, we had the opportunity to explore the associations between maternal and paternal ages and a wide range of mental disorders. In particular, we were interested in the relative influence of older vs younger parents and maternal vs paternal age with respect to different disorders.

## Methods

### Study Population

The Danish Civil Registration System was established in 1968,[18] when all people alive and living in Denmark were registered. This register includes the personal identification number, information on sex and date and place of birth, continuously updated information on vital status, and the parent's personal identifiers. The personal identification number is used in all national registers, enabling accurate linkage between registers. Our study population included all persons born in Denmark from January 1, 1955, through December 31, 2006, whose parents were born in Denmark.

### Assessment of Mental Illness

Persons within the study cohort and their parents and siblings were linked via their personal identification number to the Danish Psychiatric Central Research Register[19] to obtain information about mental illness. The Danish Psychiatric Central Research Register was computerized in 1969 and contains data on all admissions to Danish psychiatric inpatient facilities and, from 1995, information on outpatient visits to psychiatric departments. From 1969 to 1993, the diagnostic system used was the Danish modification of the *International Classification of Diseases, Eighth Revision* (*ICD-8*)[20]; from 1994, the *International Statistical Classification of Diseases, 10th Revision, Diagnostic Criteria for Research* (*ICD-10-DCR*).[21] Cohort members were classified as having a mental disorder if they had been admitted to a psychiatric hospital or had received outpatient care. The spectrum of mental disorders considered is shown in the Supplement (eTable 1). For each mental disorder, the date of onset was defined as the first day of the first contact (inpatient or outpatient) for the diagnosis of interest. In light of comorbidity between different disorders, multiple disorders were recorded (ie, the same individual may appear in >1 comparison). In this study, we examined the following range of disorders and specific disorders according to the following *ICD-10-DCR* criteria:

1. Any psychiatric diagnosis (codes F00-F99).
2. Mental and behavioral disorders due to psychoactive substance abuse (codes F10-F19), with separate analyses for mental and behavioral disorders due to alcohol use (F10) and mental and behavioral disorders due to cannabis use (F19).
3. Schizophrenia and related disorders (codes F20-F29), with separate analyses for schizophrenia (F20) and schizoaffective disorder (F25).
4. Mood disorders (codes F30-F39), with a separate analysis for bipolar disorder (F30 and F31).
5. Neurotic, stress-related, and somatoform disorders (codes F40-F48).
6. Eating disorders (code F50), with a separate analysis for anorexia nervosa (F50.0).
7. Specific personality disorders (code F60).
8. Mental retardation (codes F70-F79).
9. Pervasive developmental disorders (code F84), with a separate analysis for childhood autism (F84.0).
10. Behavioral and emotional disorders with onset usually occurring in childhood and adolescence (codes F90-F98), with a separate analysis for hyperkinetic disorder (F90).

### Assessment of Maternal and Paternal Ages

Maternal and paternal ages at the time of the child's birth were categorized as 12 to 19, 20 to 24, 25 to 29, 30 to 34, 35 to 39, 40

to 44, and 45 years or older. Because of limited power, the oldest category was not used regarding maternal age.

### Study Design and Statistical Analysis

For each psychiatric disorder, individuals were observed from the earliest age at which they may possibly develop the specific disorder or January 1, 1995 (whichever came last), until onset of the outcome in question, death, emigration from Denmark, or December 31, 2011 (whichever came first). Because persons were followed up from 1995 onward only, persons having diagnoses before 1995 were excluded. The findings were therefore based entirely on incident cases diagnosed according to the more operational *ICD-10-DCR* classification system (during a period when inpatient and outpatient information was used), except that the *ICD-8* classification and the first year of the operation of the *ICD-10-DCR* classification was used to exclude persons with a diagnosis before 1995. Because many of the child psychiatric disorders were only registered in outpatient settings, for the analyses of child psychiatric disorders, the study cohort was restricted to persons born during 1993 or later. We included only persons who were alive and resided in Denmark at the initiation of follow-up, thereby effectively controlling for the increased risk of mental disorders associated with immigration.[22]

The incidence rate ratios (IRRs) for each mental disorder outcome were estimated by log linear Poisson regression.[23,24] All IRRs were adjusted for the calendar period (at onset), age (at onset), and sex of the offspring. In keeping with standard survival analysis techniques, age and calendar period were treated as time-dependent variables,[25] whereas all other variables were treated as being independent of time. As planned sensitivity analyses, we also examined the degree of urbanization of the place of birth[26] and a history of mental illness in a parent or sibling as potential confounders.[27] We calculated *P* values and 95% confidence intervals based on likelihood ratio tests.[25] The adjusted-score test[28] suggested that the regression models were not subject to overdispersion. In total, we consider 18 different categories of mental disorders. Owing to the many tests performed, we will denote estimates as statistically significant if the *P* value is less than .0025, thus approximating a Bonferroni correction for multiple testing across psychiatric disorders. All personal information from the registers is anonymized when used for research purposes, and the project was approved by the Danish Data Protection Agency.

## Results

A total of 2 894 688 persons born in Denmark from 1955 through 2006 were followed up from 1995 through 2011. Overall, the cohort was followed up for 42.7 million person-years, during which 218 441 members of the cohort had their first psychiatric contact for any psychiatric disorder. The number of persons who developed the disorders according to maternal and paternal ages is shown in the Supplement (eTable 2).

The **Table** shows the IRRs for each of the psychiatric outcomes across the categories of maternal and paternal ages at the time of the child's birth, adjusted for the age and sex of the offspring, calendar year of birth year, and age of the other parent. Children whose parent was 25 to 29 years of age at the time of the child's birth were chosen as the reference category. The same analyses without the adjustment for the age of the other parent are shown in the Supplement (eTable 3).

Considering the broadest category of any psychiatric diagnosis (*ICD-10-DCR* codes F00-F99) as the outcome of interest, the offspring of the youngest mothers were at the highest risk for any mental disorders. Compared with the offspring of mothers aged 25 to 29 years, the offspring of mothers aged 12 to 19 years had a 51% increased risk of having a mental disorder (IRR, 1.51 [95% CI, 1.48-1.54]). No significantly increased risk for the offspring of older mothers was found. In contrast, paternal age showed a U-shaped relationship, with the offspring of teenaged fathers having a 28% increased risk for a psychiatric disorder (IRR, 1.28 [95% CI, 1.24-1.32]), whereas the offspring of the fathers 45 years or older had a 34% increased risk (1.34 [1.30-1.39]). **Figure 1** shows the relationship between maternal and paternal ages and the risk for any mental disorder when not adjusted and when adjusted for age of the other parent. We refer to the results adjusted for age of the other parent only below.

Remarkably, maternal and paternal ages were significantly ($P < .0025$) associated with all categories of mental disorders examined except schizoaffective disorder, bipolar disorder, and eating disorders/anorexia. Paternal but not maternal age was significantly associated with autism. However, **Figure 2** and **Figure 3** reveal subtle differences in the patterns of association between parental age and different disorders.

Some disorders were clearly more prominent in the offspring of younger parents. For example, the offspring of teenaged parents were most at risk for the broad category of mental and behavioral disorders due to psychoactive substance abuse (*ICD-10-DRC* codes F10-F19). Inspection of separate analyses for mental and behavioral disorders due to alcohol and cannabis use were consistent with the overall pattern but with increased effect sizes related to cannabis use. Also, the offspring of teenaged parents were most at risk for the broad category of behavioral and emotional disorders and the more specific diagnosis of hyperkinetic disorder.

With respect to mood disorders, the patterns were more subtle and imprecise. For the general category of mood disorders, the offspring of teenaged mothers or fathers and the offspring of older fathers had small but significantly increased risks (compared with the reference category). Within this group, we found no prominent association between parental age and the risk for bipolar disorder.

The risk for schizophrenia and related disorders was associated with older fathers (≥45 years vs the reference category; IRR, 1.54 [95% CI, 1.41-1.69]). We found significantly increased risks in the offspring of teenaged fathers (IRR, 1.16 [95% CI, 1.04-1.28]) and teenaged mothers (1.47 [1.38-1.56]).

For the broad group of neurotic and stress-related disorders (*ICD-10-DRC* codes F40-F48), the offspring of teenaged mothers were at the highest risk (IRR, 1.49 [95% CI, 1.45-

Table. IRR for Psychiatric Disorders by Parental Age[a]

| Diagnostic Categories | Parent | IRR (95% CI) by Parental Age Range[b] | | | | | | *P* Value[c] |
|---|---|---|---|---|---|---|---|---|
| | | 12-19 y | 20-24 y | 30-34 y | 35-39 y | 40-44 y | ≥45 y | |
| Any psychiatric disorder | Mother | 1.51 (1.48-1.54) | 1.21 (1.19-1.22) | 0.94 (0.93-0.95) | 0.94 (0.92-0.96) | 0.98 (0.94-1.02) | | <.001 |
| | Father | 1.28 (1.24-1.32) | 1.12 (1.10-1.13) | 1.00 (0.99-1.01) | 1.09 (1.07-1.11) | 1.19 (1.16-1.22) | 1.34 (1.30-1.39) | <.001 |
| Mental and behavioral disorders due to psychoactive substance use | Mother | 1.73 (1.65-1.80) | 1.28 (1.24-1.31) | 0.95 (0.92-0.98) | 0.95 (0.90-1.00) | 1.06 (0.97-1.17) | | <.001 |
| | Father | 1.48 (1.39-1.58) | 1.19 (1.15-1.22) | 1.03 (1.00-1.06) | 1.10 (1.05-1.14) | 1.18 (1.11-1.24) | 1.23 (1.14-1.33) | <.001 |
| Mental and behavioral disorders due to alcohol use | Mother | 1.51 (1.43-1.59) | 1.19 (1.15-1.24) | 0.99 (0.95-1.03) | 1.01 (0.95-1.08) | 1.14 (1.02-1.27) | | <.001 |
| | Father | 1.39 (1.29-1.51) | 1.15 (1.11-1.20) | 1.03 (0.99-1.06) | 1.07 (1.02-1.12) | 1.10 (1.02-1.18) | 1.16 (1.06-1.27) | <.001 |
| Mental and behavioral disorders due to cannabis use | Mother | 2.22 (2.05-2.41) | 1.38 (1.31-1.46) | 0.88 (0.83-0.94) | 0.90 (0.81-1.00) | 1.05 (0.86-1.27) | | <.001 |
| | Father | 1.58 (1.40-1.79) | 1.21 (1.14-1.28) | 1.03 (0.97-1.09) | 1.09 (1.01-1.18) | 1.26 (1.13-1.41) | 1.33 (1.14-1.55) | <.001 |
| Schizophrenia and related disorders | Mother | 1.47 (1.38-1.56) | 1.16 (1.12-1.21) | 0.99 (0.95-1.03) | 0.96 (0.90-1.02) | 0.97 (0.86-1.09) | | <.001 |
| | Father | 1.16 (1.04-1.28) | 1.05 (1.00-1.09) | 1.04 (1.00-1.08) | 1.19 (1.13-1.26) | 1.34 (1.25-1.44) | 1.54 (1.41-1.69) | <.001 |
| Schizophrenia | Mother | 1.45 (1.34-1.57) | 1.18 (1.12-1.23) | 0.96 (0.91-1.02) | 1.00 (0.92-1.09) | 0.94 (0.79-1.11) | | <.001 |
| | Father | 1.12 (0.97-1.28) | 1.07 (1.01-1.13) | 1.08 (1.03-1.13) | 1.21 (1.13-1.30) | 1.40 (1.28-1.54) | 1.47 (1.29-1.67) | <.001 |
| Schizoaffective disorder | Mother | 1.17 (0.96-1.43) | 1.04 (0.93-1.18) | 1.02 (0.88-1.17) | 1.14 (0.93-1.39) | 1.19 (0.82-1.67) | | .52 |
| | Father | 0.92 (0.63-1.30) | 1.07 (0.93-1.22) | 1.10 (0.97-1.25) | 1.29 (1.10-1.52) | 1.26 (1.00-1.58) | 1.40 (1.04-1.87) | .06 |
| Mood disorders | Mother | 1.35 (1.30-1.40) | 1.12 (1.09-1.14) | 0.98 (0.95-1.00) | 0.99 (0.96-1.03) | 1.01 (0.94-1.08) | | <.001 |
| | Father | 1.20 (1.13-1.27) | 1.10 (1.08-1.13) | 1.03 (1.01-1.05) | 1.11 (1.08-1.14) | 1.20 (1.15-1.25) | 1.25 (1.18-1.32) | <.001 |
| Bipolar disorder | Mother | 1.20 (1.08-1.33) | 1.06 (0.99-1.13) | 1.02 (0.95-1.10) | 1.08 (0.97-1.21) | 1.10 (0.89-1.34) | | .03 |
| | Father | 1.19 (0.99-1.40) | 1.04 (0.97-1.12) | 1.06 (0.99-1.13) | 1.06 (0.97-1.16) | 1.03 (0.90-1.17) | 1.24 (1.05-1.45) | .09 |
| Neurotic, stress-related, and somatoform disorders | Mother | 1.49 (1.45-1.53) | 1.18 (1.16-1.20) | 0.95 (0.93-0.96) | 0.98 (0.95-1.01) | 1.04 (0.98-1.10) | | <.001 |
| | Father | 1.25 (1.19-1.30) | 1.12 (1.10-1.14) | 1.01 (0.99-1.03) | 1.08 (1.06-1.11) | 1.16 (1.12-1.20) | 1.31 (1.25-1.37) | <.001 |
| Eating disorders | Mother | 0.94 (0.85-1.04) | 0.99 (0.95-1.04) | 1.08 (1.02-1.13) | 1.03 (0.95-1.12) | 0.97 (0.80-1.16) | | .05 |
| | Father | 1.18 (0.99-1.40) | 1.04 (0.98-1.10) | 1.01 (0.96-1.06) | 0.99 (0.92-1.05) | 1.13 (1.03-1.25) | 1.05 (0.91-1.21) | .06 |
| Anorexia nervosa | Mother | 0.76 (0.60-0.95) | 0.97 (0.88-1.06) | 1.13 (1.04-1.24) | 1.15 (1.00-1.33) | 1.07 (0.77-1.47) | | .005 |
| | Father | 0.75 (0.47-1.13) | 0.91 (0.81-1.02) | 1.07 (0.98-1.17) | 0.98 (0.87-1.10) | 1.14 (0.96-1.35) | 0.90 (0.68-1.16) | .049 |
| Specific personality disorders | Mother | 1.68 (1.61-1.76) | 1.25 (1.21-1.28) | 0.93 (0.90-0.96) | 0.91 (0.86-0.95) | 0.96 (0.87-1.05) | | <.001 |
| | Father | 1.35 (1.26-1.44) | 1.14 (1.11-1.17) | 1.02 (0.99-1.05) | 1.14 (1.09-1.18) | 1.30 (1.23-1.37) | 1.59 (1.48-1.71) | <.001 |
| Mental retardation | Mother | 1.88 (1.69-2.08) | 1.43 (1.35-1.52) | 0.90 (0.85-0.96) | 0.95 (0.87-1.04) | 1.34 (1.16-1.55) | | <.001 |
| | Father | 1.22 (1.02-1.44) | 1.01 (0.94-1.08) | 1.07 (1.01-1.13) | 1.29 (1.20-1.38) | 1.59 (1.44-1.75) | 2.02 (1.78-2.28) | <.001 |
| Pervasive developmental disorders | Mother | 1.37 (1.15-1.63) | 1.26 (1.18-1.35) | 0.96 (0.90-1.01) | 1.00 (0.93-1.09) | 0.97 (0.82-1.15) | | <.001 |
| | Father | 0.85 (0.60-1.16) | 1.05 (0.96-1.15) | 1.00 (0.94-1.06) | 1.07 (0.99-1.15) | 1.26 (1.14-1.39) | 1.58 (1.38-1.80) | <.001 |
| Childhood autism | Mother | 1.50 (1.07-2.05) | 1.23 (1.07-1.40) | 0.94 (0.85-1.04) | 1.04 (0.90-1.19) | 1.03 (0.77-1.36) | | .004 |
| | Father | 0.54 (0.24-1.05) | 1.00 (0.84-1.20) | 1.06 (0.96-1.18) | 1.09 (0.95-1.24) | 1.42 (1.19-1.69) | 1.80 (1.42-2.25) | <.001 |
| Behavioral and emotional disorders with onset usually occurring in childhood and adolescence | Mother | 2.40 (2.21-2.62) | 1.61 (1.54-1.68) | 0.80 (0.77-0.83) | 0.77 (0.73-0.81) | 0.79 (0.69-0.89) | | <.001 |
| | Father | 1.43 (1.24-1.63) | 1.32 (1.25-1.39) | 0.96 (0.92-1.00) | 1.03 (0.98-1.08) | 1.14 (1.06-1.23) | 1.43 (1.29-1.57) | <.001 |
| Hyperkinetic disorders | Mother | 2.30 (2.05-2.56) | 1.61 (1.53-1.70) | 0.78 (0.74-0.82) | 0.74 (0.68-0.80) | 0.74 (0.63-0.88) | | <.001 |
| | Father | 1.44 (1.19-1.72) | 1.36 (1.27-1.45) | 0.96 (0.91-1.01) | 0.99 (0.93-1.06) | 1.09 (0.99-1.20) | 1.32 (1.16-1.51) | <.001 |

Abbreviation: IRR, incidence rate ratio.

[a] Includes persons born January 1, 1955, through December 31, 2006, and followed up from January 1, 1995, through December 31, 2011. The IRRs are adjusted for age and sex of the offspring, calendar year, and other parent's age. Mothers 45 years or older were excluded from the analyses owing to limited power.

[b] Parents aged 25 to 29 years represent the reference category.

[c] The *P* values measure the likelihood ratio test for an overall effect of maternal or paternal age.

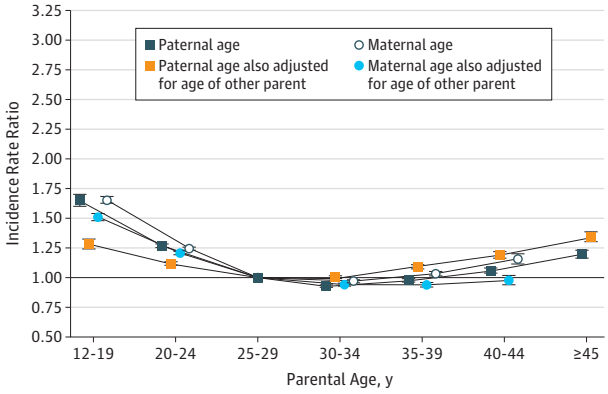
1.53]). With respect to this category of disorders and paternal age, small but significantly increased risks for the offspring of teenaged fathers and older fathers were found (IRRs, 1.25 and 1.31, respectively).

For personality disorders (*ICD-10-DRC* code F60), the highest risks were found in the offspring of teenaged mothers (IRR, 1.68 [95% CI, 1.61-1.76]) and fathers 45 years or older (1.59 [1.48-1.71]). A similar pattern was found for the broad category mental retardation (*ICD-10-DRC* codes F70-F79); the highest risks were seen in the offspring of teenaged mothers (IRR, 1.88 [95% CI, 1.69-2.08]) and in the offspring of fathers 45 years or older (2.02 [1.78-2.28]). With respect to pervasive developmental dis-

order (*ICD-10-DRC* code F84), we again see the pattern of highest risks in the offspring of teenaged mothers (IRR, 1.37 [95% CI, 1.15-1.63]) and in the offspring of fathers 45 years or older (1.58 [1.38-1.80]).

When adjusted for the degree of urbanization of the place of birth, the general pattern of findings remained essentially unchanged (Supplement [eTable 4]). When adjusted for history of mental illness in a parent or sibling, most effect sizes were slightly attenuated (Supplement [eTable 5]). For some disorders, this attenuation was most prominent for the effect sizes associated with teenaged mothers (but not with older fathers). For example, the risk of neurotic stress-related and somatoform disorders in the offspring of mothers aged 12 to 19 years before and after adjustment for family history of mental disorders was 1.49 (95% CI, 1.45-1.53) and 1.37 (95% CI, 1.34-1.41), respectively. For the risk of behavioral and emotional disorders (with onset usually occurring in childhood and adolescence), the comparable estimates were 2.40 (95% CI, 2.21-2.62) and 1.91 (1.75-2.07), respectively.

Figure 1. Incidence Rate Ratios (IRRs) for Any Psychiatric Disorder by Parental Age




Psychiatric disorders were identified by codes F00 to F99 from the *International Statistical Classification of Diseases, 10th Revision, Diagnostic Criteria for Research*, by parental age. Persons identified were born from January 1, 1955, through December 31, 2006, and followed up from January 1, 1995, through December 31, 2011. All IRRs are adjusted for age, sex, and calendar year. Tick marks indicate 95% confidence intervals.

## Discussion

In addition to the recent attention accorded to the risk for mental disorders in the offspring of older fathers, our study shows a more complex and nuanced pattern of association between maternal and paternal ages and the risk for mental illness in the offspring. For many disorders, the risk for mental disorders in the offspring of young (especially teenaged) mothers is comparable to that seen in the offspring of older fathers. The offspring of teenaged fathers are also at risk for some disorders. For disorders such as schizophrenia and pervasive developmental disorder, the association between the variables of interest is J-shaped, with a higher risk found in the oldest group (≥45 years). This pattern has been reported for schizophrenia[1,29] and for the overall mortality rate in the offspring.[30]

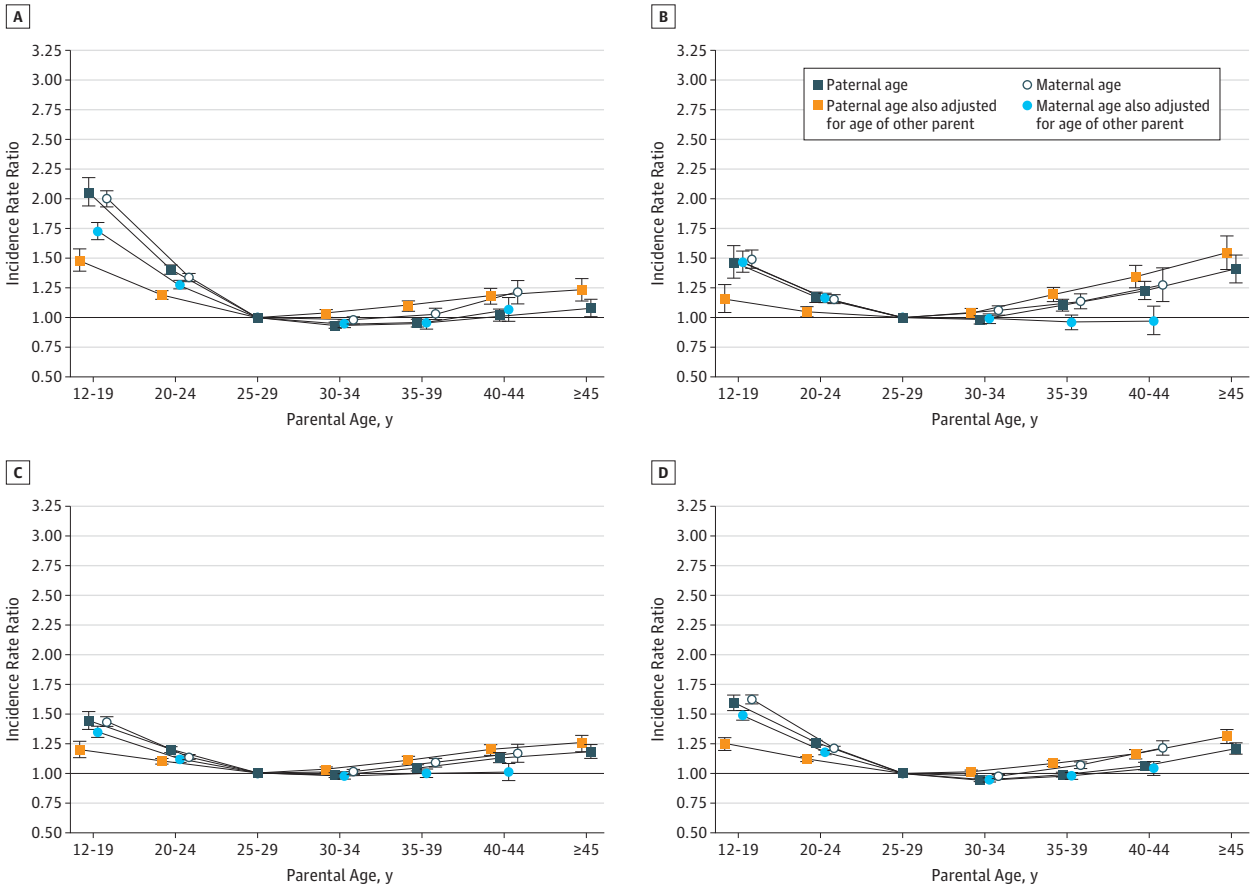
Although our study cannot determine the factors underpinning the pattern of associations, some novel inferences can be made based on the range of disorders examined in this study. Some mental disorders appear to have little or no association with maternal or paternal age (eg, schizoaffective disorder, bipolar disorder, eating disorders/anorexia). In contrast, other disorders have distinct patterns of association. For example, with respect to maternal age, several disorders have an increased risk in the offspring of younger (teenaged) mothers but no marked increased in the offspring of older mothers, plus an increased risk in the offspring of older (≥45 years) fathers but little or no marked increase in the offspring of younger fathers. In other words, an increased risk for a set of mental disorders in the offspring appears to be associated with younger mothers and older fathers.

Our study draws particular attention to the links between younger mothers and a range of mental disorders. Young mothers have been linked to an increased risk for hyperkinetic disorder[31-33] and behavioral and emotional disorders.[34] The offspring of teenaged fathers and mothers have an increased risk for hyperkinetic disorder and behavioral and emotional disorders; however, the effect size is significantly higher for younger mothers compared with younger fathers (the 95% confidence intervals do not overlap). The increased risk for substance use and personality disorder in the offspring of younger parents may reflect shared parent-offspring risk factors (genetics and/or environmental exposures). The attenuation of effect sizes associated with the increased risk for certain disorders in the offspring of teenaged mothers suggests that maternal mental health (before or after the birth of the proband) may contribute to the increased risk for certain disorders in the offspring of younger mothers.

Generally, studies have suggested that early parenthood can interfere with education and employment aspirations.[14] Having a child at an earlier age may contribute to a cascade of events related to socioeconomic exclusion. Some commentators have suggested that a larger proportion of pregnancies in teenaged women (compared with pregnancies in older women) are unplanned.[35] Teenaged parenthood has been associated with a broad range of adverse health, educational, social, and crime-related outcomes in the mothers and their offspring. However, ascribing these outcomes directly to the ages of the parents vs a wide range of confounding factors is difficult.[36] As with many behaviors, young parenthood as a trait can be identified across several generations,[16] further highlighting the complex and socially patterned web of causation that may link the variables of interest.

The pattern of association between parental age and mental retardation was particularly interesting. The offspring of teenaged and older (40-44 years) mothers had significantly increased risks for mental retardation. The link with older mothers may reflect the well-known association with Down syndrome.[37] With respect to paternal age, we found a steady and linear increase in the risk for each age

Figure 2. Incidence Rate Ratios (IRRs) for Diagnoses Due to Psychoactive Substance Abuse, Schizophrenia, Mood Disorders, and Neurotic Disorders by Parental Age



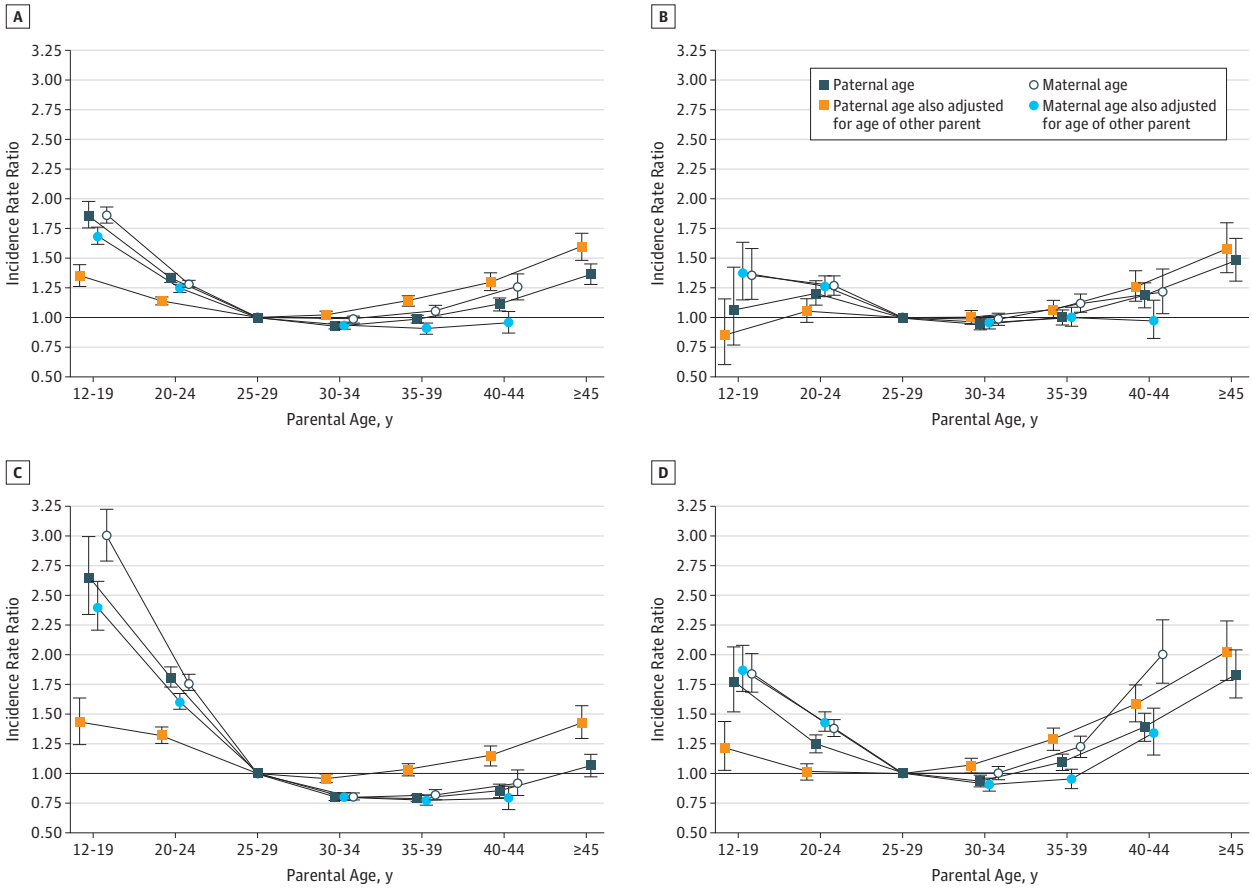

Persons identified were born from January 1, 1955, to December 31, 2006, and followed up from January 1, 1995, to December 31, 2011. All IRRs are adjusted for age, sex, and calendar year. Tick marks indicate 95% confidence intervals. A, Mental and behavioral disorders due to psychoactive substance abuse (*International Statistical Classification of Diseases, 10th Revision, Diagnostic Criteria for Research* codes F10-F19). B, Schizophrenia and related disorders (F20-F29). C, Mood disorders (codes F30-F39). D, Neurotic, stress-related, and somatoform disorders (codes F40-F48).

strata above the reference category (25-29 years). Recent studies have confirmed that approximately 80% of de novo mutations are paternal in origin and that the total number of mutations strongly correlates with paternal age.[4] Experimental studies in mice have demonstrated that the offspring of older sires have altered behavioral outcome,[38,39] altered brain structure,[38] and increased de novo copy number variants.[40] In addition, paternal age-related de novo mutations that affect spermatogonial proliferation have been proposed to be differentially selected and thus skew the biological sequelae of these mutations.[41]

Although mechanisms related to psychosocial and cultural factors can plausibly account for the increased risk for mental disorders in the offspring of younger parents, biological and genetic factors should also be considered. Exposure to prenatal smoking, alcohol, or illicit drugs may compromise fetal growth[42,43] or contribute to de novo mutations in the germ cells.[44] Although the body of evidence implicating age-related de novo mutations and the risk for schizophrenia is growing, other mechanisms may also operate. For example, studies that have adjusted for age at first fatherhood find that advanced paternal age at the time of subsequent births is not associated with an increased risk.[45,46] This finding suggests that factors associated with delayed first fatherhood (eg, schizotypal traits in the father) may contribute to the link between advanced paternal age and the risk for schizophrenia. A wide range of biological and culturally mediated factors may also influence the association between parental age and the risk for mental illness in the offspring. These factors could be as diverse as birth order, maternal age, obstetric complications, fecundability, age-related epigenetic factors, pregnancy wantedness, and de facto/married status at the time of birth.[47-49]

Our main analyses adjusted for key variables (in particular, the age of the other parent), but we did not include other variables in the models (eg, socioeconomic factors and parental education). Future studies might explore the relative influence of these variables on the range of mental disorders examined in this study. Although the nationwide registration of severe mental disorders is almost complete (there are no pri-

Figure 3. Incidence Rate Ratios (IRRs) for Personality Disorders, Developmental Disorders, Childhood-Onset Behavioral and Emotional Disorders, and Mental Retardation by Parental Age




Persons identified were born from January 1, 1955, to December 31, 2006, and followed up from January 1, 1995, to December 31, 2011. All IRRs are adjusted for age, sex, and calendar year. Tick marks indicate 95% confidence intervals. A, Specific personality disorders (code F60). B, Pervasive developmental disorders (code F84). C, Behavioral and emotional disorders with onset usually occurring in childhood and adolescence (codes F90-F98). D, Mental retardation (codes F70-F79).

vate psychiatric hospitals in Denmark), milder common mental disorders that receive treatment only via general practitioners (eg, depression and anxiety disorders) will be underrepresented in the Danish Psychiatric Central Research Register. We restricted the childhood-onset disorder to those born in 1993 or later because most childhood development disorders were registered in the Danish Psychiatric Central Research Register after this date. The smaller sample size may have reduced our ability to detect small effects with confidence. With respect to the validity of the mental disorders, systematic studies have not been conducted on all outcomes, but validation studies for some diagnoses (eg, schizophrenia, a single depressive episode, affective disorder, dementia, and autism) have been performed with good results.[50-55]

## Conclusions

Younger mothers and older fathers are associated with an increased risk of mental disorders in their offspring. However, the nature of the outcomes varies in a complex fashion. Several mental disorders (eg, schizoaffective disorder, bipolar disorder, and eating disorders/anorexia) show little or no association with parental age. Our findings suggest that paternal age–related de novo mutations and/or adverse sociocultural factors associated with young parents are less likely to contribute to the risk of these disorders. Although the links between advanced paternal age and disorders such as schizophrenia and autism are well appreciated, our study demonstrates that the risks for several disorders (eg, hyperkinetic disorders and substance use disorders) are significantly increased in the offspring of younger mothers. The association between parental age and risk of various mental disorders in the offspring may be confounded by a range of factors (eg, parental mental health). When integrating the sweep of information from the epidemiology of risk factors, recommendations about optimal age of parenthood need to consider a broad range of biologically and psychosocially mediated variables that may be associated with younger and older parents.

## ARTICLE INFORMATION

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*Study concept and design:* McGrath, Petersen, Agerbo, Pedersen.
*Acquisition of data:* Mortensen, Pedersen.
*Analysis and interpretation of data:* McGrath, Agerbo, Mors, Pedersen.
*Drafting of the manuscript:* McGrath, Pedersen.
*Critical revision of the manuscript for important intellectual content:* All authors.
*Statistical analysis:* McGrath, Agerbo, Pedersen.
*Obtained funding:* McGrath, Mortensen.
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