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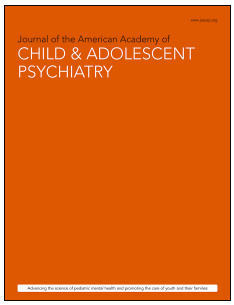

Parental Age and Differential Estimates of Risk for Neuropsychiatric Disorders: Findings From the Danish Birth Cohort

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PII: S0890-8567(19)30126-1

DOI: https://doi.org/10.1016/j.jaac.2018.09.447

Reference: JAAC 2475

To appear in: *Journal of the American Academy of Child & Adolescent Psychiatry*

Received Date: 23 February 2018

Revised Date: 27 August 2018

Accepted Date: 7 September 2018

Please cite this article as: Janecka M, Hansen SN, Modabbernia A, Browne HA, Buxbaum JD, Schendel DE, Reichenberg A, Parner ET, Grice DE, Parental Age and Differential Estimates of Risk for Neuropsychiatric Disorders: Findings From the Danish Birth Cohort, *Journal of the American Academy of Child & Adolescent Psychiatry* (2019), doi: https://doi.org/10.1016/j.jaac.2018.09.447.

Parental Age and Differential Estimates of Risk for Neuropsychiatric Disorders: Findings From the Danish Birth Cohort

RH = Parental Age and Psychiatric Disorders

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Supplemental Material

Accepted September 14, 2018

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This work was supported by the Lundbeck Foundation Initiative for Integrative Psychiatric Research (to D.S.), the National Institutes of Health (grant HD073978 to A.R. and MH097849 to J.D.B.), the Mindich Child Health and Development Institute (to D.E.G. and J.D.B), the Friedman Brain Institute (to D.E.G.), the Seaver Foundation (to J.D.B., A.R., D.E.G., and M.J.), and the Stanley Center for Psychiatric Research (to D.E.G.).

Drs. Hansen and Parner served as the statistical expert for this research.

The authors would like to thank Therese Koops Grønborg, PhD, of Aarhus University, for her assistance with the statistical procedures.

Disclosure: Drs. Janecka, Hansen, Modabbernia, Browne, Buxbaum, Schendel, Reichenberg, Parner, and Grice report no biomedical financial interests or potential conflicts of interest.

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Abstract

Objective: Parental age at birth has been shown to affect the rates of a range of neurodevelopmental disorders, but the understanding of the mechanisms through which it mediates different outcomes is still lacking. We used a population-based cohort to assess differential effects of parental age on estimates of risk across pediatric-onset neuropsychiatric disorders: autism spectrum disorder (ASD), attention-deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD) and Tourette syndrome/chronic tic disorder (TS/CT).

Method: Our study cohort included all singleton births in Denmark between 1980 and 2007 with full information on parental ages (N=1,490,745), followed through December 31, 2013. Cases of ASD, ADHD, OCD and TS/CT were identified in the Danish Psychiatric Central Register and the National Patient Register. Associations with parental age were modeled using a stratified Cox regression, allowing for changes in baseline diagnostic rates across time.

Results: Younger parental age was significantly associated with increased estimates of risk for ADHD and TS/CT, while older parental age was associated with ASD and OCD. Except for OCD, we did not observe any evidence for differential effects of parental ages on male vs. female offspring.

Conclusion: We provide novel evidence for the association between age at parenthood and TS/CT and OCD, and show for the first time in a population-based sample that parental age confers differential risk rates for pediatric-onset psychiatric disorders. Our results are consistent with a model of both shared and unshared risk architecture for pediatric-onset neuropsychiatric conditions, highlighting unique contributions of maternal and paternal ages.

Key words: parental age, maternal age, paternal age, neurodevelopmental disorders, psychiatric disorders

Introduction

Extensive evidence suggests that parental age at child's birth affects the estimates of risk for a range of neurodevelopmental and psychiatric disorders in offspring.[1,2] Across different population-based cohorts, advanced parental age has been associated with autism spectrum disorder (ASD)[3–5] and schizophrenia.[6,7] Similarly, children of very young parents have elevated rates of adverse neurobehavioral outcomes, including ADHD and intellectual disability.[8,9] Some of these results were corroborated in meta-analyses,[10,11] and supported by animal models of these disorders[12,13] and studies on social skills in the general population.[14,15] Nevertheless, the underlying mechanisms remain unknown.

Risk conferred by parental age may be mediated through a number of different mechanisms, both genetic and non-genetic. Reproduction at a younger age is associated with parenting behaviors and home environments that may adversely impact child development.[16] The association between early parenthood and negative offspring outcomes could be also mediated by factors pertaining to the biology of the reproductive system,[17] or familial genetic factors – for example, whereby conceiving at a young age indicates an underlying genetic liability for neuropsychiatric disorders.[18]

Similarly, several mechanisms could underlie risk for psychiatric disorders in offspring of older parents. These factors can emerge as a consequence of age and impact the germline and reproductive system, or relate to parental characteristics influencing decisions about delaying parenthood[4,19] - mirroring the familial contribution hypothesized to play a role in young parental age effects.

"Parental age effects" could therefore encompass a range of genetic and environmental factors, with possibly qualitatively different contributions to neuropsychiatric disorders. Nevertheless,

distentangling how these mechanisms affect the risk of adverse outcomes in offspring remains challenging, not least due to conflicting findings emerging from the epidemiological studies. Lack of consensus about early vs. late, and maternal vs. paternal effects in different disorders hinders research on overlapping and distinct underpinnings of these associations.

Although effects of advanced paternal age in ASD and ASD-like behaviours have been validated in a number of cohorts[20–23] and animal models,[12,13] disorder risk among offspring of young fathers, as well as maternal age contribution to these effects, remain equivocal. The few studies that examine parental age and risk for OCD, TS/CT and ADHD have yielded variable results, reporting an effect of paternal and/or maternal age only,[24–26] as well as no association.[27] Different analytical approaches, variable operational definitions of parental age (categorical vs. continuous variable) and important confounders (e.g. different measures of socioeconomic status), and use of samples too small to afford statistical power to reliably establish presence or absence of significant effects, constitute major challenges in examining differential effects of parental age across psychiatric disorders. To our knowledge, the largest samples reported in the parental age literature to date include 12,159 cases of ASD,[28] 2,861 cases of ADHD,[1] and 1,358 and 1,195 cases of OCD and TS/CT, respectively,[29] although a majority of the studies rely on samples considerably smaller than those.

The present study was designed to address the above challenges and limitations. We used a single population-based cohort to assess the role of parental age in risk across four common pediatric psychiatric disorders: OCD, TS/CT, ASD, and ADHD. A powerful resource for studies such as this, Denmark has over 200 health and administrative registries with individual-level information collected prospectively. A comparative and trans-diagnostic approach allows us to examine the effect of parental age on estimates of risk for several disorders in the same large

population cohort. Such observations of distinct effects of parental ages on offspring outcomes may inform hypothesis generation regarding shared and unshared mechanisms, contributing to the design of further molecular investigations.

METHOD

The Danish Data Protection Agency, the Danish National Board of Health, and the Mount Sinai Institutional Review Board approved this study. To protect privacy and minimize risk for identification of individuals, we report counts of less than one percent of the cohort as <1%.

Study population

We identified all singleton births in Denmark from 1 January 1980 through 31 December 2007 in the Danish Medical Birth Registry[30] totaling 1,500,270 individuals. Information on death, parental ages, and family linkages was obtained from the Danish Civil Registration System.[31] Excluding 9,525 individuals with incomplete parental age data yielded a population cohort of 1,490,745.

Outcomes

Psychiatric diagnoses were obtained by linkage to the Danish Psychiatric Central Register (DPCR)[32] and the National Patient Register (NPR)[33]. The DPCR records all inpatient admissions to psychiatric hospitals since 1969 and all outpatient admissions since 1995. The NPR records all somatic inpatient admissions since 1977 and all outpatient and emergency room admissions since 1995. We thus identified all individuals who had contact with healthcare specialists in the national healthcare system and who carried the diagnoses of interest made by specialized clinicians. In Denmark, children suspected of having mental or behavioral disorders are referred

by general practitioners or school psychologists to a child and adolescent psychiatric department for an evaluation, and are assigned a diagnosis by a child and adolescent psychiatrist; Danish health care is universal and free of charge. All diagnoses are reported to the DPCR.

The International Classification of Diseases, Eighth Revision (ICD-8,WHO 1965) was used in Denmark until 1993, with ICD-10 (WHO 1992) used subsequently. From the DPCR and NPR we obtained information on ASD, ADHD, OCD and TS/CT diagnoses, both primary and subsidiary, for all individuals in the cohort (see **Table S1, available online,** for the codes). Individuals diagnosed with more than one of the diagnoses of interest were included in all relevant outcome analyses. Follow-up began at birth and continued until diagnosis of ASD, ADHD, OCD and/or TS/CT, death, or the end of follow-up (December 31, 2013), whichever occurred first. Because most individuals had multiple clinical visits over the study period, <1.5% of those diagnosed with ASD, OCD or TS/CT retained only an ICD-8 diagnosis; ADHD was not represented in ICD-8. For parents of all diagnosed individuals, we collected information on any psychiatric diagnosis (ICD-8 codes: 290-315; ICD-10 codes F00-F99).

Parental age and covariates

Maternal and paternal ages were derived from the Danish Central Population Register. Parental age effects were examined by age category (<27.5, 27.5-32.5 (referent), 32.5-37.5, >37.5). We investigated the potential confounders obtained from the DMBR or DPCR, including parity, sex, and parental psychiatric history (yes, no) defined as any psychiatric diagnosis before birth of the child. In the supplementary analyses, we also investigated the outcomes associated with extreme parental age categories (<22.5 and >42.5), as well as the role of other factors that may be associated with age at parenthood (maternal smoking during pregnancy; gestational age; parental

immigration). In supplementary analysis we also explored the estimates of risk for neuropsychiatric disorders in relation to parental age difference. Categories were created by subtracting maternal age from paternal age (less than -12.5, -12.5 to -7.5, -7.5 to -2.5, -2.5 to 2.5 (referent), 2.5 to 7.5, 7.5 to 12.5, more than 12.5 - where a negative difference indicated an older mother, and a positive one an older father).

Statistical Analysis

Statistical analyses were carried out using Stata/SE 13.1. We quantified the association between parental age and risk for ASD, ADHD, OCD, and TS/CT in stratified Cox regression, in which each birth year has its own baseline diagnostic rate. We performed tests for a linear trend separately in maternal and paternal effects on the log-rate scale, and tested for an interaction between those effects and offspring sex, allowing us to investigate possible sexually dimorphic effects of parental ages. All analyses were performed using maternal/paternal age at child's birth as the only predictor (crude models), as well as adjusted for the covariates. For offspring in all four parental age groups we computed the disorder-specific hazard ratios (HRs), relative to offspring of parents in the reference age category. We then tested whether those HRs across parental age categories indicate significant trend effects. Finally, parental age effects were estimated in an interaction analysis including both maternal and paternal age at child's birth, which allowed us to observe their independent and synergistic effects on estimates of disorders' risk in offspring.

Given high levels of comorbidity in the cohort, all analyses were also run in subsamples of individuals diagnosed with only one of the disorders of interest throughout the follow-up period. For these analyses, only the 'cases with no comorbidity' were considered in the estimation of

parental age risk for the relevant diagnosis. At the time of the relevant case diagnosis, knowledge about the lack of potential other diagnoses in the remaining follow-up period is used, i.e. we are conditioning on the knowledge of no future other diagnoses when determining cases. For this reason, these analyses were treated only as exploratory.

Parental age difference effects were investigated using analogous procedures to those employed in the main parental age analyses.

RESULTS

Cohort

In our cohort, we identified 16,083 cases of ASD, 25,307 of ADHD, 5,324 of OCD, and 4,666 of TS/CT. **Table S2, available online,** presents characteristics of those clinical groups, as well as the rest of the cohort. Among individuals with diagnoses of ASD, ADHD, and TS/CT we observed an enrichment of male patients; conversely, OCD diagnosis was more common in female patients. Individuals with any of the four disorders were more likely to have parents with a psychiatric history, compared with the general birth cohort.

The role of parental age in ASD, ADHD, OCD, and TS/CT

Parental age at child's birth was differentially associated with each of the four disorders. ASD and OCD showed an association with advanced parental age (**Figures 1, 2**). After adjustment for the covariates, the estimates of risk for OCD were increased only among the offspring of older mothers, but not older fathers (HR_{mat}=1.23, 1.07-1.42; **Figure 2**), although sex-specific analyses indicated that paternal age effects were likely present, but only in male offspring (HR_{female}=1.04,

0.92-1.16; HR_{male}=1.14, 1.00-1.31; $p_{agexsex}$=0.009; **Table S3, available online**). In the adjusted analyses, significant effects of maternal age on OCD risk estimates were observed across all paternal age categories, except for when the father was younger than 27.5 (**Table S4, available online**). Similarly, after adjustment, increased estimates of risk for ASD was observed among offspring of both older men and women, irrespective of the other parent's age, except for offspring born to older women and men younger than 27.5 (**Table S4, available online**). Although there was also an indication of an association between ASD and young parental age, those effects were relatively weak and near non-significant in the adjusted models (HR_{mat}=1.04, 1.00-1.08; HR_{pat}=1.03, 0.99-1.08; **Figure 1**).

The estimates of risk for both ADHD and TS/CT were elevated in the offspring of younger parents (**Figures 3, 4**), although the latter effect diminished in size after controlling for the covariates (ADHD: HR_{mat}=1.70, 1.66-1.75; HR_{pat}=1.63, 1.58-1.68; TS/CT: HR_{pat}=1.09, 1.01-1.18; HR_{mat}=1.12, 1.04-1.20; **Figure 3**). The estimates of risk for those disorders was highest in the couples where both parents were very young at child's birth (HR=2.08, 2.00-2.17), but diminished if either parent was aged >27.5 **(Table S4, available online)**.

After including the additional covariates and separating out the most extreme parental ages (<22.5 and >42.5 years), all effects described above remained significant (**Table S5, available online**).

Excluding individuals with any comorbidities left 11,549 cases of ASD, 20,015 of ADHD, 4,267 of OCD and 2,540 of TS/CT. All results remained significant after excluding individuals with multiple diagnoses, with an exception of TS/CT (**Table S6, available online**) for which we observed the most substantial decrease in sample size after excluding all comorbid cases (nearly 50%). Conversely, the associations between parental ages and ASD or ADHD, became even stronger after exclusion of comorbid cases.

In contrast with elevated estimates of risk described above, young age of either parent at child's birth was associated with lower odds of OCD (HR_{mat}=0.93, 0.87-0.99; HR_{pat}=0.90, 0.84-0.96; **Figure 2**), while offspring of older parents had lower estimates of ADHD risk (HR_{mat}=0.84, 0.78-0.90; HR_{pat}=0.84, 0.81-0.88; **Figure 3**).

Parental age difference was associated with higher odds of both ASD and ADHD, irrespective of which parent was older at child's birth **(Table S7, available online)**.

DISCUSSION

Our study provides robust evidence for distinct patterns of disorder risk associated with early vs. late parenthood, separately in mothers and fathers. Applying standardized analytical procedures in a large, population-based cohort, we observe a varying relationship between parental age at birth and estimates of risk for four pediatric-onset neuropsychiatric disorders. This approach suggests differential interactions between age at parenthood and factors involved in the etiology of ADHD, ASD, OCD and TS/CT, including familial genetic effects, *de novo* mutations and environmental factors. Furthermore, for the first time in a population-based sample we demonstrate that younger parental age increased the estimates of risk for TS/CT in offspring, while advanced parental age is associated with higher risk estimates for OCD. With regard to

parental age gap, we observed that larger age differences are associated with both ASD and ADHD, irrespective of which parent was older at child's birth.

In our study, young parental age was linked with higher estimates of risk for ADHD and TS/CT. The association between ADHD and early parenthood has been observed in some[25,26] but not all[1] previous studies, however, no similar effects have been reported for TS/CT. The TS/CT effects became non-significant after excluding individuals with another comorbid disorder, likely due to the substantial reduction of our sample size – although we cannot exclude the possibility that the parental age effects on offspring TS/CT odds were driven by associations with the comorbid disorders.

Similar effects of young parental age on both ADHD and TS/CT are in line with previously recorded shared etiological pathways for these disorders – including both genetic[34,35] and environmental[36,37] risk factors - and frequent co-occurrences observed between these conditions.[38] However, given co-morbidity between ADHD, TS/CT and OCD[38] it was of interest that young age at child's birth had opposite effects on the risk for those disorders. This notwithstanding, such dissociation can provide useful clues for designing future experiments to dissect the mechanisms through which young parental age can differentially affect the offspring risk for these disorders.

Advanced age of either parent was associated with higher estimates of risk for ASD and OCD. Many epidemiological studies have indicated that advancing parental age, and, in particular, advancing paternal age, contribute to offspring risk for ASD and other neuropsychiatric disorders.[5,39] Association between late fatherhood and both ASD and OCD may offer insights into shared pathways leading to these disorders, echoing the literature that highlights the overlap between the behavioral traits underlying ASD and OCD conditions.[40] Our results suggest that

maternal age effects were independent of those that could be attributed to paternal age, indicating distinct mechanisms through which these parental effects operate in ASD. Consistently with the patterns reported previously by Sandin et al. (2015)[10] and McGrath et al. (2014),[41] we observed a U-shaped risk profile for ASD associated with maternal age at birth.

Our findings underscore differential mechanisms through which age at parenthood can impact offspring development and outcomes. Below we consider these mechanisms in more detail, relate them to the biological processes underlying the disorders at hand, and examine support from previous epidemiological studies. The mechanisms considered below likely interact with each other, as well as with other genetic and environmental factors that are independent of parental age and child's birth, influencing the offspring onto distinct trajectories for neuropsychiatric disorders.

Mechanism underlying "paternal age effects"

Socioeconomic and family factors

Compared to children of older parents, those born to young parents are more often exposed to disadvantageous home environments and parenting behavior, parental smoking[42] and substance abuse.[43,44] These environmental factors have been associated with higher risk for ADHD and TS/CT,[45,46] and with regard to ADHD, could account for the shared parental contribution we observed.

The independent and synergistic nature of the effects of different socioeconomic (SES) and family factors on offspring risk for neuropsychiatric disorders remains to be explored. Work by Rutter et al.[47] suggested that it is the composite measure of early adversity, rather than any one factor in particular, that increases risk of ADHD, a finding replicated in a more recent study.[48]

Sensitive designs will be necessary to establish whether the same holds for TS/CT, and to resolve whether similar convergence of environmental effects can be observed on a molecular level.

Antenatal complications

Antenatal complications include preterm birth, low birth weight, and preeclampsia, all of which have been associated with both early and late motherhood,[17,49] as well as TS/CT,[50] ASD[51] and ADHD[52], but not OCD.[53] As such, these factors could mediate the associations observed in our and other epidemiological studies of maternal age effects. It is important to emphasize that these factors could themselves result from other environmental exposures – including smoking[54] or psychosocial stress[55] - as well as familial genetic liabilities.[56] Thus, future research will have to establish the extent of their mediating vs. independent role in the parental age effects.

***De novo* genetic effects**

Advanced paternal, and recently also maternal, age has been linked with a steady accrual of *de novo* point mutations in the germline DNA.[57,58] Owing to the different rates of replicative events in spermatogonia and oocytes, age-related increase in *de novo* burden is approximately three times higher in men than women.[58] This is likely further exacerbated by selection mechanisms, which may endow spermatogonial stem cells carrying certain mutations with a replicative advantage.[59] Although as a consequence, the majority of *de novo* mutations in offspring are paternal in origin,[60] maternal contributions should receive more attention in the future studies of parental age effects.

The contribution of *de novo* mutations to risk is particularly plausible in ASD, given that case-control studies demonstrate enrichment of such mutations in at least a subset of the probands.[60,61] Exploring different assumptions regarding the mechanisms underlying the associations between advanced paternal age and ASD/schizophrenia, Gratten et al. (2016) highlighted that age-related

de novo mutations likely contribute only 10-20% to the observed increases in the odds of the disorder. This is consistent with the notion from the experimental genetic studies that those mutations play a role only in a subset of ASD cases. Although emerging evidence suggests contribution of *de novo* mutations also to TS/CT[62] – which in our sample was not associated with advancing parental age - such effects have not been reliably demonstrated for ADHD or OCD. This implies that the mediating role of *de novo* mutations could be specific to the association between ASD and advanced parental age.

Although the evidence for the contribution of *de novo* point mutations to risk is most robust, other age-related molecular events could include accumulation of epigenetic alterations[63] and copy number variations.[64] Both of these have been linked with ASD,[65,66] representing plausible mechanisms that contribute to the association between parental age and offspring disorder.

Familial effects

Several groups propose that the association between age at parenthood and neuropsychiatric disorders in offspring is mediated not by *de novo*, but familial genetic factors.[4,19] The underlying assumption behind such notion is that there is a correlation between genetic factors underpinning psychiatric disorders and age at conception. This posits that individuals with a higher genetic liability for some conditions – and thus more likely to have a child with a similar disorder - may also be more likely to conceive early/late in life.

Consistently, several groups demonstrated that the effects of advanced paternal age are relevant only to familial, but not sporadic forms of ASD,[67] or that they disappear after controlling for the age at birth of the first child.[4] More directly, Mehta and colleagues showed that early and late age at motherhood is associated with an increased polygenic risk for schizophrenia.[18] Similarly, Mullins et al. (2017)[68] found that higher genetic load for autism is associated with older age at

first child, while ADHD load is associated with younger age, consistent with our results. Although, to the best of our knowledge, such studies with regard to the other disorders considered herein are absent, work by Gratten et al. (2016)[19] suggests that these mechanisms could be relevant to a wider range of psychiatric disorders.

Given the complexity of the disorders considered in the current study, the mechanisms discussed above are unlikely to be mutually exclusive. The estimates of heritability vary between the studies,[69–71] but ASD, ADHD, OCD and TS/CT have all been consistently shown to arise due to a combination of both genetic and environmental factors. Although we expect certain effects to be more prominent in some disorders, we do not suggest that they generally operate in isolation – either from each other or a broader set of environmental and genetic factors. In the light of the heterogeneity of these disorders, it is even plausible that parental age exerts its effects on any given disorder via a number of different routes - for example, the association between paternal age and ASD could be due to considerably different mechanisms in sporadic and familial cases[72]. Although our study did not have a scope to elucidate such effects, we hope to open up a platform for further research and scientific debate to explore those mechanisms.

It remains to be seen whether consistent associations between parental age effects and different neurodevelopmental disorders in offspring are underpinned by the same or distinct mechanisms, as well as whether estimates of risk and protective effects we uncovered arose due to factors on the same or distinct causal pathways. Given the cross-diagnostic overlap between the effects we report, it will also be on interest whether comorbidity patterns vary as a function of parental age at birth, as well as how parental age affects the behavioral traits underlying those neurodevelopemental disorders in non-clinical samples.

This study has several notable strengths. First, we take advantage of diagnostic data on over 1.4 million individuals (of whom over 25,000 had diagnoses of interest). Second, the study is based on a national healthcare system structured to provide specialized no-cost psychiatric care to all citizens. Third, in this cohort, diagnostic data, parental age and other important confounders are collected prospectively, minimizing problems associated with ascertainment biases.

Limitations of this study include the potential omission or misdiagnosis of the individual. Although the Danish national healthcare system provides psychiatric care to all citizens at no cost, and this structure supports broad inclusion of the clinical population within the registries, those with subthreshold clinical disorders or those who do not seek treatment would not be included herein. Although the validity for childhood autism, schizophrenia and OCD in Danish registers is over 90%,[73–75] and 83% for ADHD,[76] TS/CT diagnoses have yet to be validated. Of note, such validation has been achieved in a similar Swedish health care system[77]. Given the evidence for lower validity of mild to moderate psychiatric problem in the Danish registry, we decided not to study the effects of parental age on other childhood-onset mood and anxiety disorders, although we acknowledge that such study would provide an extremely useful contribution to the field. Furthermore, due to the long follow-up period of the study, some of the individuals in our cohort could receive their diagnosis only in adulthood, and we acknowledge that as such our samples are not of purely "pediatric" disorders – a limitation that is likely particularly pertinent to OCD.

Finally, given the association between young parental age and SES factors, and well-established effects of the latter on offspring outcomes, it remains controversial whether one should control for those factors while investigating parental age effects.[10] This is contingent upon the nature of association between SES and those psychiatric outcomes: if SES is on a causal pathway between

parental age and offspring disorders, then such adjustment could introduce bias into the estimates of the effect sizes. Therefore, in our study we did not include SES as another covariate, although we do acknowledge that the relationship between those factors requires further interrogation.

In conclusion, we used a comparative and trans-diagnostic approach in a large, population-based national sample, adjusting for important potential confounders, and found differential risk patterns across ASD, ADHD, TS/CT and OCD related to parental age at birth. We discuss possible mechanisms and models to understand these differential estimates of risk, and conclude that our results are consistent with a model of both shared and unshared risk architecture for pediatric-onset neuropsychiatric disorders.

FIGURES

Figure 1. Parental Age Effects on Autism Spectrum Disorder (ASD)
Note: Full models were adjusted for parity, sex, and parental psychiatric history at birth. X-axis is shown on a logarithmic scale.

Figure 2. Parental Age Effects on Obsessive-Compulsive Disorder (OCD)
Note: Full models were adjusted for parity, sex, and parental psychiatric history at birth. X-axis is shown on a logarithmic scale.

Figure 3. Parental Age Effects on Attention-Deficit/Hyperactivity Disorder (ADHD)
Note: Full models were adjusted for parity, sex, and parental psychiatric history at birth. X-axis is shown on a logarithmic scale.

Figure 4. Parental Age Effects on Tourette Disorder/Chronic Tic Disorder (TS/CT)
Note: Full models were adjusted for parity, sex, and parental psychiatric history at birth. X-axis is shown on a logarithmic scale.

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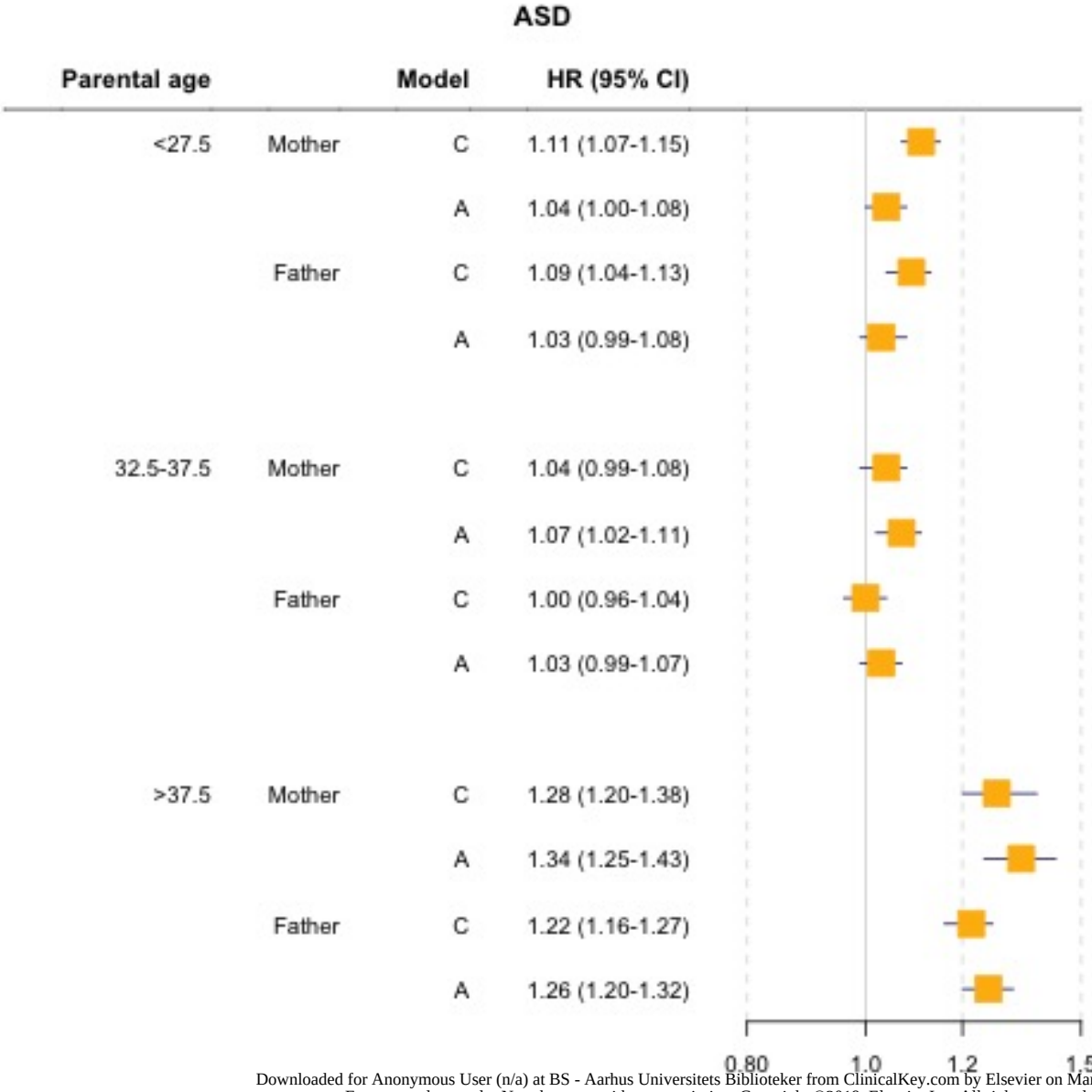

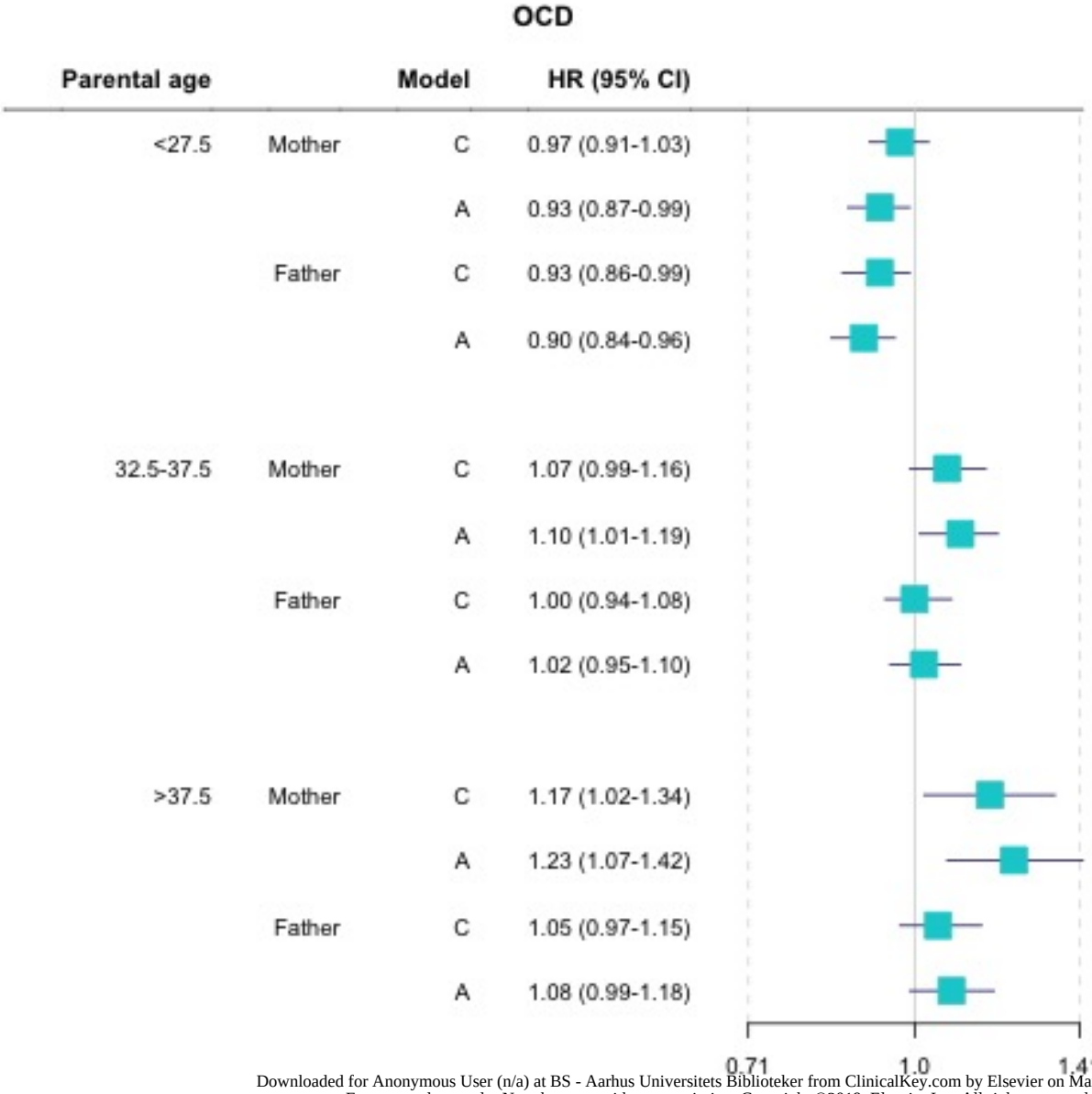

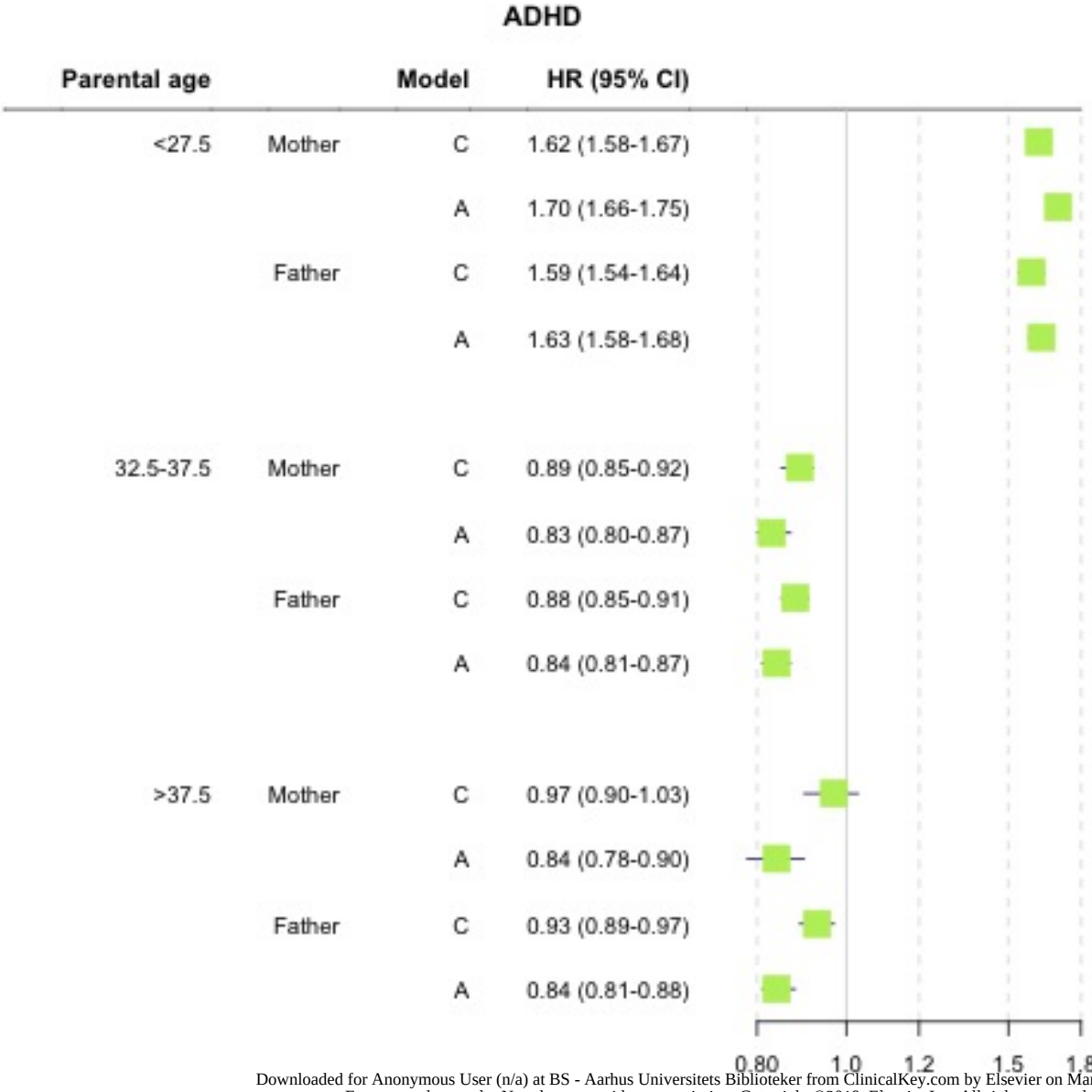

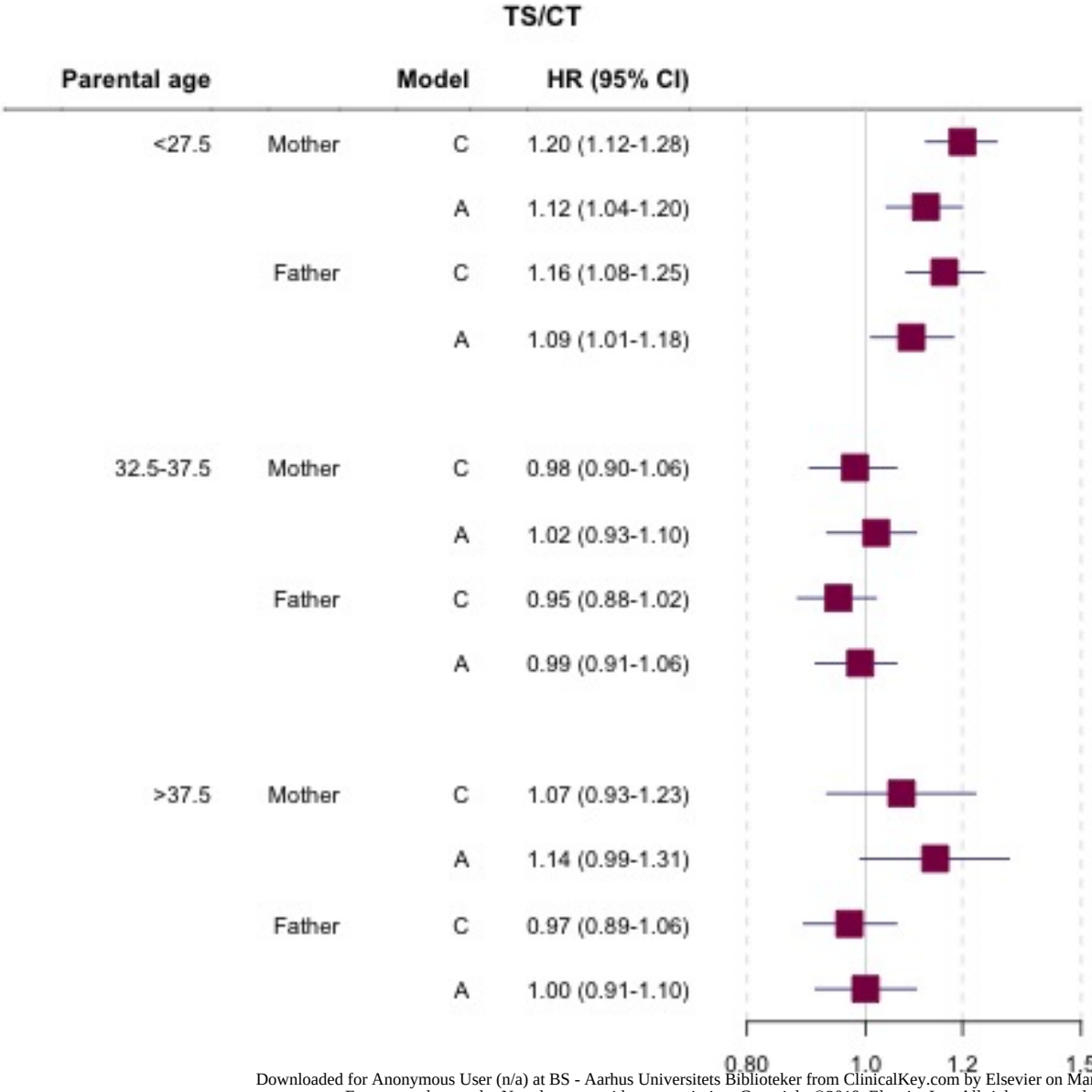

FUNDING: This work was supported by the Lundbeck Foundation Initiative for Integrative Psychiatric Research (to D.S.), the National Institutes of Health (grant HD073978 to A.R. and MH097849 to J.D.B.), the Mindich Child Health and Developmental Institute (to D.E.G. and J.D.B), the Friedman Brain Institute (to D.E.G.) the Seaver Foundation (to J.D.B., A.R., D.E.G. and M.J.) and Stanley Center for Psychiatric Research (to D.E.G.).

ACKNOWLEDGEMENTS: We would like to thank Therese Koops Grønborg, PhD, Aarhus University, for her assistance with the statistical procedures.

CONFLICT OF INTEREST: The authors declare no conflict of interest.