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Parental Age and Autism Spectrum Disorders

ERIK THORLUND PARNER, MSc, PhD, SIMON BARON-COHEN, PhD, MARLENE B. LAURITSEN, MD, META JØRGENSEN, MD, LAURA A. SCHIEVE, PhD, MARSHALYN YEARGIN-ALLSOPP, PhD, AND CARSTEN OBEL, PhD

PURPOSE: We sought to study the possible association between parental age and autism spectrum disorder (ASD) by using both a cohort design and a sibling design.
METHODS: Our cohort included all singleton births in Denmark from January 1, 1980, through December 31, 2003, a total of 1,311,736 children. Cases of ASDs were obtained from the Danish National Psychiatric Register using International Classification of Diseases (ICD)-8 and ICD-10.
RESULTS: A total of 9556 children were diagnosed with an ASD. Both maternal and paternal age were associated with a greater risk of ASD in the offspring (hazard ratios ranging from 1.21 (1.10–1.34) to 1.65 (1.09–2.48) depending on combinations of parental age categories; <35, 35–39, and 40+ years). For mothers younger than 35 years, the risk of ASD increased with increasing father's age group. For fathers younger than 35 years, the risk of ASD increased with increasing maternal age.
CONCLUSIONS: We found an association between parental age and ASD in the cohort study, but the combined underlying mechanisms through which paternal and maternal age impact ASD risk do not seem to act synergistically. The results of the sibling analysis suggest that the association between parental age and ASD found in the cohort study cannot be accounted for by common genetic and environmental factors.
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KEY WORDS: ASD, Autism Spectrum Disorder, Effect Measure Modification, Interaction, Maternal Age, Paternal Age.

INTRODUCTION

Autism spectrum disorders (ASDs) are neurodevelopmental disorders characterized by difficulties in social interaction and communication alongside stereotypic, repetitive behavior and narrow interests. The reported prevalence of ASD in children has increased during the last two decades. The current prevalence of ASD is estimated to be approximately 1% (1–3). At least part of the explanation for the increasing ASD prevalence is likely to be related to factors such as changing diagnostic criteria, greater awareness, improved case identification, and changes in age of diagnosis (4). In the same time period, however, parental age has also increased in many countries, and in a number of studies researchers suggest that older parental age is associated with an increased risk of ASD (5–14).

Although ASDs are strongly genetic, twin studies indicate there must also be environmental factors (15–17). As mentioned previously, the authors of several studies from different cultures have reported greater parental age as a risk factor for ASD. However, the results from these studies are quite inconsistent; after adjusting for other potential confounders, some reported the role of advanced paternal age only (7, 9), another group reported the role of advanced maternal age only (6), and some others point to advanced age of both parents (10–13). In addition, in one study researchers found no effect of either maternal age or paternal age (8), and in one study including only maternal age, authors found no statistical significant effect of maternal age (5). It is unclear whether this association reflects biological causation or whether this association is attributable to confounding. Part of the inconsistency may be caused by the fact that many studies covered a wide time span but few adjusted for the increasing prevalence of ASD and the

From the School of Public Health, Department of Biostatistics, University of Aarhus, Denmark (E.T.P.); Autism Research Centre, Department of Psychiatry, University of Cambridge, UK (S.B.-C.); Regional Centre for Child and Adolescent Psychiatry, Aarhus University Hospital, Risskov, Denmark (M.B.L., M.J.); Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities, Atlanta, GA (L.A.S., M.Y.-A.); School of Public Health, Department of General Practice, University of Aarhus, Denmark (C.O.); and School of Public Health, Center of Mental Childhealth, University of Aarhus, Denmark (C.O.).

Address correspondence to: Erik Thorlund Parner, MSc, PhD, Department of Public Health, Section for Biostatistics, University of Aarhus Address: Bartholins Allé 2, DK-8000 Aarhus C, Denmark. Phone: +45 8716 7995. Fax: +45 8716 7305. E-mail: parner@biostat.au.dk.

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360 Park Avenue South, New York, NY 10010

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Selected Abbreviations and Acronyms

ASD = autism spectrum disorder
DMBR = Danish Medical Birth Registry
CPR = central population registry
DCPR = Danish Central Population Register
aHR = adjusted hazard ratio
CI = confidence interval

authors of only one study assessed the potential modification effect between maternal and paternal age (14).

To our knowledge, no previous study has attempted to replicate the finding in a sibling design, where the association between parental age and ASD is estimated within siblings in the family. The sibling design appears to be one of the most efficient epidemiological designs to substantially reduce the potential confounding caused by environment and genetic factors within the family (18). Couples with a genetic disposition to ASD may simply have their children later. Similarly, giving birth at a later age may could be an indicator of shared social environmental factors that include the possibility of greater awareness of ASD and a subsequent greater likelihood of ASD diagnosis.

In this paper we aimed to study associations between both maternal age, paternal age, and the combined maternal–paternal age effect by using both a population cohort design and a sibling design. The sibling design allowed us to control for potential common environmental and genetic factors within the family, which may confound the association.

METHODS

Study Population and Study Design

The study cohort included all singleton births in Denmark from January 1, 1980, through December 31, 2003, identified in the Danish Medical Birth Registry (DMBR), a total of 1,311,736 children. The DMBR includes information on the course of pregnancy, delivery, and selected demographic variables for all live births and stillbirths by women with permanent residence in Denmark (19). Data on sex, gestational age, and birth weight were obtained from the DMBR. All live-born children in Denmark are assigned a central population registry (CPR) number, a unique, 10-digit number used for all official personal registrations in Denmark since 1968. Information on all Danish residents, including CPR number, date of birth, and parent identification and dates of birth, sex, and migration status (in- and out-migration), are included in the Danish Central Population Register (DCPR) since 1968 (20). Data on parental age and birth order were obtained from the DCPR. Here, we report the finding of 99.4% of the births between 1980 and 2003 with CPR identification of both parents, a total of 1,304,132 children. Because the date of birth can be abstracted from the CPR identification number, the parental ages were available for the whole study cohort.

A sibling subcohort was identified as children born in the same time period January 1, 1980, through December 31, 2003 with the same mother and father in the DCPR, in families with at least two siblings, of which at least one child is diagnosed with ASD. If either of the mother or father changed, the subsequent siblings were defined as a new family (9% of all mothers were included in a second family), hence each family consisted of full siblings. The sibling subcohort included in total 7005 families (0.9% of families in the cohort), with 16,588 children (1.3% of children in the cohort).

On the basis of the CPR number the data from the DMBR were linked to the DPCR to obtain neuropsychiatric outcomes. The DPCR includes all inpatient admissions and, from January 1, 1995, also includes all outpatient visits to psychiatric hospitals and clinics in Denmark (21). For children, inpatient admissions correspond to overnight hospital stays or daily hospital visits during an extended period for diagnostic evaluation and treatments, whereas outpatient admissions correspond to clinic visits on a less regular or long-term basis.

Children suspected to have ASD by general practitioners or school psychologists are referred to a child psychiatric clinic, where they are diagnosed by a child psychiatrist. In Denmark, a specialized diagnostic assessment of children suspected to have an ASD is generally necessary to be enrolled in special services, and the diagnostic evaluation and treatment are free of charge. The DPCR includes data on clinical diagnoses, dates of admission and discharge, and terms of admission. ICD-8 diagnostic criteria were used during the time period up to 1994, and ICD-10 diagnostic criteria have been used since 1994, which closely corresponds to *Diagnostic and Statistical Manual of Mental Disorders*-IV (22).

ASDs included the following ICD-8 diagnoses: 299.00, psychosis proto-infantilis; 299.01, psychosis infantilis posterior; 299.02, psychosis limitaris infantilis; and 299.03, psychosis infantilis non specificata. In Denmark, the ICD-8 diagnostic codes 299.01, 299.02, and 299.03 were considered to include most children with autism spectrum disorders other than childhood autism. The code 299.00 corresponds to childhood autism. The ICD-10 diagnoses included F84.0, childhood autism, and the other autism spectrum disorders F84.1, atypical autism, F84.5, Asperger syndrome, F84.8, other pervasive developmental disorders, and F84.9, pervasive developmental disorders, unspecified. Follow-up for the diagnosis of ASD or childhood autism began for all children from birth and continued until death, or the end of follow-up, on December 31, 2009, whichever occurred first. Parental psychiatric history was defined here as either of the parents having a psychiatric diagnosis recorded before the birth of the child (ICD-8 diagnoses: 290-315 and ICD-10 diagnoses: F00-F99).

Parental age was divided into the three age groups: <35, 35–39, and 40+ years. In a secondary analysis the parental age group <35 years were further divided into smaller age subgroups <25, 25–29, and 30–34 years. Potential confounders included: gestational age (<32, 32–36, 37-40, 41+ weeks), birth weight (≤2.500, 2.501–3.000, 3.001–4.000, >4.000 kg), birth order (1, 2–3, ≥4), sex, parental psychiatric history at birth (yes, no). The study was approved by the Danish National Board of Health and the Danish Data Protection Agency.

Statistical Analyses

In the population cohort design, the hazard ratio for ASDs associated with parental age was estimated using Cox regression, with separate baseline diagnostic rates (stratum) for each birth year group. The outcome variable consist of a pair, time to ASD diagnosis, or end of follow-up, whichever came first, and an ASD indicator (yes/no). The exposure variable was parental ages. The hazard ratio may be interpreted as relative risk because ASD are relatively rare disorders (23). Control for the lack of independence of children within the same family was obtained using a robust (Huber-White) variance estimator. We investigated whether the association between parental age and ASD was modified by year of birth and sex of the child.

For the sibling subcohort, we performed stratified Cox regression. The stratified Cox regression includes a separate stratum for each family; thus, each family has its own baseline rate function reflecting the family's shared genetic and environmental factors. The association between parental age group and ASD is analyzed among siblings in the same family and therefore adjusted for genetic and environmental factors that are shared among the siblings. Hence, only families in the sibling subcohort with at least two siblings born in different parental age groups contributed information to the association between parental age group and ASD, corresponding to 2,608 families, with 6704 children and 2732 ASD cases.

The stratified Cox regression model is an extension of the paired binomial model, taking differences in follow-up time into account. In the sibling-matched analyses adjustment for the increasing autism prevalence (which is at least 10-fold over the study period 1980 to 2003) (24) was achieved by including for the birth date a cubic spline with 10 knots (25). The sibling analysis was only performed for the ASDs, as only few cases were found in the older age group for childhood autism.

RESULTS

A total of 9556 children were diagnosed with an ASD, of which 2446 were diagnosed with childhood autism (Table 1). Of the total 739,122 families, 9036 families had one ASD child, 241 families had two ASD children, 10 families had three ASD children, and 2 families had four ASD children. Cohort characteristics show that children with an ASD and childhood autism diagnosis were more likely to be born prematurely, have a lower birth weight, be male, and have parents with a psychiatric diagnosis prior to the child's birth. The children in the sibling subcohort had a similar distribution with respect to gestational age, birth weight, birth order, gender, and parental psychiatric history. The proportion of parents of 35–39 and 40+ years of age increased consistently over the study time period (Fig. 1). The number of children, ASD, and childhood autism cases by parental age group are shown in Table 2. Although the parental ages showed a high correlation (Pearson correlation equal to 0.68), there were 18 or more cases in all nine parental age groups to compare the ASD diagnostic rate in both the cohort and sibling subcohort.

We found that increased maternal age as well as paternal age were associated with a greater risk of ASD diagnosis in the offspring, and this finding was consistently independent of the birth year group (Fig. 2, test for trend: $p = .70$ for maternal age, and $p = .31$ for paternal age). The finding of increased risk of ASD with both increasing maternal

TABLE 1. Description of the cohort and sibling subcohort

	Cohort			Sibling subcohort	
	ASD	Childhood autism	All other births	ASD	All other births
No.	9,556	2,446	1,294,576	7,272	16,588
Gestational age weeks, %					
<32	0.8	1.3	0.5	0.7	0.7
32–36	4.8	4.9	3.7	4.6	4.1
37–40	65.7	65.4	66.7	65.9	66.7
41+	27.4	27.1	27.2	27.7	27.2
Missing	1.3	1.2	1.9	1.2	1.3
Birth weight kg, %					
≤2.500	5.4	6.2	4.0	4.9	4.3
2.501–3.000	12.9	13.4	13.0	12.3	12.2
3.001–4.000	63.1	61.2	67.0	63.6	64.8
>4.000	18.0	18.2	15.6	18.6	18.0
Missing	0.7	0.9	0.5	0.7	0.7
Birth order					
1	43.3	37.0	39.7	41.4	38.6
2–3	50.6	54.9	54.1	53.1	54.8
≥4	4.8	6.4	5.2	4.2	5.5
Missing	1.3	1.7	1.0	1.3	1.1
Sex, %					
Boys	80.4	81.4	51.2	80.2	63.6
Girls	19.6	18.6	48.8	19.8	36.4
Parental psychiatric history, %					
Yes	7.3	7.6	4.1	6.3	6.2
No	92.7	92.4	95.9	93.7	93.8

ASD = autism spectrum disorder.

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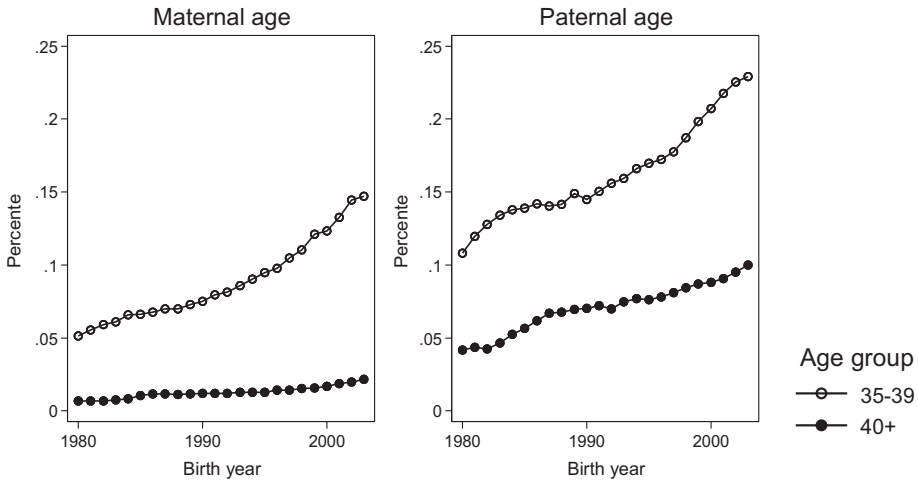

FIGURE 1. Percent of the population of 35–39 and 40+ years of age at child's birth, Denmark, 1980–2003.

and paternal age was independent of the sex of the child (Table 3). The associations were in general slightly stronger for childhood autism compared with ASD. The parental age group <35 years were further divided into smaller age groups <25, 25–29, 30–34 years, but showed very similar risk of ASD in the age groups <25, 25–29, 30–34 years (data not shown).

In the population cohort design older parental age was generally a risk factor for ASD (Table 4); most CIs for parents where one parent's age is older than 39 years do not contain the adjusted hazard (aHR) ratio of one. For mothers younger than 35 years of age, the risk of ASD increased with father's age group (aHR,1.27; 95% CI, 1.19–1.35) for fathers aged 35–39 years and aHR, 1.44 (95% CI, 1.31–1.58) for fathers ages 40+ years, test for trend *p*-value <.001). Similarly, for fathers younger than 35 years of age, the risk of ASD increased with mother's age group (aHR, 1.27; 95% CI, 1.12–1.45) for mothers ages 35 to 39 years and aHR,1.65 (95% CI, 1.09–2.48) for mothers aged 40+ years, test for trend *p*-value <.001). For fathers 35 to 39 years of age, the risk of ASD was independent of the mother's age (aHR, 1.27; 95% CI, 1.19–1.35) for mothers aged <35; aHR, 1.21 (95% CI, 1.10–1.34) for mothers aged 35-39 and aHR, 1.28 (95% CI, 0.91–1.80) for mothers aged 40+, test for trend $p = .52$); for fathers of age 40+ years of age the risk of ASD was also independent of the mother's age (aHR, 1.44 (95% CI, 1.31–1.58) for mothers aged <35; aHR, 1.37 (95% CI, 1.22–1.54) for mothers aged 35–39 and aHR, 1.55 (95% CI, 1.28–1.89) for mothers aged 40+, test for trend $p = .85$). Similarly, for mothers 35–39 years of age, the risk of ASD was independent of the father's age (aHR, 1.27; 95% CI, 1.12–1.45) for fathers aged <35; aHR,1.21 (95% CI, 1.10–1.34) for fathers aged 35–39 and aHR, 1.37 (95% CI, 1.22–1.54) for fathers aged 40+, test for trend $p = .33$); for mothers 40+ years of age, the risk of ASD was also independent of the father's age (aHR, 1.65 (95% CI, 1.09–2.48) for fathers aged <35; aHR, 1.28 (95% CI, 0.91–1.80) for fathers aged 35-39 and aHR, 1.55 (95% CI, 1.28–1.89) for fathers aged 40+, test for trend $p = .86$). The associations between parental age and

TABLE 2. Number of children, ASD and CA cases by parental age group*

	Paternal age, years		
	<35	35–39	40+
No. children, no. ASD cases (%), no. CA cases (%)			
Cohort study			
Maternal age, years no. (%)			
<35	965,517	155,738	48,487
	6,560 (0.7)	1,335 (0.9)	499 (1.0)
	1,583 (0.2)	352 (0.2)	148 (0.3)
35–39	28,676	54,547	34,351
	249 (0.9)	427 (0.8)	314 (0.9)
	70 (0.2)	133 (0.2)	99 (0.3)
40+	2,174	3,946	10,696
	25 (1.1)	37 (0.9)	110 (1.0)
	12 (0.6)	10 (0.3)	39 (0.4)
Sibling study			
Maternal age, years no. (%)			
<35	2,844	1,827	468
	1,067 (37.5)	799 (43.7)	199 (42.5)
	216 (7.6)	223 (12.2)	58 (12.4)
35–39	269	684	439
	112 (41.6)	291 (42.5)	183 (41.7)
	38 (14.1)	90 (13.2)	66 (15.0)
40+	18	44	111
	8 (44.4)	23 (52.3)	50 (45.0)
	5 (27.8)	5 (11.4)	21 (18.9)

ASD = autism spectrum disorder; CA = childhood autism.
*In the sibling study the number of children, ASD and CA cases are counted among the informative families: at least two siblings in the family of which one child is diagnosed with ASD, with at least two siblings born in different parental age groups.

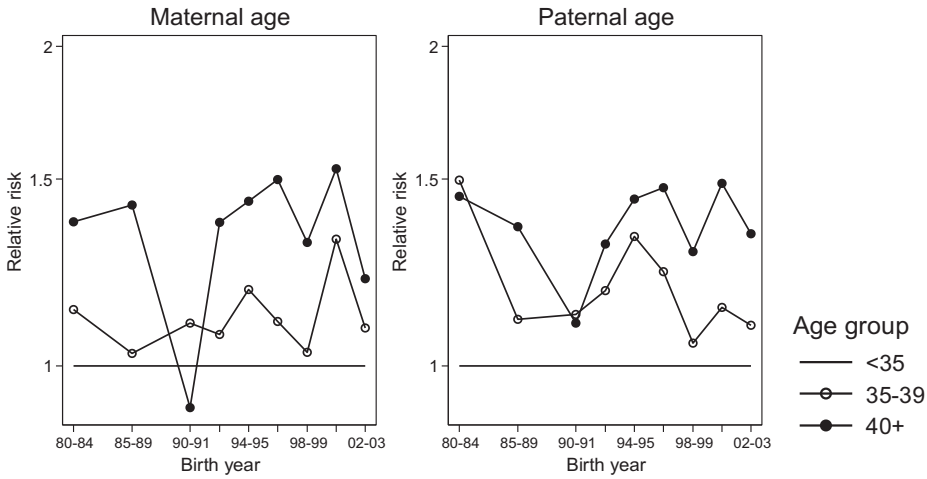

FIGURE 2. The relative risk for ASD in parental age group 35–39 and 40+ years compared to the reference age group <35 years by birth year.

childhood autism showed a similar pattern of results by maternal versus paternal age. The adjusted associations of maternal and paternal age in the sibling sub-cohort showed a similar pattern as compared to the full cohort (Table 5).

DISCUSSION

We found that the risk for ASD was similar for children born to mothers of advanced age, fathers of advanced age, and both parents of advanced age. Our study did not indicate that having two parents of advanced age increased the risk above having only one parent of advanced age. The associations between parental age and childhood autism showed a similar pattern of effect as for ASD. In the sibling subcohort, which adjusted for common genetic and environmental factors within the family, the pattern of mother's and father's age were similar as in the full cohort.

The association between maternal and paternal age and autism has previously most often been explained by an increased occurrence of spontaneous genomic alterations

TABLE 3. Unadjusted parental age effect, and stratified by sex of the child in the Cohort analysis

	Other parent's age, years				
	<35	35–39	40+	*p*-value*	*p*-value†
Autism spectrum disorders					
Maternal age					
All	1.00 (reference)	1.11 (1.04–1.19)	1.35 (1.16–1.57)	<.001	
Sex					
Boys	1.00 (reference)	1.07 (0.99–1.15)	1.26 (1.06–1.50)		.06
Girls	1.00 (reference)	1.28 (1.11–1.48)	1.74 (1.28–2.36)		
Paternal age					
All	1.00 (reference)	1.17 (1.11–1.23)	1.35 (1.26–1.45)	<.001	
Sex					
Boys	1.00 (reference)	1.15 (1.09–1.22)	1.31 (1.21–1.41)		.24
Girls	1.00 (reference)	1.25 (1.11–1.41)	1.53 (1.32–1.78)		
Childhood autism					
Maternal age					
All	1.00 (reference)	1.23 (1.09–1.39)	1.75 (1.36–2.26)	<.001	
Sex					
Boys	1.00 (reference)	1.20 (1.05–1.37)	1.79 (1.35–2.37)		.75
Girls	1.00 (reference)	1.36 (1.04–1.79)	1.60 (0.85–3.00)		
Paternal age					
All	1.00 (reference)	1.22 (1.10–1.35)	1.59 (1.41–1.81)	<.001	
Sex					
Boys	1.00 (reference)	1.24 (1.11–1.38)	1.50 (1.30–1.73)		.10
Girls	1.00 (reference)	1.12 (0.88–1.43)	2.01 (1.54–2.63)		

*Test for no parental age effect.
†Test for no interaction between parental age group and sex.

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TABLE 4. Unadjusted and adjusted parental age effect in the Cohort analysis, adjusting for gestational age, birth weight, birth order, sex, and parental psychiatric history at birth

	Paternal age, years			
	<35	35–39	40+	*p*-value*
Autism spectrum disorders				
Maternal age, years				
Unadjusted age effect				
<35	1.00 (reference)	1.21 (1.14–1.28)	1.42 (1.30–1.56)	<.001
35–39	1.20 (1.06–1.36)	1.09 (0.99–1.20)	1.25 (1.12–1.40)	.52
40+	1.58 (1.07–2.35)	1.29 (0.94–1.78)	1.43 (1.18–1.72)	.84
p-value*	<0.001	0.18	0.42	
p-value†	0.002			
Adjusted age effect				
<35	1.00 (reference)	1.27 (1.19–1.35)	1.44 (1.31–1.58)	<.001
35–39	1.27 (1.12–1.45)	1.21 (1.10–1.34)	1.37 (1.22–1.54)	.33
40+	1.65 (1.09–2.48)	1.28 (0.91–1.80)	1.55 (1.28–1.89)	.86
p-value*	<0.001	0.52	0.85	
p-value†	0.002			
Childhood autism				
Maternal age, years				
Unadjusted age effect				
<35	1.00 (reference)	1.23 (1.10–1.38)	1.67 (1.41–1.97)	<.001
35–39	1.24 (0.98–1.58)	1.25 (1.05–1.49)	1.47 (1.20–1.80)	.25
40+	2.90 (1.65–5.12)	1.28 (0.69–2.38)	1.89 (1.37–2.59)	.48
p-value*	<0.001	0.85	0.93	
p-value†	0.02			
Adjusted age effect				
<35	1.00 (reference)	1.23 (1.09–1.38)	1.59 (1.33–1.89)	<.001
35–39	1.21 (0.94–1.54)	1.27 (1.06–1.52)	1.45 (1.18–1.79)	.23
40+	2.63 (1.45–4.78)	1.00 (0.50–2.01)	1.76 (1.26–2.45)	.64
p-value*	0.004	0.99	0.90	
p-value†	0.05			

*Test for trend *p*-values.
†Test for interaction *p*-values.

(9, 26). However, if spontaneous genomic alterations in parents was the sole causal mechanism we might expect to find a higher ASD and/or autism risk when both parents ages were advanced than when just one parent's age was advanced. Because our results did not follow such a pattern, our study suggests genomic alternation is not the main

TABLE 5. Unadjusted and adjusted effect of parental age in the sibling subcohort, adjusting for gestational age, birth weight, birth order and sex

	Paternal age, years			
	<35	35–39	40+	*p*-value*
Autism spectrum disorders				
Maternal age, years				
Unadjusted age effect				
<35	1.00 (reference)	1.12 (0.97–1.29)	1.21 (0.92–1.60)	.10
35–39	1.14 (0.84–1.56)	1.09 (0.88–1.35)	1.12 (0.83–1.51)	.97
40+	0.95 (0.32–2.80)	1.41 (0.71–2.80)	1.05 (0.63–1.75)	.84
p-value*	0.49	0.93	0.53	
p-value†	0.79			
Adjusted age effect				
<35	1.00 (reference)	1.18 (1.01–1.39)	1.39 (1.01–1.90)	.02
35–39	1.13 (0.80–1.60)	1.13 (0.89–1.44)	1.25 (0.89–1.76)	.64
40+	1.16 (0.32–4.14)	1.69 (0.76–3.74)	1.28 (0.71–2.31)	.86
p-value*	0.49	0.97	0.63	
p-value†	0.81			

*Test for trend *p*-values.
†Test for interaction *p*-values.

mechanism through which parental age impacts ASD risk. However, we cannot rule out the possibility that spontaneous genomic alterations nonetheless play some role, in combination with other factors. Parental age is a nonspecific risk factor and thus, there might be several underlying reasons for its association with ASD which might all be in play to varying degrees in the population. These include various etiologic-related pathways (eg, [as stated] genetic alterations; longer timeframe for cumulative build-up of environmental and occupational exposures in either or both parents; increased incidence or impact of maternal infections or autoimmune disorders; increased incidence of other conditions or medication use for chronic conditions in one or both parents; increased incidence of infertility conditions and/or use of infertility treatments that might impact the maternal hormonal profile), and nonetiologic pathways (eg, older parents might be more health conscious and seek services for children with developmental delays sooner than younger parents; similarly, older parents with a second or later child might be more familiar with developmental milestones).

The sibling analysis suggested that association between parental ages and ASD cannot fully be explained by genetic and/or environment factors that are shared between siblings. For example, one hypothesis to potentially explain the parental age effects is that parents with autistic traits might tend to reproduce later in life, perhaps because they tend to find a partner later in life as compared with the general population. The persistence of the parental age association in the sibling subset does not support this hypothesis as the predominant mechanism of effect. In this subset, among families with two siblings with discordant parental ages at birth (ie, at first child's birth both parents were young, whereas at second child's birth one or both parents was of advanced parental age), the later child had a higher risk of ASD than the earlier child.

In several studies from different cultures, investigators have reported either maternal age or paternal age as a risk factor for ASD with somewhat inconsistent results. In only one study (18) did the authors consider the potential interaction between maternal and paternal age; they found that increasing maternal age increases the risk of autism independent of father's age, whereas increasing father's age increases the risk of autism primarily for mothers younger than 30, with little, if any evidence for an effect in mothers older than 30 years of age. In the present study we found that when paternal age is younger than 35 years, increasing maternal age increases the risk of ASD and similarly, when maternal age is younger than 35 years, increasing paternal age increases the risk of ASD.

The results of this study were based on an ethnically homogeneous population of children born in Denmark from 1980 to 2003. The parental ages were available for almost the whole study population and both are considered accurate since they are obtained from the mother's and father's CPR identification number. The diagnostic data were obtained from nationwide registers, based on standardized diagnostic reporting procedures. The use of register data made it possible to include a large number of individuals. The quality of childhood autism ICD-10 diagnoses found in the DPCR has recently been validated (27); after evaluating nearly 500 medical records of children registered with childhood autism in the DPCR, 94% of the children met the criteria for a correct diagnosis. The quality of the ASD diagnosis in DPCR is otherwise unknown, but expected to be high; in this study we observed a prevalence of ASDs for 9- to 10–year-old children (born 1998–1999) to be 96.7 per 10,000, an estimate similar to the prevalence of 110 per 10,000 in U.S. children ages 3 to 17 years based on parent report (1) or about 1% among 8-year old U.S. children based on the ADDM Network (http://www.cdc.gov/ncbddd/autism/data.html). However, registers of clinical diagnoses can never be as complete as systematic community surveys. Since the DPCR only includes out-patient visits from 1995 some ASD cases are likely to be missed in the early birth cohorts. However, we did not see any trend in parental age effect over calendar time.

The sibling analysis is based on a small fraction of children in the cohort study, consisting of only families with at least two children, where at least one child is diagnosed with ASD. The sibling subcohort can thus potentially be a select group of the total population in which the association between parental age group and ASD is different than in the full cohort.

In conclusion, we find an association between parental age and ASD in the cohort study, but the combined underlying mechanisms through which paternal and maternal age impact ASD risk do not seem to act synergistically. The association between parental age and ASD in the cohort study does not seem to be accounted for by common genetic and environmental factors within the family that do not change over time, as shown in the sibling subcohort, but there are several etiologic and non-etiologic potential explanatory pathways that could be different between younger and older siblings.

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