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Parental Age in Relation to Offspring's Neurodevelopment

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ABSTRACT

Objective: Advanced parenthood increases the risk of severe neurodevelopmental disorders like autism, Down syndrome and schizophrenia. Does advanced parenthood also negatively impact offspring's general neurodevelopment?

Method: We analyzed child-, father-, mother- and teacher-rated attention-problems (N = 38,024), and standardized measures of intelligence (N = 10,273) and educational achievement (N = 17,522) of children from four Dutch population-based cohorts. The mean age over cohorts varied from 9.73–13.03. Most participants were of Dutch origin, ranging from 58.7%-96.7% over cohorts. We analyzed 50% of the data to generate hypotheses and the other 50% to evaluate support for these hypotheses. We aggregated the results over cohorts with Bayesian research synthesis.

Results: We mostly found negative linear relations between parental age and attention-problems, meaning that offspring of younger parents tended to have more attention problems. Maternal age was positively and linearly related to offspring's IQ and educational achievement. Paternal age showed an attenuating positive relation with educational achievement and an inverted U-shape relation with IQ, with offspring of younger and older fathers at a disadvantage. Only the associations with maternal age remained after including SES. The inclusion of child gender in the model did not affect the relation between parental age and the study outcomes.

Conclusions: Effects were small but significant, with better outcomes for children born to older parents. Older parents tended to be of higher SES. Indeed, the positive relation between parental age and offspring neurodevelopmental outcomes was partly confounded by SES.

During the past few decades, postponing parenthood to advanced age has been a persistent trend in the US (Bui & Miller, 2018) as well as Europe and many other developed countries. In the Netherlands, for example, women nowadays first give birth around age 30, while in 1970 the mean age was 24 (Centraal Bureau voor de Statistiek (CBS), 2019). Concerns about this postponement are understandable and growing, as a large body of research has shown that offspring of older parents are at increased risk for developing severe neurodevelopmental disorders, such as schizophrenia, Down syndrome, and autism (Merikangas et al., 2017, 2016). One important question is whether these effects generalize to the more common neurodevelopmental outcomes. In a recent population-based study, we found no negative effects of advanced parenthood on internalizing and externalizing problems, but observed that children of older parents tended to show fewer externalizing behavior problems than children of younger parents (Zondervan et al., 2019). In the current study, we focused on neurodevelopmental outcomes and investigated whether offspring of older parents are at increased risk for more attention problems and lower intelligence and educational achievement.

While the risk of high parental age on offspring schizophrenia, Down syndrome, and autism seems well-established, no consistent pattern exists for attention problems. Attention problems are an important component of Attention Deficit Hyperactivity Disorder (ADHD), one of the most common neurodevelopmental disorders in childhood (Faraone et al., 2003). There are studies that show a reverse association, suggesting that offspring of younger parents are more at risk. Mikkelsen et al. (2016) found in a population-based sample (N = 943,785) that

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All analysis scripts and data are available at https://osf.io/dh9p2/. For data-related questions, please contact d.i.boomsma@vu.nl for NTR, generationr@erasmusmc.nl for Generation-R, RADAR@uu.nl for RADAR and trails@umcg.nl for TRAILS.

offspring of mothers who gave birth to children early in their reproductive lives were more vulnerable to develop ADHD. This same outcome was also observed in a case-control (*N* = 10,409; *N* = 39,125) study by Chudal et al. (2015) and in population-based cohort studies (*N* = 1,495,543; *N* = 1,490,745) by Chang et al. (2014) and Janecka et al. (2019). The results are more diverse for fathers; while Mikkelsen et al. (2016) found no effect for fathers' age, D'Onofrio et al. (2014) reported in a population-based study (*N* = 2,615,081) that offspring of fathers 45 years and older were at higher risk for ADHD. Chudal et al. (2015), however, found that the relationship between paternal age and offspring ADHD showed high risk for young fathers (<25), lowest risk for fathers around 30, and a somewhat increased risk for fathers older than 40. Taken together, most studies point to an adverse effect of paternal age. Some studies suspect a curvilinear effect with adverse scores in both extremes of the age distribution as they compare odds ratios for different age groups. However, none of the studies mentioned here actually tested a linear versus curvilinear model. The relation between parental age and attention problems might thus differ for fathers and mothers and might also differ from those found in research on more extreme neurodevelopmental problems, such that offspring of younger parents could also be more at risk.

For intelligence and academic achievement, earlier studies showed mixed results. Saha et al. (2009) found in a sample of 33,437 children that intelligence at age 7 was lower for offspring of older fathers. Although only non-linear models are presented, Saha et al. conclude that the relation between intelligence and paternal age is near-linear. Gajos and Beaver (2017) reported an inverted U-shaped association between paternal age and verbal IQ scores in sons (*N* = 480), but not daughters (*N* = 449). The quadratic age factor in this study becomes non-significant after the addition of a set of covariates like father's race and mother's income. McGrath et al. (2013) found that both younger and older fathers had children with lower IQ scores than fathers aged 25–29, suggesting an inverted U shape (*N* = 169,009). On the other hand, D'Onofrio et al. (2014) observed with a proportional hazards regression that children of fathers aged 45 or older were more vulnerable for low academic achievement (indexed by e.g., low educational attainment and failing grades). Regarding maternal age, some studies indicated that offspring of older mothers (and not fathers) had a higher chance of cognitive disability (Cohen, 2014), while other studies suggested that older mothers have offspring with higher IQ scores (McGrath et al., 2013). Saha et al. (2009) conclude that the relation between maternal age and child IQ is curvilinear, with a generally steep increase up to some point between the ages of 20 and 25 and a less steep increase at older ages. Again, linear tests are not presented in Saha et al. (2009). Like attention problems, effects of parental age on cognitive ability need to be further clarified.

The present study looks into the relation between parental age and three neurodevelopmental outcomes. We analyzed parent-, teacher- and self-reported attention problems (*N* ≤ 38,024), psychometric IQ (*N* = 10,273), and educational achievement assessed by national standardized tests (*N* = 17,522) of school-aged children from four large population-based cohort studies. Our neurodevelopmental outcomes are particularly important in the school age years as they are critical for future educational attainment and work opportunities. We investigated paternal and maternal age with and without taking child gender and family SES into account. Given mixed results in previous research, and the large number of data we had available, we employed a cross-validation approach to generate hypotheses based on one half of the data, and evaluated next how much support each of these hypotheses obtained in the other half of the data. It is interesting to evaluate and compare the relative support for each of the hypotheses by each of the studies separately. However, we were also interested in the aggregated results over the cohorts, as this shows us the support for each of the hypotheses by all cohort simultaneously. Bayesian research synthesis results in measures of robust support for each hypothesis, as they show the support over different samples and measurement methods.

Method

Participants

Four Dutch cohorts contributed to this study: the Netherlands Twin Register (NTR), Generation R (Gen-R), the Research on Adolescent Development and Relationships-Young cohort (RADAR-Y), and the Tracking Adolescents' Individual Lives Survey (TRAILS). The number of participants differed over dependent variables (See Table 1). All cohort studies were approved by medical ethical committees of the associated universities.

NTR recruits newborn twins from all regions in the Netherlands shortly after birth and has registered about 52% of all Dutch twin pairs born after 1986. Data on attention problems and educational achievement were collected through surveys completed by parents and teachers, who did not get any reward. Data on IQ were collected in in-depth phenotyping studies (Ligthart et al., 2019). Data from children with a severe handicap that interfered with daily functioning were excluded in the current sample. For attention problems (*N* = 25,396),

Table 1. Mean, SD and sample size for the dependent variables.

Variable	Gen-R (*N* = 9,901)		NTR (*N* = 25,396)		RADAR-Y (*N* = 497)		TRAILS (*N* = 2,230)	
Informant	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)	*N*
Attention Problems								
Child	3.41 (2.49)	4,357	-	-	-	-	4.33 (2.74)	2,197
Mother	3.25 (3.20)	4,920	2.95 (3.05)	22,045	8.94[1] (8.37)	489	4.36 (3.47)	1,964
Father	3.29 (3.08)	3,555	2.62 (2.88)	14,725	-	-	-	-
Teacher		-	6.74 (7.87)	12,573	-	-	0.53[2] (0.58)	1,927
IQ	100.70 (15.18)	6,111	103.44 (14.21)	1,495	102.05 (11.80)	446	97.19 (15.00)	2,221
Educational Achievement	538.40 (9.44)	2,655	538.00 (8.55)	14,867	-	-	-	-

The total cohort sample size is presented between brackets. The sample size for each outcome variable is presented in the columns to provide insight in the amount of missing values. For IQ in NTR and Educational Achievement in Gen-R, a complete cases subset was created.

Unless otherwise specified, Gen-R, NTR and TRAILS used the ASEBA questionnaires (YSR, CBCL, and TRF) to measure attention problems (Achenbach, 1991; Achenbach & Rescorla, 2001). In Gen-R, IQ was measured with the Snijders-Oomen nonverbal intelligence test (Tellegen et al., 2005). In NTR, IQ was measured at ages 5, 7, 9, 10, 12, 17 and 18 using the RAKIT, WISC-R(-III), Raven or WAIS (see Franić et al., 2014). For the children in NTR with multiple assessments, the mean over all IQ assessments was taken. In TRAILS and Radar-Y, IQ was assessed with the block design and the vocabulary subtests of the WISC-III-R. Educational achievement was assessed by the CITO End of Primary Education Test

[1]Radar-Y measured mother-rated attention problems with a Dutch adaptation of Teacher ratings of DSM-III-R symptoms for the disruptive behavior disorders (DPD; Pelham et al., 1992), by Oosterlaan et al. (2000).

[2]TRAILS uses a 1-item adapted version of the TRF (scale and range = 0–2), see Measures section for more information.

we included data of children who were born between 1986 and 2008. The children had a mean age of 9.95 (*SD* = 0.51), ranging from 7.83 to 11.95. For educational achievement (*N* = 14,867), data of twins and their siblings came from a nation-wide standardized test assessed around age 12. For psychometric IQ (*N* = 1,495), data of twins and their siblings measured at ages 5, 7, 9, 10, 12, 17 and 18 were included under the assumption that IQ is a stable construct. Parents were mostly born in the Netherlands (95.7% of fathers and 96.7% of mothers). Mother's educational level was low (i.e., no education or primary education) for 4.6% of the sample, intermediate (i.e., secondary school, vocational training) for 67.0%, and high (i.e., bachelor's degree, university) for 28.4%.

Gen-R recruited pregnant women and their partners through midwifes and General Practitioners in the city of Rotterdam with an expected delivery date between April 2002 and January 2006. The inclusion criterion was that the mothers were resident in the study area (i.e., the city of Rotterdam) at their delivery date. After birth, families were contacted through telephone calls and postal questionnaires, including a parental consent form. There were no incentives for filling out the questionnaire. For attention problems (*N* = 9,901), the age of the children ranged from 8.68 to 12.47 (*M* = 9.73, *SD* = 0.33). For educational achievement (*N* = 2,655), Gen-R analyzed data obtained from a nation-wide standardized test assessed around age 12. IQ (*N* = 6,111) was measured at 6 years. In the overall dataset, 58.7% of the sample was of Dutch or other European ancestry, other groups included Moroccan, Dutch Antilles, and Cape-Verdian. Mother's educational level was low for 4.1% of the sample, intermediate for 39.4%, and high for 56.6%.

RADAR-Y participants were 497 Dutch children. The participants were drawn from a large cohort that was assessed before the RADAR-Y study was initiated. Specifically, 429 elementary schools were randomly selected in the area of Utrecht and four large cities in the mid-west of the Netherlands (i.e., Amsterdam, Rotterdam, The Hague, and Almere). Of the randomly selected schools, 296 agreed to participate. Due to logistic reasons, data was collected at 230 schools. Of the 1,544 assessed children, 497 met the inclusion criteria for the RADAR-young project (i.e., living with both of their parents and having at least one sibling who was 10 years or older at the onset of the study). Children with increased externalizing behavior problems at age 12 were purposefully oversampled. Participants received €10,- (equivalent to approximately 11USD, -) upon completion of the questionnaires. Data on attention problems and IQ were included for all participants from the first wave of data collection (born between 1990 and 1995). Their mean age was 13.03 (*SD* = 0.46), ranging from 11.01–15.56. The sample consisted mainly of children with parents born in the Netherlands (93.3%). The other children had parents born in Surinam (1.8%), Indonesia (1%), and Dutch Antilles (0.8%). Mother's educational level was low for 3.2% of the sample, intermediate for 56.7%, and high for 40.1%.

The TRAILS sample (*N* = 2,230) was recruited in both rural and urban Northern regions of the Netherlands. Data on attention problems and IQ were included from all participants from the first wave of data collection (born between 1990 and 1991). During the first wave, 135 schools were contacted, and 122 schools agreed to participate in the study. Parents at participating schools were sent brochures with information about the study, and a TRAILS staff member visited participating schools to inform eligible children about the study. Of all children approached for participation, 6.7% were excluded from the study because they were unable to participate due to mental disability or serious physical problems, or because no Dutch-speaking parent or guardian was available and it was not possible to administer measures in the parent's language. The remaining 2,230 children were included in the study. Well-trained interviewers visited the home of one of the parents or guardians (95.6% were mothers) to conduct interviews regarding their child's developmental history and somatic health and about parental psychopathology. Parents also completed a written questionnaire. Children completed questionnaires in groups at school, under the supervision of at least one research assistant. Teachers were asked to complete a questionnaire for all TRAILS-participating youth in their class. The average age of the children was 11.11 (*SD* = 0.56) and ranged between 10.01 and 12.58. The majority of participants had parents who were born in the Netherlands (86.5%), with others from Surinam (2.1%), Indonesia (1.7%), Antilles (1.7%), Morocco (0.7%), Turkey (0.5%), and other (6.9%). Mother's educational level was low for 6.6% of the sample, intermediate for 64.3%, and high for 25.9%.

Measures

Predictors

Maternal and paternal age at birth. The age of the biological parents at birth of the child was measured in years up to two decimals for each cohort. The mean age differed somewhat over cohorts and measures, for mothers it ranged from 29.92–32.25 with a total age range from 15.27–48.61. For fathers, it ranged from 32.00–33.76 with a total age range from 14.87–68.18 (see Table 2).

Outcomes

Attention problems. In Gen-R, NTR, and TRAILS, attention problems were measured with the ASEBA questionnaires: the child-rated Youth Self Report (YSR; Achenbach & Rescorla, 2001), the parent-rated Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001; Achenbach, 1991 for earlier birth cohorts), and the teacher-rated Teacher Report Form (TRF; Achenbach & Rescorla, 2001). Radar-Y measured mother-rated attention problems with a Dutch adaptation of Teacher ratings of DSM-III-R symptoms for the disruptive behavior disorders (DPD; Oosterlaan et al., 2000; Pelham et al., 1992). In TRAILS, teachers rated child behavior on a five-point scale for: "fails to finish things he/she starts, can't concentrate, can't pay attention for long, is confused, daydreams, has learning difficulties, is clumsy or poorly coordinated, is inattentive, is easily distracted, underachieves, fails to carry out tasks".

Table 2. Parental age at offspring birth.

Variable	Maternal age at birth child		Paternal age at birth child	
	Range	*M (SD)*	Range	*M (SD)*
Attention Problems				
Gen-R	15.61–46.85	30.36 (5.35)	15.01–68.67	33.45 (6.01)
NTR	17.36–47.09	31.35 (3.95)	18.75–63.61	33.76 (4.71)
RADAR-Y	17.80–48.61	31.38 (4.43)	20.34–52.52	33.70 (5.10)
TRAILS	16.34–44.88	29.32 (4.58)	18.28–52.09	32.00 (4.71)
IQ				
Gen-R	15.61–46.85	30.36 (5.35)	15.01–68.67	33.45 (6.01)
NTR	19.26–45.63	30.18 (3.81)	19.68–57.00	32.54 (4.45)
RADAR-Y	17.80–48.61	31.38 (4.43)	20.34–52.52	33.70 (5.10)
TRAILS	16.34–44.88	29.32 (4.58)	18.28–52.09	32.00 (4.71)
Educational Achievement				
Gen-R	17.30–46.85	31.69 (4.70)	17.05–68.67	34.38 (5.49)
NTR	17.15–45.63	31.02 (3.80)	18.71–63.61	33.40 (4.52)
RADAR-Y	-	-	-	-
TRAILS	-	-	-	-

Gen-R and NTR had different datasets for attention problems, IQ, and EA, therefore all descriptive statistics for parental age are given, since these are key variables in our study.

This item was derived from the set of TRF items on attention. All in all, child-rated attention problems were available in Gen-R and TRAILS, mother-rated attention problems were available in all cohorts, father-rated attention problems were available in Gen-R and NTR, and teacher-rated attention problems were available in NTR and TRAILS. See Table 1 for descriptive statistics.

IQ. In Gen-R, IQ was measured at six years by the Snijders-Oomen nonverbal IQ test (Tellegen et al., 2005). In NTR, IQ was measured at ages 5, 7, 9, 10, 12, 17 and 18 by the RAKIT, WISC-R(-III), Raven or WAIS (Franić et al., 2014). For children in NTR with multiple observations, the mean over all IQ assessments was taken. In Radar-Y and TRAILS, IQ was assessed at age 13 and 11 respectively, with the block design and vocabulary subtests of the WISC-III-R (Legerstee et al., 2004; Silverstein, 1972). See Table 1 for descriptive statistics. The range for IQ was 50.0–150.0 in Gen-R, 47.7–148.5 in NTR, 47.7–-148.5 in TRAILS and 69.0–133.0 in RADAR-Y.

Educational achievement. Educational achievement was available in two cohorts: Gen-R and NTR. Scores came from a 3-day nation-wide standardized test which is administered around age 12 at the end of primary school (Citogroep, 2019) by most schools in the Netherlands. See Table 1 for descriptive statistics.

Covariates

Socio-economic status (SES) and child gender. In Gen-R, SES was defined as a continuous variable (principal component) based on parental education (i.e., up to elementary school, up to secondary school, higher education phase 1, higher education phase 2) and household income (i.e., up to €1,600; €1,600-€2,400; €2,400-€3,200; €3,200-€4,800, more than €4,800). In NTR, SES was a 5-level ordinal variable based on parental occupational level (i.e., low skill level, lower secondary education level, upper secondary education level, higher vocational/bachelor's degree level, scientific level). In TRAILS, SES was a 3-level ordinal variable (i.e., low, middle, high) based on parental education, parental occupational status and household income. In RADAR-Y SES was a dichotomous variable based on parents' occupational level (i.e., low versus middle & high). Child gender was coded as male = 0 and female = 1.

Missing Data and Data Imputation

Missing data were imputed (Schafer & Graham, 2002; Van Buuren, 2018) with the mice package (Van Buuren & Groothuis-Oudshoorn, 2011) in R (R Core Team, 2018). The imputation was conducted separately for attention and the cognitive functioning datasets, all of which included variables on paternal age, maternal age, SES and child gender. Datasets were split into an exploratory and confirmatory half (see analytical strategy). Except for participant and family ID, all variables in the datasets were selected as predictors in the imputation model if the correlation was larger than. 10 with the to-be-imputed variable. The data were imputed 100 times (Van Buuren, 2018, Chapter 2.8), and analysis results were pooled over these datasets with the mice package. The imputation in Gen-R and NTR was family based, instead of per participant, to ensure equal information for twins and siblings on parental age and SES. The (non-twin) sibling data were imputed as individual scores.

Detailed quantities and proportions of missing data per cohort for each variable in each analysis are provided in Supplementary Tables S1-S3 (also available at osf.io/dh9p2). Table 1 includes information on the total sample size and the number of participants with complete information on the three dependent variables in this study. Over the four attention measures and cohorts, missing data on attention problems ranged from 1.5% to 64.1% with a mean of 30.5% and a median of 27.8% (see also Table 1 and S1). In NTR, IQ was analyzed in a subset of children for whom (at least one) IQ assessment was present (see also Table 1). Consequently, the percentages of missing IQ data in the analysis of IQ were 38.3 for Gen-R, 0.0 for NTR, 10.3 for RADAR-Y, and 0.4 for TRAILS. For educational achievement, Gen-R data was analyzed in a subset of the overall dataset containing participants with complete educational achievement data (see also Table 1), and the percentage of missing data in NTR was 5.3. For maternal age, the percentage of missing information ranged from 0.0 to 5.1 (median = 0.4%) over all cohorts and analyses. For paternal age, missing data ranged from 0.7% up to 25.0% (median = 11.9%). Imputation quality was monitored by inspecting imputation trace plots and fraction of missing information quantities.

Analytical Strategy

The analytical strategy consisted of four steps that were executed for each of the neurological outcomes separately: (1) exploratory data analysis, (2) informative hypothesis generation, (3) Bayesian hypothesis evaluation in confirmatory data per cohort, and (4) Bayesian research synthesis over cohorts.

Exploratory Data Analysis

As previous research is mixed about the relations between parental age and the outcome variables, we started with exploratory data analyses. In each cohort, the datasets were randomly divided into an exploratory and a confirmatory part. In the exploratory data, linear regression analyses were conducted in R with standardized paternal age and paternal age squared, or maternal age and maternal age squared as predictors. The dependent variables were attention problems (reported by either child, father, mother, or teacher), child IQ, and educational achievement. The analyses were first conducted without covariates. Next, gender was added as a covariate, and lastly, SES. For the datasets including twins or siblings (i.e., Gen-R and NTR), data were split based on Family ID to create independent datasets (so that all siblings are in one dataset), and linear regression analyses were cluster-corrected based on Family ID with the lavaan R-package (Rosseel, 2012).

Informative Hypothesis Generation

Informative hypotheses are hypotheses that contain information about the parameters of interest in the model, like that a regression parameter is positive (Hoijtink, 2012). Based on the direction and significance of the exploratory regression analyses, competing informative hypotheses were composed stating that the β_{age} and $\beta_{age}{}^2$ parameters were either negative, equal to zero, or positive. In the set of competing hypotheses, two hypotheses were included by default: the null informative hypothesis: $\beta_{age} = 0, \beta_{age}{}^2 = 0$, and the unconstrained alternative hypothesis: $\beta_{age}, \beta_{age}{}^2$. The unconstrained alternative hypothesis (estimated in addition to the informative hypotheses) entails that "anything goes", that is: $\beta_{age}, \beta_{age}{}^2$ can take on any value. This alternative hypothesis is a fail-safe hypothesis that will receive most support when the informative hypotheses in the set do not represent the data well.

Bayesian Hypothesis Evaluation in Confirmatory Data per Cohort

In the confirmatory data, linear regression analyses were conducted with mean-centered paternal or maternal age and age squared as predictors, and the same dependent variables and covariates as before. Using the bain statistical software (Gu et al., 2019), the relative support of each informative hypothesis versus the unconstrained alternative (i.e., β_{age}, $\beta_{age}{}^2$) was computed. Posterior model probabilities (PMPs) represented the relative probability of each of the evaluated hypotheses in the set. Together, the PMPs for all competing hypotheses sum up to 1.00.

Bayesian Research Synthesis over Cohorts

Next, results were aggregated over cohorts, meaning that PMPs of one cohort were used as prior model probabilities in the next cohort. In practice, we can do this by taking the product of PMPs over models and divide by the sum of all PMP products (Kuiper et al., 2012; Zondervan-Zwijnenburg et al., 2019). Thus, no other elements were used to calculate the aggregated results than each cohort's PMPs per analysis. In this manner, we evaluated which informative hypothesis was best supported by all cohorts simultaneously. Note that in this method, there is no need to pool or merge the data: all datasets independently contribute. Assessing how much the hypotheses are supported by all cohorts evaluates support for hypotheses irrespective of the population and measurement specifics of separate cohorts. To apply Bayesian Research Synthesis and interpret the aggregated result, it is important that: 1) there is one underlying population for the included samples (e.g., Dutch children), and 2) the measures represent the same construct such that support for the same informative hypothesis can be expected. We believe that in our study each of the cohorts is a subpopulation of a larger population of Dutch children, even though the regions or family compositions (e.g., families with twins) vary between the cohort studies. Furthermore, we investigate three separate neurological constructs: attention problems, intelligence and educational achievement. We believe that the measures that we use, even though they can vary between cohorts, all measure the associated constructs appropriately.

Results

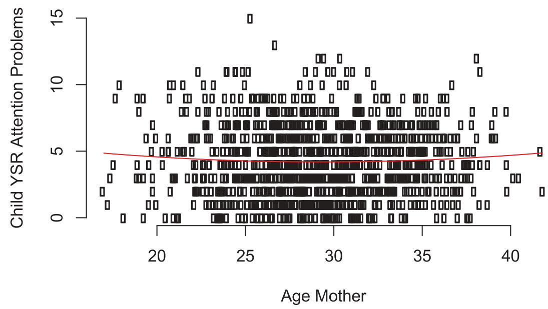
Exploratory Data Analyses

In general, the results of the exploratory analyses indicated that child-reported attention problems were not predicted by parental age (results are provided in Supplementary Tables S4-S18). For all other reporters, age had a significant negative relation with attention problems, accompanied by a significant positive quadratic factor in about half of the analyses across raters and cohorts. The negative direction of the linear relation indicated that offspring of younger parents had on average more attention problems. In case of significant quadratic factors, the regression either became U-shaped, indicating that offspring of the youngest and oldest parents had most attention problems or had a steeper decline in the beginning that attenuated over time, indicating that offspring of the youngest parents had the most attention problems (see for example, Figure 1a-b). For parental age with IQ and educational achievement the linear relations were positive: offspring of older parents had on average higher IQ or educational achievement. Also, significant quadratic factors were now negative resulting in either a bow-shape (inverse U), indicating that offspring of the youngest and oldest parents had the lowest IQ and educational achievement scores or had a steeper increase in the beginning that attenuated over time. Offspring of the youngest parents had the lowest IQ and educational achievement (see for example, Figure 1c-d). Adding gender as a covariate to the model did not generally change the patterns. When SES was added to the model, about half of the significant relations between age and attention problems disappeared.

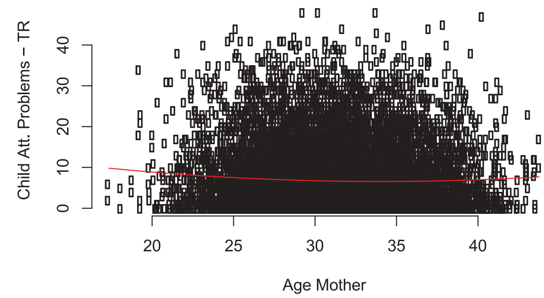
Informative Hypothesis Generation in Exploratory Data

A set of these competing hypotheses was drafted for each combination of predictor (paternal age or maternal age), dependent variable (i.e., attention rated by mother, father, teacher, child; IQ; educational achievement), and set of covariates (i.e., none or gender and SES). For example, for teacher reported attention problems regressed on maternal age, we found $\beta_1 < 0$, $\beta_2 > 0$ in NTR and $\beta_1 < 0$, $\beta_2 = 0$ in TRAILS. As a fail-safe, we always evaluated H_1: $\beta_1 = 0$, $\beta_2 = 0$, and H_a: β_1, β_2 (see Analytical Strategy section). Hence, we evaluated the four hypotheses as the set of competing hypotheses with the confirmatory data in all cohorts for the regression of teacher reported attention problems on maternal age. See Supplementary Table S19 for the exact hypotheses for attention problems per rater, before and after adjustment for gender and SES. Note that in the confirmatory analyses, we composed hypotheses and ran analyses with both gender and SES in the model at once, because the exploratory analyses showed that gender by itself hardly affected any of the relations in the model. Based on the exploratory results, the overall set of hypotheses for attention problems was:

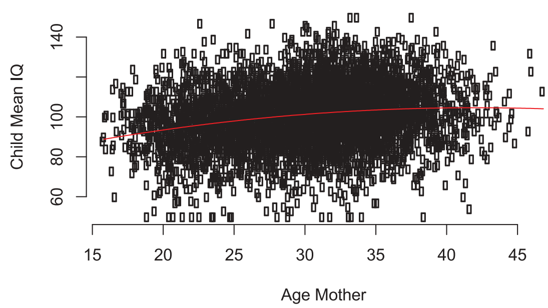
- H_1: $\beta_1 = 0$, $\beta_2 = 0$. Age is unrelated (i.e., the classical null model).



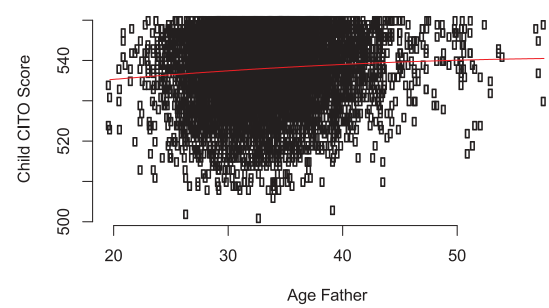
(a) Child-reported attention by TRAILS with $\beta_1 = 0, \beta_2 = 0$



(b) Teacher reported Attention by NTR with $\beta_1 < 0, \beta_2 > 0$



(c) IQ regressed on mother age by Gen-R with $\beta_1 > 0, \beta_2 < 0$



(d) Educational Achievement by NTR with $\beta_1 > 0, \beta_2 = 0$

Figure 1. Exploratory plots. (a) Child-reported attention by TRAILS with $\beta_1 = 0$, $\beta_2 = 0$, (b) Teacher reported Attention by NTR with $\beta_1 < 0$, $\beta_2 > 0$. (c) IQ regressed on mother age by Gen-R with $\beta_1 > 0$, $\beta_2 < 0$. (d) Educational Achievement by NTR with $\beta_1 > 0$, $\beta_2 = 0$.

- H_2: $\beta_1 < 0, \beta_2 = 0$. Age has a negative linear relation, there is no quadratic relation.
- H_3: $\beta_1 < 0, \beta_2 > 0$. Age has a negative linear relation, and a positive quadratic relation.
- H_4: $\beta_1 = 0, \beta_2 > 0$. Age has a positive quadratic relation, there is no linear relation.
- H_a: β_1, β_2. The relation with age can be anything.

For IQ and educational achievement, the overall set of hypotheses was:

- H_1: $\beta_1 = 0, \beta_2 = 0$. Age is unrelated (i.e., the classical null model).
- H_2: $\beta_1 > 0, \beta_2 = 0$. Age has a positive linear relation, there is no quadratic relation.
- H_3: $\beta_1 > 0, \beta_2 < 0$. Age has a positive linear relation, and a negative quadratic relation.
- H_4: $\beta_1 = 0, \beta_2 < 0$. Age has a negative quadratic relation, there is no linear relation.
- H_a: β_1, β_2. The relation with age can be anything.

See Supplementary Table S20 for the exact hypotheses for IQ and educational achievement before and after adjustment for gender and SES.

Bayesian Hypothesis Evaluation and Research Synthesis in Confirmatory Data

Cohort-specific and robust results are provided in Tables 3-8. Cohort-specific results are fully described in the Supplementary Tables S21-S29. We focus on the robust results across cohorts.

First, for attention problems, child-reported data showed no relation with parental age across cohorts. For all other

Table 3. Posterior model probabilities for parental age predicting attention problems.

		Age Father					Age Mother				
Rater	Cohort	H_1	H_2	H_3	H_4	H_a	H_1	H_2	H_3	H_4	H_a
Child	Gen-R	*.97*	.03	-	-	.00	*1.00*	-	-	-	.00
	TRAILS	*.93*	.07	-	-	.00	*1.00*	-	-	-	.00
	All	**1.00**	.00	-	-	.00	**1.00**	-	-	-	.00
Mother	Gen-R	*.70*		.12	.13	.04	.20	*.31*	*.39*	-	.11
	NTR	.04	-	*.73*	.00	.23	.00	*.58*	.33	-	.09
	TRAILS	*.78*	-	.12	.06	.04	.01	*.78*	.17	-	.05
	RADAR-Y	*.71*	-	.12	.13	.04	.06	*.56*	.31	-	.08
	All	**.92**	-	.07	.00	.00	.00	**.92**	.08	-	.00
Father	Gen-R	*.13*	*.65*	.17	-	.06	.20	*.43*	.30	-	.08
	NTR	.09	*.77*	.11	-	.04	.01	*.84*	.12	-	.03
	All	.02	**.94**	.03	-	.00	.00	**.90**	.09	-	.01
Teacher	NTR	*.94*	.06	-	-	.00	*.91*	.08	.01	-	.00
	TRAILS	.02	*.95*	-	-	.04	*.00*	*.41*	*.47*	-	.12
	All	.25	**.75**	-	-	.00	.00	**.93**	.07	-	.01

Numbers in *italic* font represent the highest posterior model probability per cohort. Numbers in **bold** font represent the highest results after Bayesian updating.Dashes indicate that the hypothesis was not among the set of evaluated hypotheses based on the exploratory analyses.

Table 4. Posterior model probabilities for parental age predicting attention problems after correction for covariates.

		Age Father					Age Mother				
Rater	Cohort	H_1	H_2	H_3	H_4	H_a	H_1	H_2	H_3	H_4	H_a
Child	Gen-R	*1.00*	-	-	-	.00	*1.00*	-	-	-	.00
	TRAILS	*1.00*	-	-	-	.00	*1.00*	-	-	-	.00
	All	***1.00***	-	-	-	.00	**1.00**	-	-	-	.00
Mother	Gen-R	*.91*	.04	.05	.00	.00	*.86*	.02	.00	.11	.00
	NTR	.33	*.62*	.04	.01	.01	.03	*.85*	.10	.00	.03
	TRAILS	*.91*	.04	.00	.04	.00	*.42*	*.36*	.10	.09	.03
	RADAR-Y	*.55*	.31	.05	.07	.02	.11	*.60*	.19	.05	.05
	All	**1.00**	.00	.00	.00	.00	.20	**.80**	.00	.00	.00
Father	Gen-R	*.53*	*.46*	-	-	.01	*.90*	.10	-	-	.01
	NTR	*.66*	.34	-	-	.01	.43	*.57*	-	-	.01
	All	**.69**	.31	-	-	.00	**.88**	.12	-	-	.00
Teacher	NTR	1.00	-	-	-	.00	*.97*	-	-	.03	.00
	TRAILS	*.98*	-	-	-	.02	*.31*	-	-	*.38*	*.31*
	All	**1.00**	-	-	-	.00	**.96**	-	-	.04	.00

See Table 3.

Table 5. Posterior model probabilities for parental age predicting IQ.

	Age Father					Age Mother				
Cohort	H_1	H_2	H_3	H_4	H_a	H_1	H_2	H_3	H_4	H_a
Gen-R	.00	.00	*.76*	.00	.24	.00	.25	*.61*	.00	.14
NTR	*.56*	.27	.06	.10	.02	*.53*	.30	.06	.09	.02
TRAILS	.00	*.76*	.19	.00	.06	.00	*.62*	.31	.00	.08
RADAR-Y	*.41*	.09	*.32*	.13	.04	.05	.06	*.36*	*.43*	.09
All	.00	.01	**.99**	.00	.01	.00	.42	**.58**	.00	.00

See Table 3.

Table 6. Posterior model probabilities for parental age predicting IQ after correction for covariates.

	Age Father					Age Mother				
Cohort	H_1	H_2	H_3	H_4	H_a	H_1	H_2	H_3	H_4	H_a
Gen-R	*.71*	.26	.01	.01	.00	.27	*.72*	-	-	.01
NTR	*.82*	.10	.01	.07	.00	*.87*	.12	-	-	.00
TRAILS	*.65*	.29	.02	.04	.01	.02	*.94*	-	-	.04
RADAR-Y	*.51*	.10	.09	.27	.03	*.38*	*.34*	-	-	.28
All	**1.00**	.00	.00	.00	.00	.06	**.94**	-	-	.00

See Table 3.

Table 7. Posterior model probabilities for parental age predicting educational achievement.

	Age Father					Age Mother				
Cohort	H_1	H_2	H_3	H_4	H_a	H_1	H_2	H_3	H_4	H_a
Gen-R	.00	.00	*.77*	-	.23	.00	.07	*.76*	-	.17
TRAILS	-	-	-	-	-	-	-	-	-	-
NTR	.00	.31	*.52*	-	.17	.00	*.70*	.24	-	.06
RADAR-Y	-	-	-	-	-	-	-	-	-	-
All	.00	.00	**.91**	-	.09	.00	.21	**.75**	-	.05

See Table 3.

Table 8. Posterior model probabilities for parental age predicting educational achievement after correction for covariates.

	Age Father					Age Mother				
Cohort	H_1	H_2	H_3	H_4	H_a	H_1	H_2	H_3	H_4	H_a
Gen-R	*.65*	.35	-	-	.01	*.86*	.14	-	-	.00
TRAILS	-	-	-	-	-	-	-	-	-	-
NTR	*.54*	*.45*	-	-	.01	.09	*.89*	-	-	.02
RADAR-Y	-	-	-	-	-	-	-	-	-	-
All	**.70**	.30	-	-	.00	.39	**.61**	-	-	.00

See Table 3.

informants, results without covariates supported a negative linear relation between parental age and attention problems, i.e. fewer attention problems in offspring of older parents. One exception is that overall, there was no relation between paternal age and mother-reported attention problems. When including gender and SES in the model, we found most support for no relation between attention problems and parental age. One exception was the relation between mother-reported problems and maternal age, where older mothers reported fewer attention-problems; even after including covariates. Second, for IQ, most support was found for a quadratic relation with paternal age with slightly lower scores for younger and older fathers (inverted U; see Figure 2a-c), or a relation that attenuated with older age (see Figure 2d). A positive quadratic attenuating relation between maternal age and IQ was found. After taking child gender and SES into account, the relation with IQ disappeared for paternal age, but the linear relation was still best supported for maternal age. Third, for educational achievement, the findings of the two largest cohorts (Gen-R and NTR) indicated that there was a quadratic relation with parental age, in which children of younger fathers (see Figure 3a-b) and younger mothers (see Figure 3c-d) were disadvantaged. Offspring of older mothers had higher educational achievement. For fathers, the associations disappeared after taking child gender and SES into account, but for mothers a positive linear relation was preserved.

Discussion

We found that older parents tend to have children with fewer attention problems and that they benefit offspring IQ and educational achievement. In contrast to being disadvantaged from a biological point of view (e.g., Malaspina, 2001), older parents seem to provide benefits

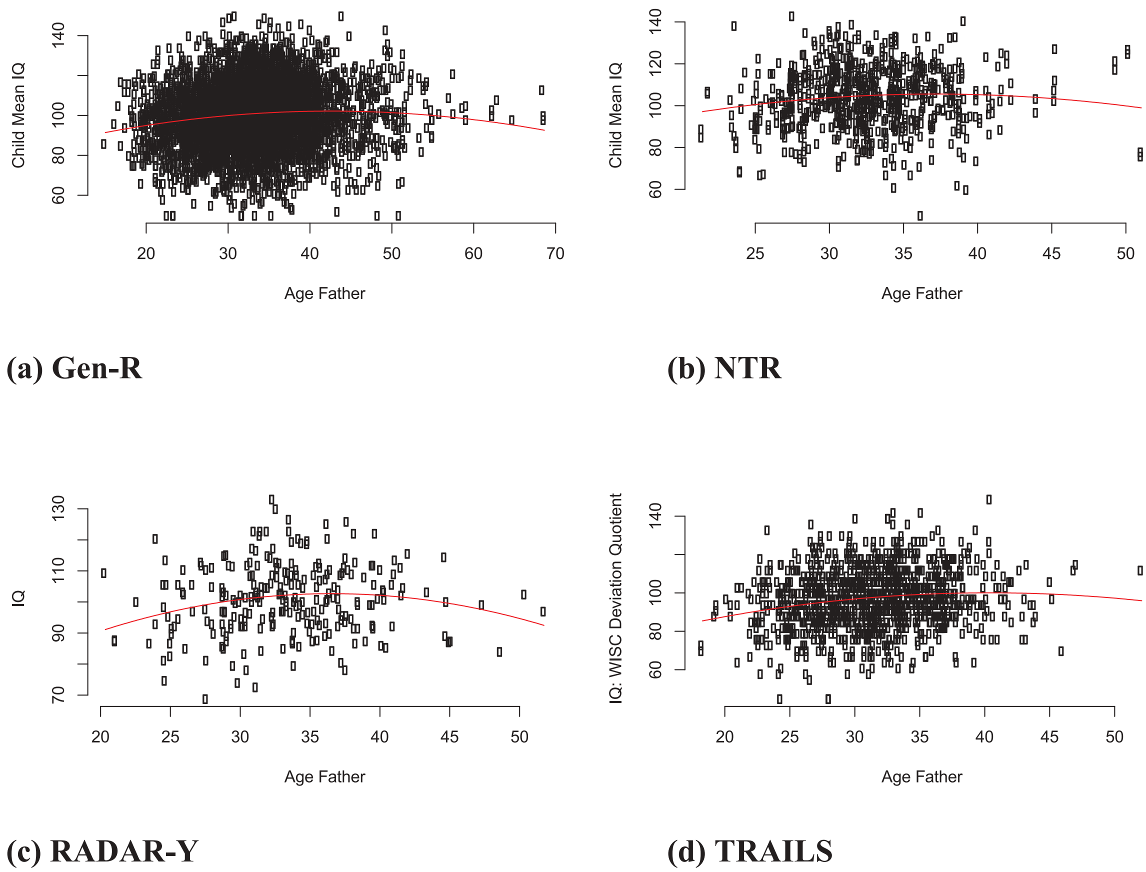
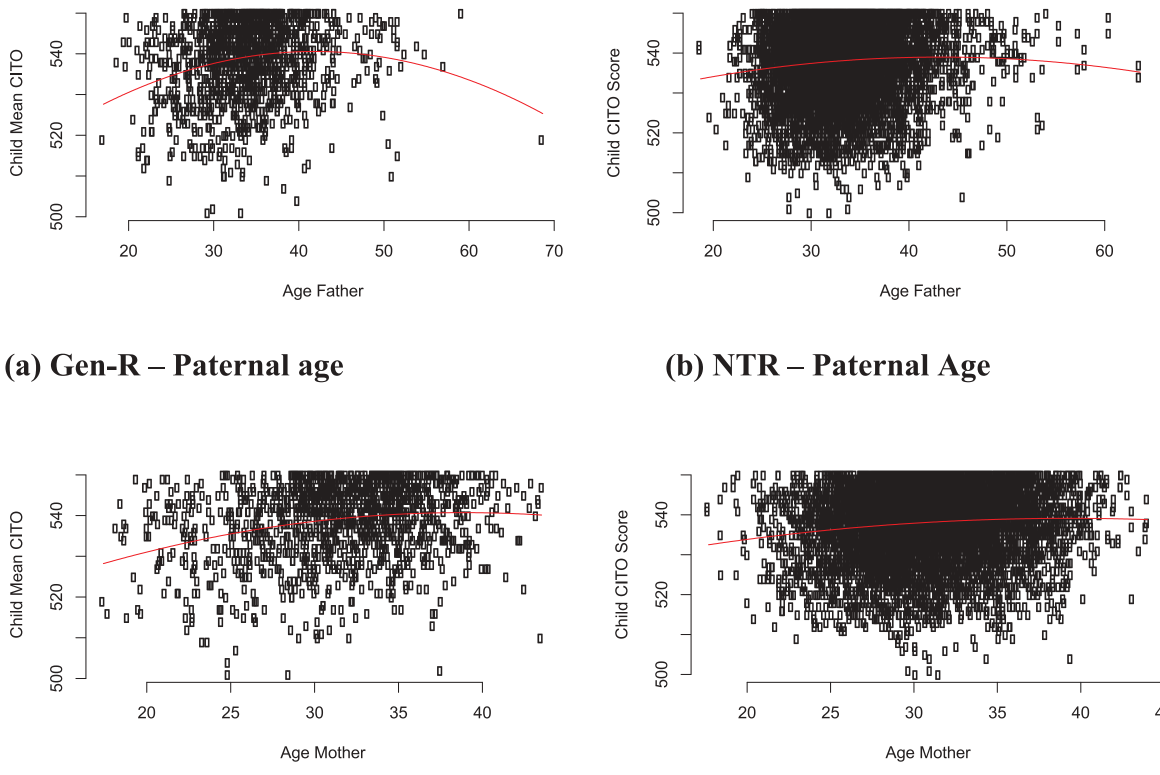


Figure 2. Confirmatory plots for age father with IQ. (a) Gen-R, (b) NTR, (c) RADAR-Y, (d) TRAILS.

for offspring on a psychosocial or contextual level improving neurocognitive functioning (Janecka et al., 2019; Noble et al., 2007). Parents who postpone parenthood are typically highly educated with higher incomes at the time they start a family. Also, single parenthood (e.g., teenage pregnancies, divorce) is more frequent in younger than older parents. This puts older parents in a better position to have more day-to-day involvement with their children (e.g., parents discussing school events with children) and provide their children with a more stimulating environment (e.g., more books at home; van Bergen et al., 2017), which has been positively associated with educational attainment (Jeynes, 2005; Kong et al., 2018; Melhuish et al., 2008). We observed no disadvantageous associations with advanced parental age, which suggests that biological disadvantages appear compensated by the positive contextual factors for attention, IQ and educational achievement. This might not be the case for the more severe neurodevelopmental disorders, such as autism, where adverse effects of advanced parenthood have been found in multiple studies (reviewed by e.g., De Kluiver et al., 2017). However, our findings are in line with the support for an advantageous relation between older age and offspring's reduced externalizing problem behavior that we found in our earlier study (Zondervan et al., 2019).

Associations between child attention problems, IQ, educational achievement and paternal age disappeared when SES was taken into account. For maternal age, the support for a beneficial association diminished, but persisted to be the best hypothesis. Associations that attenuate after taking SES into account suggest that part of the effect of parental age on offspring development is due to genetic and environmental effects on child outcome mediated through parental SES. Because it is not clear which genetic and environmental effects SES captures (Kendler & Baker, 2007), we argue that it is important to present results both with and without controlling for SES. Furthermore, we know that low SES tends to be associated with young parenthood, parental ADHD and lower IQ, and that low SES may reflect a more general (genetic or environmental) liability that influences both age at having offspring and offspring outcome. Alternatively, SES could affect at what age offspring is born, which in turn influences offspring outcome. In that case, adjusting for SES could introduce bias (Janecka et al., 2019). Hence, we conclude that older parents tend to have offspring with fewer attention problems, higher IQ, and educational achievement, but for



(a) Gen-R – Paternal age **(b) NTR – Paternal Age**

(c) Gen-R – Maternal age **(d) NTR – Maternal Age**

Figure 3. Confirmatory plots for parental age with educational achievement. (a) Gen-R – Paternal age, (b) NTR – Paternal Age, (c) Gen-R – Maternal age, (d) NTR – Maternal Age.

fathers the associations are small and mostly explained by higher SES. Nonetheless, optimal neurodevelopmental outcomes are important for children's educational and work opportunities, and in turn, these predict future healthy years and life expectancy (e.g., Barkley & Fischer, 2019; Davey Smith et al., 1998) including longer maintenance of cognitive health. Thus, even though the effects in our study were small, they may be important at the population level, and are directly linked to these well-established associations that encompass the full lifespan. This implies that that the associations between parental age, SES and offspring neurodevelopmental outcomes should become part of the wider knowledge base of the potential risks and benefits associated with low and high parental age and how this is intertwined with SES. That said, however, we emphasize that our findings are associations and that preventive and interventive measures can only be effective after thorough knowledge on causality has been established.

Besides environmental transmission, parent and child characteristics are associated due to direct genetic transmission. For example, Swagerman et al. (2017) found resemblance between parents and children in reading ability was solely due to genetic transmission. Both ADHD and IQ are heritable traits. Individuals with ADHD and/or low IQ have an increased risk of impulsive behavior, which could lead to early pregnancies (Østergaard et al., 2017). Offspring of young parents may thus have a genetic liability to develop ADHD and lower IQ. Support for this hypothesis was also reported by Chang et al. (2014) and Mikkelsen et al. (2016). Individuals who become parents at later ages tend to have higher educational attainment, and these parents pass on favorable education-related genetic variants.

In the exploratory phase, the four cohorts consistently showed associations in the same direction (offspring of older parents performed better), but these associations were small and did not consistently reach significance despite large samples. Our cross-cohort differences may relate to birth-cohort differences. For example, Goisis et al. (2017) found that the association between advanced maternal age and children's cognitive ability changed from negative to positive in different birth-cohorts because of changing parental characteristics. RADAR-Y and TRAILS represent an early nineties cohort, and Gen-R a cohort from after 2000. Our largest cohort, NTR, included children from the 80's, 90's, and 2000's. It is unclear, however, whether there is a birth-cohort effect within this range of twenty years. Other reasons for cross-cohort differences may be structural differences between the populations, and reliability and validity of measures. Although the cohorts had some different properties, and results sometimes differed, the cohorts did not yield contradictory findings. Moreover, our Bayesian updating strategy enabled us to summarize the evidence per hypothesis over cohorts that together are representative of the Netherlands, leading to robust conclusions. It is important to acknowledge that our conclusions likely generalize to relatively well-off (European) countries. We recommend studies in relatively poor societies where SES and parental age may be less intertwined to assess to what extend these results replicate.

Previous studies regarding attention problems, IQ, and educational achievement showed mixed results, but these studies used different populations, measures, covariates, etcetera. A strength of our study is that we had standardized assessments in large population cohorts and applied Bayesian research synthesis, allowing us to combine evidence from multiple cohort studies. As a result, we were able to identify consistent results and hypotheses that received the most support across cohorts. The overall outcomes pointed toward robust findings, as they were supported by all cohorts, irrespective of the characteristics of the populations or specifics of the measurements used. Furthermore, we included large population-based samples, handled missing data by means of multiple imputation, and used cross-validation. A limitation of our study is that we were not able to directly study the mechanisms playing a role in our finding that SES is important in the relation between parental age and neurodevelopmental outcomes. SES can be a proxy for, or the result of, many other factors, or a confounder, rather than a primary cause (Jeynes, 2011). In addition, future work should focus on untangling SES and parental age. and aim to identify malleable mechanisms that are associated with increased risk outcomes for youth in order to promote more positive developmental outcomes. A final limitation is that the effects of parental age and SES may differ across child age. In the present study we did not investigate this, given that within-cohort age differences were rather narrow. This should be pursued in future research, ideally with longitudinal data. In conclusion, we found support for older parents having offspring with fewer or equal attention problems, and higher IQ and educational achievement scores; and younger parents having offspring with more or equal levels of attention problems, and lower IQ and educational achievement scores. Only paternal age had a clear inverted U-shaped relation with educational achievement, with both offspring of younger and older fathers being disadvantaged. More resources and more education-elevating genetic variants in older parents may compensate for possible biological disadvantages. Genetic effects in which ADHD, cognitive functioning, and young parenthood come together may explain why lower parental age goes together with more offspring problems. After including SES in the model, most of the associations with parental age disappeared. Hence, SES takes on an important role, which may be due to SES reflecting a general genetic liability influencing both age at having offspring and offspring outcome, or SES influencing parental age, which, in turn, influences offspring outcome. Based on this population-based multi-cohort study, we conclude that offspring of older parents, who are increasingly common in many societies, are not disadvantaged with respect to the investigated cognitive constructs, at least where this pertains to mild outcomes as studied in the general population.

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Disclosure statement

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