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Paternal Age at Childbirth and Eating Disorders in Offspring

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Drs. Javaras, Rickert, Thornton, Peat, Baker, Birgegård, Almqvist, Lichtenstein, and D'Onofrio report no competing interests.

Ethical Standards: The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation.

Paternal Age at Childbirth and Eating Disorders in Offspring

Abstract

Background—Advanced paternal age at childbirth is associated with psychiatric disorders in offspring, including schizophrenia, bipolar disorder, and autism. However, few studies have investigated paternal age's relationship to eating disorders in offspring. In a large, population-based cohort, we examined the association between paternal age and offspring eating disorders, and whether that association remains after adjustment for potential confounders (e.g., parental education level) that may be related to late/early selection into fatherhood and to eating disorder incidence. **Methods—**Data for 2,276,809 individuals born in Sweden 1979-2001 were extracted from Swedish population and healthcare registers. The authors used Cox proportional hazards models to examine the effect of paternal age on the first incidence of healthcare-recorded anorexia nervosa (AN) and all eating disorders (AED) occurring 1987-2009. Models were adjusted for sex, birth order, maternal age at childbirth, and maternal and paternal covariates including country of birth, highest education level, and lifetime psychiatric and criminal history. **Results—** Even after adjustment for covariates including maternal age, advanced paternal age was associated with increased risk, and younger paternal age with decreased risk, of AN and AED. For example, the fully-adjusted hazard ratio for the 45+ (versus the 25-29) paternal age category was 1.32 (95% CI: 1.14, 1.53) for AN and 1.26 (1.13, 1.40) for AED. **Conclusions—**In this large, population-based cohort, paternal age at childbirth was positively associated with eating disorders in offspring, even after adjustment for potential confounders. Future research should further explore potential explanations for the association, including *de novo* paternal germline mutations.

INTRODUCTION

Advanced paternal age (at childbirth) is associated with an increased risk of offspring having schizophrenia and psychotic disorders (Malaspina *et al.* 2001; Buizer-Voskamp *et al.* 2011; D'Onofrio *et al.* 2014; McGrath *et al.* 2014), autism (Buizer-Voskamp *et al.* 2011; Hultman *et al.* 2011; Rahbar *et al.* 2012; D'Onofrio *et al.* 2014; McGrath *et al.* 2014), bipolar disorder (Frans *et al.* 2008; Menezes *et al.* 2010; D'Onofrio *et al.* 2014; McGrath *et al.* 2014), and numerous other psychiatric disorders (D'Onofrio *et al.* 2014; McGrath *et al.* 2014). However, few studies have investigated whether advanced paternal age is associated with eating disorders. A case study of hospitalized individuals with anorexia nervosa (AN) defined by the Feighner research criteria (Feighner *et al.* 1972) found that these individuals typically had older fathers (and mothers) than general population controls (Halmi 1974). Similarly, two population-based studies reported positive associations between paternal age and offspring eating disorders. In a population-based cohort from Western Australia, paternal age at birth was positively associated with meeting full or partial criteria for DSM-IV eating disorders, albeit only at a trend level once other predictors were included in the model (Allen *et al.* 2009). In a population-based study of U.S. twins age 8 to 17 years and in mid-puberty or beyond, paternal age at birth was associated with a lifetime history of an eating disorder and with current eating disorder symptoms, even after adjustment for maternal age at birth, fertility treatment, parental psychiatric history, familial socio-economic status, and participant body mass index (Racine *et al.* 2014). In contrast to the aforementioned studies, a large Danish register-based study did not find a strong association between advanced paternal age and AN or between advanced paternal age and all eating disorders, either before or after adjustment for maternal age, urbanization at the place of birth, or parental and sibling history of mental disorders (McGrath *et al.* 2014).

To extend and clarify the literature on paternal age and offspring eating disorders, we examined the association between paternal age at birth and the incidence of AN or all eating disorders, in a sample of over two million individuals included in the Swedish population and healthcare registers. Further, we examined whether the association remained after adjustment for covariates (e.g., birth order), including potential confounders that may be related to late or early selection into fatherhood (e.g., paternal education level).

METHOD

Procedure

Using the unique personal identification number assigned to all Swedish residents at birth, we linked data from multiple population-based registers and healthcare registers, including: (1) the Medical Birth Register, which has detailed information on more than 99% of pregnancies in Sweden since 1973; (2) the National Patient Register (NPR), which provides national coverage of Swedish public and private hospital inpatient admissions beginning in 1973 (full coverage from 1986 on) and outpatient specialist care beginning in 2001; (3) the Riksät- National Quality Register for Eating Disorders Treatment (Swedish Association of Local Authorities and Regions 2007) and Stepwise quality assurance register for eating disorders (Birgegård *et al.* 2010), which first entered patient information in 1999 and 2005, respectively, and currently include information from almost all specialized eating disorder units in Sweden (≈90% as of 2009) and many non-specialized general psychiatric units; (4) the Multi-Generation Register, which can be used to determine biological and adoptive relationships for all individuals living in Sweden since 1932; (5) the Migration Register, which records information on emigration from or immigration to Sweden since 1901; (6) the Cause of Death Register, which contains the date and principal

and contributing cause(s) of deaths occurring since 1952; (7) the National Crime Register, which includes detailed information about all criminal convictions since 1973; and (8) the Education Register, which contains information on highest level of completed formal education through 2008. Additional information about the registers and variables derived from them are provided elsewhere (D'Onofrio *et al.* 2013a; Javaras *et al.* 2015).

Sample

Our population cohort included individuals who were born in Sweden between January 1, 1979 and December 31, 2001 and had relevant data available. We used the Medical Birth Register to identify live-born offspring born in this time frame, but retained data only for 2,295,947 individuals with a valid maternal identifier, valid (non-zero) birth order, and non-missing data for sex, gestational age and birth weight. Following linkage with the Multi-Generation Register, we further excluded 16,299 individuals with missing paternal identifiers and 2,839 individuals with undetermined paternal birthdate. The resulting sample of n = 2,276,809 offspring included 110,385 individuals with at least one emigration and 17,684 individuals with date of death prior to the end of the study (December 31, 2009), who were retained and treated as right-censored in analyses. This cohort of offspring was born to 1,226,801 distinct biological fathers and 1,221,979 distinct biological mothers.

Inclusion in the Swedish registers does not require informed consent. However, patients included in the Stepwise Register must give informed consent (via an opt-out procedure) for those data to be used for research purposes; if patients decline, their data are excluded from research use only (Birgegård *et al.* 2010; Runfola *et al.* 2014). The Regional Ethical Review

Board in Stockholm, Sweden, the University of North Carolina Biomedical Institutional Review Board, and the Indiana University Institutional Review Board all approved this study.

Eating Disorder Outcomes

We examined two outcomes: the age at first diagnosis of AN and the age at first diagnosis of any eating disorder (AED), based on diagnoses appearing in any of the healthcare registers (NPR, Riksät, and Stepwise) between January 1, 1987 and December 31, 2009. Diagnoses in the NPR were made by physicians at hospital discharge, using the WHO *International Classification of Diseases, Ninth Revision* (ICD-9; 1987-1996) (WHO, World Health Organization 1978) and *ICD-Tenth Revision* (ICD-10; 1997-2009) (WHO, World Health Organization 1992). Diagnoses in Riksät and Stepwise were made by clinicians once intent to treat was established, using the DSM-IV, with criteria frequently assessed via structured interview (American Psychiatric Association 2013). For the outcomes used here, AN diagnoses included AN (e.g., ICD-9 307B, ICD-10 F50.0, and DSM-IV AN) and atypical AN (e.g., ICD-10 F50.1 and DSM-IV eating disorder not otherwise specified (EDNOS) with subthreshold AN symptoms). AED diagnoses included the AN diagnoses, as well as bulimia nervosa (BN) (e.g., ICD-10 F50.2 and DSM-IV BN), atypical BN (e.g., ICD-10 F50.3 and DSM-IV EDNOS with subthreshold BN symptoms), "other eating disorders" (ICD-9 307F), "eating disorder, unspecified" (ICD-10 F50.9), and EDNOS other than atypical AN and BN. To avoid diagnostic misclassification (i.e., with feeding difficulties of childhood), we examined only AN and AED diagnoses occurring at age 8 or older.

Statistical Analysis

Models for the relationship between paternal age and offspring eating disorders were fit to the overall (combined-sex) sample. Although we did not have sufficient power to test for a sex by paternal age interaction, we also performed analyses stratified by sex to examine the sex-specific associations between paternal age and offspring eating disorders.

More specifically, we used PROC PHREG in SAS 9.3 (SAS Institute, Inc., Cary, NC) to fit Cox proportional hazards models for the effect of paternal age on the offsprings' age at first diagnosis of AN or (separately) AED, after adjusting for covariates. Individuals who did not receive an eating disorder diagnosis during the calendar years included in our analyses (January 1, 1987 and December 31, 2009) were censored at their earliest age of emigration, death, or end-of-study period (i.e., December 31, 2009). Age was measured in years rounded to the nearest 0.001. Paternal age was treated as categorical because models that treated it as continuous did not support a linear relationship between paternal age and the log-hazards of offspring eating disorder risk (see Appendix A in the online supplemental materials). The paternal age categories included <20, 20-24, 25-29, 30-34, 35-39, 40-44, and 45+ (years), with 25-29 selected as the reference category for comparability with existing studies (McGrath *et al.* 2014).

In addition to the predictor of interest (i.e., paternal age), models also included covariates, which were treated as categorical variables unless noted otherwise below. (See Table 1 for the categories and corresponding frequencies for each covariate.) All models were adjusted for participant sex. In addition, all models were adjusted for calendar year (treated as a continuous, time-varying covariate, and measured in units of years rounded to the nearest digit), because prior research reveals that incidence rates for AN and AED increase dramatically after 2000 due to expanded coverage of the healthcare registers to psychiatric outpatient settings (Javaras *et al.*

2015). To examine the effects of adjusting for potential confounders (of the relationship between paternal age and offspring eating disorders), we fit a series of models with the following additional covariates: Model A (the 'baseline model') included only participant sex and calendar year; Model B included all Model A covariates and participant birth order; Model C included all Model B covariates and maternal age; and Model D (the 'fully-adjusted model') included all Model C covariates and several fixed maternal and paternal covariates [country of birth (Sweden or other country); highest level of education attained; lifetime history of severe psychiatric disorders (i.e., ICD diagnoses for schizophrenia or bipolar disorder); and lifetime criminality (i.e., conviction for any crime at 15 years or older)]. We chose to include these particular parental variables as covariates because they fulfill criteria for being potential confounders: (i) the variable might be associated with late (or early) selection into parenthood, based on past research; and (ii) the variable might be associated with a higher risk of eating disorders in offspring, based on past research that found an association between the parental variable and eating disorders in offspring or eating disorders in the parent himself/herself (which, since eating disorders are familial, translates into a higher risk of eating disorders in offspring) (Smith *et al.* 1989; Striegel-Moore & Bulik 2007; Hudson *et al.* 2008; Mustelin *et al.* 2016; Yao *et al.* 2016). For example, individuals with bipolar disorder who have children are more likely to fall into the very early parenthood category (i.e., <20) compared with 'control' individuals with children (Laursen & Munk-Olsen 2010), and parents with bipolar disorder are also more likely to have offspring with eating disorders because bipolar disorder and eating disorders co-aggregate in families (Smith *et al.* 1989; Hudson *et al.* 2008). Thus, even in the absence of any true causal effect of paternal age, failing to adjust for severe parental psychiatric disorders could lead to a spurious association between early paternal age and eating disorder risk in offspring.

To determine the effect of each paternal age category on AN and AED incidence, we examined the categories' hazard ratio estimates and confidence intervals in Models A-D. Further, to determine the overall effect of paternal age, we compared the AIC (Akaike 1974) values for the fully-adjusted model with paternal age and the fully-adjusted model without paternal age.

RESULTS

Table 1 presents frequencies and percentages for the paternal age categories and the covariate categories for the total sample (n = 2,276,809) and for those participants with diagnoses of AN (n = 8,137) or AED (n = 16,405).

Figure 1 presents hazard ratios for AN (panel A) and AED (panel B). (The results for AN and AED are also presented in table form in Appendix B in the online supplemental materials.) For both AN and AED, the AIC values for the fully-adjusted model with paternal age (219,049 for AN; 438,653 for AED) are smaller than the analogous values for the fully-adjusted model without paternal age (219,060 for AN; 438,673 for AED), suggesting that paternal age has significant explanatory power, even above the contributions of calendar year, sex, birth order, maternal age, and parental covariates. For both AN and AED, the hazard ratio estimates generally increase for successively older paternal age categories, with the exception of the 40-44 category, where the estimate is similar to (or even slightly smaller than) the estimate for the 35-39 category. Adjusting for birth order and fixed parental covariates has relatively little effect, with the hazard ratio estimates for the paternal age categories becoming (if anything) slightly larger in magnitude and more significant. In contrast, adjusting for maternal age at birth substantially attenuates the hazard ratio estimates for paternal age, not surprisingly given the high correlation (0.69) between paternal and maternal age at birth and the positive association

between maternal age and offspring eating disorder risk in our sample. (The results for maternal age are presented in Appendix C in the online supplemental materials.) However, in all AN and AED models, including those adjusted for maternal age, the hazard ratio for the 45+ category (versus the 25-29 category) is significantly greater than one, and the hazard ratio estimates for the <20 and 20-24 categories (relative to the 25-29 category) are less than one, significantly so for the 20-24 category.

Sex-specific results for AN and AED are presented in Tables D.1 and D.2, respectively, in the online supplemental materials. For females, results follow a similar pattern to those described above for the overall (combined-sex) sample, not surprisingly given that the vast majority of participants diagnosed with eating disorders in our sample are women. For males, the older paternal age categories exhibit similar, albeit stronger, positive associations with AN and AED risk, compared with the associations in the overall and female samples. However, for males, hazard ratio estimates for the youngest paternal age categories are greater than one and not significant, in contrast to the overall sample and female subsample, where hazard ratios for the two youngest paternal age categories are less than one and, in some cases, significantly so.

DISCUSSION

In a large, population-based cohort born in Sweden between 1979-2001, individuals with older fathers were at increased risk for the onset of eating disorders occurring between the ages of 8 and 30 years. Further, this increased risk remained even after adjustment for numerous potential confounders including birth order, maternal age at birth, and maternal and paternal country of birth, education, lifetime psychiatric hospitalization, and lifetime criminality. For example, in the fully adjusted model, the estimated hazard ratio for the 45+ paternal age category

(relative to the 25-29 reference category) was 1.32 (95% CI: 1.14, 1.53) for AN and 1.26 (95% CI: 1.13, 1.40) for AED. The increased risk of eating disorders among offspring of older fathers was present for both male and female offspring, with some suggestion that the association was especially strong for male offspring.

Previous population-based studies have found that advancing paternal age is associated with increased risk of eating disorders (Allen *et al.* 2009; Racine *et al.* 2014). In contrast, a recent Danish register-based study did not find a clear pattern of increasing risk with advanced paternal age for either AN or AED, in contrast to findings for the other psychiatric disorders examined (McGrath *et al.* 2014). Although the Danish study is similar to the present study in many ways, a large portion of the Danish cohort was not observed until after adolescence and young adulthood, missing the peak period of risk for eating disorders. In contrast, all cases in our study occurred prior to age 30 (inclusive). Also, the Danish study included all ICD-10 codes relevant to problems of eating (e.g., F50.5, "vomiting associated with other psychological disturbances") for the AED outcome, whereas our study included only ICD-10 codes representing AN, BN, and EDNOS (including binge-eating disorder), disorders typically characterized by a desire to control weight, shape, or eating (Fairburn *et al.* 2003). Thus, the association between advanced paternal age and eating disorder incidence would be expected to be stronger in our study if advanced paternal age were most strongly associated with what we consider to be the prototypic eating disorders occurring during adolescence and young adulthood. Although it is difficult to compare numerical values across studies due to differences in methodology, this pattern of association (between advanced paternal age and risk of eating disorders in offspring) has also been found for numerous other psychiatric disorders in offspring, including schizophrenia and psychotic disorders (Malaspina *et al.* 2001; Buizer-Voskamp *et al.*

2011; D'Onofrio *et al.* 2014; McGrath *et al.* 2014), autism (Buizer-Voskamp *et al.* 2011; Hultman *et al.* 2011; Rahbar *et al.* 2012; D'Onofrio *et al.* 2014; McGrath *et al.* 2014), bipolar disorder (Frans *et al.* 2008; Menezes *et al.* 2010; D'Onofrio *et al.* 2014; McGrath *et al.* 2014), and childhood behavioral and emotional disorders (McGrath *et al.* 2014).

Our results also suggest that, conversely, younger paternal age at birth (<20 and 20-24 years) is associated with slightly reduced risk of AN and AED, at least in females. For example, in the fully adjusted model, the estimated hazard ratio for the 20-24 paternal age category (relative to the 25-29 reference category) was 0.91 (95% CI: 0.83, 0.99) for AN and 0.93 (95% CI: 0.87, 0.98) for AED, with similar estimates for the <20 paternal age category. Interestingly, our sex-specific results suggest that this 'protective' effect of younger paternal age may be present only for female, and not for male, offspring. Only one other study, the Danish study, has examined the effect of younger (versus typical) paternal age categories on eating disorder risk in offspring. The results of the Danish study are partially consistent with ours since risk ratios for the youngest paternal age categories were less than one (albeit not significantly so) for AN, but not for AED (McGrath *et al.* 2014). Interestingly, this pattern of reduced risk for younger paternal age categories has generally not been found for other psychiatric disorders, with the exception of autism (Buizer-Voskamp *et al.* 2011; McGrath *et al.* 2014).

The present study has significant strengths. The sample is a large, national cohort of all individuals born in Sweden during a two-decade period, making our study the largest investigation of paternal age and prototypic eating disorders to date. Further, thanks to the availability of rich datasets with national coverage, measures of paternal age and important potential confounders are from public records rather than (retrospective) self-report or other-report.

The study has several limitations that may diminish the generalizability of findings. For one, outcomes included only healthcare-system-detected and healthcare-register-recorded eating disorders. However, the registers detect eating disorder diagnoses made in multiple contexts (e.g., in the emergency room), not only in the context of eating disorder or psychiatric treatment. Further, given the relatively low incidence of eating disorders in Sweden (Javaras *et al.* 2015), it is likely that only a small proportion of the cohort had an eating disorder that was not detected or recorded. Second, we could not examine the association between paternal age and incidence of specific eating disorders other than AN (e.g., BN) because ICD-9 in Sweden included them under a single diagnostic code. Third, although we presented sex-specific results for the relationship between paternal age and eating disorders in offspring, the relatively small number of male participants with eating disorders, especially in the less common paternal age categories, limited power and precluded formal tests of sex by paternal age interactions. Thus, our sex-specific results should be interpreted with caution.

Finally, the observational nature of our study precludes causal interpretation of findings: it is possible that factors associated with advanced paternal age are responsible for its positive relationship with eating disorder incidence, and, likewise, that factors associated with younger paternal age are responsible for its negative relationship with eating disorder incidence in females with eating disorders. Although we were able to adjust for several such factors (birth order, maternal age at birth, and parental educational, psychiatric, and criminal history) in our analyses, there may be other factors that were not measured or included in analyses (e.g., familial traits that predispose individuals toward later fatherhood and toward eating disorders). Previous studies have sought to eliminate the effects of factors associated with late (or early) selection into fatherhood by focusing on second- and later-born offspring and adjusting for "paternal age at the

birth of *first* offspring" (Petersen *et al.* 2011). However, we did not employ this approach because it can introduce collider stratification bias (Hernán *et al.* 2004) into estimates of the effects of paternal age on disease risk. Further, because eating disorder incidence increases dramatically with calendar year in our data (Javaras *et al.* 2015), we were unable to use a sibling design, which can eliminate the influence of confounding factors shared among offspring (Rutter 2007; D'Onofrio *et al.* 2013b), including factors associated with late (or early) selection into fatherhood. Because paternal age and calendar year are highly correlated within paternal sibling groups (i.e., siblings born when the father is older pass through the period of risk for disease incidence during later calendar years), sibling designs can produce biased estimates (of the effects of paternal age on disease risk) in samples, like ours, where disease incidence varies systematically with calendar year. However, the population-based associations between advanced paternal age and offspring eating disorders found in our study are similar in pattern to the population-based associations for autism and bipolar disorder found in another Swedish register-based study (D'Onofrio *et al.* 2014) where sibling-based associations were even larger than population-based associations for both disorders.

Future studies should use sibling and other extended family designs (Rutter 2007; D'Onofrio *et al.* 2013b) to shed additional light on whether paternal age has a causal effect on the incidence of eating disorders in offspring, or if late (or early) selection into fatherhood accounts for the association (Petersen *et al.* 2011; D'Onofrio *et al.* 2014; Jaffe *et al.* 2014; Gratten *et al.* 2016). If the association does appear to be causal, it will be important for future research to explore the mechanisms by which advanced paternal age confers increased risk for offspring eating disorders. One frequently-posited mechanism is *de novo* mutations in the paternal germline (Malaspina *et al.* 2001; Frans *et al.* 2008; Buizer-Voskamp *et al.* 2011;

Hultman *et al.* 2011), which increase in frequency with paternal age at conception (Kong *et al.* 2012) and have been associated with psychiatric disorders including schizophrenia and autism (Kong *et al.* 2012; Ronemus *et al.* 2014). However, no study has directly examined the role of (measured) *de novo* mutations in eating disorders, and recent simulations do not support a role for *de novo* mutations in the association between paternal age and other psychiatric disorders in offspring (Gratten *et al.* 2016). Other potential mechanisms include alternative biological mechanisms, such as increased epigenetic dysfunction with advanced paternal age (Hultman *et al.* 2011), as well as various social mechanisms (Schmidt *et al.* 2012; Racine *et al.* 2014).

In summary, in the present study, advanced paternal age at childbirth is associated with an increased risk of eating disorders in offspring during adolescence and young adulthood. Future research should further explore the causal nature and potential mechanisms of this association.

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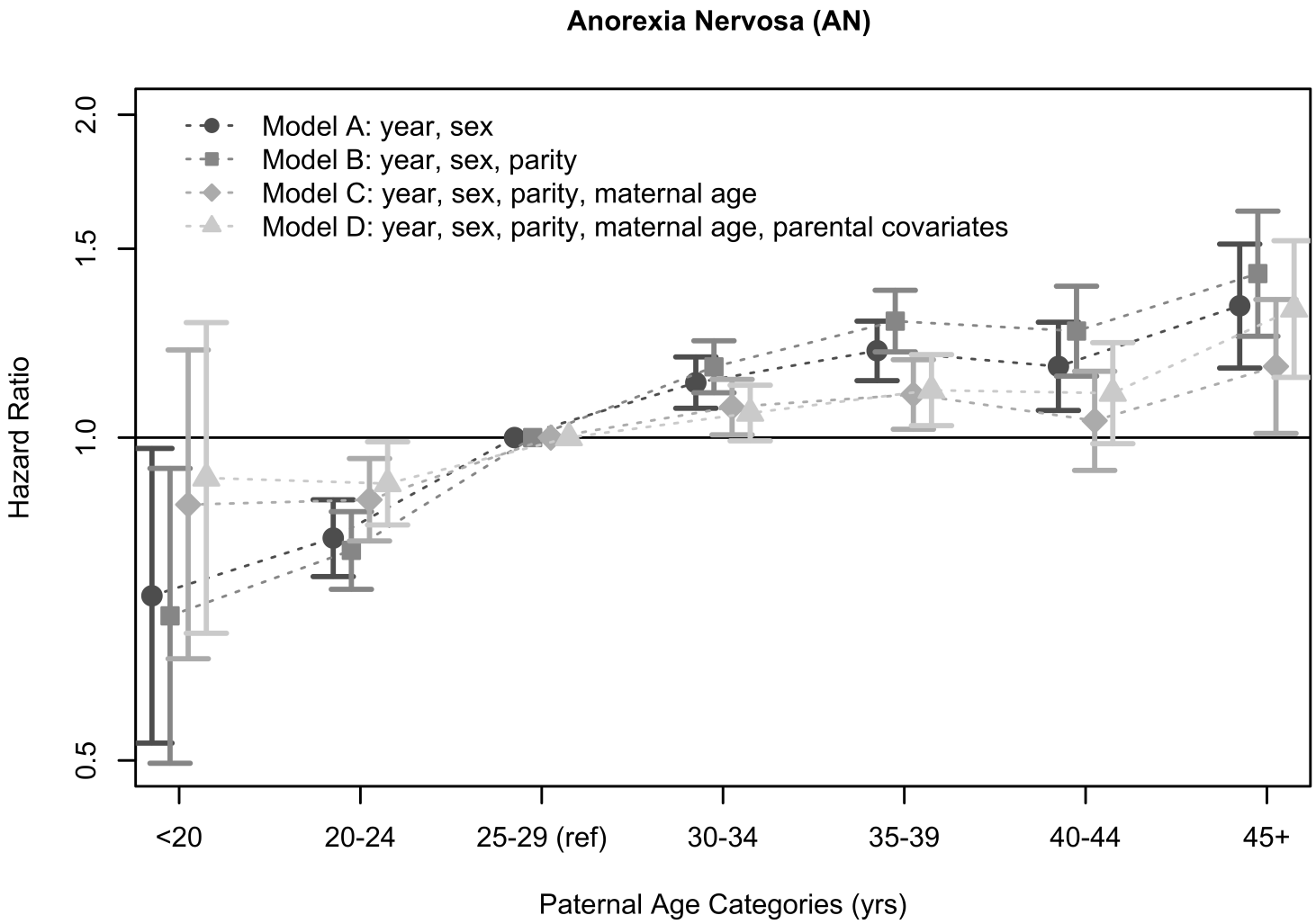
Figure 1. Hazard Ratios for First Incidence of Anorexia Nervosa or Any Eating Disorder as a Function of Paternal Age, With Adjustment for Covariates. Members of the cohort were born in Sweden between January 1, 1979 and December 31, 2001 and followed up from January 1, 1987 to December 31, 2009 (or emigration or death). Filled shapes represent estimates of the hazard ratio for the paternal age categories (relative to the reference category of 25-29 years), and crossbars represent bounds of the 95% confidence intervals for the hazard ratio. Hazard ratios for Models A-D (represented by different colors) are adjusted for the covariates described in the legend. (A) Anorexia Nervosa, which includes diagnoses for anorexia nervosa (ICD-9 307B; ICD-10 50.0; DSM-IV 307.1) and atypical anorexia nervosa (ICD-10 50.1). (B) Any Eating Disorder, which includes diagnoses for anorexia nervosa (ICD-9 307B; ICD-10 50.0; DSM-IV 307.1), atypical anorexia nervosa (ICD-10 50.1), bulimia nervosa (ICD-10 50.2; DSM-IV 307.51), atypical bulimia nervosa (ICD-10 50.3), “other eating disorders” (ICD-9 307F), “eating disorder, unspecified” (ICD-10 50.9), and eating disorder not otherwise specified (DSM-IV 307.50).

Part A


Anorexia Nervosa (AN)
Model A: year, sex
Model B: year, sex, parity
Model C: year, sex, parity, maternal age
Model D: year, sex, parity, maternal age, parental covariates
Hazard Ratio
0.5
1.0
1.5
2.0
<20
20-24
25-29 (ref)
30-34
35-39
40-44
45+
Paternal Age Categories (yrs)

Part B

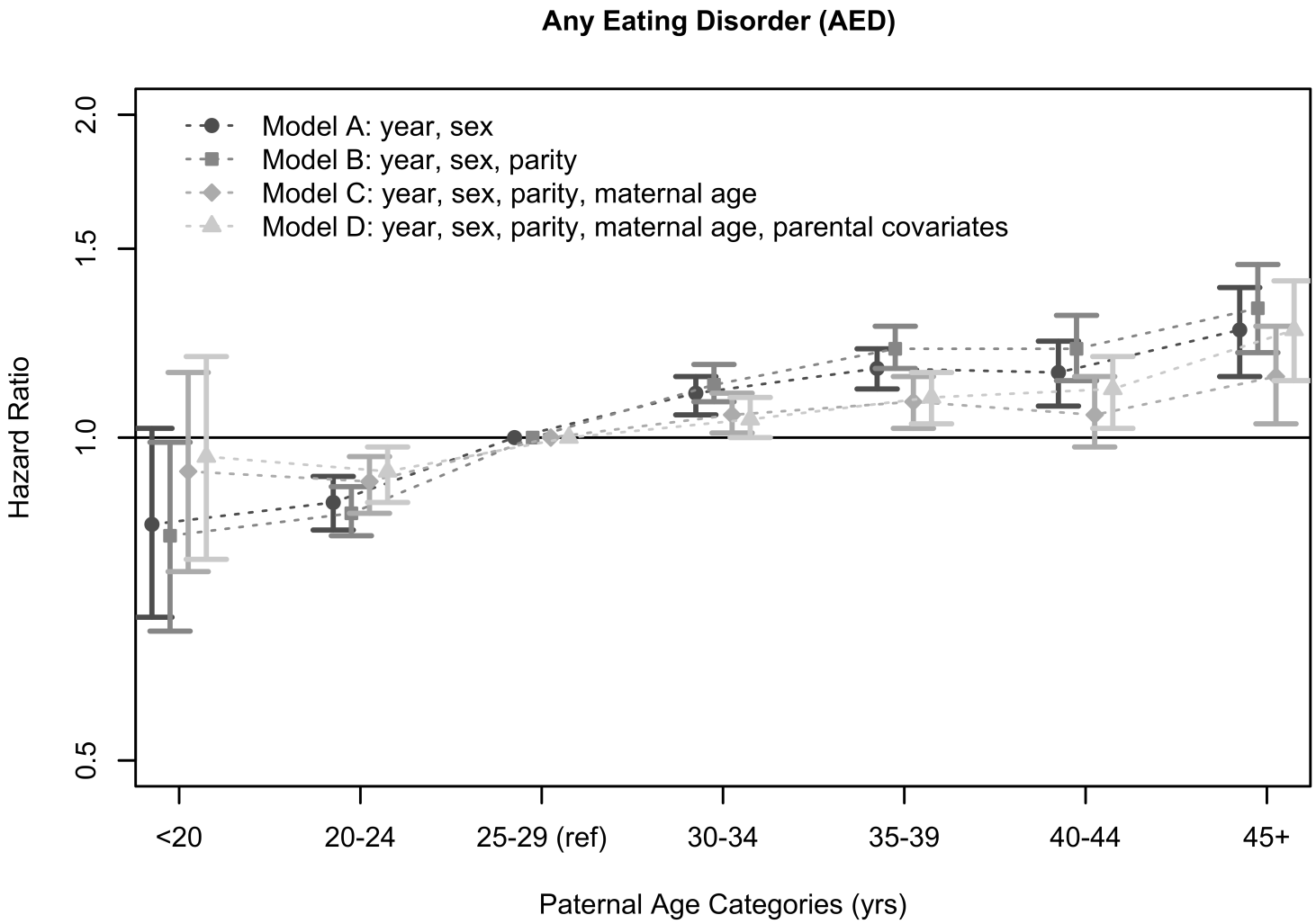


Table 1. Descriptive statistics for *N*=2,276,809 live-born individuals born between January 1, 1979 and December 31, 2001

Model Covariates		Total Sample (N = 2,276,809)		Anorexia Nervosa (N = 8,137)		Any Eating Disorder (N = 16,405)	
		N	%	N	%	N	%
Individual-level							
	Female	1,107,095	48.6	7,672	94.3	15,418	94.0
	Birth order						
	1st	929,433	40.8	3,387	41.6	6,730	41.0
	2nd	828,973	36.4	2,987	36.7	6,044	36.8
	3rd	364,807	16.0	1,278	15.7	2,599	15.8
	4+	153,596	6.7	485	6.0	1,032	6.3
Paternal							
	Age at birth of offspring						
	<20 years old	15,410	0.7	39	0.5	94	0.6
	20-24 years old	245,105	10.8	734	9.0	1,627	9.9
	25-29 years old (reference)	700,621	30.8	2,440	30.0	4,991	30.4
	30-34 years old	726,448	31.9	2,660	32.7	5,284	32.2
	35-39 years old	388,368	17.1	1,508	18.5	2,935	17.9
	40-44 years old	140,421	6.2	517	6.4	1,022	6.2
	45+ years old	60,436	2.7	239	2.9	452	2.8
	Country of birth						
	Sweden	1,941,354	85.3	7,360	90.5	14,657	89.3
	Highest education						
	<9 years	110,379	4.8	319	3.9	734	4.5
	completed 9 years	317,703	14.0	941	11.6	2,032	12.4
	upper secondary (any)	1,144,309	50.3	3,578	44.0	7,447	45.4
	post-secondary (any)	682,819	30.0	3,254	40.0	6,098	37.2
	missing	21,599	0.9	45	0.6	94	0.6
	Lifetime history of severe psychiatric disorder	37,897	1.7	157	1.9	364	2.2
	Lifetime history of criminal conviction	947,116	41.6	3,067	37.7	6,708	40.9
Maternal							
	Age at birth of offspring						
	<20 years old	64,479	2.8	162	2.0	393	2.4
	20-24 years old	483,678	21.2	1,560	19.2	3,415	20.8
	25-29 years old (reference)	834,813	36.7	3,009	37.0	5,941	36.2
	30-34 years old	614,485	27.0	2,269	27.9	4,513	27.5
	35-39 years old	237,336	10.4	989	12.2	1,847	11.3
	40-44 years old	40,551	1.8	142	1.7	283	1.7
	45+ years old	1,467	0.1	6	0.1	13	0.1
	Country of birth						
	Sweden	1,955,643	85.9	7,440	91.4	14,845	90.5
	missing	1,923	0.1	4	0.0	9	0.1
	Highest education						
	<9 years	58,562	2.6	128	1.6	268	1.6
	completed 9 years	217,096	9.5	598	7.3	1,339	8.2

upper secondary (any)	1,137,034	49.9	3,545	43.6	7,482	45.6
post-secondary (any)	846,204	37.2	3,860	47.4	7,285	44.4
missing	17,913	0.8	6	0.1	31	0.2
Lifetime history of severe psychiatric disorder	39,551	1.7	182	2.2	422	2.6
Lifetime history of criminal conviction	279,506	12.3	895	11.0	1,948	11.9

Appendix A: Combined-Sex Results for (Continuous) Paternal Age at Birth

Supplemental Table A.1. Association Between (Continuous) Paternal Age and First Incidence of Anorexia Nervosa, With Adjustment for Covariates.

		Model A[a]			Model B[b]			Model C[c]			Model D[d]		
	Paternal Age Term	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI	
Linear[e]	PA	1.02	1.02	1.02	1.02	1.02	1.03	1.01	1.00	1.01	1.01	1.01	1.02
Quadratic[f]	PA	1.03	1.02	1.04	-	-	-	-	-	-	-	-	-
	$(PA)^2$	1.00	1.00	1.00	-	-	-	-	-	-	-	-	-

Abbreviation: CI, confidence interval; HR, hazard ratio; PA, paternal age

[a] Model A is adjusted for the time-varying covariate calendar year and the fixed covariate participant sex.

[b] Model B is adjusted for the time-varying covariate calendar year and the fixed covariates participant sex and participant birth order.

[c] Model C is adjusted for the time-varying covariate calendar year and the fixed covariates participant sex, participant birth order, and maternal age.

[d] Model D is adjusted for the time-varying covariate calendar year and the fixed covariates participant sex, participant birth order, maternal age, and maternal and paternal country of birth, highest level of education attained, lifetime history of psychiatric hospitalization, and lifetime criminality.

[e] AIC for Model A with a linear PA term only is 219,930.9.

[f] AIC for Model A with linear and quadratic PA terms is 219,910.2.

Supplemental Table A.2. Association Between (Continuous) Paternal Age and First Incidence of Any Eating Disorder, With Adjustment for Covariates.

		Model A[a]			Model B[b]			Model C[c]			Model D[d]		
	Paternal Age Term	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI	
Linear[e]	PA	1.01	1.01	1.02	1.02	1.02	1.02	1.01	1.00	1.01	1.01	1.01	1.01
Quadratic[f]	PA	1.02	1.02	1.03	-	-	-	-	-	-	-	-	-
	$(PA)^2$	1.00	1.00	1.00	-	-	-	-	-	-	-	-	-

Abbreviation: CI, confidence interval; HR, hazard ratio; PA, paternal age

[a] Model A is adjusted for the time-varying covariate calendar year and the fixed covariate participant sex.

[b] Model B is adjusted for the time-varying covariate calendar year and the fixed covariates participant sex and participant birth order.

[c] Model C is adjusted for the time-varying covariate calendar year and the fixed covariates participant sex, participant birth order, and maternal age.

[d] Model D is adjusted for the time-varying covariate calendar year and the fixed covariates participant sex, participant birth order, maternal age, and maternal and paternal country of birth, highest level of education attained, lifetime history of psychiatric hospitalization, and lifetime criminality.

[e] AIC for Model A with a linear PA term only is 439,784.7.

[f] AIC for Model A with linear and quadratic PA terms is 439,770.2.

Appendix B: Combined-Sex Results for (Categorical) Paternal Age at Birth

Supplemental Table B.1. Association Between Paternal Age and First Incidence of Anorexia Nervosa, With Adjustment for Covariates.

	Model A[a]			Model B[b]			Model C[c]			Model D[d]		
Paternal Age Category (years)	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI	
<20	0.71	0.52	0.98	0.68	0.50	0.94	0.87	0.62	1.21	0.92	0.66	1.28
20-24	0.81	0.74	0.88	0.79	0.72	0.85	0.88	0.80	0.96	0.91	0.83	0.99
25-29 (ref.)	1.00	.	.	1.00	.	.	1.00	.	.	1.00	.	.
30-34	1.13	1.07	1.19	1.16	1.10	1.23	1.07	1.01	1.13	1.05	0.99	1.12
35-39	1.21	1.13	1.28	1.28	1.20	1.37	1.10	1.02	1.18	1.11	1.03	1.20
40-44	1.17	1.06	1.28	1.26	1.14	1.38	1.04	0.93	1.15	1.10	0.99	1.23
45+	1.33	1.16	1.52	1.42	1.24	1.63	1.17	1.01	1.35	1.32	1.14	1.53

Abbreviation: CI, confidence interval; HR, hazard ratio.

[a] Model A is adjusted for the time-varying covariate calendar year and the fixed covariate participant sex.

[b] Model B is adjusted for the time-varying covariate calendar year and the fixed covariates participant sex and participant birth order.

[c] Model C is adjusted for the time-varying covariate calendar year and the fixed covariates participant sex, participant birth order, and maternal age.

[d] Model D is adjusted for the time-varying covariate calendar year and the fixed covariates participant sex, participant birth order, maternal age, and maternal and paternal country of birth, highest level of education attained, lifetime history of psychiatric hospitalization, and lifetime criminality.

Supplemental Table B.2. Association Between Paternal Age and First Incidence of Any Eating Disorder, With Adjustment for Covariates

	Model A[a]			Model B[b]			Model C[c]			Model D[d]		
Paternal Age Category (years)	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI	
<20	0.83	0.68	1.02	0.81	0.66	0.99	0.93	0.75	1.15	0.96	0.77	1.19
20-24	0.87	0.82	0.92	0.85	0.81	0.90	0.91	0.85	0.96	0.93	0.87	0.98
25-29 (ref.)	1.00	.	.	1.00	.	.	1.00	.	.	1.00	.	.
30-34	1.10	1.05	1.14	1.12	1.08	1.17	1.05	1.01	1.10	1.04	1.00	1.09
35-39	1.16	1.11	1.21	1.21	1.16	1.27	1.08	1.02	1.14	1.09	1.03	1.15
40-44	1.15	1.07	1.23	1.21	1.13	1.30	1.05	0.98	1.14	1.11	1.02	1.19
45+	1.26	1.14	1.38	1.32	1.20	1.45	1.14	1.03	1.27	1.26	1.13	1.40

Abbreviation: CI, confidence interval; HR, hazard ratio.

[a] Model A is adjusted for the time-varying covariate calendar year and the fixed covariate participant sex.

[b] Model B is adjusted for the time-varying covariate calendar year and the fixed covariates participant sex and participant birth order.

[c] Model C is adjusted for the time-varying covariate calendar year and the fixed covariates participant sex, participant birth order, and maternal age.

[d] Model D is adjusted for the time-varying covariate calendar year and the fixed covariates participant sex, participant birth order, maternal age, and maternal and paternal country of birth, highest level of education attained, lifetime history of psychiatric hospitalization, and lifetime criminality.

Appendix C: Combined-Sex Results for (Categorical) Maternal Age at Birth

Supplemental Table C.1. Association Between Maternal Age and First Incidence of Anorexia Nervosa, With Adjustment for Covariates.

	Model A[a]			Model B[b]			Model C[c]			Model D[d]		
Maternal Age Category (years)	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI	
<20	0.64	0.55	0.75	0.59	0.51	0.70	0.67	0.56	0.79	0.83	0.70	0.99
20-24	0.82	0.78	0.88	0.79	0.74	0.84	0.84	0.78	0.89	0.94	0.88	1.01
25-29 (ref.)	1.00	-	-	1.00	-	-	1.00			1.00		
30-34	1.11	1.05	1.17	1.17	1.10	1.23	1.13	1.06	1.20	1.03	0.97	1.09
35-39	1.27	1.18	1.36	1.41	1.30	1.51	1.35	1.24	1.47	1.17	1.07	1.28
40-44	1.07	0.91	1.27	1.23	1.04	1.46	1.17	0.98	1.40	1.00	0.83	1.20
45+	1.34	0.60	2.99	1.62	0.73	3.61	1.49	0.67	3.34	1.26	0.56	2.83

Abbreviation: CI, confidence interval; HR, hazard ratio.

[a] Model A is adjusted for the time-varying covariate calendar year and the fixed covariate participant sex.

[b] Model B is adjusted for the time-varying covariate calendar year and the fixed covariates participant sex and participant birth order.

[c] Model C is adjusted for the time-varying covariate calendar year and the fixed covariates participant sex, participant birth order, and paternal age.

[d] Model D is adjusted for the time-varying covariate calendar year and the fixed covariates participant sex, participant birth order, paternal age, and maternal and paternal country of birth, highest level of education attained, lifetime history of psychiatric hospitalization, and lifetime criminality.

Supplemental Table C.2. Association Between Maternal Age and First Incidence of Any Eating Disorder, With Adjustment for Covariates, for Both Sexes Combined.

	Model A[a]			Model B[b]			Model C[c]			Model D[d]		
Maternal Age Category (years)	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI	
<20	0.77	0.69	0.85	0.73	0.66	0.81	0.79	0.71	0.89	0.91	0.81	1.02
20-24	0.90	0.87	0.94	0.88	0.84	0.92	0.92	0.88	0.96	1.00	0.95	1.04
25-29 (ref.)	1.00			1.00			1.00			1.00		
30-34	1.12	1.08	1.16	1.16	1.12	1.21	1.13	1.08	1.18	1.06	1.01	1.10
35-39	1.21	1.15	1.27	1.30	1.23	1.37	1.25	1.18	1.33	1.13	1.06	1.20
40-44	1.10	0.98	1.24	1.21	1.07	1.37	1.15	1.01	1.31	1.03	0.91	1.18
45+	1.52	0.88	2.61	1.72	1.00	2.97	1.60	0.93	2.78	1.44	0.83	2.49

Abbreviation: CI, confidence interval; HR, hazard ratio.

[a] Model A is adjusted for the time-varying covariate calendar year and the fixed covariate participant sex.

[b] Model B is adjusted for the time-varying covariate calendar year and the fixed covariates participant sex and participant birth order.

[c] Model C is adjusted for the time-varying covariate calendar year and the fixed covariates participant sex, participant birth order, and paternal age.

[d] Model D is adjusted for the time-varying covariate calendar year and the fixed covariates participant sex, participant birth order, paternal age, and maternal and paternal country of birth, highest level of education attained, lifetime history of psychiatric hospitalization, and lifetime criminality.

Appendix D: Sex-Specific Results for (Categorical) Paternal Age at Birth

Supplemental Table D.1. Association Between Paternal Age and First Incidence of Anorexia Nervosa, With Adjustment for Covariates, Stratified by Sex.

	Model A[a]						Model B[b]						Model C[c]						Model D[d]					
	Men			Women			Men			Women			Men			Women			Men			Women		
Paternal Age Category (years)	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI	
<20	1.94	0.79	4.74	0.65	0.46	0.91	1.86	0.76	4.57	0.62	0.44	0.88	2.44	0.92	6.51	0.79	0.56	1.13	2.50	0.93	6.72	0.84	0.59	1.20
20-24	1.07	0.76	1.51	0.79	0.73	0.86	1.05	0.74	1.48	0.77	0.71	0.84	1.16	0.80	1.67	0.86	0.79	0.94	1.17	0.81	1.70	0.89	0.81	0.98
25-29 (ref.)	1.00			1.00			1.00			1.00			1.00			1.00			1.00			1.00		
30-34	1.25	0.98	1.59	1.12	1.06	1.18	1.29	1.01	1.66	1.16	1.09	1.23	1.18	0.91	1.53	1.06	1.00	1.13	1.19	0.91	1.54	1.05	0.98	1.11
35-39	1.50	1.14	1.97	1.19	1.11	1.27	1.62	1.23	2.15	1.27	1.18	1.36	1.32	0.96	1.81	1.09	1.01	1.17	1.39	1.01	1.92	1.09	1.01	1.18
40-44	1.37	0.92	2.04	1.16	1.05	1.27	1.51	1.01	2.26	1.24	1.13	1.37	1.14	0.73	1.78	1.03	0.93	1.15	1.29	0.82	2.02	1.09	0.98	1.22
45+	2.86	1.88	4.35	1.24	1.08	1.43	3.13	2.05	4.78	1.33	1.15	1.53	2.34	1.46	3.75	1.10	0.94	1.28	2.90	1.79	4.71	1.23	1.06	1.44

Abbreviation: CI, confidence interval; HR, hazard ratio.

[a] Model A is adjusted for the time-varying covariate calendar year and the fixed covariate participant sex.

[b] Model B is adjusted for the time-varying covariate calendar year and the fixed covariates participant sex and participant birth order.

[c] Model C is adjusted for the time-varying covariate calendar year and the fixed covariates participant sex, participant birth order, and maternal age.

[d] Model D is adjusted for the time-varying covariate calendar year and the fixed covariates participant sex, participant birth order, maternal age, and maternal and paternal country of birth, highest level of education attained, lifetime history of psychiatric hospitalization, and lifetime criminality.

Supplemental Table D.2. Association Between Paternal Age and First Incidence of Any Eating Disorder, With Adjustment for Covariates, Stratified by Sex.

	Model A[a]						Model B[b]						Model C[c]						Model D[d]					
	Men			Women			Men			Women			Men			Women			Men			Women		
Paternal Age Category (years)	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI	
<20	1.36	0.67	2.74	0.80	0.65	0.99	1.28	0.63	2.59	0.78	0.63	0.97	1.51	0.71	3.21	0.90	0.72	1.13	1.48	0.70	3.15	0.93	0.74	1.17
20-24	1.10	0.88	1.38	0.85	0.81	0.91	1.06	0.85	1.33	0.84	0.79	0.89	1.16	0.91	1.48	0.89	0.84	0.95	1.15	0.90	1.47	0.91	0.86	0.97
25-29 (ref.)	1.00			1.00			1.00			1.00			1.00			1.00			1.00			1.00		
30-34	1.17	0.99	1.38	1.09	1.05	1.14	1.21	1.02	1.42	1.12	1.07	1.16	1.13	0.94	1.34	1.05	1.01	1.10	1.14	0.95	1.35	1.04	0.99	1.09
35-39	1.24	1.02	1.50	1.15	1.10	1.21	1.30	1.07	1.58	1.21	1.15	1.27	1.12	0.90	1.40	1.08	1.02	1.14	1.15	0.92	1.44	1.09	1.03	1.15
40-44	1.33	1.02	1.74	1.14	1.06	1.22	1.40	1.07	1.84	1.20	1.12	1.29	1.12	0.83	1.52	1.05	0.97	1.14	1.18	0.87	1.60	1.10	1.02	1.19
45+	2.01	1.46	2.78	1.21	1.09	1.34	2.11	1.52	2.92	1.27	1.15	1.41	1.63	1.14	2.33	1.11	0.99	1.23	1.78	1.23	2.57	1.22	1.09	1.37

Abbreviation: CI, confidence interval; HR, hazard ratio.

[a] Model A is adjusted for the time-varying covariate calendar year and the fixed covariate participant sex.

[b] Model B is adjusted for the time-varying covariate calendar year and the fixed covariates participant sex and participant birth order.

[c] Model C is adjusted for the time-varying covariate calendar year and the fixed covariates participant sex, participant birth order, and maternal age.

[d] Model D is adjusted for the time-varying covariate calendar year and the fixed covariates participant sex, participant birth order, maternal age, and maternal and paternal country of birth, highest level of education attained, lifetime history of psychiatric hospitalization, and lifetime criminality.