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Advanced Paternal Age at Birth: Phenotypic and Etiologic Associations with Eating Pathology in Offspring

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Abstract

Background—Advanced paternal age at birth has been linked to several psychiatric disorders in offspring (e.g., schizophrenia), and genetic mechanisms are thought to underlie these associations. This study is the first to investigate whether advanced paternal age at birth is associated with eating disorder risk using a twin study design capable of examining both phenotypic and genetic associations.

Methods—In a large, population-based sample of female twins ages 8–17 years in mid-puberty or beyond (N = 1,722), we investigated whether advanced paternal age was positively associated with disordered eating symptoms and an eating disorder history (i.e., anorexia nervosa, bulimia nervosa, or binge eating disorder) in offspring. Biometric twin models examined whether genetic and/or environmental factors underlie paternal age effects for disordered eating symptoms.

Results—Advanced paternal age was positively associated with disordered eating symptoms and an eating disorder history, where the highest level of pathology was observed in offspring born to fathers ≥ 40 years old. Results were not accounted for by maternal age at birth, body mass index, socioeconomic status, fertility treatment, or parental psychiatric history. Twin models indicated decreased genetic, and increased environmental, effects on disordered eating with advanced paternal age.

Conclusions—Advanced paternal age increased risk for the full spectrum of eating pathology, independent of several important covariates. However, contrary to leading hypotheses, environmental rather than genetic factors accounted for paternal age-disordered eating associations. These data highlight the need to explore novel (potentially environmental) mechanisms underlying the effects of advanced paternal age on offspring eating disorder risk.

Keywords

advanced paternal age; eating disorders; disordered eating; genetic; environmental; twin study

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Advanced paternal age at birth is a risk factor for psychiatric disorders in offspring, including schizophrenia, autism, and bipolar disorder (Malaspina *et al.*, 2001, Reichenberg *et al.*, 2006, Frans *et al.*, 2008). These relationships have been confirmed in meta-analytic studies (Wohl and Gorwood, 2007, Hultman *et al.*, 2011, Miller *et al.*, 2011) and are independent of important confounds (i.e., maternal age at birth, socioeconomic status (SES), parental psychiatric history) that increase psychiatric risk and are associated with later entry into parenthood (Byrne *et al.*, 2003, Croen *et al.*, 2007, Menezes *et al.*, 2010). Recent data also link paternal age to obesity (Eriksen *et al.*, 2012). Despite these robust effects, advanced paternal age has never been examined as a risk factor for eating disorders in offspring. Examining this possibility could provide new insights into the complex etiology of eating disorders.

Leading theories propose that de novo genetic mutations are primary mechanisms underlying paternal age-psychiatric risk associations (Malaspina *et al.*, 2002). The increased probability of DNA copy error problems with each sperm replication (~610 replications by age 40), and the accumulation of mutations in the germline of older fathers, are thought to lead to disease phenotypes in offspring (Crow, 2000). Genetic studies indicate that offspring de novo mutation rates are influenced by paternal age at conception (Kong *et al.*, 2012), and de novo mutations are implicated in schizophrenia and autism (Awadalla *et al.*, 2010, Xu *et al.*, 2011, Iossifov *et al.*, 2012). However, to our knowledge, no study has directly confirmed that de novo mutations underlie paternal age-offspring psychiatric risk associations.

Twin studies can be used to indirectly examine the role of de novo mutations in paternal age-psychiatric disorder relationships. Because monozygotic (MZ) twins share 100% of their genes, and dizygotic (DZ) twins share, on average, half of their segregating genetic material, MZ twins would be expected to share all de novo mutations, whereas DZ twins would almost never share genetic mutations given their rarity (Zhao *et al.*, 2007, Liu *et al.*, 2010, Ronald and Hoekstra, 2011). If de novo mutations underlie paternal age–psychiatric risk associations, larger differences between MZ and DZ twin correlations should be observed with advancing paternal age since DZ co-twins should become less similar as mutation rates increase.

One previous study examined these processes by investigating twin similarity for autism across paternal age (Lundström *et al.*, 2010). Importantly, differences in MZ/DZ concordance for autism *decreased* with advanced paternal age, implicating environmental rather than genetic processes. Although results were limited by a small number of cases in each age category (Ns = 3–44), they highlight the need to test hypotheses regarding mechanisms for paternal age effects. Twin registries are excellent, low-cost resources for such investigations, as they can indirectly examine whether de novo mutations or other competing processes most likely underlie paternal age-psychiatric risk associations.

The current study investigated phenotypic and etiologic associations between advanced paternal age and disordered eating symptoms (e.g., weight/shape concerns) in a large, population-based sample of female twins. These symptoms are core features of eating disorders and prospectively predict the development of diagnoses (Jacobi *et al.*, 2004); thus, results should inform risk models of eating disorders. Exploratory analyses examining

associations between advanced paternal age and an eating disorder history (anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED)) were also conducted to investigate whether results generalize across categorical and continuous eating disorder dimensions (American Psychiatric Association, 2000; Insel *et al.*, 2010). Several covariates were included (e.g., maternal age, body mass index (BMI) percentile, SES, fertility treatment, parental psychiatric history) to ensure that associations were not due to confounding factors. Finally, we compared twin similarity for disordered eating across paternal age to explore mechanisms (i.e., genetic/environmental) underlying paternal age-disordered eating associations.

Methods

Participants

Participants were 1,722 female twins (488 (28%) MZ, 611 (35%) same-sex DZ, and 623 (36%) opposite-sex) between the ages of 8–17 years (M (S.D) = 13.86 (2.39)) from the on-going *Michigan Twins Project* (MTP), a study conducted within the Michigan State University Twin Registry (MSUTR; Klump and Burt, 2006, Burt and Klump, 2013). Twins were recruited using birth records and driver's license databases (see Klump & Burt (2006)). MTP recruitment began in 2008, and response rates (~56%) are on par with those for other population-based twin registries (Kendler *et al.*, 1992, Lichtenstein, 2002).

Because increases in genetic influences on disordered eating are observed during puberty in females (Klump *et al.*, 2007, Culbert *et al.*, 2009), we only included twins who were in mid-puberty or beyond (i.e., score ≥ 2.5 on the Pubertal Development Scale; Petersen *et al.*, 1988). Twins spanned a range of racial/ethnic backgrounds (e.g., Caucasian, Black/African American, Asian/Pacific Rim), but consistent with the region (see http://www.michigan.gov), most (87%) were Caucasian.

Measures

All data came from the MTP questionnaire completed by the twins' mother or father (93% biological mothers, 6% biological fathers, 1% step/adoptive parents).

Zygosity—Similar to other twin registries (Kendler *et al.*, 1992, Lichtenstein, 2002), zygosity was determined using five physical similarity items. These items have demonstrated over 95% accuracy when compared to genotyping (Lykken *et al.*, 1990).

Parental Age at Birth—Paternal and maternal ages at offspring birth were calculated using birth dates. Average ages at birth (Paternal M (S.D) = 32.70 (5.92), range = 15–55; Maternal M (S.D) = 30.49 (4.77), range = 17–48) were similar to those from other studies examining parental age effects (e.g., Paternal M (S.D) = 31.5 (6.8), range = 13–70; Maternal M (S.D) = 28.8 (5.9), range = 12–53) (Croen *et al.*, 2007).

Disordered Eating Symptoms—Disordered eating was assessed using 9 items from the Eating Disorder Examination-Questionnaire (EDE-Q; Fairburn and Beglin, 1994) (see Table 1). The EDE-Q assesses core eating disorder symptoms including weight/shape concerns, dietary restraint, binge eating, and compensatory behaviors. EDE-Q items were included if

they: 1) represented key attitudinal and behavioral symptoms; 2) exhibited significant correlations with the EDE-Q Global Score (mean r = .76); and 3) were developmentally appropriate for pre- and early-adolescent participants. Importantly, these symptoms are well-established risk factors for eating disorders (Jacobi *et al.*, 2004).

EDE-Q items were modified for use in this large-scale, mail-in twin registry. Parent, rather than child, reports were collected in order to keep the MTP questionnaire brief and easy to complete. This was necessary for recruiting as many families as possible into the registry (which serves as a participant bank – see Burt and Klump (2013)). Although parent reports of disordered eating are less commonly used than parent reports of other psychiatric symptoms, data from another on-going MSUTR study (Klump *et al.*, 2010) show that the parent-child correlation for the MTP disordered eating items (r = .52) is similar or better than parent-child correlations for externalizing/internalizing symptoms (r's = .14–.48) (Kolko and Kazdin, 1993, Youngstrom *et al.*, 2000). EDE-Q parent reports also demonstrated expected correlations with external correlates in the Klump *et al.* (2010) sample (i.e., BMI, r = .58; depressive symptoms, r = .35).

Parents rated their children's disordered eating based on what they "generally are like" using a three-point scale ("not true", "sometimes true", "certainly true") rather than the original EDE-Q format (i.e., number of days a symptom was present in past month). This was necessary to match other MTP items and to index trait- rather than state-levels of disordered eating. Our data suggest that this rating format does not substantially affect the validity of the EDE-Q. In a sub-sample of twins whose mothers rated disordered eating using the MTP EDE-Q and the original EDE-Q, ratings were highly correlated (r = .59) despite occurring an average of 1.5 years apart (SD = 0.77; range = 0.23–2.90 years).

Internal consistency for the MTP items was excellent (α = .86). There was significant variability in disordered eating, as the rate at which most symptoms were "sometimes" or "certainly" true ranged from 10–35% (see Table 1). Levels of disordered eating were on par with those from other MSUTR studies examining a similar age range, but using the original EDE-Q (item endorsement = 7–42%) (Klump *et al.*, 2010, Klump *et al.*, 2013). As would be expected in a population-based, adolescent sample (Wade *et al.*, 2008), attitudinal symptoms (e.g., fear of fatness) were the most highly endorsed, although behaviors (e.g., dieting, binge eating) also showed sufficient variation. Correlations with BMI were in the low-to-moderate range (range = .009–.42; mean r = .25; average percent variance shared = 6%), suggesting that our measure taps disordered eating symptoms that are not merely a reflection of weight status/obesity.

Eating Disorder Diagnosis—Lifetime histories of eating disorders (AN, BN, or BED) were assessed via parent report. Of the 1,668 twins with available data, 11 (1%) had a history of an eating disorder (6/11 (55%) AN, 4/11 (36%) BED, 1/11 (9%) AN and BN), of which 7 (64%) received previous treatment and 4 (36%) did not. These percentages are on par with the prevalence of eating disorders in female children/adolescents (Merikangas *et al.*, 2010, Swanson *et al.*, 2011). As expected, twins with an eating disorder history had substantially higher MTP disordered eating scores (M (SD) = 7.81 (5.98)) than those with no history (M (SD) = 2.31 (3.16); p = .01; Cohen's d = 1.15). Disordered eating scores did not

meaningfully differ between patients with a history of AN (or AN/BN) (M (S.D) = 8.14 (7.40)) vs. BED (M (S.D) = 7.25 (2.98)).

Covariates—Several covariates were examined to ensure that associations between paternal age and eating pathology were not accounted for by confounding factors. Covariates included: twin age, ethnicity, and BMI percentile (i.e., BMI adjusted for age); SES; parental fertility treatment and psychiatric history. Selected covariates have been associated with disordered eating and/or later paternal age at birth (Hare and Moran, 1979, Lilenfeld *et al.*, 1998, O'Dea and Caputi, 2001, Croll *et al.*, 2002, Doornbos *et al.*, 2007, Sobotka, 2010, Eriksen *et al.*, 2012). Parent reports of twin height and weight, which correlate highly with laboratory measurements (r's = .79–.81; Huybrechts *et al.*, 2011), were used to calculate BMI. BMI values were transformed to percentiles (see www.cdc.gov) in order to capture age-related variation in our child/adolescent sample. Family yearly income and parental education (i.e., highest level of education achieved by mother or father) were used to assess SES. A history of depression, anxiety disorder (i.e., panic, obsessive-compulsive, post-traumatic stress, separation anxiety), or eating disorder (i.e., AN, BN, BED) in the biological mother and/or father was assessed using a family history checklist coded "yes" if at least one parent suffered from one or more disorder or "no" if neither parent reported a history of the disorders.

Statistical Analyses

Phenotypic Associations—Paternal age at birth was examined as a predictor of disordered eating symptoms and history of an eating disorder. Paternal age was modeled continuously as well as categorically (i.e., < 25 years, 25–29 years, 30–34 years, 35–39 years, ≥ 40 years) to increase statistical power and identify particularly high-risk age thresholds (e.g., paternal age > 35 years - see Wohl and Gorwood (2007)).

Generalized linear mixed models (GLMMs) were used as they could account for the non-independence of twin data (i.e., by nesting a level 1 variable (individual twin) within a level 2 unit (family)) and could examine both continuous and categorical outcomes. GLMM linear models (normal distribution with identity link) and binary logistic regressions (binomial distribution with logit link) were used to examine disordered eating and eating disorder history, respectively. We standardized all variables prior to analysis in order to interpret unstandardized coefficients as standardized coefficients.

GLMMs were run twice: 1) controlling only for maternal age at birth, and 2) controlling for all covariates. This two-step process allowed us to identify the effects of covariates on paternal age-eating pathology associations, while always controlling for maternal age, since maternal age correlated highly with paternal age (r = .72)[1] and is associated with other psychiatric disorders (Croen *et al.*, 2007, Menezes *et al.*, 2010). Controlling for maternal age also ensured that our independent variable (i.e., paternal age at birth) and dependent variables (i.e., parent-reported eating pathology) were not confounded, as 93% of MTP questionnaires were completed by biological mothers.[2]

[1]We tested for multi-collinearity due to the high correlation between paternal and maternal age at birth, but tolerance and the variance inflation factor (VIF) were well within the acceptable range (tolerance = .50, threshold = < .10; VIF = 2.01, threshold = >10).

Genetic Associations—We investigated genetic influences on paternal age effects by comparing MZ and DZ twin similarity for disordered eating as a function of paternal age at birth. Given that very few participants had an eating disorder history, analyses focused on disordered eating symptoms. Further, although same-sex and opposite-sex twins were included in phenotypic analyses, twin analyses included same-sex twins only, as male co-twins of opposite-sex females were not examined due to low eating disorder prevalence in males (Swanson *et al.*, 2011).

Twin intraclass correlations were calculated in the full sample and each paternal age category to provide an initial indication of genetic/environmental effects on disordered eating across paternal age. Additive genetic effects (A; genetic influences that add across genes) are indicated if the MZ twin correlation is approximately twice the DZ twin correlation, while non-additive genetic effects (D; interaction of genetic effects at same locus) are suggested if MZ correlations are more than double DZ correlations. De novo mutations are considered a non-additive genetic process in twin studies, as DZ twins would share far less than half of their mutations because of their rarity (Liu *et al.*, 2010). Therefore, if de novo mutations underlie paternal age-disordered eating relationships, we would expect larger MZ/DZ differences with advanced paternal age.

Twin studies also decompose variance into two forms of environmental effects. Shared environmental influences (C; factors that make co-twins similar to one another) are inferred if MZ and DZ twin correlations are approximately equal, while non-shared environmental influences (E; factors that make co-twins different from one another, including measurement error) are implied if the MZ correlation is less than 1.0. If differences between MZ/DZ correlations decrease with paternal age, shared environmental processes would be implicated, as co-twins would increase in similarity regardless of genetic sharing. Finally, decreases in the MZ correlation would indicate non-shared environmental influences on paternal age-disordered eating effects.

We then used twin moderation models (see Purcell, 2002) to statistically quantify the degree to which genetic/environmental influences on disordered eating vary by paternal age (the moderator). ACE and ADE models were examined in order to test for differences in both additive and non-additive genetic effects. Model fitting was conducted using full information maximum-likelihood raw data techniques with Mx statistical software (Neale, 1997).

Following previous recommendations (Purcell, 2002), we fit “full” ACE and ADE moderator models that included linear and non-linear moderators to directly test whether genetic/environmental estimates vary linearly or non-linearly with paternal age. We compared full models to two more restrictive models: 1) linear moderation models that dropped non-linear moderation coefficients, and 2) no moderation models that estimated only genetic/environmental paths. To minimize the number of models fit, we did not drop individual moderation coefficients one by one. Instead, we determined whether each

[2]Results remained unchanged when excluding participants whose biological father completed the questionnaire (6% of the sample; data not shown).

etiologic influence varied by paternal age by examining whether confidence intervals for moderator estimates overlapped with zero.

The best fitting model was determined using both the difference in minus twice the log likelihood (Δ-2lnL) and Akaike's Information Criteria (AIC). Δ-2lnL was used to compare full and nested moderation models, and AIC was used to compare the unnested ACE and ADE models. Statistically significant differences in-2lnL suggest that dropping moderator coefficients results in significantly worse model fit, whereas lower AIC values indicate better model fit.

Although definition variables can be used to account for covariate effects in twin models (Neale *et al.*, 2006), it was not possible to simultaneously include all eight covariates as definition variables in one model, as this would reduce statistical power to detect differences in etiologic effects across paternal age (Agrawal *et al.*, 2010). Consequently, we ran individual models that included each covariate as a definition variable one by one to examine individual covariate effects. Because findings were unchanged in each run of the model, we focused our results on models that included maternal age at birth as the definition variable in order to mirror our first set of phenotypic analyses described above.

Results

Phenotypic Associations

Consistent with hypotheses, paternal age was positively associated with disordered eating symptoms in female offspring, even after controlling for several important covariates (e.g., maternal age, BMI percentile; see Table 2). Similar to other disorders (Byrne *et al.*, 2003), a threshold effect was detected, such that mean levels of disordered eating were significantly higher in offspring of fathers ≥ 40 years compared to offspring of younger fathers (see Table 2). Effect sizes indicate that the phenotypic effect of paternal age on disordered eating is small-to-medium in magnitude (*beta's* =.08–.09; *d's* =.18–.41).[3]

Exploratory analyses revealed that paternal age at birth, measured continuously, also predicts a lifetime eating disorder history. Small sample sizes prevented examining paternal age as a categorical predictor of eating disorder diagnosis; however, there were a disproportionate number of cases in older age categories (see Table 2), and this effect was not driven by a specific diagnosis (i.e., AN and BED were both present in the older age groups).

Genetic Associations

Similar to previous research in pubertal females (Klump *et al.*, 2007, Culbert *et al.*, 2009), higher MZ than DZ correlations and an MZ correlation less than 1.0 indicated the presence of genetic and non-shared environmental influences on disordered eating in the full sample. However, differences in MZ/DZ correlations across paternal age suggested significant

[3]Advanced maternal age at birth was not associated with offspring eating pathology. Maternal age exhibited a modest, negative association with disordered eating (b = −.06, p = .03), but this association became non-significant after controlling for covariates (b = −.03, p =.15). Further, maternal age at birth did not significantly predict history of an eating disorder diagnosis (b = .21; p = .48).

heterogeneity in etiologic effects (see Table 3). Before age 35, the MZ correlation was twice the DZ correlation, suggesting additive genetic effects but little-to-no shared environmental or non-additive genetic influences. By contrast, after age 35, the DZ correlation increased and was comparable to most of the MZ correlations, indicating a complete lack of additive or non-additive genetic effects but significant shared environmental influences. The lower MZ correlation in the oldest paternal age group could reflect greater non-shared environmental effects, although conclusions are hard to draw given the group's small sample size (n = 16 pairs) and the fact that this correlation does not significantly differ from MZ correlations in most younger paternal age groups (as evidenced by overlapping confidence intervals; see Table 3). Overall, twin correlations suggest increasing shared environmental influences on disordered eating after age 35, arguing against increases in genetic or de novo mutation effects with advanced paternal age.

Because twin correlations suggested no differences in etiologic effects until age 35, we created two paternal age groups for analyses (< 35 years versus ≥ 35 years) to maximize power and capture key etiologic differences across paternal age.[4] Non-linear moderation cannot be examined with only two moderator levels, so we focused on linear and no moderation models. ACE models fit better than ADE models (i.e., lower AICs), which is not surprising given that non-additive genetic effects were non-significant (i.e., 95% confidence intervals included 0).

Within ACE models, a statistically significant Δ-2lnL indicated that the linear moderation model fit better than the no moderation model and that genetic/environmental influences on disordered eating varied by paternal age. Following previous recommendations (Purcell, 2002), we report unstandardized path and moderator estimates in Table 4 and Figure 1 in order to depict absolute changes in genetic/environmental influences rather than changes in proportions of total variance. Nonetheless, in order to compare genetic/environmental estimates to previous twin studies of disordered eating, we also report standardized estimates (calculated by squaring the path coefficients in the < 35 group, and squaring the sum of the moderator estimates plus the path coefficients in the ≥ 35 group; see percentages below).

As shown in Table 4, a, c, and e moderator estimates were statistically significant, suggesting that all three differ across paternal age. The most substantial change occurs for additive genetic and shared environmental influences (see Figure 1). Before age 35, additive genetic effects primarily contributed to disordered eating (A = 75%), with the remaining variance due to the non-shared environment (E = 25%). In stark contrast, after age 35, the variance in disordered eating was entirely due to shared and non-shared environmental factors (C = 59%; E = 41%).[5]

[4]We also tested the five paternal age categories in order to ensure that dichotomizing paternal age did not unduly influence results. Results were identical to those presented herein (data not shown), where genetic effects decreased, and shared environmental effects increased, with older paternal age.

[5]We examined whether the same pattern of results (i.e., decrease in additive genetic effects, increase in shared environmental effects, with paternal age) was observed when twins in the paternal age >40 year group were excluded from analyses given the low MZ correlation in this age group. Results were identical, in that the ACE linear moderation model was best fitting, and both additive genetic and shared environmental moderation coefficients were significant and in the same direction as in the original models.

Discussion

Using a large, population-based sample of female twins, we demonstrated for the first time that advanced paternal age at birth is a significant risk factor for offspring eating pathology. This phenotypic effect was quite robust, in that it was present for eating disorder symptoms and diagnoses, and effects were independent of several important covariates (e.g., maternal age, BMI percentile, SES, parental psychiatric history). We also examined differences in etiologic influences across paternal age to investigate whether genetic factors (more specifically, de novo mutations) might underlie paternal age-disordered eating relationships. However, results strongly suggested that genetic contributions to disordered eating decreased, rather than increased, with paternal age.

Findings contribute to a growing body of literature implicating advanced paternal age in offspring psychiatric risk, as indicated for schizophrenia, autism, and bipolar disorder (Malaspina *et al.*, 2001, Reichenberg *et al.*, 2006, Frans *et al.*, 2008). A relationship with disordered eating is novel and suggests that eating disorders may share some, perhaps more general, etiologic risk factors with these disorders. This is important given that socio-cultural influences (e.g., pressures for thinness) have led to views that eating disorders are etiologically distinct from “neuropsychiatric” illnesses (Klump *et al.*, 2009). Instead, eating disorders may be uniquely associated with both the internalizing and neuropsychiatric spectrums of psychopathology. This possibility is being explored by researchers investigating social/cognitive similarities between AN and autism (Zucker *et al.*, 2007) as well as other neuropsychiatric disorders (Steinglass *et al.*, 2007).

De novo mutations have been proposed as a potential biological mechanism underlying paternal age-psychiatric risk associations, although our results argue against de novo mutation effects for paternal age-disordered eating relationships. We observed a sharp decrease in the magnitude of genetic influences on disordered eating in the paternal age ≥ 35 group, as DZ twins (who would not share de novo mutations) became more rather than less similar with paternal age. Our results converge with those of an autism twin study (Lundström *et al.*, 2010), and together, suggest that de novo mutations may not account for paternal age effects. However, if only the frequency (rather than the location) of mutations confers risk, paternal-age related mutations could theoretically increase the similarity of DZ twins born to older fathers, as DZ twins may have a similar mutation burden but, unlike MZ twins, would not share specific mutations. We presumed that sharing specific mutations, rather than frequency alone, would influence twin similarity for eating pathology, consistent with the prediction that de novo mutations increase heritability estimates in twin studies (Liu *et al.*, 2010, Ronald and Hoekstra, 2011). Nonetheless, we cannot definitively rule out the importance of de novo mutations. Future twin and molecular genetic studies are needed to further examine the mutation hypothesis for paternal age-psychiatric disorder relationships.

Another leading mechanism proposed to underlie paternal age-psychiatric disorder associations is disruptions in epigenetic processes (i.e., activation-inactivation of genes and/or changes to chromatin structure) that occur with advanced paternal age (Perrin *et al.*, 2007). While epigenetic mechanisms have been implicated in eating disorders and other psychiatric illnesses (e.g., Schanen, 2006, Frieling *et al.*, 2010), epigenetic disruptions that

accumulate in the male germline and are passed to twin offspring should increase MZ/DZ twin differences. Indeed, MZ twins, formed from one sperm, should share these epigenetic errors at a higher rate than DZ twins who develop from two different sperm. Thus, similar to studies showing greater epigenetic similarity for MZ vs. DZ twins (Kaminsky *et al.*, 2009), paternal-age related epigenetic errors would be expected to increase genetic influences on disordered eating. We instead observed an increase in DZ twin similarity, and thus shared environmental effects with paternal age, arguing against epigenetic mechanisms. Of course, replication, particularly with molecular genetic designs, is needed.

Several covariates examined (e.g., maternal age, SES) could contribute to paternal age effects by decreasing genetic and increasing shared environmental influences on disordered eating. However, these factors did not account for paternal age-disordered eating associations and are unlikely to be strong mechanistic candidates. Additional unexamined factors that could account for paternal age effects and increased shared environmental influences include birth/obstetric complications and paternal weight concerns/behaviors. First, older paternal age has been associated with several birth/obstetric complications in offspring (e.g., pre-term birth, pre-eclampsia, cesarean section) (Harlap *et al.*, 2002, Tang *et al.*, 2006, Sartorius and Nieschlag, 2010, Shah, 2010), and birth/obstetric complications are linked to risk for eating disorders and other psychiatric illnesses (Cannon *et al.*, 2002, Favaro *et al.*, 2006). These paternal age and birth/obstetric complication associations are present after controlling for maternal age (Harlap *et al.*, 2002; Tang *et al.*, 2006), suggesting that they might account for the unique effects of paternal age on offspring psychiatric risk. However, maternal age has been shown to be a stronger predictor of birth/obstetric complications than paternal age (Harlap *et al.*, 2002; Shah, 2010), and the lack of association between maternal age and disordered eating in our data makes it less likely that birth/obstetric complications could entirely account for our findings.

Second, longitudinal research suggests that weight concerns and dieting increase with age in men, such that these attitudes/behaviors are higher in older adulthood than earlier adulthood (Keel *et al.*, 2007). In older fathers, weight concerns and dieting may be highest when children are being raised and could be transmitted environmentally to offspring in the form of paternal expectations and/or criticism. Importantly, although older women continue to report significant weight/shape concerns and eating disorder behaviors in mid-life (Gagne *et al.*, 2012), longitudinal data suggest that women experience a relative decrease in weight concerns/behaviors with advancing age (Keel *et al.*, 2007). Sex differences in these longitudinal trajectories could potentially explain differential relationships between paternal and maternal ages at birth and offspring eating pathology. Clearly, these possibilities are speculative, particularly given that paternal weight concerns/behaviors may have genetic (and/or gene-environment interaction) effects on offspring disordered eating as well. Future research is necessary to examine whether these types of mechanisms environmentally contribute to paternal age-eating pathology associations.

Despite notable strengths of our study (e.g., large, population-based twin sample, examination of confounding factors), our study was not without limitations. Given that the maximum age of our participants was 17 years, we were unable to capture the entire period of risk for eating disorders which can extend up until at least age 25 (Lewinsohn *et al.*,

2000). However, disordered eating symptoms are present as early as childhood and increase across the pubertal period in females (Maloney *et al.*, 1989, Killen *et al.*, 1992). Therefore, meaningful variance in disordered eating was likely captured in our sample of twins who are in mid-puberty and beyond. Nonetheless, future research should examine young adult samples to ensure results generalize to other periods of risk.

Eating disorder symptoms and diagnoses, as well as covariates, were assessed via parent report. Parent reports allowed us to collect data on a large sample of twins, which was necessary for twin models investigating mechanisms underlying paternal age effects. However, parent reports may miss significant eating disorder symptoms/diagnoses that would be captured by self-reports, and limiting assessment of all covariates to a single parent report could introduce error due to shared method variance. Fortunately, our identified eating disorder cases performed as expected on measures of disordered eating and external correlates, and initial MSUTR data suggest that parent-child concordance for disordered eating is better than that observed for other phenotypes routinely assessed via parent report (see Methods). Future studies should nevertheless confirm that advanced paternal age predicts eating pathology when examining self-reported symptoms/diagnoses using questionnaire and interview data. Using multiple methods to assess covariates (e.g., laboratory height/weight measures) could also help minimize potential influences of shared method variance.

Finally, given the small number of twins with eating disorder histories, phenotypic links between paternal age and eating disorder diagnoses could only be cursorily examined, and paternal age-diagnosis relationships were not investigated using twin models. Although the symptoms we examined are risk factors for eating disorders (Jacobi *et al.*, 2004), additional studies with larger samples are needed to investigate phenotypic and etiologic relationships between paternal age and the broad eating disorder category as well as the specific diagnoses of AN, BN, and BED. Such analyses could increase understanding of the role of paternal age in eating disorder risk and identify specific mechanisms contributing to differential symptom presentations.

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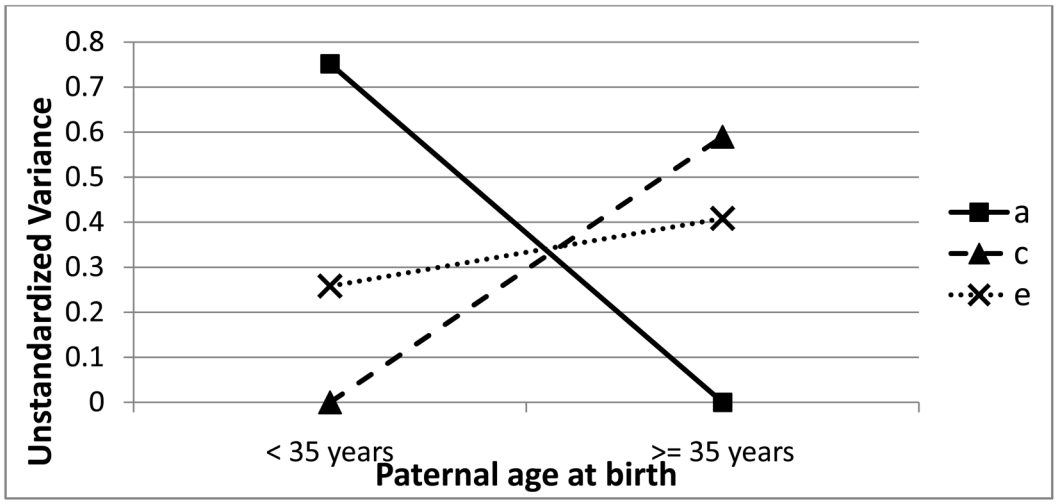

Figure 1. Unstandardized Additive Genetic, Shared Environmental, and Non-shared Environmental Variance Contributions to Disordered Eating by Paternal Age at Birth
a = additive genetic; c = shared environment; e =non-shared environment

Table 1

Disordered Eating Items and Frequency of Item Endorsement

	Item Endorsement Frequency (% of twins)		
Disordered Eating Items	**0 (Not True)**	**1 (Somewhat True)**	**2 (Certainly True)**
1. Feels fat	70.7	21.4	7.9
2. Definite fear of gaining weight or of becoming fat	66.3	25.3	8.5
3. Has a strong desire to lose weight	77.1	17.1	5.9
4. Diets to control weight	86.2	11.2	2.6
5. Very dissatisfied with his/her body weight or shape	65.1	24.9	10.0
6. Body weight and/or shape influences how thinks about (judges) him/herself as a person	69.7	25.1	5.2
7. Feels guilty about what he/she eats because of the effect on body weight and/or shape	80.1	16.6	3.3
8. Eats lots of food and can’t stop	89.5	8.7	1.9
9. Has vomited to control his/her weight	99.4	.20	.30

Table 2

Paternal Age at Birth as a Predictor of Disordered Eating Symptoms and Lifetime Eating Disorder History in Offspring

Paternal Age			Maternal Age Only				Full Covariate Model			
	n (%)		Coefficient (S.E.)	*t* (df)	*p*	*d*	Coefficient (S.E.)	*t* (df)	*p*	*d*
			Disordered Eating Symptoms							
Continuous Categorical	1722		.09 (.04)	2.37 (1719)	**.02**	--	.08 (.03)	2.44 (1709)	**.01**	--
< 25	128 (7.4)		−.02 (.10)	−2.08 (1716)	**.04**	.28	−.06 (.10)	−2.53 (1706)	**.01**	.30
25–29	439 (25.5)		−.15 (.05)	−4.14 (1716)	**<.001**	.41	−.10 (.06)	−3.98 (1706)	**<.001**	.31
30–34	589 (34.2)		.01 (.04)	−3.10 (1716)	**.002**	.27	.04 (.06)	−2.89 (1706)	**.004**	.18
35–39	383 (22.2)		.04 (.06)	−2.80 (1716)	**.005**	.32	.05 (.07)	−2.85 (1706)	**.004**	.18
≥ 40	183 (10.6)		.29 (.08)	--	--	--	.28 (.09)	--	--	--
			Lifetime Eating Disorder (ED) History							
	ED n (%)	No ED n (%)								
Continuous Categorical	11	1, 657	.64 (.32)	2.01 (1666)	**.04**	--	.67 (.31)	2.14 (1655)	**.03**	--
< 25	1 (9.1)	122 (7.4)	--	--	--	--	--	--	--	--
25–29	0 (0)	422 (25.5)	--	--	--	--	--	--	--	--
30–34	5 (45.5)	566 (34.2)	--	--	--	--	--	--	--	--
35–39	2 (18.2)	369 (22.3)	--	--	--	--	--	--	--	--
≥ 40	3 (27.3)	178 (10.7)	--	--	--	--	--	--	--	--

The “Maternal Age Only” model controlled for maternal age at birth only. The “Full Covariate” model controlled for maternal age at birth, child age, child ethnicity, child body mass index percentile, family education and income, fertility treatment, and parental psychiatric history. Coefficient = standardized beta in continuous paternal age models; standardized mean in categorical paternal age models. The ≥ 40 years group was coded as the reference group for t-test comparisons in categorical paternal age models.

Table 3

Twin Correlations for Disordered Eating by Paternal Age Category

	MZ (95% CI) [N]	DZ (95% CI) [N]	Z	*p*
Full sample	.69 (.63, .75) [227]	.43 (.35, .50) [269]	4.28	**<.001**
Paternal age				
< 25	.73 (.50, .87) [26]	.32 (−.03, .66) [17]	1.76	**.04**
25–29	.67 (.53, .79) [67]	.36 (.21, .50) [77]	2.54	**.005**
30–34	.77 (.67, .84) [72]	.33 (.18, .46) [88]	4.18	**<.001**
35–39	.65 (.50, .79) [46]	.57 (.41, .70) [54]	0.62	.24
≥ 40	.30 (−.01, .56) [16]	.64 (.46, .78) [33]	−1.35	.99

MZ = monozygotic twins; DZ = dizygotic same-sex twins; CI = confidence interval; N = number of twin pairs; Z = test of equality examining whether MZ correlation is higher than DZ twin correlations. *p* = one-tailed significance value for Z test of equality. Maternal age at birth was regressed from each twin's disordered eating score, and standardized residual scores were used to calculate twin correlations.

Table 4

Unstandardized Parameter Estimates and Test Statistics for the Comparison of Linear Moderation and No Moderation Models

	Parameter Estimates			Test Statistics					
Model	A	C/D	E	-2lnL	df	Δ-2lnL	Δdf	*p*	AIC
ACE									
Linear Moderation				2594.36	982	--	--	--	630.36
Path estimates	.87 (.75, .95)	0 (-.42, .42)	.50 (.44, .56)						
Linear moderators	-.87 (-1.47, -.26)	.77 (.27, 1.21)	.14 (.02, .23)						
No Moderation				2607.80	985	13.44	3	**.004**	637.80
Path estimates	.75 (.60,.88)	.37 (-.57,.57)	.54 (.50,.60)						
ADE									
Linear Moderation				2606.36	982	--	--	--	642.36
Path estimates	.79 (.30, .94)	-.37 (-.82, .82)	.50 (.45, .56)						
Linear moderators	0 (-.24, .49)	.74 (-1.04, 1.04)	.09 (-.01, .20)						
No Moderation				2609.70	985	3.34	3	.34	639.76
Path estimates	.84 (.69, .90)	0 (-.47, .47)	.53 (.49, .58)						

A = additive genetic; C = shared environmental; D = non-additive genetic; E = non-shared environmental; −2lnL = minus twice the log likelihood; df = degrees of freedom; Δ-2lnL = change in minus twice the log likelihood; Δdf = change in degree of freedom; AIC = Akaike Information Criteria; Linear Moderation = genetic, shared environmental, and non-shared environmental parameter estimates vary linearly by paternal age at birth; No Moderation = genetic, shared environmental, and non-shared environmental parameter estimates do not vary by paternal age at birth; Best-fitting model is denoted by boxed-in text. Significant paths and moderator estimates are indicated by confidence intervals that do not overlap with 0.