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A Genetically Informed Study of the Associations between Maternal Age at Childbearing and Adverse Perinatal Outcomes

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Abstract

We examined associations of maternal age at childbearing (MAC) with gestational age and fetal growth (i.e., birth weight adjusting for gestational age), using two genetically informed designs (cousin and sibling comparisons) and data from two cohorts, a population-based Swedish sample and a nationally representative United States sample. We also conducted sensitivity analyses to test limitations of the designs. The findings were consistent across samples and suggested that, associations observed in the population between younger MAC and shorter gestational age were confounded by shared familial factors; however, associations of advanced MAC with shorter gestational age remained robust after accounting for shared familial factors. In contrast to the gestational age findings, neither early nor advanced MAC was associated with lower fetal growth after accounting for shared familial factors. Given certain assumptions, these findings provide support for a causal association between advanced MAC and shorter gestational age. The results also suggest that there are not causal associations between early MAC and shorter gestational age, between early MAC and lower fetal growth, and between advanced MAC and lower fetal growth.

Keywords: gestational age, birth weight, fetal growth, maternal age at childbearing, genetically informed designs, quasi-experiments

Adverse perinatal outcomes (e.g., short gestational age and poor fetal growth) are major public health concerns because these problems predict mortality (e.g., Blennow et al., 2009; Crump, Sundquist, Sundquist, & Winkleby, 2011; D'Onofrio, Class, et al., 2013) and morbidity across the lifespan, including a variety of psychological, health, academic, social, and economic difficulties (e.g., Class, Rickert, Langstrom, Lichtenstein, & D'Onofrio, 2014; Mathiasen, Hansen, Anderson, & Greisen, 2009). For example, previous research has shown that preterm birth is associated with decreased cognitive functioning in childhood (Bhutta, Cleves, Casey, Cradock, & Anand, 2002) and psychiatric medication use in adulthood (Crump, Winkleby, Sundquist, & Sundquist, 2010), and poor fetal growth is associated with psychiatric diagnoses in childhood (e.g., autism and ADHD; Class, Rickert, Larsson, Lichtenstein, & D'Onofrio, 2014) and adult health problems (e.g. cardiovascular disease and diabetes; Baker, Olsen, & Sorensen, 2008). Thus, given that both short gestational periods and poor fetal growth predict short- and long-term problems, it is important that research be conducted to gain a better understanding of the etiology of these adverse perinatal outcomes.

Previous studies have shown that both early (e.g., Geronimus & Korenman, 1993; Gibbs, Wendt, Peters, & Hogue, 2012; Rosenzweig & Wolpin, 1995) and advanced maternal age at childbearing (MAC; e.g., Carolan, 2013; Cnattingius, Forman, Berendes, & Isotalo, 1992; Newburn-Cook & Onyskiw, 2005) are associated with low birth weight, fetal growth restriction, and shorter gestational age. This has led to speculation of causal associations between MAC and poor perinatal outcomes through several mechanisms, such as maternal-fetal competition for nutrients in younger pregnant women (Gibbs et al., 2012) and more prevalent diseases (e.g., hypertension or diabetes; Balasch & Gratacos, 2012) and poor maternal-fetus oxygen exchange (Odibo, Nelson, Stamilio, Sehdev, & Macones, 2006) in older pregnant women.

There are, however, significant limitations to prior research on the associations of MAC with perinatal outcomes and the causal interpretations that researchers have made from these associations. The social selection hypothesis posits that biopsychosocial factors influence both MAC and offspring development (Coley & Chase-Lansdale, 1998; Coyne & D'Onofrio, 2012; Jaffee, Caspi, Moffitt, Belsky, & Silva, 2001), and, thus, may confound the associations between MAC and perinatal outcomes. For instance, behavior genetics studies have suggested that age at first childbearing is heritable (Rodgers, Bard, & Miller, 2007), which indicates that genetic factors could be a common cause of both MAC and perinatal outcomes. Furthermore, social factors (e.g., socioeconomic status, education level, race/ethnicity, and marital status) related to MAC (e.g., Alan Guttmacher Institute, 2010; Mersky & Reynolds, 2007; Nilsen, Waldenstrom, Hjelmsted, Rasmussen, & Schytt, 2012) could influence both MAC and perinatal outcomes, thereby accounting for the associations between MAC and perinatal outcomes (Gibbs et al., 2012). The majority of studies on MAC and perinatal outcomes have relied on controlling for measured covariates, but such designs cannot realistically account for all plausible confounding factors (Academy of Medical Sciences Working Group, 2007; Rutter, 2007). Thus, researchers should explore whether the previously identified associations could be due to unmeasured confounding factors.

Given the possibility that unmeasured environmental and genetic confounding could account for the observed association between both early and advanced MAC and offspring perinatal outcomes, researchers should use designs that can help rule out these alternative explanations when randomized control trials are not feasible. Because there are large biological differences between humans and other animals related to parturition, findings from non-human animal studies on the effects of MAC may not generalize to humans (Mitchell & Taggart, 2009).

Scientific working groups (Academy of Medical Sciences Working Group, 2007) and researchers spanning a variety of disciplines, including psychiatry (Kendler, 2005), psychology (D'Onofrio, Lahey, Turkheimer, & Lichtenstein, 2013; Rutter, Pickles, Murray, & Eaves, 2001) , epidemiology (Susser, Eide, & Begg, 2010), sociology (Freese, 2008), and economics (Duncan, 2012), have stressed the importance of using genetically informed designs that help account for genetic and environmental confounding in order to advance causal understanding. Genetically informed designs, which compare differntially exposed individuals within the same nuclear or extended family, control for all unmeasured genetic and environmental factors shared by the family members. A finding that a population-wide association remains robost in a model that compares individuals from the same family suggests that the association is not explaind by familial confounding and, thus, provides support for a causal inference.

There are a number of different types of genetically informed quasi-experimental methods that use design features to help rule out genetic and environmental confounding (D'Onofrio, Lahey, et al., 2013; Knopik, 2009). To our knowledge, there are only three genetically informed studies that have assessed the associations of MAC with fetal growth and gestational age (Bacci, Bartolucci, Chiavarini, Minelli, & Pieroni, 2014; Geronimus & Korenman, 1993; Rosenzweig & Wolpin, 1995). Two of these studies used the Children of the National Longitudinal Study of Youth 1979 (CNLSY). The CNLSY is an ongoing study of all offspring born to women who were approximately 15-21 years old in 1979 and is one of the datasets used in the present manuscript. In the first study (N = 784 mothers), Geronimus and Korenman (1993) found that teenage childbearing (i.e., MAC $\leq$ 19 years), compared to non-teenage childbearing (i.e., MAC between 20 and 31 years), was associated with an increased risk for an offspring having low birth weight (i.e., less than 2,500 grams). However, among

differentially exposed cousins, teenage childbearing was not associated with an increased risk for low birth weight offspring. The authors concluded that the results provided preliminary support to suggest that the observed population-wide increased risk for children of teenage mothers being born with low birth weight was confounded by genetic and environmental factors. Limitations of the study included low statistical power (none of the estimates were statistically significant) and a restricted range of MAC.

In the second genetically informed study (N = 3,110 mothers), Rosenzweig and Wolpin (1995) used the CNLSY dataset to test the association of teenage childbearing with gestational age (in weeks) and fetal growth (i.e., ounces per weeks of gestation). Models, which assessed association among unrelated individuals and controlled for maternal behavior and race, showed that, compared to offspring born to mothers older than 19 years, offspring born to teenagers had shorter gestational age and restricted fetal growth. Unlike the comparison among unrelated individuals, a cousin comparison did not show an association of MAC with either outcome, and a sibling comparison suggested that compared to offspring born to mothers greater than 19 years, offspring born to teenagers had shorter gestational age and *greater* fetal growth.

There were major limitations to these studies conducted with the CNLSY. Because the studies were conducted fairly early in the CNLSY (i.e., over two decades ago), the sample sizes were relatively small and the children were disproportionally born to younger mothers. Thus, the studies lacked statistical power, and there are concerns about the generalizability of findings from a sample with restricted range of MAC. The effects of advancing MAC could not be evaluated in these studies because data on older MAC was not available. It is also important to note that more recent genetically informed studies using the CNLSY dataset to assess the association of MAC with other outcomes (i.e., disruptive behaviors; D'Onofrio et al., 2009)

have reached different conclusion from early CNLSY studies using the same methods (Geronimus, Korenman, & Hillemeier, 1994; Turley, 2003), indicating that studies based on earlier subsets of CNLSY may have drawn incorrect conclusions.

More recently, Bacci and colleagues (2014) assessed the association of MAC with birth weight using an Italian sample of 792 mothers who had two births between 2005 and 2008. They found that after controlling for maternal demographic characteristics, characteristics that may make pregnancies different (e.g., prenatal care), gestational age, and offspring sex, there was no statistically significant association between differences in MAC and birth weight in first and second born siblings. Major limitations of this study include a relatively small sample size and an inability to control for birth order. Furthermore, the study tested a narrow range of MAC (the mean MAC for the first birth was 29.4 years and the average difference in MAC between the first and second childbirth was 2.1 years). As such, the study was not able to assess the associations with advanced MAC.

Given the limitations of the few genetically informed studies on associations between MAC and perinatal outcomes, the aim of present study was to conduct rigorous genetically informed studies to test the associations of MAC with both gestational age (GA) and birth weight for gestational age (BWGA), a proxy for fetal growth. To assess potential familial confounding, we used cousin and sibling comparisons and controlled for measured covariates that may vary within families. We also explored associations with both early and advanced MAC and addressed the generalizability of our findings by fitting the models to data from two samples with different cultures, races, ethnicities, economic backgrounds, and health care coverage. Finally, we conducted several sensitivity analyses to examine how assumptions and limitations of sibling and cousin comparisons could influence our interpretation of the results.

Methods

We conducted analyses on a population-based Swedish dataset and a nationally representative United States dataset. More details about both of these datasets and the variables are provided in previous publications (D'Onofrio, Class, et al., 2013; D'Onofrio et al., 2009).

Swedish Dataset

Sample

Data for the Swedish sample was obtained by linking information available in the following population-based registers: (1) the Medical Birth Register, which includes data on more than 96% of births in Sweden since 1973; (2) the Multi-Generation Register, which contains information about biological relationships for all individuals living in Sweden since 1961; (3) the Patient Register, which provides diagnoses for all inpatient psychiatric hospital admissions in Sweden since 1987 and outpatient care since 2001; (4) the National Crime Register, which includes detailed information about all criminal convictions since 1973; and (5) the Education Register, which contains information on highest level of completed formal education through 2008.

Individuals included in the Swedish cohort were born between January 1, 1973 and December 31, 2008. We selected birth-related data from the Medical Birth Register for 3,369,058 live-born singletons with non-missing birth weight and gestational age who were born to mothers between 13 and 56 year of age. After merging information from the Education register and Multi-Generation registers, we dropped 34,011 individuals with missing data on mother's highest level of education and 2,832 individuals with insufficient data to establish mother's age at first childbirth (i.e., the Multi-Generation Register was used to determine offspring born to each mother before 1973). The resulting cohort of 3,332,215 individuals

represents approximately 92% of the targeted population and includes offspring from 1,773,026 distinct mothers, 1,761,846 distinct fathers, and 1,173,556 distinct maternal-side grandmothers.

Measures

See Table I for the distributions of the characteristics of the study population. At the birth of each offspring, MAC, GA, and birth weight were recorded. We also had measures of offspring birth order and parental characteristics, which were included as covariates in the models. Birth order was categorized into first, second, third, or fourth born or higher. Measured maternal and paternal covariates included indices of highest level of completed education (categorized into six levels), Swedish country of birth, history of any criminal convictions, lifetime history of severe psychiatric problems (either Schizophrenia or Bipolar Disorder), history of any suicide attempts, and history of any inpatient substance abuse treatment. Paternal age at childbearing (ordinally grouped into six categories) was also included as a covariate. Missingness indicators were included for paternal covariates. Offspring birth order was the only covariate included in the baseline population models; all covariates were included in the adjusted population models; and covariates that may differ within families were included in the models comparing individuals within in the same family. In additional sensitivity analyses, maternal age at first childbirth was included as a covariate to test carry-over effects (i.e., to test whether maternal age at first childbirth influenced the interpretation of the main findings).

United States Dataset

Sample

Data for the U.S. sample was obtained from the children of the National Longitudinal Survey of Youth 1979 (Bureau of Labor Statistics, 2012). The National Longitudinal Survey of Youth 1979 (NLSY79) sampled males and females between the ages of 14 and 22 years. A

stratified and clustered household probability sampling approach was used to select participants and the sample included a nationally representative sample of 6,111 individuals and an over-sample of 3,652 Hispanic and African American individuals. From 1979 to 1994 assessments occurred annually. Following 1994, assessments occurred biennially (i.e., every other year). The initial NLSY79 assessment had a response rate of 90% and the NSLY79 retention rates for the first 16 waves were over 90%. Beginning in 1986, the offspring of the female NLSY79 participants were recruited to participate in biennial assessments. This sample is referred to as the children of the NLSY79 (CNLSY). Ninety-five percent of families participated in the initial CNLSY assessment and, on average, 90% participated in subsequent waves. Because the original NLSY79 sample targeted all eligible individuals in each household, multiple females from the same households were included. Thus, related individual (e.g., siblings and cousins) can be identified in the CNLSY.

We started with the original sample of 11,497 offspring and sequentially deleted cases from multiple births (252), cases with missing MAC or MAC of 13 years or less (8), cases with missing GA or GA of 25 weeks or less (1,332), and cases with missing birth weight, birth weight less than 225 grams, or birth weight more than 8,000 grams (387). Analyses were conducted on a final sample of 9,518 cases (83% of the original CNLSY sample), which included offspring from 4,723 distinct mothers and 4,054 distinct maternal-side grandmothers. Given that the U.S. sample was obtained using a stratified and clustered household probability sampling approach, we used probability weights for the population-based analyses. Probability weights based on maternal demographic characteristics were available in the CNLSY and we adjusted the weights for the sample used in this study.

Measures

See Table I for the descriptive summary of measures in the study. Mothers reported on their age at childbearing, as well as the birth weight and GA of each of their offspring**.** In 2004 the women reported their highest level of education (i.e., the number of years of school completed). When the women were 30 years old, family income was assessed based on income from all adults in the household at that time point. In 1980, the women completed the Armed Services Vocational Aptitude Battery of intellectual assessment. When the women were between 15 and 22 years old, the Self-Reported Delinquency (SRD) interview (Elliott & Huizinga, 1983) was used to assess their participation in 12 delinquent behaviors. In 1992, the women completed the Center for Epidemiological Studies-Depression (CES-D; Randloff, 1977) measure to assess symptoms of depression. In 1994, alcohol abuse and dependency symptoms were assessed and the sum of reported symptoms was used to evaluate women's lifetime history of alcohol use and dependence.

Covariates included in the analyses were offspring birth order (first, second, third, or fourth birth or higher), maternal education (less than 12 years, 12 years or more, or 16 years or more), maternal race (Hispanic, African American, or white, non-Hispanic), maternal delinquency (categorized into low, medium or high), maternal depression (categorized into low, medium or high), any maternal lifetime alcohol use and dependency, maternal intelligence (categorized into low, medium or high), and household income in 1986 dollars measured when the mothers were 30 years old (categorized into low, medium or high). Additionally, maternal age at first childbirth was included as a covariate in a sensitivity analysis to test carry-over effects. Missingness indicators were included for covariate variables with missing data.

Analyses

Main Analyses

All main analyses used linear regression models to evaluate the association of MAC with GA and BWGA. Because we used BWGA as a proxy for fetal growth, all models predicting birth weight included gestational age and gestational age squared as covariates. In the Swedish sample, we first fit models using MAC categorized into 6 groups, with 25 to 29 years of MAC designated as the reference group, to predict continuous measures of GA and birth weight. Using the categorical designation for MAC enabled us to explore complex non-linear associations, particularly when exploring association with very young (e.g., teenage) and advanced (e.g., greater than 40 years) MAC. For both the Swedish and U.S. samples, we also fit quadratic models using continuous variables of MAC (centered at 25 years) and MAC squared. Using the continuous designation of MAC provided more statistical power, which was particularly important for the analyses of the CNLSY dataset. Every model included offspring birth order to adjust for the well-established associations with perinatal outcomes (Astolfi & Zonta, 1999; Swamy, Edwards, Gelfand, James, & Miranda, 2012).

Model 1 provided baseline estimates of the association between MAC and each outcome in the population. We present the results in meaningful units (i.e., the unstandardized estimates are in units of weeks for gestational age or grams for birth weight). To provide further insight about the magnitude of these associations, we also report unbiased effect size estimates using Hedges' g, which is a standardized measure that takes into account sample size (Hedges & Olkin, 2014; Hedges & Vevea, 1998). In Model 2 the population association was adjusted for all available measured covariates. Model 3 compared all differentially exposed cousin pairs, defined as pairs of offspring who shared a maternal grandmother identifier, but differed on the maternal identifier, while controlling for all available measured covariates not shared by cousins (i.e., we excluded race as a covariate in the U.S. analyses because all cousins' mothers shared the same

race in the U.S. sample). The model included cousin pair means and within cousin pair deviation scores for all predictor variables in the model. Thus, Model 3 examined the association between MAC and perinatal outcomes while adjusting for all measured covariates that may differ between pairs of cousins and unmeasured covariates that are constant within pairs of cousins. Lastly, Model 4 compared all differentially exposed siblings defined using maternal identifiers, while controlling for all available measured covariates that may differ among siblings (i.e., birth order in the U.S. sibling comparison and birth order and paternal covariates in the Swedish sibling comparison). The model included a random intercept, nuclear family means, and within nuclear family deviation scores for all covariates in the model. Thus, Model 4 provided estimates of the associations adjusted for all measured covariates that may differ among siblings and all unmeasured covariates that are constant within groups of siblings. (For additional details about fixed-effects estimation see Allison, 2009.)

Sensitivity Analyses

First, in order to test carry-over effects, we excluded first-born offspring and fit a model that controlled for maternal age at *first* childbirth while estimating the associations with MAC for each later-born child in both the Swedish and U.S. samples. Second, to test whether the associations may be due to birth cohort effects we fit a population model in both samples that controlled for offspring year of birth. Offspring year of birth was not included in the main analyses because differences in year of birth would be almost perfectly correlated with differences in MAC in the sibling comparison models. Third, in the Swedish sample we estimated the population and sibling comparison models without parental covariates to explore the role of unmeasured confounding and the role of measured paternal covariates. Fourth, to provide an additional test of the influence of birth order, we fit a cousin comparison restricted to

first-born individuals in the Swedish sample. Finally, to further examine the clinical significance of the findings, in the Swedish sample we fit Models 1 through 4 using the categorized MAC predictors to predict the log-odds of preterm birth (PTB), which we defined as GA less than 37 weeks.

Results

For each outcome (GA and BWGA) we first present the categorical MAC results from the Swedish analyses, then the continuous MAC results from the Swedish analyses, and finally the continuous MAC results from the U.S. analyses. Because different patterns of findings emerged for young and advanced MAC, we present the findings for each separately.

Gestational Age

Early MAC

Categorical Analyses for Early MAC *in Sweden.* (See Table II and the first row of Figure 1). The population model (Model 1) showed that younger MAC was associated with shorter GA. GA of offspring born to teenage mothers was, on average, 0.09 weeks less than the GA of offspring born to 25 to 29 year old mothers. It is important to note, however, that the effect size for this group difference was small (Hedges' g = 0.05). Unlike Model 1, which suggested that younger MAC was associated with shorter GA, the adjusted population model (Model 2), showed a slight positive association with younger MAC. The cousin comparison model (Model 3) also showed a small positive association between younger MAC and GA. For example, Model 3 showed that the GA of offspring born to teenage mothers was, on average, 0.03 weeks longer than the GA of offspring born to 25 to 29 year old mothers. Similarly, the sibling comparison model (Model 4) showed younger MAC was associated with a slightly longer GA. Thus, the results from models that controlled for measured covariates, and compared differentially exposed

cousins and siblings, respectively, suggested that confounding factors account for the observed association between younger MAC and shorter GA in the population.

Continuous Analyses for Early MAC *in Sweden.* (See Table II and the middle row of Figure 1). Results from the quadratic models fit to the continuous measurement of MAC were comparable to the categorical results. In Model 1, younger MAC was associated with shorter GA. The model that controlled for measured covariates (Model 2) showed little association between younger MAC and GA. The models that compared differentially exposed cousins (Model 3) and siblings (Model 4), however, found that younger MAC was associated with a slightly longer GA, though the magnitude of the association was small.

Continuous Analyses for Early MAC *in the U.S.* (See Table II and the bottom row of Figure 1). The population-wide model (Model 1) showed a curvilinear association between MAC and GA for younger MAC, such that there was a peak in GA at about 20 years of MAC. The effect size for the group difference between GA of offspring born to teenagers and offspring born to 20 to 29 year old women was small (-0.10 weeks; Hedges' g = 0.04). Furthermore, the adjusted population model (Model 2), the cousin comparison model (Model 3), and the sibling comparison model (Model 4) all showed similar results as Model 1 and suggested that younger MAC was, if at all, weakly associated with GA.

Summary of Analyses for Early MAC and GA. In Sweden, there was a small population-wide association between early MAC and shorter GA; however, once measured covariates and shared familial factors were accounted for there no longer was an association between early MAC and shorter GA. In all four models fit to the U.S. dataset, there were weak associations between early MAC and GA. Thus, these findings do not provide support for a causal association between early MAC and shorter GA.

Advanced MAC

Categorical Analyses for Advanced MAC *in Sweden.* (See Table II and the first row of Figure 1). The population model (Model 1) showed that advanced MAC was associated with shorter GA. GA of offspring born to 30 to 34 year old mothers (-0.04 weeks; Hedges' g = 0.03), 35 to 39 year old mothers (-0.16 weeks; Hedges' g = 0.10), and mothers 40 years or older (-0.35 weeks; Hedges' g = 0.22) were all less than GA of offspring born to 25 to 29 year old mothers. Results from the adjusted population model (Model 2) were similar to results from Model 1, indicating the association of shorter GA with advancing maternal age was robust to the influence of the measured covariates. Results from the cousin comparison (Model 3) and sibling comparison (Model 4) models were similar to results from the previous models, indicating the association was independent of measured covariates and unmeasured familial factors.

Continuous Analyses for Advanced MAC *in Sweden.* (See Table II and the middle row of Figure 1). The population model (Model 1) showed that older MAC was associated with shorter GA. This association remained robust in the adjusted population model (Model 2), in the cousin comparison model (Model 3), and in the sibling comparison model (Model 4).

Continuous Analyses for Advanced MAC *in the U.S.* (See Table II and the bottom row of Figure 1). The population model (Model 1) indicated that advancing MAC was strongly associated with shorter GA, and the magnitude of the association was larger than in the Swedish sample. For example, the effect size for the group difference between GA of offspring born to women 30 years or over and offspring born to women 20 to 29 years old was moderate (-0.45 weeks; Hedges' g = 0.22). The adjusted population model (Model 2), the cousin comparison model (Model 3), and the sibling comparison model (Model 4) all showed a relatively strong associations between advanced MAC and shorter GA. Thus, the results indicated that the

association between advancing MAC and shorter GA was robust to the measured covariates and unmeasured shared familial factors, consistent with the results from the Swedish dataset.

Summary of Analyses for Advanced MAC and GA. In both the U.S. and the Swedish analyses there was a strong population-wide association between advanced MAC and shorter GA. This association remained robust in models that accounted for measured covariates and unmeasured shared familial factors. Thus, the results from these analyses provide support for a causal association between advanced MAC and shorter GA.

Birth Weight for Gestational Age

Early MAC

Categorical Analyses for Early MAC *in Sweden.* (See Table II and the first row of Figure 2). The population model (Model 1) showed that younger MAC was associated with lower BWGA. For example, BWGA of offspring born to 25 to 29 year old mothers and BWGA of offspring born to teenage mothers was, on average, 45.45 grams less than the BWGA of offspring born to 25 to 29 year old mothers (Hedges' g = 0.25). However, the adjusted population model (Model 2) showed little indication of an association between young MAC and BWGA. The cousin comparison (Model 3) indicated that offspring born to teenage mothers were on average slightly heavier (i.e., 3.79 grams) when controlling for factors shared by cousins. The sibling comparison (Model 4) indicated that a sibling born to a mother when she was younger, particularly a teenager (i.e., 25.93 grams), tended to have slightly higher BWGA, than a sibling born to the same mother when she was 25 to 29 years old.

Continuous Analyses for Early MAC *in Sweden.* (See Table II and the middle row of Figure 2). The population model (Model 1) suggested that younger MAC was associated with lower BWGA. However, the adjusted population model (Model 2) showed little association

between younger MAC and BWGA. The cousin comparison (Model 3) also showed that the association was attenuated compared to Model 1 and the sibling comparison (Model 4) showed a slight positive association between younger MAC and BWGA.

Continuous Analyses for Early MAC *in the U.S.* (See Table II and the bottom row of Figure 2). The population model, (Model 1) suggested that younger MAC was associated with lower BWGA. For example, the effect size for the group difference between BWGA of offspring of teenage mothers and offspring of 20 to 29 year old mothers was moderate (-149.15 grams; Hedges' g = 0.25). The adjusted population model (Model 2) showed that younger MAC was associated with lower BWGA; however, this association was attenuated compared to Model 1. The cousin comparison model (Model 3) also showed that earlier MAC was associated lower BWGA. However, the sibling comparison (Model 4) showed little association between early MAC and BWGA.

Summary for Early MAC and BWGA. In both samples there was a population-wide association between early MAC and lower BWGA. However, once familial factors were accounted for, there was little association between early MAC and lower BWGA. Thus, these results do not provide support for a causal association between early MAC and lower BWGA.

Advanced MAC

Categorical Analyses for Advanced MAC *in Sweden.* (See Table II and the first row of Figure 2). The population model (Model 1) showed that there was a small association between advancing MAC and BWGA, suggesting that offspring born to 30 to 34 year old mothers (14.07 grams; Hedges' g = 0.05), to 35 to 39 year old mothers (14.5 grams; Hedges' g = 0.04), and to 40 year old or older mothers (4.62 grams; Hedges' g = 0.02) had slightly higher BWGA than offspring born to 25 to 29 year old mothers. In the adjusted population model (Model 2), these

differences were largely attenuated. The cousin (Model 3) and sibling comparisons (Model 4) showed a similar pattern of result—advancing MAC was not strongly associated with BWGA.

Continuous Analyses for Advanced MAC *in Sweden.* (See Table II and the middle row of Figure 2).The population model (Model 1) showed that for older MAC there was a curvilinear association between MAC and BWGA, such that BWGA peaked for offspring born to mothers in their mid thirties and decreased for both offspring born to younger mothers and for offspring born to older mothers. While Model 1 suggested an association between advanced MAC and BWGA, the model that adjusted for numerous measured covariates (Model 2) did not. The cousin and sibling comparisons (Models 3 and 4, respectively) showed similar patterns of results as Model 2.

Continuous Analyses for Advanced MAC *in the U.S.* (See Table II and the bottom row of Figure 2). The population model (Model 1) showed a curvilinear association between MAC and BWGA for older MAC, such that BWGA peaked for offspring born to mothers in their early to mid thirties and then following this period advancing MAC was associated with lower BWGA. Still, associations were weak; the effect size for the group difference between BWGA of offspring born to women 30 years or over and offspring born to women 20 to 29 year old was small (35.25 grams; Hedges' g = 0.06). Similar to Model 1, the adjusted population model (Model 2) and the cousin comparison (Model 3) showed advancing MAC was inversely associated with BWGA, although the confidence intervals were wide. However, unlike the previous models, the sibling comparison (Model 4) indicated that advancing MAC was not associated with lower BWGA.

Summary for Advanced MAC and BWGA. The population models showed a weak association between advanced MAC and BWGA. However, once familial confounding was

accounted for, there was little association between advanced MAC and BWGA. Thus, the results do not provide support for a causal association between advanced MAC and BWGA.

Sensitivity Analyses

First, we tested carry-over effects (i.e., the influence of maternal age of first childbearing on later-born offspring) in both samples by restricting the samples to second- and later-born offspring and including maternal age at first childbearing as a covariate (see Appendix A). These results suggested that, in general, maternal age at first childbearing did not account for the population-wide associations with MAC, although maternal age at first childbearing may partially account for the population-wide association between younger MAC and BWGA. Second, we tested the influence of birth cohort effects in both samples by including year of birth in a population-wide model (see Appendix B). The population–wide associations were similar in models that did and did not include offspring year of birth as a covariate, suggesting that MAC associations with year of birth are unlikely to change the interpretation of the main results. Third, to assess the possible influence of paternal covariates, which we could not control for in the U.S. analyses, we fit Swedish population models and Swedish sibling models without paternal covariates and compared the results of these models to Swedish models that did include paternal covariates (see Appendix C). The patterns of results were similar, suggesting that measured paternal covariates did not account for the associations of MAC in the Swedish sample. Fourth, to test birth order effects, we conducted cousin comparisons on a subsample of the Swedish data consisting of only first-born individuals (see Appendix D). The results from these analyses showed the same patterns as the results from the full-cousin comparisons, suggesting that the associations of MAC with GA and with BWGA were not due to birth order effects. Lastly, we examined a dichotomized clinical outcome (i.e., PTB) using the same models that we used in the

main analyses (see Appendix E). The results were consistent with the results we observed for the GA findings. After adjusting for measured covariates and unmeasured shared familial factors, younger MAC was not associated with PTB; however, advancing MAC was associated with increased risk for PTB. Thus, these results provide support for a causal association between advanced MAC and PTB and suggest that early MAC is not causally linked to PTB.

Discussion

Consistent with previous research we found younger MAC was associated with shorter GA and lower BWGA in both samples, although the magnitudes of the associations were relatively small. The results of models that controlled for measured covariates and unmeasured confounds shared by cousins and siblings in both datasets suggested that early MAC is unlikely to cause shorter GA and lower fetal growth, which is consistent with few extant genetically informed studies that have explored these associations (Geronimus & Korenman, 1993; Rosenzweig & Wolpin, 1995). As such, the results of our analyses suggest that younger MAC does not have a causal effect on these perinatal outcomes.

The results of the population estimates from both samples, as well as models that accounted for measured and unmeasured confounds, indicated that advanced MAC was not highly associated with BWGA. However, our population estimates suggest that advancing MAC was associated with shorter GA. Furthermore, the association was robust to the influence of the measured covariates, as well as the genetic and environmental factors shared by cousins and siblings. The model fitting results in both samples, therefore, are consistent with a causal association (assuming no residual confounding) between advanced MAC and shorter GA. The results from the sensitivity analyses predicting PTB showed that, even after adjusting for measured covariates and unmeasured familial confounding, advanced MAC was associated with

PTB (see Table EI and Figure E1); thus, indicating that the independent association between advanced MAC and shorter GA is clinically significant. Our findings add to and extend the findings from other epidemiologic studies exploring the association between advancing MAC and GA (Balasch & Gratacos, 2012; Carolan, 2013; Cnattingius et al., 1992; Newburn-Cook & Onyskiw, 2005; Odibo et al., 2006).

There were several strengths to our study. We conducted analyses of two samples, which allowed us to show that the findings generalized across samples with different cultures, races, ethnicities, economic backgrounds, and health care coverage. Furthermore, our sample sizes were large, especially the Swedish sample, which enabled us to obtain more precise estimates of the magnitude of the associations. We also examined both early and advanced MAC. To our knowledge, no previous study had evaluated the association of advanced MAC with perinatal outcomes using genetically informed designs. Additionally, we were able to include numerous covariates, especially in the Swedish analyses in which we adjusted for paternal covariates in addition to offspring and maternal covariates. We also used multiple genetically informed models and tested many alternative hypotheses that could explain the results we presented in the main analyses (see Appendix A through E). In particular, we assessed whether carry-over effects (i.e., the influence of maternal age at first childbearing on later-born children), birth cohort effects (i.e., offspring year of birth), measured paternal factors, or birth order effects explained our results. We also fit the same models we used in the main analyses to predict a dichotomized clinical outcome (i.e., PTB).

There were limitations to our study, including that we did not have a measure of fetal growth, but rather used BWGA as a proxy for fetal growth. There were also limitations to our study that are inherent to cousin and sibling comparison designs. Comparisons of related

individuals, especially sibling comparisons, require large samples for adequate statistical power (Gauderman, Witte, & Thomas, 1999). The large Swedish dataset enabled us to obtain precise parameter estimates, but the confidence intervals around the estimates from the United States sample were large. Additionally, the results found in sibling and cousin comparisons may not generalize to other populations (e.g., to families with only one child). We, therefore, encourage researchers to use other research designs to study the mechanisms behind the associations between MAC and these perinatal outcomes. Sibling and cousin comparisons include an assumption of no carry-over effects. Although the results of our sensitivity analyses (see Appendix A) were generally not consistent with large carry-over effects, it is impossible to rule out such effects definitively. Furthermore, sibling and cousin comparisons cannot account for factors that vary within families, which could confound the associations, and, perhaps, bias the estimates. In particular, it is impossible to disentangle associations with year of birth and MAC in sibling comparisons; though we also conducted additional analyses to explore this assumption (see Appendix B). We also included measured covariates to control for potential confounds that are not accounted for by sibling and cousin comparisons and ran a sensitivity analyses to explore the influence of paternal covariates (see Appendix C), but it is impossible to know if we have measured every salient confound that may differ within families. Therefore, we can only conclude that our finding that advancing MAC is associated with shorter GA independent of the measured covariates and genetic and environmental factors shared by siblings is consistent with a causal influence. Our interpretation is strengthened by our use of multiple genetically informed designs and analyses in two different datasets; however, we cannot definitively make conclusions about causal effects.

In sum, our findings suggested that small population-wide associations of young MAC with GA and fetal growth do not reflect a causal influence. As such, future studies should try to identify the familial confounding factors that account for the associations between young MAC and these perinatal outcomes. The observed associations with advancing MAC provide support (assuming no residual confounding) for a causal link between advancing MAC and shorter GA and suggest that research should explore the specific factors that account for or mediate the association between advanced MAC and shorter GA. Specifically, future research should try to identify factors that vary within siblings, are correlated with MAC, and are correlated with GA. Possible factors include maternal diseases (e.g., hypertension or diabetes; Balasch & Gratacos, 2012) or quantity of oxygen and nutrients received during the prenatal period (Gibbs et al., 2012; Odibo et al., 2006). Furthermore, even though we did not find evidence that offspring year of birth influenced the association between MAC and these outcomes, future research should explore potential cohort effects in more detail, especially given that societal changes related to childbearing may have occurred over time.

Many studies are now exploring the consequences of prenatal risks, such as short gestation and low fetal growth. The results from the current study highlight the importance of considering the genetic and environmental origins of these factors because these perinatal outcomes do not occur at random.

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Table I.

Demographic Characteristics

	Swedish	U.S.
	Mean (SD)	Mean (SD)
Offspring birth weight (grams)	3533.2 (551.5)	3312.2 (596.7)
Offspring gestational age (weeks)	39.5 (1.8)	38.68 (2.2)
Maternal age at childbearing (years)	28.4 (5.2)	24.6 (5.5)
Maternal age at first childbirth (years)	25.6 (4.7)	21.7 (4.9)
Paternal age at childbearing (years)	31.7 (6.1)	
	Range	Range
Offspring year of birth	1973 - 2008	1972-2008
	N (%)	N (%)
Preterm birth	158,361 (4.8%)	
Small for gestational age	93,881 (2.8%)	
Offspring sex (female)	1,625,715 (48.8%)	4,653 (48.9%)
Offspring birth order		
First born	1,410,452 (42.3%)	4377 (46.0%)
Second born	1,223,809 (36.7%)	3057 (32.1%)
Third born	496,570 (14.9%)	1392 (14.6%)
Fourth born or later	201,384 (6.0%)	692 (7.3%)
Maternal age at childbearing (years)		
<20	108,358 (3.3%)	
20 - 24	703,759 (21.1%)	
25 - 29	1,187,715 (35.6%)	
30 - 34	909,554 (27.3%)	
35 - 39	357,448 (10.7%)	
≥ 40	65,381 (2.0%)	
< 20		1830 (19.3%)
20 -29		5802 (61.0%)
≥ 30		1886 (19.8%)
Maternal education		
Primary and lower secondary education, less than 9 years	126,863 (3.8%)	
Primary and lower secondary education, 9 years	323,340 (9.7%)	
Upper secondary education, 1 – 2 years	1,016,477 (30.5%)	
Upper secondary education, 3 years	600,402 (18.0%)	
Post-secondary education, less than 3 years	489,316 (14.7%)	
Post-secondary education, 3 years or longer or postgraduate education	775,817 (23.3%)	
<12 years of education		740 (7.8%)
12 -15 years of education		5858 (61.6%)
≥16 years of education		2911 (30.6%)
Missing		9 (0.1%)

Maternal race		
Swedish nationality	2,866,506 (86.0%)	
White, Non-Hispanic		5123 (53.8%)
Hispanic		1775 (18.7%)
African American		2620 (27.5%)
Maternal delinquency		
Any maternal criminal conviction	381,897(11.46%)	
Low		2127 (22.4%)
Medium/ Low		2261 (23.8%)
Medium/ High		2258 (23.7%)
High		2350 (24.7%)
Missing		522 (5.5%)
Maternal mental health		
Severe psychiatric problems	55,847 (1.68%)	
Maternal depression - Low		1939 (20.4%)
Maternal depression - Medium/ Low		2044 (21.5%)
Maternal depression - Medium/ High		1897 (19.9%)
Maternal depression - High		1828 (19.1%)
Maternal depression - Missing		1810 (19.0%)
Any maternal suicide attempts	85,906 (2.58%)	
Maternal substance abuse requiring inpatient care	68,256 (2.05%)	
Maternal alcohol abuse/ dependency - None		4999 (52.5%)
Maternal alcohol abuse/ dependency - Any		2663 (28.0%)
Maternal alcohol abuse/ dependency - Missing		1856 (19.5%)
Maternal IQ		
Low		2347 (24.7%)
Medium/ Low		2239 (23.5%)
Medium/ High		2261 (23.8%)
High		2220 (23.3%)
Missing		451 (4.7%)
Family income		
Low		1970 (20.7%)
Medium/ Low		2009 (21.1%)
Medium/ High		2009 (21.1%)
High		2026 (21.3%)
Missing		1504 (15.8%)
Paternal age at childbearing (years)		
<20	24,409 (0.7%)	
20 - 24	364,051 (10.3%)	
25 - 29	1,008,727 (30.5%)	
30 - 34	982,105 (29.7%)	
35 - 39	561,687 (16.9%)	
$\geq$ 40	296,486 (8.9%)	
Missing	26,622 (0.8%)	
Paternal nationality Swedish	2,834,493 (84.8%)	
Paternal nationality missing	26,622 (0.8%)	

Paternal education	
Primary and lower secondary education, less than 9 years	220,010 (6.6%)
Primary and lower secondary education, 9 years	419,260 (12.6%)
Upper secondary education, 1 – 2 years	1,079,015 (32.4%)
Upper secondary education, 3 years	546,476 (16.4%)
Post-secondary education, less than 3 years	432,402 (13.0%)
Post-secondary education, 3 years or longer or postgraduate education	590, 405 (17.7%)
Paternal education missing	44,647 (1.3%)
Any paternal criminal conviction	1,275,462(38.9%)
Paternal criminal conviction missing	18 (0.0%)
Severe paternal psychiatric problems	52,980 (1.6%)
Severe paternal psychiatric problems	42 (0.0%)
Paternal substance abuse requiring inpatient care	129,380 (3.9%)
Paternal substance abuse requiring inpatient care missing	39 (0.0%)
Any paternal suicide attempts	61,328 (1.8%)
Any paternal suicide attempts missing	448 (0.0%)

Note. Total offspring in Swedish sample = 3,332,215. Total offspring in U.S. sample = 9,518. All percentages are based on the number of offspring.

Table II.

Main Analyses

	Model 1			Model 2			Model 3			Model 4		
	b	*LCL*	*UCL*	*b*	*LCL*	*UCL*	*b*	*LCL*	*UCL*	*b*	*LCL*	*UCL*
GA[a] (in weeks)												
Sweden												
Binned MAC[b]												
< 20	-0.09	-0.10	-0.08	0.02	0.01	0.03	0.03	0.01	0.06	0.07	0.05	0.08
20 - 24	-0.01	-0.02	-0.01	0.03	0.02	0.04	0.03	0.01	0.04	0.03	0.02	0.04
25 - 29	ref			ref			ref			ref		
30 - 34	-0.04	-0.05	-0.04	-0.06	-0.06	-0.05	-0.04	-0.05	-0.03	-0.05	-0.05	-0.04
35 - 39	-0.16	-0.17	-0.16	-0.17	-0.17	-0.16	-0.10	-0.12	-0.08	-0.17	-0.18	-0.16
≥ 40	-0.35	-0.37	-0.34	-0.35	-0.36	-0.33	-0.19	-0.23	-0.16	-0.36	-0.38	-0.34
Continuous												
MAC[b]	0.00	0.00	0.01	-0.01	-0.01	-0.01	-0.02	-0.02	-0.01	-0.02	-0.02	-0.01
MAC[2 b]	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U.S.												
Continuous												
MAC[b]	-0.03	-0.04	-0.02	-0.04	-0.05	-0.03	-0.02	-0.05	0.00	-0.01	-0.04	0.02
MAC[2 b]	0.00	0.00	0.00	0.00	0.00	0.00	-0.00	-0.01	0.00	0.00	0.00	0.00
BWGA[c] (in grams)												
Sweden												
Binned analyses												
MAC[b]												
< 20	-45.45	-48.29	-42.60	3.88	0.69	7.08	3.79	-2.54	10.12	25.93	22.23	29.63
20 - 24	-23.37	-24.71	-22.02	-2.15	-3.63	-0.68	-3.58	-6.58	-0.57	2.31	0.54	4.08
25 - 29	ref			ref			ref			ref		
30 - 34	14.07	12.83	15.32	3.47	2.13	4.81	1.69	-1.19	4.56	8.45	6.76	10.14
35 - 39	14.52	12.79	16.26	2.41	0.46	4.37	-1.90	-6.35	2.55	11.59	8.77	14.40
≥ 40	4.62	1.02	8.22	-3.76		0.04	-19.51	-27.81	-10.21	6.39	1.37	11.42
Continuous												
MAC[b]	5.02	4.86	5.19	0.40	0.19	0.62	0.93	0.44	1.41	-1.09	-1.46	-0.72
MAC[2 b]	-0.23	-0.25	-0.22	-0.02	-0.04	0.00	0.00	-0.04	0.03	0.12	0.10	0.14
U.S.												
Continuous												
MAC[b]	13.21	10.15	16.27	4.74	1.27	8.20	8.20	2.87	13.52	5.37	0.10	10.64
MAC[2 b]	-0.88	-1.23	-0.53	-0.46	-0.80	-0.11	-1.06	-1.65	-0.47	0.04	-0.33	0.40

Note. Model 1 is a population model, which controlled for offspring birth order. Model 2 is a population model, which controlled for all available covariates. Model 3 is a cousin comparison model, which controlled for all available covariates (except for maternal race in the U.S. analyses). Model 4 is a sibling comparison model, which controlled for offspring birth order in both samples as well as paternal covariates in the Swedish sample. LCL = lower confidence limit. UCL = upper confidence limit. [a]GA = gestational age. [b]MAC = maternal age at childbearing. MAC was centered at 25 years in the continuous analyses. [c]BWGA = birth weight adjusted for gestational age. BWGA was defined as birth weight adjusted for gestational age and gestational age squared.

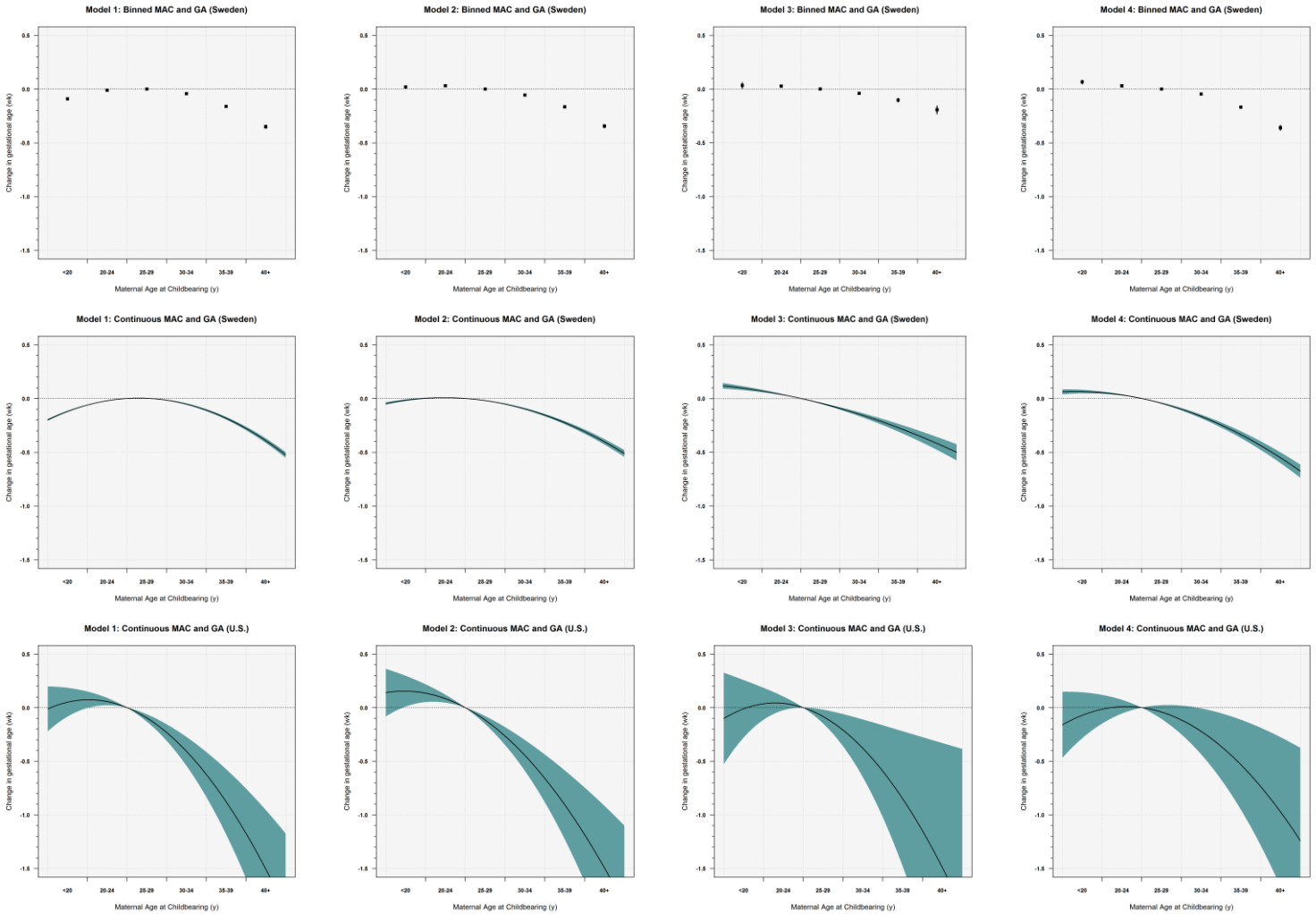

Figure 1. Gestational age. Model 1 is a population model, which controlled for offspring birth order. Model 2 is a population model, which controlled for all available covariates. Model 3 is a cousin comparison model, which controlled for all available covariates (except for maternal race in the U.S. analyses). Model 4 is a sibling comparison model, which controlled for offspring birth order in both samples as well as paternal covariates in the Swedish sample. Ninety-five percent confidence intervals are shown for the binned Swedish models. The shaded regions on the Swedish and U.S. continuous models represent 95% confidence intervals.

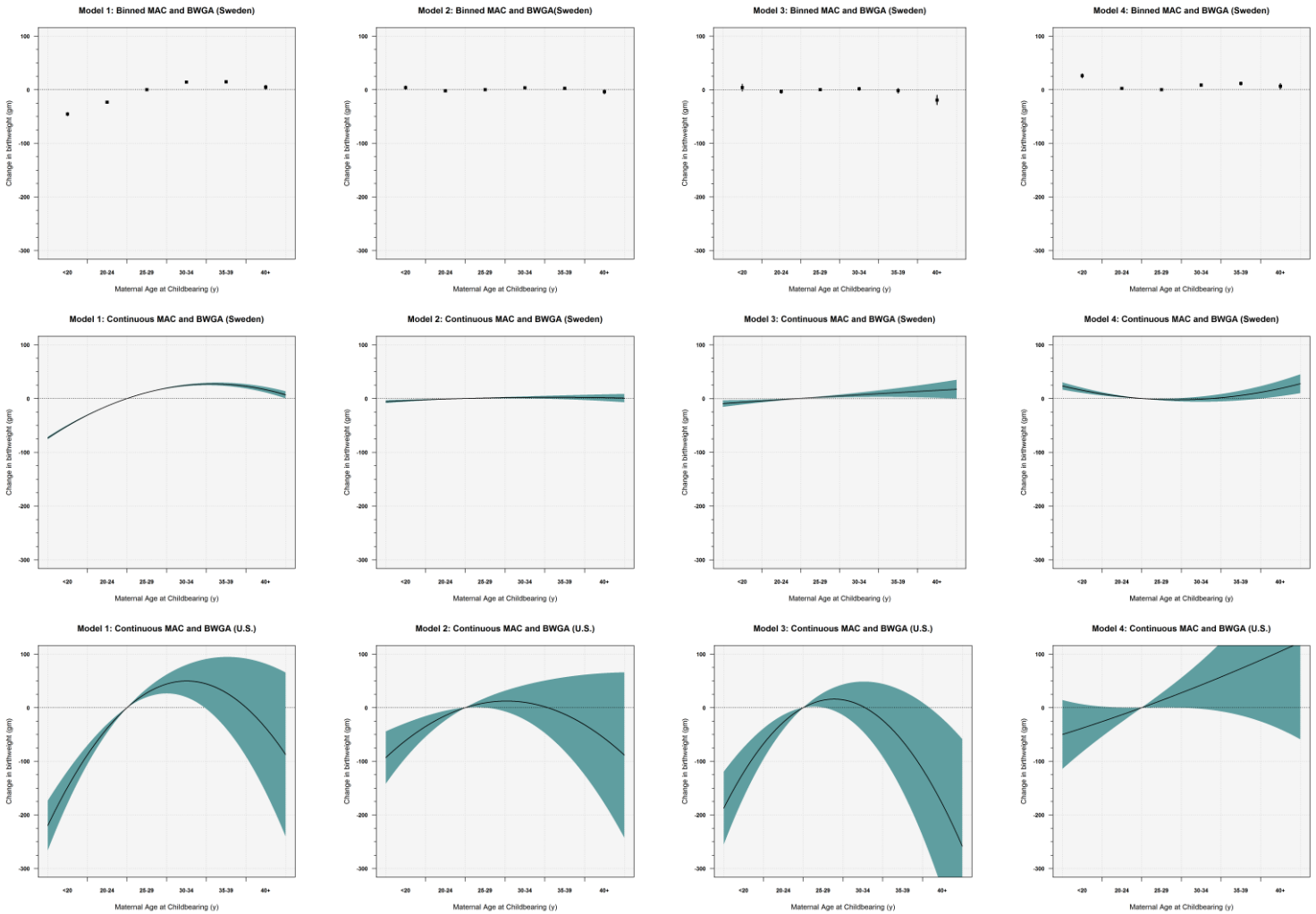

Figure 2. Birth weight for gestational age. Model 1 is a population model, which controlled for offspring birth order. Model 2 is a population model, which controlled for all available covariates. Model 3 is a cousin comparison model, which controlled for all available covariates (except for maternal race in the U.S. analyses). Model 4 is a sibling comparison model, which controlled for offspring birth order in both samples as well as paternal covariates in the Swedish sample. Ninety-five percent confidence intervals are shown for the binned Swedish models. The shaded regions on the Swedish and U.S. continuous models represent 95% confidence intervals.

Appendix A

In order to test carry-over effects, we fit a model that controlled for maternal age at *first* childbirth and birth order in a subsample of the data that excluded first-born offspring. We compared the results from this model to Model 1, the population model, which only controlled for birth order (see Figure A1 and A2). In general, the analyses controlling for maternal age at first childbirth (shown in the second column of Figure A1 and A2) were consistent with the results in the main text. The models showed a similar pattern of results for the association between MAC and GA, suggesting that differences in GA among offspring were not due to when a woman had her first child. Furthermore, the models showed similar results for the association between older MAC and BWGA. However, including maternal age at first childbirth as a covariate slightly attenuated the associational between younger MAC and BWGA, suggesting that maternal age at first childbirth may partially account for the observed population-wide association between younger MAC and BWGA.

Table AI.

Test of Carry-Over Effects

	b	*LCL*	*UCL*
GA[a] (in weeks)			
Sweden			
Binned MAC[b]			
< 20	-0.26	-0.30	-0.22
20 - 24	-0.02	-0.03	-0.02
25 -29	ref		
30 - 34	-0.05	-0.06	-0.05
35 - 39	-0.15	-0.16	-0.14
≥ 40	-0.30	-0.32	-0.28
U.S.			
Continuous			
MAC[b]	0.01	-0.04	0.05
MAC^{2} [b]	0.00	-0.01	0.00
BWGA[c] (in grams)			
Sweden			
Binned analyses			
MAC[b]			
< 20	-16.32	-26.04	-6.60
20 - 24	1.47	-0.85	3.79
25 -29	ref		
30 - 34	-5.85	-7.60	-4.11
35 - 39	-17.39	-19.90	-14.89
≥ 40	-29.52	-34.05	-24.99
U.S.			
Continuous			
MAC[b]	6.99	-4.20	18.18
MAC^{2} [b]	-0.57	-1.21	0.07

Note. LCL = lower confidence limit. UCL = upper confidence limit. [a]GA = gestational age. [b]MAC = maternal age at childbearing. MAC was centered at 25 years in the continuous analyses. [c]BWGA = birth weight adjusted for gestational age. BWGA was defined as birth weight adjusted for gestational age and gestational age squared.

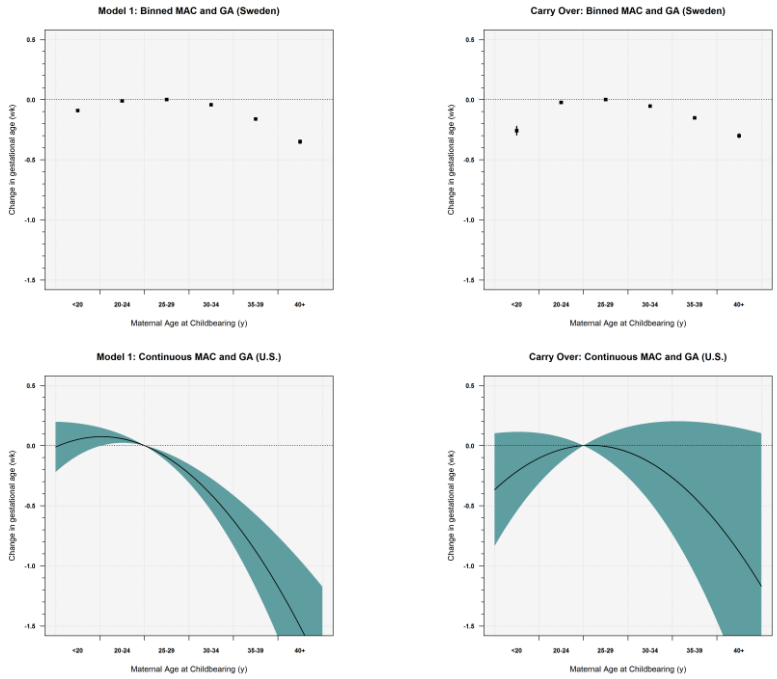

Figure A1. Gestational age. The first column shows Model 1, the population model that only controlled for offspring birth order. The second column shows models that controlled for maternal age at *first* childbirth and offspring birth order in a subsample of the data that excluded first-born offspring. Ninety-five percent confidence intervals are shown for the binned Swedish models. The shaded regions on the U.S. continuous models represent 95% confidence intervals.

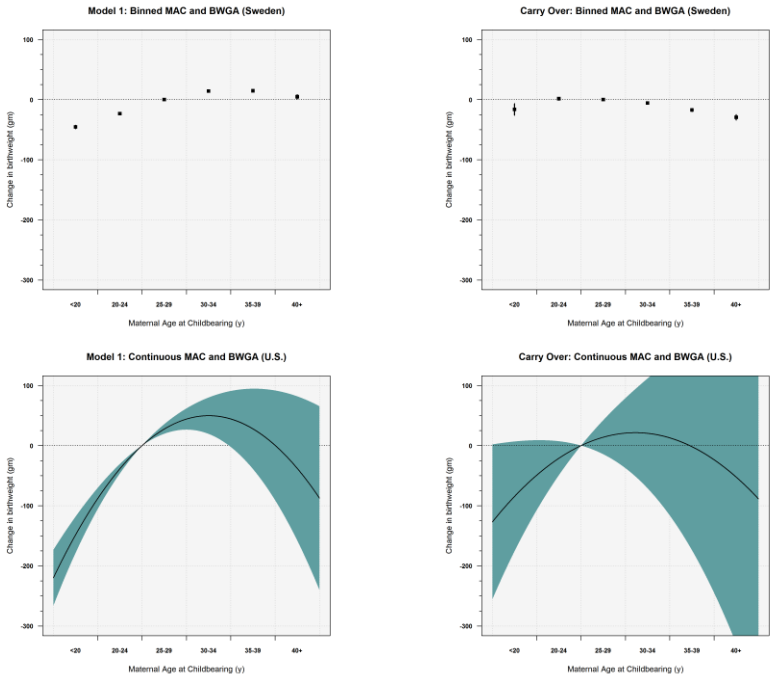

Figure A2. Birth weight for gestational age. The first column shows Model 1, the population model that only controlled for offspring birth order. The second column shows models that controlled for maternal age at *first* childbirth and offspring birth order in a subsample of the data that excluded first-born offspring. Ninety-five percent confidence intervals are shown for the binned Swedish models. The shaded regions on the U.S. continuous models represent 95% confidence intervals.

Appendix B

We did not include offspring year of birth as a covariate in the main analyses because differences in offspring year of birth would be almost perfectly correlated with differences in MAC in the sibling comparison models. Thus, in order to test whether associations may be due to birth cohort effects (i.e., changes in society that have occurred over time) we fit population models that controlled for offspring year of birth. The population-wide models with (shown in the second column of Figure B1 and B2) and without (shown in the first column of Figure B1 and B2) year of birth included as a covariate yielded the same pattern of results, suggesting that birth cohort effects did not bias our interpretation of the results in the main text.

Table BI.

Test of Birth Cohort Effects

	b	*LCL*	*UCL*
GA[a] (in weeks)			
Sweden			
Binned MAC[b]			
< 20	-0.14	-0.15	-0.13
20 - 24	-0.04	-0.04	-0.03
25 -29	ref		
30 - 34	-0.01	-0.02	-0.01
35 - 39	-0.11	-0.12	-0.11
≥ 40	-0.29	-0.31	-0.28
U.S.			
Continuous			
MAC[b]	0.00	-0.03	0.03
MAC^{2} [b]	0.00	-0.01	0.00
BWGA[c] (in grams)			
Sweden			
Binned analyses			
MAC[a]			
< 20	-24.55	-27.40	-21.71
20 - 24	-12.31	-13.66	-10.96
25 -29	ref		
30 - 34	1.34	0.09	2.59
35 - 39	-5.49	-7.24	-3.75
≥ 40	-18.44	-22.03	-14.84
U.S.			
Continuous			
MAC[b]	9.31	1.73	16.90
MAC^{2} [b]	-0.87	-1.23	-0.52

Note. LCL = lower confidence limit. UCL = upper confidence limit. [a]GA = gestational age. [b]MAC = maternal age at childbearing. MAC was centered at 25 years in the continuous analyses. [c]BWGA = birth weight adjusted for gestational age. BWGA was defined as birth weight adjusted for gestational age and gestational age squared.

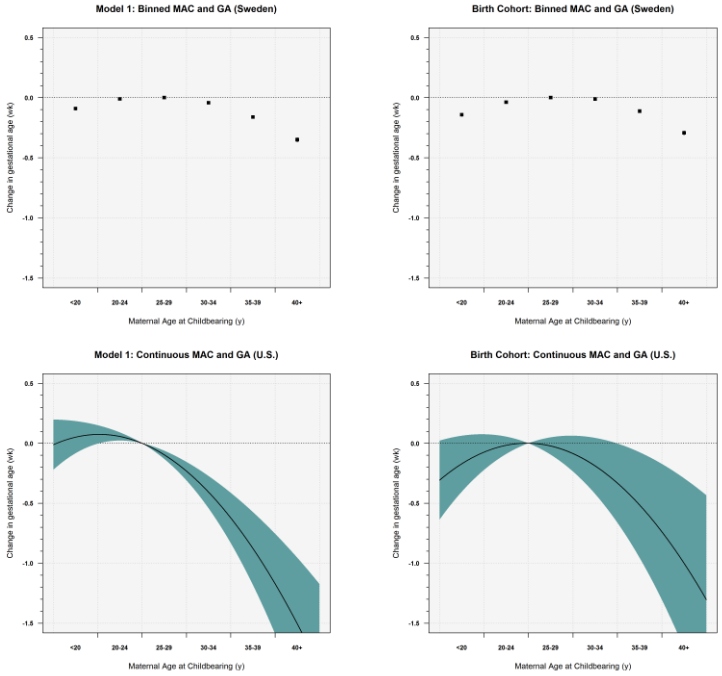

Figure B1. Gestational age. The first column shows Model 1, the population model that only controlled for offspring birth order. The second column shows population models, which controlled for offspring birth order and offspring year of birth. Ninety-five percent confidence intervals are shown for the binned Swedish models. The shaded regions on the U.S. continuous models represent 95% confidence intervals.

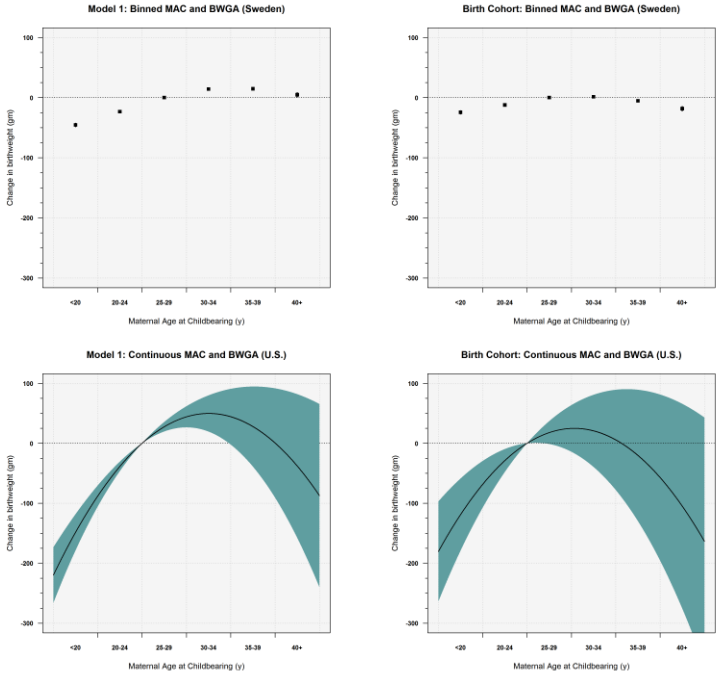

Figure B2. Birth weight for gestational age. The first column shows Model 1, the population model that only controlled for offspring birth order. The second column shows population models, which controlled for offspring birth order and offspring year of birth. Ninety-five percent confidence intervals are shown for the binned Swedish models. The shaded regions on the U.S. continuous models represent 95% confidence intervals.

Appendix C

We re-ran the adjusted population models (Model 2) and the sibling comparison models (Model 4) in the Swedish sample, leaving out paternal covariates to examine the role of measured paternal characteristics (see Figure C1 and C2 for population models and Figure C3 and C4 for sibling comparison models). The model provided us with some insight into the possible confounding roles of measured paternal factors, which we did not have access to in the US sample. The models without paternal covariates (see column two of Figure C1 to C4) showed the same patterns of findings as the models with paternal covariates (see column one of Figure C1 to C4), suggesting that measured paternal characteristics did not account for the results in the Swedish analyses.

Table CI.

	Population Model without Paternal Covariates			Sibling Comparison without Paternal Covariates		
	b	*LCL*	*UCL*	*b*	*LCL*	*UCL*
Gestational Age (in weeks)						
Binned MAC[a]						
< 20	-0.03	-0.04	-0.01	0.06	0.04	0.07
20 - 24	0.02	0.01	0.03	0.03	0.03	0.04
25 -29	ref			ref		
30 - 34	-0.06	-0.06	-0.05	-0.06	-0.06	-0.05
35 - 39	-0.18	-0.19	-0.17	-0.19	-0.20	-0.18
≥ 40	-0.37	-0.38	-0.35	-0.39	-0.41	-0.37
Fetal Growth[b] (in grams)						
Binned analyses MAC						
< 20	-9.55	-12.43	-6.67	27.61	24.21	31.01
20 - 24	-8.16	-9.52	-6.80	2.52	0.85	4.19
25 -29	ref			ref		
30 - 34	6.88	5.63	8.13	9.66	8.08	11.24
35 - 39	7.30	5.56	9.04	14.10	11.57	16.63
≥ 40	0.28	-3.31	3.87	10.06	5.39	14.72

Note. LCL = lower confidence limit. UCL = upper confidence limit. [a]GA = gestational age. [b]MAC = maternal age at childbearing. [c]BWGA = birth weight adjusted for gestational age. BWGA was defined as birth weight adjusted for gestational age and gestational age squared.

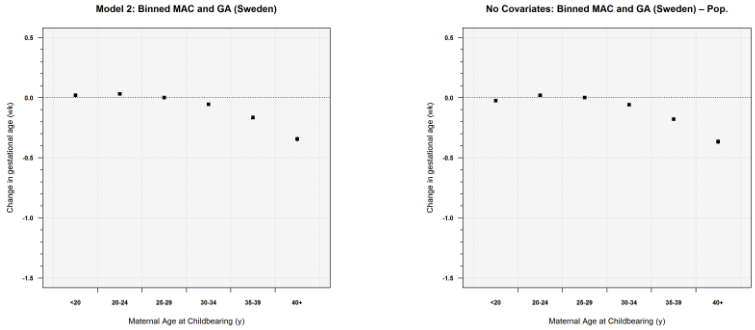

Figure C1. Gestational age. The first columns shows population models, which control for offspring, maternal, and paternal covariates. The second column shows population models, which controlled for offspring and maternal covariates; paternal covariates were not included. Ninety-five percent confidence intervals are shown.

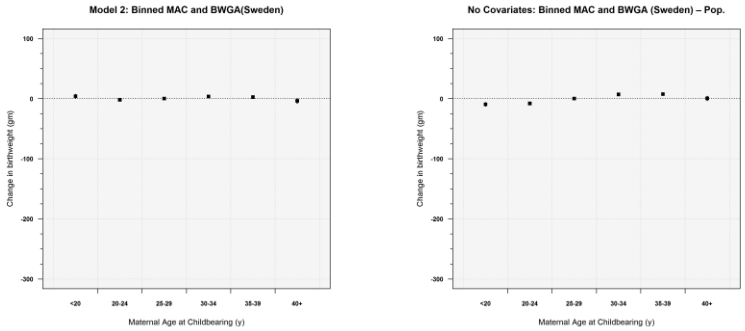

Figure C2. Birth weight for gestational age. The first columns shows population models, which control for offspring, maternal, and paternal covariates. The second column shows population models, which controlled for offspring and maternal covariates; paternal covariates were not included. Ninety-five percent confidence intervals are shown.

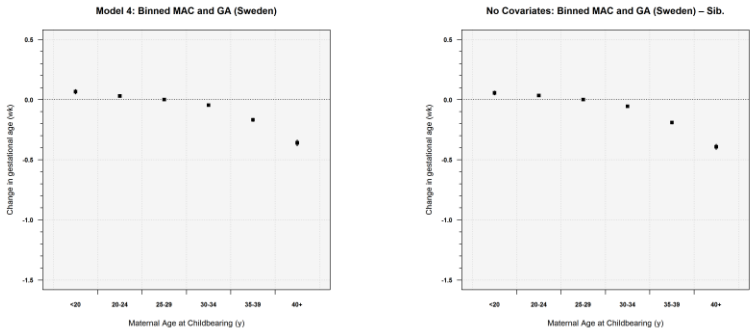

Figure C3. Gestational age. The first column shows sibling comparison models, which control for offspring birth order and paternal covariates. The second column shows sibling comparison models, which controlled for offspring birth order; paternal covariates were not included. Ninety-five percent confidence intervals are shown.

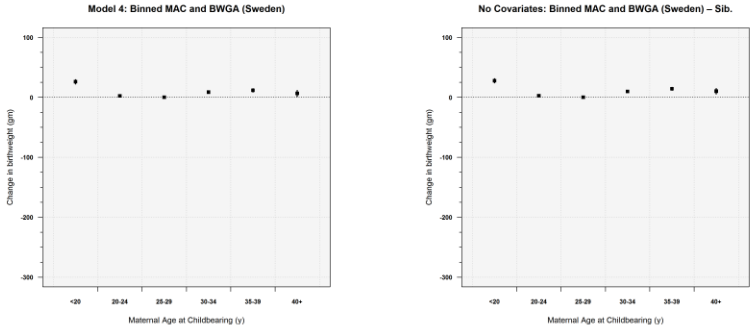

Figure C3. Birth weight for gestational age. The first column shows sibling comparison models, which control for offspring birth order and paternal covariates. The second column shows sibling comparison models, which controlled for offspring birth order; paternal covariates were not included. Ninety-five percent confidence intervals are shown.

Appendix D

Because GA and birth weight are correlated with birth order we fit a cousin comparison models restricted to the subsample of first-born individuals in the Swedish dataset (see Figure D1 and D2) to assess whether birth order may have influenced the main results. The first-born cousin comparisons (see column two of Figure D1 and D2) showed the same patterns of findings as the main analyses full-cousin comparisons (Model 3; see column one of Figure D1 and D2), suggesting that our main results were not due to birth order effects.

Table DI.

Test of Birth Order Effects

	b	*LCL*	*UCL*
GA[a] (in weeks)			
Binned MAC[b]			
< 20	0.12	0.09	0.16
20 - 24	0.09	0.07	0.11
25 -29	ref		
30 - 34	-0.04	-0.07	-0.02
35 - 39	-0.13	-0.17	-0.09
≥ 40	-0.30	-0.39	-0.21
BWGA[c] (in grams)			
Binned analyses MAC[b]			
< 20	-11.67	-18.61	-4.72
20 - 24	-2.89	-7.00	1.21
25 -29	ref		
30 - 34	-12.19	-17.05	-7.34
35 - 39	-22.98	-31.46	-14.50
≥ 40	-18.54	-38.32	1.23

Note. LCL = lower confidence limit. UCL = upper confidence limit. [a]GA = gestational age. [b]MAC = maternal age at childbearing. [c]BWGA = birth weight adjusted for gestational age. BWGA was defined as birth weight adjusted for gestational age and gestational age squared.

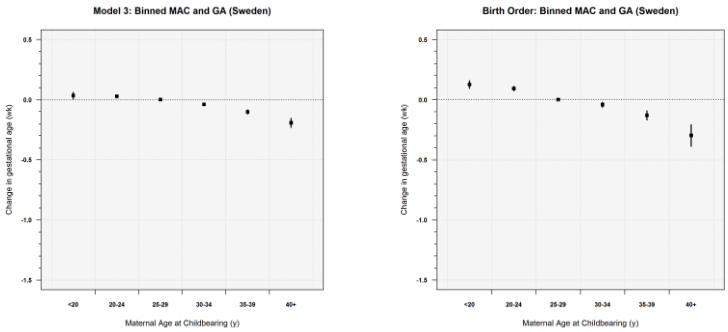

Figure D1. Gestational age. The first column shows the full-cousin comparison model and the second column shows the cousin comparison, which included only first-born cousins. Ninety-five percent confidence intervals are shown.

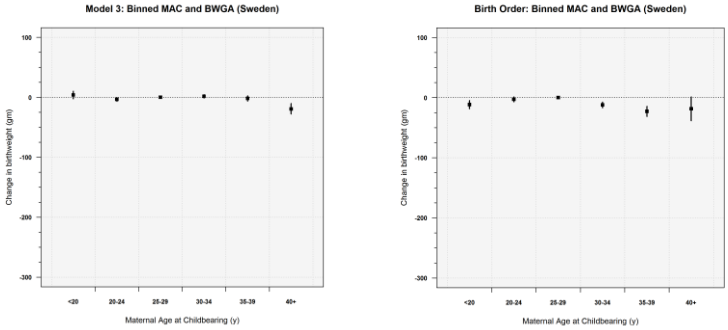

Figure D2. Birth weight for gestational age. The first column shows the full-cousin comparison model and the second column shows the cousin comparison, which included only first-born cousins. Ninety-five percent confidence intervals are shown.

Appendix E

To examine the clinical significance of the finding further, in the Swedish sample we re-ran models used in the main analyses to predict the log-odds of PTB (see Figure E1) and found that the results were consistent with the GA findings from the main analyses. The results suggested the observed population-wide association between early MAC and increased risk for PTB was confounded by familial factors. However, the association between advanced MAC and increased risk for PTB was observed in all models, thus, providing support for an association between advanced MAC and increased risk for PTB, independent of measured covariates and unmeasured shared familial factors.

Table EI.

	Population			Adjusted Population			Cousin Comparison			Sibling Comparison		
	OR	*LCL*	*UCL*	*OR*	*LCL*	*UCL*	*OR*	*LCL*	*UCL*	*OR*	*LCL*	*UCL*
PTB[a]												
Binned MAC[b]												
< 20	1.30	1.26	1.33	1.03	1.00	1.06	1.07	1.01	1.14	0.79	0.75	0.84
20 - 24	1.06	1.04	1.07	0.96	0.94	0.97	1.00	0.97	1.03	0.90	0.88	0.93
25 - 29	ref			ref			ref			ref		
30 - 34	1.06	1.05	1.08	1.10	1.09	1.12	1.06	1.03	1.09	1.12	1.09	1.15
35 - 39	1.29	1.27	1.31	1.33	1.30	1.36	1.21	1.16	1.27	1.41	1.35	1.47
≥ 40	1.53	1.48	1.59	1.54	1.49	1.60	1.32	1.21	1.44	1.77	1.64	1.91

Note. LCL = lower confidence limit. UCL = upper confidence limit. [a]PTB = preterm birth. [b]MAC = maternal age at childbearing.

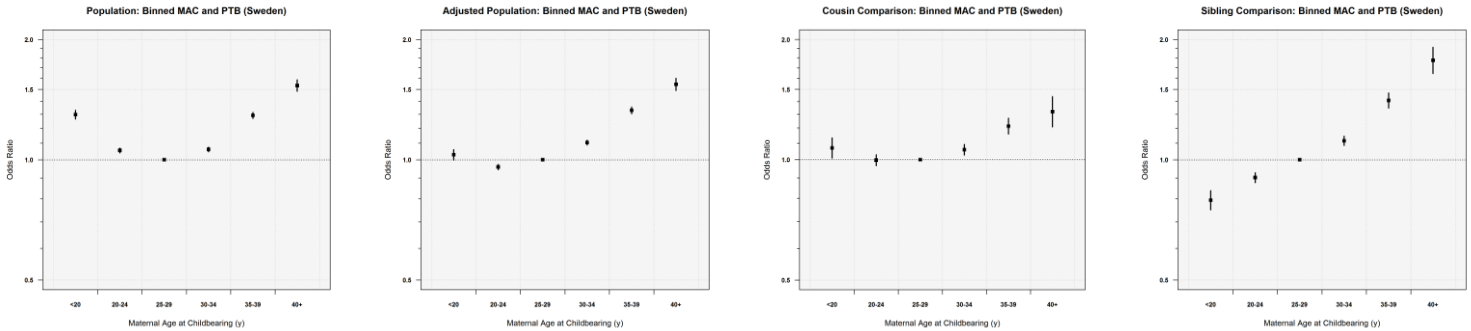

Figure E1. Preterm birth. Ninety-five percent confidence intervals are shown.