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Birthweight, time-varying adiposity growth and early menarche in girls: A Mendelian randomisation and mediation analysis

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ABSTRACT

Objective: To explore the causal effect of time-varying z-BMI growth on early menarche using Mendelian randomisation (MR); to identify critical adiposity predictors of early menarche; to compare the effects of birthweight and time-varying z-BMI growth as mediators of the path from genes to early menarche using mediation analysis.
Methods: We used data from the Taiwan Children Health Study with 21 obesity-related single-nucleotide polymorphisms (SNPs) to yield genetic (instrumental variable)IVs for adiposity. Children with available data on genotyping, birthweight, adiposity, and menarcheal age were included.
Results: In MR analyses, results based on the time-varying z-BMI growth show more statistical power and capture more information of adiposity growth ($p = 0.01$) than those based on single point z-BMI ($p = 0.02$). Among adiposity measures, critical predictors of early menarche are fat free mass (RR = 1.33, 95% CI 1.07–1.65) and waist/height ratio (RR = 1.27, 95% CI 1.03–1.56). Other potential predictors of early menarche are sum of skinfold (RR = 1.24, 95% CI 1.03–1.48) and total body fat (RR = 1.20, 95% CI 1.05–1.38). In both one-mediation and multi-mediation analyses, time-varying z-BMI growth in the prepubertal years plays a crucial mediator in the pathway from the genes to early menarche.
Conclusions: This study discovered that greater prepubertal adiposity growth is a crucial mediator in the path from genes to early menarche. For girls with genes positively associated with obesity; and/or of lower birthweight, a strategy to prevent childhood adiposity should be implemented in order to avoid early menarche development.

Introduction

Childhood obesity has been linked to early menarche, which further leads to health events in later life such as fertility impairment [1], cardiometabolic diseases [2], breast cancer [3] and mortality [4]. Many developed countries have rising trends of childhood obesity [5] and declining trends of age at menarche [6], leading to speculation that adiposity and sexual maturation may be causally related. While most observational studies have found that girls with large body weight in childhood experienced an earlier age of menarche [7–9], the pathway from genes to early menarche via birthweight and adiposity growth is less clear.

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Mendelian randomisation (MR) analysis may be a desirable approach for causal inference analysis. Causal inference analysis in observational studies may be particularly susceptible to the effects of biases such as residual or unmeasured confounding and reverse causation [10], and adiposity exposures are difficult to study using randomised control trials (RCTs). Mumby et al. conducted a MR study using a proxy measure of adiposity (BMI at age 20) [11] but their study was limited in that only BMI data from a single arbitrary time point was used, and therefore it was unable to adequately capture time-varying adiposity growth. Although current studies have measured BMI at some time points [8,9], the use of such irregular and sparse longitudinal data may undervalue relationship inferences, not merely due to the measurement error in the exposure, but also due to a failure to capture its long-term change [12]. Therefore, current methodical studies have proposed a new approach, principal analysis by conditional expectation (PACE) [12,13], wherein original time points are recovered and smoothed, the cumulative effect of the time-varying exposure variable is calculated, and an MR analysis is performed.

Incomplete measurements of adiposity throughout infant and childhood may underestimate or overestimate the influence of birthweight and childhood adiposity on menarcheal timing [8]. For example, many studies report that lower birthweight is a risk for early menarche [8,14]; but that girls of a low fetal and early childhood body weight had a lower risk of early menarche [8,9]. However, their studies were limited by not assessing prepubertal body weight at multiple time points and misattributing sequential causation. Thus, studies with complementary measures of adiposity during prepubertal years are needed to determine whether the processes that relate prepubertal adiposity to timing of menarche.

Our study has three aims: (1) to explore the effect of single point z-BMI and time-varying z-BMI growth on early menarche using MR; (2) to discover critical adiposity predictors of early menarche using MR; (3) to further explore the mediating pathway from genes, birthweight and prepubertal time-varying z-BMI growth to early menarche and thereby reveal the critical factors influencing early menarche development.

Subjects, materials and methods

Cohort description

The Taiwan Children Health Study (TCHS) is a nationwide school-based cohort study consisting of two cohorts. Containing a menarcheal outcome, the second cohort with an open cohort design was used in this study. The menarcheal outcome and demographic information about girls and their family were reported from interviews in school. Adiposity measures were conducted by our trained members. Oral mucosa samples were collected to extract genomic DNA for identifying BMI SNPs. These data and samples were collected in 2010. Detailed procedures have been described in previous articles [15].

Definitions

Maternal gestational exposures are defined as girls whose was in was in fetal conditions [8]. The prenatal exposure was defined as exposures at birth. Prepubertal exposures are defined as adiposity measures before/at the age of menarche [35]. The menarche outcome is defined as the first menstrual bleeding in girls.

Menarcheal outcome

The Chinese version of the Puberty Category Score (PCS) was used to define early menarche [16]. Menarche was asked as either yes or no. When children answered the question with “yes”, each was asked an open question (age at menarche) at the end. Probit analysis based on the status quo method was used to observe a distribution of age of menarche [17]. The ages of 25th percentile [18] for menarche were 10.8 years, which was defined as early menarche.

Adiposity measures

General and abdominal adiposity measurements were obtained annually [19]. To standardise measurements, each was converted into age sex-specific z-scores according to our cohort reference [19]. BMI was converted into BMI z-scores according to the WHO Growth Standards [20]. Adiposity indices, including body fat, fat free mass, sum of skinfolds, waist circumference, hip, waist/hip ratio, and waist/height ratio, were described in the supplemental information.

Genotyping

Obesity-related SNPs were chosen from either the Asian Genome-Wide Association Study (GWAS) meta-analysis [21], or the Chinese child study (see the supplemental information) [22]. FTO genes are strong adiposity-related genes in the Chinese population [23]. Therefore, the 21 candidate SNPs were grouped as FTO genes (2 SNPs) and Non-FTO genes (19 SNPs).

Confounders

We identified potential confounders by reference to previous literature [24], and included maternal gestational factors (e.g., age, weight gain, and diabetes), breastfeeding, birthweight, parental education and household cigarette smoke. These confounders were adjusted for generalised estimating equations (GEE) analysis.

Data analysis

A weighted genetic risk score (GRS) based on the allele dosages and the coefficients was calculated [25]. A principal analysis through conditional expectation (PACE) was used to handle our time-varying individualised growth (see supplemental information) [12,13]. The strength of the association between genetic variants with time-varying z-BMI growth and single point z-BMI was compared using linear regression analysis with assumptions (see Fig. S1 and Table S3).

Basic characteristics of each SNP, including minor allele frequency and F statistics were determined with Plink v2.0. Linear regression analyses were used to examine relationships between genetic variants and adiposity measures (Table S1), and genetic variants and numeric confounders (Table S2). A logistic regression model was used to explore the relationships between genetic variants and binary confounders (Table S2), and genetic variants and binary outcomes (Table S1). A GEE approach taking into account intra-subject correlation of responses was used to estimate the relationship between repeated measures (adiposity measures) and menarcheal outcome (early menarche) (Table 3).

The two-stage least squares (2SLS) method is widely used in MR analysis, and is applicable for binary exposures and outcomes [26]. We performed this method to estimate the causal direction between adiposity exposures and early menarche (Fig. 1 and Tables 2 and 3). Further, sensitivity analyses (Fig. S3 and Table S4) and meta-analyses (Fig. S2) were implemented for supporting the robustness of the causal conclusions from the MR analysis (see supplemental information).

One-mediation and multi-mediation analyses were used to further understand the causal pathways leading to a risk of early menarche (Figs. 2). To compare the effect of a birthweight and

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