Research Article

Mendelian Randomisation Study of Childhood BMI and Early Menarche

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To infer the causal association between childhood BMI and age at menarche, we performed a mendelian randomisation analysis using twelve established "BMI-increasing" genetic variants as an instrumental variable (IV) for higher BMI. In 8,156 women of European descent from the EPIC-Norfolk cohort, height was measured at age 39–77 years; age at menarche was self-recalled, as was body weight at age 20 years, and BMI at 20 was calculated as a proxy for childhood BMI. DNA was genotyped for twelve BMI-associated common variants (in/near *FTO, MC4R, TMEM18, GNPDA2, KCTD15, NEGR1, BDNF, ETV5, MTCH2, SEC16B, FAIM2* and *SH2B1*), and for each individual a "BMI-increasing-allele-score" was calculated by summing the number of BMI-increasing alleles across all 12 loci. Using this BMI-increasing-allele-score as an instrumental variable for BMI, each $1 \, \text{kg/m}^2$ increase in childhood BMI was predicted to result in a 6.5% (95% CI: 4.6–8.5%) higher absolute risk of early menarche (before age 12 years). While mendelian randomisation analysis is dependent on a number of assumptions, our findings support a causal effect of BMI on early menarche and suggests that increasing prevalence of childhood obesity will lead to similar trends in the prevalence of early menarche.

1. Introduction

Early age at menarche, the onset of menstrual periods in girls, is associated with increased risks of adverse health outcomes such as breast, ovarian, and endometrial cancer, hypertension, type 2 diabetes, and cardiovascular disease [1, 2]. Earlier age at menarche is also associated with increased risk for a number of psychosocial outcomes in adolescence including depression, eating disorders, substance abuse, sexual risk-taking and teenage pregnancy [3].

It has been suggested that childhood BMI has a causal effect on the risk for early menarche and there are a number of strongly plausible biological mechanisms [4, 5]. However, discordant secular trends in obesity and age at menarche have raised doubts about the causal nature of these associations. In developed countries, a long-term trend towards earlier menarche has been observed from the late 1800s to the mid 1900s [6]. In many countries these trends appear to

have slowed or even stopped since around 1950 [6] while the prevalence of childhood overweight and obesity has increased since the 1980s [7]. It is possible, therefore, that the apparent association between higher BMI and earlier age at menarche might be confounded by other factors such as diet or exposure to endocrine disruptors [8]. The association could also be explained by reverse causality as the progression of puberty in girls is accompanied by rapid gains in body weight and body fat [9].

Mendelian randomisation, using robust genetic variants as "instrumental variables" [10], has been suggested as an approach to avoid the problems of confounding, residual confounding and specificity that are experienced by traditional epidemiological studies [11]. For example, Mendelian randomisation studies have demonstrated the causal effects of low-density lipoprotein (LDL) cholesterol on risk of myocardial infarction [12], apparent protective effects of high-density lipoprotein (HDL) cholesterol on

coronary heart disease [13], and lack of a causal effect of C-reactive protein (CRP) on ischemic cerebrovascular disease and carotid intimamedia thickness [14]. Similar approaches, using BMI-increasing variants at *FTO* and *MC4R* have reported apparent causal effects of BMI on hypertension [15] and markers of atherosclerosis [16]. In recent years, large scale genome wide association (GWA) studies have identified several common genetic variants that are robustly associated with increased BMI [17–20]. Furthermore, two large studies have reported that some of these genetic variants for higher BMI are also associated with earlier age at menarche [21, 22]. We therefore used a mendelian randomisation approach to assess the likely causal nature of the observed association between higher BMI and risk of early menarche [11].

2. Materials and Methods

2.1. The EPIC-Norfolk Study. The European Prospective Investigation into Cancer and Nutrition-(EPIC-) Norfolk study is a large, predominantly ethnically homogenous, white European population-based cohort study, which is part of a multicentre international study designed to investigate the relationship between diet and chronic disease. The design of the EPIC-Norfolk study has been described in detail previously [23]. The EPIC-Norfolk study was approved by the Norwich local research ethics committee and informed consent was given by all participants.

Age at menarche in completed whole years and weight at age 20 years were ascertained by recall in the baseline questionnaire which women completed at age 39–77 years old. Weight at age 20 was recalled and adult height measured at baseline by trained nurses. The measures were used to calculate BMI at age 20 (recalled weight in kg divided by height squared in metres). This was used as a proxy for childhood BMI. Genotype information was available for 12 variants in the first 12 loci that were identified in the first three waves of GWA studies for BMI [17–20]; these variants were rs91121980 (in/near to gene *FTO*); rs17782313 (*MC4R*), rs6548238 (*TMEM18*), rs10938397 (*GNPDA2*), rs368794 (*KCTD15*), rs32568958 (*NEGR1*), rs10838738 (*MTCH2*), rs925946 (*BDNF*), rs7498665 (*SH2B1*), rs10913469 (*SEC16B*), rs10938397 (*FAIM2/BCDIN3D*) and rs7647305 (*ETV5*). Genotyping was performed by custom TaqMan SNP Genotyping Assays (Applied Biosystems, Warrington, UK) or (markers rs10938397 and rs10838738) Sequenom iPLEX Gold standard chemistry (Sequenom, San Diego, CA) as previously described [24]. Call rates were >95% and each locus genotyped was under HW equilibrium given $\alpha = 0.05$.

In the EPIC-Norfolk study, 10,957 women had DNA available for genotyping. Of these, only 6,709 women had complete genotype data on all 12 SNPs, however a further 3,972 women had genotype data on at least 9 SNPs and for these women we imputed genotype data on their missing (up to 3) SNPs using the mean number of BMI-increasing alleles at each SNP as the individual values (we excluded 276 women who lacked genotype data on more than 3 SNPs). Of the 10,681 women with complete or imputed genotype data, 10,136 had data on recalled age at menarche within the physiological range of 8–18 years, and of these 8,387 women had data on their recalled body weight at age 20 years, and 8,156 also had data on measured height in order to calculate BMI at age 20. All analyses were therefore based on 8,156 women, who were slightly younger, taller and lighter at their baseline visit compared to excluded women, but had very similar recalled weight and (calculated) BMI at age 20 and recalled age at menarche (Table 1).

2.2. Statistical Analyses

2.2.1. Mendelian Randomisation. The outcome variable "early menarche" was defined as menarche before age 12 years, as previously described [25, 26]. As the association of interest was between prepubertal BMI and age at menarche, BMI at age 20 years was used as a proxy for prepubertal BMI. The directly observed increase in risk of early menarche per $1 \, kg/m^2$ change in BMI at age 20 was assessed by logistic regression (to estimate an odds ratio), and by binomial regression (to estimate an absolute increase in risk), with adjustment for age at baseline.

To represent an instrumental variable (IV) for higher BMI, a "BMI-increasing-allele-score" was created in EPIC-Norfolk by summing the number of BMI-increasing alleles across all 12 loci in each person. The association between the BMI-increasing-allele-score and BMI at age 20 was analysed by linear regression, with adjustment for age at baseline. The association between the BMI-increasing-allele-score and risk of early menarche was analysed by logistic regression.

The IV-predicted risk for early menarche per $1 \, kg/m^2$ change in BMI and was calculated using the *ivprobit* command in STATA with a maximum likelihood estimator in order to calculate the predicted absolute risk probabilities. All analyses were conducted using STATA version 10.1 StataCorp., College Station, TX).

3. Results

3.1. The BMI-Increasing-Allele-Score. Associations between the individual variants and BMI at age 20 years in EPIC-Norfolk women are shown in Table 2. All 12 variants showed directionally consistent associations with BMI at age 20 as expected from the original reports [17–20]. The BMI-increasing-allele-score ranged from 3 to 20 alleles and was normally distributed (Figure 1). Because few women had a score below 6 ($n = 51$) or above 17 ($n = 25$) in Figure 1 these scores were collapsed into the categories: "less than or equal to 6" and "greater than or equal to 17" and imputed SNP counts were rounded to the nearest whole number for the figure. On average, each additional BMI-increasing allele was associated with $0.12 \, kg/m^2$ higher BMI at age 20 (95% CI: 0.10–0.15, $P = 6.8 \times 10^{-19}$), but showed no association with adult height ($P = .3$).

3.2. Mendelian Randomisation. 1,766 (21.7%) EPIC-Norfolk women reported that their menarche occurred before age 12 years (early menarche). Each $1 \, kg/m^2$ higher BMI at age 20

Table 1: Characteristics of EPIC-Norfolk women included in the current study.

	Included women			Excluded women			
	n	Mean	SD	n	Mean	SD	*P value
Age at baseline visit (years)	8,156	58.2	9.2	2,801	59.8	9.3	<.001
Height at baseline visit (cm)	8,156	161.1	6.2	2,503	160.5	6.2	<.001
Weight at baseline visit (kg)	8,150	67.6	11.5	2,510	68.3	12.1	.004
Weight at age 20 (kg)	8,156	56.8	8.0	804	56.5	7.8	.2
BMI at age 20 (kg/m^2)	8,156	21.9	2.8	559	21.7	2.6	.2
Age at menarche (years)	8,156	13.0	1.6	2,241	13.0	1.6	.04

Inclusion criteria were complete genotype data on at least 9 SNPs, available height measurement and recalled information on age at menarche between 8 to 18 years, and body weight at age 20 years.
*P values for unpaired t-test.

Table 2: Associations between individual BMI-increasing variants and BMI at age 20 years in 8,156 EPIC-Norfolk women.

Nearby gene	SNP	Chromosome	Position	B* (kg/m^2/allele)	Lower CI	Upper CI
SEC16B	rs10913469	1	176180142	0.28	0.17	0.38
TMEM18	rs6548238	2	624905	0.21	0.10	0.32
FTO	rs1121980	16	52366748	0.20	0.11	0.29
FAIM2	rs7132908	12	48549415	0.15	0.06	0.23
BDNF	rs925946	11	27623778	0.13	0.03	0.22
MC4R	rs17782313	18	56002077	0.13	0.03	0.23
GNPDA2	rs10938397	4	45023455	0.10	0.01	0.19
SH2B1	rs7498665	16	28790742	0.09	0.00	0.18
NEGR1	rs2568958	1	72477137	0.08	−0.01	0.16
ETV5	rs7647305	3	187316992	0.08	−0.03	0.18
MTCH2	rs10838738	11	47619625	0.08	−0.02	0.17
KCTD15	rs368794	19	39012292	0.06	−0.03	0.15

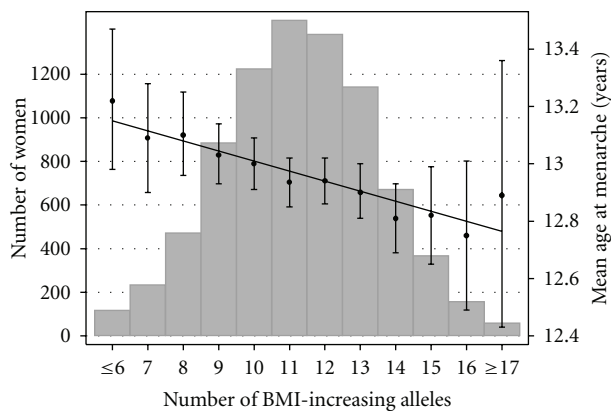*B: regression coefficient from additive genetic models for the previously reported BMI-increasing allele.

Figure 1: Histogram showing the distribution of the BMI-increasing-allele-score in EPIC-Norfolk women ($n = 8,156$). Within each allele score category, the mean and 95% CI for age at menarche are shown by circles and error bars. The trend line shows the inverse linear trend between mean age at menarche and allele score category.

was directly associated with an 11% (95% CI: 9–14%) higher relative risk of early menarche, or in terms of absolute risk 1.7% higher (1.5 to 2.0%).

The BMI-increasing-allele-score was positively associated with the relative risk of early menarche (OR = 1.06 per allele, 95% CI =1.03–1.08, $P = 5.8 \times 10^{-6}$). When using the BMI-increasing-allele-score as an instrumental variable for BMI, each 1 kg/m^2 increase in BMI at age 20 was predicted to result in a 6.5% (95% CI: 4.6–8.5%) increase in the absolute risk of early menarche.

We performed a sensitivity analysis by calculating a "weighted BMI-increasing-allele-score", where the contribution of each genotype to the score was weighted by its individual association with BMI at age 20. Using this weighted BMI-increasing-allele-score, each 1 kg/m^2 increase in BMI at age 20 was predicted to result in a 6.7% (95% CI: 5.0–8.4%) higher absolute risk of early menarche.

4. Discussion

The results of this mendelian randomisation analysis infers a causal effect of higher BMI on increased risk of early menarche (at age <12 years), and that the observed association is unlikely to be explained by positive confounding or by reverse causality.

It is not suggested that such genetic instrumental variable approaches can replace randomised controlled trials, but rather that they support the causal inference from observational studies. This is because mendelian randomisation

TABLE 3: Longitudinal studies reporting the association between childhood BMI and subsequent age at menarche.

Reference (country)	Number of participants	Mean age at BMI assessment	Mean age at followup	Findings			
Ong et al. 2009 (UK) [33]	1,781	9 mo 19 mo	13 y	Mean ± SE BMI by age at menarche			
					<12 y	12-13 y	>13 y	*P* value for trend
				(i) 9 mo	17.5 ± 0.1	17. 3 ± 0.1	17.3 ± 0.1	.007
				(ii) 19 mo	16.9 ± 0.1	16.7 ± 0.1	16.7 ± 0.1	.09
Buyken et al. 2009 (Germany) [34]	87	7.7 y (Interquartile range 6.5–8.8)	13 y	Age at menarche (mean, 95% CI) by BMI z-score 1 year before height "take-off"			
				(i) Lowest BMI quartile	12.9 y	(12.4–13.4)	*P* value for trend
				(ii) Quartiles 2 and 3	11.7 y	(11.4–12.1)	.03
				(iii) Highest BMI quartile	12.4 y	(11.9–12.8)	
Lee et al. 2007 (USA) [36]	354	3.0 y 4.5 y 6-7 y	12 y	Odds ratio (95% CI) for early menarche (by age 12 y) per +1 BMI z-score			
				(i) 3.0 y	OR = 1.45	(1.10–1.93)	
				(ii) 4.5 y	OR = 1.50	(1.14–1.97)	
				(iii) 6-7 y	OR = 1.85	(1.38–2.47)	
Must et al. 2005 (USA) [35]	307	12.0 y (SD 1.2)	15 y	Age at menarche showed an inverse trend with premenarche BMI Correlation coefficient = −0.10; *P* = .08.			
Freedman et al. 2003 (USA) [31]	771 Whites 408 Blacks	8.7 y (SD 2) whites 8.9 y (SD 2) blacks	17 y	Odds ratio (95% CI) for early menarche (<12 y) per +1 BMI z-score			
				White girls	OR = 2.0	(1.6–2.5)	
				Black girls	OR = 2.1	(1.5–3.0)	

relies on several assumptions [11]. Firstly, that there is a reliable association between the genetic variant and the exposure, childhood BMI. While we did not have information on childhood BMI in this study, the effect size of our 12-variant BMI-increasing-allele-score on BMI at 20 years (+0.12 kg/m^2 per allele, or around 0.04 of an SD) is identical to that in 9–15-year-old children with research clinic measurements in the European Youth Heart Study (0.04 SD per allele; $n = 2,042$ children) [27], and is similar to the effect size of a 10-variant score at age 9 years in the ALSPAC study (BMI: 0.07 SD per allele; weight 0.05 SD per allele [28]. We are therefore confident that our genetic score is a valid instrumental variable for childhood BMI. Secondly, the genetic variants should not have pleiotropic effects on different biological processes, or be in linkage disequilibrium with other genetic variants that might directly affect the outcome [11]. We would expect that pleiotropic effects (i.e., mediated by independent biological processes) on BMI and timing of menarche are infrequent among BMI variants. In contrast, a recent very large study in 87,000 women reported that individually 9 of the 12 BMI-increasing variants that we studied here showed significant associations with lower age at menarche [29]. As most BMI-increasing variants are associated with lower age at menarche, we consider that pleiotropy is unlikely and therefore our findings indicate a causal pathway linking higher BMI, or the growth and developmental processes that lead to higher BMI, to earlier menarche.

It is unclear why our IV-predicted association, based on the genetic score, was even stronger than the directly observed association between BMI and early menarche. The mechanisms of action for these variants are yet unknown and it is possible that some might indeed have direct effects on the timing of menarche. Alternatively, the observed association between childhood BMI and age at menarche might have been artificially diminished due to negative confounding or due to our imprecise estimate of childhood BMI. In this case, the IV-predicated association may actually be closer to true size of the causal association between childhood BMI and age at menarche.

The lack of direct assessments of growth during childhood was a limitation of our study. Recalled body weight at age 20 years was used to calculate a proxy measure of childhood BMI. However, other studies have demonstrated that recall of early adult weight in this age group is reliable [30] and that BMI at age 20 is well-correlated with childhood BMI [31]. Furthermore in our IV analyses, BMI at 20 is only used in order to estimate the effect size of the genetic score on childhood BMI, and the result was very similar to that found in earlier childhood studies (discussed above).

Our inference of a causal relationship between higher BMI and early menarche is supported by other sources of evidence. One randomised control trial showed that reduction in childhood obesity led to avoidance of early menarche [32]. However, the lifestyle intervention used in that trial lead to changes in fruit and vegetable consumption, duration of physical activity and sedentary behaviour, and it is therefore not possible to specify any one causal factor. Most longitudinal studies, while small in numbers, consistently report that higher BMI during childhood is associated with

subsequent increased risk of early menarche [31, 33–36] (Table 3). In those longitudinal studies, associations with earlier menarche were seen with childhood BMI at various ages from 9 months through to 12 years. One study reported that greater weight gain even in the first weeks and months of life was associated with earlier age at menarche [33]. Further longitudinal studies are needed to identify the relative effects of rapid weight during different childhood ages, up to and including the pubertal years, on the timing of menarche.

In a separate birth cohort study [37] we recently examined the relationship between the age at menarche genetic variant in *LIN28B* to measures of growth and weight gain from birth to age 53 years. In that study, that the menarche-lowering allele was associated with higher BMI in women from ages 15–43 years, but not before age 15. That finding is therefore consistent with our current analysis in supporting a causal direction of childhood BMI on puberty timing, although puberty timing may in turn influence BMI beyond puberty.

Together, these findings indicate that the occurrence of early menarche is likely to increase as the prevalence of childhood overweight and obesity increases. An expert panel assembled to assess the evidence for an ongoing secular trend in age at menarche since 1940 failed to reach a consensus, although the majority concluded that there was sufficient evidence for an ongoing decline [6]. The rapid reductions in mean age at menarche from the late 1800s to the mid 1900s have been attributed to the avoidance of under-nutrition, while the effects of overnutrition on further advancing age at menarche may result in relatively slower yet continuing trends to earlier menarche [38].

5. Conclusions

Our genetic IV analysis infers a strong causal effect of higher childhood BMI on the risk of early menarche. While mendelian randomisation analysis is dependent on a number of assumptions, our conclusions are supported by the findings of longitudinal studies and suggest that increasing trends in childhood obesity will lead to increasing prevalence of early menarche.

Conflict of Interests

The authors declare no conflict of interest.

Acknowledgments

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