Age at menarche and adult body mass index: a Mendelian randomization study

Dipender Gill1*, Christopher F. Brewer2, Fabiola Del Greco M3, Prasanthi Sivakumaran2, Jack Bowden4, Nuala A. Sheehan5, Cosetta Minelli6

1Department of Clinical Pharmacology and Therapeutics, St. Mary’s Hospital, Imperial College Healthcare NHS Trust, London, UK; 2Faculty of Medicine, Sir Alexander Fleming Building, Imperial College London, London, UK; 3Institute for Biomedicine, Eurac Research, Bolzano, Italy; 4MRC Integrative Epidemiology Unit, University of Bristol, Bristol, United Kingdom; 5Department of Health Sciences, University of Leicester, Leicester, UK; 6Population Health and Occupational Disease, NHLI, Imperial College London, London, UK

*Corresponding author: Dr Dipender Gill MA (Oxon), BM BCh, MRCP (UK)
Postgraduate Centre, St. Mary’s Hospital, London, W2 1NY, United Kingdom
Phone: +44 (0) 7904 843 810
E-mail: dipender.gill@imperial.ac.uk

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DG affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.
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Abstract

Background: Pubertal timing has psychological and physical sequelae. While observational studies have demonstrated an association between age at menarche and adult body mass index (BMI), confounding makes it difficult to infer causality.

Methods: The Mendelian randomization (MR) technique is not limited by traditional confounding and was used to investigate the presence of a causal effect of age at menarche on adult BMI. MR uses genetic variants as instruments under the assumption that they act on BMI only through age at menarche (no pleiotropy). Using a two-sample MR approach, heterogeneity between the MR estimates from individual instruments was used as a proxy for pleiotropy, with sensitivity analyses performed if detected. Genetic instruments and estimates of their association with age at menarche were obtained from a genome-wide association meta-analysis on 182,416 women. The genetic effects on adult BMI were estimated using data on 80,465 women from the UK Biobank. The presence of a causal effect of age at menarche on adult BMI was further investigated using data on 70,692 women from the GIANT Consortium.

Results: There was evidence of pleiotropy among instruments. Using UK Biobank data, after removing instruments associated with childhood BMI that were likely exerting pleiotropy, fixed-effect meta-analysis across instruments demonstrated that a one year increase in age at menarche reduces adult BMI by 0.38 kg/m² (95%CI 0.25 to 0.51 kg/m²). However, evidence of pleiotropy remained. MR-Egger regression did not suggest directional bias, and similar estimates to the fixed-effect meta-analysis were obtained in sensitivity analyses when using a random-effect model, MR-Egger regression, a weighted median estimator and a weighted mode-based estimator. The direction and significance of the causal effect were replicated using data from the GIANT Consortium.

Conclusion: MR provides evidence to support the hypothesis that earlier age at menarche causes higher adult BMI. Complex hormonal and psychological factors may be responsible.

Abstract Word count: 300

Key words: Mendelian randomization, puberty, menarche, body mass index, obesity
Introduction

Following current trajectories, almost one fifth of the global population will be obese by 2030 (1), emphasising the importance of understanding predisposing factors for obesity. Pubertal timing has come under increasing attention due to the associated psychological and physical sequelae (2, 3), and early menarche in particular has been shown to be a risk factor for eating disorders (4), depression (5), type 2 diabetes (6), cardiovascular disease and mortality (7). Earlier pubertal timing in girls has been associated with higher body mass index (BMI) in adulthood (3). However, childhood obesity is a risk factor for adult obesity, and adjusting for this variable has resulted in inconsistent effect estimates of the association between pubertal timing and adult BMI, ranging from a modest reduction of adult BMI with delayed pubertal timing (8-10), to complete loss of statistical evidence (11). Thus, it is difficult to decipher whether age at menarche indeed has a causal effect on adult obesity, or whether the association is wholly attributable to confounding factors that also affect the timing of menarche, such as pubertal adiposity or individual socio-economic factors (10, 12).

The Mendelian randomization (MR) technique uses genetic variants as instruments (“proxies”) for a risk factor of interest, which here is age at menarche. As these genetic variants are allocated randomly at the time of conception, MR may be used in this situation to disentangle a causal effect of age at menarche on adult BMI from spurious associations attributable to confounding (13). Indeed, this approach has recently been used to demonstrate causal effects of age at menarche on adolescent depression (14), time spent in education (15), adolescent and adult lung function (16), and risk of breast cancer and endometrial cancer (17). A critical assumption of MR analysis is that the instrumental variables do not affect the outcome via a pathway other than the risk factor of interest. Genetic variants can violate this assumption if they exert their effects on the outcome through different biological pathways in a phenomenon known as horizontal pleiotropy (18). Although there are methods that address horizontal pleiotropy, these must be carefully selected and appropriately interpreted because they vary in their underlying assumptions and power to identify a causal effect (19, 20). Indeed, while recent work has used MR to suggest that higher age at menarche results in lower adult BMI, causal effect estimates and possible bias resulting from horizontal pleiotropy were not explored in this analysis (17).

In this study, we use a two-sample MR approach with single nucleotide polymorphism (SNP)-age at menarche and SNP-adult BMI association estimates to investigate the causal effect of age of menarche on adult BMI. We also perform sensitivity analyses that address the issue of horizontal pleiotropy and assess the robustness of the findings.

Materials and Methods

A published genome-wide association (GWA) meta-analysis of 57 studies incorporating 182,416 women was used to identify SNPs for use as instruments for age at menarche, and to obtain estimates of the magnitude of their association (21). Onset of menarche was established from questionnaires, with analysis adjusted for birth year (for secular trends) and genomic control (for population stratification). A total of 122 independent SNPs situated at 106 genomic loci were identified to be associated with age at menarche at genome-wide significance level (p value < 5 x 10^{-8}). We calculated
the F statistic of each SNP, which reflects magnitude and precision of the genetic effect, to evaluate its strength as an instrument (22, 23).

SNP-adult BMI association estimates for each of the 122 instruments were obtained from the UK Biobank, a prospective study performed across 22 assessment centres (24). We include 80,465 women aged 40-69 recruited in 2006–2010, who had BMI (kg/m², calculated using height and weight measurements) and GWA data available. Analyses were adjusted for age, age², 10 ancestry principal components and study centre.

The presence of a causal effect of age at menarche on adult BMI was further investigated using SNP-adult BMI summary data made publicly available by the Genetic Investigation of Anthropometric traits (GIANT) Consortium, which included Metabochip and GWA studies on 70,692 women aged less than 50 years (25, 26). Here BMI was based on either measured or self-reported height and weight (26), and the analyses were adjusted for age and age² (25). Due to the use of a rank-based inverse normal transformation of BMI in the original analyses, we could not obtain an MR estimate in an interpretable unit of measurement using these summary data, since back transformation to values in kg/m² is not possible without access to the individual-level data. For this reason, although we performed a similar MR analysis to the one performed with UK Biobank data, we only report results in terms of direction of the causal effect and statistical significance to allow comparison with the results obtained for UK Biobank.

All genetic association analyses assume an additive genetic model, as well as no interactions for both SNP-age at menarche and SNP-adult BMI associations.

Mendelian randomization estimates

The MR effect estimates for each instrument were derived using the Wald estimator (27), which is the ratio of the SNP-BMI estimate over the SNP-age at menarche estimate, with the Delta method used to estimate the standard error (28). A fixed-effect inverse-variance weighted meta-analysis (IVW) was then used to combine individual MR estimates across SNPs and generate an overall estimate of the effect of age at menarche on adult BMI.

Investigation of pleiotropy

The MR analysis is based on the assumption of no horizontal pleiotropy, that is each SNP exerts its effect on adult BMI through variations in the timing of menarche, and not by any other independent pathway (29). Violation of this assumption can be assessed by evaluating, as a proxy, the variability in MR estimates across different SNPs beyond what can be expected by chance alone, using the $I^2$ statistic (called here $I^2_{MR}$) and Cochran’s Q test (30). In this analysis, an $I^2_{MR}$ value of greater than 25% or a Cochran’s Q test p<0.05 was used to identify the presence of horizontal pleiotropy. If detected, further sensitivity analysis methods that operate under differing, weaker assumptions relating to horizontal pleiotropy were performed to investigate the robustness of the findings.

MR-Egger regression is one such method (31). It performs a linear regression of the SNP-outcome association estimates on the SNP-exposure association estimates. If the assumptions of the model are met, the intercept of this regression represents an estimate for the directional bias due to horizontal pleiotropy. An intercept estimate close to zero suggests that either there is no horizontal pleiotropy, or that the horizontal pleiotropy between different SNPs is balanced and thus effectively “cancels
out”. In the latter case, a random-effect IVW meta-analysis is then sufficient to address the observed
pleiotropy (19), which is generally far more efficient than MR-Egger (20).

MR-Egger, fixed-effect IVW meta-analysis and random-effect IVW meta-analysis all rely on the
assumption that the effect of the instruments on age at menarche is independent of any possible
horizontal pleiotropic effects that they may exert, the Instrument Strength Independent of Direct
Effect (InSIDE) assumption (31), although MR-Egger is much more sensitive to violations of InSIDE (20).
In our scenario, a potential pleiotropic mechanism is through childhood BMI, and it might be that SNPs
associated with age at menarche have a proportionate association with childhood BMI, which would
violate the InSIDE assumption. For this reason, if there was an $I^2_{MR}$ value of greater than 25% or a
Cochran’s Q test p<0.05 following the initial fixed-effect IVW meta-analysis of all 122 age at menarche
instruments, sensitivity analysis using fixed-effect IVW regression-based multivariable MR was also
performed, to adjust for the effects of the age at menarche instruments on childhood BMI when
estimating their effect on adult BMI (32, 33) (Figure 1). Furthermore, those SNPs also associated with
childhood BMI were consequently excluded from MR analyses. SNP-childhood BMI association
estimates for each of the 122 age at menarche instruments were contributed by the Early Growth
Genetics (EGG) Consortium from a GWA meta-analysis that used age- and sex-adjusted standard
deviation scores (34). We considered SNPs associated with childhood BMI using a p-value threshold
of $4 \times 10^{-4}$, after accounting for multiple testing (Bonferroni correction for the 122 SNPs).

Two further sensitivity analyses that do not rely on the InSIDE assumption were also performed. First,
the IVW median estimator calculates the mid-point of the distribution of MR estimates, while
considering their relative precision, and is consistent when more than 50% of the information for the
analysis comes from valid instruments (35). The IVW median estimator approach is preferred to the
simple median estimator (which gives ratio estimates from all instruments equal weighting) in this
context, due to its greater efficiency when the precision of estimates vary (35). Second, an IVW mode-
based estimator is robust when the largest number of similar weighted causal effect estimates is
derived from valid instruments, even in scenarios where most instruments are not (36). We prefer the
IVW mode-based estimator over its unweighted (simple) counterpart in this context because of its
superior precision (36).

Bias due to winner’s curse

SNP-age at menarche estimates that are generated from discovery rather than replication analysis
(which had a sample size 20 times smaller, 8,689 versus 182,416) (21), may result in upward bias in
these estimates (“winner’s curse”) (37). This would lead to underestimation of the true causal effect
of age at menarche on adult BMI, which in our two-sample MR study is estimated using the Wald
estimator, i.e. the ratio of the SNP-adult BMI association over the SNP-age at menarche association.
An unweighted allele score analysis, which is not affected by bias resulting from winner’s curse, can
be used to address this (38). As a further sensitivity analysis, we therefore performed a fixed-effect
meta-analysis of SNP-adult BMI association estimates across instruments, which is equivalent to
performing an unweighted allele score analysis with all SNPs.

All analyses were performed using Stata 14 (StataCorp LP). The weighted median estimator and the
weighted mode-based estimator were performed using the mrrobust package (39).
Results

All 122 instruments demonstrated a strong association with age at menarche, with F statistics ranging from 25 to 576 (Supplementary Table 1). They all exceed the recommended threshold of 10 for MR analyses and provide assurance that the results are probably not affected by weak instrument bias (22, 23). The individual effect estimates of each instrument on age of menarche and adult BMI (UK Biobank data) are detailed in Supplementary Tables 1 and 2 respectively. Supplementary Table 3 shows the causal effect estimate of age of menarche on adult BMI for each instrument, using SNP-adult BMI association estimates from the UK Biobank.

The main MR analyses were performed using SNP-adult BMI association estimates from the UK Biobank data. The fixed-effect IVW meta-analysis using all 122 instruments demonstrated a causal effect of age at menarche on adult BMI, with a one year increase in age at menarche causing a reduction in adult BMI of 0.56kg/m² (95% CI 0.44 to 0.68kg/m², p value = 7 x 10⁻¹⁹). There was strong evidence of heterogeneity suggesting the presence of horizontal pleiotropy, with an $I^2_{MR}$ statistic of 70% (95% CI 64% to 75%) and a Cochran’s Q test p value of 3 x 10⁻³¹. Sensitivity analysis using fixed-effect IVW regression-based multivariable MR that adjusted for the effects of the age at menarche instruments on childhood BMI (Supplementary Table 4) supported a smaller effect of a one year increase in age at menarche causing a reduction in adult BMI of 0.26kg/m² (95%CI 0.13 to 0.39kg/m², p value = 1 x 10⁻⁴), and also suggested that childhood BMI was exerting horizontal pleiotropy (p = 3 x 10⁻⁶⁵). For this reason, the 12 age at menarche instruments also associated with childhood BMI (p < 4 x 10⁻⁴, Supplementary Table 4) were consequently excluded from further sensitivity analyses.

The fixed-effect IVW meta-analysis using the remaining 110 instruments also demonstrated a causal effect of age at menarche on adult BMI, with a one year increase in age at menarche causing a reduction in adult BMI of 0.38kg/m² (95% CI 0.25 to 0.51kg/m², p value = 6 x 10⁻⁹). There remained moderate evidence of heterogeneity to suggest the presence of horizontal pleiotropy, with an $I^2_{MR}$ statistic of 46% (95% CI 33% to 57%) and a Cochran’s Q test p value of 1 x 10⁻⁷. MR-Egger regression analysis using these 110 instruments did not produce evidence of directional horizontal pleiotropy (intercept estimate -0.001, 95% CI -0.018 to 0.015, p value = 0.878), and identified a similar causal effect of age at menarche on adult BMI of 0.38kg/m² (95% CI 0.001 to 0.75, p value = 0.049). A random-effect IVW meta-analysis was performed as a sensitivity analysis in the context of possible balanced pleiotropy, and gave a similar causal effect estimate (0.40kg/m², 95%CI 0.21 to 0.58kg/m², p value = 2 x 10⁻⁵). Sensitivity analysis using the IVW median and IVW mode-based estimator methods also demonstrated similar causal effects, with a one year increase in age at menarche causing a reduction in adult BMI of 0.41kg/m² (95%CI 0.19 to 0.63kg/m², p value = 3 x 10⁻⁴) and 0.41kg/m² (95%CI 0.11 to 0.71kg/m², p = 0.007), respectively.

An unweighted allele score for the 110 age at menarche instruments (after excluding the 12 pleiotropic instruments also associated with childhood BMI) using the UK Biobank data showed an association with adult BMI (p value = 2 x 10⁻⁹). This supports the causal effect of age at menarche on adult BMI identified in our main MR analysis, and is unlikely to be attributable to “winner’s curse” bias due to the use of SNP-age at menarche estimates from discovery stage results, as the unweighted allele score does not use these estimates. Results from all the analyses performed in UK Biobank are presented in Table 1.
The fixed-effect IVW meta-analysis of MR estimates across all 122 instruments using data from the GIANT consortium confirmed an effect of age at menarche on adult BMI (p value = 3 x 10^{-22}), with direction consistent with that found in UK Biobank; it also showed strong evidence of heterogeneity (I^2_{MR} statistic of 72%, Cochran’s Q test p value = 5 x 10^{-36}). When repeating the analysis after excluding the 12 SNPs associated with childhood BMI, the p value was 1 x 10^{-9}, with moderate evidence of heterogeneity (I^2_{MR} statistic of 43%, Cochran’s Q test p value = 2 x 10^{-6}).

Discussion

In this study, we performed an MR analysis using UK Biobank to estimate the causal effect of age of menarche on adult BMI. There was evidence of horizontal pleiotropy, and various sensitivity analyses that make differing weaker assumptions relating to this were consequently performed to investigate the robustness of the findings. Multivariable MR that accounted for the effects of the instruments on childhood BMI supported a causal effect of age at menarche on adult BMI, whilst also providing evidence that childhood BMI was contributing to the pleiotropy. After excluding the 12 age at menarche instruments also associated with childhood BMI, fixed-effect IVW meta-analysis using the remaining 110 instruments demonstrated that a one year increase in age at menarche caused a reduction in adult BMI of 0.38 kg/m². However, there remained moderate evidence of horizontal pleiotropy, which may be introducing bias into this MR analysis (30). MR-Egger regression analysis did not produce any evidence of directional pleiotropy (20, 40), and sensitivity analysis with random-effect IVW meta-analysis, which can address balanced horizontal pleiotropy (19), also provided a similar estimate to the fixed-effect model. Furthermore, MR-Egger regression, the IVW median estimator and the IVW mode-based estimator all also produced a causal estimate in keeping with both IVW meta-analysis methods and multivariable MR, to further strengthen the evidence. Our findings for presence and direction of a causal effect of age at menarche in UK Biobank, which includes women aged 40 to 69 years, could be replicated using publicly available data from the GIANT Consortium on women aged less than 50 years.

Our findings support those of previous observational studies, which have shown a similar inverse relationship between the onset of menarche and adult obesity (3). Of particular note is the Framingham Heart Study (41), which investigated the association of age at menarche with BMI and adiposity in a sample of 1,456 women over the age of 40. The researchers adjusted the analyses for lifestyle factors and exogenous hormone exposure, although they note causal interpretation was limited because it was not also possible to adjust for childhood adiposity due to lack of data. Other studies, including the Bogalusa Heart Study (10), and the 1950’s Aberdeen Cohort (8), were able to adjust the analyses for childhood BMI using longitudinal data, although their estimates of the impact of this confounding effect differed markedly (60-75% and 11% attenuation of the association of interest, respectively). Furthermore, whilst these studies adjusted for various other confounding factors, it is likely that some unknown confounders may remain. In addition, the authors of both papers note that selection bias due to loss of follow up or missing data may have impacted on the results. In this study, we used genetic variants as instruments in an MR analysis to overcome these limitations of observational research. While recent work has already demonstrated a strong inverse genetic correlation between age at menarche and adult BMI, with MR used to explore the causal effect of age at menarche on adult BMI (17), our current study goes further beyond this to estimate the...
magnitude of this effect, and also uses a number of sensitivity analyses to show that it is robust to the
presence of horizontal pleiotropy.

Explanations for the detrimental health outcomes in adulthood attributable to earlier age at puberty
span a range of domains (42). Early menarche hastens exposure to gonadal steroids, invoking
accelerated physical and psychological changes. Oestrogen and progesterone receptors are widely
expressed in adipose tissue, and are thought to mediate variations in body habitus patterns between
genders (43). Pre-pubertal girls with greater abdominal fat have been shown to have increased plasma
levels of total oestradiol compared to their leaner peers (44). Interestingly, these girls also had an
accelerated progression through pubertal stages, implicating gonadal steroids as mediators of the
faster maturation seen with earlier menarche (45). However observational studies of women using
oestrogen-based hormonal contraceptives have failed to identify any dose-related effect on weight
gain, suggesting that adiposity changes are unlikely to be solely oestrogen-dependant (46).

Hyperandrogenemia (excessively high androgen concentrations) may also play a role in mediating
increased adult BMI (47), although the contribution of individual androgens remains to be established.
A cross-sectional study by Bleil and colleagues found that the association between pubertal timing
and adult obesity was attenuated after accounting for biologically active testosterone levels (48). In
contrast, a more recent study by Gallachio and colleagues found relatively little attenuation after this
adjustment, although they note that other androgens such as dehydroepiandrosterone-sulfate (DHEA-S)
may have a role (49). Supporting the androgen hypothesis, evidence from studies on precocious
puberty show that early adrenarche (maturational increase in adrenal androgen production) is
associated with ovarian hyperandrogenism (50). The cause of the hyperandrogenaemia is unclear,
however it may in part be due to positive feedback regulation on gonadotrophin release in the
hypothalamus from elevated oestrogen levels (51). The roles of androgens in insulin resistance and
obesity have also been well-described (52).

The effects of an altered hormonal environment may also impact on the psychological development
of adolescent girls, which may in turn increase susceptibility for weight gain (42). Enduring the
accelerated physical changes of puberty discordantly with peers can predispose to negative effects in
early adolescence (45). Of particular interest is the association with depressive disorders, which have
a complex bi-directional relationship with obesity (53). A meta-analysis by Blaine et al found that
female adolescent depression increased the risk of adult obesity by more than two-fold (54). Proposed
explanations for this effect include emotional eating behaviours, less time spent engaging in physical
activity, and changes in adiposity secondary to antidepressant use. Weight gain at this age is
stigmatizing, reinforcing discrimination and social isolation from others (55). This in turn may
exacerbate depression and precipitate adult obesity. Early maturing girls have also been shown to
achieve poorer academic and employment outcomes in relation to their peers (56). This has been
partly attributed to accelerated involvement in romantic relationships and truant behaviour,
distracting girls from academic work and leading to school absenteeism (42). Schooling provides
consistently timetabled physical activity, as well as encouraging children to take part in sports outside
of lesson time. Whilst the efficacy of school programmes on limiting obesity remain controversial,
overall estimates show a beneficial effect (57).

Schulz et al. provide another theory bridging these models that attributes the psychological outcomes
to varying gonadal steroid exposure during early adolescence (58). They propose that hormonal
organising events on the brain are chronologically influenced, due to declining neural plasticity
following the postnatal period. Girls who undergo earlier menarche may develop emotional responses discordantly with the cognitive control systems that are achieved later in adolescence (59, 60). This may predispose them to negative interpretation of environmental and social events, giving rise to detrimental psychological outcomes that persist into adult life. It is indeed likely that the psychological and biological consequences of early puberty synergise to create an at-risk phenotype for excessive weight gain. The propensity to follow this path may be dictated by the environmental and social context.

The effects of common genetic variants are typically modest and this was the case with age at menarche in our current MR study, where adequate instrument strength could only be achieved because of the large sample size of the GWA study. For this reason, we used SNP-age at menarche estimates generated from the discovery (rather than the replication) analysis, but these might be affected by the upward bias typical of the discovery stage (winner’s curse bias) (37), resulting in overestimation of the SNP-age at menarche association to pull the MR estimate towards the null and give a false positive result. Reassuringly however, our sensitivity analysis suggested that the identified causal effect of age at menarche and adult BMI is not attributable to such possible bias.

In conclusion, this study demonstrates a causal effect of age at menarche on adult BMI. This supports previous research and helps provide further mechanistic insight into the influence pubertal timing has on adult obesity. We propose elevated gonadal hormones and adverse psychological outcomes as possible mediators for the observed effect.
Conflict of Interest

All authors declare no conflict of interest. Specially, no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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References


Figure Legend

Figure 1. A directed acyclic graph depicting the application of multivariable Mendelian randomization in this context. The instruments for age at menarche may also have a causal effect on childhood BMI, and thus affect adulty BMI through this pathway. The multivariable Mendelian randomization approach allows adjustment for the effects of the age at menarche instruments on childhood BMI when estimating their effect on adult BMI. An assumption in this model is that all instruments affect adult BMI only through age at menarche or childhood BMI, and no other pathway.

Table Legend

Table 1. MR estimates of the causal effect from the analyses performed in UK Biobank.
Supplementary Table Legends

Supplementary Table 1. Estimates of the SNP-age at menarche association for all 122 SNPs, from Perry et al. (1). EA: effect allele; EAF: effect allele frequency; F: F statistic, a function of the magnitude and precision of the genetic effect estimated as: F=GX²/GX SE² (2); GX: per-allele genetic effect on age at menarche (years); GX SE: standard error of GX; p: p value of GX

Supplementary Table 2. Estimates of the SNP-adult BMI association for all 122 SNPs (reported to four decimal places), from the UK Biobank (3). EA: effect allele; GY: per-allele genetic effect on adult BMI (kg/m²); GY SE: standard error of GY; p: p value of GY

Supplementary Table 3. MR estimates of the causal effect of age at menarche on adult BMI for all 122 SNPs. EA: effect allele; Beta: estimate of the effect of one year increase in age at menarche on BMI (kg/m²); Beta SE: standard error of beta; p: p value of Beta

Supplementary Table 4. Estimates of the SNP-childhood BMI association for all 122 SNPs, from Felix et al. (4). EA: effect allele; GZ: per-allele genetic effect on childhood BMI (standard deviation score); GZ SE: standard error of GZ; p: p value of GZ