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BMI Loci and Longitudinal BMI from Adolescence to Young Adulthood in an Ethnically Diverse Cohort

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Abstract

Objective—The association of obesity susceptibility variants with change in body mass index (BMI) across the life course is not well understood.

Subjects—In ancestry stratified models of 5,962 European American (EA), 2,080 African American (AA), and 1,582 Hispanic American (HA) individuals from the National Longitudinal Study of Adolescent to Adult Health (Add Health), we examined associations between 34 obesity SNPs with per year change in BMI, measured by the slope from a growth-curve analysis of two or more BMI measurements between adolescence and young adulthood. For SNPs nominally associated with BMI change ($p<0.05$), we interrogated age differences within data collection Wave and time differences between age categories that overlapped between Waves.

Results—We found SNPs in/near *FTO, MC4R, MTCH2, TFAP2B, SEC16B, and TMEM18* were significantly associated ($p<0.0015 \approx 0.05/34$) with BMI change in EA and the ancestry-combined meta-analysis. Rs9939609 in *FTO* met genome-wide significance at $p<5e-08$ in the EA

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MG, KEN, EML and PG-L designed the study. MG, ASR, and KMY contributed to data analysis. PG-L and KEN are responsible for data acquisition. MIG, EML, KEN, and PG-L drafted the manuscript. All authors contributed to data interpretation and writing of the manuscript. MIG, KEN and PG-L had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors have approved the final version of the manuscript.

and ancestry combined analysis, respectively [Beta(se)=0.025(0.004);Beta(se)=0.021(0.003)]. No SNPs were significant after Bonferroni correction in AA or HA, although 5 SNPs in AA and 4 SNPs in HA were nominally significant ($p<0.05$). In EA and the ancestry-combined meta-analysis, rs3817334 near *MTCH2* showed larger effects in younger respondents, while rs987237 near *TFAP2B*, showed larger effects in older respondents across all Waves. Differences in effect estimates across time for *MTCH2* and *TFAP2B* are suggestive of either era or cohort effects.

Conclusion—The observed association between variants in/near *FTO, MC4R, MTCH2, TFAP2B, SEC16B, and TMEM18* with change in BMI from adolescence to young adulthood suggest that the genetic effect of BMI loci varies over time in a complex manner, highlighting the importance of investigating loci influencing obesity risk across the life course.

Keywords

Gene-environment interactions; adolescence; obesity; BMI change; African-American; Hispanic-American

INTRODUCTION

The transition from adolescence to young adulthood is a period of high risk for weight gain and development of obesity [1–3], with high rates of incident obesity (24.1%) and severe obesity (7.9%) [3]. Genome-wide association (GWAS) studies of over 200,000 European descent adults, have identified several independent loci associated with BMI [4, 5]. While recent studies have analyzed BMI loci across the lifecycle [6–14], few longitudinal studies have examined BMI loci associated with *change* in body mass index (BMI) in the period between adolescence and young adulthood. Several studies have examined the association of *FTO* and *MC4R*, two of the earliest identified BMI susceptibility variants, with longitudinal change in BMI from childhood into adulthood [6–8, 15]. Results for BMI change with *FTO and MC4R* suggest stronger estimated effects encompassing the early adolescent to young adult period compared to later in adulthood [6, 7, 15]. Further, childhood growth trajectories from age one to 16 years have been shown to be associated with established BMI susceptibility loci as a risk score [13], suggesting that genetic determinants associated with BMI at cross-sectional periods are also associated with changes in BMI across the life course. Studies of the influence of genetic variants on BMI change have not yet been interrogated during the late adolescent to early adulthood transition, a developmental period associated with substantial BMI change. More research is warranted to determine the impact of BMI genetic variants across this phase of the life course.

In this study, we examined the association between 34 established BMI variants and change in BMI derived from measured height and weight assessed from adolescence to early adulthood in youth enrolled in an ethnically diverse, nationally representative cohort, the National Longitudinal Study of Adolescent to Adult Health (Add Health), followed for 13 years across three time points, which we call Waves, between 1996 and 2008 when the cohort fell between the ages of 13 years and 34 years. We hypothesized that carriers of obesity risk alleles would have a greater rate of change in increasing BMI across the adolescent and early-adulthood time period. In addition, because of increasing environmental influences that might mask genetic ones as we age, we speculated that some

variants might have comparatively stronger estimated effects at earlier versus later ages of the period between adolescence and young adulthood.

METHODS

Add Health

Participants—Add Health is a nationally representative school-based cohort of US adolescents (Wave I: 1994–95, n=20,745, aged 11–20 y, mean age 15.9 y) drawn from a probability sample of 80 high schools and 52 middle schools, representative of US schools in 1994–95 with respect to region, urban setting, school size and type, and race or ethnic background. Wave II (1996, n = 14,738, aged 12–21 y, mean age 16.5 y) included by design Wave I adolescents still of school age, including those currently in high school and high school dropouts. Oversampled subgroups include related and non-related adolescents sharing a Wave I household (n=5,524 Wave I respondents living in 2,639 households) [16] and several race/ethnic subpopulations, including Chinese, Cubans, Puerto Ricans, and Filipinos. Wave III (2001–2002, n= 15,197, aged 18–27 y, mean age 22.3 y) and Wave IV (2008–2009, n=15,701, aged 23–32 y, mean age 28.9 y) followed all Wave I respondents, regardless of Wave II participation. The most recent data collection (Wave IV) included follow-up interviews from 15,701 respondents drawn from 19,962 of the original 20,745 Wave I respondents and included DNA collection and banking for future studies. Survey procedures have been described elsewhere [17–19], and were approved by the Institutional Review Board, University of North Carolina at Chapel Hill.

Literature-based SNPs and Genotyping—We selected 34 SNPs associated with BMI reported by the Genetic Investigation of ANthropometric Traits (GIANT) consortium (Supplementary Table 1) and other studies in European adults [4, 20–24]. Familial relationships were classified according to participant and parental self-report. Twin zygosity was confirmed by 11 molecular genetic markers [25]. Genotyping was performed using TaqMan assays and the ABI Prism 7900® Sequence Detection System (Applied Biosystems, Foster City, CA, USA). Sequences for primers and TaqMan probes are available upon request. Procedures for genotyping (call rate 98%, discordance 0.3%) have been detailed elsewhere [26].

Ancestry—Ancestry was constructed using race and ethnic background and family relationship status (i.e. country of origin, ancestry, and adoption): European American (EA), African American (AA), and Hispanic American (HA), with indicators for subpopulation (e.g., Mexican, Cuban) and immigrant status (e.g., US and non-US born), given differences in BMI by immigrant status [27, 28].

Analysis sample

We included individuals with phenotype data in at least two Waves of data collection, and those that had at least 80% of the SNPs genotyped (n=10,710). In addition, we excluded one from each twin pair (n=142 pairs) with the fewest genotypes SNPs, Asian, Native American or other race/ethnicity (n=719); disabled (n=76); and individuals missing covariate data (n=125) or pregnant at all BMI observations available (n=18). BMI was set to missing for

women who were pregnant at a particular observation. The final analytic sample included 9,624 individuals measured at Waves II, III, and/or IV with DNA data (Supplementary Figure 1). Wave I included only self-reported height and weight and was only one year prior to Wave II, thus we did not include these self-reported observations. Within each of three ethnic groups, sample sizes were comprised of 5,962 EA, 2,080 AA, and 1,582 HA. When analyzing AAs, we excluded 12 of 34 SNPs (rs2568958, rs1514175, rs1555543, rs887912, rs2890652, rs13078807, rs2112347, rs4929949, rs4771122, rs11847697, rs571312, rs29941; see notes in all tables) that did not show evidence of association at $p<0.20$ and consistent direction of effect in AA GWAS [29, 30]. Given the lack of large GWAS in Hispanics, and the observation that 75% of GWAS SNPs for complex traits were replicated in Hispanics [31], all 34 SNPs were considered in analyses of this population.

Statistical analysis

Outcome Measure: Change in Body Mass Index (BMI)—BMI (kg/m^2) was calculated from measured height and weight taken at Waves II, III and IV during in-home surveys using standardized procedures. Self-reported height and weight (r=0.95/0.94 with measured weight/height [32]) were substituted for those refusing measurement and/or weighing more than scale (Health-o-meter 844KL digital scale, Jarden Corporation; Rye, NY) capacity (n=163 at Wave II, n=371 at Wave III, and n=82 at Wave IV). The maximum scale at all waves was 200 kg / 440 lbs maximum. We used BMI rather than Z-scores as is common in the literature [33–35], which allows more straightforward interpretation. Individual participant linear slopes were derived using the best linear unbiased prediction method ("BLUP"), regressing BMI on age as both a fixed and random effect. We also adjusted for current smoking at the indicated Wave, and an indicator for whether or not height and weight was self-reported as fixed effects. Models were run by sex to account for sex-specific differences in weight across time and by ancestry to account for ancestry differences in weight gain over time. Of the 9,624 individuals in the analyses, 6,403 had 3 BMI measurements used to create the slope and 3,221 had 2 BMI measurements (1,296 with BMI at Wave II and Wave IV, 1,913 with BMI at Wave III and Wave IV, and 12 with BMI at Wave II and Wave III) to create their slope.

Association analyses—Ancestry-stratified association analyses between change in BMI and SNP genotype were conducted using linear mixed models incorporated in Stata, version 12.1 (Stata Corp, College Station, TX. Each SNP was modeled under an additive model, with SNPs scored for the number of copies of the established (from prior GWAS) risk allele or 'BMI-increasing' allele. Covariates included baseline age, sex, geographic region, oversampling of highly educated AAs (n=520), Hispanic ancestry: Cuban (n=284), Puerto Rican (n=275), Central/South American (n=160), Mexican (n=863), other Hispanic (n=102), and if the participant was foreign born (n=432). Study design effects and relatedness were accounted for using random effects for school and family (of the 9,624 total individuals, 1744 (18%) were related or shared a household with another individual in the sample). Effect estimates were combined and meta-analyzed in METAL using the inverse standard-error weighted approach [36]. For each SNP association, we evaluated heterogeneity between race/ethnic groups using Cochran's Q. We considered evidence for heterogeneity when the chi-square $p<0.10$ or I^2 index >50[37, 38]. While we examined all nominally

significant findings ($p<0.05$), we corrected for multiple testing: $\alpha = 0.05$/number of SNPs tested ($p\leq0.0015$ in EA, $p\leq0.0015$ in HA, and $p\leq0.0023$ in AA, and $p\leq0.0015$ in the combined meta-analyzed sample). We also ran models without including any SNPs (Supplementary Table 2).

For SNPs with nominally significant effects ($p<0.05$) on the change in BMI, we interrogated two additional sets of analyses to assess whether the effects on change in BMI were due to different effects across age groups or points in time, the latter for which we use Wave of data collection. Given the narrow age range among participants (approximately 10 year age-span) within each Wave of data collection, cohort and age effects are highly collinear. Thus, to interrogate whether SNP effects vary by age, we performed SNP-by-age interaction analyses on cross-sectional BMI at each Wave. This set of analyses considered that a locus might have a stronger effect in younger compared to older individuals within the full age range studied (e.g., 12–21 years at Wave II) or vice versa. To keep the sample size constant when testing for the SNP-by-age interaction at each Wave, we included a subsample of participants with measured anthropometry at Waves II, III and IV. This reduced our sample size to 6,190 (3,155 females and 3,035 males). To aid in interpretation of the SNP-by-age interaction results, we plotted the results by year of age at each Wave, except for ages 13–14 and ages 18–21, which we combined due to smaller sample sizes. Second, we examined the main genetic effects of each SNP on cross-sectional BMI between individuals at similar ages but at a different Wave of data collection Wave, to verify that the main effect of the SNP on BMI is changing from one Wave to the next (i.e., across time periods). We attempted to age match the groups when testing the same ages between 2 different Waves (i.e. time points). Given the small sample sizes we combined age groups that overlapped including ages 18–20 as one group, both in Wave II and Wave III, and ages 25–26 as a second group, both in Wave III and Wave IV. Then we ran interaction models by testing the SNP×Wave effect separately in each of the two age groupings.

RESULTS

The participants (47% females) were an average of 16.1 years of age (ranging from 13–21 years) in 1996 (Wave II) and 28.5 years (ranging from 25–34 years) in 2008 (Wave IV). Mean BMI in 1996 ranged from 22.9±4.9 kg/m^2 in EA to 24.1±5.7 kg/m^2 in AA, while in 2008 mean BMI ranged from 28.5±7.1 kg/m^2 in EA to 30.5±8.4 kg/m^2 in AA (Table 1). The average change per year was largest in AA, 0.54±28 kg/m^2 and smallest in EA, 0.45±22 kg/m^2. Analyses using a model without SNPs (Supplementary Table 2) showed significant associations with age, sex, and in most cases random effect parameters. Sampling based on education in Africans was not significant. Foreign born and ancestry variables in Hispanics were not significant except that Cuba had significantly lower change in BMI compared to Puerto Ricans (the referent).

In EA, *FTO* SNP rs9939609 was genome-wide significantly associated (p=2.42e-09) with the slope of BMI (e.g. change in BMI over time), suggesting a 0.025 kg/m^2 per year of age increase in BMI for each additional copy of the established risk allele compared to non-carriers (Table 2). Similar results were seen for variants (in/near) rs571312 *(MC4R)*, rs3817334 *(MTCH2)*, rs6548238 (*TMEM18*), rs987237 *(TFAP2B)*, and rs543874

(SEC16B), with estimated effect sizes suggesting increases in BMI ranging from 0.014 to 0.025 kg/m^2 per year for each additional copy of their respective established risk alleles as compared to non-risk allele carriers (Table 2). These results were significant after correcting for 34 tests ($p<0.0015$). Thirty-two of 34 SNPs displayed positive effect estimates on BMI change (consistent with the established risk alleles being associated with higher cross-sectional BMI in prior reports) and 13 of these were at least nominally significant, which is more than expected by chance alone (binomial p=3.9E-09). In AA, no SNPs were significantly associated with BMI slope. However, 17 of 24 tested had positive beta estimates and 5 of these variants in/near *SEC16B* (rs543874), *GNPDA2* (rs10938397), *ETV5* (rs7647305), *LRRN6C* (rs10938397), and *MAP2K5* (rs2241423) were also nominally significant, which is more than expected by chance (binomial p=0.005). In HA, no SNPs were significantly associated with BMI slope, but 22 of 34 SNPs had positive beta estimates, and four were nominally significant (rs1514175, rs543874, rs9939609, rs12444979, respectively in/near *TNNI3K, SEC16B, FTO* and *GPRC5B).* In the all ancestry meta-analysis, 31 of 34 SNPs had positive effect estimates for the established risk allele on change in BMI and six SNPs in/near *MC4R* (rs571312), *MTCH2* (rs3817334), *TMEM18* (rs6548238), *TFAP2B* (rs987237), *FTO* (rs9939609), and *SEC16B* (rs543874) displayed significant associations after correcting for multiple testing (Figure 1). Again, *FTO* met genome-wide significance. While the statistical significance estimates in the meta-analyses for these 6 loci were dominated by the larger EA results, effect estimates were largely consistent across ethnic groups. Two notable exceptions were for *FTO* SNP rs9939609 and *TFAP2B* SNP rs987237, where the effect estimates in AA were noticeably smaller compared to EA and HA (Table 2), possibly because these SNPs are not tagging the relevant signal in Africans. We calculated the variance explained by each SNP based on our meta-analysis results. We calculated the variance explained for a one year change in BMI for each SNP based on our European ancestry analysis results (Table 2). The cumulative variance explained by the six SNPs that met Bonferroni significance or by the 15 SNPs that met nominal significance ($p<0.05$), is 0.09% 0.37%, respectively.

We next considered whether the loci significantly associated ($p<0.05$) with change in BMI within each ancestry might have different magnitudes of effect at younger compared to older ages. Therefore, we tested a SNP-by-age interaction on cross-sectional BMI at each of Waves II, III and IV for nine SNPs in EA and two SNPs each in AA and HA. In EA, we found two interactions that remained statistically significant after correction for multiple testing ($p<0.05/9$ SNPs=0.0056); a negative estimated SNP-by-age interaction effect on BMI at Wave II for rs3817334 (in *MTCH2*; $\beta_{interaction}\pm$[se] = −0.192[0.065]) and a positive estimated interaction effect for rs987237 (in *TFAP2B;* $\beta_{interaction}\pm$[se] = 0.308[0.085]) (Table 3 and Supplementary Table 3). Thus, the SNP near *TFAP2B* had a stronger influence on BMI in EA adolescents who were older, while *MTCH2* had a stronger influence on BMI in EA adolescents who were younger. No other SNP-by-age interactions on BMI at any Wave were significant, although SNP-by-age interaction estimates for *MTCH2* and *TFAP2B* on BMI were consistent in direction of effect but smaller in magnitude at Waves III and IV compared to Wave II.

To aid in interpretation of these effect estimates, we estimated the main effect associations between BMI and rs3817334 (in *MTCH2*) and rs987237 (in *TFAP2B*), by age group at each

Wave (Figure 2). For rs3817334 (in *MTCH2*), estimated main effects were comparatively larger in younger respondents across all Waves, with an increasing range in differences by age across time. The magnitude of the estimated effect appears to be driven by the individuals who were younger compared to older (e.g. aged ≤ 15 years versus ≥16 years), with increased variability in effect estimates in 2001 (Wave II) and again in 2008 (Wave III) [Figure 2]. The magnitudes of the estimated main effects were highest across all Waves in the youngest participants that were recruited to Add Health and who were age 13–14 years at Wave II. For rs987237 (in *TFAP2B*), the estimated main effects were comparatively larger in older respondents across all Waves. We then compared effect sizes in all participants who were similar ages but at different points in time (i.e. those who were aged 18–20 years in Wave II versus Wave III or 25–26 years in Waves III versus Wave IV). While no SNPs were significant for SNP-by-Wave interactions after correcting for multiple testing, both rs3817334 in *MTCH2* (stronger effects in Wave III than Wave II) and rs987237 in *TFAP2B* (weaker effects in Wave III than Wave II) had nominally significant SNP-by-Wave interactions when comparing aged 18–20 year olds between Waves II and III (Table 4 and Supplementary Table 4).

DISCUSSION

Over the past decade, numerous common genetic loci have been reported to be associated with BMI in primarily European descent adults, as well as in other ancestral groups, and at one or more phases of the life course including adulthood [4, 21, 29, 39–41], childhood [7, 42–44] and adolescence [7, 26, 45]. We extended these findings to interrogate 34 known obesity-related loci for association with change in BMI across the transition from adolescence to adulthood in an ethnically diverse, nationally representative cohort of adolescents followed over 13 years into adulthood.

Among EA, we observed statistically significant positive associations with change in BMI (when oriented on the obesity susceptibility allele) from adolescence into adulthood for 6 of 34 known obesity loci tested, including one *FTO* variant (rs9939609) that met genome-wide significance. Results were similar in the meta-analyses including EA, HA and AA. Among six Bonferroni-corrected significant SNPs, only *FTO, MC4R, TFAP2B*, and *SEC16B* have been shown to be associated with cross-sectional measures of BMI during adolescence in this cohort [26]. The variance explained for a one year change in BMI the by six Bonferroni-corrected significant SNPs or the 15 SNPs that met nominal significance is clinically rather small. How this extends beyond one year is not something we can extrapolate here. However, we have only tested a selection of SNPs and there are likely others that influence change in BMI in addition to those tested here. Our work confirms previous findings in younger children (ages one to 16 years) of European descent of positive associations between BMI-related loci and BMI trajectories of at least nominal significance with *FTO, MC4R, SEC16B, TMEM18, TFAP2B* and *MTCH2* [13]. Other analysis of *FTO* variant rs9939609 and *MC4R* variant rs17782313 (R^2=0.96 with the *MC4R* SNP rs571312 we tested) associations with change in BMI from childhood into adulthood in a sample of 2,479 European descent individuals suggested comparatively stronger association with BMI from age two to 20 years and then weakening to age 53 [7]. In our study, *FTO* variant rs9939609 and *MCR4* variant rs571312 were positively associated with change in BMI, however,

though consistent in direction with the prior report, the effects of these variants in higher vs. lower ages in Wave-stratified age-by-SNP interaction analyses were not significant. A longitudinal study in over 41,000 European descent adults from three studies, mean ages 60, 45, and 58 years, found no statistically significant association with *FTO* and change in BMI across a 10-year period of time [46]. Thus, *FTO* may play a comparatively less prominent role in relation to weight change in later adulthood. A recent study comparing genome-wide genetic effects on BMI in younger adults <=50 years versus older adults (>50 years) showed 11 of 15 loci with greater estimated effects on younger adults [43]. None of the 11 loci were associated with birth weight, yet all but one were nominally associated with increased risk of childhood obesity and BMI in 16-to-25 year-olds, suggesting that some loci exert genetic effects relatively early in life and into young adulthood. Among the 11 loci were variants in *FTO, MC4R, SEC16B*, and *TMEM18* that are in high linkage disequilibrium (R^2>0.8) with those identified in the current study.

Change in BMI over time, and the effects of genotype on this change, is likely impacted by many factors including changes in age and environment. Many of the specific environmental factors are either unknown or difficult to adequately measure and/or represent in a social epidemiological study. Over the past couple of decades, there has been a profound increase in obesity in both adolescent and adult populations due to a number of external factors strongly associated with the time period. In our study, like most social and epidemiological longitudinal studies, the impact of change in age and general change in environment captured by year of study (Wave) are highly confounded. In addition to assessing longitudinal change in BMI, we also performed Wave-stratified age-by-SNP interactions and age-matched Wave-by-SNP interactions between adjacent Waves to attempt to tease apart this confounding. Our findings suggest that the etiology for the observed strengthening associations between established BMI variants and BMI during the period of adolescence and young-adulthood is complex and may be a function of both the aging process and exposure to an increasingly obesogenic environment[47]. The interaction between rs987237 (near *TFAP2B*) and age suggests that this variant has stronger effects on BMI in older adolescents/young adults (in the 13–21 year age range at Wave II, the estimated increase in BMI from each established risk allele is 2.5kg/m^2 greater for those at age 21 compared to those at age 13). On the other hand, for *MTCH2* variant rs3817334, we observed evidence for stronger estimated effects on BMI at younger ages as suggested by the significant interaction of age and rs3817334 during Wave II when participants ranged from 13 to 21 years old. Given the main and interaction effect sizes, the estimated increase in BMI per T allele of rs3817334 is 1.5kg/m^2 greater in those who are 13 years at Wave II versus those who are 21 years at Wave II. Interestingly, we also found supporting evidence for this same variant having stronger effects on BMI in later Waves (e.g. stronger in Wave II vs. Wave III) in age-matched participants. For *TFAP2B* variant rs987237, the effects appear to be stronger in earlier Waves among age-matched participants. *MTCH2* is highly expressed in white adipose tissue and adipocytes, and thought to play a regulatory role in adipocyte differentiation and biology, while *TFAP2B* mRNA expression has been shown to be correlated negatively with leptin and positively with IL-6 expression in both subcutaneous and omental adipose tissues [48]. Possibly *MTCH2* might influence younger individuals more in playing a role during puberty while *TFAP2B* might have a stronger effect in older

individuals in that cytokines (e.g. IL-6) have markedly lower levels in children versus adults [49]. For the other variants associated with change in BMI, we found no significant evidence pointing to differential effects across ages or year of study.

While our study capitalizes on an ancestrally diverse, nationally representative cohort measured during a unique period of the lifecycle, there are limitations. There is a lack of established obesity loci in HA and power in HA for common loci in our study was limited by smaller sample sizes. In addition, the age range of our participants limited our ability to separate differences in effect by age that might be due to cohort, time, and or age. The Add Health sample is largely comprised of post-pubertal adolescents. For example <1% of Add Health females had not achieved menarche by wave I. Nonetheless we conducted a sensitivity analysis with (and without) adjustment for age at menarche in women (we have no such comparable measure for men) (Supplementary Table 5). This sensitivity analysis suggests little difference and therefore would infer that there is little confounding from lack of adjustment for puberty. We were unable to test periods of the life course that might be defined as childhood or middle- to late-adulthood, making comparisons with other studies difficult. However, these questions extend beyond the scope of the current study given our sample. Finally, while it is possible, most common variants are not affected by pop stratification in Europeans which is where we find most results. We are not well powered to detect effects in these samples. Thus, it is not likely that we are reporting any false positives.

In conclusion, we demonstrated that several established BMI variants are positively associated with change in BMI during the period of adolescence and young-adulthood. Through stratified analyses, we demonstrate that *MTCH2* variant rs3817334 has stronger effects on BMI in younger participants and in later Wave (i.e. time periods), and that *TFAP2B* variant rs987237 has stronger effects in older participants and in earlier Waves. Due to the confounding between age and Wave in longitudinal analyses, stratified analyses were necessary to tease apart these directionally conflicted findings for both variants. Our results suggest that the genetic effect of BMI loci varies over time in a complex manner, highlighting the importance of investigating loci influencing obesity risk across the life course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

SNP	Single Nucleotide Polymorphism
GWA	Genome-Wide Association
EA	European American
AA	African American
HA	Hispanic American

REFERENCES

1. Dietz W. Critical periods in childhood for the development of obesity. Am J Clin Nutr. 1994; 59(5): 955–959. [PubMed: 8172099]
2. Gordon-Larsen P, Adair LS, Nelson MC, P BM. Five-year obesity incidence in the transition period between adolescence and adulthood: the National Longitudinal Study of Adolescent Health. American Journal of Clinical Nutrition. 2004; 80(3):569–575. [PubMed: 15321794]
3. Suchindran C, North KE, Popkin BM, Gordon-Larsen P. The, N.S. Association of adolescent obesity with risk of severe obesity in adulthood. JAMA. 2010; 304(18):2042–2047. [PubMed: 21063014]
4. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet. 2010; 42(11):937–948. [PubMed: 20935630]
5. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature. 2015; 518(7538):197–206. [PubMed: 25673413]
6. Hallman DM, Friedel VC, Eissa MA, Boerwinkle E, Huber JC Jr, Harrist RB, et al. The association of variants in the FTO gene with longitudinal body mass index profiles in non-Hispanic white children and adolescents. Int J Obes (Lond). 2012; 36(1):61–68. [PubMed: 21986706]
7. Hardy R, Wills AK, Wong A, Elks CE, Wareham NJ, Loos RJ, et al. Life course variations in the associations between FTO and MC4R gene variants and body size. Hum Mol Genet. 2010; 19(3): 545–552. [PubMed: 19880856]
8. Liu G, Zhu H, Dong Y, Podolsky RH, Treiber FA, Snieder H. Influence of common variants in FTO and near INSIG2 and MC4R on growth curves for adiposity in African- and European-American youth. Eur J Epidemiol. 2011; 26(6):463–473. [PubMed: 21544599]
9. Loos RJ, Lindgren CM, Li S, Wheeler E, Zhao JH, Prokopenko I, et al. Common variants near MC4R are associated with fat mass, weight and risk of obesity. Nat Genet. 2008; 40(6):768–775. [PubMed: 18454148]
10. Bradfield JP, Taal HR, Timpson NJ, Scherag A, Lecoeur C, Warrington NM, et al. A genome-wide association meta-analysis identifies new childhood obesity loci. Nat Genet. 2012; 44(5):526–531. [PubMed: 22484627]
11. Wing MR, Ziegler J, Langefeld CD, Ng MC, Haffner SM, Norris JM, et al. Analysis of FTO gene variants with measures of obesity and glucose homeostasis in the IRAS Family Study. Hum Genet. 2009; 125(5–6):615–626. [PubMed: 19322589]
12. Mei H, Chen W, Jiang F, He J, Srinivasan S, Smith EN, et al. Longitudinal replication studies of GWAS risk SNPs influencing body mass index over the course of childhood and adulthood. PLoS One. 2012; 7(2):e31470. [PubMed: 22355368]
13. Warrington NM, Howe LD, Wu YY, Timpson NJ, Tilling K, Pennell CE, et al. Association of a body mass index genetic risk score with growth throughout childhood and adolescence. PLoS One. 2013; 8(11):e79547. [PubMed: 24244521]
14. Croteau-Chonka DC, Marvelle AF, Lange EM, Lee NR, Adair LS, Lange LA, et al. Genome-wide association study of anthropometric traits and evidence of interactions with age and study year in Filipino women. Obesity (Silver Spring). 2011; 19(5):1019–1027. [PubMed: 20966902]

15. Kaakinen M, Laara E, Pouta A, Hartikainen AL, Laitinen J, Tammelin TH, et al. Life-course analysis of a fat mass and obesity-associated (FTO) gene variant and body mass index in the Northern Finland Birth Cohort 1966 using structural equation modeling. Am J Epidemiol. 2010; 172(6):653–665. [PubMed: 20702506]
16. Harris KM, Halpern CT, Smolen A, Haberstick BC. The National Longitudinal Study of Adolescent Health (Add Health) twin data. Twin Res Hum Genet. 2006; 9(6):988–997. [PubMed: 17254442]
17. Harris KM. An integrative approach to health. Demography. 2010; 47(1):1–22. [PubMed: 20355681]
18. Miller WC, Ford CA, Morris M, Handcock MS, Schmitz JL, Hobbs MM, et al. Prevalence of chlamydial and gonococcal infections among young adults in the United States. JAMA. 2004; 291(18):2229–2236. [PubMed: 15138245]
19. Resnick MD, Bearman PS, Blum RW, Bauman KE, Harris KM, Jones J, et al. Protecting adolescents from harm. Findings from the National Longitudinal Study on Adolescent Health. JAMA. 1997; 278(10):823–832. [PubMed: 9293990]
20. Thorleifsson G, Walters G, Gudbjartsson D, Steinthorsdottir V, Sulem P, Helgadottir A, et al. Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. Nature Genetics. 2009; 41(1):18–24. [PubMed: 19079260]
21. Willer CJ, Speliotes EK, Loos RJ, Li S, Lindgren CM, Heid IM, et al. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. Nat Genet. 2009; 41(1):25–34. [PubMed: 19079261]
22. Lindgren CM, Heid IM, Randall JC, Lamina C, Steinthorsdottir V, Qi L, et al. Genome-wide association scan meta-analysis identifies three Loci influencing adiposity and fat distribution. PLoS Genet. 2009; 5(6):e1000508. [PubMed: 19557161]
23. Heard-Costa NL, Zillikens MC, Monda KL, Johansson A, Harris TB, Fu M, et al. NRXN3 is a novel locus for waist circumference: a genome-wide association study from the CHARGE Consortium. PLoS Genet. 2009; 5(6):e1000539. [PubMed: 19557197]
24. Heid IM, Jackson AU, Randall JC, Winkler TW, Qi L, Steinthorsdottir V, et al. Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. Nat Genet. 2010; 42(11):949–960. [PubMed: 20935629]
25. The Add Health Biomarker Team. Biomarkers in Wave III of the Add Health Study. In: Manhart, LE., editor. 1999. p. 57
26. Graff M, North KE, Mohlke KL, Lange LA, Luo J, Harris KM, et al. Estimation of genetic effects on BMI during adolescence in an ethnically diverse cohort: The National Longitudinal Study of Adolescent Health. Nutrition and Diabetes. 2012; 2:e47. [PubMed: 23168566]
27. Bates LM, Acevedo-Garcia D, Alegria M, Krieger N. Immigration and generational trends in body mass index and obesity in the United States: results of the National Latino and Asian American Survey: 2002–2003. Am J Public Health. 2008; 98(1):70–77. [PubMed: 18048787]
28. Harris KM, Perreira KM, Lee D. Obesity in the transition to adulthood: predictions across race/ethnicity, immigrant generation, and sex. Arch Pediatr Adolesc Med. 2009; 163(11):1022–1028. [PubMed: 19884593]
29. Monda KL, Chen GK, Taylor KC, Palmer C, Edwards TL, Lange LA, et al. A meta-analysis identifies new loci associated with body mass index in individuals of African ancestry. Nat Genet. 2013; 45(6):690–696. [PubMed: 23583978]
30. Kang SJ, Chiang CW, Palmer CD. Genome-wide association of anthropometric traits in African- and African-derived populations. Human Molecular Genetetics. 2010; 19(13):2725–2738.
31. Carlson CS, Matise TC, North KE, Haiman CA, Fesinmeyer MD, Buyske S, et al. Generalization and dilution of association results from European GWAS in populations of non-European ancestry: the PAGE study. PLoS Biol. 2013; 11(9):e1001661. [PubMed: 24068893]
32. Goodman E, Hinden BR, Khandelwal S. Accuracy of teen and parental reports of obesity and body mass index. Pediatrics. 2000; 106(1 Pt 1):52–58. [PubMed: 10878149]
33. Heo M, Faith MS, Mott JW, Gorman BS, Redden DT, Allison DB. Hierarchical linear models for the development of growth curves: an example with body mass index in overweight/obese adults. Stat Med. 2003; 22(11):1911–1942. [PubMed: 12754724]

34. Kakinami L, Henderson M, Chiolero A, Cole TJ, Paradis G. Identifying the best body mass index metric to assess adiposity change in children. Arch Dis Child. 2014; 99(11):1020–1024. [PubMed: 24842797]
35. Sovio U, Mook-Kanamori DO, Warrington NM, Lawrence R, Briollais L, Palmer CN, et al. Association between common variation at the FTO locus and changes in body mass index from infancy to late childhood: the complex nature of genetic association through growth and development. PLoS Genet. 2011; 7(2):e1001307. [PubMed: 21379325]
36. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics. 2010; 26(17):2190–2191. [PubMed: 20616382]
37. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002; 21(11): 1539–1558. [PubMed: 12111919]
38. Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol Methods. 2006; 11(2):193–206. [PubMed: 16784338]
39. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science. 2007; 316(5826):889–894. [PubMed: 17434869]
40. Vasan SK, Fall T, Neville MJ, Antonisamy B, Fall CH, Geethanjali FS, et al. Associations of variants in FTO and near MC4R with obesity traits in South Asian Indians. Obesity (Silver Spring). 2012
41. Wen W, Cho YS, Zheng W, Dorajoo R, Kato N, Qi L, et al. Meta-analysis identifies common variants associated with body mass index in east Asians. Nat Genet. 2012; 44(3):307–311. [PubMed: 22344219]
42. Wang J, Mei H, Chen W, Jiang Y, Sun W, Li F, et al. Study of eight GWAS-identified common variants for association with obesity-related indices in Chinese children at puberty. Int J Obes (Lond). 2012; 36(4):542–547. [PubMed: 22083549]
43. Zhao J, Bradfield JP, Zhang H, Sleiman PM, Kim CE, Glessner JT, et al. Role of BMI-associated loci identified in GWAS meta-analyses in the context of common childhood obesity in European Americans. Obesity (Silver Spring). 2011; 19(12):2436–2439. [PubMed: 21779088]
44. Zhao J, Grant SF. Genetics of childhood obesity. J Obes. 2011; 2011:845148. [PubMed: 21773009]
45. den Hoed M, Ekelund U, Brage S, Grontved A, Zhao JH, Sharp SJ, et al. Genetic susceptibility to obesity and related traits in childhood and adolescence: influence of loci identified by genome-wide association studies. Diabetes. 2010; 59(11):2980–2988. [PubMed: 20724581]
46. Hertel JK, Johansson S, Sonestedt E, Jonsson A, Lie RT, Platou CG, et al. FTO, type 2 diabetes, and weight gain throughout adult life: a meta-analysis of 41,504 subjects from the Scandinavian HUNT, MDC, and MPP studies. Diabetes. 2011; 60(5):1637–1644. [PubMed: 21398525]
47. Ravussin E, Bouchard C, et al. Human genomics and obesity: finding appropriate drug targets. Eur J Pharmacol. 2000; 410(2–3):131–145. [PubMed: 11134665]
48. Ugi S, Nishio Y, Yamamoto H, Ikeda K, Kobayashi M, Tsukada S, et al. Relation of the expression of transcriptional factor TFAP2B to that of adipokines in subcutaneous and omental adipose tissues. Obesity (Silver Spring). 2010; 18(7):1277–1282. [PubMed: 20019683]
49. Lilic D, Cant AJ, Abinun M, Calvert JE, Spickett GP. Cytokine production differs in children and adults. Pediatr Res. 1997; 42(2):237–240. [PubMed: 9262229]

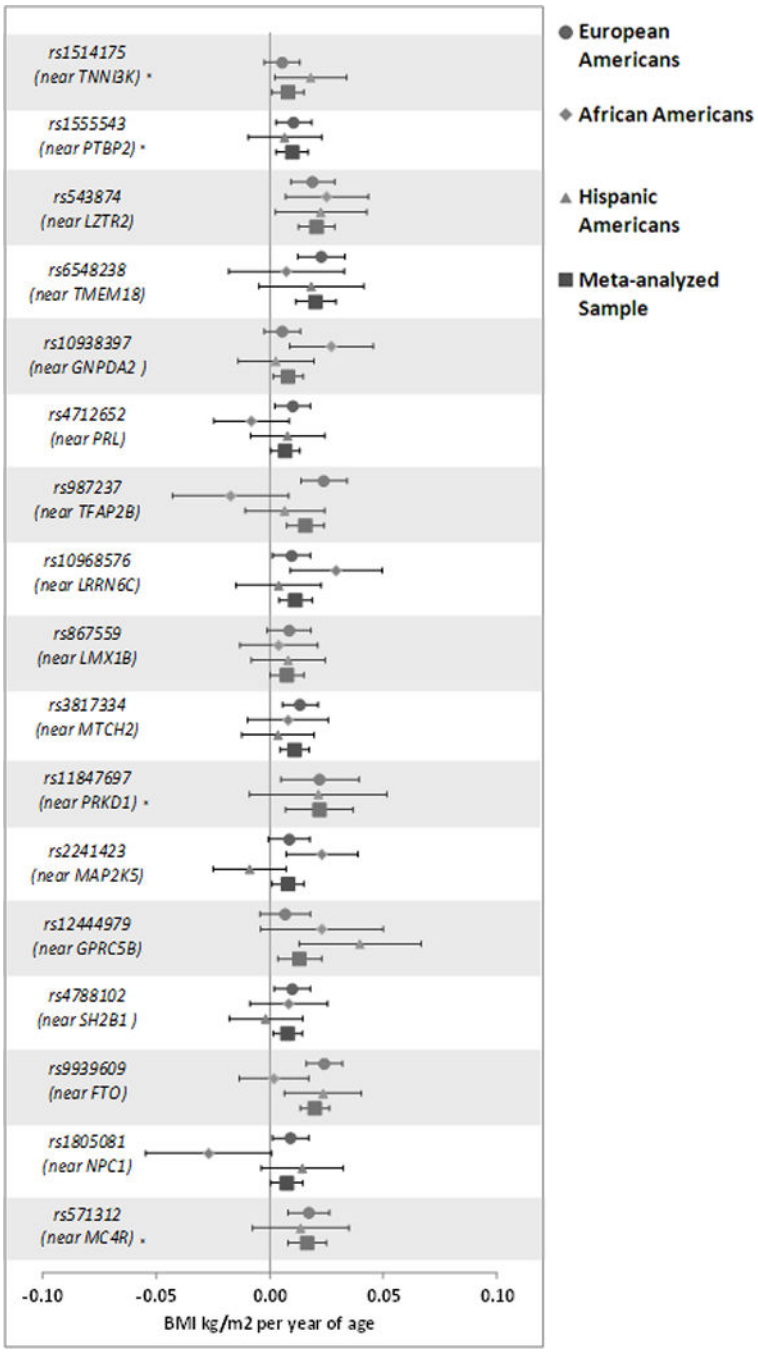

Figure 1.

For SNPs that achieved statistical significance at $p<0.05$ across the meta-anlayzed sample, effect estimates for per allele change in slope of BMI across adolescence to young adulthood for the Add Health cohort by ethnic/race group and combined.

*Denotes SNPs that do not generalize to African Americans and thus were not considered.

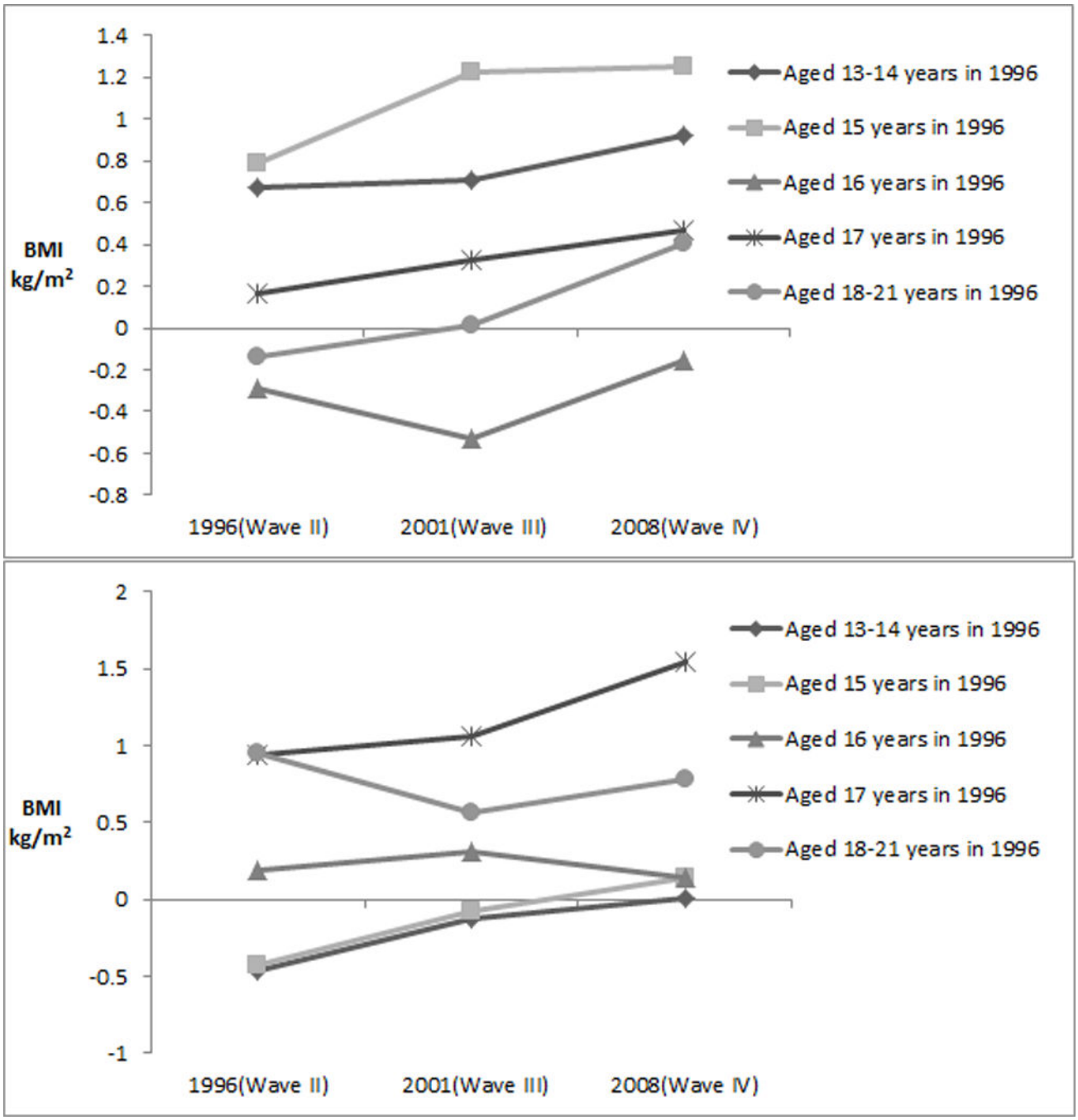

Figure 2.

Effect estimates of (a) rs3817334 (near *MTCH2*) and (b) rs987237 (near *TFAP2B*) with cross-sectional measures of BMI at each Wave by age group at Wave II.[a]

[a] To aid in interpretation, we plotted the results by year of age at each Wave, except for those aged 13–14 and aged 18–21 which we combined due to smaller sample sizes.

Sample sizes for MTCH2:

Aged 13–14 in 1996 (N=961 in Wave II, N=836 in Wave III, N=975 in Wave IV)

Aged 15 in 1996 (N=961 in Wave II, N=836 in Wave III, N=975 in Wave IV)

Aged 16 in 1996 (N=1007 in Wave II, N=840 in Wave III, N=1023 in Wave IV)
Aged 17 in 1996 (N=960 in Wave II, N=782 in Wave III, N=974 in Wave IV)
Aged 18–21 in 1996 (N=1022 in Wave II, N=904 in Wave III, N=1069 in Wave IV)
Sample sizes for TFAP2B:
Aged 13–14 in 1996 (N=966 in Wave II, N=843 in Wave III, N=980 in Wave IV)
Aged 15 in 1996 (N=835 in Wave II, N=715 in Wave III, N=845 in Wave IV)
Aged 16 in 1996 (N=1009 in Wave II, N=842 in Wave III, N=1025 in Wave IV)
Aged 17 in 1996 (N=967 in Wave II, N=789 in Wave III, N=981 in Wave IV)
Aged 18–21 in 1996 (N=1028 in Wave II, N=908 in Wave III, N=1075 in Wave IV)

Table 1

Descriptive information for the Add Health analytic sample, by race/ethnicity and in the total sample

	European Americans (N=5,962)				African Americans (N=2,080)				Hispanic Americans (N=1,582)				Total Sample (N=9,624)			
	Females		Males		Females		Males		Females		Males		Females		Males	
Variable	**N**	**Mean (SD) / %**	**N**	**Mean (SD) / %**	**N**	**Mean (SD) / %**	**N**	**Mean (SD) / %**	**N**	**Mean (SD) / %**	**N**	**Mean (SD) / %**	**N**	**Mean (SD) / %**	**N**	**Mean (SD) / %**
Age in Wave II, years	2,532	15.94 (1.6)	2,304	16.24 (1.63)	882	16.08 (1.63)	744	16.21 (1.67)	624	16.35 (1.66)	625	16.49 (1.60)	4,038	16.03 (1.62)	3,673	16.27 (1.64)
Age in Wave III, years	2,746	21.69 (1.77)	2,445	21.95 (1.76)	991	21.74 (1.71)	797	21.96 (1.84)	670	22.15 (1.74)	679	22.27 (1.76)	4,407	21.77 (1.76)	3,921	22.01 (1.78)
Age in Wave IV, years	2,987	28.18 (1.76)	2,831	28.43 (1.75)	1,103	28.29 (1.75)	929	28.44 (1.83)	766	28.64 (1.75)	783	28.78 (1.72)	4,856	28.28 (1.76)	4,543	28.49 (1.77)
BMI in Wave II, kg/m2	2,532	22.66 (4.9)	2,304	23.09 (4.76)	882	24.45 (6.03)	744	23.51 (5.07)	624	23.57 (5.32)	625	24.08 (5.10)	4,038	23.19 (5.29)	3,673	23.34 (4.90)
BMI in Wave III, kg/m2	2,746	25.96 (6.43)	2,445	26.28 (5.48)	991	28.4 (7.68)	797	26.61 (6.01)	670	27.14 (6.47)	679	27.42 (5.55)	4,407	26.69 (6.81)	3,921	26.55 (5.62)
BMI in Wave IV, kg/m2	2,987	28.3 (7.74)	2,831	28.66 (6.41)	1,103	31.83 (9.11)	929	29.01 (7.13)	766	29.58 (7.73)	783	30.23 (6.67)	4,856	29.30 (8.20)	4,543	29.00 (6.63)
One year change (slope) in BMI, kg/m2	3,131	0.44 (0.26)	2,831	0.46 (0.17)	1,145	0.61 (0.28)	935	0.45 (0.24)	797	0.47 (0.24)	785	0.51 (0.22)	5,073	0.48 (0.27)	4,551	0.46 (0.20)
Region, N (%)																
West	484	15.46	411	14.52	158	13.8	140	14.97	342	42.91	305	38.85	984	19.4	856	18.8
Midwest	1,142	36.47	1,032	36.45	215	18.78	172	18.4	59	7.4	58	7.39	1416	27.9	1,262	27.7
South	1,026	32.77	976	34.48	700	61.14	575	61.5	300	37.64	310	39.49	2026	39.9	1,861	40.9
Northeast	479	15.3	412	14.55	72	6.29	48	5.13	96	12.05	112	14.27	647	12.8	572	12.6

Abbreviations: BMI (body mass index), SD (standard deviation)

Table 2

Association results for the slope of BMI[a] with each SNP in the Add Health participants by race/ethnicity and in the combined meta-anlayzed sample.[b]

SNP information					European ancestry				African ancestry[c]				Hispanic ancestry				Meta-analyzed sample, All Ancestries[d]					
SNP	*Gene*	Chr	BP	Effect/ other allele [e]	EAF	Beta(SE) slope of BMI as kg/m^2 per year	Pvalue	N	EAF	Beta(SE) slope of BMI as kg/m^2 per year	Pvalue	N	EAF	Beta(SE) slope of BMI as kg/m^2 per year	Pvalue	N	EAF	Beta(SE) slope of BMI as kg/m^2 per year	Pvalue	N	HetISq	Variance explained [f]
rs2568958	*NEGR1*	1	72765116	A/G	0.6283	0.009 (0.004)	0.0363343449806959	5899					0.6946	−0.006 (0.009)	0.537930934892836	1571	0.6409	0.006 (0.004)	0.1026	7470	52.3	0.0008
rs1514175	*TNNI3K*	1	74991644	A/G	0.44	0.006 (0.004)	0.120431702081817	5928					0.5349	0.017 (0.008)	0.0426338583368813	1572	0.458	0.008 (0.004)	0.02171	7500	20.2	0.00001
rs1555543	*PTBP2*	1	96944797	C/A	0.5873	0.01 (0.004)	0.0150685657529825	5915					0.5688	0.007 (0.008)	0.395956543682014	1563	0.5861	0.009 (0.004)	0.0106	7478	0	0.0007
rs543874	***SEC16B, LZTR2***	**1**	**177889480**	**G/A**	**0.1993**	**0.019 (0.005)**	**0.000137710423790072**	**5927**	**0.241**	**0.027 (0.01)**	**0.00512916970442667**	**2064**	**0.1875**	**0.024 (0.01)**	**0.018689836407328**	**1567**	**0.2058**	**0.022 (0.004)**	**0.0000001724**	**9558**	**0**	**0.0004**
rs6548238	***TMEM18***	**2**	**634905**	**C/T**	**0.8297**	**0.024 (0.005)**	**8.31800216993805E-06**	**5937**	**0.8928**	**0.012 (0.013)**	**0.390540350175295**	**2070**	**0.8695**	**0.019 (0.012)**	**0.113699082451912**	**1572**	**0.8429**	**0.022 (0.005)**	**0.000002315**	**9579**	**0**	**0.00001**
rs713586	*POMC*	2	25158008	C/T	0.4837	0.009 (0.004)	0.0299801260334576	5901	0.8423	−0.007 (0.011)	0.520232429627132	2060	0.4306	−0.014 (0.008)	0.097795157849865	1564	0.5047	0.003 (0.004)	0.3457	9525	71.3	0.00004
rs887912	*FANCL*	2	59302877	T/C	0.2803	0.003 (0.005)	0.491160421613799	5930					0.1879	0.004 (0.011)	0.707969631936108	1575	0.2663	0.003 (0.004)	0.4354	7505	0	0.0001
rs2890652	*LRP1B*	2	142959931	C/T	0.1642	0.007 (0.006)	0.217162797065839	5920					0.1261	0.009 (0.012)	0.448557465796797	1569	0.1548	0.007 (0.005)	0.1506	7489	0	0.0001
rs13078807	*CADM2*	3	85884150	G/A	0.1981	0.01 (0.005)	0.0474965470274247	5925					0.147	−0.005 (0.012)	0.683265705532463	1576	0.192	0.008 (0.005)	0.09861	7501	26.8	0.0002
rs7647305	*ETV5*	3	185834290	C/T	0.7916	0.006 (0.005)	0.234131380762947	5916	0.597	0.021 (0.008)	0.00933554847364504	2062	0.8128	0.002 (0.01)	0.864315826922167	1568	0.749	0.009 (0.004)	0.02417	9546	35.9	0.00001
rs10938397	*GNPDA2*	4	45182527	G/A	0.4303	0.008 (0.004)	0.0644008335362849	5914	0.2411	0.031 (0.01)	0.0013579608823584	2067	0.3709	0.001 (0.009)	0.8868425665692	1571	0.3955	0.01 (0.004)	0.005698	9552	67	0.0007
rs13107325	*SLC39A8*	4	103188709	T/C	0.08068	0.012 (0.007)	0.105182944382441	5938	0.0154	0.006 (0.034)	0.851949875091347	2073	0.04119	0.005 (0.021)	0.822042856372413	1576	0.0732	0.011 (0.007)	0.1084	9587	0	0.00001
rs2112347	*FLJ3577, HMGCR*	5	75015242	T/G	0.6334	0.004 (0.004)	0.386300046195639	5909					0.6295	0.013 (0.009)	0.123905991663066	1572	0.63	0.006 (0.004)	0.1455	7481	0	0.0005
rs1077393	*NCR3, AIF1, BAT2*	6	31610529	G/A	0.4867	0.002 (0.004)	0.655112788718038	5883	0.345	−0.001 (0.009)	0.904136178479392	2052	0.4852	−0.006 (0.008)	0.488099423487185	1562	0.4687	0.0001 (0.003)	0.9701	9497	0	0.0001
rs206936	*NUDT3*	6	34302869	G/A	0.2098	0.006 (0.005)	0.218320267301597	5939	0.5357	−0.002 (0.008)	0.82655403883952	2067	0.3989	0.006 (0.008)	0.497745024011879	1568	0.3196	0.004 (0.004)	0.2523	9574	0	0.0001
rs987237	***TFAP2B***	**6**	**50803050**	**G/A**	**0.176**	**0.024 (0.005)**	**7.96402874936319E-06**	**5936**	**0.09875**	**−0.011 (0.014)**	**0.42707797684036**	**2070**	**0.2718**	**0.007 (0.009)**	**0.457200851773043**	**1572**	**0.1925**	**0.016 (0.004)**	**0.0001747**	**9578**	**71.6**	**0.0004**
rs10968576	*LRRN6C*	9	28414339	G/A	0.3103	0.011 (0.004)	0.0137325873208902	5888	0.1722	0.026 (0.011)	0.0129824960281197	2058	0.2352	0.005 (0.01)	0.605760679610998	1558	0.2825	0.012 (0.004)	0.00151	9504	18.3	0.0001
rs867559	*LMX1B*	9	129465325	G/A	0.1912	0.007 (0.005)	0.181945816557514	5926	0.2988	0.006 (0.009)	0.536527080574311	2063	0.3307	0.008 (0.008)	0.356649140521792	1575	0.2409	0.007 (0.004)	0.08423	9564	0	0.0003
rs4929949	*RPL27A, TUB*	11	8604593	C/T	0.5077	0.005 (0.004)	0.225799407987264	5904		0.008 (0.008)	0.312288924912817	2065	0.4853	0.006 (0.008)	0.455108051652104	1562	0.506	0.005 (0.004)	0.1565	7466	0	0.0005
rs10767664	*BDNF*	11	27725986	A/T	0.7888	0.006 (0.005)	0.266481925639808	5921	0.93374	0.002 (0.017)	0.895613080276965	2064	0.8079	0.007 (0.01)	0.510800725004547	1566	0.8031	0.006 (0.004)	0.2019	9551	0	0.00001
rs3817334	***MTCH2***	**11**	**47650993**	**T/C**	**0.4026**	**0.014 (0.004)**	**0.000597839313208892**	**5901**	**0.2601**	**0.006 (0.009)**	**0.531830133787902**	**2067**	**0.3894**	**0.005 (0.008)**	**0.537861556694164**	**1568**	**0.3795**	**0.011 (0.003)**	**0.0008378**	**9536**	**0**	**0.00001**
rs7138803	*FAIM2*	12	50247468	A/G	0.3782	0.008 (0.004)	0.0496305504077867	5820	0.1689	0.013 (0.011)	0.235457647729183	2045	0.2715	−0.011 (0.009)	0.260324258382214	1543	0.3405	0.006 (0.004)	0.1003	9408	47.8	0.0003
rs4771122	*MTIF3*	13	28020180	G/A	0.2199	0.006 (0.005)	0.181961568445123	5906					0.2016	0.009 (0.01)	0.408092615576273	1574	0.2164	0.007 (0.004)	0.1189	7480	0	0.0011
rs11847697	*PRKD1*	14	30515112	T/C	0.05325	0.023 (0.009)	0.00957949081714604	5939					0.07183	0.024 (0.016)	0.126117365353668	1580	0.055	0.024 (0.008)	0.00263	7519	0	0.0001
rs10146997	*NRXN3*	14	79945162	G/A	0.7909	−0.007 (0.005)	0.165654039718296	5943	0.6413	0.005 (0.008)	0.520134912588576	2070	0.7901	−0.004 (0.01)	0.659218936596024	1580	0.7565	−0.004 (0.004)	0.336	9593	0	0.00001
rs2241423	*MAP2K5*	15	68086838	G/A	0.7672	0.01 (0.005)	0.0416373735766462	5930	0.6242	0.022 (0.008)	0.00800851227675126	2068	0.5804	−0.01 (0.008)	0.239675502326333	1575	0.7025	0.008 (0.004)	0.02577	9573	73.7	0.0001
rs2444217	*ADCY9*	16	4038387	A/G	0.57	0.001 (0.004)	0.809051948917954	5924	0.76	−0.002 (0.01)	0.870364048427314	2062	0.43	−0.007 (0.008)	0.395081963932239	1568	0.5694	−0.001 (0.003)	0.8358	9554	0	0.00001
rs12444979	*GPRC5B*	16	19933600	C/T	0.8562	0.008 (0.006)	0.143422025867003	5901	0.91064	0.027 (0.014)	0.0590406874232221	2062	0.90834	0.039 (0.014)	0.00471861566537712	1570	0.8727	0.015 (0.005)	0.003194	9533	60	0.0001
rs4788102	*SH2B1*	16	28873398	A/G	0.3923	0.011 (0.004)	0.00550841945096625	5928	0.2801	0.013 (0.009)	0.153339943320713	2061	0.4032	−0.002 (0.008)	0.812178517765675	1573	0.3758	0.009 (0.003)	0.006001	9562	11.1	0.0007
rs9939609	***FTO***	**16**	**53820527**	**A/T**	**0.3929**	**0.025 (0.004)**	**2.41962405667095E-09**	**5907**	**0.4731**	**0.004 (0.008)**	**0.590061046533582**	**2067**	**0.3283**	**0.025 (0.009)**	**0.00475208845717967**	**1570**	**0.3952**	**0.021 (0.003)**	**0.0000000005377**	**9544**	**62.5**	**0.0002**
rs571312	***MC4R***	**18**	**57839769**	**A/C**	**0.2347**	**0.018 (0.005)**	**0.000145767338018077**	**5923**					**0.1638**	**0.017 (0.011)**	**0.125813734**	**1571**	**0.2188**	**0.018 (0.004)**	**0.0000425**	**7494**	**0**	**0.0001**

SNP information					European ancestry				African ancestry[c]				Hispanic ancestry				Meta-analyzed sample, All Ancestries[d]					
SNP	*Gene*	Chr	BP	Effect/ other allele [e]	EAF	Beta(SE) slope of BMI as kg/m^2 per year	Pvalue	N	EAF	Beta(SE) slope of BMI as kg/m^2 per year	Pvalue	N	EAF	Beta(SE) slope of BMI as kg/m^2 per year	Pvalue	N	EAF	Beta(SE) slope of BMI as kg/m^2 per year	Pvalue	N	HetISq	Variance explained [f]
rs29941	*KCTD15*	19	34309532	G/A	0.6803	0.004 (0.004)	0.315950807178992	5900					0.6435	0.015 (0.009)	0.125813734270379	1563	0.672	0.006 (0.004)	0.09793	7463	12.3	0.0001
rs2287019	*QPCTL*	19	46202172	C/T	0.8167	0.011 (0.005)	0.0374216237136888	5932	0.8833	0.003 (0.013)	0.839650890441376	2064	0.8702	−0.005 (0.012)	0.657435105815855	1574	0.8343	0.008 (0.005)	0.09055	9570	0	0.0008
rs3810291	*TMEM160*	19	47569003	A/G	0.6685	0.001 (0.004)	0.872282995109245	5915	0.208	0.002 (0.01)	0.843750665430601	2060	0.5625	0.011 (0.008)	0.203871204936517	1568	0.5938	0.003 (0.004)	0.4567	9543	0	0.0001

Abbreviations: SNP (single nucleotide polymorphism), EAF: Effect Allele Frequency, Chr: Chromosome, BP: base pair position based on NCBI build 37 (hg19), BMI (body mass index), SE (standard error)

[a]Individual participant linear slopes for BMI change were derived using the best linear unbiased prediction method ("BLUP"), regressing BMI on age as both a fixed and random effect. We also adjusted for current smoking at each Wave, and an indicator for whether or not height and weight was self-reported as fixed effects.

[b]Beta and standard error (SE) estimates are presented for the slope of BMI change: Multivariable linear models of slope of BMI regressed baseline age, sex, geographic region. Models in Hispanic Americans also adjusted for an indicator for foreign born and country of origin, and models in African Americans also adjusted for an indicator for selection for high education group (oversampling for education). Random intercepts allowed for individual, family and school. Models were run separately for each SNP.

[c]SNPs that are missing in African American stratum were excluded because it did not generalize based on published African American GWAS (Monda et al. 2012).

[d]Meta-analyzed results were done in METAL software (Willer et al 2012), by combining effect estiamtes from each of the 3 ancestries shown using the inverse-weighted approach.

[e]Effect allele oriented to BMI increasing allele

[f]The variance explained by SNP was calcuated in European ancestry individuals and based on the R-squared after regressing each SNP on the residual of the slope. The residual was calculated by adjusted for fixed effects of baseline age, smoking, gender, self-reported height or weight, and region, and random effects for school and family.

Table 3

The SNPx Age association results with cross-sectional BMI at each wave for SNPs associated with slope of BMI at Pvalue<0.05 within each race/ethnic group and the meta-analyzed sample.[a]

SNP	*Gene*	Chr	BP (hg19)	Effect/ other allele[b]	EAF	N	Wave 2		Wave 3		Wave 4	
							Beta(SE) SNPxAge	Pvalue SNPxAge	Beta(SE) SNPxAge	Pvalue SNPxAge	Beta(SE) SNPxAge	Pvalue SNPxAge
European Ancestry												
rs2568958	*NEGR1*	1	72765116	A/G	0.6276	3833	−0.095 (0.067)	0.15839675	−0.116 (0.085)	0.174223	−0.143 (0.099)	0.15002094
rs1555543	*PTBP2*	1	96944797	C/A	0.588	3841	0.063 (0.065)	0.33022502	0.045 (0.082)	0.58172959	0.079 (0.095)	0.40798848
rs543874	*SEC16B /LZTR2*	1	177889480	G/A	0.1973	3847	−0.038 (0.079)	0.63267938	0.032 (0.102)	0.75043498	−0.012 (0.118)	0.92137839
rs6548238	*TMEM18*	2	634905	C/T	0.8298	3853	−0.071 (0.079)	0.36787556	−0.059 (0.102)	0.56182566	−0.032 (0.117)	0.78259877
rs713586	*RBJ/ADCY3/ POMC*	2	25158008	C/T	0.4827	3825	−0.081 (0.064)	0.20255856	−0.053 (0.082)	0.51419235	−0.177 (0.095)	0.06133292
rs987237	***TFAP2B***	**6**	**50803050**	**G/A**	**0.174**	**3858**	**0.308 (0.085)**	**0.0002692**	**0.172 (0.109)**	**0.11352658**	**0.188 (0.125)**	**0.13101385**
rs10968576	*LRRN6C*	9	28414339	G/A	0.3143	3823	−0.036 (0.068)	0.59219184	−0.086 (0.087)	0.32343075	0.007 (0.101)	0.94512972
rs867559	*LMX1B*	9	129465325	G/A	0.1917	3842	0.003 (0.078)	0.96787912	0.065 (0.101)	0.51830464	0.08 (0.117)	0.4948819
rs3817334	***MTCH2***	**11**	**47650993**	**T/C**	**0.4056**	**3832**	**−0.192 (0.065)**	**0.00312145**	**−0.157 (0.083)**	**0.05902117**	**−0.124 (0.095)**	**0.19345613**
rs11847697	*PRKD1*	14	30515112	T/C	0.05271	3856	−0.052 (0.135)	0.69691654	−0.1 (0.174)	0.56412162	−0.027 (0.203)	0.8952082
rs4788102	*SH2B1*	16	28873398	A/G	0.3924	3854	−0.069 (0.064)	0.28107862	−0.129 (0.081)	0.11123961	−0.178 (0.094)	0.05777997
rs9939609	*FTO*	16	53820527	A/T	0.3923	3834	0.066 (0.067)	0.32476931	0.074 (0.084)	0.37519525	0.04 (0.098)	0.67997773
rs571312	*MC4R*	18	57839769	A/C	0.2345	3846	0.03 (0.076)	0.69118432	0.065 (0.096)	0.50288313	0.09 (0.111)	0.41517632
rs2287019	*QPCTL/GIPR*	19	46202172	C/T	0.8132	3852	−0.047 (0.083)	0.57410085	0 (0.106)	0.99808789	0.052 (0.122)	0.66672612
African Ancestry												
rs543874	*SEC16B /LZTR2*	1	177889480	G/A	0.2411	1242	−0.401 (0.156)	0.01016935	−0.28 (0.195)	0.15141702	−0.424 (0.225)	0.05926957
rs7647305	*ETV5/SFRS10/DGKG*	3	185834290	C/T	0.5983	1238	0.028 (0.136)	0.83665072	0.173 (0.171)	0.30973571	0.04 (0.202)	0.84448894
rs10938397	*Gene desert;GNPDA2*	4	45182527	G/A	0.2465	1238	−0.004 (0.155)	0.97974832	0.017 (0.197)	0.93280467	−0.091 (0.227)	0.68798342
rs10968576	*LRRN6C*	9	28414339	G/A	0.1732	1237	−0.006 (0.171)	0.97360567	0.17 (0.216)	0.43110424	0.256 (0.249)	0.30517407
rs2241423	*MAP2K5/LBXCOR1*	15	68086838	G/A	0.621	1244	0.033 (0.138)	0.80981145	0.02 (0.174)	0.90700752	−0.128 (0.199)	0.52115135
Hispanic Ancestry												
rs1514175	*TNNI3K*	1	74991644	A/G	0.5425	955	−0.127 (0.14)	0.36563463	−0.131 (0.167)	0.43285491	−0.058 (0.198)	0.76942165
rs543874	*SEC16B /LZTR2*	1	177889480	G/A	0.1864	951	−0.076 (0.18)	0.67358686	0.011 (0.216)	0.95944761	−0.321 (0.258)	0.21238977
rs12444979	*GPRC5B/IQCK*	16	19933600	C/T	0.91275	955	0.089 (0.237)	0.70626811	−0.317 (0.282)	0.26089037	−0.166 (0.333)	0.61751673
rs9939609	*FTO*	16	53820527	A/T	0.3247	955	−0.115 (0.144)	0.42517715	−0.035 (0.172)	0.84068492	0.048 (0.203)	0.81177089

SNP	Gene	Chr	BP (hg19)	Effect/ other allele[b]	EAF	N	Wave 2 Beta(SE) SNPxAge	Wave 2 Pvalue SNPxAge	Wave 3 Beta(SE) SNPxAge	Wave 3 Pvalue SNPxAge	Wave 4 Beta(SE) SNPxAge	Wave 4 Pvalue SNPxAge
Meta-analyzed sample, all ancestries[c]												
rs1514175	*TNNI3K*	1	74991644	A/G	0.504921987105307	6051	0.037 (0.054)	0.4869	0.014 (0.067)	0.8402	0.076 (0.079)	0.3348
rs1555543	*PTBP2*	1	96944797	C/A	0.554255430649694	6034	−0.029 (0.054)	0.594	−0.072 (0.068)	0.2858	−0.005 (0.079)	0.9536
rs543874	*LZTR2*	1	177889480	G/A	0.204572292940982	6040	−0.107 (0.066)	0.1025	−0.028 (0.083)	0.7403	−0.132 (0.097)	0.1736
rs6548238	*TMEM18*	2	634905	C/T	0.850095966275417	6053	−0.01 (0.07)	0.8867	0.013 (0.088)	0.8798	0.043 (0.102)	0.6765
rs10938397	*GNPDA2*	4	45182527	G/A	0.383783088113738	6032	−0.013 (0.056)	0.8194	0.024 (0.07)	0.7318	0.044 (0.081)	0.5878
rs987237	***TFAP2B***	**6**	**50803050**	**G/A**	**0.173825852206976**	**6058**	**0.253 (0.07)**	**0.0003112**	**0.136 (0.088)**	**0.1255**	**0.195 (0.102)**	**0.05577**
rs10968576	*LRRN6C*	9	28414339	G/A	0.273630186807737	6005	−0.027 (0.059)	0.6502	−0.032 (0.075)	0.6723	0.061 (0.087)	0.4863
rs867559	*LMX1B*	9	129465325	G/A	0.23544250289304	6041	−0.009 (0.062)	0.8858	−0.003 (0.079)	0.9732	0.021 (0.091)	0.8227
rs3817334	***MTCH2***	**11**	**47650993**	**T/C**	**0.373131542403703**	**6026**	**−0.14 (0.054)**	**0.009652**	**−0.127 (0.069)**	**0.0641**	**−0.116 (0.079)**	**0.1431**
rs11847697	*PRKD1*	14	30515112	T/C	0.112226528351794	6058	−0.104 (0.092)	0.2561	−0.077 (0.118)	0.5112	−0.005 (0.136)	0.9684
rs2241423	*MAP2K5*	15	68086838	G/A	0.706667680608365	6047	−0.03 (0.06)	0.6108	0.041 (0.075)	0.5837	−0.019 (0.087)	0.8315
rs12444979	*GPRC5B*	16	19933600	C/T	0.874909173417094	6032	−0.068 (0.079)	0.3853	−0.067 (0.099)	0.4956	−0.143 (0.114)	0.2106
rs4788102	*SH2B1*	16	28873398	A/G	0.372053116217557	6049	−0.052 (0.054)	0.3358	−0.076 (0.068)	0.2646	−0.079 (0.079)	0.3165
rs9939609	*FTO*	16	53820527	A/T	0.397909621425029	6031	0.06 (0.055)	0.2711	0.078 (0.068)	0.2519	0.083 (0.08)	0.2973
rs571312	*MC4R*	18	57839769	A/C	0.246872689700777	6043	0.012 (0.063)	0.8455	0.012 (0.079)	0.8812	0.006 (0.092)	0.947

Abbreviations: SNP (single nucleotide polymorphism), EAF: Effect Allele Frequency, Chr: Chromosome, BP: base pair position based on NCBI build 37 (hg19), SE (standard error)

[a] Beta and standard error (SE) estimates are presented for the SNP×Age interaction model: Multivariable linear models of cross-sectional BMI regressed on SNP and Age in years, with SNP by Age interaction term, controlling for sex, current smoking (at least one cigarette every day for 30 days), geographic region, and self-reported heights and weights (n=39). Random intercepts allowed for family and school with no sample weighting. Models were run separately for each SNP. Models in Hispanic Americans also adjusted for an indicator for foreign born and country of origin, and models in African Americans also adjusted for an indicator for selection for high education group (oversampling for education).

[b] Effect allele oriented to BMI increasing allele.

[c] Meta-analyzed results were done in METAL software (Willer et al 2012), by combining effect estiamtes from each of the 3 ancestries shown using the inverse-weighted approach.

Table 4

The SNPx Wave associations with BMI for age-matched individuals across 2 waves for SNPs associated with slope of BMI at p<0.05 within each race/ethnic group and the meta-analyzed sample.[a]

SNP	*Gene*	Chr	BP	Effect/ other allele[b]	EAF	Ages 18–20, Waves II and III			Ages 25 and 26, Waves III and IV		
						N	Beta(SE) SNPxWave	Pvalue SNPxWave	N	Beta(SE) SNPxWave	Pvalue SNPxWave
European Ancestry											
rs2568958	*NEGR1*	1	72765116	A/G	0.6276	2380	0.489 (0.328)	0.1360018	1320	0.227 (0.683)	0.7394976
rs1555543	*PTBP2*	1	96944797	C/A	0.588	2383	−0.159 (0.318)	0.61759384	1327	0.46 (0.666)	0.48956544
rs543874	*SEC16B /LZTR2*	1	177889480	G/A	0.1973	2392	0.445 (0.39)	0.25413935	1328	0.383 (0.876)	0.66231479
rs6548238	*TMEM18*	2	634905	C/T	0.8298	2394	0.346 (0.408)	0.3963025	1329	−0.392 (0.845)	0.64237252
rs713586	*RBJ/ADCY3/ POMC*	2	25158008	C/T	0.4827						
rs987237	***TFAP2B***	**6**	**50803050**	**G/A**	**0.174**	**2399**	**−0.852 (0.412)**	**0.0387382**	**1332**	**−0.908 (0.923)**	**0.3251806**
rs10968576	*LRRN6C*	9	28414339	G/A	0.3143	2369	0.144 (0.343)	0.67426563	1320	−0.283 (0.713)	0.69180913
rs867559	*LMX1B*	9	129465325	G/A	0.1917	2389	−0.378 (0.378)	0.3181291	1327	−0.028 (0.817)	0.97297023
rs3817334	***MTCH2***	**11**	**47650993**	**T/C**	**0.4056**	**2379**	**0.783 (0.317)**	**0.01356331**	**1317**	**0.53 (0.673)**	**0.4306055**
rs11847697	*PRKD1*	14	30515112	T/C	0.05271	2397	0.153 (0.674)	0.8202924	1329	−0.508 (1.34)	0.70483292
rs4788102	*SH2B1*	16	28873398	A/G	0.3924	2392	0.246 (0.315)	0.43535528	1330	0.464 (0.657)	0.47997764
rs9939609	*FTO*	16	53820527	A/T	0.3923	2381	−0.369 (0.322)	0.25094021	1320	0.31 (0.686)	0.6520413
rs571312	*MC4R*	18	57839769	A/C	0.2345	2390	0.056 (0.375)	0.88096245	1330	0.464 (0.766)	0.54458768
rs2287019	*QPCTL/GIPR*	19	46202172	C/T	0.8132	2392	0.265 (0.401)	0.50840104	1327	1.22 (0.879)	0.16527409
African Ancestry											
rs543874	*SEC16B /LZTR2*	1	177889480	G/A	0.2411	806	0.832 (0.724)	0.25057022	429	0.223 (1.403)	0.8734678
rs7647305	*ETV5/SFRS10/DGKG*	3	185834290	C/T	0.5983						
rs10938397	*Gene desert;GNPDA2*	4	45182527	G/A	0.2465	810	0.755 (0.741)	0.30796107	430	0.201 (1.23)	0.87001824
rs10968576	*LRRN6C*	9	28414339	G/A	0.1732	804	1.114 (0.81)	0.16906801	428	1.022 (1.459)	0.48371119
rs2241423	*MAP2K5/LBXCOR1*	15	68086838	G/A	0.621	808	0.705 (0.64)	0.27127539	427	2.152 (1.139)	0.05887978
Hispanic Ancestry											
rs1514175	*TNNI3K*	1	74991644	A/G	0.5425	573	0.44 (0.672)	0.51292985	288	0.276 (1.078)	0.79756657
rs543874	*SEC16B /LZTR2*	1	177889480	G/A	0.1864	568	0.059 (0.89)	0.94708825	285	−1.002 (1.488)	0.50085972
rs12444979	*GPRC5B/IQCK*	16	19933600	C/T	0.91275	571	0.433 (1.17)	0.7117468	289	1.131 (1.902)	0.55187899
rs9939609	*FTO*	16	53820527	A/T	0.3247	571	0.637 (0.684)	0.35131988	287	−1.046 (1.155)	0.36502999

SNP	Gene	Chr	BP	Effect/ other allele[b]	EAF	Ages 18–20, Waves II and III			Ages 25 and 26, Waves III and IV		
						N	Beta(SE) SNPxWave	Pvalue SNPxWave	N	Beta(SE) SNPxWave	Pvalue SNPxWave
Meta-analyzed sample, all ancestries[c]											
rs1514175	*TNNI3K*	1	74991644	A/G	0.504921987105307	3778	−0.202 (0.259)	0.4347	2049	0.054 (0.52)	0.9178
rs1555543	*PTBP2*	1	96944797	C/A	0.554255430649694	3759	0.065 (0.262)	0.8027	2038	0.418 (0.521)	0.423
rs543874	*LZTR2*	1	177889480	G/A	0.204572292940982	3766	0.471 (0.321)	0.1418	2042	0.071 (0.665)	0.9154
rs6548238	*TMEM18*	2	634905	C/T	0.850095966275417	3777	0.03 (0.352)	0.9316	2047	0.173 (0.676)	0.7976
rs10938397	*GNPDA2*	4	45182527	G/A	0.383783088113738	3767	0.096 (0.272)	0.7234	2040	−0.709 (0.523)	0.1752
rs987237	***TFAP2B***	**6**	**50803050**	**G/A**	**0.173825852206976**	**3780**	**−0.61 (0.335)**	**0.06899**	**2050**	**−0.397 (0.666)**	**0.5509**
rs10968576	*LRRN6C*	9	28414339	G/A	0.273630186807737	3739	0.079 (0.293)	0.7881	2033	−0.431 (0.571)	0.4511
rs867559	*LMX1B*	9	129465325	G/A	0.23544250289304	3774	0.023 (0.296)	0.9389	2044	0.433 (0.584)	0.4589
rs3817334	***MTCH2***	**11**	**47650993**	**T/C**	**0.373131542403703**	**3759**	**0.594 (0.264)**	**0.02449**	**2035**	**0.312 (0.523)**	**0.5506**
rs11847697	*PRKD1*	14	30515112	T/C	0.112226528351794	3784	−0.077 (0.445)	0.8618	2051	0.466 (0.814)	0.5669
rs2241423	*MAP2K5*	15	68086838	G/A	0.706667680608365	3772	−0.26 (0.283)	0.3585	2048	0.794 (0.576)	0.168
rs12444979	*GPRC5B*	16	19933600	C/T	0.874909173417094	3768	0.355 (0.388)	0.3593	2039	0.201 (0.801)	0.8017
rs4788102	*SH2B1*	16	28873398	A/G	0.372053116217557	3772	0.301 (0.263)	0.2529	2045	0.869 (0.524)	0.09725
rs9939609	*FTO*	16	53820527	A/T	0.397909621425029	3761	−0.156 (0.262)	0.5513	2037	−0.147 (0.525)	0.7795
rs571312	*MC4R*	18	57839769	A/C	0.246872689700777	3769	0.087 (0.305)	0.7749	2047	−0.009 (0.594)	0.9875

Abbreviations: SNP (single nucleotide polymorphism), EAF: Effect Allele Frequency, Chr: Chromosome, BP: base pair position, BMI (body mass index), SE (standard error)

[a] Beta and standard error (SE) estimates are presented for the SNP×Wave interaction model: Multivariable linear models of cross-sectional BMI regressed on SNP and wave of data collection in years, with SNP by Wave interaction term, controlling for sex, current smoking (at least one cigarette every day for 30 days), geographic region, and self-reported heights and weights (n=39). Random intercepts allowed for family and school with no sample weighting. Models were run separately for each SNP. Models in Hispanic Americans also adjusted for an indicator for foreign born and country of origin, and models in African Americans also adjusted for an indicator for selection for high education group (oversampling for education).

[b] Effect allele oriented to BMI increasing allele.

[c] Meta-analyzed results were done in METAL software (Willer et al 2012), by combining effect estiamtes from each of the 3 ancestries shown using the inverse-weighted approach.