

# The Influence of Obesity-Related Single Nucleotide Polymorphisms on BMI Across the Life Course

## The PAGE Study

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Evidence is limited as to whether heritable risk of obesity varies throughout adulthood. Among >34,000 European Americans, aged 18–100 years, from multiple U.S. studies in the Population Architecture using Genomics and Epidemiology (PAGE) Consortium, we examined evidence for heterogeneity in the associations of five established obesity risk variants (near *FTO*, *GNPDA2*, *MTCH2*, *TMEM18*, and *NEGR1*) with BMI across four distinct epochs of adulthood: 1) young adulthood (ages 18–25 years), adulthood (ages 26–49 years), middle-age adulthood (ages 50–69 years), and older adulthood (ages  $\geq 70$  years); or 2) by menopausal status in women and stratification by age 50 years in men. Summary-effect estimates from each meta-analysis were compared for heterogeneity across the life epochs. We found heterogeneity in the association of the *FTO* (rs8050136) variant with BMI across the four adulthood epochs ( $P = 0.0006$ ), with larger effects in young adults relative to older adults ( $\beta$  [SE] = 1.17 [0.45] vs. 0.09 [0.09] kg/m<sup>2</sup>, respectively, per A allele) and smaller

intermediate effects. We found no evidence for heterogeneity in the association of *GNPDA2*, *MTCH2*, *TMEM18*, and *NEGR1* with BMI across adulthood. Genetic predisposition to obesity may have greater effects on body weight in young compared with older adulthood for *FTO*, suggesting changes by age, generation, or secular trends. Future research should compare and contrast our findings with results using longitudinal data. *Diabetes* 62:1763–1767, 2013

In the past 5 years, genome-wide association studies have identified common genetic loci associated with BMI (in kilograms per meters squared) mainly in European populations (1–4). It has been suggested that genetic effects of BMI risk variants vary by age (1–7). However, most studies about age-varying effects have focused on childhood and adolescence or contrasted these developmental periods to adulthood (3–8). While it is known that adulthood weight changes are substantial, with weight gain common in earlier to mid-age adulthood and unintentional weight loss in later adulthood, evidence is limited for any differences in the heritable variation of weight across the transition from young adulthood to older adulthood. A few studies have begun to interrogate the importance of genetic susceptibility variants across the life course, using both cross-sectional and longitudinal designs, but only for a limited number of genetic variants (6,7,9)—for example, for *FTO* and *MC4R*. Studies of BMI susceptibility variants during childhood (0–18/20 years) are the most common (other than middle-aged adults) and, using cross-sectional data, have shown mixed results (3–8). A few cross-sectional studies over shorter periods of the life cycle suggest a stronger genetic association during childhood or adolescence compared with middle-aged adults (5,8). Two longitudinal studies have shown larger effect estimates for *FTO* around late adolescence and young adulthood compared with childhood (6,7) or beyond young adulthood (7). There have been few life-course studies of distinct genetic effects operating across adulthood (20–90 years) within large population-based samples, and for the most part, little difference in BMI has been associated with genetic variants (10).

In our previous work in the Population Architecture using Genomics and Epidemiology (PAGE) Study, we replicated the effects of genome-wide association studies

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obesity risk variants on adult BMI, in particular for five single nucleotide polymorphisms (SNPs) near *FTO* and one SNP near each of *MC4R*, *TMEM18*, *GNDPA2*, *NEGR1*, and *MTCH2* (11). This sample of European American individuals ranged from 18–100 years of age, spanning the life course from young adulthood (ages 18–25 years), a period with increased risk of weight gain (12), to older adulthood (age ≥70 years), a period of declining steroid hormone levels, loss of lean body mass, and abdominal fat accumulation (13,14). For the current study, we interrogated the evidence for heterogeneity of genetic effects in five of six previously replicated obesity loci by contrasting cross-sectional associations across four age groups within PAGE: young adulthood (ages 18–25 years), adulthood (ages 26–49 years), middle-age adulthood (ages 50–69 years), and older adulthood (ages ≥70 years). We also examined whether observed genetic effects differed in females according to menopausal status during a period in the life course associated with increased risk of weight gain and obesity (15). Similarly, we investigated genetic effects among men stratified by age 50 years (i.e., <50 or ≥50 years) as a comparison with age at onset of menopause in women and to consider the potential impact of declining testosterone levels in males associated with aging (16).

**RESEARCH DESIGN AND METHODS**

**Study populations.** PAGE involves several studies, described in detail elsewhere (17) and on the PAGE Web site (<https://www.pagestudy.org>). Briefly, the PAGE Study consists of four sites: Genetic Epidemiology of Causal Variants Across the Life Course Consortium, Epidemiologic Architecture of Genes Linked to Environment (EAGLE), Multiethnic Cohort (MEC), and Women’s Health Initiative (WHI). From the Genetic Epidemiology of Causal Variants Across the Life Course Consortium, we used European Americans from the Atherosclerosis Risk in Communities, Coronary Artery Risk Development in Young Adults, and Cardiovascular Health Studies with men and women from diverse regions in the U.S., ranging in age from childhood to advanced age. EAGLE is based on three National Health and Nutrition Examination Surveys with information on demographics, phenotypes, and environmental exposures. MEC contains five major ethnic groups of older men and women in Hawaii and California. WHI contains postmenopausal women who have been genotyped.

European ancestry was self-reported and confirmed using ancestry informative markers in majority of study samples as described previously (11,18). Underweight (BMI <18.5 kg/m<sup>2</sup>) and extremely overweight (BMI >70 kg/m<sup>2</sup>) individuals were excluded for all PAGE sites, because they could be attributed to illness, a rare mutation associated with obesity, or data-coding errors. After applying the above exclusion criteria, our sample included 34,053 participants of European descent from the PAGE consortium. Sample size, age, and BMI for men and women by study cohort for each life epoch are provided in Supplementary Table 1.

**Anthropometric measurements.** In MEC, self-reported height and weight were used to calculate baseline BMI (calculated as weight [kg]/height [m]<sup>2</sup>). Multiple studies have described systematic biases in self-reported compared with measured height and weight; yet in general, these differences are small (<1.0 kg/m<sup>2</sup>) and unlikely to affect any conclusions drawn from analyses using self-reported data (19,20). At all other sites, BMI was calculated from height and weight measured at study enrollment in a clinic setting, with the exception of 140 WHI subjects whose first available measurements were collected 1 or 3 years after enrollment. Each participant contributed one cross-sectional observation for height and weight within one of the four life-cycle periods of study.

**SNP selection and genotyping.** For five of the six loci (*FTO*, *TMEM18*, *GNDPA2*, *NEGR1*, and *MTCH2*) previously associated with BMI in the European Americans of the PAGE study, SNPs were available for individuals across four periods of adulthood: 1) young adulthood, between age 18 and 25 years; 2) adulthood, between ages 26 and 50 years; 3) middle-age adulthood, between ages 51 and 70 years; and 4) older adulthood, between ages 71 and 100 years. The SNPs at the five loci included the following: rs10838938 (near *MTCH2*), rs10938397 (near *GNDPA2*), rs2815752 (near *NEGR1*), rs6548238 (near *TMEM18*), and rs8050136 (near *FTO*). We did not include rs12970134 (near *MC4R*) because it was not available for individuals <50 years of age, thus limiting comparisons across life epochs. Each PAGE site used different genotyping platforms, with similar quality-control criteria as described previously (11). All sites used appropriate internal and external controls and excluded SNPs deviating from Hardy-Weinberg expectations or with low concordance (typically <95–99%).

**Statistical analysis.** BMI was natural-log transformed prior to analysis to stabilize the variances and improve normality assumptions. Each cohort estimated the association between each SNP and BMI using linear regression with robust SEs, assuming an additive genetic model. All analyses were stratified by sex and life epoch of adulthood or for the secondary analyses by menopausal status in women or stratified by age 50 years in men. Models were adjusted for 10 principal components calculated from ancestry informative markers, study center or clinic, age, current smoking (yes or no), and the possible correlation among family members recruited within a subset of studies. Ancestry-specific linkage disequilibrium patterns were compared for selected SNPs in HaploView 4.2 (Broad Institute, Cambridge, MA) (17) using data from the International HapMap Project (Version 3, Release R2) (21).

**Meta-analysis.** To provide combined summary measures across life epoch and sex, effect estimates for BMI–SNP associations from each cohort were meta-analyzed separately by life epoch and sex using the inverse variance–weighted method. Using meta-regression, we tested summary effect estimates for BMI–SNP associations across each life epoch for heterogeneity with a significance level of *P* < 0.05 (Bonferroni correction for testing five loci was *P* < 0.01). A similar strategy was used for meta-analyses of menopausal status and age among men (i.e., <50 or ≥50 years). Results from BMI–SNP associations were meta-analyzed across all cohorts by menopausal status in women and stratified by age 50 years in men. Using meta-regression, we tested for heterogeneity of effect estimates between pre- and postmenopausal women and <50- or ≥50-year-old men. We used METAL software for all meta-analyses with the inverse variance–weighted method (22).

**RESULTS**

Table 1 provides a description of the study population age and BMI. Supplementary Table 1 shows mean age and BMI

TABLE 1  
Demographic characteristics of European American PAGE participants by life epoch

| Sex             | Life epoch    | N      | Mean age (years) | SD (age) | Mean BMI | SD (BMI) |
|-----------------|---------------|--------|------------------|----------|----------|----------|
| Male and female | 18–25 years   | 1,382  | 22.31            | 2.07     | 24.63    | 4.53     |
|                 | 26–49 years   | 5,544  | 39.46            | 3.54     | 26.59    | 5.15     |
|                 | 50–69 years   | 18,006 | 59.75            | 4.81     | 28.77    | 5.92     |
|                 | ≥70 years     | 9,121  | 74.44            | 3.58     | 27.35    | 5.14     |
| Female          | Premenopausal | 4,186  | 38.87            | 6.41     | 26.02    | 5.60     |
|                 | Menopausal    | 19,723 | 64.74            | 7.33     | 28.85    | 6.45     |
| Male            | Age <50 years | 2,282  | 37.69            | 6.53     | 27.31    | 5.58     |
|                 | Age ≥50 years | 7,724  | 58.93            | 6.05     | 26.98    | 4.04     |
| All             | 18–70+ years  | 34,053 | 58.86            | 4.16     | 27.87    | 5.53     |

Included cohorts: Atherosclerosis Risk in Communities Study, Coronary Artery Risk in Young Adults, Cardiovascular Health Study, EAGLE, MEC, and WHI. Minimum BMI was 18.5 for all sites and ancestry groups.

within each life epoch by sex. BMI was lowest in young adults ages 18–25 years (24.6 kg/m<sup>2</sup>) and highest in adults between 50 and 69 years of age (28.8 kg/m<sup>2</sup>). In older adults (aged ≥70 years), the mean BMI was lower at 27.4 kg/m<sup>2</sup>. Premenopausal women had a lower BMI than postmenopausal women: 26.02 and 27.31 kg/m<sup>2</sup>, respectively. BMI was similar between men aged <50 (27.31 kg/m<sup>2</sup>) and ≥50 years (26.98 kg/m<sup>2</sup>).

Associations and heterogeneity for BMI across the four life epochs with each of the five SNPs are shown in Table 2, Fig. 1, and Supplementary Table 2. Allele frequencies for each SNP are presented for the whole sample because they differed little by life epoch. The association of BMI with four of the five loci—*TMEM18*, *GNPDA2*, *NEGR1*, and *MTCH2*—did not significantly differ across the four life epochs (heterogeneity  $P > 0.05$ ) in men and women combined or stratified by sex. We found evidence for heterogeneity in the effect estimate for the association between BMI and *FTO* SNP (rs8050136) for men and women together ( $P = 0.0006$ ) (Table 2) and separately in men ( $P = 0.01$ ) with a tendency in women ( $P = 0.08$ ) (Supplementary Table 2). The largest effect was seen for young adults (ages 18–25 years:  $\beta$  [SE] = 1.17 [0.45] kg/m<sup>2</sup> per risk allele) epoch and smaller in each successive life epoch with no effect in adults ≥70 years ( $\beta$  [SE] = 0.09

[0.09] kg/m<sup>2</sup> per risk allele). We found no evidence that the distinct *FTO* genetic effects across the life course for BMI were specifically related to menopausal status in women (Supplementary Table 3) or differed in men around the comparable age cutoff of 50 years, although the effect size was larger in premenopausal compared with menopausal women and in men aged <50 years compared with men aged ≥50 years due to the overall trend across the four epochs.

## DISCUSSION

Using five loci previously associated with BMI in adults (1–3) and replicated in our study population (11), we evaluated evidence for heterogeneity of the associations with BMI across four distinct phases of adulthood: young adulthood (ages 18–25 years), adulthood (ages 26–49 years), middle-aged adulthood (ages 50–69 years), and older adulthood (ages ≥70 years) using the 34,053 European Americans in the PAGE study. In addition, we conducted secondary analyses that considered whether BMI–SNP associations differed according to menopausal status in women or age 50 years in men.

In this cross-sectional analysis, we found evidence of heterogeneity in the BMI–SNP associations across life epochs for rs8050136 (*FTO*), with effect estimates that

TABLE 2

Effect estimates for BMI–SNP associations across life epoch in men and women combined and tested for interaction with  $\chi^2$  for heterogeneity ( $P_{\text{het}} < 0.05$ )

| SNP        | Gene          | Effect/<br>other<br>allele | Sex                | Life epoch (age)        | N      | EAF  | $\beta$ (kg/m <sup>2</sup> )<br>per<br>allele | SE<br>(kg/m <sup>2</sup> )<br>per<br>allele | P value  | Difference<br>across four<br>life epochs |                  |
|------------|---------------|----------------------------|--------------------|-------------------------|--------|------|---|---|----------|--|------------------|
|            |               |                            |                    |                         |        |      |   |   |          | $\chi^2_{\text{het}}$                    | $P_{\text{het}}$ |
| rs10838738 | <i>MTCH2</i>  | A/G                        | Male and<br>female | All ages (18–70+ years) | 22,589 | 0.65 | −0.142  | 0.056                                       | 0.01     | 0.71                                     | 0.87             |
|            |               |                            |                    | 18–25 years             | 1,055  |      | −0.218  | 0.166                                       |          |  |                  |
|            |               |                            |                    | 26–49 years             | 2,242  |      | −0.053  | 0.136                                       |          |  |                  |
|            |               |                            |                    | 50–69 years             | 11,456 |      | −0.158  | 0.089                                       |          |  |                  |
|            |               |                            |                    | ≥70 years               | 7,836  |      | −0.136  | 0.096                                       |          |  |                  |
| rs10938397 | <i>GNPDA2</i> | A/G                        | Male and<br>female | All ages (18–70+ years) | 19,276 | 0.56 | −0.122  | 0.064                                       | 0.06     | 5.43                                     | 0.14             |
|            |               |                            |                    | 18–25 years             | 1,052  |      | 0.002   | 0.161                                       |          |  |                  |
|            |               |                            |                    | 26–49 years             | 2,256  |      | 0.088   | 0.131                                       |          |  |                  |
|            |               |                            |                    | 50–69 years             | 10,201 |      | −0.283  | 0.101                                       |          |  |                  |
|            |               |                            |                    | ≥70 years               | 5,767  |      | −0.104  | 0.129                                       |          |  |                  |
| rs2815752  | <i>NEGR1</i>  | T/C                        | Male and<br>female | All ages (18–70+ years) | 29,464 | 0.63 | 0.106   | 0.045                                       | 0.02     | 0.38                                     | 0.95             |
|            |               |                            |                    | 18–25 years             | 1,061  |      | 0.188   | 0.163                                       |          |  |                  |
|            |               |                            |                    | 26–49 years             | 4,102  |      | 0.104   | 0.096                                       |          |  |                  |
|            |               |                            |                    | 50–69 years             | 16,465 |      | 0.107   | 0.063                                       |          |  |                  |
|            |               |                            |                    | ≥70 years               | 7,836  |      | 0.085   | 0.093                                       |          |  |                  |
| rs6548238  | <i>TMEM18</i> | T/C                        | Male and<br>female | All ages (18–70+ years) | 30,298 | 0.17 | −0.244  | 0.056                                       | 1.54E-05 | 2.25                                     | 0.52             |
|            |               |                            |                    | 18–25 years             | 1,066  |      | −0.393  | 0.215                                       |          |  |                  |
|            |               |                            |                    | 26–49 years             | 4,043  |      | −0.141  | 0.125                                       |          |  |                  |
|            |               |                            |                    | 50–69 years             | 16,490 |      | −0.309  | 0.084                                       |          |  |                  |
|            |               |                            |                    | ≥70 years               | 8,699  |      | −0.164  | 0.107                                       |          |  |                  |
| rs8050136  | <i>FTO</i>    | A/C                        | Male and<br>female | All ages (18–70+ years) | 27,652 | 0.40 | 0.384   | 0.047                                       | 8.61E-16 | 17.53                                    | 5.49E-04         |
|            |               |                            |                    | 18–25 years             | 246    |      | 1.173   | 0.450                                       |          |  |                  |
|            |               |                            |                    | 26–49 years             | 3,080  |      | 0.621   | 0.120                                       |          |  |                  |
|            |               |                            |                    | 50–69 years             | 16,481 |      | 0.444   | 0.063                                       |          |  |                  |
|            |               |                            |                    | ≥70 years               | 7,845  |      | 0.090   | 0.093                                       |          |  |                  |

EAF, frequency of effect allele;  $P_{\text{het}}$ ,  $P$  value for  $\chi^2$  test of heterogeneity;  $\chi^2_{\text{het}}$ ,  $\chi^2$  value for test of heterogeneity across age groups.

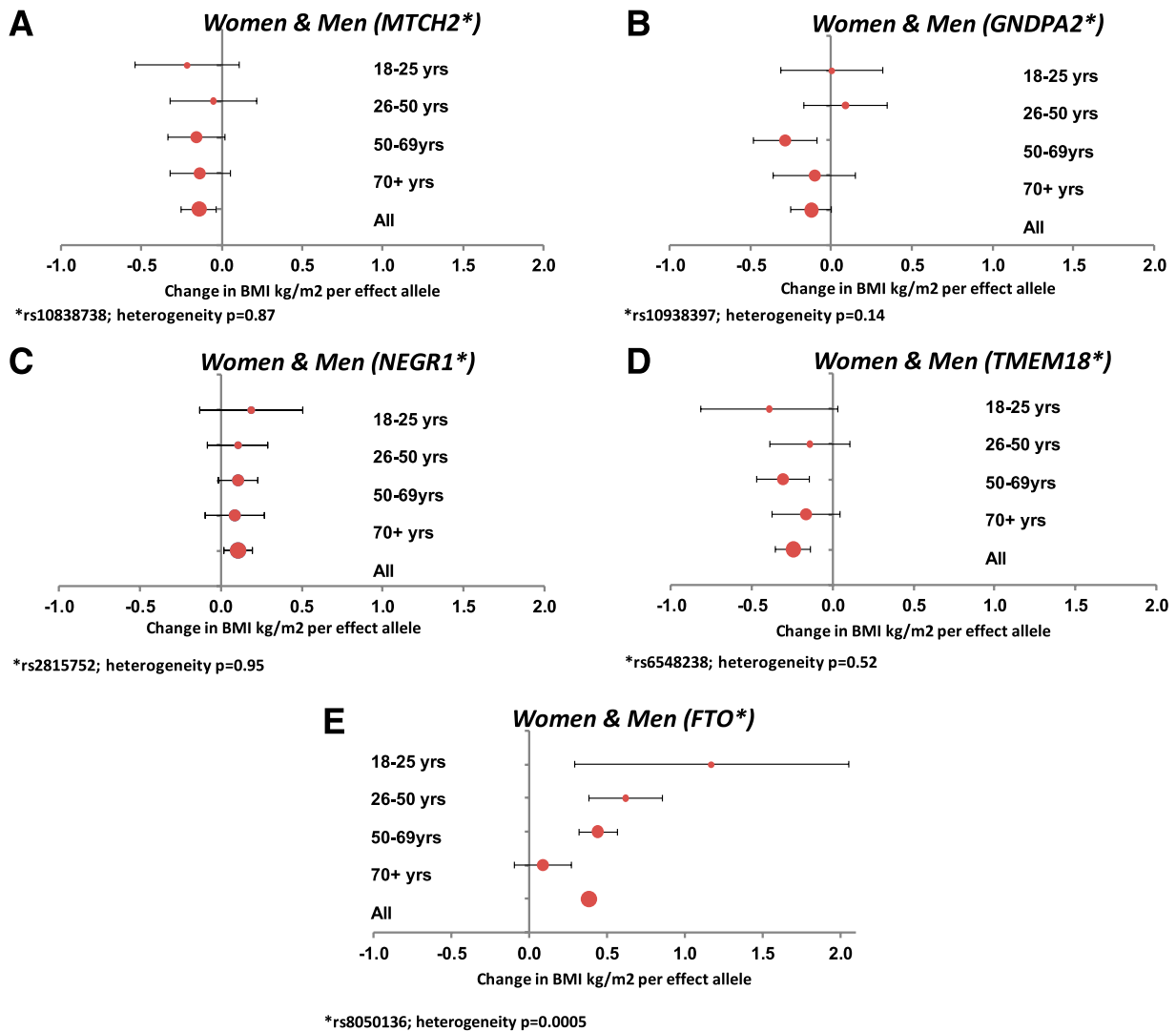


FIG. 1. A–E: Effect estimates ( $\beta$  [95% CI]) across life epoch in men and women combined and tested for interaction with  $\chi^2$  for heterogeneity ( $P$  value for  $\chi^2$  test of heterogeneity  $<0.05$ ). (A high-quality color representation of this figure is available in the online issue.)

were strongest in young adults relative to each successive life epoch of adulthood. We did not find any statistically significant evidence of an interaction for the *FTO* variant and menopausal status, suggesting that our findings are not related to hormonal changes that occur at menopause. However, the trend for effect sizes is consistent with age-group comparison showing the larger effect sizes in premenopausal women and men aged  $<50$  years compared with the older women and men. These results suggest that *FTO* genotype has a comparatively stronger association with BMI in young to middle-aged adulthood relative to older adulthood, in which no effect was seen. It is possible that at older ages, genetic and physiological processes related to aging might bear greater influence on BMI. In addition, it is likely that environmental factors play a comparatively stronger role in shaping BMI or have a comparatively longer period to influence BMI earlier in the life cycle. It is also possible that cohort differences, which we do not directly address in our analysis, have differential influence on BMI in our sample. Our findings for differences in genetic effects by life epoch for *FTO* may suggest changes by age, secular or generational

differences, or a combination of these which we cannot address in this study.

Our findings of genotype-by-life-course interaction for *FTO* are part of a growing literature suggestive of varying genetic effects for *FTO* across the life course, with studies pointing to stronger associations in adolescence and young adulthood compared with childhood (6,7) or middle-aged adulthood (7,8). A recent study that examined associations of *FTO* variants with BMI across the life course (birth to age 53 years) in a 1946 birth cohort found comparatively stronger associations in adolescence and young adulthood compared with childhood or beyond the young adult years (7). Results from a cross-sectional study in suggested larger effect sizes for *FTO* and other BMI susceptibility loci in adolescents compared with middle-aged adults (8). Still another study reported larger genetic effects for the BMI-*FTO* association at age 17 years (adolescence) compared with age 8 years (childhood) in non-Hispanic white children (6). In contrast to our study findings, a new study of European adults, aged 20–90 years, did not find a *FTO*-by-age interaction with cross-sectional BMI (10). However, the youngest and oldest individuals were

not as well-represented in these data compared with our study.

No other interactions across life epoch were noted. The other loci considered in this paper have been associated with obesity in adult Caucasians (1–3) and, with the exception of *MTCH2*, in children (3,5–7). As *FTO* is well-known to display the largest magnitude of effect on BMI across populations, it is not completely unexpected that only *FTO* demonstrates a statistically significant genotype-by-life-course interaction. Indeed, we may have had limited power to detect interaction effects for the other five variants interrogated, as their effect sizes with BMI are smaller and therefore harder to detect. Further study in larger populations of individuals and with more of the well-established BMI loci are warranted.

Our study sample, particularly for the young adult and older adult age groups, limits our ability to provide robust estimates in sex-stratified analyses and detect smaller differences between effect estimates that may indeed be present. For *FTO*, we are unable to evaluate why effect sizes may vary across life epochs but can speculate that the underlying genetic predisposition to obesity may attenuate, as body weight is increasingly determined by other genetic and cumulative environmental exposures. Indeed, the contribution of behavioral and environmental factors directly and indirectly by influencing genetic contributions on body weight across phases of adulthood are valid scientific questions in understanding changes to heritability of body weight over the life course. For example, a few studies have found that the association between *FTO* and BMI varies according to physical activity levels (23,24) and dietary intake (25,26).

Using longitudinal data that span life epochs will be helpful in further understanding the role of genes in developmental trajectories across the life course, trajectories that may operate at an optimal rate within a particular window, among specific genotypes and specific environmental contexts.

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M.G. wrote the manuscript, contributed individual cohort analyses, and conducted meta-analyses. P.G.-L. and S.V. wrote the manuscript. U.L., J.H.F., M.F., M.D.R., S.B., T.C.M., D.C.C., U.P., and K.E.N. wrote the manuscript and contributed individual cohort analyses. S.-A.L. contributed individual cohort analyses and conducted meta-analyses. L.R.W., R.L.P., J.P., K.M., J.E.M., L.L.M., L.H.K., L.N.K., C.P.H., B.E.H., J.H., M.D.G., R.G., N.F., C.S.C., P.B., L.A.H., and C.A.H. contributed individual cohort analyses. K.E.N. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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