

FTO variant and age at menarche simultaneously predict measures of obesity in young and late adulthood

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Obesity is a major risk factor for morbidity and mortality in cardiovascular disease. The discovery of genetic variants previously associated with measures of obesity in recent genome-wide association studies of female pubertal timing, such as those in the Fat Mass- and Obesity-Associated (*FTO*) gene, has raised questions about such variants' effects over the life course. We constructed two explanatory models to examine the total and direct effects of *FTO* variants on young- and older-adult body mass index (BMI) with and without adjustment for age at menarche (AAM) in ~4,750 Caucasian female participants in the Atherosclerosis Risk in Communities Study (ARIC). Genotype data from the Affymetrix 6.0 platform passed standard quality control thresholds. Natural log (ln) transformation of BMI, additive risk allele coding, and adjustments for age, current smoking at baseline, recruitment site, and population stratification using principal components were applied to all models. AAM was defined as a women's age of first self-reported menstrual period, and reports <9 or >17 years were excluded as potential outliers (n=34). BMI was self-reported at age 25 and measured at the ARIC baseline exam (ages 44-66 years), and both measurements were transformed to correct for a non-normal distributions. Of the women with genotype information, 2.7% were obese (BMI>30 kg/m²) at age 25 (n=4755) and 22.6% at ARIC baseline (n=4769). Because of the high linkage disequilibrium among *FTO* variants, we used rs9939609 as a proxy for the region. AAM was significantly associated with this variant (p=0.0009). The SNP effect estimate for lnBMI was 0.008 for each copy of A allele in early adulthood (p=7x10⁻³) and 0.016 per allele in later adulthood (p=7x10⁻⁵). This corresponded to a 52% increase in the SNP effect on lnBMI relative to early adulthood. When continuous AAM was used as a covariate in the *FTO*-lnBMI models, both AAM (p<7x10⁻⁶) and its SNP interaction term (p=0.01) were significantly associated with young- and older-adult BMI. For both BMI measurements, the SNP-lnBMI effect was larger in women with AAM ≤12 years than in those >12 years. The AAM-adjusted effect of rs9939609 on lnBMI in early adulthood remained less (β=0.06/allele) than the effect in later adulthood (β=0.09/allele). In summary, we found evidence that the magnitude of effect of *FTO* on body mass may change over the life course, and that some of the *FTO* effect on BMI is modified by AAM.