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Physical activity modifies genetic susceptibility to obesity in postmenopausal women

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Abstract

Objective—We conducted a gene-environment interaction study to evaluate whether the association of body mass index (BMI) associated meta-GWAS SNPs (as a genetic risk score) and BMI is modified by physical activity and age.

Methods—In 8206 women of European ancestry from the Women's Health Initiative (WHI), we used linear regression to examine main effects of the 95 SNP BMI genetic risk score (GRS) and physical activity on BMI, and evaluated whether genetic associations are modified by physical activity (two-way interaction) and age (three-way interaction).

Results—We found evidence for modification of the BMI GRS-BMI association according to both physical activity and age. We observed a significant two-way interaction of BMI GRS $\times$ physical activity in the crude model (p -interaction=0.05); where a smaller effect of the BMI GRS on BMI with increasing physical activity. The beta coefficient was 0.05 (standard error (SE)=0.02), $p=0.01$ for the high activity group compared to beta=0.13 (SE=0.02), $p=4.8 \times 10^{-9}$ for the sedentary group. The three-way interaction was statistically significant (adjusted p -interaction=0.01). Notably, in the 70+ age group, the BMI GRS-BMI association was attenuated and no longer significant in the high activity group; the beta coefficient for the 70+ high activity

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group was relatively small and non-significant ($\beta=0.02$, $SE=0.03$, $p=0.58$) compared to 70⁺ sedentary group ($\beta=0.17$, $SE=0.03$, $p=2.5\times10^{-7}$).

Conclusion— Our study suggests that physical activity attenuates the influence of genetic predisposition to obesity, and this effect is more profound in the oldest age group.

Keywords

epidemiology; exercise; obesity; body mass index; genetic susceptibility; physical activity

Introduction

As obesity continues to be a global epidemic, progress is being made in recognizing genetic susceptibility to obesity (1–3). Several novel genetic associations with obesity have been identified, replicated and meta-analyzed in very large samples of Europeans for body mass index (BMI) (3), albeit with small overall influences on obesity phenotypes, via the genome-wide association study (GWAS) approach. Also important is the influence of lifestyle behaviors on obesity, including excess energy intake and physical inactivity (4), resulting in a positive energy balance. The robust gene-BMI associations (1–3) provide a groundwork on which to build on our knowledge of gene-environment interactions.

While heritability studies suggest that the genetic influence on BMI increases from childhood to early adulthood (5, 6), relatively little is known about the effect of obesity genes later in life, especially whether genetic predisposition can be mitigated by healthy anti-obesogenic behaviors such as physical activity. Guo et al showed that in the presence of physical activity, the genomic influence on BMI is smaller compared to physically inactive individuals (7).

Given the robust, polygenic evidence for genetic susceptibility to obesity, we studied the potential modifying effect of physical activity on the BMI genetic associations in the form of a genetic risk score to further expand our knowledge of the genetic architecture of obesity. A few studies suggest that physical activity can blunt the influence of genetic predisposition (7–10); however there is limited representation of older women in these studies. Our study extends this investigation in the Women's Health Initiative (WHI) that is comprised exclusively of postmenopausal women. Herein, we conducted a gene-environment interaction study to evaluate whether the association of BMI and 98 meta-genome-wide significant obesity predisposition SNPs in the form of a polygenic risk score is mitigated by physical activity and age in a sample of postmenopausal European American women.

Methods

Women's Health Initiative sample

Our study includes European American women who participated in the hormone therapy (HT) clinical trials and consented to genotyping as part of two WHI sub-studies. The first is the WHI Genomics and Randomized Trials Network (GARNET) study, a sub-study of WHI with an overarching goal to identify novel genetic factors that contribute to incidence of myocardial infarction, stroke, venous thrombosis, and diabetes through large-scale GWAS of

treatment response in a randomized clinical trial of hormone therapy. The second is the WHI Memory Study (WHIMS+) study, which included women in the HT trial who did not participate in GARNET and consented to genotyping, and mainly consisted of women in the WHI Memory Study (11). Our study is focused on phenotypic data collected at WHI baseline, irrespective of the health outcomes that occurred during study follow-up. We obtained all of the necessary approvals from the WHI and dbGaP for data access. The study was approved by the University at Buffalo Health Sciences IRB and all participants provided written informed consent.

In the GARNET sub-sample, 4936 unique participant DNA samples extracted from buffy coat were submitted for genotyping on the Omni 1M array; of which high-quality genotype data were available on 4929. Further cleaning for imputation excluded certain gross chromosomal anomalies or when the chromosome-specific missing call rate was >5%, samples where the missing call rate across all chromosomes was >2%, and samples that fell outside of a homogenous EA group using principal components (PC) analysis. This resulted in 4313 samples for analysis from GARNET.

The WHIMS+ sub-sample (n=5740) was genotyped on the HumanOmniExpressExome-8v1_B genotyping array and underwent initial quality control at the Broad Institute. Genetic quality control for imputation was carried out by the WHI Clinical Coordinating Center using the GENEVA protocol. Samples were removed if the call rate was <0.97. We excluded women for whom genome-wide imputed data was not available, resulting in 5687 participants from WHIMS+.

In summary, among a total of 10,676 women from the GARNET and the WHIMS+, the genotype quality and imputation-based cleaning procedures excluded 6% (n=676) women, resulting in 10,000 women with robust genetic data.

Construction of the BMI genetic risk score (GRS)

We constructed a genetic risk score using only those SNPs that met strict criteria for genome-wide significance in published BMI meta-GWAS (1). We considered 97 SNPs for BMI which remained genome-wide significant ($p < 5 \times 10^{-8}$) in combined discovery and follow-up cohorts from meta-GWAS for BMI (1).

Of the 97 published SNPs associated with BMI (1), 55 were genotyped and 38 were imputed in GARNET. Similarly, 47 SNPs were genotyped in WHIMS+ and 48 were imputed. Three BMI SNPs had poor imputation quality (dosage $r^2 < 0.8$) (rs2112347, rs2245368, rs2650492) and one SNP (rs1016287) was not available. We successfully identified two proxies (rs10057967 and rs759250) for rs2112347 and rs1016287, respectively, based on r-squared LD=1 in CEU 1000G pilot data and the results from a query using the Broad Institute's SNAP tool (<http://www.broadinstitute.org/mpg/snap/>). Two SNPs (rs2245368, rs2650492) had no suitable proxy and thus were not included in the BMI genetic risk score.

We estimated both unweighted and weighted genetic risk scores. The genetic risk score was calculated as a weighted allele count using the 95 meta-GWAS significant SNPs, with weights based on the effect of each BMI-increasing allele, quantified by the beta coefficient

(1). We divided by the mean beta coefficients across all GRS SNPs. The weighted risk score is a sum of the number of risk alleles at each SNP (0,1,2) (or the “best guess” for imputed SNPs) multiplied by their weights, i.e., $\beta/\text{mean } \beta$ of the 95 SNPs.

Measurement of BMI, physical activity, and covariates

Height and weight used for BMI calculations (kg/m^2) were measured by trained staff at the WHI baseline visit according to standardized protocols. Extensive data was collected from WHI participants at baseline and included demographics, medical history, lifestyle and behavioral characteristics, diet (12), and physical activity (13, 14). Information on expenditure of energy from recreational physical activity was summarized as a variable representing MET-minutes/week as previously reported (15). Briefly, women were asked to provide frequencies and duration for the different speeds of walking outside the home for more than 10 minutes without stopping. For recreational physical activity, women were asked how frequency, duration and intensity (strenuous, moderate and mild intensity). These responses were used to classify women into the following categories: “sedentary”, <100 MET-min/week; “low activity”, >100 -500 MET-min/week; “moderate activity”, >500 -1200 MET-min/week; and “high activity”, >1200 MET-min/week (15). The moderate activity category represents approximately 150 minutes per week, the minimum recommended amount of physical activity.

Variables that we considered in linear regression models include baseline age, age², U.S. region, WHI sample (GARNET or WHIMS+), physical function score, alcohol servings/week, smoking pack years, hormone therapy use (ever, never, current), education, income, hours of sleep per night, as well as dietary factors such as total energy intake, grain intake, fruit intake, vegetable intake, fiber intake, percent saturated fat intake from the WHI baseline food frequency questionnaire (12). These dietary variables were chosen because they have been shown to be associated with BMI in the WHI cohort (15).

Participants were not included in the analysis ($n=316$) if they had missing values in any typed SNP that is needed for construction of the BMI genetic risk score, and excluded 67 women for whom race was self-reported as “other” or “missing.” Additionally, we excluded three samples with genetic missingness >0.02 , six samples with questionable ethnicity as identified by a principal component analysis, and 29 related subjects. With consideration of missing phenotype variables unique to our analysis, we excluded 502 women with self-reported diabetes and 59 women who reported being treated for diabetes at WHI baseline, 610 women who were missing a baseline BMI or physical activity information, and 202 women who reported their health limits walking 1 block a little (or missing) based on a cutoff of 70 in a physical function construct score 70 because these women were sedentary due to physical limitations (15). These exclusions resulted in a final sample of 8206 women for the BMI GRS $\times$ physical activity (gene-environment) interaction analysis.

Statistical analyses

We estimated descriptive statistics to characterize the sample according to physical activity categories using ANOVA or chi-square tests, as appropriate. We examined the main effects of the BMI genetic risk scores (weighted and unweighted) and physical activity (categories)

on BMI using linear regression models (adjusting for age, age², region, cohort, physical function score, alcohol servings/wk, pack year of smoking, hormone therapy use, education, income, hours of sleep/night, energy, grain and fiber intake, percent calories from saturated fat) prior to examination of genetic risk score $\times$ physical activity interactions. We then assessed multiplicative interaction using regression models including their cross product terms, where the GRS was a continuous variable, physical activity was a categorical variable (representing their respective marginal effects), and the product term. Given the established interaction between physical activity and age in women in the WHI (15), we also examined the three-way interaction (BMI GRS $\times$ physical activity $\times$ age), including main effects and lower interaction terms in the model. In age-stratified analyses, we considered the BMI GRS, physical activity, and age marginal effects and lower interaction term in the model. We considered interaction terms statistically significant at $p \leq 0.05$. We used R version 3.3.1 for all analyses.

Results

Descriptive characteristics for our sample of postmenopausal women according to physical activity categories are reported in Table 1. At WHI baseline, the age range for overall sample ranged from 50-81 years; the mean was 67.8 years (standard deviation (SD)=6.4). The mean age was <1 year different between “sedentary” and “high” physical activity categories. Higher physical activity was associated with a lower BMI; we observed a difference of 4 kg/m² between the sedentary and high physical activity groups ($p < 0.001$). Self-reported daily energy intake was similar across physical activity groups ($p = 0.76$). No relation was observed between physical activity groups and the (weighted or unweighted) BMI genetic risk score ($p > 0.49$). Further, the crude correlation between physical activity (MET-min/wk) and the BMI GRS was -0.02 .

Table 2 shows the estimates from linear regression models, where we observed statistically significant main effects for the association of BMI, physical activity, and age with the BMI GRS (per BMI-increasing risk allele). Here, we replicated the published association of BMI-increasing risk alleles in the form of a genetic risk score (1); we observed an approximate 0.09 kg/m² higher BMI per GRS risk allele ($p = 2.00 \times 10^{-16}$). As expected, BMI was lower with increasing physical activity. Women in the highest category of physical activity had on average a 1.91 kg/m² lower BMI than women who were sedentary in the fully adjusted model. We observed lower BMI with increasing age; women in the 70+ group had almost a 2.8 kg/m² lower BMI compared to women aged 50-59. These main effects of the BMI GRS, physical activity, and age associations with BMI were very similar after adjustment for potential confounding variables.

We observed statistically significant evidence for a two-way interaction of the BMI GRS and physical activity (p -for interaction=0.049 for the weighted BMI GRS, and 0.02 for the unweighted BMI GRS. Both the weighted and unweighted GRS interactions became no longer significant with adjusted for the full set of variables (p -for interaction=0.4).

We observed a statistically significant three-way interaction of physical activity, BMI GRS and age in adjusted models; the three-way interaction p -values ranged from 0.06 in

unadjusted model to 0.01 in the fully adjusted model; Table 3. This led us to evaluate and present the associations stratified by age. Table 3 and Figure 1 show the associations between the BMI GRS and BMI stratified by physical activity (sedentary, low, moderate, high) and age (50-59, 60-69, 70+). The overall patterns of lower BMI can be seen across the three age panels and with increasing physical activity, representing the main effects of age and physical activity, respectively. Specifically, in the 50-59 year age strata, we observed no influence of physical activity since the beta coefficients (slopes in the figure) are essentially unchanged and displayed no clear attenuation with increasing physical activity. In the 60-69 year age group, we observed an attenuation of the association of the BMI GRS with increasing physical activity, and significant evidence for interaction within this age strata (p for interaction=0.069); however the moderate activity group is the exception. The age 60-69 moderate activity group had the beta coefficient with the smallest p -value, suggesting that the BMI GRS is associated with the largest change in BMI in this particular group. In the 70+ group, we observed a trend in smaller beta coefficients with increasing physical activity, where the influence of the GRS on BMI is the smallest and becomes not significant (adjusted p -value=0.58) in women with high physical activity. The p -for interaction was 0.002 for the 70+ group, corroborating the attenuation of the genetic associations with increasing physical activity. The results are similar whether the weighted or unweighted BMI GRS is considered. Adjusting for covariables had no appreciable influence on the significance of the two- and three-way interactions.

Discussion

Genetic associations on BMI, studied using the largest known set of 95 obesity-associated loci (identified via GWAS), are strongest in postmenopausal women who are sedentary, and are weakest in postmenopausal women who report high recreational physical activity. Further, we observed that genetic predisposition to obesity is not only mitigated by physical activity, but also by age, where physical activity attenuated the gene-obesity associations in women aged 70+.

Our findings suggest that age is an important player in the gene-obesity interaction; this is not surprising given the known changes in body composition accompanied by menopause, namely increases in fat mass and decreases in physical activity (16). In another analysis of WHI data on the trajectory of physical activity, it was shown that higher physical activity results in less weight gain from women age 50-59 and less weight loss in women age 70-79 (15), which may translate to decreased health risks resulting from adiposity (17) and frailty (18), respectively. In the context of our study, where we include consideration of genetic predisposition to obesity, higher physical activity may mitigate the genetic influence on obesity, even in older age women. However, we recognize that it is difficult to tease apart the effects of age, the dynamics of BMI change in older women, and the exposure to an obesogenic environment across the life span. Winkler et al was the first group to investigate at a large scale (>320,000 individuals) whether the established BMI genetic associations differ by age (19). Using a cutpoint of age 50, they found that 15 of the more than 100 genetic polymorphisms identified in the Genetic Investigation of Anthropometric Traits (GIANT) consortium (1, 2) significantly differed by age. The effects were smaller in the older group and the authors speculate that the smaller effect sizes in the over age 50 group

may be due to the accumulation of environmental and lifestyle influences on obesity. A more recent large-scale obesity $\times$ physical activity genome-wide interaction study identified that physical activity (dichotomous; physically active or not) modified the genetic associations of *FTO* and BMI by approximately 30% (20). While these authors focused on single SNP associations rather than a genetic risk score, the findings suggests that it is not likely that other single SNPs interact with effects as large as they identified with *FTO* $\times$ physical activity. Nonetheless, this line of investigation can be improved with consideration of more accurate and quantitative measurements of physical activity.

In the Framingham Heart Study, Guo et al estimated the proportion of BMI variance due to genome-wide SNPs using the genome-wide complex trait analysis (GCTA) approach and evaluated changes with age and the influence of physical activity (7). These authors report a weaker genetic influence with older age (lowest in >60 y group), and a smaller genomic influence on BMI for those who are physically active compared to those who are not physically active in the 21-50 age group. However, the important difference in our findings is with respect to the oldest age groups. Guo et al did not find differences in the genetic effects on BMI according to physical activity in the >50 group. Among sedentary individuals, the genetic influence is approximately equal in magnitude in older women (70+) versus the youngest women (50-59 y). Further, while our most interesting findings are what appears to be an attenuation of the BMI genetic association in the oldest women (70+), our study perhaps highlights the importance of a physical activity in older age.

Our study may be better powered to detect these associations in older women, based on large variability with respect to physical activity in our postmenopausal sample, and parameterization of age and the 95 SNP BMI GRS, which enabled our detection of significant interactions. Notwithstanding, it is important to note the limitation of BMI in the assessment of obesity and adiposity in older women; further studies should differentiate the influence of proportions of lean body mass and adiposity in gene-environment interaction studies.

Li et al examined a 12-SNP obesity GRS $\times$ physical activity interaction in EPIC-Norfolk and reported a 40% lower odds per risk allele of obesity in physically active compared to inactive individuals (21). Ahmad et al conducted a replication study using the 12 loci GRS in 111,421 individuals of European ancestry from 11 cohorts and reported a significant interaction with physical activity that was driven by the North American cohorts (22). The reasons for this are not clear; however collectively, these studies and our own are in solid support of the presence of the interaction and the importance in recognizing the relative influence of genetic and non-genetic risk factors on obesity.

One meta-analysis of more than 218,000 adults showed a 27% attenuation of the *FTO*-obesity associations with higher physical activity (23). In a more recent study of European adults, Celis-Morales et al in agreement with earlier studies, showed that the influence of *FTO* on both BMI and waist circumference is reduced in physically active individuals (24). Collectively, this evidence, while focused on a single gene instead of multiple polymorphisms via a genetic risk score, supports our findings of attenuation of the genetic influence on BMI in adults in the presence of physical activity.

Our use of the largest set of BMI-associated SNPs in the form of a GRS, allowed us to comprehensively evaluate interactions while exploiting the whole set of SNPs identified to date. Although the use of a genetic risk score is limiting in that we cannot determine whether certain SNPs are driving the interaction or whether the interaction is due to SNPs involved in certain biologic pathways, our study provides an overall picture of genetic predisposition to obesity in the presence of physical activity in postmenopausal women. Further, use of the GRS is beneficial since we are not limited by the need to adjust for multiple testing. In an exploratory analysis of single SNP interactions, we found that none survived a Bonferroni correction; however one SNP in particular in *ATP2A1* showed significant two- and three-way interactions (both p-for interactions <0.048).

The latest estimates on how well genetic variants contribute to BMI variability come from Yang et al (25), who studied the contribution of both common and rare variants plus imputed variants to BMI variance and shed light on ‘missing heritability’ (26). The authors report that with inclusion of 1000 Genomes Project imputed variants, 27% of BMI variance is explained by genetic factors; representing slightly less of the heritability forecasted by family and twin studies on BMI (40-60%). While our study focused rather on the common variants associated with BMI, we believe that our approach is still a valuable representation of genetic liability toward higher BMI and well powered to detect interactions with physical activity. Our study was effectively unable to analyze the contribution of rare (MAF<0.01) variants to BMI and whether they interact with physical activity.

A notable limitation of our study relates to self-reported physical activity that only includes recreational activity. In addition, we had no measure of objective activity and we have shown previously in WHI that participants tend to overreport activity when self-report is used (27). However, the questionnaire used in the WHI has shown good reliability (14). Another important limitation is our focus on BMI, rather than more specific compartments of body composition, such as fat mass, bone, and lean mass. As our knowledge of genes linked to specific body compartments grows, specifically those related to muscle and sarcopenia, we will be able to test different hypotheses about interactions of physical activity with genetic susceptibility to muscle loss with age. Other important limitations to our study include the generalizability, given that WHI includes only postmenopausal European American and our focus on a single time point (WHI baseline). In addition, one may argue that women who survived may have a lower genetic risk of obesity from those who died and were not represented in our oldest age group (70+). However, we estimated the mean GRS for each age group and found no statistically significant differences; the mean (SD) GRS for the youngest group (50-59 years) and the oldest age group (70+) are 86.5 y (SD=6.1) and 86.3 (SD=6.3), respectively. This suggests that survival to the 70+ age group is not associated with more favorable obesity genetic risk profile. However, some degree of survival bias may remain.

Conclusion

In summary, our findings suggest that genetic predisposition to obesity is not wholly deterministic; rather physical activity may attenuate the influence of inherited obesity susceptibility alleles and suggest that healthy behaviors are still important later in life. In

principle, studies like this may provide impetus for further development of tailored lifestyle recommendations coupled with the use of genetic information. Further, our findings point to the importance of promoting and maintaining healthy behaviors in particular in older adults to maximize quality of life.

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References

1. Locke AE, Kahali B, Berndt SI, et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature*. 2015; 518(7538):197–206. [PubMed: 25673413]
2. Shungin D, Winkler TW, Croteau-Chonka DC, et al. New genetic loci link adipose and insulin biology to body fat distribution. *Nature*. 2015; 518(7538):187–96. [PubMed: 25673412]
3. Speliotes EK, Willer CJ, Berndt SI, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet*. 2010; 42(11):937–48. [PubMed: 20935630]
4. Hill JO, Wyatt HR, Reed GW, Peters JC. Obesity and the environment: where do we go from here? *Science*. 2003; 299(5608):853–5. [PubMed: 12574618]
5. Haworth CM, Carnell S, Meaburn EL, Davis OS, Plomin R, Wardle J. Increasing heritability of BMI and stronger associations with the FTO gene over childhood. *Obesity*. 2008; 16(12):2663–8. [PubMed: 18846049]
6. Jacobson KC, Rowe DC. Genetic and shared environmental influences on adolescent BMI: interactions with race and sex. *Behav Genet*. 1998; 28(4):265–78. [PubMed: 9803019]
7. Guo G, Liu H, Wang L, Shen H, Hu W. The genome-wide influence on human BMI depends on physical activity, life course, and historical period. *Demography*. 2015; 52(5):1651–70. [PubMed: 26319003]
8. McCaffery JM, Papandonatos GD, Bond DS, Lyons MJ, Wing RR. Gene $\times$ environment interaction of vigorous exercise and body mass index among male Vietnam-era twins. *The Am J Clin Nutr*. 2009; 89(4):1011–8. [PubMed: 19225119]
9. Mustelin L, Silventoinen K, Pietilainen K, Rissanen A, Kaprio J. Physical activity reduces the influence of genetic effects on BMI and waist circumference: a study in young adult twins. *Int J Obesity*. 2009; 33(1):29–36.
10. Reddon H, Gerstein HC, Engert JC, et al. Physical activity and genetic predisposition to obesity in a multiethnic longitudinal study. *Sci Rep*. 2016; 6:18672. [PubMed: 26727462]

11. Shumaker SA, Reboussin BA, Espeland MA, et al. The Women's Health Initiative Memory Study (WHIMS): a trial of the effect of estrogen therapy in preventing and slowing the progression of dementia. *Control Clin Trials*. 1998; 19(6):604–21. [PubMed: 9875839]
12. Patterson RE, Kristal AR, Tinker LF, Carter RA, Bolton MP, Agurs-Collins T. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. *Ann Epidemiol*. 1999; 9(3):178–87. [PubMed: 10192650]
13. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. *Control Clin Trials*. 1998; 19(1):61–109. [PubMed: 9492970]
14. Meyer AM, Evenson KR, Morimoto L, Siscovick D, White E. Test-retest reliability of the Women's Health Initiative physical activity questionnaire. *Med Sci Sport Exer*. 2009; 41(3):530–8.
15. Sims ST, Larson JC, Lamonte MJ, et al. Physical activity and body mass: changes in younger versus older postmenopausal women. *Med Sci Sport Exer*. 2012; 44(1):89–97.
16. Sowers M, Zheng H, Tomey K, et al. Changes in body composition in women over six years at midlife: ovarian and chronological aging. *J Clin Endocr Metab*. 2007; 92(3):895–901. [PubMed: 17192296]
17. Manson JE, Willett WC, Stampfer MJ, et al. Body weight and mortality among women. *New Engl J Med*. 1995; 333(11):677–85. [PubMed: 7637744]
18. Blaum CS, Xue QL, Michelon E, Semba RD, Fried LP. The association between obesity and the frailty syndrome in older women: the Women's Health and Aging Studies. *J Am Geriatr Soc*. 2005; 53(6):927–34. [PubMed: 15935013]
19. Winkler TW, Justice AE, Graff M, et al. The influence of age and sex on genetic associations with adult body size and shape: a large-scale genome-wide interaction study. *PLoS Genet*. 2015; 11(10):e1005378. [PubMed: 26426971]
20. Graff M, Scott RA, Justice AE, et al. Genome-wide physical activity interactions in adiposity - A meta-analysis of 200,452 adults. *PLoS Genet*. 2017; 13(4):e1006528. [PubMed: 28448500]
21. Li S, Zhao JH, Luan J, et al. Physical activity attenuates the genetic predisposition to obesity in 20,000 men and women from EPIC-Norfolk prospective population study. *PLoS Med*. 2010; 7(8)
22. Ahmad S, Rukh G, Varga TV, et al. Gene $\times$ physical activity interactions in obesity: combined analysis of 111,421 individuals of European ancestry. *PLoS Genet*. 2013; 9(7):e1003607. [PubMed: 23935507]
23. Kilpelainen TO, Qi L, Brage S, et al. Physical activity attenuates the influence of FTO variants on obesity risk: a meta-analysis of 218,166 adults and 19,268 children. *PLoS Med*. 2011; 8(11):e1001116. [PubMed: 22069379]
24. Celis-Morales C, Marsaux CF, Livingstone KM, et al. Physical activity attenuates the effect of the FTO genotype on obesity traits in European adults: The Food4Me study. *Obesity*. 2016; 24(4): 962–9. [PubMed: 26921105]
25. Yang J, Bakshi A, Zhu Z, et al. Genetic variance estimation with imputed variants finds negligible missing heritability for human height and body mass index. *Nat Genet*. 2015; 47(10):1114–20. [PubMed: 26323059]
26. Manolio TA, Collins FS, Cox NJ, et al. Finding the missing heritability of complex diseases. *Nature*. 2009; 461(7265):747–53. [PubMed: 19812666]
27. Neuhouwer ML, Di C, Tinker LF, Thomson C, et al. Physical activity assessment: biomarkers and self-report of activity-related energy expenditure in the WHI. *Am J Epidemiol*. 2013; 177(6):576–85. [PubMed: 23436896]

Figure 1. Unadjusted linear regression models for BMI genetic risk score predicting BMI stratified by baseline age. Shaded areas indicate 95% confidence intervals.

Table 1

Characteristics of the WHI BMI GRS interaction study, N=8206. Mean (SD) or N (%).

Characteristic	N Missing	Physical Activity Categories				P-value*
		Sedentary (<100 MET-min/wk) N=1993	Low (100-500 MET-min/wk) N=2489	Moderate (500-1200 MET-min/wk) N=2182	High (>1200 MET-min/wk) N=1542	
Age, yr	0	66.7 (0.15)	66.9 (0.13)	67.7 (0.13)	67.5 (0.16)	3.62e-07
BMI, kg/m ²	0	30.6 (0.14)	29.0 (0.11)	27.7 (0.11)	26.6 (0.12)	2.20e-16
Education	32					
<High school		145 (0.07)	148 (0.06)	61 (0.03)	54 (0.04)	2.20e-16
High school/GED		524 (0.26)	591 (0.24)	457 (0.21)	242 (0.16)	
>High school		825 (0.41)	985 (0.40)	881 (0.4)	6 (0.40)	
College degree		487 (0.24)	757 (0.30)	776 (0.36)	617 (0.40)	
Total energy expenditure, MET-min/week	0	17.4 (0.69)	285.2 (2.36)	807.3 (4.12)	1968.2 (20.46)	2.20e-16
Smoking status						
Never	86	991 (0.50)	1325 (0.53)	1130 (0.52)	706 (0.46)	2.20e-16
Past		717 (0.36)	902 (0.36)	902 (0.41)	728 (0.47)	
Current		270 (0.14)	236 (0.09)	127 (0.06)	86 (0.06)	
Pack years of smoking	86	13.5 (0.52)	11.8 (0.42)	9.7 (0.40)	10.3 (0.48)	7.63e-09
Alcohol intake, servings/week	25	2.27 (0.13)	2.41 (0.11)	2.97 (0.12)	3.53 (0.16)	4.95e-12
Dietary energy intake, kcal/day	20	1642.6 (16.0)	1636.3 (13.9)	1620.4 (14.2)	1631.9 (18.3)	0.76
Dietary fiber, g	20	13.9 (0.14)	15.1 (0.13)	16.3 (0.15)	17.4 (0.19)	2.20e-16
% calories from saturated fat	20	12.4 (0.08)	11.5 (0.07)	10.8 (0.07)	10.1 (0.08)	2.20e-16
Hormone therapy use	8					
Never		1086 (0.54)	1353 (0.54)	1124 (0.52)	792 (0.51)	2.37e-05
Past		798 (0.40)	934 (0.38)	882 (0.40)	595 (0.39)	
Current		106 (0.05)	201 (0.08)	175 (0.08)	152 (0.10)	
BMI genetic risk score (weighted)	0	86.4 (6.3)	86.3 (6.3)	86.4 (6.1)	86.2 (6.3)	0.80
BMI genetic risk score (unweighted)	0	90.21 (6.16)	90.1 (6.26)	90.18 (6.03)	89.91 (6.14)	0.49

* P-values obtained from ANOVA or chi-square tests.

Table 2

Main effects of BMI genetic risk score, physical activity and age on BMI (n=8206).

	Model	Mean difference in BMI (SE)	P-value
BMI GRS, per allele	Model 1 [†]	0.09 (0.01)	2.00e-16
	Model 2 [‡]	0.09 (0.01)	2.00e-16
Physical activity category [*]	Model 1 [†]		
	<i>Sedentary</i>	Reference	
	<i>Low</i>	−1.59 (0.16)	2.00e-16
	<i>Moderate</i>	−2.71 (0.17)	2.00e-16
	<i>High</i>	−3.79 (0.18)	2.00e-16
	Model 2 [‡]		
	<i>Sedentary</i>	Reference	
	<i>Low</i>	−0.70 (0.16)	1.00e-05
	<i>Moderate</i>	−1.26 (0.17)	1.40e-13
	<i>High</i>	−1.91 (0.19)	2.00e-16
Age category [*]	Model 1 [†]		
	<i>50-59</i>	Reference	
	<i>60-69</i>	−0.49 (0.19)	0.009
	<i>70+</i>	−1.87 (0.19)	2.00e-16
	Model 2 [‡]		
	<i>50-59</i>	Reference	
	<i>60-69</i>	−0.90 (0.18)	3.58e-7
	<i>70+</i>	−2.79 (0.18)	2.00e-16

[†]Model 1: adjusted for age, age², region and cohort.[‡]Model 2: adjusted for age, age², region, cohort, physical function score, alcohol servings/week, pack years, hormone therapy use (ever, never, current), education, income, hours of sleep per night, energy intake, grain intake, fruit intake, vegetable intake, fiber intake, percent calories from saturated fat.^{*}Age category models are not adjusted for age.

Table 3

Association between weighted BMI GRS and BMI, and stratified by physical activity and age.*

	Sedentary			Low			Moderate			High		2-Way Interaction (GRS × physical activity) P-value Weighted (unweighted)	3-Way Interaction (GRS × physical activity × age) P-value Weighted (unweighted)
	N	Beta (SE)	P-value	N	Beta (SE)	P-value	N	Beta (SE)	P-value	N	Beta (SE)	P-value	
All ages	Unadjusted	1993	0.13 (0.02)	4.80e-09	2489	0.09 (0.02)	1.3e-07	2182	0.11 (0.02)	2.54e-09	0.05 (0.02)	0.01	0.06 (0.01)
	Adjusted*	1856	0.10 (0.02)	1.07e-06	2350	0.08 (0.02)	1.1e-06	2048	0.10 (0.02)	5.94e-09	0.05 (0.02)	0.004	0.01 (0.01)
50-59	Unadjusted	328	0.09 (0.06)	0.14	365	0.11 (0.06)	0.06	249	0.11 (0.06)	0.06	0.17 (0.05)	0.001	
	Adjusted*	313	0.05 (0.06)	0.46	345	0.11 (0.06)	0.06	227	0.16 (0.06)	0.009	0.20 (0.06)	0.0003	
60-69	Unadjusted	941	0.10 (0.03)	0.001	1225	0.09 (0.02)	0.0003	1034	0.16 (0.03)	1.60e-09	0.05 (0.03)	0.11	
	Adjusted*	881	0.08 (0.03)	0.008	1156	0.08 (0.02)	0.001	982	0.14 (0.03)	9.9e-08	0.06 (0.03)	0.04	
70+	Unadjusted	724	0.17 (0.03)	2.48e-07	899	0.08 (0.03)	0.002	899	0.05 (0.02)	0.027	0.02 (0.03)	0.51	
	Adjusted*	662	0.15 (0.03)	4.10e-06	849	0.07 (0.03)	0.005	839	0.05 (0.02)	0.06	0.02 (0.03)	0.005 (0.007)	0.002 (0.007)

* Adjusted for age, age², region, cohort, physical function score, alcohol servings/week, pack years, hormone therapy use (ever, never, current), education, income, hours of sleep per night, energy intake, grain intake, fruit intake, vegetable intake, fiber intake, percent calories from saturated fat.