Genetic Susceptibility, Change in Physical Activity, and Long-term Weight Gain

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Whether change in physical activity over time modifies the genetic susceptibility to long-term weight gain is unknown. We calculated a BMI–genetic risk score (GRS) based on 77 BMI–associated single nucleotide polymorphisms (SNPs) and a body fat percentage (BF%)–GRS based on 12 BF%–associated SNPs in 9,390 women from the Nurses’ Health Study (NHS) and 5,291 men from the Health Professionals Follow-Up Study (HPFS). We analyzed the interactions between each GRS and change in physical activity on BMI/body weight change within five 4-year intervals from 1986 to 2006 using multivariable generalized linear models with repeated-measures analyses. Both the BMI–GRS and the BF%–GRS were associated with long-term increases in BMI/weight, and change in physical activity consistently interacted with the BF%–GRS on BMI change in the NHS (P for interaction = 0.025) and HPFS (P for interaction = 0.001). In the combined cohorts, 4-year BMI change per 10-risk allele increment was −0.02 kg/m² among participants with greatest increase in physical activity and 0.24 kg/m² among those with greatest decrease in physical activity (P for interaction < 0.001), corresponding to 0.01 kg versus 0.63 kg weight changes every 4 years (P for interaction = 0.001). Similar but marginal interactions were observed for the BMI–GRS (P for interaction = 0.045). Our data indicate that the genetic susceptibility to weight gain may be diminished by increasing physical activity.

Obesity has been rapidly increasing over the past few decades and has become a major public health threat and the leading cause of disabilities around the world (1). Changes in lifestyle, such as decrease in physical activity, are considered to be among the major driving force behind the global obesity pandemic (2). Obesity is commonly defined by BMI; however, it has been recognized that BMI may not adequately represent adiposity because it does not distinguish lean from fat mass (3). More sophisticated measures, such as body fat percentage (BF%), have been also widely used to reflect body fat (4).

Recent genome-wide association studies (GWAS) have identified different sets of single nucleotide polymorphisms (SNPs) that are associated with BMI and BF% (5,6). Earlier studies on the association between BMI–associated genetic variants and weight change have revealed contradictory results (7–9). Besides, no study has investigated the association between BF%–associated genetic variants and longitudinal weight change. In addition, our previous analyses have shown that physical activity significantly modified the genetic predisposition to higher BMI (10); however, it remains unknown whether temporal change in physical activity may modify the associations of genetic variations of BMI and BF% with weight change and whether such modification effects are different for the two genetic variations.

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In the current study, we analyzed the associations of the genetic variations of BMI and BF%, assessed by two genetic risk scores (GRSs) based on 77 BMI-associated SNPs and 12 BF%-associated SNPs recently identified through GWAS (5,6), respectively, with long-term BMI change. In addition, we particularly examined the interaction between each GRS and change in physical activity on long-term BMI change in two independent cohorts: the Nurses’ Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS).

RESEARCH DESIGN AND METHODS

Study Design and Population

The NHS is a cohort of 121,701 female registered nurses from 11 U.S. states aged 30–55 years at enrollment in 1976 (11). The HPFS is a cohort of 51,529 male health professionals from all 50 states aged 40–75 years at enrollment in 1986 (12). Participants were followed with the use of biennial validated questionnaires concerning medical history and lifestyle. For this analysis, the baseline year in the NHS and HPFS was 1986, the first year when detailed information was available on physical activity, diet, and smoking habits. Between 1989 and 1990, a blood sample was collected from 32,826 women in the NHS. Similarly, a blood sample was obtained between 1993 and 1995 from 18,225 men in the HPFS. The current analysis included 9,390 women in the NHS and 5,291 men in the HPFS of European ancestry who had complete baseline information and available genotype data based on GWAS (13–17) and were free of diabetes, cancer, or cardiovascular disease at baseline. The current study was approved by the institutional review boards of Brigham and Women’s Hospital and Harvard T.H. Chan School of Public Health. All participants provided written informed consent.

Assessment of Physical Activity

Detailed assessments of physical activity in the NHS and HPFS were first obtained by questionnaires in 1986 and every 2 years thereafter. Participants reported the average amount of time they spent per week on leisure-time physical activities, including walking, jogging, running, bicycling, swimming, calisthenics or use of a rowing machine, lap squash or racquet ball, and tennis. Physical activity was assessed with average weekly energy expenditure in MET-hours (MET-h) based on the validated information (18). Change in physical activity was calculated as the difference in physical activity (MET-h/week) between the beginning and the end of each 4-year interval, with positive difference representing increased levels, and negative difference, decreased levels. The reproducibility and validity of the physical activity questionnaire have been described elsewhere (19).

Changes in BMI and Body Weight

Height and body weight were assessed by questionnaire administered at enrollment, and weight was requested on each follow-up questionnaire. In a validation subsample, questionnaire-reported and staff-measured weights were highly correlated ($r = 0.97$ for men and women) (20). BMI was calculated as weight in kilograms divided by the square of height in meters. Changes in BMI and weight were calculated as the differences in BMI and weight between the beginning and the end of each 4-year interval, with positive difference representing weight gain, and negative difference, weight loss.

Assessment of Covariates

Information about demographics, medical history, and lifestyle factors was derived from the biennial questionnaires. Detailed dietary information was collected from a validated 131-item semiquantitative food frequency questionnaire, administered in 1986 and every 4 years thereafter (21). Diet quality was assessed by using the Alternative Healthy Eating Index (AHEI), with a higher score indicating a healthier diet (22).

Genotyping and GRS Calculation

We selected 77 SNPs that represent all 77 loci associated with BMI in individuals of European ancestry (Supplementary Table 2) (5) and 12 SNPs that represent all 12 loci that have been identified to be associated with BF% (Supplementary Table 1) (6). SNP genotyping and imputation have been described in detail previously (13–17). We used MACH (http://www.sph.umich.edu/csg/abecasis/mach) to impute SNPs on chromosomes 1–22, with National Center for Biotechnology Information build 36 of phase II HapMap CEU data (release 22) as the reference panel. All of the SNPs were genotyped or had a high imputation quality score ($r^2 \geq 0.8$) (23).

In calculations of the GRSs, each SNP was weighted by its relative effect size ($\beta$-coefficient) obtained from the previously GWAS (5,6):

1. BMI-GRS = (\beta_1 \times SNP_1 + \beta_2 \times SNP_2 + \ldots + \beta_{77} \times SNP_{77}) \times (77/\text{sum of the } \beta\text{-coefficients}), where SNP_i is the risk allele number of each SNP associated with higher BMI.

2. Of the 12 BF%-associated SNPs, two near PLA2G6 and in CRTCI were identified in men-specific and women-specific GWAS, respectively; thus, there were 11 SNPs included in the BF%-GRS for men and women. BF%-GRS = (\beta_1 \times SNP_1 + \beta_2 \times SNP_2 + \ldots + \beta_{11} \times SNP_{11}) \times (11/\text{sum of the } \beta\text{-coefficients}), where SNP_i is the risk allele number of each SNP associated with higher BF%. We weighted each SNP using its sex-specific $\beta$-coefficients in the GRS calculation for men and women.

The BMI-GRS ranges from 0 to 154 and the BF%-GRS 0 to 22; higher scores indicate a greater genetic predisposition to obesity.

Statistical Analyses

Data were analyzed within five 4-year intervals over a period of 20 years, i.e., five measures during the period
from 1986 to 2006 in both the NHS and HPFS. The associations of the two GRSs or physical activity at the beginning of each 4-year interval with attained BMI at the end of the same 4-year interval and the associations of the two GRSs or change in physical activity within 4-year intervals with concurrent BMI change were assessed by multivariable generalized linear models with repeated-measures analyses, and all of the independent variables were treated as continuous variables. Generalized estimating equations procedure was used to fit the model, the REPEATED statement was used to specify covariance structures for repeated measurements on subjects, and the empirical SE estimates were used. Change in physical activity, BMI, and other continuous covariates were winsorized at the 0.5 and 99.5 percentiles to minimize the influence of outliers. Missing data during any follow-up period were coded as a missing indicator category for categorical variables, such as smoking status, and with carried-forward values for continuous variables except for physical activity and BMI. Missing values for physical activity and BMI were carried forward only once and after that the follow-up was censored. Relationships of each 10-risk allele increment of each GRS with change in BMI stratified according to quartiles of change in physical activity, and relationships of each 10 MET-h/week increment of physical activity with change in BMI stratified according to quartiles of each GRS were estimated by generalized linear models with repeated-measures analysis, and all of the independent variables were treated as continuous variables. The effect of interaction between each GRS and change in physical activity on BMI change was tested by including the respective interaction terms in the models, with the main effects included in the models as well. We analyzed the interaction between the GRS (G) and change in physical activity (P) using the model: BMI change = \beta_0 + \beta_GG + \beta_PP + \beta_G \times P + e, where \beta_G is the interaction effect. We also tested the genetic associations and interactions on change in body weight. For sensitivity analyses:

1. We tested the interaction using quantitative or quartile scale of change in physical activity.
2. Because the mean effect size of the BF%-variants (0.036, range 0.021–0.058) was greater than that of the BMI variants (0.028, 0.017–0.082), we selected a subset of BMI variants with comparable effect sizes (n = 42, mean 0.035, range 0.023–0.082) to calculate a GRS (mean ± SD 36.5 ± 3.8) to test the interaction.
3. Five SNPs of the BMI- and BF%-associated variants are the same or in linkage disequilibrium: TOMM40 rs20775650, SEC16B rs543874, MC4R rs6567160, TMEM18 rs13021737, and FTO rs1558902. We also analyzed the interaction using a GRS (mean ± SD 5.1 ± 1.3) based on the five SNPs.
4. Given possible confounding due to age- or smoking-related weight change, we performed sensitivity analyses to test the genetic associations and interactions in participants younger than 65 years by censoring participants who were 65 and in participants who had never smoked throughout the follow-up period.

The results across the two cohorts were pooled by means of inverse variance-weighted fixed-effects meta-analyses. Heterogeneity in meta-analyses was assessed by the I^2 measure. All reported P values are nominal and two-sided. Statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS
Baseline Characteristics and Change in BMI
Table 1 presents baseline characteristics and the first 4-year (1986–1990) changes in BMI and lifestyle according to quartiles of concurrent change in physical activity. The mean (SD) BMI changes during the first 4-year interval were 0.4 (2.0) kg/m² for women in the NHS and 0.2 (1.3) kg/m² for men in the HPFS. Compared with participants with decreased physical activity, those who became more physically active had less concurrent increases in BMI and body weight.

The mean (SD) BF%-GRS was 11.5 (2.1) in the NHS and 9.7 (2.2) in the HPFS, and the difference between the two cohorts mainly due to the sex-specific effect sizes (β-coefficients) used to weight each SNP in the GRS calculation (Supplementary Fig. 1). The mean (SD) BMI-GRS was 69.5 (5.5) in the NHS and 69.3 (5.6) in the HPFS (Supplementary Fig. 2).

Main Effects of the GRSs and Physical Activity on BMI
Attained BMI
A higher GRS was associated with a higher BMI at the end of each 4-year interval in the combined cohorts: 1.49 kg/m² (SE 0.16; P < 0.001) and 0.91 kg/m² (0.06; P < 0.001) per 10-risk allele increment of the BF%-GRS and BMI-GRS, respectively. The genetic associations with baseline BMI at the beginning of each 4-year interval were similar to those for attained BMI. Each increment of 10 MET-h/week physical activity at the baseline of each 4-year interval was associated with −0.12 kg/m² (0.01; P < 0.001) lower BMI at the end of the same interval (Fig. 1A). Corresponding associations with body weight are shown in Supplementary Table 3.

Change in BMI
Each GRS was positively associated with BMI change every 4 years in the combined data: 0.06 kg/m² (SE 0.02; P = 0.011) and 0.02 kg/m² (0.01; P = 0.018) per 10-risk allele increment of the BF%-GRS and BMI-GRS, respectively. Each 10 MET-h/week increase in physical activity within each 4-year interval was associated with −0.03 kg/m² (0.002; P < 0.001) change in BMI (Fig. 1B). Corresponding associations with weight change are shown in Supplementary Table 3.

Genetic Associations With BMI Change According to Change in Physical Activity
As shown in Table 2, we found consistently significant interactions between the BF%-GRS and change in physical activity.
activity on BMI change in both the NHS and HPFS (P for interaction = 0.025 and 0.001, respectively). In the combined cohorts, 4-year BMI changes per 10-risk allele increment of the BF%-GRS were 0.24 (SE 0.06), −0.02 (0.06), 0.05 (0.06), and −0.02 (0.06) kg/m² across increasing quartiles of change in physical activity (P for interaction < 0.001). No statistically significant heterogeneity in the interaction effects was observed between the two cohorts (P for heterogeneity > 0.05). We found similar interactions on weight change (Supplementary Table 4).

In the combined cohorts, each 10-risk allele increment of the BMI-GRS was associated with 4-year BMI increases of 0.05 (0.02), 0.03 (0.02), 0.02 (0.02), and 0.01 (0.02) kg/m² across increasing quartiles of physical activity change (P for interaction = 0.045) (Table 3). Similar results for weight change are shown in Supplementary Table 5.

Table 1—Characteristics according to the first 4-year change in physical activity among 14,681 U.S. women and men in the two prospective cohorts

| NHS       | Change in physical activity, MET-h/week* |
|-----------|-----------------------------------------|
| Overall   | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 |
| Age, years| 55.1 ± 6.6 | 55.1 ± 6.8 | 55.8 ± 6.5 | 55.9 ± 6.6 | 54.7 ± 6.6 |
| Initial physical activity, MET-h/week | 28.5 ± 26.2 | 28.5 ± 26.2 | 8.3 ± 10.8 | 7.2 ± 10.1 | 12.2 ± 14.1 |
| BMI change, kg/m² | 26.5 ± 19.0 | 35.6 ± 24.6 | 26.0 ± 5.2 | 25.8 ± 5.1 | 25.3 ± 4.6 |
| Initial weight, kg | 6.8 ± 13.7 | 67.4 ± 12.8 | 69.5 ± 14.7 | 68.9 ± 14.2 | 67.4 ± 13.0 |
| Weight change, kg | 1.0 ± 1.9 | 1.0 ± 1.9 | 0.3 ± 2.2 | 0.3 ± 2.0 | 0.2 ± 1.9 |
| Initial alcohol intake, g/day | 6.3 ± 10.7 | 6.1 ± 10.7 | 6.0 ± 10.6 | 6.2 ± 10.5 | 6.7 ± 11.1 |
| Change in alcohol intake, g/day | −1.1 ± 6.5 | −1.2 ± 6.3 | −1.0 ± 6.5 | −1.0 ± 6.5 | −1.2 ± 6.8 |
| Current smoker, % | 17.4 | 15.2 | 19.4 | 17.7 | 17.4 |
| Remaining current smoker, % | 12.7 | 11.4 | 14.4 | 13.4 | 11.7 |
| Total energy intake, kcal/day | 1,783 ± 518 | 1,791 ± 525 | 1,783 ± 519 | 1,793 ± 511 | 1,767 ± 518 |
| Change in total energy intake, kcal/day | −13 ± 433 | −14 ± 452 | −26 ± 418 | −13 ± 431 | −1 ± 430 |
| AHEI score | 51.6 ± 11.1 | 53.5 ± 11.2 | 49.3 ± 10.6 | 50.3 ± 10.6 | 52.8 ± 11.4 |
| Change in AHEI score | 1.7 ± 8.6 | 1.2 ± 8.8 | 1.6 ± 8.5 | 2.0 ± 8.5 | 2.0 ± 8.8 |
| BF%-GRS | 11.5 ± 2.1 | 11.5 ± 2.2 | 11.5 ± 2.1 | 11.5 ± 2.1 | 11.5 ± 2.1 |
| BMI-GRS | 69.5 ± 5.5 | 69.2 ± 5.5 | 69.4 ± 5.5 | 69.7 ± 5.6 | 69.5 ± 5.5 |

Change in Physical Activity and BMI Change According to Genetic Susceptibility

In the combined cohorts, 4-year BMI changes per 10 MET-h/week increase in physical activity were −0.015 (SE 0.004), −0.027 (0.005), −0.026 (0.004), and −0.035 (0.005) kg/m² across increasing quartiles of the BF%-GRS (Fig. 2A). The findings were broadly similar for the BMI-GRS (Fig. 2B).

Mean of BMI Change According to Joint Categories of Change in Physical Activity and the GRSs

In the combined cohorts, participants with the highest GRSs and the greatest decrease in physical activity had the greatest increases in BMI every 4 years. Compared with participants who had the highest BF%-GRS and the greatest decrease in physical activity, those with the lowest BF%-GRS
and the greatest increase in physical activity exhibited 0.25 kg/m² less increase in BMI, corresponding to 0.70 kg less weight gain; similar findings were observed for the BMI-GRS (Fig. 3).

**Sensitivity Analyses**

The findings of interactions were consistent by using quartile scale or quantitative scale of change in physical activity (Supplementary Table 6). The interactions tested by using the GRSs based on a subset of BMI variants with effect sizes comparable to that of BF% variants and five overlapped SNPs of the BMI- and BF%-associated variants were similar to the main interactions (Supplementary Tables 7 and 8). In addition, we observed similar but weaker genetic associations and interactions between GRSs and change in physical activity in relation to BMI change in participants younger than 65 years and in participants who had never smoked throughout the follow-up period (Supplementary Table 9).

**DISCUSSION**

In two large cohorts of U.S. men and women, both the BMI-GRS and the BF%-GRS were positively associated with increases in BMI and body weight every 4 years over 20 years of follow-up; notably, the BF%-GRS showed stronger associations. Moreover, we found consistently significant interactions between change in physical activity and genetic susceptibility on changes in BMI and body weight over time. The genetic associations appeared to be attenuated by increased physical activity; the inverse association between increasing physical activity and BMI change was more prominent in individuals with greater genetic risk.

Recent GWAS have identified multiple genetic variants associated with BMI and BF% (5,6), which have been largely based on analyses of one-time measurements in these obesity traits. Previous studies on genetic associations of BMI variants with weight change have provided inconsistent results (7–9), which may be partly due to the differences

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**Figure 1**—Relationships of BF%-GRS, BMI-GRS, and physical activity with attained BMI at the end of each 4-year interval and BMI changes every 4 years in the two prospective cohorts. Data are $\beta \pm SE$ (kg/m²), based on 20 years of follow-up (1986–2006) in the NHS and HPFS. Results were adjusted for age and genotyping source for panel A and were further adjusted for baseline BMI (quintile) at the beginning of each 4-year interval for panel B. Results for the two cohorts were pooled by means of inverse variance–weighted fixed-effects meta-analysis ($I^2$ ranged from 0.0 to 98.0%).
in numbers of genetic variants, sample size, and characteristics of study participants. In the current study, we took advantage of repeated measures and the updated genetic variants to show consistent results that genetic variations of BMI and BF% were both associated with long-term changes in BMI and body weight in two independent cohorts.

Additionally, we applied change-on-change analysis in examining the gene–physical activity interaction on changes in BMI and body weight. Several weight-loss trials (24–26) and one longitudinal study (27) have reported interactions of physical activity or lifestyle interventions including physical activity with genetic predisposition to obesity (most used a single locus, FTO gene) on weight change and revealed inconsistent results. Possible reasons for the inconsistent results are the heterogeneity of study design and a relatively small proportion of genetic variation explained by the FTO genotype. Besides, the weight-loss trials have typically enrolled overweight or obese individuals who received short-term lifestyle intervention, therefore limiting the generalizability of the findings to normal populations and to the interactions that determine long-term weight change. As compared with previous studies using single time measures (both exposures and BMI), such change-on-change analysis has several strengths in testing gene–environment interactions and may generate more robust and biologically plausible relations between lifestyle and long-term weight gain (28). Weight gain often occurs gradually over decades, and individuals may achieve a new steady-state weight after changes in lifestyle behaviors. The repeated and well-validated measures of lifestyle and body weight allowed us to assess changes in BMI and physical

Table 2—BMI change per 10-risk allele increment of the BF%-GRS every 4 years, according to quartiles of change in physical activity

|          | Change in physical activity, MET-h/week |         |         |         |   |
|----------|----------------------------------------|---------|---------|---------|---|
|          | Quartile 1                             | Quartile 2 | Quartile 3 | Quartile 4 | P for interaction |
| NHS      |                                        |         |         |         |   |
| Model 1† | 0.18 ± 0.08                            | −0.10 ± 0.09 | 0.11 ± 0.09 | 0.06 ± 0.08 | 0.011 |
| Model 2† | 0.19 ± 0.08                            | −0.10 ± 0.09 | 0.13 ± 0.09 | 0.07 ± 0.08 | 0.025 |
| HPFS     |                                        |         |         |         |   |
| Model 1† | 0.31 ± 0.08                            | 0.03 ± 0.08 | 0.01 ± 0.08 | −0.11 ± 0.08 | <0.001 |
| Model 2† | 0.31 ± 0.08                            | 0.03 ± 0.08 | −0.01 ± 0.08 | −0.10 ± 0.08 | 0.001 |
| Pooled results§ |                                    |         |         |         |   |
| Model 1† | 0.24 ± 0.06                            | −0.03 ± 0.06 | 0.05 ± 0.06 | −0.03 ± 0.06 | <0.001 |
| Model 2† | 0.24 ± 0.06                            | −0.02 ± 0.06 | 0.05 ± 0.06 | −0.02 ± 0.06 | <0.001 |

Data are β ± SE (kg/m²), based on 20 years of follow-up (1986–2006) in the NHS and HPFS. †Model 1 was adjusted for age, genotyping source, and baseline BMI (quintiles) at the beginning of each 4-year interval. ‡Model 2 was further adjusted for baseline lifestyle factors at the beginning of each 4-year interval (physical activity [quartiles], smoking status [never, former, current], alcohol intake [0, 0.1–4.9, 5.0–9.9, 10.0–14.9, ≥15 g/day], total energy intake [quintiles], AHEI score [quintiles]) and concurrent changes in lifestyle factors (smoking status [never to never, never to current, past to past, past to current, current to past, current to current], alcohol intake [quintiles], total energy intake [quintiles], and AHEI score [quintiles]). §Results for the two cohorts were pooled by means of inverse variance–weighted fixed-effects meta-analysis (I² ranged from 0.0 to 68.3%).

Table 3—BMI change per 10-risk allele increment of the BMI-GRS every 4 years, according to quartiles of change in physical activity

|          | Change in physical activity, MET-h/week |         |         |         |   |
|----------|----------------------------------------|---------|---------|---------|---|
|          | Quartile 1                             | Quartile 2 | Quartile 3 | Quartile 4 | P for interaction |
| NHS      |                                        |         |         |         |   |
| Model 1† | 0.03 ± 0.03                            | 0.01 ± 0.04 | 0.02 ± 0.03 | 0.02 ± 0.03 | 0.189 |
| Model 2‡ | 0.02 ± 0.03                            | 0.01 ± 0.04 | 0.02 ± 0.03 | 0.02 ± 0.03 | 0.289 |
| HPFS     |                                        |         |         |         |   |
| Model 1† | 0.07 ± 0.03                            | 0.05 ± 0.03 | 0.03 ± 0.03 | −0.03 ± 0.03 | 0.018 |
| Model 2‡ | 0.07 ± 0.03                            | 0.04 ± 0.03 | 0.03 ± 0.03 | −0.01 ± 0.03 | 0.027 |
| Pooled results§ |                                    |         |         |         |   |
| Model 1† | 0.05 ± 0.02                            | 0.03 ± 0.02 | 0.03 ± 0.02 | −0.01 ± 0.02 | 0.021 |
| Model 2‡ | 0.05 ± 0.02                            | 0.03 ± 0.02 | 0.02 ± 0.02 | 0.01 ± 0.02 | 0.045 |

Data are β ± SE (kg/m²), based on 20 years of follow-up (1986–2006) in the NHS and HPFS. †Model 1 was adjusted for age, genotyping source, and baseline BMI (quintiles) at the beginning of each 4-year interval. ‡Model 2 was further adjusted for baseline lifestyle factors at the beginning of each 4-year interval (physical activity [quartiles], smoking status [never, former, current], alcohol intake [0, 0.1–4.9, 5.0–9.9, 10.0–14.9, ≥15 g/day], total energy intake [quintiles], and AHEI score [quintiles]) and concurrent changes in lifestyle factors (smoking status [never to never, never to current, past to past, past to current, current to past, current to current], alcohol intake [quintiles], total energy intake [quintiles], and AHEI score [quintiles]). §Results for the two cohorts were pooled by means of inverse variance–weighted fixed-effects meta-analysis (I² ranged from 0.0 to 51.9%).
activity rather than prevalent variables, and it has been demonstrated that the analysis of changes in lifestyle factors such as physical activity with long-term weight change may be more relevant to the physiological time course of weight change and the potential biological effects (29, 30). In addition, from a public health perspective, such analysis is important because it may be feasible to encourage populations to make improvement in their overall levels of physical activity and make efforts to prevent weight gain or promote weight loss.

Our data also showed that although the whole population exhibited greater weight loss by increasing physical activity, individuals who were genetically susceptible to higher BMI or BF% might benefit more than those with lower genetic susceptibility. These findings suggest that individuals with a greater genetic predisposition to obesity may respond better to enhancing physical activity on weight loss and lend support to precision interventions using genetic information in the future (31). Although the magnitude of weight change associated with the GRSs or change in physical activity was relatively modest, in the aggregate, the genetic susceptibility and change in physical activity would be associated with a greater weight change. In addition, many individuals may find it difficult to lose weight, and thus simply maintaining weight from adulthood onward, as compared with gaining weight, is an important goal and could have a substantial impact on population health.

In the present analysis, the BF%-GRS showed stronger association with BMI change than that of the BMI-GRS. Compared with the GWAS for BMI, the GWAS for BF% is considerably smaller and, thus, the effect sizes are stronger for the genetic variants that have been detected. However, the mechanisms underlying the observed difference in the genetic associations remained unclear. Moreover, the interaction between the BF%-GRS and change in physical activity appeared to be more prominent than that for the BMI-GRS. High levels of physical activity affect weight loss mainly through lowering fat mass (32, 33), which is better indicated by BF% than by BMI (represents both fat mass and lean mass); thus, individuals who are genetically predisposed to elevated BF% may be more susceptible to the weight-loss effect of physical activity than are individuals who are genetically predisposed to higher BMI.

To the best of our knowledge, this is the first investigation showing that the associations of genetic variations of BMI and BF% with long-term changes in BMI and body weight could be modified by change in physical activity over time. The strengths of the study included the large cohorts, the use of repeated measurements of lifestyle and BMI collected by well-validated questionnaires over 20 years of follow-up, the comprehensive coverage of the well-established BMI- and BF%-associated SNPs, and the consistent results across two independent cohorts. Our study has several potential limitations. First, although we adjusted for the major lifestyle and dietary factors in the analyses, we could not rule out the possible influence of unmeasured or unknown confounders. Second, the data are observational in nature, and the results could be influenced by potential reverse causality. For example, evidence from a longitudinal study and a Mendelian randomization study support that individuals who gained weight might become less physically active (34, 35), leading to reverse bias with respect to the observed associations. Third, the GRSs captured the combined information on all BF%- and BMI-associated SNPs to date, but the identified SNPs account for only a small amount of the variations of these adiposity traits (about 0.6% for BF% and 2.7% for BMI) (5, 6). In addition, due to modest effect sizes for each 1 unit of the GRSs, we presented effect sizes for a 10 allele difference in the GRSs, which is of large genetic difference. Fourth, our study cohorts were restricted to U.S. professionals with

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**Figure 2**—Relationship between each increment of 10 MET-h/week physical activity and BMI change every 4 years, according to quartiles of BF%-GRS and BMI-GRS. Data are \( \beta \pm SE \) (kg/m²), based on 20 years of follow-up (1986–2006) in the NHS and HPFS. Results were adjusted for age, genotyping source, baseline BMI (quintiles), lifestyle factors at the beginning of each 4-year interval (physical activity [quintiles], smoking status [never, former, current], alcohol intake [0, 0.1–4.9, 5.0–9.9, 10.0–14.9, ≥15 g/day], total energy intake [quintiles], and AHEI score [quintiles]), and concurrent changes in lifestyle factors (smoking status [never to never, never to current, past to past, past to current, current to past, current to current], alcohol intake [quintiles], total energy intake [quintiles], and AHEI score [quintiles]). Results for the two cohorts were pooled by means of inverse variance–weighted fixed-effects meta-analysis (I² ranged from 0.0 to 82.8%).
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**Author Contributions.** T.W. performed analyses and drafted the manuscript. T.W. and L.Q. conceived and designed the study. M.K.J., J.H.K., J.L.W., L.R.P., E.B.R., J.E.M., F.B.H., W.C.W., and L.O. acquired the data. All authors contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. L.O. 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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European ancestry, and future analyses in other demographic or ethnic populations are warranted to validate our findings.

In summary, taking advantage of the repeated assessments of 20-year follow-up data from two independent cohorts, we found that both the genetic variations of BMI and BF% were associated with long-term increases in BMI and body weight. In addition, the genetic associations might be attenuated by increasing physical activity, highlighting the importance of promoting physical activity in the prevention of obesity, particularly in genetically predisposed individuals.
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