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The *Fat-Mass and Obesity-Associated (FTO)* Gene, Physical Activity, and Risk of Incident Cardiovascular Events in Caucasian Women

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Abstract

Background—Variation in the *Fat-Mass and Obesity-Associated (FTO)* gene has been associated with obesity, diabetes and hypertension. However, its association with cardiovascular disease (CVD) in healthy populations and any interaction with physical activity remain unclear.

Methods—The *FTO* rs8050136 allele was determined in a prospective cohort study of 21,674 apparently healthy Caucasian US women in the Women's Genome Health Study.

Results—During a mean follow-up of 12.7 ± 2.0 years, 664 incident CVD events occurred. The risk allele (A) was associated with higher prevalence of hypertension, diabetes, and metabolic syndrome (all P<0.05). In a multivariate model, there was significant association of the risk allele with CVD (hazard ratio [HR] per allele copy 1.14 [95% confidence interval, 1.01–1.28]) that was no longer significant after additional adjustment for body mass index (BMI) (HR 1.10 [0.97–1.23]). There was statistical evidence of an interaction between *FTO* and physical activity, P=0.048. We found a significant association of *FTO* with CVD only among less active (≤8.8MET-hrs/wk) women (HR 1.19 [1.02–1.38]) in multivariate analyses that included BMI. More active women did not have this increased risk (HR 0.96 [0.79–1.16]). In a model that adjusted for BMI, less active/high-risk (A/A) women were at 54% increased risk of developing CVD (HR 1.54 [1.13–2.11]), compared to more active/low risk (T/T) women.

Conclusions—Carriers of the *FTO* risk allele have an increased risk of CVD, mediated by BMI. There appears to be an interaction with physical activity, such that this risk increase is only in less active women.

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Potential Financial Conflicts of Interest

Dr. Lee serves as a consultant to Virgin HealthMiles, and sits on its Scientific Advisory Board.

The prevalence of obesity worldwide has reached epidemic proportions, contributing to the global burden of type 2 diabetes, hypertension, the metabolic syndrome (MetS), and atherosclerotic cardiovascular disease (CVD).¹ Recent studies have shown that common variation in the *Fat Mass and Obesity Associated (FTO)* gene is strongly associated with higher body mass index (BMI) and obesity in several populations across the world.² Studies have also suggested that the adiposity related risk alleles at *FTO* may predispose individuals to diabetes, hypertension and cardiovascular events in high risk populations.^{3–5} However, there are scarce data on whether risk alleles at *FTO* increase the risk of the MetS and CVD among individuals at usual risk. Studies have also suggested that the obesogenic effects of *FTO* may be offset by higher levels of physical activity.^{6, 7} Thus, it is plausible that any increased risk of CVD associated with the *FTO* gene may be attenuated by increased levels of physical activity.

We therefore sought to investigate the association between variation in the *FTO* gene and CVD among middle-aged, apparently healthy women, and to examine whether this association is modified by physical activity.

Methods

Participants

Participants were from the Women's Genome Health Study (WGHS),⁸ a prospective genetic evaluation of women in the Women's Health Study (WHS), a completed randomized trial testing aspirin and vitamin E for the prevention of CVD and cancer.⁹ Briefly, beginning in 1993, 39,876 female health professionals in the United States, aged 45 years and older, and free of CVD, cancer, or other major illnesses were randomized in the WHS to receive 100 mg of aspirin or placebo, and 600 IU of vitamin E or placebo, every other day. Total caloric intake, intake of saturated fat and fiber was estimated using a validated 131-item semi-quantitative food frequency questionnaire previously described.¹⁰ Nutrient intake was computed by multiplying the intake frequency of each unit of food by the nutrient content of the specified portion size according to food composition tables from the Harvard School of Public Health, Boston, MA.¹¹ Smoking, menopausal status, hormone use, treatment for high cholesterol, alcohol intake and parental history of myocardial infarction were self-reported at study entry. Diagnoses of hypertension and type 2 diabetes also were self-reported at baseline; such self-reports have been shown to be reliable.¹²

Participants were asked to provide a blood sample before randomization; 28,345 (71%) did so. The baseline characteristics of all women in the WHS and those providing blood were largely similar. Genotype data were available for 22,051 women in the WGHS. For this study, we included 21,674 Caucasian (self-reported European ancestry, verified on the basis of a principal component analysis of 1443 ancestry informative SNPs) women for whom data on *FTO* rs8050136 genotype, BMI and physical activity were available. Participants provided informed consent and the study was approved by the institutional review board, Brigham and Women's Hospital.

Genotyping

DNA samples were genotyped with the Infinium II technology from Illumina (Human HAP300 panel) previously described.⁸ The call rate for rs8050136 was >99%.

Assessment of Physical Activity

Physical activity was assessed using a validated questionnaire with test-retest correlation over two years of 0.59 in a random sample of nurses from another study.^{13, 14} The correlation of physical activity reported on the questionnaire as compared with 4 past-week

recalls of physical activity spaced over one year prior to questionnaire administration was 0.79; as compared with activity diaries kept for 4 weeks over a year, 0.62.^{13, 14} Participants were asked to estimate the average time per week over the past year spent on 8 groups of recreational activities (walking/hiking, jogging, running, bicycling, aerobic exercise/dance, lap swimming, tennis/squash/racquetball, and lower-intensity exercise) and the number of flights of stairs climbed daily.¹⁵ A metabolic equivalent (MET) score was assigned to each activity based on the energy cost of that activity (1 MET is the energy cost of sitting quietly). The energy expended on each activity was then estimated by multiplying its MET score by hours/week of participation, and the total energy expenditure was estimated by summing across all activities.

Laboratory Analysis

Blood samples were assayed for total cholesterol, high density lipoprotein (HDL-C), direct low density lipoprotein (LDL-C) and triglyceride (TG) levels in a core laboratory certified by the National Heart Lung and Blood Institute/Centers for Disease Control and Prevention Lipid Standardization Program. High-sensitivity C-reactive protein (hsCRP) was measured using a validated immunoturbidometric method (Denka Seiken, Tokyo, Japan).

Definition of Metabolic Syndrome

According to the Adult Treatment Panel III (ATP III) guidelines, women with ≥ 3 of the following traits are defined as having metabolic syndrome (MetS): (1) Waist circumference ≥ 88 cm; (2) triglycerides ≥ 150 g/dL; (3) HDL-C < 50 mg/dL; (4) blood pressure $\geq 130/85$ mm Hg; and (5) abnormal glucose metabolism as identified by a fasting blood glucose level ≥ 100 mg/dL.^{16, 17} For this study, we used a modified ATP III definition of MetS.^{12, 18} This definition included using a BMI (self-reported weight and height) > 26.7 kg/m² (corresponding to the same percentile cut-point for women with waist circumference 88 cm, reported at 6-years' follow-up) instead of waist circumference, which was not available at baseline. Blood pressure at baseline was self-reported and has been shown to be accurate.¹⁹ The diagnosis of hypertension was based on self-reported systolic blood pressure of ≥ 130 mm Hg, or diastolic blood pressure of ≥ 85 mm Hg. Because fasting glucose levels were unavailable, we conservatively used a diagnosis of type 2 diabetes at baseline or during follow-up as a surrogate. This modified definition of MetS yields almost identical proportions of women in the WGHS with increasing numbers of characteristics of the metabolic syndrome, compared with data from NHANES which uses the ATP III definition.¹⁸ We additionally included hsCRP of ≥ 3 mg/dL in the list of metabolic traits as studies in this cohort have shown hsCRP to add clinically important prognostic information.¹⁸

Ascertainment of Cardiovascular Disease

The criteria for CVD assessment have been previously reported.⁹ Briefly, women reported the occurrence of diseases of interest, including CVD (nonfatal myocardial infarction, nonfatal ischemic stroke, and coronary revascularization procedures) on questionnaires every 6 months during the first year, and annually thereafter. Deaths were reported by relatives or postal authorities. An endpoints committee of physicians reviewed medical records for all participants reporting CVD. Deaths due to cardiovascular causes were confirmed using all available information from medical records, death certificates, autopsy reports, and information from family members. For this study, participants were followed through February 2008 for the occurrence of the composite end point of first major cardiovascular event (nonfatal myocardial infarction, nonfatal ischemic stroke, coronary revascularization, or cardiovascular death). Only confirmed endpoints were analyzed (n=664).

Statistical Analysis

All analyses were carried out using SAS/Genetics 9.1 package (SAS Institute Inc, Cary, NC). We calculated allele frequencies at rs8050136 and performed Hardy-Weinberg equilibrium tests using the χ^2 test. We first compared baseline characteristics among women in the A/A, A/C and C/C genotype groups using χ^2 tests for categorical variables and Kruskal-Wallis tests for continuous variables.

In cross-sectional analyses, we used multivariable logistic regression analysis to find the odds, per *FTO* risk allele, of the presence of the following metabolic traits: BMI >30 kg/m², HDL-C <50 mg/dL, TG ≥150 mg/dL, hsCRP ≥3 mg/dL, hypertension, diabetes and the metabolic syndrome. We controlled for age and randomized treatment. In additional analyses, we controlled for BMI, a likely variable in the causal pathway linking *FTO* genotype to the metabolic traits.

In prospective analyses, we used multivariable Cox proportional hazards regression to estimate the hazard ratio (HR) of incident CVD per *FTO* risk allele, assuming an additive model of inheritance. A crude model adjusted for age and randomized treatment only. Next, on an a priori basis, we additionally adjusted for potential confounders that are not thought to be in the causal pathway, calling this Model 1: intake of total calories, fat and fiber, and parental history of myocardial infarction. In another model, Model 2, we further adjusted for BMI and BMI² (to more completely adjust for BMI, likely in the causal pathway relating *FTO* to risk of cardiovascular disease; we included a quadratic term since BMI demonstrated some non-linearity in its relationship with CVD). A final model, Model 3, additionally adjusted for other variables that may also be in the causal pathway: treatment for high cholesterol, total cholesterol, LDL-C, HDL-C, triglyceride, hsCRP, menopausal status, hormone therapy, hypertension, diabetes, and MetS.

To assess whether physical activity modified the association of *FTO* genotype with CVD risk, we stratified physical activity using an a priori cut-point, the median level (8.8 MET-hr/week) in the cohort. We tested for interaction between *FTO* genotype and physical activity by including an interaction term between *FTO* genotype and physical activity, classified as ≤8.8 versus >8.8 MET-hr/wk, in Model 1. In sensitivity analyses, we repeated the analysis using two other cut-points for physical activity: 7.5 MET-hours/week, the minimum recommended by the federal government²⁰ and 10 MET-hr/week, congruent with previous guidelines from the Centers for Disease Control and Prevention/American College of Sports Medicine.²¹

Finally, we examined the joint associations of *FTO* genotype and physical activity with CVD risk: those with two copies of the *FTO* risk allele were labeled genetically ‘high-risk’ (A/A); those with one copy of the risk allele, ‘medium-risk’ (A/C); and those with no copies of the risk allele, being ‘low-risk’ (C/C). We compared groups of women classified jointly by their *FTO* genotype and physical activity against a common referent group: women with a low-risk genotype (C/C) expending >8.8 MET-hr/wk in physical activity.

Multiple comparisons were not adjusted for and p-values were set at 0.05 for statistical significance.

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(Cambridge, MA). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Results

The frequency of the risk allele (A) *FTO* rs8050136 was 0.40; allele frequencies in this population did not deviate from Hardy-Weinberg equilibrium ($\chi^2=0.03$, d.f.=1, $p=0.88$). Table 1 shows the baseline characteristics of participants according to their *FTO* genotypes. There was a strong association of the *FTO* risk allele with BMI, with high-risk (A/A) participants having a median BMI that was 1.0 kg/m² higher than the low-risk (C/C) participants. The risk allele also was associated with lower HDL-C levels, higher hsCRP levels, and higher prevalence of hypertension, diabetes and MetS ($p\leq 0.01$ for all). There were no significant associations among *FTO* genotypes and total or saturated fat and alcohol intakes, parental history of myocardial infarction (MI), cholesterol treatment, smoking, menopausal status, hormone therapy, total cholesterol, LDL-C and TG.

The odds, per risk allele, of metabolic traits amongst the cohort are shown in Table 2. The risk allele was associated with significantly increased odds of obesity (BMI>30kg/m²), HDL-C <50mg/dL, hypertension, diabetes, and MetS. These associations were no longer significant after adjusting for BMI.

Table 3 shows the associations between *FTO* genotype and the risk of developing CVD. During a mean follow-up of 12.7 (standard deviation, 2.0 years), 664 women developed CVD. The hazard ratio (HR) for CVD per risk allele was 1.14 (95% CI, 1.01–1.28) in Model 1. The association between *FTO* and CVD was not significant after adjustment for BMI (Model 2) (HR 1.10 [0.97–1.23]). Further addition of other intermediate variables (Model 3) did not materially change these results (HR 1.09 [0.97–1.23]).

When we examined modification of the association between *FTO* and CVD by physical activity levels, we found statistically significant evidence of interaction ($P=0.048$). We therefore performed a stratified analysis, separating women according to the median level of physical activity in the cohort. In those who exercised >8.8 MET-hrs/wk, we found no association between the risk allele and CVD (Model 1 HR 0.98 [0.81–1.18] per copy of risk allele, Table 3). In less active women, there was a significant association (Model 1 HR 1.26 [1.08–1.46]). This increased risk of CVD was attenuated once adjustments were made for BMI (HR 1.19 [1.02–1.38]) and other CVD risk factors (HR 1.19 [1.02–1.39]), but remained statistically significant. In sensitivity analyses, we used alternate, clinically relevant classifications of physical activity: 7.5²⁰ and 10 MET-hr/wk.²¹ The results were similar to those in Table 3 (data not shown).

Finally, we examined the joint associations of *FTO* genotype and physical activity with CVD risk (Table 4). After controlling for variables in Model 1, women with the high-risk genotype (A/A) who were less active were at an 83% increased risk of developing CVD, compared with low-risk genotype (C/C) women who were more active (HR 1.83 [1.34–2.50]). This risk was significantly attenuated, but remained significant, after additionally controlling for BMI and other CVD risk factors (HR 1.54 [1.13–2.11] and 1.49 [1.09–2.05] in Models 2 and 3, respectively). None of the other groups of women, defined by both genotype and physical activity, were at significantly increased risk of CVD.

Discussion

In this prospective study of apparently healthy US Caucasian middle-aged women, variation in the *FTO* gene was significantly associated with increased risk of adverse metabolic traits, including low HDL-C, diabetes, hypertension and the metabolic syndrome. These

associations appeared to be mediated by the effect of *FTO* on BMI. We also found an association of *FTO* with increased risk of CVD. There was significant modification of this association by physical activity, such that carriers of the risk allele had an increased risk of CVD only if they were less active, but not if they were more active.

Three recent studies report an association between *FTO* and CVD amongst high-risk individuals with carriers of the risk allele having up to twice the risk of CVD.^{4, 5, 22} For one of these studies,⁴ the use of statins appeared to ameliorate this association, and in a second study,⁵ the increased risk was only amongst men. The current study extends our knowledge by examining women at usual risk for CVD.

We confirmed previous reports of associations between the *FTO* risk allele with low HDL, hypertension, diabetes and the metabolic syndrome.^{23–25} As in other studies, these associations in the WGHS appear to be driven by the effect of *FTO* on body weight.^{3, 4} We further observed that the association of the *FTO* risk allele with increased CVD risk was modified by level of physical activity. When jointly classified by *FTO* genotype and physical activity, women with a high-risk genotype who were less active had up to an 83% greater risk than women with a low-risk genotype who were more active. Furthermore, our study replicated observations from recent studies among diabetics showing that even after adjustment for BMI and obesity-related covariates, there remained a significant, although attenuated, association of the *FTO* genotype with CVD.^{4, 5} This is an interesting finding because in the present study, the association between *FTO* and atherogenic conditions, such as dyslipidemia, diabetes and hypertension, were completely explained by its effect on BMI. Whether this finding can be explained by ‘off-target’ effects of *FTO* (i.e., effects on targets other than those regulating adiposity) will be likely clarified as we understand more about the mechanism of action of this risk region.

The mechanism of action of the *FTO* variant on increased weight gain, risk of metabolic traits and CVD is currently uncertain. The rs8050136 SNP is likely not a causal variant; SNPs in the first intron of the *FTO* gene that are in linkage disequilibrium with this variant have been found to be associated with obesity phenotypes in multiple populations.² It is unclear whether these changes influence *FTO* expression or splicing, or act as cis regulatory elements. Recent basic science studies have implicated *FTO* as the causal gene underlying this association. The expression of *FTO* is particularly high in the hypothalamus and appears to be involved in energy balance.²⁶ A mouse model with a dominant mutation that reduced *FTO* protein levels in tissue had reduced fat mass, increased energy expenditure, unchanged physical activity and an improved inflammatory profile.²⁷ Another study showed that the loss of *FTO* in mice led to postnatal growth retardation and a significant reduction in adipose tissue and lean body mass. The leanness of *FTO*-deficient mice despite no increase in physical activity and no reduction in caloric intake led authors to suggest that this may be mediated through increased systemic sympathetic activation.²⁸ It is uncertain how applicable these animal findings are to humans.

Several limitations of this study must be considered. First, the study only includes Caucasian women and may not be generalizable to other groups. Second, we lacked genotyping for other *FTO* variants, such as the most commonly associated polymorphism, rs9939609. Third, we did not have baseline waist circumference and fasting glucose levels in all participants and so used BMI and the diagnosis of incident diabetes as a surrogate in our definition of metabolic syndrome. However, this definition has been used in this cohort before and shown to be conservative.^{12, 18} Fourth, physical activity, weight, height, diabetes and hypertension were assessed by self-report. Imprecise reporting of the variables may have occurred; however, any misclassification would be expected to bias the results towards the null since the self-reports predated the occurrence of CVD. Lastly, cardiovascular risk

biomarkers were measured using one fasting sample and may not adequately capture the true risk associated; however, this imprecision is again likely to have attenuated findings.

In conclusion, these data show that carriers of the risk variants in the *FTO* gene have increased risk of developing CVD. Further, this association appears to be modified by physical activity, such that the increase in CVD risk is observed only among women with low levels of physical activity. The effect of *FTO* on CVD risk in these less active women appears to be mediated only partially along pathways related to BMI. An important implication of the present findings, if replicated, is that modifiable aspects of the environment – in this case, physical activity – can offset an adverse risk profile conferred by inherited genes – in this case, *FTO* risk alleles – on increased CVD risk. These results also add to the already large body of evidence supporting a role of regular physical activity for health.

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Table 1Baseline Characteristics of the Study Population by *FTO* Genotype

	A/A (high-risk) N=3,495	A/C (medium-risk) N=10,403	C/C (low-risk) N=7,776	P*
Age, y	52.0 (48.0–58.0)	52.0 (48.0–59.0)	52.0 (48.0–58.0)	0.90
BMI, kg/m ²	25.6 (22.8–29.3)	24.9 (22.5–28.3)	24.6 (22.3–28.1)	<0.0001
Physical activity, MET-hrs/week	8.86 (2.85–20.37)	8.70 (2.85–20.47)	8.91 (2.95–20.90)	0.51
Caloric intake, kcal/d	1680 (1346–2082)	1677 (1355–2049)	1680 (1361–2046)	0.80
Saturated fat intake, g/d	18.6 (14.2–24.0)	18.6 (14.1–24.0)	18.5 (14.1–24.1)	0.92
Alcohol consumption, %				
Rarely	44.0	43.1	42.5	
1–3 drinks/mo	11.9	13.4	13.6	0.14
1–6 drinks/wk	33.9	32.6	33.1	
≥ 1 drinks/d	10.3	10.9	10.8	
Parental history of myocardial infarction, %	13.6	13.0	12.7	0.46
Treatment for high cholesterol, %	3.1	3.2	3.4	0.60
Current smoking, %	11.8	11.7	11.4	0.80
Post-menopausal, %	54.4	54.3	54.0	0.90
Post-menopausal hormone therapy, %	42.6	43.5	44.4	0.16
Total cholesterol, mg/dl	208 (184–235)	209 (184–236)	208 (184–236)	0.60
HDL-C, mg/dl	51.1 (42.4–61.5)	51.9 (43.3–62.3)	52.4 (43.5–62.7)	<0.001
LDL-C, mg/dl	120.9 (100.5–144.0)	121.3 (100.9–144.5)	122.2 (99.9–144.4)	0.78
Triglycerides, mg/dl	121 (85–176)	118 (84–176)	118 (83–174)	0.37
C-reactive protein, mg/dl	2.1 (0.9–4.6)	2.0 (0.8–4.3)	1.9 (0.8–4.3)	0.01
Hypertension, %	27.3	24.5	23.1	<0.0001
Diabetes, %	3.1	2.7	2.1	0.001
Metabolic syndrome, %	26.6	22.8	21.7	<0.0001

Values shown for continuous variables are medians (IQR).

* Using χ^2 test for categorical variables and Kruskal-Wallis test for continuous variables.

Table 2Adjusted Odds Ratios (OR) (95% Confidence Intervals, CI) for Metabolic Traits per Copy of the *FTO* Risk Allele (A)

Characteristic	No. with characteristic	OR* (95% CI)	P	OR (95% CI) [†]	P
BMI ≥30 kg/m ²	3,788	1.23 (1.17–1.29)	<0.0001	-	-
HDL-C <50 mg/dL	9,568	1.04 (1.00–1.08)	0.04	0.97 (0.93–1.01)	0.16
TG ≥150 mg/dL	7,501	1.02 (0.98–1.06)	0.36	0.96 (0.92–1.00)	0.053
hsCRP ≥3 mg/dL	7,970	1.04 (0.99–1.08)	0.09	0.95 (0.91–0.99)	0.01
Hypertension	5,297	1.12 (1.07–1.17)	<0.0001	1.05 (1.00–1.10)	0.06
Diabetes	553	1.25 (1.11–1.41)	0.0003	1.13 (1.00–1.27)	0.054
Metabolic syndrome	4,775	1.13 (1.08–1.19)	<0.0001	0.99 (0.93–1.05)	0.66

* Adjusted for age and randomized treatment assignment.

[†] Additionally adjusted for BMI.

Table 3

Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Incident Cardiovascular Disease per copy of the *FTO* Risk Allele (A)

All Women			
	No. of events	HR for CVD (95% CI)	P
Crude model (n=21,674)	664	1.11 (0.99–1.24)	0.06
Model 1* (n=19,004)	560	1.14 (1.01–1.28)	0.03
Model 2 [†] (n=19,004)	560	1.10 (0.97–1.23)	0.13
Model 3 [‡] (n=18,826)	555	1.09 (0.97–1.23)	0.15
Women Expending >8.8 MET hours/week			
Crude model (n=10,841)	263	1.01 (0.85–1.20)	0.92
Model 1* (n=9,486)	223	0.98 (0.81–1.18)	0.82
Model 2 [†] (n=9,486)	223	0.96 (0.79–1.16)	0.68
Model 3 [‡] (n=9,486)	222	0.96 (0.79–1.16)	0.67
Women Expending ≤ 8.8 MET hours/week			
Crude model (n=10,833)	401	1.18 (1.02–1.35)	0.02
Model 1* (n=9,518)	337	1.26 (1.08–1.46)	0.004
Model 2 [†] (n=9,518)	337	1.19 (1.02–1.38)	0.03
Model 3 [‡] (n=9,431)	333	1.19 (1.02–1.39)	0.03

Crude model adjusted for age and randomized treatment assignment.

* Model 1: crude model additionally adjusted for alcohol use, caloric intake, saturated fat and fiber intake, smoking, and parental history of myocardial infarction.

[†] Model 2: Model 1, additionally adjusted for BMI and BMI².

[‡] Model 3: Model 2, additionally adjusted for cholesterol lowering medication, total cholesterol, LDL-C, HDL-C, TG, hsCRP, menopausal status, post-menopausal hormone therapy, hypertension, diabetes and the metabolic syndrome.

Table 4
Risk of Cardiovascular Disease According to *FTO* Genotype Risk Categories and Physical Activity Level

	>8.8 MET-hours/week			8.8 MET-hours/week		
	Low-Risk C/C	Medium-Risk A/C	High-Risk A/A	Low-Risk C/C	Medium-Risk A/C	High-Risk A/A
N	3,913	5,173	1,755	3,863	5,230	1,740
Mean BMI, kg/m ² (±SD)	24.84 (4.22)	24.89 (4.17)	25.57 (4.73)	26.31 (5.03)	26.90 (5.45)	27.82 (5.86)
No. of Events	104	107	52	131	186	84
Crude Model	1.0	0.78 (0.60–1.03)	1.13 (0.81–1.57)	1.34 (1.04–1.73)	1.39 (1.09–1.76)	1.91 (1.44–2.55)
P-value		0.08	0.48	0.03	0.008	<0.0001
Model 1 [*]	1.0	0.78 (0.58–1.05)	1.06 (0.73–1.54)	1.14 (0.86–1.52)	1.22 (0.93–1.58)	1.83 (1.34–2.50)
P-value		0.10	0.75	0.37	0.15	0.0001
Model 2 [†]	1.0	0.79 (0.59–1.05)	1.01 (0.70–1.46)	1.06 (0.79–1.41)	1.09 (0.84–1.42)	1.54 (1.13–2.11)
P-value	-	0.10	0.96	0.71	0.52	0.007
Model 3 [‡]	1.0	0.78 (0.59–1.05)	1.02 (0.70–1.47)	1.04 (0.77–1.38)	1.04 (0.79–1.36)	1.49 (1.09–2.05)
P-value	-	0.10	0.94	0.82	0.77	0.01

Crude model adjusted for age and randomized treatment assignment.

^{*} Model 1: crude model additionally adjusted for alcohol use, caloric intake, saturated fat and fiber intake, smoking, and parental history of myocardial infarction.

[†] Model 2: Model 1, additionally adjusted for BMI and BMI².

[‡] Model 3: Model 2, additionally adjusted for cholesterol lowering medication, total cholesterol, LDL-C, HDL-C, TG, hsCRP, menopausal status, post-menopausal hormone therapy, hypertension, diabetes and the metabolic syndrome.