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Weight gain prevention buffers the impact of *CETP* rs3764261 on high density lipoprotein cholesterol in young adulthood: The Study of Novel Approaches to Weight Gain Prevention (SNAP)

Jeanne M. McCaffery, **Jose M. Ordovas**, **Gordon S. Huggins**, **Chao-Qiang Lai**, **Mark A. Espeland**, **Deborah F. Tate**, and **Rena R. Wing**

Department of Psychiatry and Human Behavior, Alpert School of Medicine at Brown University (J.M.M., R.R.W.); JM-USDA-HNRCA at Tufts University, IMDEA Alimentacion, Madrid (J.M.O.); Sackler School of Biomedical Science, Tufts University (G.S.H.); USDA-ARS, JM-USDA Human Nutrition Research Center on Aging at Tufts University (C-Q.L); Department of Biostatistical Sciences, Wake Forest School of Medicine (M.A.E.); Gillings School of Global Public Health, University of North Carolina (D.F.T.)

Abstract

Background and Aims—Two weight gain prevention strategies, one targeting small changes to diet and physical activity and a second targeting large changes, significantly reduced weight gain in young adulthood. We examined whether weight gain prevention blunts genetic risk for body weight increase and/or high density lipoprotein cholesterol (HDL-C) lowering over two years.

Methods and Results—Participants were 524 male and female young adults (mean age=28.2, SD=4.3; mean BMI=25.5, SD=2.6). Obesity-related SNPs accounting for >= 0.04% of the variance were genotyped and combined into a genetic risk score. For HDL-C, SNPs within *CETP, LIPC* and *FADS2* were genotyped. The obesity-related genetic risk score did not predict change in BMI independently or in interaction with treatment arm. However, consistent with the prior literature, each copy of the HDL-C risk, C, allele at *CETP* rs3764261 was associated with lower HDL-C at baseline. Moreover, significant interaction between SNP and treatment arm for change in HDL-C was observed (p=0.02). In the control group, HDL-C change was dependent upon rs3764261 (p=0.004) with C allele carriers showing a continued reduction in HDL-C. In contrast, within the two intervention groups, HDL-C increased on average with no differential effect of rs3764261 (p >0.24). Notably, even among carriers of the CC genotype, small and large change arms were associated with increased HDL-C and the control arm a reduction (p=0.013).

Corresponding Author: Jeanne McCaffery, Ph.D., University of Connecticut, Department of Allied Health Sciences, Koons Hall Room #320, 358 Mansfield Rd, Unit 1101, Storrs, CT 06269-1101; Phone: 860 486-2190; jeanne.mccaffery@uconn.edu.

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Authors' contributions to the manuscript: JMM, JMO, GH, RW designed research; JMM, RW, MAE, DFT conducted research; JMO, C-QL provided essential reagents or provided essential materials; JMM performed statistical analysis; JMM, RW wrote paper; JMM had primary responsibility for final content. All authors read and approved the final manuscript.

Conclusions—The C allele at *CETP* rs3764261 is a strong risk factor for low HDL-C in young adulthood but weight gain prevention may mitigate this risk.

Clinical Trial Registry number and website—clinicaltrials.gov Identifier: NCT01183689, https://clinicaltrials.gov/

Keywords

Prevention; body mass index; genetics; high-density lipoprotein cholesterol; young adulthood

Introduction

Young adulthood is a critical period for weight gain and the development of obesity.[1–3] The Coronary Artery Risk Development in Young Adults (CARDIA) study, for example, found that young adults gain 30 pounds on average between the ages of 20–35[4], although more recent data suggest that the rate of weight gain may be decreasing.[5, 6] This weight gain leads to worsening in cardiovascular risk factors, including a lowering of HDL-C[4, 7].

The Study of Novel Approaches to Weight Gain Prevention (SNAP)[8] was designed to determine whether two randomized weight gain prevention treatments, based upon “Small” and “Large” change self-regulation strategies, could prevent weight gain and the associated change in cardiovascular risk in young adulthood compared to a “self-guided” control condition. Both the Small Change and Large Change self-regulation approaches resulted in significant weight losses over an average of three-years of follow-up compared to the control condition; the Large Change program further produced significantly greater weight loss compared to the Small Change condition[9]. Although the changes in cardiometabolic risk factors from baseline to 2 years did differ significantly across groups, many of the risk factor changes were strongly related to changes in weight over this interval[10]. Percent weight change was strongly related to change in HDL-C at year 2, ranging from a 0.11 mmol/l [4.21 mg/dL] average increase in HDL-C among participants who lost 5% or more of their initial weight to a decrease of −0.03 mmol/l [1.24 mg/dL] on average among participants who gained 5% or more of their initial weight[10].

Genetic factors are well-known to contribute to adiposity and cardiovascular disease risk. Genome-wide association studies (GWAS) have discovered common genetic variants that account for 2.7% of the variance in adult body mass index (BMI)[11] and 9–12% of the variance in serum lipids[12, 13]. Gene × environment interaction has also been demonstrated for body weight and HDL-C. Physical activity blunts the effects of obesity-related genetic variation on BMI[14]. Body weight and physical activity further interact with genetic risk factors for low HDL-C[15–17], in one study accounting for additional 3% of the variance in HDL-C above and beyond the variance associated with the genetic markers alone[16]. Huggins and colleagues[18] similarly demonstrated that improvement in HDL-C during behavioral weight loss treatment (combining diet and physical activity) varies by *CETP* rs3764261, *LIPC* rs8034802 and *FADS2* rs1535.

We hypothesized that weight gain prevention may blunt genetic risk for obesity and/or low HDL-C. We genotyped select SNPs associated with obesity or HDL-C in GWAS in the

SNAP study to explore whether successful weight gain prevention can mitigate genetic risk. The SNPs selected included those accounting for 0.04% of variance or greater in BMI in prior research (N=12; jointly 1.04% of total variance[11]) as well as HDL-C related SNPs previously shown to interact with weight loss intervention[18].

Methods

Study Participants

Participants were 524 men and women, ages 18–35, with a BMI of 21–30.9 kg/m^2 who participated in the SNAP randomized controlled trial, a 3-arm parallel randomized controlled clinical trial, with equal allocation, comparing self-regulation with small daily behavior changes (Small Changes), self-regulation with large periodic behavior changes (Large Changes), and a minimal treatment control condition[8]. The coordinating center at Wake Forest School of Medicine randomized 599 participants using a simple, variable block-length algorithm stratified by clinic, gender and race between August 2010 and February 2012.

The 524 participants included in this analysis represent the subset who consented for genetic analyses. At baseline, 178, 177 and 169 participants in the control, Small Changes and Large Changes treatment arms were included in this analysis. At year 2 follow-up, 137, 138 and 140 participants in the control, Small Changes and Large Changes arms, respectively, were included, for a total of 415 participants. Primary reasons for missing data at year 2 included pregnancy and missed visits.

A full description of the methods for the SNAP trial have been published previously[19]. Briefly, both Small and Large Changes interventions were framed in a self-regulation model. To encourage self-regulation, participants were instructed to weigh themselves daily and submit their weight via the study website, text message or email. They received monthly email feedback on their weight, which was based on a color-coded system and reinforced their success, encouraged problem-solving, or recommended strategies to reverse weight gain. Participants in Small Changes were taught to make daily small changes (approximately 100 kcal/day) in both diet (e.g. select lower calorie coffee drinks, reduce portion sizes) and physical activity (e.g. park further from store, use stairs). Large Changes focused on losing 5 – 10 lbs. during the initial four-month program to create a buffer against subsequent weight gain. To achieve this, participants were prescribed a calorie goal based on a 500 to 1000 kcal deficit from baseline. They were also encouraged to gradually increase moderate intensity physical activity to a goal of 250 minutes/week, the level recommended for weight loss maintenance[20], and to maintain this over time. Both the Small and Large arms began with 10 face-to-face group meetings over 4 months. Subsequently, the interventions were delivered primarily online. The Control group attended one face-to-face meeting where they were introduced to both the small and large changes approaches to prevention of weight gain, but this group did not receive any further assistance with weight gain prevention. Participants received a $50 honorarium for follow-up assessments.

The study involved 2 clinical sites (Providence, RI and Chapel Hill, NC) and a coordinating center (Winston-Salem, NC), and was approved by each Institutional Review Board.

Measures

All assessments were completed by staff blinded to treatment arm. Weight was measured on a calibrated scale in light clothes, without shoes; height was assessed with a wall-mounted stadiometer. Two measures were taken and averaged. Serum lipids were analyzed using standard methods at baseline and year 2.

SNP Selection and Genotyping

Select single nucleotide polymorphism (SNP) were targeted for genotyping based on prior associations with body weight or HDL-C in GWAS. For BMI, we represented 12 genetic regions accounting for 0.04% or more of the variance in BMI in the most recent, multi-ethnic GWAS[11]. These included (nearest gene, SNP): *BDNF* rs11030104; *SEC16B* rs543874, *FTO* rs1558902; *ETV5* rs1516725; *TFAP2B* rs2207139; *NEGR1* rs3101336; *ATP2A1* rs3888190; *MC4R* rs6567160; *BCDIN3D* rs7138802; *ADCY3* rs10182181; *GNPDA* rs10938397; *TMEM18* rs13021737). We created an obesity genetic risk score by summing the additive allele dose at each SNP weighted by the strength of association with BMI[11].

For HDL-C, we selected SNPs identified in GWAS as associated with HDL-C[12, 13] but also shown to interact with weight loss intervention in our previous work[18]. Specifically, *CETP* rs3764261, *FADS2* rs1535 and *LIPC* rs8034802 were genotyped.

All SNP assays were performed using Taqman assays as recommended by the manufacturer.

Statistical approach

Baseline SNP associations with BMI were determined by linear regression with clinic, race and Hispanic ethnicity as covariates. For change over 2 years, hierarchical linear regression was used to examine change in BMI at year 2 from baseline as function of clinic, race, Hispanic ethnicity, treatment arm, SNP allele dose and SNP allele dose by treatment arm interaction. Similar models were run for HDL-C at baseline and year 2 with the addition of oral contraceptives as a covariate. Participants taking lipid-lowering medications were excluded from lipid analyses. The covariate set is consistent with the SNAP primary outcome paper[9] with the addition of self-reported race and Hispanic ethnicity to mitigate the potential for population stratification and oral contraceptives to mitigate potential impact on lipid parameters.

Results

Study Population

Table 1 presents demographic and baseline characteristics for the sample. Participants were on average approximately 28 years of age. The majority of participants identified as female (78%) with 26% reporting a minority racial or ethnic background. Participants were on average slightly overweight (BMI: mean = 25.5 kg/m^2; SD=2.59) and had lipid and glucose levels in the normal range. Twenty-two participants (4.2%) reported taking lipid-lowering medications at some point during the two years and 34.4% (44.2% of female participants)

reported taking oral contraceptives over the same period. No differences by treatment arm in demographic or baseline characteristics were observed (p >0.12).

At year 2, change in BMI differed significantly across treatment group (p=0.003). Both the Small and Large Change interventions reduced BMI (−0.85 kg/m^2 (SD=4.74) and −1.60 kg/m^2 (SD=5.01), respectively), whereas the control group showed a small increase in BMI (0.34 kg/m^2 (SD=4.83)). HDL-C tended to increase at year 2 in the Small and Large Changes arms relative to the control arm (Small Changes: 0.04 mmol/l, SD=0.25; Large Changes: 0.05 mmol/l, SD=0.25; Self-Guided Control: −0.01 mmol/l, SD=0.27) but the difference across treatment arms did not achieve statistical significance (p=0.15). Glucose also tended to differ across the three arms at year 2 (p=0.04) with a small decline in the Large Changes condition (Large Changes: −0.02 mmol/l, SD=0.32), a small increase in Small Changes condition (Small Changes: 0.03 mmol/l, SD=0.36) and a larger increase in the control arm (Self-Guided Control: 0.09 mmol/l, SD=0.32). Little difference across treatment arms emerged for triglycerides (p=0.476), total cholesterol (p=0.86) and low-density lipoprotein cholesterol (LDL-C; p=0.83).

Obesity Genetic risk score

Baseline—The weighted genetic risk score did not significantly predict baseline BMI (p=0.99).

Change from baseline to Year 2—The weighted obesity genetic risk score also did not predict change in BMI at year 2 independently (p = 0.77) or in interaction with treatment arm (p = 0.30).

High Density Lipoprotein Cholesterol

Baseline—Each copy of the risk, C, allele at *CETP* rs3764216 was associated with lower baseline HDL-C (−0.07 mmol/l, standard error (SE)=0.026, p = 0.008). Neither *LIPC* rs8034802 nor *FADS2* rs1535 were significantly associated with baseline HDL-C (p's > 0.45).

Change from Baseline to Year 2—An interaction between *CETP* rs3764216 and treatment arm was observed for year 2 change in HDL-C (ΔR^2= 0.02, p = 0.02). Genotypic models to explore the interactions within treatment group are presented in Figure 1. HDL-C tended to increase on average in both the small (0.04 mmol/l, SD=0.25, p = 0.05) and large change (0.05 mmol/l, SD=0.25, p = 0.04) arms with no differential effect of rs3764261 (p > 0.24). In the control group, HDL-C did not change significantly on average −0.01 mmol/l, SD=0.27, p = 0.71) but change was dependent upon rs3764261 (p=0.004). The highest risk, CC genotype was associated with a reduction of −0.05 mmol/l, (SD=0.024), the AC genotype with an intermediate response (0.01 mmol/l, SD=0.26) and the AA genotype with an increase in HDL-C (0.20 mmol/l, SD=0.32) in the control group.

Notably, even in analyses limited to the group at highest risk for low HDL-C, those with the CC genotype at *CETP* rs3764216, treatment arm remained a significant predictor of HDL-C change (p=0.013), with small and large change arms associated with increased HDL-C

(Small changes: 0.05 mmol/l, SD=0.27; Large Changes: 0.06 mmol/l, SD=0.19, respectively) and the control arm a reduction (−0.05 mmol/l, SD=0.24).

Although not associated with HDL-C at baseline, *LIPC* rs8034802 significantly predicted change in HDL-C over 2 years (ΔR^2= 0.02, p = 0.008) but did not interact with treatment arm (ΔR^2= 0.001, p = 0.85). Across arms, each copy of the T allele, previously associated with low HDL-C, predicted a decline of HDL-C of −0.05 mmol/l (SE=0.02) at year 2.

FADS2 rs1535 did not predict change in HDL-C year 2 overall or interact with treatment arm (p's > 0.45).

Total cholesterol, LDL cholesterol, triglycerides and glucose

Baseline—None of the SNPs related significantly to total cholesterol, LDL cholesterol, triglycerides or glucose levels (p=0.06).

Change from baseline to Year 2—An interaction between *CETP* rs3764216 and treatment arm was observed for year 2 change in total cholesterol levels (ΔR^2= 0.02, p = 0.02). Total cholesterol did not change in either the small (p = 0.60) or large change (0.05 mmol/l, SD=0.25, p = 0.40) arms and no effect of rs3764261 was observed within these arms (p > 0.29). Total cholesterol also did not change significantly on average in the control group (0.01 mmol/l, SD=0.49, p = 0.99) but a differential effect of rs3764261 on total cholesterol change was observed (p=0.048). The CC genotype (highest risk for low HDL-C) was associated with a reduction of −0.04 mmol/l, (SD=0.43), the AC genotype with an intermediate response (0.02 mmol/l, SD=0.49) and the AA genotype with an increase in total cholesterol (0.32 mmol/l, SD=0.39) in the control group. As this finding may have been driven by the observed changes in HDL-C and the association of *CETP* rs3764126 is most prominent with HDL-C, we tested whether statistically controlling HDL-C altered the strength of the interaction. After adding change in HDL-C as a covariate, the interaction of rs3764126 and treatment arm in predicting change in total cholesterol was no longer significant (p=0.19).

No other SNPs associations with changes in total cholesterol, LDL cholesterol, triglycerides or glucose levels at year 2, either independently (p > 0.06) or in interaction with treatment arm (p > 0.18), were observed.

Discussion

The goal of this paper was to examine the potential for weight gain prevention to mitigate genetic risk for weight gain and lowering of HDL-C. We found that the effect of *CETP* rs3764261 on a lowering of HDL-C over time could be blunted by weight gain prevention. Intriguingly, even in highest risk group for low HDL-C, the *CETP* rs3764261 CC genotype, both weight gain prevention treatments were associated with an increase in HDL-C, whereas the self-guided control group showed the expected decrease in HDL-C. No effect of the obesity-related genetic variants on BMI at baseline or changes in BMI from baseline to 2 years were observed and there were no significant interactions with treatment arm. These results identify SNP × environment interaction contributing to 2 year change in HDL-C

among young adults. Moreover, they suggest that low HDL-C associated with the *CETP* locus may be mitigated by weight gain prevention strategies.

CETP rs3764261 is the strongest association with HDL-C observed in GWAS, with the major C allele accounting for −0.088 mmol/l lower HDL-C per copy[13]. In this study, each copy of the C allele predicted −0.07 mmol/l lower HDL-C at baseline, confirming the prior association with a similar effect size in young adulthood. The cholesteryl ester transfer protein, coded by *CETP*, regulates reverse cholesterol transport, exchanging cholesterol esters and triglycerides between HDL-C and triglyceride-rich very low-density lipoproteins. Increased expression of the *CETP* gene has been associated with low HDL-C. *CETP* rs3764261 is located upstream in the 5' region, wherein major alleles, including the C allele at *CETP* rs3764261, are associated with greater *CETP* expression and lower HDL-C[21]. Obesity further creates a triglyceride-rich environment, leading to greater CETP activity, clearance of triglyceride-rich HDL-C and lower HDL-C[22]. Taken together, it is plausible that higher body weight provides a substrate rich in triglycerides that varies in its impact on HDL-C based upon genetic variation, including *CETP* rs3764261. Weight gain prevention may negate the triglyceride-rich environment and therefore alter the role of *CETP* rs3764261 in predicting HDL-C leading to SNP × weight gain prevention interaction.

It is notable that the obesity genetic risk score did not predict baseline BMI or change in BMI in this study. This lack of effect may have occurred for several reasons. First, the control group gained less weight than anticipated. In CARDIA, for example, weight gain was approximately 1 kg per year across young adulthood[23], whereas 0.34 kgs over two years was observed in this study[9]. It is possible that the initial educational session and feedback on weight and risk factors may have blunted weight gain in the control group and thereby genetic effects of weight gain. Second, genetic risk for obesity appears modifiable by high levels of physical activity[14]. The SNAP cohort participated in remarkably high levels of moderate-to-vigorous physical activity at baseline, with 60% already meeting physical activity guidelines using conservative objective measurement[24]. As such, it is also plausible that the high levels of moderate to vigorous physical activity may have overshadowed the impact of obesity-related genetic variation on weight gain. Lastly, BMI was the only measure of adiposity available in the present study. It remains possible that the obesity genetic risk score may show stronger association with other indices of adiposity, such as waist circumference, waist-to-hip ratio or visceral fat.

Despite limitations, including a small sample size, self-reported race and ethnicity and limited genotyping, we find a novel interaction of *CETP* rs3764261 with randomized weight gain prevention techniques in predicting HDL-C. In the broader context of epidemiologic studies reliably demonstrating strong interaction of BMI with HDL-C related genetic variation, we provide a novel example of the interplay of body weight and genetics for HDL-C and demonstrate for the first time that the impact of *CETP* rs3764261 on low HDL-C may be reversible with weight gain prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

None

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Abbreviations

ADCY3	Adenylate Cyclase 3
ATP2A1	ATPase Sarcoplasmic/Endoplasmic Reticulum Ca2+ Transporting 1
BCDIN3D	BCDIN3 Domain Containing RNA Methyltransferase
BDNF	brain derived neurotrophic factor gene
BMI	body mass index
CARDIA	Coronary Artery Risk Development in Young Adults Study
CETP	Cholesteryl Ester Transfer Protein
LIPC	Lipase C, Hepatic Type
ETV5	ETS Variant 5
FADS2	Fatty Acid Desaturase 2
FTO	fat mass and obesity gene
GNPDA	Glucosamine-6-Phosphate Deaminase 1
GWAS	genome-wide association study
HDL-C	high density lipoprotein cholesterol
kcal	kilocalories
kg	kilograms
LDL-C	low density lipoprotein cholesterol
MC4R	melanocortin 4 receptor gene
NEGR1	Neuronal Growth Regulator 1
SEC16B	SEC16 Homolog B, Endoplasmic Reticulum Export Factor gene
SNAP	Study of Novel Approaches to Weight Gain Prevention
SNP	single nucleotide polymorphism
TFAP2B	Transcription Factor AP-2 Beta
TMEM18	Transmembrane Protein 18

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Highlights

- Randomized weight gain prevention strategies blunted the impact of *CETP* rs3764261, representing the region mostly strongly associated with high density lipoprotein cholesterol (HDL-C) in genome-wide association studies, on lowering of HDL-C over two years in young adulthood
- Even among those with the highest risk genotype for low HDL-C, the CC genotype, randomized weight gain prevention produced an increase in HDL-C whereas lowering was observed in the control group.

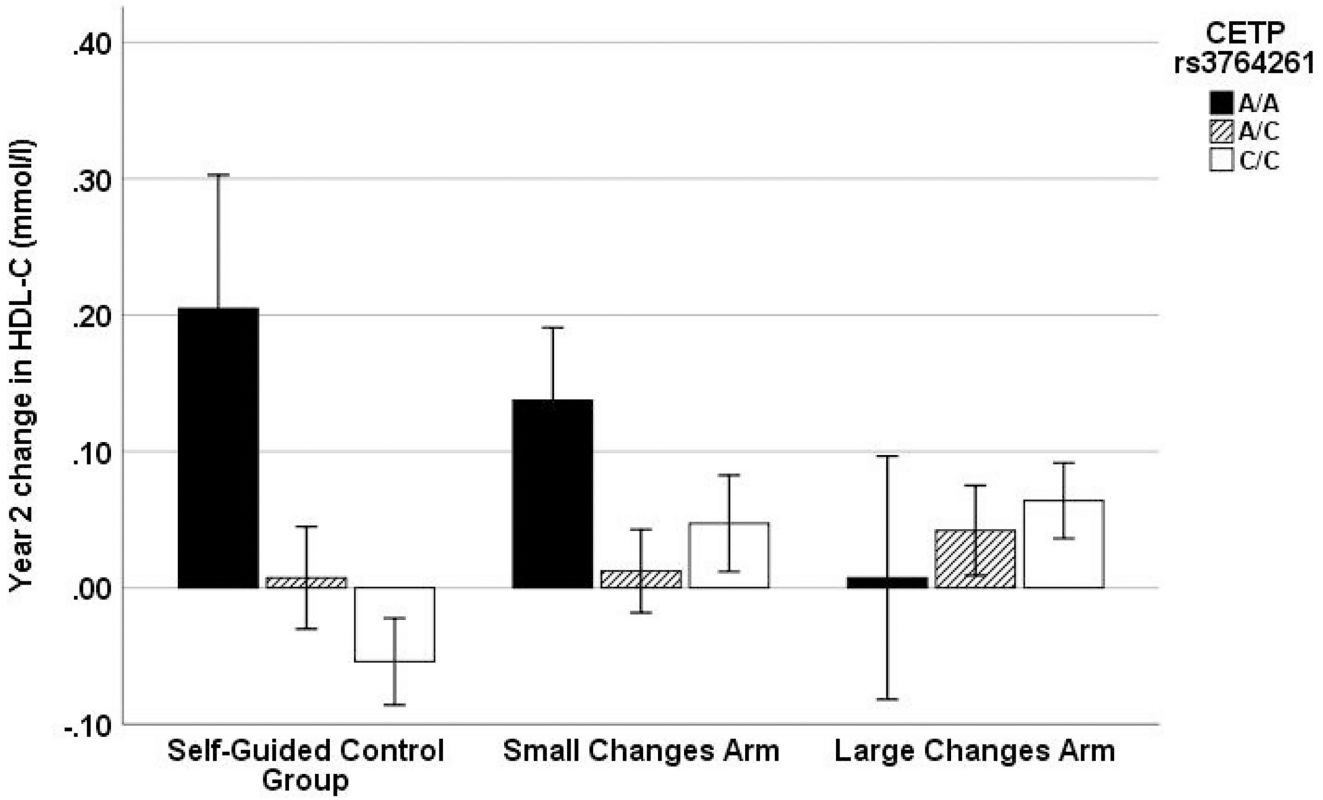

Figure 1.

Year 2 change in HDL-C cholesterol (in mmol/l) by *CETP* rs3764261 and weight gain prevention treatment arm. Error bars reflect +/− one standard error.

Table 1

Descriptive statistics and baseline characteristics

	Mean or %	SD
Age (years)	28.2	4.35
Female (%)	78.0%	
Race and Ethnicity		
White	74.0%	
African American or Black	9.7%	
Hispanic ethnicity	7.6%	
Other race or ethnicity	8.2%	
BMI (kg/m^2)	25.5	2.4
Total cholesterol (mmol/l)	4.5	0.8
HDL cholesterol (mmol/l)	1.5	0.4
LDL cholesterol (mmol/l)	2.5	0.7
Triglycerides (mmol/l)	1.0	0.5
Glucose (mmol/l)	5.0	0.4
Lipid-lowering medications	4.2%	
Oral contraceptives	34.4%	