Variants in APOA5 and ADIPOQ Moderate Improvements in Metabolic Syndrome during a One-Year Lifestyle Intervention

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Abstract

Background: Metabolic syndrome (MetS) comprises a cluster of risk factors including central obesity, hypertension, dyslipidemia, and impaired glucose homeostasis. Lifestyle interventions that promote improvements in diet quality and physical activity represent a first line of therapy for MetS. However, varying responses to lifestyle interventions are well documented and may be partially explained by underlying genetic differences. The aim of this study was to investigate if variants in genes previously associated with MetS influence the magnitude of change in MetS risk during a 1-year lifestyle intervention. Methods: The present study used data collected from the Canadian Health Advanced by Nutrition and Graded Exercise study cohort (n = 159 men and women) to investigate the effect of 17 candidate single nucleotide polymorphisms (SNPs) on response to a 1-year lifestyle intervention. Associations between SNPs and the continuous MetS (cMetS) score, as well as individual MetS components, were examined. Results: Reductions in cMetS score at both 3 months and 1 year were significantly associated with 2 variants: rs662799 (A/G) in apolipoprotein A5 (APOA5) and rs1501299 (G/T) in adiponectin (ADIPOQ). Individuals carrying a minor T allele in rs1501299 experienced a greater reduction in cMetS score at both 3 months and 1 year, whereas major allele AA homozygotes in rs662799 experienced greater reductions in cMetS score during the intervention. No associations were identified between the aforementioned SNPs and individual components of MetS. Both unweighted and weighted genetic risk scores (GRS) using these 2 SNPs revealed that individuals carrying none of the risk alleles experienced significantly greater reductions in cMetS score after 1 year. Conclusions: The findings from the current study suggest that individuals with certain genotypes may benefit more from a lifestyle intervention for MetS and that specific variants, either independently or as part of a GRS, could be used as a nutrigenomic tool to tailor the intervention to reduce the risk of MetS.
Introduction

Metabolic syndrome (MetS) encompasses a cluster of factors that contribute to the risk for developing type 2 diabetes (T2D) and cardiovascular disease [1]. The prevalence of MetS is estimated to be as high as 40% in some populations, particularly in developed countries and older generations [2]. Although nuances exist regarding the definitions for MetS proposed by various organizations, the condition is generally defined as the clinical manifestation of 3 or more of the following 5 risk factors: central obesity (defined using waist circumference), elevated fasting blood glucose, hypertension, elevated triglycerides, and reduced high-density lipoprotein cholesterol (HDL-C) [3]. Diagnosing MetS is generally done by examining whether the five aforementioned risk factors lie above or below defined threshold values. However, the use of dichotomous assessments is not without criticism, which prompted the development of a continuous MetS (cMetS) score [4]. Specifically, the cMetS score was developed by Hillier and colleagues as a practical method to evaluate MetS risk using principal component analysis. These authors demonstrated that each standard deviation (SD) increase in the cMetS score was associated with an increased risk of T2D and cardiovascular disease.

Initial treatment for MetS typically includes a lifestyle intervention comprising changes in diet and physical activity, which has been shown to reduce both the severity of MetS and dependency on pharmacological therapy [5]. While lifestyle interventions for MetS are generally successful, a wide range of responses are observed between people, with some individuals showing great improvements, while others show little-to-no improvement [6–8]. These variable responses to lifestyle interventions may stem, in part, from underlying genetic differences [6]. Indeed, hundreds of single nucleotide polymorphisms (SNPs) have been associated with MetS as a whole, as well as with the individual MetS components [1]. Moreover, many of these SNPs have also been reported to influence a person’s response to lifestyle interventions [6]. Consequently, it stands to reason that SNPs may influence the degree of improvement experienced by individuals undergoing lifestyle modifications for MetS [9].

The Canadian Health Advanced by Nutrition and Genomic Strategies (CHANGE) feasibility study evaluated a year-long tailored lifestyle intervention for individuals with MetS [10]. We previously reported that the CHANGE study resulted in a 19% reversal of MetS [10]; however, it is unknown if genetic variants moderate improvements in MetS risk. The primary objective of the present study was to examine the influence of SNPs previously found to be associated with MetS on changes in cMetS score, as well as individual MetS components, during a 1-year lifestyle intervention. A secondary objective was to develop un-weighted (uw) and weighted (w) genetic risk scores (GRS) to examine their impact on changes in cMetS score. We hypothesized that genetic variants would moderate improvements in cMetS score in response to a lifestyle intervention. We anticipate that our findings will help to further personalize lifestyle interventions that aim to reduce MetS risk.

Materials and Methods

CHANGE Feasibility Study Overview

The data used for the current analyses corresponds to the subset of individuals enrolled in the CHANGE feasibility study who provided a DNA sample (Fig. 1). For a thorough description of the CHANGE feasibility study, as well as inclusion and exclusion criteria, please refer to Jeejeebhoy et al. [10]. The CHANGE feasibility study was a prospective, longitudinal before-after demonstration study carried out at 3 primary healthcare clinics across Canada, recruiting individuals with MetS between 2012 and 2014. The primary objective of the CHANGE study was to reverse MetS and improve its components by the end of the intervention period. This year-long personalized lifestyle intervention used a team-based approach comprising a primary care physician, a kinesiologist, and a dietician. The goal of the intervention was to create sustainable behavioral changes within the cohort by adhering to an individual diet plan broadly based on the Mediterranean diet principles and a combination of weekly aerobic, resistance, and flexibility exercises [11, 12]. Diet quality was assessed using the Canadian Healthy Eating Index (HEI-C), which provides a score ranging from 0 to 100 based on a person’s adherence to Canada’s Food Guide recommendations [13]. Dieticians met with participants to create individualized dietary plans based on a care map that integrated evidence-based dietary advice with principles from behavior change models [12]. Participants also met with kinesiologists to develop individualized fitness plans that included supervised and unsupervised activities to improve aerobic, resistance, and flexibility training [11]. Aerobic capacity was evaluated using maximal oxygen consumption (VO2max) [14]. All participants attended weekly visits (over the first 3 months) and monthly visits (over the final 9 months) with a diettitian and kinesiologist, and were followed by a primary physician quarterly. Standard blood clinical measurements were completed at baseline, 3- and 12-months to monitor common biomarkers of metabolic health (e.g., lipids, glucose). The cMetS score was calculated by combining the weighted effects of waist circumference, triglycerides, blood glucose, and systolic blood pressure using the approach developed by Hillier and colleagues [4]. Written and oral informed consent was obtained from all eligible patients before inclusion. This protocol was approved by a Research Ethics Board of the participating clinics and affiliated universities.
DNA Extraction and Genotyping

Blood samples were drawn at baseline, 3 months and 12 months and stored at −80°C until analysis. DNA was extracted from whole blood using the Qiagen PAXgene Blood DNA kit, according to manufacturer instructions (Qiagen, Toronto, ON, Canada). DNA quantity was determined using a NanoDrop 2000c (Fisher Scientific, Waltham, MA, USA) and quality was visually assessed on a 1% agarose gel. DNA samples were collected from each participant at baseline and 12 months; therefore, the sample with the highest quality was used for genotyping.

SNP Selection

SNPs of interest were selected based on an extensive search of the existing literature. The search criteria included SNPs that have been previously associated with MetS in genome-wide association studies, lifestyle intervention studies, and/or meta-analyses. Only SNPs with a minor allele frequency > 10% according to the 1000 Genomes Project (http://www.internationalgenome.org/; accessed 09/2016) were selected. A panel of 17 SNPs corresponding to 12 genes was chosen for the present analysis (Table 1) [1, 6, 15–24].

SNP Analysis

All DNA samples were diluted to a concentration of 20 ng/µL. Genotyping was performed at the Centre for Applied Genomics (The Hospital for Sick Children, Toronto, ON, Canada) using the Sequenom MassARRAY platform, which is based on detection through MALDI-TOF MS (Mass Array, Sequenom, San Diego, CA, USA). Positive and negative controls, made up of a Yoruban HapMap trio and water samples, respectively, were used for quality control. Twelve DNA samples were randomly selected for replication and 100% concordance was achieved. Hardy-Weinberg equilibrium was evaluated for all SNPs using a χ² test.

Genetic Risk Score

The SNPs used to build un-weighted (uw) and weighted (w) GRSs were identified based on associations between individual SNPs and change in cMetS score. An uwGRS ranging from 0 to 2 was built, where a participant’s GRS was calculated by summing the number of risk alleles for 2 SNPs: rs662799 (G) and rs1501299 (G). A GRS = 0 corresponds to a participant carrying no risk alleles, GRS = 1 corresponds to a participant carrying one risk allele, and a GRS = 2 corresponds to a participants carrying both risk alleles. The wGRS was built by taking into account the effect size (β/stANDARD error) of each SNP, as revealed from the individual additive models for rs662799 and rs1501299.

Statistical Analyses

Linear regressions were used to investigate associations between SNPs and cMetS score, as well as between SNPs and individual MetS components. Models accounted for the following covariates: age, sex, BMI, ethnicity, change in HEI-C, participating site, and baseline medication. Medication was treated as a dichotomous variable (Y/N), where participants using any medication related to a MetS component were considered “Y”. BMI was not included as a covariate when investigating cMetS score and waist circumference. We constructed both dominant (MM vs. Mm + mm) and additive (MM vs. Mm vs. mm) genetic models for all regression analyses. The term “minor allele carrier” is used throughout the manuscript to refer to participants who are either

### Table 1. Candidate SNPs associated with individual MetS components selected

| MetS component       | Gene     | SNP          | Major/ minor allele | MAF based on 1000 Genomes | MAF in CHANGE study participants | Ref. |
|----------------------|----------|--------------|---------------------|---------------------------|-----------------------------------|------|
| Blood pressure       | ATP2B1   | rs17249754   | G/A                | 0.2095                    | 0.1572                             | 15   |
|                      | ACE      | rs4343       | A/G                | 0.3568                    | 0.4840                             | 16   |
| Fasting blood glucose| GLUT2    | rs5400       | G/A                | 0.2153                    | 0.1604                             | 17   |
|                      | TCF7L2   | rs12255372   | G/T                | 0.2139                    | 0.2830                             | 6    |
|                      | ADIPOQ   | rs7903146    | C/T                | 0.2278                    | 0.3050                             | 1    |
|                      |          | rs1501299    | G/T                | 0.3033                    | 0.2642                             | 18   |
| Dyslipidemia         | FADS1    | rs174537     | G/T                | 0.3029                    | 0.3584                             | 19   |
|                      | CETP     | rs1800775    | A/C                | 0.4535                    | 0.4748                             | 20   |
|                      | CETP     | rs247617     | C/A                | 0.2680                    | 0.2893                             | 21   |
|                      | rs5882   | G/A          | 0.4661              | 0.2987                    | 22   |
|                      | APOC3    | rs2854117    | C/T                | 0.4992                    | 0.2642                             | 23   |
|                      | APOA5    | rs662799     | A/G                | 0.1629                    | 0.0912                             | 6    |
|                      | rs964184 | C/G          | 0.2222              | 0.1792                    | 6    |
|                      | APOA1    | rs670        | C/T                | 0.1885                    | 0.1950                             | 24   |
| Waist circumference  | MCar     | rs12970134   | G/A                | 0.2075                    | 0.2421                             | 1    |
|                      | FTO      | rs9939609    | T/A                | 0.3401                    | 0.4308                             | 6    |

MAF, minor allele frequency.
heterozygous or minor homozygous carriers for a given SNP. The change in cMetS score at 3 and 12 months was calculated as “cMetS score at 3-months – cMetS score at baseline” and “cMetS score at 12-months – cMetS score at baseline” respectively. Since we chose to not account for multiple testing, we only considered associations that were statistically significant at both time points, and in both dominant and additive models, to reduce the risk of reporting false positives.

Prior to analyses, data were assessed for normality using a Shapiro-Wilk test. A Friedman’s repeated measures test was used when analyzing continuous data in study participants at baseline, 3- and 12-months. A χ^2 test was used to compare categorical data when analyzing continuous data in study participants at baseline, or were missing either a DNA sample or both dominant and additive genetic models. Individuals heterozygous or minor homozygous carriers at both time points (Fig. 2a). In contrast, individuals carrying a minor T allele in rs1501299 (GT + TT) experienced greater reductions in cMetS score compared to AG + GG carriers at both time points (Fig. 2a). In contrast, individuals carrying a minor T allele in rs1501299 (GT + TT) experienced greater reductions in cMetS score at both time points (Fig. 2b). Significant associations were observed between other SNPs and the change in cMetS score at both 3- and 12-months. Specifically, triglyceride levels were reduced (p = 0.0006) and HDL-C levels were increased (p < 0.0001). These improvements aligned with trends in other blood lipid markers, that is, a reduction in LDL-C (p = 0.07) and an increase in APOA1 (p = 0.07). Waist circumference decreased significantly after 3 months (p < 0.0001), which reflected reductions in BMI. Both systolic and diastolic blood pressure were reduced after 3 months (both p < 0.0001) and these reductions persisted at 12 months. Fasting blood glucose (p = 0.3) was the only MetS component that did not change during the intervention.

**SNPs Influence the Magnitude of Change in the cMetS Score**

Seventeen candidate SNPs previously reported in the literature to be associated with individual MetS components were analyzed in the present investigation. All SNPs but one (rs17782313) were in Hardy-Weinburg equilibrium. No significant associations were observed between the 17 candidate SNPs and the cMetS score at baseline (data not shown). However, examining the change in cMetS score at both 3 and 12 months revealed several statistically significant and consistent associations with various SNPs (Table 3). In particular, rs662799 (A/G) in APOA5 and rs1501299 (G/T) in ADIPOQ were associated with change in cMetS score at both 3- and 12-months. Furthermore, these associations were significant in both dominant and additive genetic models. Individuals homozygous for the major A allele for rs662799 experienced greater reductions in cMetS score compared to AG + GG carriers at both time points (Fig. 2a). In contrast, individuals carrying a minor T allele in rs1501299 (GT + TT) experienced greater reductions in cMetS score at both time points (Fig. 2b). Significant associations were observed between other SNPs and the change in cMetS score; however, these associations were not consistent

**Results**

**Characterization of the CHANGE Cohort**

Participants who did not meet our criteria for MetS at baseline, or were missing either a DNA sample or 12-month cMetS data, were excluded from the present analysis (Fig. 1). The final sample size for the present analyses was 159 (77 males and 82 females). The mean age of participants was 60.7 ± 0.73 years (median of 62; range 18–75). The majority of the study population was Caucasian (n = 131, 82.4%), while the remainder of the cohort comprised of 16 (10%) individuals of European/Sub-Saharan African/Mediterranean/Arab ethnicity, 10 (6.3%) individuals of Asian/South Central American ethnicity, and 2 (1.3%) individuals of unknown ethnicity.

Baseline, 3- and 12-month characteristics for the 159 participants are presented in Table 2. Consistent with the original CHANGE feasibility study, in this subset of patients both the HEI-C and estimated VO_2_{max} improved significantly by 3 months and these improvements were maintained at 12 months (p < 0.0001 for both). The cMetS score decreased at 3 months and the reduction was maintained at 12 months (p < 0.0001). Individual MetS components significantly improved across the duration of the study in our subset of participants. Blood lipid profiles were improved at 3 months and maintained at 12 months. Specifically, triglyceride levels were reduced (p = 0.0006) and HDL-C levels were increased (p < 0.0001). These improvements aligned with trends in other blood lipid markers, that is, a reduction in LDL-C (p = 0.07) and an increase in APOA1 (p = 0.07). Waist circumference decreased significantly after 3 months (p < 0.0001), which reflected reductions in BMI. Both systolic and diastolic blood pressure were reduced after 3 months (both p < 0.0001) and these reductions persisted at 12 months. Fasting blood glucose (p = 0.3) was the only MetS component that did not change during the intervention.

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across time points and/or models. Therefore, these SNPs were not considered in the construction of GRSs.

**Genetic Risk Score and Change in the cMetS Score**

We established GRSs corresponding to the 2 aforementioned SNPs: rs662799 and rs1501299. These 2 SNPs were associated with a change in cMetS score at both 3- and 12-months using both dominant and additive genetic models. At baseline, no associations were identified between the uwGRS (or wGRS) and cMetS score (data not shown). In contrast, the 12-month change in cMetS score was significantly associated with uwGRS ($p = 0.0006$; Fig. 3), with a similar trend seen at 3 months ($p = 0.005$; data not shown). Individuals with an uwGRS of 0 (i.e., carrying no risk alleles) showed greater reductions in their cMetS score compared to individuals with at least 1 risk allele (0 vs. 1, $p = 0.05$; 0 vs. 2, $p = 0.004$). Although we did not detect statistical differences between individuals carrying 1 or 2 risk alleles, it appears that the change in cMetS score is reduced as the number of risk alleles increases.

### Table 2. Characteristics of participants at baseline, 3, and 12 months

| Characteristics                                                                 | Baseline ($n = 159$) | 3 months ($n = 148$) | 12 months ($n = 159$) | $p$ value |
|---------------------------------------------------------------------------------|----------------------|----------------------|-----------------------|-----------|
| Age, years                                                                       | 60.7±0.73            | –                    | –                     | –         |
| Female, $n$ (%)                                                                  | 82 (51.6)            | –                    | –                     | –         |
| BMI, kg/m²                                                                       | 31.0±0.27$^a$        | 30.4±0.27$^b$        | 30.1±0.29$^b$         | <0.0001   |
| Current smoker, $n$ (%)                                                           | 14 (8.8)             | 13 (8.8)             | 12 (7.55)             | 0.9       |
| HEI-C                                                                            | 58.2±1.2$^a$         | 68.4±1.0$^b$         | 68.6±1.1$^b$          | <0.0001   |
| VO$_{2\text{max}}$ mL/kg/min                                                     | 32.2±0.57$^a$        | 34.9±0.57$^b$        | 35.2±0.55$^b$         | <0.00001  |
| LDL-C, mmol/L                                                                   | 2.54±0.08            | 2.49±0.09            | 2.49±0.08             | 0.07      |
| APOA1, mmol/L*                                                                  | 1.43±0.02            | Not measured         | 1.46±0.02             | 0.06      |
| cMetS score                                                                      | 2.36±0.08$^a$        | 1.79±0.08$^b$        | 1.94±0.09$^b$         | <0.0001   |

**Metabolic syndrome criteria**

1. Elevated blood pressure or using pharmacotherapy, $n$ (%)  
   Systolic blood pressure, mm Hg  
   Diastolic blood pressure, mm Hg  
   Received pharmacotherapy for elevated blood pressure, $n$ (%)  

2. Elevated fasting blood glucose or using pharmacotherapy, $n$ (%)  
   Blood glucose, mmol/L  
   Received pharmacotherapy for elevated blood glucose levels, $n$ (%)  

3. Elevated triglycerides or using pharmacotherapy, $n$ (%)  
   Triglyceride level, mmol/L  
   Pharmacotherapy for dyslipidemia, $n$ (%)  

4. Reduced HDL-C, $n$ (%)  
   HDL-C, mmol/L  

5. Large waist circumference, $n$ (%)  
   Waist circumference, cm

Values denote mean ± SE. Continuous data were analyzed using a Friedman’s repeated measures test, while categorical data were compared using a $\chi^2$ test. Values within a row that have a different superscript letter are statistically significantly different from one another ($p < 0.05$).

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; HEI-C, Healthy Eating Index-Canadian; LDL-C, low-density lipoprotein cholesterol; VO$_{2\text{max}}$, maximal oxygen consumption.

* APOA1 was not measured at 3 months; therefore, a Wilcoxon repeated measures test was used. *Metabolic syndrome criteria were defined as follows: blood pressure ≥130/85 mm Hg or receiving pharmacotherapy; fasting blood glucose ≥5.6 mmol/L or receiving pharmacotherapy; triglyceride level ≥1.7 mmol/L or receiving pharmacotherapy; male patients with an HDL-C level <1.0 mmol/L or female patients with an HDL-C level <1.3 mmol/L; waist circumference as determined by a prespecified technique ( Europid, white, sub-Saharan African, Mediterranean, middle eastern [Arab] patients ≥94 cm for men, 80 cm for women; Asian and South Central American patients ≥90 cm for men, 80 cm for women; white American and Canadian patients ≥102 cm for men, 88 cm for women. 

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Table 3. Associations between candidate SNPs and change in cMetS score at 3 and 12 months

| Gene | SNP       | 3-month change in cMetS score | 12-month change in cMetS score |
|------|-----------|-------------------------------|-------------------------------|
|      |           | additive model, p, β value    | dominant model, p, β value     | additive model, p, β value | dominant model, p, β value |
| ATP2B1 | rs17249754 | 0.99, 0.01                    | 0.67, 0.04                    | 0.27, 0.09                  | 0.36, –0.07                 |
| ACE   | rs4343    | 0.81, 0.10                    | 0.46, –0.06                   | 0.56, 0.05                  | **0.02, –0.19**             |
| GLUT2 | rs5400    | 0.86, 0.01                    | 0.85, 0.02                    | 0.74, –0.03                 | 0.61, –0.04                 |
| TCF7L2 | rs12255372 | **0.05, –0.17**               | 0.07, –0.15                   | 0.24, –0.10                 | 0.33, –0.08                 |
|       | rs7903146 | 0.10, –0.14                   | 0.21, –0.11                   | 0.25, –0.10                 | 0.35, –0.08                 |
| ADIPOQ | rs1501299 | **0.02, 0.2**                 | **0.05, 0.16**                | **0.006, 0.22**             | **0.01, 0.21**              |
| FADS1 | rs174537  | 0.76, 0.03                    | 0.14, 0.12                    | 0.66, –0.04                 | 0.56, 0.05                 |
| CETP  | rs1800775 | 0.83, 0.02                    | 0.55, –0.05                   | 0.44, –0.07                 | 0.28, –0.09                 |
|       | rs247617  | 0.96, 0.01                    | 0.87, 0.01                    | 0.09, 0.14                 | 0.14, 0.13                 |
|       | rs5882    | 0.8, –0.02                    | 0.77, –0.02                   | 0.31, –0.08                 | 0.38, –0.07                 |
| APOC3 | rs2854117 | 0.06, –0.16                   | 0.19, –0.11                   | **0.02, –0.19**             | 0.13, –0.12                 |
| APOA5 | rs662799  | **0.02, 0.19**                | **0.03, 0.18**                | **0.004, 0.23**             | **0.02, 0.19**              |
|       | rs964184  | 0.23, –0.1                    | 0.27, –0.09                   | 0.1, –0.13                 | 0.15, –0.12                 |
| APOA1 | rs670     | 0.21, 0.1                     | **0.05, 0.16**                | 0.13, 0.12                 | **0.02, 0.19**             |
| MC4R  | rs12970134| 0.98, –0.01                   | 0.96, 0.01                    | 0.7, 0.03                   | 0.43, 0.06                 |
|       | rs17782313| 0.84, –0.02                   | 0.80, –0.02                   | 0.71, 0.03                 | 0.75, 0.03                 |
| FTO   | rs9939609 | 0.83, 0.02                    | 0.5, –0.06                    | 0.18, –0.11                 | 0.32, –0.08                 |

Data corresponding to dominant and additive genetic models for all linear regressions are presented. Models accounted for the following covariates: HEI-C, BMI, age, ethnicity, gender, recruitment site, and baseline medication. Statistically significant associations are highlighted with bold font (p < 0.05).
The wGRS showed similar results, with significant associations seen with the 12-month change in cMetS ($p = 0.003$) and the 3-month change in cMetS ($p = 0.002$).

**Discussion**

The present study examined whether genetic variants influence the magnitude of the reduction in cMetS score during a year-long lifestyle intervention in a subset of participants from the CHANGE feasibility study. The primary findings of this investigation were: (1) 2 SNPs were consistently associated with change in cMetS score, where 0 corresponds to individuals carrying no risk alleles, 1 corresponds to individuals carrying one risk allele, and so on. Bars sharing letters are not significantly different from one another ($p < 0.05$). The number of individuals in each group: GRS = 0 ($n = 56$), GRS = 1 ($n = 87$), and GRS = 2 ($n = 16$).

Although not the primary objective of this genetic-based study, the improvements in biochemical measures and dietary behaviors observed within our subset of individuals mirror the findings from the entire CHANGE study cohort as previously reported [10]. The decrease in cMetS score, increase in HEI-C and VO$_{2\text{max}}$, as well as improvements in all MetS components except fasting blood glucose, highlight the effectiveness of the lifestyle intervention used in the CHANGE feasibility study. The current investigation revealed that the magnitude of the reduction in cMetS score in response to the lifestyle intervention is moderated by common SNPs in 2 genes.

APOA-V is an important regulator of circulating triglyceride levels through 2 primary mechanisms. First, circulating APOA-V can interact with lipoprotein lipase on the luminal side of endothelial cells to promote the hydrolysis of triglyceride-rich lipoproteins. Second, APOA-V, can bind the hepatic LDL-receptor to encourage the clearance of lipoprotein remnants [25]. Previous reports have shown that MetS prevalence and the risk of MetS is increased in individuals carrying the minor G allele in rs662799 (also known as –1131T>C), a SNP located in the upstream promoter region of the APOA5 gene [26–29]. Specifically, people carrying the minor allele have been shown to have elevated triglyceride levels and, in some instances, reduced HDL-C levels in both healthy and unhealthy individuals [29, 30].

In the present study, minor allele carriers showed smaller reductions in cMetS score in response to the lifestyle intervention compared to major allele homozygotes. These findings align with previous reports investigating the modifying effect of this SNP on triglyceride levels during lifestyle and/or dietary interventions. For example, a 3-year trial in which Korean individuals with impaired fasting glucose or newly diagnosed T2D replaced all refined white rice with whole grains, barley, or legumes and increased vegetable intake, showed that those carrying the minor allele had lower plasma APOA-V levels and higher triglyceride levels at both baseline and following the intervention compared to individuals carrying the major allele [31]. Additionally, a 3-month intervention consisting of diet quality improvements and regular walking in individuals with hypertriglyceridemia showed greater improvements in major allele carriers for both APOA-V and triglyceride levels compared to minor allele carriers, despite a similar degree of compliance [32]. In contrast, the aforementioned genotype effect in response to a lifestyle intervention was not observed in a Japanese cohort [33]. Collectively, these studies suggest a potential moderating effect for rs662799 on blood triglyceride levels in response to longer-term lifestyle interventions. Interestingly, previous reports suggest that the frequency of the minor “risk” allele is more common in the Asian population compared to other ethnicities.
to those of European descent [31]. This suggests that the moderating effect of this SNP in response to a lifestyle intervention should be investigated more closely in distinct subgroups of the general population.

Adiponectin is a well-known adipokine encoded by the ADIPOQ gene. Circulating adiponectin levels have been associated with improvements in both MetS and insulin resistance, and genetic variants in ADIPOQ have been shown to influence circulating levels [34]. For example, individuals carrying the minor T allele in rs1501299 were reported to have higher adiponectin levels in both Asian and European populations [35, 36]. The present study demonstrated that rs1501299 genotype is associated with reductions in cMetS score. Specifically, individuals carrying the minor T allele (GT + TT) showed a greater response to the lifestyle intervention compared to those homozygous for the major G allele. This is intriguing, as evidence suggests that individuals homozygous for the G allele are at greater metabolic risk than T-allele carriers. For example, a recent meta-analysis of Chinese Han populations reported a greater G allele frequency in individuals with MetS [37]. Further, individuals homozygous for the GG genotype showed impaired glucose tolerance in Spanish subjects [35]. We did not identify any associations between rs1501299 and fasting glucose levels at baseline or during the intervention; therefore, we are unable to hypothesize why the change in cMetS score is influenced by the rs1501299 genotype.

Shin et al. [38] examined the association between rs1501299 and circulating adiponectin and insulin resistance in response to a 12-week weight loss intervention. In contrast to our findings, these authors showed that GG homozygotes showed significant improvements in insulin sensitivity and increases in adiponectin following the weight-loss intervention, with little-to-no change seen in carriers of the T allele. It is unclear why our results, which show that T allele carriers experienced greater improvement in metabolic health in response to the lifestyle intervention, do not align with those reported by Shin et al. [38]. Measuring plasma adiponectin levels may have provided some insight to help understand this apparent discrepancy; however, differences in the lifestyle intervention (i.e., caloric deficit versus improvement in diet quality), length of time of the intervention (3 vs 12 months), and population make-up should be acknowledged. Thus, further investigations of this particular SNP as a moderator of response to lifestyle interventions are necessary.

In addition to individual SNP associations, GRSs (both uwGRS and wGRS) provided strong correlation with the lifestyle intervention outcomes. The significantly greater reduction in cMetS score seen in individuals carrying no risk alleles (GRS = 0) compared to individuals with at least 1 risk allele highlights the need to consider overall risk scores rather than individual SNPs. To the best of our knowledge, this is one of the first studies to examine GRSs in the context of a lifestyle intervention for MetS. A recent study by San-Cristobal et al. [39] used a GRS comprised of 14 SNPs to explore associations between Mediterranean Diet adherence, blood biomarkers, and genetic background in volunteers of the Food4Me study. Individuals were categorized into “low” and “high” GRS groups, with those having a low GRS experiencing a greater reduction in total cholesterol levels after 6-months compared to those with a high GRS. The SNPs used to create a GRS in this past study are different than those used in the present study; however, the results align to suggest that individuals with a greater number of “risk” alleles would benefit from more tailored strategies to improve health outcomes. Conversely, an unfavorable genetic profile may predict an adverse response to what would be normally expected from healthy eating and exercise training.

The present study has several limitations and strengths to be considered. Primary limitations include the relatively small sample size (n = 159), minor differences in diet, and exercise alterations between individuals due to personalized advice (as opposed to a standardized lifestyle intervention), lack of information regarding alcohol intake, and the fact that all subjects had MetS at recruitment (i.e., no control group) may have limited our ability to detect certain gene associations (e.g., rs670 and HDL-C). Future studies to validate the genetic findings on subsequent MetS intervention populations are warranted. However, a major strength of the CHANGE study was the duration of the intervention and data collection at multiple time points. Furthermore, the use of 3 diverse participating sites across Canada means our results are generalizable, at minimum across North America. Moreover, having a physician, dietitian, and kinesiologist monitor each participant’s progress at regular intervals during the study, and make adjustments if necessary, was optimal to minimize risk of non-compliance. Finally, we were overly conservative in regard to the SNPs used in our GRS analyses. Specifically, both SNPs were significantly associated with changes in cMetS at both 3 and 12 months in both dominant and additive genetic models. This conservative approach reinforces the significant findings uncovered with our uwGRS and wGRS models.

In conclusion, the present study demonstrated that specific genetic variants, both alone and when combined into a GRS, influence the magnitude of change in cMetS.
score in response to a lifestyle intervention. These results reinforce the potential value of assessing genetic risk to better tailor health management and goal-setting during an intervention. Moreover, knowledge of gene-lifestyle interactions may contribute to the development and/or refinement of nutrigenomic advice for healthcare practitioners and direct-to-consumer genetic companies alike.

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Disclosure Statement

Metabolic Syndrome Canada is a not-for-profit charitable organization that funded the current study. R.D. was paid for her work on the study by Queen’s University from this grant. R.D. became an employee of Metabolic Syndrome Canada after the completion of study enrolment. D.K. received a grant as a participating site for patient enrolment and data collection from Metabolic Syndrome Canada. P.B., D.R., D.M.M., and A.T. received grants for program development from Metabolic Syndrome Canada. K.J. is on the board of directors for Metabolic Syndrome Canada and will be involved in discussions about fundraising for this non-profit organization.

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