Cardiovascular Risk Factors and Ischemic Heart Disease

Is the Confluence of Risk Factors Greater Than the Parts?
A Genetic Approach

Roberto Elosua, MD, PhD; Carla Lluís-Ganella, PhD; Isaac Subirana, PhD; Aki Havulinna, PhD; Kristi Läll, MSc; Gavin Lucas, PhD; Sergi Sayols-Baixeras, MSc; Arto Pietilä, MSc; Maris Alver, MSc; Antonio Cabrera de León, MD, PhD; Mariano Sentí, MD, PhD; David Siscovick, MD, MPH; Olle Mellander, MD, PhD; Krista Fischer, PhD; Veikko Salomaa, MD, PhD; Jaume Marrugat, MD, PhD

Background—Cardiovascular risk factors tend to aggregate. The biological and predictive value of this aggregation is questioned and genetics could shed light on this debate. Our aims were to reappraise the impact of risk factor confluence on ischemic heart disease (IHD) risk by testing whether genetic risk scores (GRSs) associated with these factors interact on an additive or multiplicative scale, and to determine whether these interactions provide additional value for predicting IHD risk.

Methods and Results—We selected genetic variants associated with blood pressure, body mass index, waist circumference, triglycerides, type-2 diabetes mellitus, high-density lipoprotein and low-density lipoprotein cholesterol, and IHD to create GRSs for each factor. We tested and meta-analyzed the impact of additive (synergy index) and multiplicative (βinteraction) interactions between each GRS pair in 1 case–control (n=6042) and 4 cohort studies (n=17,794) and evaluated the predictive value of these interactions. We observed 2 multiplicative interactions: GRS_{LDL} × GRS_{triglycerides} (βinteraction =−0.096; SE=0.028) and nonpleiotropic GRS_{HDL} × GRS_{LDL} (βinteraction =0.091; SE=0.028). Inclusion of these interaction terms did not improve predictive capacity.

Conclusions—The confluence of low-density lipoprotein cholesterol and triglycerides genetic risk load has an additive effect on IHD risk. The interaction between low-density lipoprotein cholesterol and IHD genetic load is more than multiplicative, supporting the hazardous impact on atherosclerosis progression of the combination of inflammation and increased lipid levels. The capacity of risk factor confluence to improve IHD risk prediction is questionable. Further studies in larger samples are warranted to confirm and expand our results. (Circ Cardiovasc Genet. 2016;9:279-286. DOI: 10.1161/CIRCGENETICS.115.001255.)

Key Words: regression analysis ■ genetic association studies ■ genetic variation ■ risk assessment ■ risk factors

The Framingham Heart Study introduced the term cardiovascular risk factor1 to define traits that are associated with cardiovascular disease and have a capacity to predict future events.2 Some of these risk factors are interrelated and tend to aggregate. A paradigm of this aggregation is metabolic syndrome,3 which is associated with an increase in cardiovascular events.4,5 However, there is an open debate about whether this confluence of cardiovascular risk factors provides clinical or mechanistic information beyond the mere addition of its individual components.6–8 In other words, is the combination of risk factors more valuable than the sum of its parts?

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An ideal way to reliably assess the impact of these risk factors on cardiovascular risk, individually and in combination, would be to perform a prospective cohort study of individuals with different, stable, long-term levels of exposure to these risk factors and with different combinations of each. Alternatively, this approach could be circumvented by genetic analysis, in which variants associated with cardiovascular risk factors are used as a proxy for the risk factors themselves. Specifically, each risk factor could be represented by a genetic risk score (GRS) composed of multiple variants that are known to be robustly associated with that risk factor.9,10 Although this approach has the disadvantage of capturing a limited fraction of the total variance of the risk factor itself, it does have some important advantages. First, a GRS represents constant lifetime exposure within individuals and variable exposure between individuals, with random combinations of alleles according to Mendel’s Second Law.11 Second, it is an
efficient and economically feasible approach to this clinically important question.

In this study, we used the genetically determined variability of classical risk factors to reappraise the value of risk factor confluence in assessing ischemic heart disease (IHD) risk. Our specific aims were (1) to analyze whether GRSs associated with the individual cardiovascular risk factors interact and present more than an additive or multiplicative association with IHD and (2) to determine whether these interactions provide additional value for predicting the risk of future IHD events.

Methods

Design

A meta-analysis of 5 studies, 1 case–control and 4 prospective cohorts, was performed. The studies included the Myocardial Infarction Genetics Consortium (MIGen) and the Framingham Heart Study (FHS), the National FINRISK Study 1997 (FINRISK 1997), the National FINRISK Study 2002 (FINRISK 2002), and Estonian Biobank (EGCUT). A total of 23,836 participants were included in the meta-analysis, 6,042 from the case–control study and 17,794 from the 4 cohorts.

MIGen, an international case–control study, included 2,967 cases of early-onset myocardial infarction (men ≤50 and women ≤60 years old) and 3,075 age- and sex-matched controls (12). The FHS sample consisted of 3,557 individuals from the FHS offspring cohort attending examination 5. Genome-wide genotype and associated phenotype data from MIGen and FHS were obtained via the database of Genotypes and Phenotypes (dbGaP; http://dbgap.ncbi.nlm.nih.gov; project number 5195). The FINRISK cohorts comprise representative, cross-sectional population survey respondents. Surveys have been performed every 5 years since 1972 to assess the risk factors of chronic diseases and health behaviors in the working age population; 5,562 individuals were included from the FINRISK 1997 cohort and 2,314 from the FINRISK 2002 cohort. Finally, the EGCUT cohort of 50,750 participants recruited between 2002 and 2011 includes adults (aged 18–103 years) from all counties of Estonia, 8.5% of the Estonian average-adult population. A subset of 6,361 individuals was included in the study selected for this meta-analysis.

Single Nucleotide Polymorphism Selection

We mined published data from a series of large meta-analyses of genome-wide association studies for each of the selected phenotypes. From these studies we identified single nucleotide polymorphisms (SNPs) that were associated (P<5×10^-8) with the trait of interest and grouped these into 8 categories broadly definable as distinct cardiovascular risk factors or coronary end points (Table I in the Data Supplement): low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides (TG), blood pressure (BP), type 2 diabetes mellitus, body mass index, waist circumference, and IHD. We additionally included genetic variants associated with schizophrenia as a negative control.

Genotyping

Four different arrays and 2 reference panels were used for genotyping and imputing. The MIGen study used the Affymetrix 6.0 GeneChip and imputing was performed with MACH 1.0 using the HapMap CEU phased chromosomes as reference. The FHS used the Affymetrix 500K and 50K chips, imputing was performed using HapMap CEU as reference. FINRISK used the Illumina HumanCoreExome chip, imputation was performed using IMPUTE v221 and the 1000 Genomes Project sequencing data as a reference panel. EGCUT used the Illumina OmniExpress BeadChip, imputation was implemented in IMPUTE v2 using the 1000 Genomes Project as a reference. In all the cohorts, directly genotyped SNPs were coded as 0, 1, or 2, whereas the dosage was used for the imputed SNPs with values ranging between 0 and 2. SNPs with an imputation quality <0.4 were excluded.

Construction of the GRGs

We constructed a weighted GRS for each cardiovascular risk factor of interest and IHD independently by adding the number of risk alleles weighted by their effect sizes on the phenotype of interest (Table I in the Data Supplement). One SNP could be included in >1 GRS when associated with >1 risk factor, although with different weights.

We also constructed a weighted GRS for each cardiovascular risk factor, excluding those SNPs that were related to any trait other than that of interest (nonpleiotropic GRGs). From the list of variants associated with each trait, we included those that were associated with any other trait with a P<0.10 in the Framingham cohort.

IHD Outcomes

In the MIGen case–control study, only early-onset myocardial infarction cases were included. In the cohort studies, 2 IHD outcomes were defined: hard IHD, including fatal and nonfatal myocardial infarction and coronary death, and all IHD, additionally including angina and revascularization. The follow-up methodology in the prospective cohorts is explained in detail in the Supplementary Material. In summary, a follow-up or linkage with national databases was implemented using predefined International Classification of Disease–Ninth Revision and International Classification of Disease–Tenth Revision codes. In each cohort, cases were categorized by an event committee.

Statistical Methods

The association between each GRS and IHD was tested by a logistic regression model in the case–control study and by Cox proportional hazards models in the cohort studies. Furthermore, we analyzed all potential pairwise interactions between the GRGs of interest and IHD. In the analysis of these interactions—and from a methodological point of view—we considered their departure from additivity and multiplicativity: (1) to test for multiplicative interactions we added, one by one, all pairwise products of GRGs to the logistic or Cox regression models and (2) to analyze departure from additivity several metrics have been recommended, relative excess risk caused by interaction, attributable proportion, and synergy index (SI). We selected the SI metric because it has been proposed as the most robust when the model includes covariates to control for confounding:

\[
SI = \frac{HR_{A+B} - 1}{(HR_{A} + OR_{B} - 1) + (HR_{A} + OR_{B} - 1)}
\]

where

1. \(HR_{A} \) is the hazard ratio/odds ratio of those exposed to factor A and B compared with those nonexposed to factors A and B.
2. \(HR_{B} \) is the hazard ratio/odds ratio of those exposed to factor B but not to factor A compared with those nonexposed to factors A and B.
3. \(HR_{A+B} \) is the hazard ratio/odds ratio of those exposed to factor B but not to factor A compared with those nonexposed to factors A and B.

This index measures the extent to which the hazard or odds ratio for both exposures together exceeds 1, and whether this is greater than the sum of the extent to which each risk factor, considered separately, exceeds 1. An SI > 1 would indicate the presence of an additive interaction. Bootstrapping was used to calculate 95% confidence intervals of the estimate.

All the analyses were adjusted for age, sex, and principal genetic components to account for population stratification and family relatedness. We used a Bonferroni-adjusted P value to account for independent multiple testing. Because of the correlation between the 36 pairs of tested interactions (each GRS of interest was included in 8 different pairwise interaction terms), we estimated the number of effective independent tests according to the matrix of variance-covariance; the resulting value was 35.88. Therefore, the statistical threshold was set at 0.05/35.88=0.0014.
A meta-analysis of the results observed in the different studies was undertaken using an inverse-variance weighting under a random-effects model (DerSimonian–Laird method). Heterogeneity between studies included in this meta-analysis was also analyzed by estimating the $I^2$ and its $P$ value. To assess whether an individual study had strong effects and influenced the pooled results, a sensitivity analysis was performed by excluding 1 study at a time and calculating the multiplicative and additive interaction metrics for the remaining studies.

The improvement in the predictive capacity of the statistically significant interaction terms was evaluated by assessing improvements in discrimination and reclassification in the cohort studies:

1. The improvement in the discriminative capacity of the model was evaluated using the change in the c-statistic. We first evaluated the discriminative capacity of a multivariate model including age, sex, and all the individual GRSs of interest; additionally, we evaluated the discriminative capacity of this multivariable model, further including the significant interaction terms individually in different models.

2. The reclassification capacity of the interactions of interest was evaluated by calculating the continuous net reclassification improvement index and the integrated discrimination improvement index.

These analyses were also performed in the individual studies and meta-analyzed using an inverse-variance weighting under a random-effects model.

All statistical analyses were performed using packaged or custom functions written in R-3.02 (R Foundation for Statistical Computing, Vienna).

**Ethics Statement**

All participants gave written informed consent to be included in these studies. The study was approved by the local Clinical Research Ethics Committees.

**Results**

The characteristics of the individuals included in the 5 studies, and the number of incident coronary events (938 hard events and 1,453 events in total) and median follow-up in the 4 cohorts are shown in Table 1.

**SNP Selection and Sample Description**

From the literature sources described above, 484 independent SNPs were reported to be robustly associated with cardiovascular risk factors or coronary end points. The number of SNPs included in the GRSs ranged from 23 for type 2 diabetes mellitus to 81 for body mass index (Table I in the Data Supplement). There was a slight overlap between the different GRSs in terms of number of shared SNPs or loci but the Spearman correlation coefficient between GRSs was weak (correlation coefficient, $r=0.100$) with the exception of the associations between GRSs for TG and HDL ($r=−0.391$), IHD and LDL ($r=0.182$), TG and LDL ($r=0.170$), and HDL and LDL ($r=0.129$; Table II in the Data Supplement). When the nonpleiotropic GRSs were considered only the correlation between TG and HDL GRSs ($r=−0.142$), and between TG and LDL GRSs ($r=0.379$), remained significant. A strong and consistent association across studies between the GRS and their corresponding risk factors was observed, remaining strong and consistent for lipids and body mass index when the nonpleiotropic GRSs were analyzed (Table III in the Data Supplement).

**Association Between GRSs and IHD**

We observed significant associations between the GRS for IHD and hard coronary events in all the studies and in the meta-analysis ($P=9.4×10^{-12}$; Figure and Table IV in the Data Supplement; Figure and Table V in the Data Supplement for all IHD events). The TG, HDL, LDL, body mass index, and waist GRSs were also associated with coronary events in the meta-analyses of hard IHD events, although these associations were mainly driven by the MIGen study (Figure; Table IV in the Data Supplement). The BP, diabetes mellitus, and schizophrenia GRSs were not associated with coronary events in this meta-analysis (Figure; Table IV in the Data Supplement). When the nonpleiotropic GRSs were considered, only the association between the GRS for IHD and coronary events remained significant (Table VI in the Data Supplement).

**Assessment of Interactions Between GRSs and Impact on IHD Risk**

We tested all pairwise interactions between the GRSs of interest and IHD in the different studies. In the meta-analyses we found 2 statistically significant multiplicative interactions (Tables VII and VIII in the Data Supplement)—a negative multiplicative interaction between the LDL and TG GRSs on all IHD events (Table 2; Table VIII in the Data Supplement). When hard IHD events were considered, the magnitude of the association of the interaction term decreased, from $−0.096$ to $−0.047$ (Table 3), but this decrease was driven by the MIGen study; when that study was excluded, the effect of the interaction term on hard IHD remained similar and statistically significant ($β=−0.116; P=1.3×10^{-4}$; Table IX in the Data Supplement). A positive multiplicative interaction between the nonpleiotropic LDL and IHD GRSs on all IHD and hard IHD was also observed (Table 2) and was robust and consistent in the sensitivity analysis (Table IX in the Data Supplement).

We also analyzed the presence of additive interactions. In the meta-analysis, we did not find any statistically significant additive interaction term (Tables X and XI in the Data Supplement).

We estimated 80% statistical power to detect a multiplicative interaction regression coefficient higher or lower than $±0.077$, considering the observed SE (0.020) and a $P=0.0014$. We also estimated 80% power to detect an SI $>1.28$ or $<0.72$, considering the lower observed SE (0.07) and an SI $>2.57$ or $<−0.57$, considering the higher observed SE (0.39), always with a $P=0.0014$.

**Assessment of the Predictive Capacity of the Scores**

We evaluated improvement in the discrimination of coronary events in the different cohort studies. First, we used a model that included age, sex, the GRSs for all the cardiovascular risk factors evaluated, and the first 2 principal genetic components. Second, we added to the model, the interaction terms that were associated with IHD ($GRS_{LDL}·GRS_{TG}$ and nonpleiotropic $GRS_{LDL}·GRS_{TG}$). Including these interaction terms did not improve the discriminative or reclassification capacity of coronary events in the meta-analysis (Table 3).
Discussion

In this study, we evaluated the potential interaction effects between cardiovascular risk factors on IHD risk using a genetic approach. We tested the departure from an additive or multiplicative effect of the different 2-pair combinations of GRSs related to these risk factors and their association with coronary events. We report 2 significant multiplicative interactions related to these risk factors and their association with coronary events. We tested the departure from an additive or multiplicative effect (GRSLDL and nonpleiotropic GRSIHD) modulating coronary risk. The inclusion of these interaction terms in the multivariate model did not improve the predictive capacity of the model based on the individual effects of the GRSs of interest.

We first evaluated the association of each individual GRS with its corresponding risk factors and these associations were strong and consistent across studies. We also evaluated the effects of each individual GRS on IHD risk in each study and meta-analyzed the results. The GRS for IHD was associated with coronary events in all the studies and also in the meta-analysis. The GRSs for the different risk factors were also associated with hard coronary events in the meta-analysis, with the exception of the GRSs for BP, diabetes mellitus, and schizophrenia (which was included as a negative control). These results validate the GRSs; the lack of association of IHD events with BP and diabetes mellitus could be related to the lack of causal relationship, low statistical power in the prospective studies, or other factors.

The debate about whether the aggregation of cardiovascular risk factors provides additional information on vascular health beyond that of each individual components is still open. The paradigm for this discussion is metabolic syndrome. Our choice of a genetic approach to assess whether different risk factors interact to modulate the risk of IHD was based on the premise that a genetic score for a given risk factor captures some of its population variability; however, the extent to which this is true varies markedly between risk factors. The amount of variance in the traits of interest that is accounted for by genetic scores varies from ≈25% to 30% for LDL cholesterol down to no more than 3% for BP. However, the loss of information that this represents, with respect to measuring the phenotype itself, is counterbalanced by the fact that genetic risk is a constant exposure throughout an individual's lifespan. Some studies have suggested that selecting a list of SNPs nominally associated with a trait increases the explained variability of that trait. In this study, we selected only those SNPs consistently replicated in GWAS to be associated with the phenotypes of interest. The allelic scores that include thousands of genetic variants tend to lack specificity, and therefore should be used with caution and perhaps only to analyze proxy biological intermediates, not to analyze the association with other related clinical phenotypes, as in this study. Moreover, the list of nominally associated SNPs could vary across studies. For all these reasons, we preferred to select those variants with a statistically significant association, considering the GWAS threshold for our analyses.

In the analysis of these interactions, we considered their departure from additivity and multiplicativity and identified 2 multiplicative interaction terms, one showing a less than multiplicative effect (GRSLDL and GRSIHD) and another a more than multiplicative effect (nonpleiotropic GRSLDL and GRSIHD). The LDL and TG GRSs were slightly correlated. This association could be related to common molecular mechanisms or to the use of the Friedewald equation to estimate LDL in most epidemiological studies. Although this collinearity could decrease the statistical power of our analyses, we report a statistically significant multiplicative interaction between the genetic load for LDL
cholesterol and TG. This interaction term had a negative value, indicating that the joint effect of these 2 factors is less than multiplicative in the risk ratio scale. Moreover, as the additive interaction between these 2 factors was not statistically significant, we can assume an additive effect of these 2 factors on IHD risk in the risk ratio scale. This type of additive but not multiplicative effect of 2 risk factors has also been reported in other diseases, for example, to describe the joint effects of smoking and asbestos on lung cancer.57 The explanation of this additive effect could be related to basic lipid profile concepts.36 The lipid profile includes measurement of the total amount of the 2 most important lipids in the plasma compartment: cholesterol and TG. These lipids are not soluble in plasma and are carried in association with proteins, the so-called lipoproteins: HDL, LDL, and TG-rich lipoproteins. The TG-rich lipoproteins also transport remnant cholesterol. Triglycerides can be degraded by most cells, but cholesterol cannot; therefore, the cholesterol content of TG-rich lipoproteins, rather than increased TG levels per se, is the more likely contributor to atherosclerosis and cardiovascular disease.48 The negative multiplicative interaction indicates an additive effect between TG and LDL cholesterol on IHD risk and supports the suggestion that TG-rich particles act as an additional source of cholesterol in the arterial wall.

We also report a more than multiplicative effect between the nonpleiotropic genetic load for LDL and IHD. The IHD genetic load has been related to lipid, inflammatory and immune pathways that could potentiate the progression of atherosclerosis.57 The nonpleiotropic GRS for IHD excluded SNPs associated with lipids and mainly reflects immunoinflammatory mechanisms. Therefore, this interaction could be explained by the independent interrelationships between lipids and immunoinflammation that could trigger the deleterious consequences of these 2 factors through different mechanisms.38,39

We also analyzed the improvement in predictive capacity when the interaction terms were included in the model. However, we did not observe any improvement in the discrimination or reclassification. Recent meta-analyses focused on metabolic syndrome have shown that the population with this syndrome has a 2-fold higher risk of cardiovascular disease than the rest of the population,4,5 but the added value of this clinical constellation of risk factors is questioned.1-3 We identified 1 cross-sectional study46 and 6 cohort studies41,46 that assessed the unadjusted and adjusted association between metabolic syndrome and cardiovascular risk. When the models were adjusted for all or some of the classical cardiovascular risk factors, 3 of these studies showed an association between metabolic syndrome and cardiovascular events.41,45,46 However, Girman et al45 only adjusted for the estimated coronary risk obtained with the Framingham function, categorized as ≤20% or >20%, and McNeill et al46 did not adjust for HDL cholesterol and BP. In contrast, our analyses did not show any interaction between the GRSs related to the risk factors that define metabolic syndrome. Our results are in line with the 2 remaining studies, which specifically analyzed whether metabolic syndrome improves the predictive capacity of its individual components. Neither study reported significant improvement in discrimination capacity44,46; this shared finding calls into question the capacity of the metabolic syndrome

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**Figure.** Forest Plot of the association between the weighted genetic risk scores (GRS) for cardiovascular risk factors and ischemic heart disease and the prevalence/incidence of hard ischemic heart disease events (myocardial infarction or ischemic heart disease [IHD] death) across studies and in the meta-analysis. BMI indicates body mass index; BP, blood pressure; EGCUT, Estonian Biobank; FHS, Framingham Heart Study; FINRISK 1997, National FINRISK Study 1997; FINRISK 2002, National FINRISK Study 2002; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; MiGen, Myocardial Infarction Genetics Consortium; OR, odds ratio; T2D, type-2 diabetes mellitus; and TG, triglycerides.
that when the magnitude of the association between the 2 individual classical cardiovascular risk factors.

**Limitations**

Four main limitations should be considered. (1) The variability of the cardiovascular trait explained by the genetic scores considered in this analysis is not very high, in general, but represents lifetime exposure. Moreover, some interacting genetic variants could have been overlooked by GWAS and therefore not included in our GRSs. (2) The small number of events observed in the cohort studies limited the statistical power to explore the interactions of interest. We have also to consider that when the magnitude of the association between the 2 individual components of the interaction and the outcome of interest is small, the power to differentiate between additive and multiplicative effects is reduced. (3) IHD clinical end points are the result of a complex phenomenon, which includes endothelial dysfunction, plaque formation and growth, plaque stability, and thrombosis. Interaction could happen in the context of one of these pathways and be diluted in the observation of clinical end-points. (4) Although the approach we used could consider the presence of pleiotropic effects that are reflected in the correlation between the GRSs analyzed and that violate one of the assumptions of Mendelian randomization studies. Finally, we would note that 339 of the FINRISK participants were also included in the MIGen sample; however, this is a small proportion (<1.5%) of the whole sample, the sensitivity analyses performed are consistent, and we could consider the effect of this duplication to be minimal.

**Conclusions**

The genetic risk loads for LDL cholesterol and TG interact, suggesting that the effect of these 2 risk factors on IHD risk is additive rather than multiplicative. Moreover, the nonpleiotropic GRSs for LDL and IHD also interact on IHD risk and have a more than multiplicative effect. This interaction supports the hazardous impact on atherosclerosis progression of the combination of inflammation and increased lipid levels. Our results question the added value of the confluence of risk factors in improving the estimation of cardiovascular risk beyond the predictive capacity provided by individual risk factors. However, further studies in larger samples are warranted to confirm and expand our results, because of the limited statistical power of the present analysis.

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CLINICAL PERSPECTIVE

Cardiovascular risk factors tend to aggregate, but the biological and predictive value of this aggregation is questioned and genetics could shed light on this debate. Our aim was to test whether genetic risk scores associated with these cardiovascular risk factors interact on an additive or multiplicative scale and whether these interactions add predictive value. The genetic risk loads for low-density lipoprotein cholesterol and triglycerides interacted, but with a less than multiplicative joint effect. Therefore, the confluence of these 2 risk factors has an additive effect on ischemic heart disease risk. This result suggests that the cholesterol content of triglyceride-rich lipoproteins, rather than increased triglyceride levels per se, is the more likely contributor to atherosclerosis. The nonpleiotropic genetic risk scores for low-density lipoprotein and ischemic heart disease also interact, but have a more than multiplicative effect. This finding supports the hazardous impact on atherosclerosis progression of the combination of inflammation and increased lipid levels. The inclusion of these 2 interaction terms in a risk function did not improve the predictive capacity of the individual genetic risk loads. Our results question the added value of the confluence of risk factors to improve the estimation of cardiovascular risk beyond the predictive capacity provided by individual risk factors. However, further studies in larger samples are warranted to confirm and expand our results, because of the limited statistical power of the present analysis.