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Lifestyle Cardiovascular Risk Score, Genetic Risk Score, and Myocardial Infarction in Hispanic/Latino Adults Living in Costa Rica

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ABSTRACT

Background: A lifestyle cardiovascular risk score (LCRS) and a genetic risk score (GRS) have been independently associated with myocardial infarction (MI) in Hispanics/Latinos. Interaction or joint association between these scores has not been examined. Thus, our aim was to assess interactive and joint associations between LCRS and GRS, and each individual lifestyle risk factor, on likelihood of MI.

Methods and Results: Data included 1,534 Costa Rican adults with nonfatal acute MI and 1,534 matched controls. The LCRS used estimated coefficients as weights for each factor: unhealthy diet, physical inactivity, smoking, elevated waist:hip ratio, low/high alcohol intake, low socioeconomic status. The GRS included 14 MI-associated risk alleles. Conditional logistic regressions were used to calculate adjusted odds ratios (OR). The OR for MI was 2.72 (2.33, 3.17) per LCRS unit and 1.13 (95%CI 1.06, 1.21) per GRS unit. A significant joint association for highest GRS tertile and highest LCRS tertile and odds of MI was detected (OR=5.43 (3.71, 7.94); $p<1.00x10^{-7}$), compared to both lowest tertiles. The OR was 1.74 (1.22, 2.49) under optimal lifestyle and unfavorable genetic profile, and 5.02 (3.46, 7.29) under unhealthy lifestyle but advantageous genetic profile. Significant joint associations were observed for the highest GRS tertile and the highest of each lifestyle component risk category. The interaction term was non-significant (p=0.33).

Conclusions: Lifestyle risk factors and genetics are jointly associated with higher odds of MI among Hispanics/Latinos. Individual and combined lifestyle risk factors showed stronger associations. Efforts to improve lifestyle behaviors could help prevent MI regardless of genetic susceptibility.

Key words: Lifestyle, genetics, myocardial infarction, Hispanics/Latinos

INTRODUCTION

Coronary Heart Disease (CHD) is the leading cause of death in the Costa Rican population[1, 2], and ischemic heart disease is among the top three causes of disability-adjusted life years[3]. These high statistics likely reflect unfavorable changes in lifestyles[1, 4] in the last several decades, including unhealthy dietary behaviors as one of the main risk factors.[3] In addition to diet, the World Health Organization reported four main lifestyle risk factors for such population and risk of noncommunicable diseases: tobacco smoking, alcohol consumption, elevated blood pressure, and obesity.[1] Indeed, a lifestyle cardiovascular risk score (LCRS) that included those risk factors; namely diet, physical activity, smoking, alcohol intake, waist:hip ratio, and socioeconomic status, has been derived in a group of healthy Hispanic/Latino adults living in Costa Rica participating in a myocardial infarction (MI) case-control study, and subsequently validated in the same study among participants with a history of chronic disease, where it was shown to be associated with nearly three times the odds of having an MI[5]

In addition to lifestyle, compelling evidence indicates that genetic susceptibility alone is part of the etiology of CHD and heart-related events.[6-11] Genome-wide association studies have identified chromosomal regions and genetic variants associated with CHD.[6, 10, 12] One of the most robust genetic associations for CHD is the Chromosome 9p21 region. Several single nucleotide polymorphisms (SNPs) in this region has been associated with increased risk of CHD[6, 10, 12], such as a common sequence variant adjacent to genes CDKN2A and CDKN2B found to be associated with 1.64 times higher risk of MI.[10] Recently, we showed that genetic markers in these loci were also associated with this outcome in the same MI case-control study of Costa Rican adults, when analyzed as part of a genetic risk score (GRS).[13] Notably, the genetic predisposition conferred by MI risk alleles in the 9p21 region is seen both in persons with a positive family history of MI and in persons with a negative family history, suggesting that these variants add to the effect of a family history, and that different underlying mechanisms may be involved. The specific genes and variants responsible for the autosomal dominant inheritance of MI in families have not been identified.[14]

It has been documented that the effect of genetic factors may be partly modulated by varying levels of environmental exposures such as diet, physical activity, and smoking.[15] Previous gene-environment studies evaluating the risk of MI or related CHD outcomes determined by variations in the 9p21 chromosome showed that this risk could be modified by a prudent diet[16], smoking[17], and vegetable intake.[18] Despite the recent progress in this area, the study of complex interactions between multiple

genetic and environmental factors has been very scarce, with inconsistent results[19, 20], mostly limited to single environmental components and SNPs, and mostly conducted in European populations. Importantly, genetic background and lifestyle factors tend to be population-specific; this Hispanic/Latino population experiences unique backgrounds and lifestyle patterns[5, 11, 21, 22], warranting further scrutiny of the contribution of these two factors on MI and CHD-related events among adults in Costa Rica.

Although genetic and environmental factors have been each, independently, associated with MI in a Costa Rican population, the potential interaction or the joint association (combination of independent effects) of an overall GRS and LCRS instead of single genes or lifestyle components has not been explored. Investigating gene-environment interactions is necessary to better understand the biology of the disease and the phenotypic responses that are not mainly explained by genotypic variants. Therefore, our aim was to assess the interactive and joint associations between a LCRS and a GRS in Hispanic/Latino adults living in Costa Rica. As a secondary aim, we evaluated the association of each individual lifestyle risk factor on the likelihood of MI.

METHODS

Study population and data collection

The Costa Rica Myocardial Infarction Study is a case-control study where participants were recruited between 1994-2004 from 34 counties in the Central Valley of Costa Rica, covering a full range of socioeconomic levels, as well as urban, peri-urban, and rural lifestyles. Eligible case subjects were adult residents who were diagnosed as survivors of a first MI by two independent cardiologists at any of the six recruiting hospitals. All cases met the World Health Organization criteria for MI, which required typical symptoms plus either elevations in cardiac enzyme levels or diagnostic changes in the electrocardiogram.[23] Each case was matched with one control for age (±5 years), sex, and area of residence (county level). Controls were randomly selected using the information available at the National Census and Statistics Bureau of Costa Rica and they came from the same source population as the cases. All participants gave informed consent on documents approved by the Human Subjects Committee of the Harvard T. H. Chan School of Public Health and the University of Costa Rica. Detailed description of the study methods was published previously.[7, 24, 25]

All study participants received home visits during which trained staff collected data on sociodemographic characteristics, lifestyle behaviors (including smoking, physical activity, and alcohol intake), and medical history through questionnaires.[26-28] Dietary exposures were ascertained using a food frequency questionnaire validated against the method of triads with 24-hour recalls and biomarkers of fatty acids and carotenoids.[29] Anthropometric measurements were measured in duplicate while participants wore light clothing, and an average was recorded. Physical activity information was collected using a questionnaire that inquired about the average frequency and time spent on several occupational and leisure time activities during the last year. The questionnaire was previously validated by its ability to predict fitness level among Costa Ricans.[26, 28] Energy expenditure for each activity was calculated as the product of frequency, time, and intensity measured in METS.[27] Adipose tissue α-linolenic and total *trans* fatty acids were quantified by gas-liquid chromatography as described previously.[30]

DNA was extracted from the buffy coat fraction by QIAmp Blood Kit (Qiagen, Chatsworth, CA). Genotyping was performed using the TaqMan Allelic Discrimination system from Applied Biosystems, Inc. (Foster City, CA), using custom genotyping assays from ABI's "assays by design" service. Replicate quality control samples yielded >99% concordance, and the overall call rate was greater than 95%.

Lifestyle Cardiovascular Risk Score

The Lifestyle Cardiovascular Risk Score (LCRS) has been defined and validated previously.[5] Briefly, the LCRS was calculated by using the estimated coefficients derived from the conditional regression model with MI as outcome and the lifestyle components as predictors, as weights for each of the six lifestyle components. The LCRS components (diet, physical activity, smoking, alcohol intake, waist:hip ratio, and socioeconomic status) were selected based on a prior analysis of modifiable MI risk factors in our study population as well as World Health Organization (WHO) guidelines for healthy lifestyle (nutrition and physical activity).[7, 31, 32] The final LCRS was the sum of each component multiplied by the aforementioned regression coefficient. Because the LCRS estimated risk of MI, higher LCRS values reflect a higher risk of MI. The healthy diet component comprised six nutrients: saturated fats, dietary cholesterol, polyunsaturated fats, dietary fiber, folate, and total *trans* fats. In addition, the healthy diet score included the adipose tissue biomarker for α-linolenic acid (ALA) as a more reliable measure of long-term α-linolenic fatty acid intake, which is a strong cardio-protective marker in this population.[33]Quintiles of each dietary component were created and assigned values from 0 (highest risk quintile) to 4 (lowest risk quintile), then summed to create a dietary score ranging from 0 (lowest adherence to the

dietary recommendations) to 28 (highest adherence). Physical activity in METs was included in the LCRS as a continuous variable, defined as total METS expended over a 24-h period. Smoking was defined as a dichotomous variable (non-smokers *vs*. current smokers), and alcohol intake was expressed as g/day. Waist:hip ratio was categorized using the WHO cutoffs for women (<0.85) and men (<0.90).[34] Socioeconomic status was calculated as a comprehensive measure of education, occupation, household income, and household possessions[35], and used as a continuous variable in the score.

Genetic Risk Score

The development of the Genetic Risk Score (GRS) has been previously reported for this population. [13] Fourteen Single Nucleotide Polymorphisms (SNPs) (rs4977574, rs10757274, rs2383206, rs1333049 (*CDKN2A/2B*); rs646776, rs599839 (*CELSR2-PSRC1-SORT1*); rs501120, rs1746048 (*CXCL12*); rs2259816 (*HNF1A, C12orf43*); rs9818870 (*MRAS*); rs2048327 (*SLC22A3*); rs3127599 (*LPAL2*); rs7767084 and rs10755578 (*LPA*)) with evidence of association with coronary artery disease and/or MI were assessed to calculate the GRS. The equal contribution to odds of MI in an additive genetic model[13] suggested that each SNP was independently associated with MI. The GRS reflected the sum of the number of risk alleles at each locus, and ranged from 0 to 28. Weighed GRS did not change the association with MI.[13] In sensitivity analysis, the three SNPs showing the strongest association with MI in the Costa Rica study (rs4977574 at *CDKN2A/2B*; rs646776 at *CELSR2-PSRC1-SORT1*, and rs501120 at *CXCL12*) were selected to calculate a simplified 3-SNP GRS, although this may be biased towards a stronger association.

Statistical analysis

In total, 1,534 case-control pairs with complete information on the lifestyle factors included in the LCRS, genotype information, and potential confounders, were included in the present study. Means and risk frequencies of health factors by case-control status were compared using paired t-test and McNemar's test. Conditional logistic regression analysis matched on sex, age, and area of residence were used to calculate odds ratios (ORs) and 95% confidence intervals (CI) of MI in all analyses. When individual lifestyle factors were tested separately, we further adjusted each model for the other lifestyle components. Linear *P*-trend was tested across tertiles of LCRS and tertiles GRS. Multiplicative interactions between the GRS (in tertiles) and the LCRS (in tertiles) and each individual component (diet, in tertiles; physical activity, in tertiles; smoking, non-smokers *vs.* current; alcohol, 0 (not drinkers), 0.1–5.0, 5.1–10, >10 g/day; waist:hip ratio, <0.85 in women, and <0.90 in men; socioeconomic status, in

tertiles). The maximum likelihood test was used to compare the models with and without the interactive term. Joint association of the LCRS and the GRS on MI was also tested using conditional logistic regression models. The joint variable was calculated as a combination of the LCRS (in tertiles) and the GRS (in tertiles) resulting in a new variable with 9 categories: corresponding to each combination of low, medium, and high-risk LCRS plus each of the low, medium, and high-risk GRS. Additionally, a separate joint analysis was run for each individual lifestyle and genetic risk score (tertile) resulting in six separate regressions models. *P*-joint of the overall model was calculated. In sensitivity analysis, we used unconditional logistic regression for unmatched case-control (n=1628 control and 1563 cases). Statistical analyses were conducted using SAS version 9.4 (SAS Institute). A significance level of $P<0.05$ was used.

RESULTS

Table 1 shows the general characteristics of the study population by MI status. Compared with controls, cases had a higher LCRS (indicative of higher risk), but lower diet score (indicative of unhealthier diet) and socioeconomic status. Additionally, cases had higher prevalence of smoking, waist:hip ratio, and MI genetic predisposition. No significant differences were found between cases and controls for physical activity or alcohol intake. The GRS was significantly higher among cases.

Both the LCRS and the GRS were associated with higher OR for MI when tested in independent models; however, the point estimates were more than twice as large for the LCRS than the GRS (multivariable OR (95% CI) for third *vs.* first tertile LCRS: 3.71 (3.02, 4.55); GRS: 1.30 (1.07, 1.59); **Table 2**). Similar results were observed when the scores were modeled as continuous (per unit).

An interaction between the GRS and the LCRS for odds of MI was not detected ($P=0.33$). (**Table S1**). In the joint analysis, we found that those with the highest GRS and in the highest tertile of the LCRS had 5.43 (3.71, 7.94) higher odds of MI than those in the lowest GRS and the lowest tertile of LCRS (**Figure 1**). The OR was 1.74 (1.22, 2.49) under optimal lifestyle and worst genetic risk, while under unhealthy lifestyle and advantageous genetic profile, the odds of MI were 5.02 (3.46, 7.29). Trends for higher odds across higher GRS and LCRS were observed, with the higher odds detected for those in the high LCRS tertile, in general. The joint association was significant for the overall model at $P<1.00\text{x}10^{-7}$ (**Table S1**).

We examined interaction and joint associations for each component of the LCRS separately and controlling for each other (i.e. adjusted for the other lifestyles in the LCRS). Significant joint associations (all $P<0.01$) were found for the overall model when comparing the highest joint risk *vs*. lowest risk (reference group) categories of all components: 1.87 (1.30, 2.68) for diet, 2.11 (1.47, 3.04) for physical

activity, 3.16 (2.30, 4.35) for smoking, 2.77 (1.77, 4.34) for waist:hip ratio, and 1.58 (1.13, 2.21) for socioeconomic status (**Table 3**). While the overall model was significant for alcohol intake, the odds of MI among those in the highest category of alcohol consumption and highest genetic risk were not significant 1.25 (0.87, 1.81). None of the individual lifestyle components were found to interact significantly with the GRS. Similar results were also observed for the joint association of the lifestyle score and GRS using the 3-SNP score (**Table S2, Table S3, Table S4**). Additionally, all results were similar when we conducted the analysis using unconditional logistic regression (data not shown).

DISCUSSION

In this population of Hispanic/Latino adults living in Costa Rica, we found that poor predictive lifestyle behaviors were associated with higher odds of MI, in line with previous studies.[7, 9, 11, 36-38] The association for the GRS and higher odds of MI was consistent with previous literature analyzing SNPs in the chromosome 9p21 and higher risk of CHD and mortality. [6, 10, 12] Moreover, we observed that participants with the highest genetic risk in combination with the highest lifestyle risk factors (both all-together as well as individually) had higher odds of MI. Although the two scores contributed independently, the association of the LCRS on MI risk was stronger than the GRS, suggesting that lifestyle factors can contribute to MI more than genetic predisposition. Moreover, the genetic predisposition may be blunted if a healthy lifestyle is attained.

In our study, no statistically significant interactions were found. However, we found a statistically significant joint association between the GRS and the LCRS. Those participants in the highest risk category for the GRS and the LCRS had 5.4 times higher risk of MI, mostly due to the lifestyle. Our results underscore that MI is less likely to occur for individuals with an optimal healthy lifestyle that comprise various behaviors, even when having a high-risk genetic profile, than for those having the more advantageous GRS but an unhealthy lifestyle. Prior investigation studying the combined association of genes and other independent factors such as BMI, waist:hip ratio, physical activity, diet or other nutrients or food components, on risk of diabetes[20] and other cardiometabolic[39] outcomes have also found significant joint associations while failing to find significant interactions.[20, 39] Yet, as the majority of studies had small sample sizes, it is difficult to know whether the non-significant interaction is due to low power or no true interaction.[40] For example, a large study of 8,114 individuals (3,820 cases and 4,294 controls) from the global INTERHEART study found a significant interaction with a prudent diet when evaluating the risk of MI in the 9p21 chromosome. Specifically, the individuals who were homozygous for the risk allele of rs2383206 and have a low prudent diet score, had about twice the risk for MI ($p = 2.11 \times 10^{-9}$) when compared to the reference group.[16] However, no significant interaction or

trend was found with physical activity (P=0.23) or smoking (P=0.56) despite the large sample size. Although the previous study analyzed only four SNPs (rs10757274, rs2383206, rs10757278, rs1333049) instead of 14 in our study, we were also not able to detect significant interactions when we evaluated each lifestyle factor separately. Additionally, differences in dietary components between studies could explain why they observed a significant interaction between the genetic markers and diet but we did not.

In general, current literature about gene-environment interactions using similar risk factors as those tested here shows heterogeneous results. A study evaluating the risk of CVD morbidity and mortality by the SNP rs4977574 on chromosome 9p21 reported that this association was modified by smoking, but not by the other lifestyle factors analyzed (educational status and physical activity).[17] However, the Atherosclerosis Risk in Communities Study did not reveal a significant interaction with this SNP and smoking, possibly due to a lack of statistical power (1,653 cases vs 2,309) as may be the case in our study (1,534 cases).[41] Another study found a significant interaction between the rs4977574 and vegetable and wine intake but not with total alcohol in 3,164 cases of CVD. [18] Similarly, in our study, we could not detect a significant interaction with total alcohol intake. However, those with the highest genetic risk had higher odds of MI for any category of alcohol consumption, except for moderate intake. In addition, participants in the moderate genetic risk with moderate alcohol intake had significantly lower odds of MI compared to those with the lowest genetic risk and lowest alcohol consumption (non-alcohol consumption).

When we analyzed the joint association with each independent lifestyle component, adjusting for the other components, we found that the highest odds of MI jointly with the GRS were for smoking, followed by waist:hip ratio, diet, physical activity, and socioeconomic status. A similar gradient of population attributable risk (PAR) of only lifestyle factors was shown in a case-control study (15,152 cases and 14,820 controls) of acute MI in 52 countries, where the strongest risk factors for MI were smoking (PAR= 36%), abdominal obesity (20.1%), daily fruit and vegetables (13.7%), physical activity (12.2%), and regular alcohol consumption (7.1%).[37] In line with these results, strong evidence support that the modification of lifestyle factors could potentially decrease the risk of CHD, MI, stroke and related clinical risk factors. [7, 9, 11, 36, 42, 43] even in secondary prevention[38].

Despite the discrepancies among studies regarding the SNPs studied, the diet definition (factor analysis, guidelines or recommendations, or specific diet components), and outcomes, that limit the comparison and replication among studies, our findings indicate that improving several lifestyle factors can serve as

opportunities to reduce the likelihood of heart attacks in Costa Ricans, similar to previous studies conducted in other populations. Lifestyle modification through smoking cessation, healthy diet promotion, physical activity programs, or social assistance programs, should be the cornerstone of prevention of MI and related CHD events. More importantly, a combination of these strategies may be even more protective than single behaviors, and may partly overcome the genetic predisposition that some individuals present. Although our findings highlighted that participant with the combination of poor lifestyle and genetics factors were at substantially increased risk, the results from this analysis justify and promote the need to lifestyle intervention and modification to all population regardless of whether they carry the mutations analyzed.

Strengths of our study include the matched study design by age, sex and area of residence, thus the associations were not likely confounded by these factors. Using randomly selected population-based controls after matching, and conditional logistic regression for our matched sample also lends merit to our results. Additionally, we examined an overall GRS and overall LCRS comprised of many lifestyle risk factor rather than individual SNPs or individual foods or nutrients. This is a more comprehensive way to evaluate the multifaceted nature of our genetic makeup and environment.

We should note some limitations of our study. Although the genetic variants used in the GRS have been associated with increased risk of CHD in European populations,[6, 10, 12] they account for a modest portion of the variability in MI, and other genetic variants (for example, in genes of the inflammation response) could have stronger effect in this population. A more comprehensive evaluation of gene-environment interactions with genetic markers in additional loci warrants future investigation. Future studies with specific designs to test this hypothesis could help generate more knowledge. Another limitation is the self-reported dietary and other lifestyle information; thus, measurement error and misclassification were inevitable. However, we were able to validate the food frequency questionnaire with biomarkers of diet. In addition, to minimize potential recall bias among cases, dietary data collection was conducted in the participant's home as close as possible to hospital discharge. In any case, these issues may only attenuate the risk estimates.[44]

In conclusion, although lifestyle risk factors and genetics contribute independently and jointly to higher odds of MI, lifestyle risk factors were more strongly associated with MI among Hispanic/Latino adults living in Costa Rica. Efforts to improve lifestyle behaviors in this population, regardless of genetic susceptibility, may help prevent MI and related heart conditions.

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Table 1. General characteristics of Hispanic/Latino adults living in Costa Rica for cases of myocardial infarction and population-based controls

	Control, n=1534	Cases, n=1534	*P*-value
Age, years[*]	57.9 (11.1)	58.1 (10.9)	N/A
Female, %[*]	24.6	24.6	N/A
Area of residence,% rural[*]	25.8	25.8	N/A
Lifestyle Cardiovascular Risk Score[†]	-0.46 (0.53)	-0.18 (0.57)	$1.0x10^{-7}$
Diet score[‡]	14.5 (4.8)	13.5 (5.0)	$1.0x10^{-7}$
Physical activity, METS[§]	35.3 (14.8)	34.4 (15.6)	0.08
Current smokers, %	35.3	64.7	$1.0x10^{-7}$
Alcohol intake, g/day	6.3 (14.8)	7.4 (19.1)	0.06
Elevated waist:hip ratio, %[||]	48.1	51.9	$1.0x10^{-7}$
Socioeconomic status[#]	9.2 (3.5)	8.5 (3.5)	$1.4x10^{-6}$
Genetic Risk Score[**]	13.3 (3.7)	13.7 (3.6)	$3.9x10^{-3}$

MET, Metabolic Equivalent of Task. [*]Matching variable

[†]The Lifestyle Cardiovascular Risk Score (LCRS) was calculated by multiplying the regression coefficients of each of six lifestyle components obtained from the conditional regression with MI as outcome, by the score of each component, then summing them. LCRS estimated risk of MI, therefore higher LCRS values reflect a higher risk of MI.

[‡]A composite measure of total dietary intake of saturated fats, cholesterol, polyunsaturated fats, fiber, folate, and adipose tissue a-linolenic acid (ALA) and total *trans* fats. The total diet score range from 0 (lowest adherence to the dietary recommendations) to 28 (highest adherence).

[§]Physical activity was defined as total METS expended over a 24-h period.

[||]Elevated waist:hip ratio was >0.85 for women and >0.90 for men.

[#]Socioeconomic status is a continuous variable that accounts for education, occupation, income, and household possessions. A higher score indicates a higher socioeconomic status.

[**]The GRS included the sum of 14SNPs risk alleles: rs4977574, rs10757274, rs2383206, rs1333049 (*CDKN2A/2B*); rs646776, rs599839 (*CELSR2-PSRC1-SORT1*); rs501120, rs1746048 (*CXCL12*); rs2259816 (*HNF1A, C12orf43*); rs9818870 (*MRAS*); rs2048327 (*SLC22A3*); rs3127599 (*LPAL2*); rs7767084 and rs10755578 (*LPA*).

Table 2. Odds of myocardial infarction for the Lifestyle Cardiovascular Risk Score and the Genetic Risk Score among Hispanic/Latino adults living in Costa Rica

Lifestyle Cardiovascular Risk Score*		Genetic Risk Score*	
Tertiles (range)	OR (95% CI)	Tertiles (range)	OR (95% CI)
Low Risk (-2.02, -0.61)	Ref. (1.00)	Low Risk (8-11)	Ref. (1.00)
Medium Risk, (-0.61,-0.13)	1.71 (1.41, 2.07)	Medium Risk (13-14)	1.31 (1.09, 1.57)
High Risk (-0.13, 1.28)	3.71 (3.02, 4.55)	High Risk (16-19)	1.30 (1.07, 1.59)
P-trend	$<1.00x10^{-7}$		$1.24x10^{-3}$
Continuous (per unit)	2.72 (2.33, 3.17)		1.13 (1.06, 1.21)

*Matched on age, sex, area of residence.

Lifestyle Cardiovascular Risk Score tertiles: Low Risk, n=1022; Medium Risk, n=1023, High Risk, n=1023. Genetic Risk Score tertile (14 SNPs): Low Risk, n=889; Medium Risk, n=1283; High Risk, n=896

The LCRS used estimated coefficients as weights for each factor: unhealthy diet, physical inactivity, smoking, elevated waist:hip ratio, low/high alcohol intake, low socioeconomic status.

The GRS included the sum of 14SNPs risk alleles: rs4977574, rs10757274, rs2383206, rs1333049 (CDKN2A/2B); rs646776, rs599839 (CELSR2-PSRC1-SORT1); rs501120, rs1746048 (CXCL12); rs2259816 (HNF1A, C12orf43); rs9818870 (MRAS); rs2048327 (SLC22A3); rs3127599 (LPAL2); rs7767084 and rs10755578 (LPA).

Table 3. Joint and interaction associations of individual lifestyle cardiovascular risk factors with the genetic risk score (in tertiles) on myocardial infarction among Hispanic/Latino adults living in Costa Rica

	GRS Tertiles				
	T1= GRS 14 SNPs low risk	T2= GRS 14 SNPs medium riks	T3= GRS 14 SNPs high risk	*P*-overall joint model	*P* for interaction
Diet Score*					
High adherence	1	1.32 (0.95, 1.84)	1.38 (0.98, 1.94)	$5.8x10^{-4}$	0.36
Medium	1.04 (0.73, 1.47)	1.67 (1.21, 2.30)	1.67 (1.18, 2.35)		

adherence					
Low adherence	1.62 (1.12, 2.34)	1.86 (1.32, 2.61)	1.87 (1.30, 2.68)		
Physical activity[†]					
High	1	1.56 (1.12, 2.17)	1.52 (1.06, 2.18)	6.85×10^{-4}	0.53
Medium	1.13 (0.79, 1.62)	1.68 (1.20, 2.35)	1.63 (1.14, 2.32)		
Low	1.73 (1.22, 2.47)	1.88 (1.35, 2.64)	2.11 (1.47, 3.04)		
Smoking					
Never	1	1.45 (1.16, 1.83)	1.51 (1.19, 1.92)	$<1.00 \times 10^{-7}$	0.36
Current	2.85 (2.08, 3.90)	3.30 (2.50, 4.42)	3.16 (2.30, 4.35)		
Alcohol consumption[‡]					
Never	1	1.35 (1.06, 1.72)	1.33 (1.02, 1.72)	1.92×10^{-4}	0.87
Low	0.78(0.50, 1.22)	1.06 (0.73, 1.54)	1.15 (0.73, 1.80)		
Moderate	0.60 (0.34, 1.04)	0.68 (0.42, 1.09)	0.63 (0.38, 1.05)		
High	0.68 (0.47, 0.99)	1.02 (0.72, 1.44)	1.25 (0.87, 1.81)		
Waist:hip ratio[§]					
Normal	1	1.37 (0.80, 2.35)	1.32 (0.75, 2.34)	$<1.00 \times 10^{-7}$	0.98
Elevated	2.01(1.28, 3.14)	2.72 (1.74, 4.3)	2.77 (1.77, 4.34)		
Socioeconomic Status[‖]					
High	1	1.26 (0.91, 1.74)		$<1.00 \times 10^{-7}$	0.29
Medium	1.04 (0.74, 1.45)	1.63 (1.19, 2.25)	1.25 (0.88, 1.77)		
Low	1.46 (0.99, 2.15)	1.73 (1.22, 2.47)	1.58 (1.13, 2.21)		

Matched on age, sex, area of residence and adjusted for the other lifestyle components.

[*]A composite measure of total dietary intake of saturated fats, cholesterol, polyunsaturated fats, fiber, folate, and adipose tissue a-linolenic acid (ALA) and total *trans* fats. The total diet score range from 0 (lowest adherence to the dietary recommendations) to 28 (highest adherence).

[†]Physical activity was defined as total METS expended over a 24-h period.

[‡]Alcohol consumption categories were: never=0, low= 0.1–5.0 g/day, moderate=5.1–10 g/day, and high as > 10 g/day.

[§]Elevated waist:hip ratio were >0.85 for women and >0.90 for men.

The GRS included the sum of 14SNPs risk alleles: rs4977574, rs10757274, rs2383206, rs1333049 (CDKN2A/2B); rs646776, rs599839 (CELSR2-PSRC1-SORT1); rs501120, rs1746048 (CXCL12); rs2259816 (HNF1A, C12orf43); rs9818870 (MRAS); rs2048327 (SLC22A3); rs3127599 (LPAL2); rs7767084 and rs10755578 (LPA).

Figure Legend:

Figure 1. Odds ratio of MI risk according to joint classification of Lifestyle Cardiovascular Risk Score (in tertiles) and Genetic Risk Score (in tertiles) among Hispanic/Latino adults living in Costa Rica. OR and 95% CI were calculated by using conditional logistic regression model. The analyses were matched on age, sex, and area of residence. *P*-joint for overall model $1.00x10^{-7}$. The GRS included the sum of 14SNPs risk alleles: rs4977574, rs10757274, rs2383206, rs1333049 (*CDKN2A/2B*); rs646776, rs599839 (*CELSR2-PSRC1-SORT1*); rs501120, rs1746048 (*CXCL12*); rs2259816 (*HNF1A, C12orf43*); rs9818870 (*MRAS*); rs2048327 (*SLC22A3*); rs3127599 (*LPAL2*); rs7767084 and rs10755578 (*LPA*). The LCRS used estimated coefficients as weights for each factor: unhealthy diet, physical inactivity, smoking, elevated waist:hip ratio, low/high alcohol intake, low socioeconomic status.
LCRS + GRS: Low Risk + Low, n=290; Medium Risk + Low, n=266; High Risk + Low, n=305; Low Risk + Medium, n=387; Medium Risk + Medium, n=373; High Risk + Medium, n=356; Low Risk + High, n=345; Medium Risk + High, n=384; High Risk + High, n=362