Parental History and Myocardial Infarction Risk Across the World

The INTERHEART Study

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A parental history (PH) of coronary heart disease (CHD) is consistently associated with a higher risk of the development of CHD in several studies (1–9). It is generally accepted that this association is explained by a combination of predominantly known risk factors and genetic variants (10). Although many studies show that risk factors and genetic polymorphisms are significantly associated with myocardial infarction (MI), these studies fail to show how these associations may explain the relationship between PH and the risk of MI (11,12). Some previous studies established the independence of PH from common vascular risk factors (7); however, there are few large international studies that can establish the independence of PH from comprehensive measurements of behavioral, biological, psychosocial, and genetic risk factors, as reported in the INTERHEART study.

The aims of this analysis were: 1) to examine whether the risk associated with a score of PH of MI (increasing with the number of affected parents and prematurity of PH) is independent of behavioral, biological, psychosocial, and genetic factors; and 2) to evaluate whether these findings are consistent across sex, age groups, socioeconomic groups, and world regions.

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Methods

Participants. INTERHEART was a multinational case-control study that enrolled 15,152 cases presenting with a first MI and 14,820 controls matched for age and sex between February 1999 and March 2003. Details of selection criteria were reported previously (13). In the principal analysis of the INTERHEART study, cases and controls were excluded if they did not meet inclusion criteria (e.g., previous CHD) or had insufficient data, leaving 12,461 cases and 14,637 controls (13). For the present analysis, participants were also excluded if data on PH of cardiovascular disease (CVD) were incomplete. Therefore, 12,149 cases and 14,467 controls were included in the current analysis.

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Clinical variables. Data on demographic factors, socioeconomic status, biological risk factors (hypertension, diabetes, lipids, waist-to-hip ratio), behavioral risk factors (tobacco use, alcohol use, physical activity, fruit and vegetable intake), and psychosocial risk factors (depression, permanent stress, financial stress, stressful events, and perceived locus of control) (14) were obtained for all participants. Psychosocial risk factors were combined into a score based on categories of each of the factors listed previously, and this was detailed in a previous paper (14).

Hereafter we refer to the 9 risk factors (abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, physical activity, fruit and vegetable consumption, and alcohol consumption) as the INTERHEART risk factors. The presence or absence of a history of MI in the mother and/or father was recorded for each case and control. Participants also reported whether MI occurred before the age of 50 years in each parent.

Details of blood sampling, storage, transportation, and analyses were published previously (15). The protocol was approved by the ethics committee at each of the participating centers, and all participants provided informed consent.

Genetic analysis was performed in 8,795 (~32%) participants enrolled in INTERHEART study. This included participants from 5 ethnic groups (Arab, European, Iranian, Nepalese, and South Asian) who were genotyped using a panel of 1,536 single nucleotide polymorphisms (SNPs) from 103 genes that were chosen based on previous knowledge suggesting a relationship with MI or MI risk factors (16). Cases and controls were matched by ethnicity in addition to age (±5 years) and sex. To develop a genotype score, the relationship of each of the 1,536 SNPs was examined in models with MI as the dependent variable including age, sex, and ethnicity. The top 20 most significant SNPs ($p < 0.007$) (rs3798221, rs2113485, rs6980952, rs11679259, rs2020942, rs7015547, rs4520, rs11615630, rs5070, rs9364559, rs2972162, rs1293309, rs854548, rs1298295, rs854542, rs4073054, rs3760627, rs2239375, rs2645424, rs3813667) were tested in a multiple logistic regression model. From this model, 9 SNPs (rs7412, rs699, rs3798221, rs4420638, rs6511720, rs2972162, rs730365, rs4520, rs11679259) from 8 genes (*APOE*, *AGT*, *LPA*, *LDLR*, *PPARG*, *PON2*, *APOC3*, *INSIG2*) were found to remain significant ($p < 0.05$). The minor allele frequencies of these SNPs for each ethnic group are described in the Online Appendix. A test for Hardy-Weinberg equilibrium criteria was performed. All SNPs were in Hardy-Weinberg equilibrium in each ethnicity. The directions of associations were the same for the majority of the 9 SNPs except for rs6511720, rs7412, and rs4420638 in Nepalese compared with other ethnic groups and rs6511720 in South Asians compared with other ethnic groups. The 9 SNPS were used to calculate the genotype score (the number of risk alleles that an individual possesses). For each of the 9 significant SNPs, 0 points were allocated if no risk alleles were carried by an individual, 1 point if 1 risk allele, and 2 points if 2 risk alleles. We defined an allele as protective according to what was derived as protective in the overall dataset, and we did not use ethnicity-specific scores. Thus, the potential genotype score for each subject ranged from 0 to 18. The mean scores for controls and cases (11.9 and 12.2, respectively) are >9 because in several cases, the major allele is the risk allele. The methodology that we used to create this genotype score was similar to that described by a number of groups seeking to aggregate genetic information (17–19). A total of 3,372 cases and 4,032 controls had complete clinical and genetic data, and the characteristics of those genotyped compared with those not genotyped are included in the Online Appendix.

Statistical methods. Multiple logistic regression models were used to quantify the association between the risk of MI and PH of MI. Age, sex, and region were forced in all models. In more complex models, we adjusted for the 9 INTERHEART risk factors. We tested for significant interactions in risks among groups stratified by sex, age of participant (men 55 years and younger and women 65 years and younger), education, and country-specific economic level based on World Bank classifications for the relevant period 1999 to 2003 (20). We also examined risk stratified by overall cardiovascular risk (calculated using a risk equation derived from the Framingham cohort [21]), region, and ethnicity. In the subset of participants who were genotyped, the genotype score was included in multiple logistic regression models adjusted for age, sex, region, and the 9 INTERHEART risk factors.

We scored PH as follows: Those with no PH were designated as the reference group. The groups in order of least to most severe were: 1) history of disease in 1 parent 50 years of age or older; 2) disease in 1 parent younger than 50 years of age; 3) disease in both parents 50 years of age or older; 4) disease in 1 parent 50 years of age or older and 1 parent younger than 50 years of age; and 5) disease in both parents younger than 50 years of age. We compared risk factor levels between groups using *t* tests. All statistical tests were 2 sided. Statistical analyses and graphics were produced with the SAS system

Table 1 Characteristics of Cases and Controls From the INTERHEART Study

Characteristics	Controls	Cases
No. of individuals	14,637	12,461
Female	3,786 (26)	3,005 (24)
Age, yrs	56.9 ± 12.2	58.1 ± 12.2
Smoking		
Current	26.8	45.2
Current or past	48.1	65.2
Diabetes	7.5	18.5
Hypertension	21.9	39.0
Daily intake of fruits and vegetables	42.4	35.8
Exercise daily	19.3	14.3
Alcohol intake	24.5	24.0
Body mass index, kg/m^2	25.8 ± 4.2	26.1 ± 4.2
Waist-to-hip ratio	0.91 ± 0.08	0.93 ± 0.08
Apolipoprotein B, g/l	0.90 (0.74–1.07)	0.95 (0.78–1.13)
Apolipoprotein A-I, g/l	1.19 (1.03–1.37)	1.10 (0.96–1.36)
Apolipoprotein B/apolipoprotein A-I ratio	0.75 (0.60–0.93)	0.87 (0.70–1.05)

Values are n, n (%), mean ± SD, %, or median (interquartile range).

version 9.1 (SAS Institute Inc., Cary, North Carolina) and S-Plus version 6 (TIBSO Software Inc., Palo Alto, California).

Results

The distribution of risk factors between cases and controls was reported previously and is summarized in Table 1 (13). Genotype score was higher in cases compared with controls, and the distribution of this score is reported in Table 2. The prevalence of PH of MI in either parent was 18.1% of cases and 12.0% of controls, and the prevalence of PH of MI in both parents was 2.1% of cases and 0.9% of controls. PH of MI in the mother was reported by 7.5% of cases and 4.9% of controls and PH of MI in the father was reported by 12.7% of cases and 8.1% of controls.

Table 2 Genotype Score Distribution in Subsample of Participants From the INTERHEART Study

	Controls	Cases	p Value
No. of individuals	4,043	3,372	
Genotype score			
Mean (SD)	11.897 (1.756)	12.237 (1.697)	<0.0001
Median	12	12	
<5, %	0	0	
5–10, %	21.0	15.2	<0.0001
11–13, %	61.3	62.0	0.486
>13, %	17.7	22.8	<0.0001

Association of PH of MI with MI. The odds ratio (OR) of MI associated with a PH of MI in either parent (age, sex, and region adjusted) was 1.81 (95% confidence interval [CI]: 1.69 to 1.94). Compared with those with no PH, persons with a PH of MI at an age of 50 years or older in 1 parent had an OR for MI of 1.67 (95% CI: 1.55 to 1.81), persons with a PH of MI in 1 parent younger than 50 years had an OR for MI of 2.36 (95% CI: 1.89 to 2.95), persons with both parents with an MI 50 years or older had an OR for MI of 2.90 (95% CI: 2.30 to 3.66), persons with both parents with an MI but 1 younger than 50 years of age had an OR for MI of 3.26 (95% CI: 1.72 to 6.18), and persons with both parents with a premature MI had an OR for MI of 6.56 (95% CI: 1.39 to 30.95). This graded relationship with MI risk remained after adjusting for the 9 INTERHEART risk factors (Fig. 1). There was improvement in model fit with the addition of PH of MI (area under the curve of the model with age, sex, region, and previously described 9 risk factors was 72.9%, and with the addition of PH score, it was 73.2%; $p < 0.0001$). The population-attributable risks for a PH of MI (including the different grades of family history) were 12.4% (95% CI: 11.1% to 13.9% after adjusting for age and sex and 10.1% (95% CI: 8.5% to 12.1%) after additionally adjusting for the 9 previously mentioned risk factors.

MATERNAL VERSUS PATERNAL HISTORY OF MI ASSOCIATED WITH MI. Both maternal and paternal histories of MI were associated with increased MI risk. There were no statistical differences in the risks associated with paternal and maternal history of MI. The OR for MI associated with a paternal history of MI was 1.84 (95% CI: 1.69 to 2.0), and for a maternal history of MI, it was 1.72 (95% CI: 1.56 to 1.91), and they were not significantly different ($p = 0.692$ for heterogeneity).

CONTRIBUTION OF BEHAVIORAL, BIOLOGICAL, AND PSYCHOSOCIAL FACTORS TO THE ASSOCIATION BETWEEN PH OF MI AND MI. The OR of MI associated with a PH of MI in either parent was 1.81 after age, sex, and region adjustment and remained unchanged at 1.84 (95% CI: 1.70 to 1.98) after adding behavioral factors, 1.80 (95% CI: 1.64 to 1.97) after adding biological factors, and 1.74 (95% CI: 1.58 to 1.92) after adding psychosocial factors (Table 4). These findings suggest that the 9 INTERHEART risk factors only explain to a modest degree the relationship of PH of MI with risk of MI.

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Table 3 Characteristics of Case and Control Participants With and Without a PH of MI (Adjusted for Age, Sex, and Region)

Characteristics	Controls			Cases		
	No PH of MI (n = 12,714)	With PH of MI (n = 1,753)	p Value	No PH of MI (n = 9,935)	With PH of MI (n = 2,214)	p Value
Body mass index, kg/m^2	26.3	26.7	0.0001	26.8	27.3	<0.0001
Waist-to-hip ratio	0.90	0.89	0.0189	0.93	0.93	0.8382
Blood pressure, mm Hg						
Systolic	129	131	0.0005	122	121	0.0190
Diastolic	80	80	0.0017	74	74	0.0531
Cholesterol, mmol/l						
Total	5.28	5.57	<0.0001	5.43	5.50	0.0430
LDL	3.25	3.49	<0.0001	3.49	3.52	0.2825
Triglycerides	1.92	2.02	0.0087	1.96	2.04	0.0246
HDL	1.17	1.19	0.0877	1.06	1.07	0.3625
Apo B	0.93	0.98	<0.0001	1.00	1.01	0.0811
Apo A-I	1.27	1.30	0.0006	1.15	1.16	0.3367
Apo B/Apo A-I ratio	0.77	0.80	0.0003	0.91	0.91	0.3926
HbA_{1c}	5.85	5.86	0.7520	6.16	6.12	0.2979
Smoking						
Current or past	40.6	45.2	0.0010	58.6	62.2	0.0103
Current	16.8	15.7	0.2138	34.9	35.4	0.6772
Past	17.2	22.5	<0.0001	14.7	16.8	0.0103
Diabetes	6.6	8.1	0.0248	29.8	22.2	0.0227
Hypertension	20.2	24.6	0.0001	41.6	45.3	0.0042
Alcohol consumption	18.7	21.2	0.0180	14.0	15.7	0.0323
Physical activity	20.3	22.9	0.0199	13.6	14.4	0.3272
Consume both fruits and vegetables daily	48.0	54.3	<0.0001	38.3	43.6	<0.0001
Depression	18.8	21.8	0.0041	26.2	29.2	0.0124
Stress						
Permanent	4.1	5.2	0.0242	7.2	10.5	<0.0001
Several periods	17.7	19.2	0.1459	21.6	21.0	0.5500
Severe financial stress	9.6	7.8	0.0085	13.9	13.4	0.5271
Moderate financial stress	34.9	32.6	0.0717	37.1	34.8	0.0558
2+ stressful events	13.4	13.4	0.9353	17.6	20.2	0.0056
Least control over life	33.1	31.7	0.2924	16.7	19.2	0.0133

Values are listed as mean or %.
Apo = apolipoprotein; HbA_{1c} = glycosylated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; PH = parental history.

CONSISTENCY OF FINDINGS ACROSS SUBGROUPS AND REGIONS. The age-, sex-, and region-adjusted OR associated with a PH of MI was higher for younger individuals (men 55 years of age and younger and women 65 years of age and younger) compared with older individuals. The OR was 2.01 (95% CI: 1.84 to 2.20) for younger ages and 1.54 (95% CI: 1.38 to 1.72) for older ages (p = 0.0002 for heterogeneity). However, after adjusting for the 9 INTERHEART risk factors, the OR for younger people was 1.84 (95% CI: 1.62 to 2.08) and for older people 1.60 (95% CI: 1.38 to 1.86), and the difference in risks became insignificant (p = 0.154 for heterogeneity), suggesting that risk factor differences explained the initial heterogeneity observed. The results were consistent in fully adjusted models across geographic regions, ethnic groups, world economic regions (based on World Bank economic classification), socioeconomic groups in both sexes and all age groups and when stratified by cardiovascular risk (Framingham risk score) (Tables 5 and 6).

CONTRIBUTION OF GENETIC RISK FACTORS TO ASSOCIATION BETWEEN PH OF MI AND MI RISK. In the subset of 7,415 with complete genetic and clinical data, the OR associated with a PH of MI was unchanged after adjusting for genotype score (Table 4).

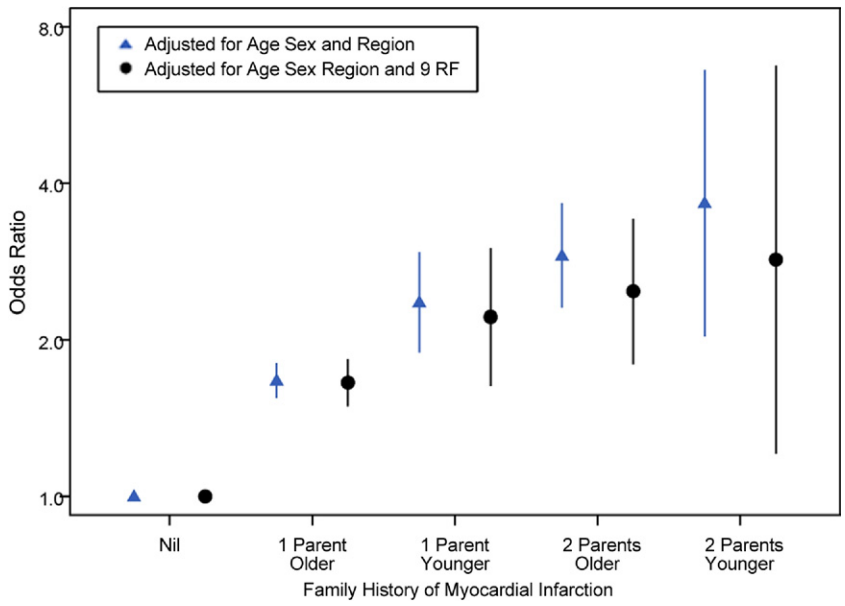

Figure 1 **Relationship of Parental History of Myocardial Infarction and Risk of Myocardial Infarction**

The 9 risk factors in the models are hypertension, diabetes, lipids, waist-to-hip ratio, tobacco use, alcohol use, physical activity, fruit and vegetable intake, and psychosocial risk factors. One parent older, disease in 1 parent, diagnosed when older than 50 years of age. One parent younger, disease in 1 parent, diagnosed when younger than 50 years of age. Two parents older, disease in both parents, diagnosed when older than 50 years of age. Two parents younger, disease in both parents, at least 1 parent diagnosed when younger than 50 years of age. Nil = no parental history; RF = risk factor.

RISK FACTORS IN THOSE WITH AND WITHOUT A PH OF MI. Risk factors were compared in participants reporting a PH of MI in at least 1 parent and those not reporting a PH of MI. Those reporting a PH of MI were younger (55.0 years vs. 57.9 years; $p < 0.0001$). Biological and psychosocial risk factors were generally more adverse in those with a PH of MI. Behaviors, however, were generally better in those with a PH of MI. The patterns of differences in risk factors between those with and without a PH of MI are similar for both cases and controls (Table 3).

Genotype score was calculated for 3,372 cases and 4,043 controls. Although the genotype score was higher in cases compared with controls (Table 2), it was not higher in those with a PH versus those without a PH of MI. The mean genotype score was 11.90 (SD = 1.75) in controls with no PH of MI, 11.84 (SD =

Table 4 **Risk of MI Associated With PH of MI and Adjustment for Behavioral, Biological, Psychosocial, and Genetic Risk Factors**

	PH of MI			
Odds Ratio	Mother	Father	Mother or Father	Mother and Father
Unadjusted	1.61 (1.45–1.78)	1.65 (1.53–1.79)	1.62 (1.51–1.73)	2.43 (1.96–3.01)
Adjusted for age, sex, region	1.73 (1.56–1.91)	1.84 (1.69–2.00)	1.81 (1.69–1.94)	2.65 (2.14–3.29)
Adjusted for age, sex, region, behavioral RFs	1.74 (1.55–1.94)	1.85 (1.69–2.02)	1.84 (1.70–1.98)	2.52 (2.00–3.17)
Adjusted for age, sex, region, behavioral and biological RFs	1.63 (1.42–1.86)	1.86 (1.67–2.08)	1.80 (1.64–1.97)	2.37 (1.77–3.15)
Adjusted for age, sex, region, 9 RFs	1.54 (1.33–1.76)	1.85 (1.65–2.07)	1.74 (1.58–1.92)	2.26 (1.68–3.06)
Adjusted for age, sex, region, 9 RFs, genotype score*	1.57 (1.34–1.86)	1.45 (1.25–1.68)	1.50 (1.32–1.70)	2.28 (1.64–3.17)

Values are odds ratio (95% confidence interval). *Analysis in 3,269 cases and 4,032 controls. All other models include 14,467 controls and 12,149 cases.
RF = risk factor; other abbreviations as in Table 3.

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Table 5 Risk of MI Associated With PH of MI and Comparisons Within Major Subgroups: Analysis of 14,467 Controls and 12,149 Cases

	PH of MI Adjusted for Age, Sex, Region	PH of MI Adjusted for 9 Risk Factors
Overall	1.81 (1.69–1.94)	1.74 (1.58–1.92)
Sex		
Women	1.62 (1.41–1.86)	1.65 (1.36–2.00)
Men	1.88 (1.73–2.04)	1.78 (1.59–1.98)
p value for heterogeneity	0.0694	0.5078
Age		
Younger (men ≤55 yrs, women ≤65 yrs)	2.01 (1.84–2.20)	1.84 (1.63–2.08)
Older (men >55 yrs, women >65 yrs)	1.54 (1.38–1.72)	1.60 (1.38–1.86)
p value for heterogeneity	0.0002	0.1539
Highest level of education completed		
Trade/college/university	1.73 (1.56–1.93)	1.75 (1.51–2.02)
9–12 yrs of education	2.04 (1.79–2.33)	1.97 (1.64–2.37)
≤8 yrs of education	2.00 (1.76–2.28)	1.69 (1.42–2.01)
p value for heterogeneity	0.098	0.4415
Household income		
Low (lowest 2 quintiles of income)	1.88 (1.64–2.15)	1.76 (1.55–2.00)
Middle (middle quintile)	1.56 (1.26–1.93)	1.78 (1.52–2.09)
High (upper 2 quintiles)	1.73 (1.47–2.06)	1.76 (1.55–2.00)
p value for heterogeneity	0.3380	0.4430
Economic development of country*		
Low income	1.69 (1.40–2.04)	1.60 (1.23–2.07)
Middle income	1.98 (1.80–2.19)	1.88 (1.66–2.13)
High income	1.60 (1.41–1.81)	1.53 (1.27–1.86)
p value for heterogeneity	0.0199	0.1699
Cardiovascular risk		
Low Framingham risk (1st tertile)	2.06 (1.79–2.37)	1.96 (1.66–2.30)
Medium Framingham risk (2nd tertile)	1.68 (1.47–1.92)	1.57 (1.35–1.83)
High Framingham risk (3rd tertile)	1.82 (1.55–2.13)	1.75 (1.46–2.10)
p value for heterogeneity	0.1210	0.1566

Values are odds ratio (95% confidence interval) unless otherwise indicated. PH of MI is self-reported history of MI in mother or father. *Economic development of each country was based on World Bank classifications for the relevant period 1999 to 2003 (http://web-worldbank.org).

Abbreviations as in Table 3.

1.81) in controls with a PH of MI, 12.26 (SD = 1.71) in cases with no PH of MI, and 12.14 (SD = 1.68) in cases with a PH of MI.

Discussion

The findings of this study indicate that a PH of MI scored on clinical history is an independent predictor of future MI. The strength of this association is minimally attenuated in models adjusted for age, sex, region, and the 9 INTERHEART risk factors. The strength of association between a PH of MI and MI risk is also consistent across geographic regions, age, sex, and socioeconomic subgroups. Differences in crude measures of strength of association (ORs) by world economic region, geographic region, or ethnicity is likely due to risk factor differences across regions as the difference in ORs became nonsignificant after adjusting for the previously mentioned 9 risk factors.

Of note is that our findings indicate that the strength of association of parental history of MI and MI risk is similar across different risk groups. Household income is a measure of socioeconomic status within a country, and our results indicate that the risk associated with a PH of MI is similar across groups of differing socioeconomic status within a country. Although we note that previous studies indicate the strength of association of family history with cardiovascular outcomes is greater in low-risk groups (22), our findings indicate that the associations are not significantly different in groups of low, medium, and high risk (as defined by tertiles of Framingham risk score). Thus, the simple self-report measure of a PH of MI confers a near doubling of MI risk regardless of background risk factors, country, and age or whether the history was from the mother or father.

The reason for the association between a PH of MI is often attributed to a combination of shared risk factors and genetics (12). Consistent with this hypothesis is the marginal attenuation of the effect of PH on the risk of MI that we observed in this study, which has also been observed in other studies (8,9). Consistent with this, other studies find that more detailed information on family history (e.g., considering the number of relatives with coronary disease, degree of relationship, lineage, and age at diagnosis) also adds to risk prediction based on risk factors and a single metric of family history (23,24). This raises the question of what PH is a measure of. Are there other factors that are unmeasured that could explain the relationship between PH of MI and risk of MI? Could other factors shared in families be the culprit? For example, early life exposures such as early life stress or early life nutrition may affect early development of atherosclerosis. Such influences may be transgenerational and hence could be causing increased MI risk (25). Home environmental factors such as exposure

Table 6 Risk of MI Associated With PH of MI by Geographic Region and Ethnicity

	PH of MI Adjusted for Age, Sex, Region	PH of MI Adjusted for 9 Risk Factors
Geographic regions		
Western Europe (656 cases, 766 controls)	1.29 (1.02–1.65)	1.36 (0.97–1.89)
Central and Eastern Europe (1,689 cases, 1,918 controls)	1.72 (1.44–2.05)	2.00 (1.58–2.53)
Middle East (1,614 cases, 1,778 controls)	1.87 (1.55–2.26)	1.53 (1.21–1.93)
Africa (561 cases, 783 controls)	2.65 (1.96–3.60)	2.09 (1.40–3.12)
South Asia (1,676 cases, 2,200 controls)	1.63 (1.36–1.95)	1.54 (1.20–1.99)
China and Hong Kong (3,014 cases, 3,054 controls)	1.93 (1.42–2.64)	1.82 (1.28–2.60)
Southeast Asia and Japan (941 cases, 1,198 controls)	2.44 (1.85–3.22)	1.95 (1.38–2.77)
Australia and New Zealand (588 cases, 677 controls)	1.93 (1.54–2.43)	2.18 (1.44–3.29)
South America and Mexico (1,184 cases, 1,847 controls)	2.02 (1.68–2.44)	1.87 (1.46–2.39)
North America (283 cases, 333 controls)	1.24 (0.90–1.71)	1.24 (0.62–2.51)
p value for heterogeneity	0.0015	0.4184
Ethnic groups		
European (3,254 cases, 3,689 controls)	1.52 (1.36–1.69)	1.76 (1.50–2.07)
Chinese (3,114 cases, 3,165 controls)	1.94 (1.46–2.58)	1.71 (1.23–2.38)
South Asian (2,100 cases, 2,565 controls)	1.67 (1.42–1.97)	1.47 (1.17–1.84)
Other Asian (850 cases, 1,072 controls)	2.37 (1.77–3.17)	1.74 (1.21–2.52)
Arab (1,292 cases, 1,476 controls)	2.08 (1.67–2.56)	1.76 (1.37–2.27)
Latin American (1,095 cases, 1,794 controls)	2.08 (1.72–2.52)	2.01 (1.56–2.60)
Black African (148 cases, 362 controls)	7.23 (1.89–27.71)	10.95 (1.83–65.72)
Colored African (304 cases, 339 controls)*	1.94 (1.33–2.83)	1.75 (1.08–2.85)
Other (49 cases, 92 controls)	1.65 (0.73–3.69)	6.65 (1.50–29.54)
p value for heterogeneity	0.0045	0.1767

Values are odds ratio (95% confidence interval) unless otherwise specified. *The colored African group in this study is predominantly from South Africa and represents a group of mixed race ancestry descending from the first South African nations, the Khoi and San people, as well as European, African, and Malaysian people.

Abbreviations as in Table 3.

to similar social factors or indoor air pollution may also contribute. Unmeasured genetic factors offer a strong potential explanation for the association between family history and MI. Although we have attempted to examine the contribution of some genetic factors through a genotype score of selected SNPs derived from a large panel of genotype variants known or hypothesized to be related to MI or its risk factors, the list of genotype variants including those from recent genome-wide associations studies related to MI is continually growing (26,27). The genotype score here only represents a small percentage of the possible genotype variants, and all but 1 of the SNPs (the one near AGT) used to derive the genotype score are in or near candidate genes that have been implicated in cholesterol metabolism. In this context, our genotype risk score probably had very limited ability to predict risk of MI independent of serum lipids levels. A higher mean genotype score was seen in cases compared with controls. It would be expected that the genotype score would also be higher in those with a PH compared with those without, if these common genotype variants contributed substantially to the relationship between PH and MI risk. However, this was not seen in either cases or controls. As currently known loci still only explain a small proportion of the variance of risk of CHD, the power to detect differences with any genotype score is likely to be very poor. It is very likely that many genetic factors are yet to be identified, and an important supporting argument for this is that twin studies in which shared environmental risk factors are largely accounted for show a clear increase in risk of CHD when the twin has CHD, which is greater among monozygotic twins and thus argues strongly for a genetic component to the explanation for the association observed between family history of MI and MI risk (28).

In our study, individuals with a PH had more adverse levels of most biological risk factors and psychosocial risk factors. However, behavioral risk factors (current and past smoking, fruit and vegetable intake, physical activity, and alcohol consumption) were more favorable in those with a

PH. The higher rates of protective behaviors in individuals with a PH could be because individuals in this study may have already changed their lifestyle due to a greater awareness of risk, although information bias may also be a possible explanation. However, the higher levels of modifiable risk factors including lipids, obesity, and diabetes indicate that clinicians should aggressively manage risk factors in those with a PH of CHD (29).

The strengths of this study are its large international coverage in ethnically and socioeconomically diverse populations, the large number of cases of MI, and the comprehensive measurement of risk factors including genetic factors. It thus has wider population implications compared with previous studies and is able to establish the independence of the measure of a PH of MI from a long list of potential confounders. Further research is required to examine whether other determinants, genetic, early life determinants, or common family level influences (e.g., environmental exposures) may explain the relationship between a PH of MI and MI risk.

Study limitations. First, only data on PH were collected in this study; data on a history of MI in siblings or other relatives were not collected. Second, we had limited measures of SNPs in a limited number of individuals from our study population. We did not have adequate numbers of individuals to derive our genotype score in a training set separate from the evaluation set, and this raises the potential of overfitting. Third, the case-control design of this study raises the possibility of recall biases influencing our results. Studies have shown that although specificity of self-reported family history is high (90% to 100%), the sensitivity of self-reported family history can be low (50% to 70%) (30). This inaccuracy could mean our estimations are an underestimation of the risk associated with family history (31). However, studies examining the risk of MI associated with a validated PH of CVD (MI/angina/stroke/other vascular disease) report results similar to ours (Lloyd-Jones et al. [9] document an age-adjusted OR for the risk of CVD associated with a validated PH of nonpremature CVD of 1.9 (95% CI: 1.2 to 3.0) in men and 1.6 (95% CI: 0.9 to 2.9) in women. In comparison in this study, the age-adjusted OR for risk of MI associated with a PH of MI is 1.88 (95% CI: 1.73 to 2.04) in men and 1.62 (95% CI: 1.41 to 1.86) in women.

We think that differential recall bias is unlikely between cases and controls because a PH of MI is likely to be an enduring memory and recalled equally by cases and controls.

Conclusions

PH of MI is an easy-to-measure risk factor that is significantly associated with a risk of MI independent of the 9 established risk factors as well as some common genetic factors, and this relationship is consistent across all world regions, income, age, and sex groups studied in the INTERHEART study. Further, clinical grading of risk determined by self-reported information from a patient on the age at onset of disease in parents and whether 1 or both parents are affected provides a simple but robust assessment of their risk in this population of patients independent of other measured risk factors.

Author Disclosures

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Key Words: family history ■ genetics ■ myocardial infarction ■ parental history.

APPENDIX

For supplemental tables, please see the online version of this article.

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