

# Lipid Profile, Plasma Apolipoproteins, and Risk of a First Myocardial Infarction Among Asians

## An Analysis From the INTERHEART Study

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- Objectives** This study sought to determine the prevalence of lipid and lipoprotein abnormalities and their association with the risk of a first acute myocardial infarction (AMI) among Asians.
- Background** Patterns of lipid abnormalities among Asians and their relative impact on cardiovascular risk have not been well characterized.
- Methods** In a case-control study, 65 centers in Asia recruited 5,731 cases of a first AMI and 6,459 control subjects. Plasma levels of lipids and apolipoproteins in the different Asian subgroups (South Asians, Chinese, Southeast Asians, and Japanese) were determined and correlated with the risk of AMI.
- Results** Among both cases and controls, mean low-density lipoprotein cholesterol (LDL-C) levels were about 10 mg/dl lower in Asians compared with non-Asians. A greater proportion of Asian cases and controls had LDL-C  $\leq$ 100 mg/dl (25.5% and 32.3% in Asians vs. 19.4% and 25.3% in non-Asians, respectively). High-density lipoprotein cholesterol (HDL-C) levels were slightly lower among Asians compared with non-Asians. There was a preponderance of people with low HDL-C among South Asians (South Asia vs. rest of Asia: cases 82.3% vs. 57.4%; controls 81% vs. 51.6%;  $p < 0.0001$  for both comparisons). However, despite these differences in absolute levels, the risk of AMI associated with increases in LDL-C and decreases in HDL-C was similar for Asians and non-Asians. Among South Asians, changes in apolipoprotein (Apo)A1 predicted risk better than HDL-C. ApoB/ApoA1 showed the strongest association with the risk of AMI.
- Conclusions** The preserved association of LDL-C with risk of AMI among Asians, despite the lower baseline levels, suggests the need to rethink treatment thresholds and targets in this population. The low HDL-C level among South Asians requires further study and targeted intervention. (J Am Coll Cardiol 2009;53:244-53) © 2009 by the American College of Cardiology Foundation

The causal link between lipid abnormalities and cardiovascular disease (CVD) is well established. Among these abnormalities, elevated levels of low-density lipoprotein

cholesterol (LDL-C) are thought to be a key determinant of CVD risk (1). However, most of the information on the contributions of various lipid fractions to CVD risk is

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derived from studies in the Caucasian population. The pattern of lipid abnormalities and their relative impact on CVD risk might vary among ethnic groups (2–8). Asians experience the largest proportion of the worldwide burden of CVD. Further, Asians include several distinct ethnic subpopulations (South Asians, Chinese, etc.), who may differ in their lipid profiles (3). These differences may be the result of both genetic and environmental factors (high-carbohydrate diets, reduced physical activity, and so on) (9,10).

There is also considerable controversy regarding the relative importance of the apolipoprotein measures (ApoB and ApoAI) in comparison to the conventionally measured lipid fractions in determining CVD risk, with practically no data in Asian populations (11–13). The higher prevalence of hypertriglyceridemia and small, dense LDL-C particles among some Asian subgroups raises the possibility that lipoprotein levels will more accurately reflect the total atherogenic particle load, and consequently, CVD risk (14,15).

The INTERHEART study, which enrolled over 5,500 cases of a first acute myocardial infarction (AMI) and nearly 6,500 control subjects from Asia, and measured both lipoproteins and apolipoproteins, provides an opportunity to explore the relative importance of these markers and the risk of AMI in Asians.

## Methods

The INTERHEART study is a case-control study that enrolled 15,152 cases of a first AMI and 14,820 age- ( $\pm 5$  years) and sex-matched control subjects from 262 centers in 52 countries. The details of the study methods, inclusion and exclusion criteria, and the overall results have been published and are also described in the Online Appendix (16–18). This analysis pertains to the individuals who were recruited from 65 centers in countries from Asia. India, Pakistan, Bangladesh, Nepal, and Sri Lanka represented the South Asian region. The Southeast Asian countries included were Singapore, Malaysia, Thailand, and the Philippines. The other countries included in this analysis were China and Hong Kong, and Japan.

**Subjects and study procedures.** Centers in Asia recruited 5,731 cases of AMI and 6,459 control subjects. All patients admitted to the hospital with a diagnosis of a first AMI, within 24 h of the initial symptoms, were eligible for enrollment. Control subjects were either hospital based (patients admitted to hospital with a noncardiac diagnosis) or community based (unrelated attendants of index patients, attendants of noncardiac patients). Control subjects neither had a history of exertional chest pain nor were known to have cardiac disease. Nonfasting blood samples were obtained from case and control subjects, and the time since the last meal and from the onset of symptoms was documented. Blood samples were obtained and centrifuged within 2 h, separated, and immediately frozen at either  $-20^{\circ}\text{C}$  or at

$-70^{\circ}\text{C}$ . Samples were periodically shipped in nitrogen vapor tanks for storage at  $-80^{\circ}\text{C}$  in China or at  $-160^{\circ}\text{C}$  in Hamilton, Ontario, Canada. The laboratory procedures involved in lipid and lipoprotein measurement have been detailed elsewhere (18) and also in the Online Appendix.

**Statistical analysis.** Continuous variables were summarized using means and were compared using analysis of variance model-based tests. For comparison of means across subgroups, values were adjusted for age and sex using analysis of covariance models. Univariate associations were explored using frequency tables and Pearson chi-square tests for independent proportions. Unconditional logistic regression with adjustment for matching factors was used to control for confounding by other risk factors. Results from unconditional analyses were similar to those from conditional and mixed-effect models analyses ( $<5\%$  variation). The results were consistent using the 2 types of controls, and so the results are presented using the overall analysis. All statistical tests were 2-sided. Statistical analyses were performed using the SAS system version 9.1 (SAS Institute Inc., Cary, North Carolina). All of our models were multivariate, and in general we adjusted for age, sex, smoking, and geographic region.

## Results

Data for LDL-C and high-density lipoprotein cholesterol (HDL-C) were available for 4,247 cases and 5,452 control subjects from Asia. Lipid data were available for 4,455 cases and 5,867 control subjects from other regions of the world. Missing samples were largely accounted for by patients who presented 24 h after the onset of symptoms (in whom blood was not drawn) and unusable samples (because of poor storage and unclear labeling). The proportion of missing samples among Asians was similar to that in the overall INTERHEART population (18). Non-Asians were more likely to be diabetic, to be hypertensive, and to have abdominal obesity, but were also more likely to exercise and to consume fruits and vegetables and alcohol regularly. Asians were more likely to be smokers (Online Appendix).

**Differences in lipid and lipoprotein levels among Asians and non-Asians.** The mean LDL-C level (mg/dl) was significantly lower among both Asian cases (126.8 vs. 136.2) and control subjects (118.7 vs. 127.1;  $p < 0.0001$  for both comparisons) compared with non-Asians (Table 1). Further, a larger proportion of Asians had a low LDL-C level. The proportion of cases and control subjects from Asia who had LDL-C levels  $\leq 100$  mg/dl was 25.5% and 32.3% respectively, compared with 19.4% and 25.3% in non-Asians (Table 2), with consistent results in both sexes and in

### Abbreviations and Acronyms

**AMI** = acute myocardial infarction

**Apo** = apolipoprotein

**CVD** = cardiovascular disease

**HDL-C** = high-density lipoprotein cholesterol

**LDL-C** = low-density lipoprotein cholesterol

**TG** = triglyceride

**Table 1** Mean (SD) LDL-C, HDL-C, Triglyceride, and Apo Levels in Subjects From Asia and Other Regions

	LDL-C* (mg/dl)		HDL-C* (mg/dl)		Triglycerides† (>8 h Fasting) (mg/dl)		ApoB* (g/l)		ApoA1 (g/l)	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Asia (n = 9,699)	126.8 (40)	118.6 (37)	39.2 (12.3)	41.2 (14.3)	148.4 (97.4)	156.7 (100.3)	0.92 (0.26)	0.87 (0.24)	1.11 (0.25)	1.21 (0.28)
Non-Asian regions (n = 10,322)	136.2 (42.4)	127.1 (39.1)	40.8 (13.2)	42.6 (15)	164.8 (104.8)	164.0 (101.8)	1.02 (0.27)	0.95 (0.25)	1.13 (0.24)	1.22 (0.28)
South Asia (n = 2,674)	125.2 (39.8)	115.4 (37.1)	32.5 (10)	33.5 (11.6)	163.3 (105.6)	169.4 (107.9)	0.95 (0.26)	0.90 (0.24)	1.01 (0.23)	1.08 (0.23)
China/Hong Kong (n = 5,232)	121.6 (36)	113.8 (33.8)	41.9 (12)	44.0 (13.3)	139.3 (91.7)	152.3 (98)	0.86 (0.23)	0.81 (0.21)	1.16 (0.25)	1.26 (0.29)
Southeast Asia (n = 1,546)	150.4 (47.6)	135.6 (41)	41.0 (12.5)	42.6 (15.5)	160.4 (95.1)	161.0 (103.5)	1.08 (0.29)	0.97 (0.25)	1.11 (0.23)	1.22 (0.26)
Japan (n = 247)	133.6 (34.6)	133.1 (30.9)	44.2 (12.8)	56.4 (13.2)	159.5 (139.5)	137.4 (71.1)	0.99 (0.23)	0.95 (0.22)	1.20 (0.30)	1.44 (0.25)

\*p < 0.0001. †p = 0.01, for both between-case and between-control comparisons between Asian and non-Asian regions. For conversion of LDL-C and HDL-C levels into mmol/l, multiply by 0.0259, and for triglycerides, multiply by 0.0113. Apo = apolipoprotein; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

all age groups. Levels of HDL-C and triglycerides (TGs) were lower among Asians (Table 1). The ApoB levels were also lower among Asians than among subjects from other regions of the world, whereas ApoA1 levels were similar between the 2 populations (Table 1).

**LDL-C, HDL-C, TG, and Apo levels among Asian subgroups.** There were large variations in the LDL-C levels among the various Asian subgroups. South Asians and people from China and Hong Kong tended to have lower LDL-C levels compared with people from Southeast Asia and Japan (Table 1). This was because of the higher prevalence of people with LDL-C levels  $\leq 100$  mg/dl among South Asians and the Chinese (Table 2). The absolute differences in LDL-C levels were large and were about 30 mg/dl lower among people from China and Hong Kong compared with those from Southeast Asia. Southeast Asians had LDL-C levels similar to people from other non-Asian regions. The Japanese also had LDL-C levels similar to non-Asian people, but this observation was based on a relatively small number of subjects (n = 247) (Tables 1 and 2).

The HDL-C levels in the South Asian population were substantially lower than in all other subgroups (Tables 1 and 2). Over 80% of both cases and control subjects in South Asia had low HDL-C levels (cases 82.3% vs. 57.4%; control subjects 81% vs. 51.6%; comparisons between South Asia and the rest of Asia; p < 0.0001 for both comparisons) (Table 2). The proportion of people with low HDL-C levels in the other Asian subgroups tended to be similar to or lower than in non-Asians. Japanese control subjects seemed to have a preponderance of normal or high HDL-C levels, but again, this observation is based on a small number of subjects (Table 2).

People from China and Hong Kong had the lowest TG levels, and South Asians had the highest (difference of 10 mg/dl) (Table 1). Whereas the former had lower TG levels when compared with people from other continents, the latter had comparable or marginally higher levels (Table 1). The TG levels among Southeast Asians and the Japanese were closer to the levels found in non-Asians.

The ApoB levels were lowest among people from China and Hong Kong. People from the other Asian regions had levels similar to those in the rest of the world. The association between LDL-C and ApoB levels was linear, and increases in LDL-C were associated with predictable increases in ApoB among all subjects. However, the absolute values corresponding to different LDL-C levels differed among subgroups. For any given LDL-C level, South Asians had the highest and the Chinese had the lowest ApoB levels when compared with the other Asian subgroups (Fig. 1A).

The ApoA1 levels were lowest among South Asians. The association between HDL-C and ApoA1 levels was linear for all populations, and higher HDL-C levels were associated with predictably higher ApoA1 levels. However, among South Asians, for any given HDL-C level, the

**Table 2** Proportion of Subjects, n (%), With Different LDL-C and HDL-C Categories in Asia and Other Regions

	LDL-C (mg/dl)						HDL-C (mg/dl)*					
	Cases			Controls			Cases			Controls		
	≤100†	>100 but ≤130	>130	≤100†	>100 but ≤130	>130	Low HDL-C	Normal or High HDL-C	Low HDL-C	Normal or High HDL-C	Low HDL-C	Normal or High HDL-C
Asia	1,084 (25.5)	1,391 (32.7)	1,773 (41.7)	1,763 (32.3)	1,852 (33.9)	1,841 (33.7)	2,843 (64.3)	1,576 (35.7)	3,406 (59.9)	2,283 (40.1)	2,283 (40.1)	2,283 (40.1)
Non-Asian regions	863 (19.4)	1,225 (27.5)	2,369 (53.2)	1,485 (25.3)	1,715 (29.2)	2,678 (45.6)	2,789 (60.0)	1,859 (40.0)	3,463 (56.3)	2,689 (43.7)	2,689 (43.7)	2,689 (43.7)
South Asia	324 (27.8)	343 (29.4)	498 (42.7)	526 (34.8)	514 (34.0)	471 (31.2)	1,010 (82.3)	217 (17.7)	1,294 (81.0)	303 (19.0)	303 (19.0)	303 (19.0)
China/Hong Kong	663 (27.5)	904 (37.5)	841 (34.9)	1,047 (37.0)	999 (35.4)	780 (27.6)	1,427 (57.6)	1,050 (42.4)	1,539 (52.7)	1,381 (47.3)	1,381 (47.3)	1,381 (47.3)
Southeast Asia	78 (13.3)	120 (20.5)	388 (66.2)	175 (18.2)	269 (28.0)	517 (53.8)	367 (58.8)	257 (41.2)	554 (54.7)	458 (45.3)	458 (45.3)	458 (45.3)
Japan	19 (21.3)	24 (27.0)	46 (51.7)	15 (9.5)	70 (44.3)	73 (46.2)	39 (42.9)	52 (57.1)	19 (11.9)	141 (88.1)	141 (88.1)	141 (88.1)

\*Low HDL-C: HDL-C <40 mg/dl (men) and <50 mg/dl (women); normal or high HDL-C: ≥40 mg/dl (men) and ≥50 mg/dl (women). †p < 0.001 for both between-case and between-control comparisons. For conversion of LDL-C and HDL-C levels into mmol/l, multiply by 0.0259, and for triglycerides, multiply by 0.0113.  
Abbreviations as in Table 1.

corresponding ApoA1 level was lower than in the other populations (p for heterogeneity <0.0001) (Fig. 1B).

**LDL-C, HDL-C, Apo, and risk of AMI.** The risk of AMI increased progressively with elevations in LDL-C levels among Asian subjects as a whole and across all subgroups of the Asian population (Fig. 2). The higher risk associated with elevations in LDL-C levels was similar to that observed in the rest of the INTERHEART population.

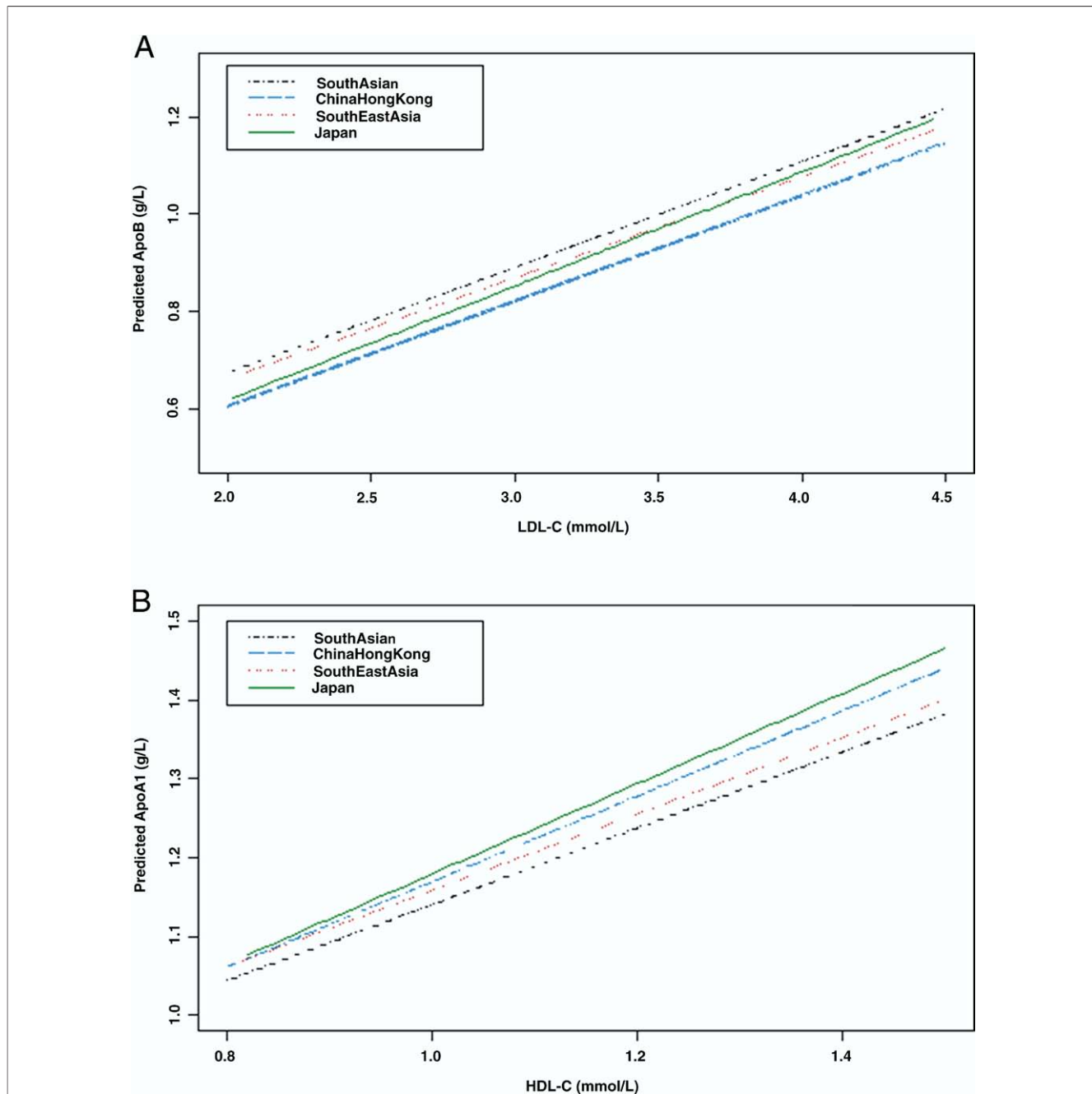
As in subjects from other regions of the world, elevations in HDL-C were associated with a decreased risk of AMI (Fig. 3). This lower risk was of a similar magnitude to that observed in other populations and was consistent across all of the Asian subgroups. However, the protective effect of higher HDL-C levels seemed to be weaker for South Asians compared with the other Asians (odds ratio [OR] for 1 SD increase in South Asians: 0.87, 95% confidence interval [CI]: 0.72 to 1.06; OR for rest of Asia: 0.77, 95% CI: 0.70 to 0.85; p for interaction = 0.25). In every LDL-C category, subjects with a normal or high HDL-C had a lower risk of AMI than those with low HDL-C levels. (Fig. 4).

The risk of AMI for 1 SD increase in ApoB levels was similar in magnitude to that associated with a similar increase in LDL-C (ORs: 1.24 and 1.25, respectively). Increases in ApoA1 levels were associated with a lower risk of AMI (OR for 1 SD increase: 0.65, 95% CI: 0.62 to 0.68), which was significantly greater than that observed with HDL-C. Further, increases in ApoA1 were equally protective among all of the Asian subgroups, unlike increases in HDL-C. Among South Asians, the lower risk of AMI associated with high ApoA1 levels was similar to that observed overall (OR: 0.67, 95% CI: 0.61 to 0.74).

**Comparison of AMI risk by lipid and Apo ratios.** The ratio of ApoB and ApoA1 had the strongest association with the risk of AMI among Asians and non-Asians. Among Asians, for a 1-SD increase in the ratio, the OR for AMI was 1.38, compared with an OR of 1.06 and 1.14 for every SD increase in the non-HDL-C/HDL-C and LDL-C/HDL-C ratios, respectively (Fig. 5). Increases in non-HDL-C and LDL-C were associated with much smaller ORs than for increases in the ApoB/ApoA1 ratio. Fasting TG levels (samples drawn >8 h after the last meal) were not associated with an increase in the risk of AMI; neither was the TG/HDL-C ratio.

## Discussion

Our data suggests that: 1) LDL-C, HDL-C, TG, and ApoB levels are lower among Asians compared with non-Asians. However, there is much heterogeneity among the various subgroups of the Asian population, with lower levels of HDL-C and LDL-C in South Asians and lower levels of LDL-C among the Chinese. 2) The associations of elevated LDL-C and lower levels of HDL-C for the risk of AMI are



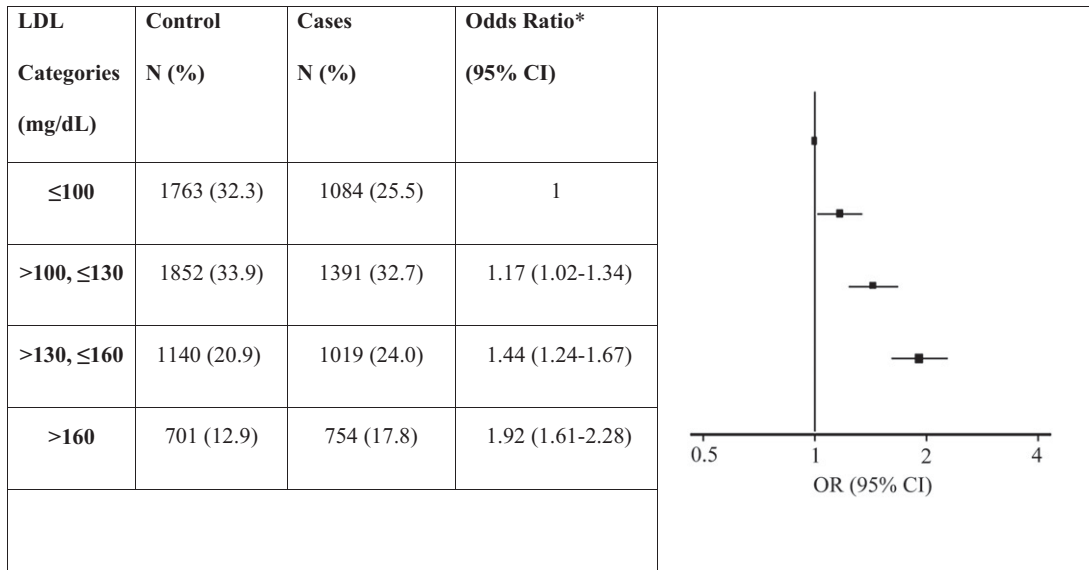
**Figure 1** Regression Plots

**(A)** Regression plot of age- and sex-adjusted apolipoprotein (Apo)B versus low-density lipoprotein cholesterol (LDL-C) by ethnic group. For any given LDL-C level, South Asians had the highest ApoB levels and the Chinese had the lowest. **(B)** Regression plot of age- and sex-adjusted ApoA1 versus high-density lipoprotein cholesterol (HDL-C) by ethnic group. For any given HDL-C level, South Asians had the lowest ApoA1 levels compared with all of the other subgroups.

broadly similar among Asians and non-Asians. 3) As in the overall INTERHEART population, the ratio of ApoB to ApoA1 had the strongest association with the risk of AMI in Asians.

**Higher prevalence of low LDL-C levels among people of Chinese and South Asian origin.** More than one-fourth of the patients with AMI from South Asia and China had levels of LDL-C  $\leq 100$  mg/dl, whereas the proportions of

people from Southeast Asia and Japan with low LDL-C levels resembled the rest of the INTERHEART population from other continents. The mean LDL-C level in the Asia Pacific collaboration study was 3.23 mmol/l (125 mg/dl), which is similar to the mean LDL-C level among cases in our analysis (8). The low mean level of LDL-C observed in our analysis is also consistent with several other cross-sectional studies from Asia (2,5,19,20).



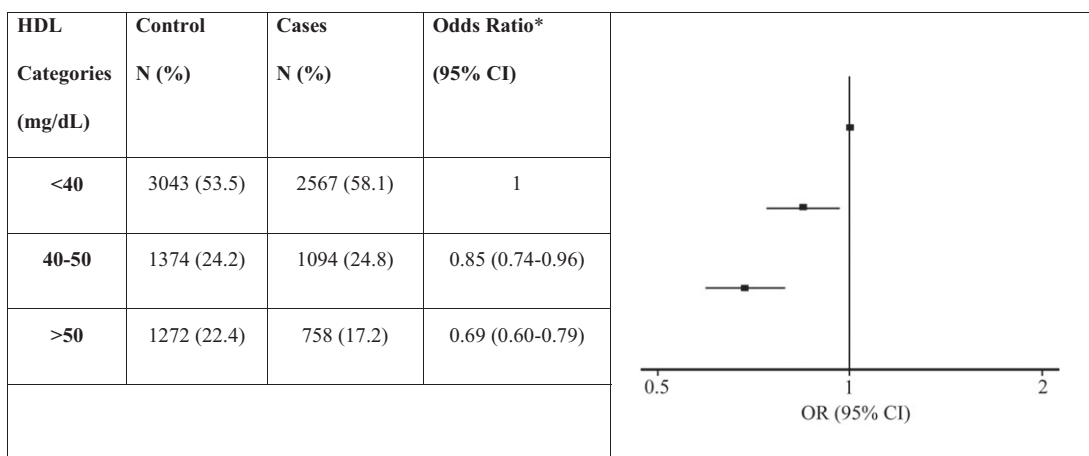
**Figure 2** ORs for Risk of First AMI With Increasing LDL-C Levels Among Asian Subjects

Increasing LDL-C levels are associated with progressively increasing odds of a first AMI among Asian subjects. \*OR adjusted for age and sex. For conversion of LDL-C levels into mmol/l, multiply by 0.0259. AMI = acute myocardial infarction; CI = confidence interval; LDL-C = low-density lipoprotein cholesterol; OR = odds ratio.

The reasons for low LDL-C levels among Asians are unknown. Lower levels of LDL-C and other lipid fractions might simply be a function of lower body mass. Indeed, a survey of Japanese men and women indicated that at the lower end of the body mass index spectrum, serum cholesterol levels were much lower than in the average Western population, but as body mass index increased toward the Western average, so did the lipid levels (21). In our analysis,

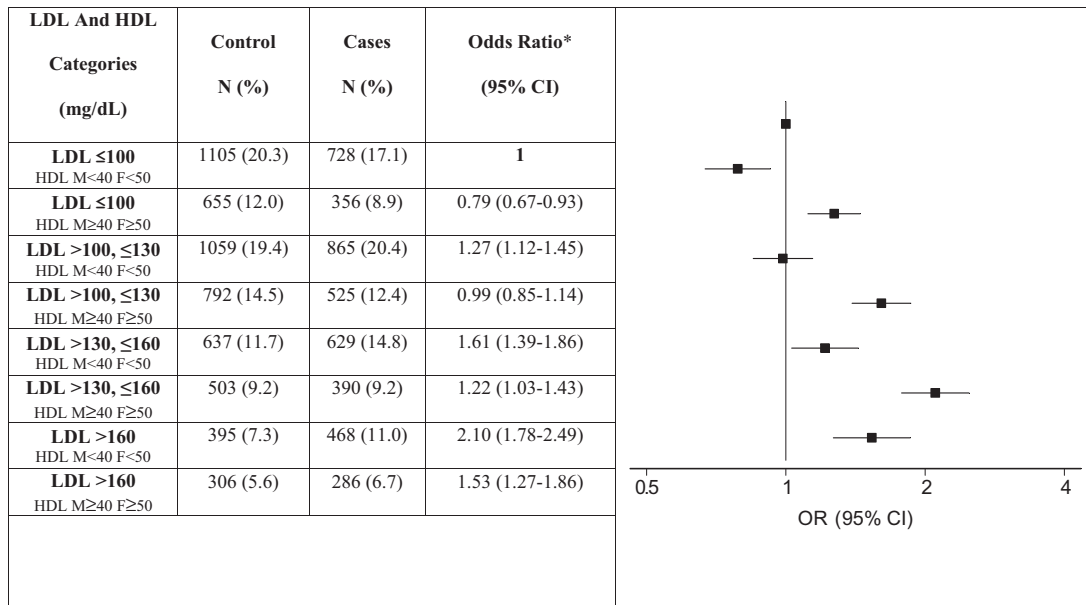
however, LDL-C levels among Asians remained lower even after adjustment for waist-hip ratio and body mass index.

Although the LDL-C levels in our study (which were calculated using the Friedwald formula) could be artifactually lower by the elevated TG levels because of a nonfasting state, this is unlikely to be a major confounder for 2 reasons. First, separate analyses of patients who had their last meal more than 8 h before blood sampling (which approximates



**Figure 3** ORs for Risk of First AMI With Increasing HDL-C Levels Among Asian Subjects

Increasing HDL-C levels are associated with a progressive decrease in the odds of a first AMI among Asian subjects. \*ORs adjusted for age and sex. For conversion of HDL-C levels into mmol/l, multiply by 0.0259. HDL-C = high-density lipoprotein cholesterol; other abbreviations as in Figure 2.



**Figure 4** ORs for Risk of First AMI in Different LDL-C Categories Adjusted to HDL-C Levels Among Asian Subjects

For any given LDL-C category, a normal or high HDL-C level is associated with a lower odds of a first AMI. \*ORs adjusted for age and sex. For conversion of LDL-C and HDL-C levels into mmol/l, multiply by 0.0259. F = female; M = male; other abbreviations as in Figures 1 and 2.

an overnight fast) indicates results that were consistent with the overall analysis. Second, the overall mean TG levels in our study were not elevated (and in some subgroups, were actually lower) compared with previous studies among Asians.

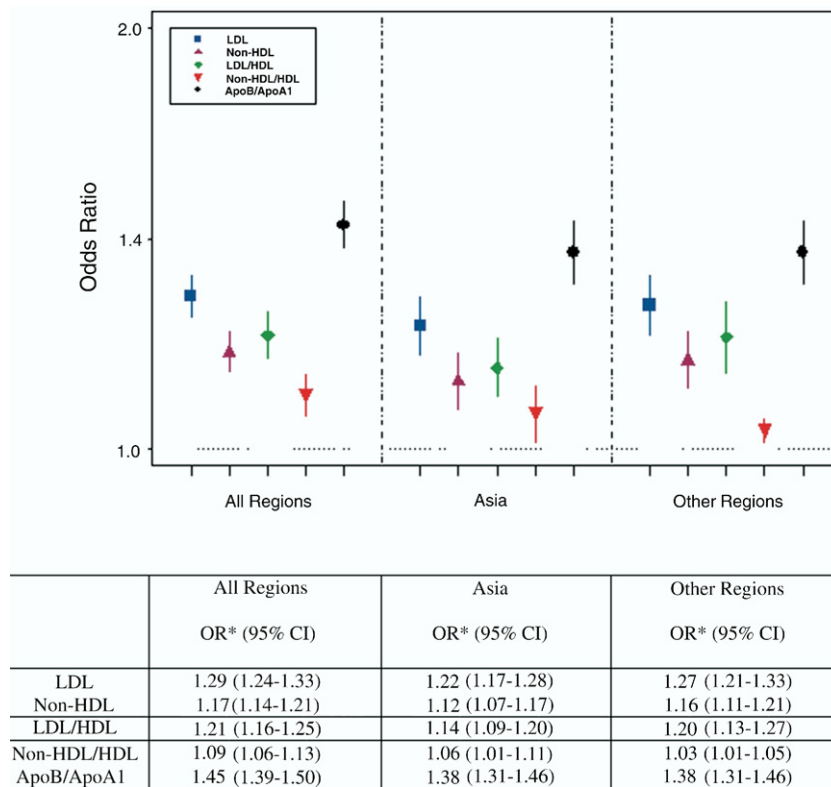
Despite the lower absolute levels, however, the risk of AMI was proportionately higher with higher LDL-C, with similar patterns in all of the Asian subgroups. The magnitude of risk increase associated with a 1-SD increase in LDL-C levels in our study is consistent with the increase in risk (hazard ratio: 1.35) of coronary heart disease-related death observed in the Asia-Pacific cohort study (8). This implies that, for a given LDL-C level, the risk of AMI may be higher among Asians compared with non-Asian populations. This finding has been a recurring theme in studies involving South Asians (2,5,19,20). This difference in atherogenicity of LDL-C in this population has been attributed to differences in particle size and density, with smaller and denser particles being more atherogenic (22). Indeed, studies among Asian Indians have shown a higher prevalence of small, dense LDL-C particles in this population compared with Caucasians (23). We did not estimate LDL-C particle size among our patients. Moreover, whether this explanation can be extrapolated to the other ethnically distinct Asian populations is not clear.

**ApoB levels among Asians.** Subjects from China and Hong Kong had the lowest ApoB levels, accounting for the lower mean levels among Asians compared with people from other regions of the world. The low ApoB

levels paralleled the low LDL-C levels in this population (Table 1, Fig. 1) On the other hand, among South Asians, who had LDL-C levels that were similar to the Chinese, ApoB levels were much higher, presumably indicating a larger atherogenic particle load and possibly smaller LDL-C particle size (Fig. 1).

**HDL-C and ApoA1 levels among Asians.** South Asians had HDL-C levels that were on average 10 mg/dl lower than those in the rest of the Asian population and other non-Asian groups. This was accompanied by lower ApoA1 levels. This predilection of South Asians to have lower HDL-C levels is well known (2), and has been attributed to the higher prevalence of insulin resistance and related metabolic abnormalities, which may be the consequence of a combination of genetic predisposition, physical inactivity, and a high-carbohydrate diet (2,9,10). By contrast, among other Asian subgroups, HDL-C levels were higher and similar to levels in non-Asians. Polymorphisms of the genes regulating cholesteryl ester transfer protein (CETP) are also known to affect HDL-C levels. But the interplay of these polymorphisms, HDL-C levels, and CVD risk among Asians is poorly understood (24).

Higher levels of HDL-C were associated with equivalent protection from AMI in Asians and non-Asians. However, among South Asians, we observed a nonsignificant tendency toward weaker protection afforded by normal or high levels of HDL-C. Other investigators have shown a similar lack of protective effect of HDL-C among Asian Indians. In a community-based cross-sectional study correlating risk factors with carotid



**Figure 5** Risk of First AMI for 1-SD Change in the Various Lipid and Apo Parameters and Ratios

Comparison of the odds of a first AMI with 1 SD change in the levels of LDL-C, non-HDL-C, the LDL-C to HDL-C ratio, the non-HDL-C to HDL-C ratio, and the ApoB to ApoA1 ratio. The ApoB to ApoA1 ratio was associated with the greatest increase in the odds of an AMI. \*ORs adjusted for age, sex, smoking, diabetes, hypertension, abdominal obesity, fruit and vegetable intake, exercise, alcohol consumption, and psychosocial index. Abbreviations as in Figures 1, 2, and 4.

intima-media thickness, higher HDL-C levels were not associated with lower intima-media thickness among Indians, as was observed in a comparator (Caucasian) population (25). Differences in the prevalence of the various HDL-C subfractions may account for some of these differences in CVD risk. At any given HDL-C level, Asian Indians have a higher prevalence of small HDL-C particles compared with Caucasians (26). Studies have suggested that smaller HDL-C particles have lower free cholesterol content, may be markers of impaired reverse cholesterol transport, and are associated with the presence of coronary artery disease (27). Interestingly, higher HDL-C levels were accompanied by lower absolute ApoA1 levels among South Asians when compared with other Asian populations (Fig. 1B). This could account for some of the lack of benefit observed with high HDL-C levels in this population. Higher ApoA1 levels, on the other hand, were just as protective among South Asians as in the overall Asian population, suggesting that it might be a better marker of AMI risk than HDL-C in this subgroup.

**TG levels among Asians.** The TG levels were lower among Asians by about 15 mg/dl when compared with the

rest of the INTERHEART population. However, most of this difference was caused by the low TG levels in China and Hong Kong. South Asians and Southeast Asians had TG levels similar to other non-Asian populations. The Asian cohort of the Asia-Pacific cohort studies (comprising a large number of Chinese subjects) also found a similar, low mean TG level (28).

**Risk of AMI by lipid and Apo fractions.** As in the rest of the INTERHEART population, the ApoB/ApoA1 ratio showed the strongest association with the risk of AMI among Asians. The stronger association is thought primarily to be caused by the ability of the ApoB/ApoA1 ratio to account for all of the atherogenic particles in plasma. Each atherogenic lipoprotein particle contains 1 molecule of ApoB; therefore, plasma ApoB best estimates the total atherogenic particle number. LDL-C accounts for the vast majority of atherogenic particles and therefore has been the fundamental index of atherogenic risk. However, when small, dense, cholesterol-depleted LDL-C particles are common, as is presumably the case among some Asian subgroups, LDL-C levels underestimate the atherogenic particle number. Further, ApoB is also present in other atherogenic lipid fractions such as very-low-density and



intermediate-density lipoproteins, which again may be present in higher concentrations in these populations and is not represented in the LDL-C measure (29). The LDL-C/HDL-C ratio was not better than LDL-C alone in predicting risk for the same reasons. Non-HDL-C has often been used as a surrogate measure of circulating atherogenic lipoproteins. However, similar to some previous reports (14), we found that neither the increases in non-HDL-C nor the increases in the non-HDL-C/HDL-C ratio were as strongly associated with the risk of AMI as the ApoB/ApoA1 ratio.

The TG/HDL-C ratio was even less discriminatory. An earlier study indicated that the TG/HDL-C ratio might be one of the best predictors of coronary artery disease-related death (8). However, this study also showed that TG levels were independent predictors of risk. We were, however, unable to show that TG or any of the TG-related ratios predicted AMI risk.

**Study strengths and limitations.** The principal strengths of our study are the large number of cases studied and the geographic and ethnic diversity within Asians represented in our study population. The large number of cases from several subgroups of Asians provides statistical power to explore the strength of association of closely related lipid parameters with the occurrence of a first AMI. However, we have refrained from performing too many subgroup analyses so as to avoid potentially spurious associations, and have been careful not to draw conclusions based on subgroups (e.g., the Japanese) with small numbers of subjects. We have also, for the first time, studied the association of lipoprotein fractions to AMI risk among Asian subjects. However, one important limitation of our analysis needs to be highlighted. Blood samples in the INTERHEART study were not fasting samples. However, measurements of ApoB and ApoA1 are recognized as being relatively unaffected by the nonfasting state. Also, total cholesterol and HDL-C change little after a meal. For the analysis of association of TG levels to the risk of AMI, we included only those samples that were obtained at least 8 h after the last meal. Acute myocardial infarction itself can alter serum lipid levels, but these changes occur after 48 h (30) and are not likely to affect the findings of our study because blood samples were drawn within 24 h of symptom onset in 87.3% of our AMI patients and within 48 h in 95.7% of them. Finally, although the case-control design of our study may introduce some potential biases, we minimized this risk by careful selection of control subjects, by using standardized methods of data collection for both cases and control subjects, and by only enrolling cases with a first AMI. Cases with a first AMI are less likely to have altered their lifestyle and diet before this event, thus ensuring lipid levels that might be reasonably representative of this population. Moreover, only 5.2% of cases and 2.2% of control subjects were on lipid-lowering medications at the time of enrollment.

## Conclusions and Clinical Implications

Despite a higher prevalence of low LDL-C levels among Asians, the association of LDL-C levels with the risk of AMI was preserved. Overall, changes in levels of HDL-C were associated with changes in risk of AMI, which were similar across all regions of the world. Among South Asians, there was a preponderance of people with low HDL-C levels, and changes in ApoA1 levels were better determinants of risk than changes in HDL-C levels. Of the various markers evaluated, the ApoB/ApoA1 ratio had the strongest association with the risk of a first AMI. Studies relating the particle size of HDL-C and LDL-C and their subtypes may further refine risk predictions. Although Asian patients are likely to benefit from lowering LDL-C, the threshold for treatment initiation and the treatment targets are conceivably lower than for Caucasians. These thresholds and targets need to be determined in future studies. Finally, given the lower levels of HDL-C among South Asians, approaches to increasing HDL-C may also be beneficial in this population.

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**Key Words:** lipids ■ lipoproteins ■ myocardial infarction.

 **APPENDIX**

**For further details regarding the study subjects and methods, please see the online version of this article.**