Isolated Low Levels of High-Density Lipoprotein Cholesterol Are Associated With an Increased Risk of Coronary Heart Disease: An Individual Participant Data Meta-Analysis of 23 Studies in the Asia-Pacific Region

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Isolated Low Levels of High-Density Lipoprotein Cholesterol Are Associated With an Increased Risk of Coronary Heart Disease

An Individual Participant Data Meta-Analysis of 23 Studies in the Asia-Pacific Region

Rachel R. Huxley, DPhil; Federica Barzi, PhD; Tai Hing Lam, MD; Sebastien Czernichow, PhD; Xianghua Fang, PhD; Tim Welborn, PhD; Jonathan Shaw, MD; Hirotsugu Ueshima, MD; Paul Zimmet, PhD; Sun Ha Jee, PhD; Jeetesh V. Patel, MD; Ian Caterson, PhD; Vlado Perkovic, PhD; Mark Woodward, PhD; for the Asia Pacific Cohort Studies Collaboration and the Obesity in Asia Collaboration

Background—Previous studies have suggested that there is a novel dyslipidemic profile consisting of isolated low high-density lipoprotein cholesterol (HDL-C) level that is associated with increased risk of coronary heart disease, and that this trait may be especially prevalent in Asian populations.

Methods and Results—Individual participant data from 220 060 participants (87% Asian) in 37 studies from the Asia-Pacific region were included. Low HDL-C (HDL <1.03 mmol/L in men and <1.30 mmol/L in women) was seen among 33.1% (95% confidence interval [CI], 32.9–33.3) of Asians versus 27.0% (95% CI, 26.5–27.5) of non-Asians ($P<0.001$). The prevalence of low HDL-C in the absence of other lipid abnormalities (isolated low HDL-C) was higher in Asians compared with non-Asians: 22.4% (95% CI, 22.2–22.5) versus 14.5% (95% CI, 14.1–14.9), respectively ($P<0.001$). During 6.8 years of follow-up, there were 574 coronary heart disease and 739 stroke events. There was an inverse relationship between low HDL-C with coronary heart disease in all individuals (hazard ratio, 1.57; 95% CI, 1.31–1.87). In Asians, isolated low levels of HDL-C were as strongly associated with coronary heart disease risk as low levels of HDL-C combined with other lipid abnormalities (hazard ratio, 1.67 [95% CI, 1.27–2.19] versus 1.63 [95% CI, 1.24–2.15], respectively). There was no association between low HDL-C and stroke risk in this population (hazard ratio, 0.95 [95% CI, 0.78 to 1.17] with nonisolated low HDL-C and 0.81 [95% CI, 0.67–1.00] with isolated low HDL-C).

Conclusion—Isolated low HDL-C is a novel lipid phenotype that appears to be more prevalent among Asian populations, in whom it is associated with increased coronary risk. Further investigation into this type of dyslipidemia is warranted. **(*Circulation*. 2011;124:2056-2064.)**

Key Words: cardiovascular diseases ■ cholesterol ■ epidemiology

The direct but opposing relationships of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) with coronary heart disease (CHD) risk are well characterized in many populations.[1–3] There is also increasing recognition of the importance of HDL-C in determining coronary risk independently of LDL-C levels.[4,5] Moreover, some studies suggest that isolated low HDL-C, a condition that describes the coexistence of low HDL-C in

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From the George Institute (R.R.H., F.B., S.C., V.P., M.W.) and Boden Institute, Sydney Medical School (I.C.), University of Sydney, Sydney, Australia; Division of Epidemiology and Community Health, University of Minnesota, Minneapolis (R.R.H.); University of Hong Kong, School of Public Health/Department of Community Medicine, Hong Kong (T.H.L.); Department of Nutrition, Ambroise Paré Hospital and University of Versailles Saint Quentin en Yvelines, Boulogne-Billancourt, France (S.C.); Department of Epidemiology and Social Medicine, Xuanwu Hospital, Capital Medical University, Beijing, China (X.F.); Department of Endocrinology and Diabetes, Sir Charles Gairdner Hospital, Nedlands, Western Australia (T.W.); Baker IDI Heart and Diabetes Institute, Melbourne, Victoria, Australia (J.S., P.Z.); Department of Health Science, Shiga University of Medical Science, Shiga, Japan (H.U.); Institute for Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, Korea (S.J.H.); Sandwell Medical Research Unit, Sandwell and West Birmingham Hospitals NHS Trust, West Bromwich, UK (J.V.P.); and Department of Epidemiology, Johns Hopkins University, Baltimore, MD (M.W.).

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Correspondence to Rachel Huxley, DPhil, Division of Epidemiology and Community Health, University of Minnesota School of Public Health, 1300 S Second St, Ste 300, Minneapolis, MN 55454. E-mail rhuxley@umn.edu

conjunction with normal LDL-C and triglyceride levels, has a coronary risk equivalent to that of elevated LDL-C.[6–8]

Clinical Perspective on p 2064

Survey data suggest that the prevalence of low HDL-C, either in isolation or in conjunction with abnormal LDL-C or triglyceride levels, differs substantially between countries and ethnic groups, and published values for the prevalence of isolated low HDL-C range from 6% to 34%.[6,9–11] However, individuals with this lipid phenotype are unlikely to be considered for pharmacotherapy partly because their LDL-C and total cholesterol levels fall within current guidelines, and partly because there is insufficient randomized evidence unequivocally demonstrating that raising HDL-C levels reduces cardiovascular risk.[12]

Here, we determine whether isolated low HDL-C is a form of dyslipidemia that occurs more frequently in Asian populations using data from 2 large-scale collaborations of prospective cohorts and cross-sectional studies from the Asia-Pacific region, namely the Asia Pacific Cohort Studies Collaboration (APCSC) and the Obesity in Asia Collaboration (OAC). We also examine whether isolated low HDL-C is independently associated with increased risk of CHD and stroke and if there is a particular phenotype associated with low HDL-C based on routinely measured clinical characteristics.

Methods

Asia Pacific Cohort Studies Collaboration

Details of APCSC, including study identification, data collection, and event verification, are given elsewhere.[13,14] All studies included in APCSC were conducted prospectively in populations from the Asia-Pacific region, had at least 5000 person-years of follow-up, and recorded age, sex, and blood pressure (BP) at baseline, as well as vital status at the end of the follow-up. Lipid measurements were determined with serum samples, which were obtained while fasting in ≈93% of participants. Information regarding the method of cholesterol analysis was available for ≈70% of all participants, of whom 96% used enzymatic methods. Most studies additionally recorded current smoking status (current/not current) at baseline. BP was measured at rest in the seated position with a standard mercury sphygmomanometer in most studies.

Obesity in Asia Collaboration

Details of OAC, including study identification, data collection, and event verification, are given elsewhere.[15,16] Studies were eligible if they contained information on age, sex, weight, height, waist circumference, hip circumference, fasting plasma glucose, and BP and measures on at least 1 lipid variable (total cholesterol, HDL-C, LDL-C, or triglycerides).

All of the included studies from both the APCSC and OAC were classified as Asian if study members were recruited from mainland China, Hong Kong, India, Japan, Korea, the Philippines, Singapore, South Korea, Taiwan, or Thailand; they were classified as Australia/New Zealand if participants were drawn from Australia or New Zealand. This classification largely represented a split by ethnicity into Asians and non-Asians.

Statistical Methods

Participants without information on lipids were excluded from these analyses. When not measured directly, LDL-C was calculated from the Friedewald formula in samples in which triglyceride levels were <400 mg/dL.[17] National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) guidelines were used to identify people with low values of HDL-C (<1.03 mmol/L in men, <1.30 mmol/L in women), high values of LDL-C (≥4.14 mmol/L), and high values of triglycerides (>2.26 mmol/L).[18] These guidelines were chosen to facilitate comparisons with previous work. Venn diagrams were constructed to illustrate the frequency of different forms of dyslipidemia within Asians and non-Asians. Because cigarette smoking is negatively associated with HDL-C levels, the frequency of lipid abnormalities was also examined by smoking status separately within Asia and Australia/New Zealand.

The outcomes analyzed in this study were fatal or nonfatal CHD (*International Classification of Disease* codes 410, 411, 412, 413, 414, and 798) and stroke (codes 430–438). Fatal CHD and stroke events were recorded in 37 studies from the APCSC using a variety of methods, most often through death registrations or personal contact with subjects or relatives. Nonfatal events were recorded in 8 studies through hospital records or personal contact. The median follow-up was 6.6 years in Asia and 8.3 years in non-Asian countries.

Individuals were divided into 3 mutually exclusive groups according to lipid levels: normal HDL-C, isolated low HDL-C, and nonisolated low HDL-C (ie, low HDL-C combined with elevated LDL-C and/or triglycerides). Differences in the distribution of BP and anthropometry across these groups were assessed with general linear models, and differences in the percentages of smoking and diabetes mellitus were assessed with logistic regression models. All models accounted for the confounding effects of age and study. Hazard ratios (HRs) for CHD and stroke events were calculated with Cox proportional hazard models, with corresponding 95% confidence intervals (CIs) derived with floating absolute risks and taking those with normal HDL-C as the reference group. The continuous relationships between HDL-C and cardiovascular outcomes are described in detail elsewhere.[4] In the main analysis, Cox models were adjusted by age, systolic BP, and current smoking and stratified by study and sex. A sensitivity analysis was performed comparing current smokers with not-current smokers separately within Asia and Australia/New Zealand in models adjusted for age and systolic BP and stratified by study and sex. In a subgroup of the population (n=64 310), information on alcohol consumption at study baseline was available (yes/no); among this group, the models were rerun stratifying by alcohol status. In secondary analyses, we examined the relationships with cardiovascular outcomes when low HDL-C level was defined according to the modified World Health Organization (WHO) guidelines (<1.0 mmol/L in men and <0.9 mmol/L in women) and the European Group for Insulin Resistance (EGIR) guidelines (<1.0 mmol/L).[19]

All analyses were conducted with SAS version 9.1 (SAS Institute, Inc, Cary, NC).

Results

Information was available on 69 145 eligible study participants from 24 studies from the APCSC (Table 1) and 150 915 from 13 studies in the OAC (Table 2). Overall, 87% of men and 86% of women were from Asia. The overall mean levels of cardiovascular risk factors for Asians and non-Asians are summarized in Table 3.

In the Asian cohorts, one third (33%) displayed low levels of HDL-C (n=63 316), and two thirds of these individuals (22% overall) had isolated levels of low HDL-C (Figure 1A). These estimates were comparable in current (Figure Ia in the online-only Data Supplement) and not-current (Figure Ib in the online-only Data Supplement) smokers. High levels of LDL-C either with or without other colipid abnormalities occurred in 13% of the population. When examined by country, the frequency of low HDL-C varied between one quarter and one third of the study population, with the notable exceptions of Singapore and India, where >50% of the

Table 1. Baseline Study Characteristics of Contributing Studies From the Asia Pacific Cohort Studies Collaboration

Cohort	Country	n	Age, y	TC, mmol/L	TG, mmol/L	HDL-C, mmol/L	LDL-C, mmol/L	BMI, kg/m^2	SBP, mm Hg	Smoking, %	Diabetes Mellitus, %	WC, cm	Hip Circumference, cm	Obesity,* %
ALSA	Australia	1121	78 (6)	5.8 (1.1)	1.5 (0.7)	1.3 (0.4)	3.8 (1.0)	25.7 (3.9)	149 (22)	8.3	7.1	. . .	. . .	13.0
ANHF	Australia	8924	43 (13)	5.5 (1.1)	1.4 (0.7)	1.3 (0.4)	3.5 (1.0)	25.3 (4.2)	126 (18)	23.8	1.7	83 (13)	100 (9)	12.2
Busselton	Australia	1585	44 (17)	5.7 (1.2)	1.2 (0.7)	1.5 (0.4)	3.6 (1.1)	24.6 (3.7)	129 (20)	24.0	7.3	. . .	. . .	8.0
Perth	Australia	5826	45 (13)	5.6 (1.1)	1.2 (0.7)	1.4 (0.4)	3.7 (1.0)	25.5 (4.2)	130 (21)	25.4	2.5	. . .	. . .	13.2
Aito town	Japan	893	52 (7)	4.7 (0.8)	1.3 (0.4)	1.4 (0.4)	2.6 (0.8)	22.6 (3.0)	139 (20)	30.8	1.7	. . .	. . .	4.5
Akabane	Japan	1819	54 (8)	5.0 (0.9)	1.2 (0.7)	1.2 (0.3)	3.2 (0.8)	22.5 (3.0)	125 (19)	27.8	2.4	. . .	. . .	4.1
Anzhen02	China	4078	47 (8)	4.7 (0.9)	1.2 (0.7)	1.4 (0.4)	2.7 (0.8)	24.0 (3.3)	122 (18)	20.6	10.7	80 (9)	97 (7)	11.1
Beijing Aging	China	1675	69 (8)	4.4 (1.0)	1.5 (0.8)	1.5 (0.6)	3.0 (1.0)	23.3 (3.9)	141 (25)	30.6	29.4	. . .	. . .	11.4
CISC	China	164	45 (9)	5.0 (0.8)	0.7 (0.6)	1.1 (0.3)	2.8 (1.2)	22.9 (2.7)	123 (20)	73.6		. . .	. . .	4.3
Civil Service Workers	Japan	8910	47 (5)	5.2 (0.9)	1.4 (0.8)	1.4 (0.4)	3.1 (0.8)	22.4 (2.7)	125 (18)	37.8	1.7	. . .	. . .	3.0
CVDFACTS	China	460	45 (16)	4.8 (1.0)	1.2 (0.7)	1.3 (0.4)	3.0 (0.9)	23.2 (3.4)	113 (19)	22.4	3.0	. . .	. . .	8.1
EGAT	Thailand	3390	43 (5)	5.7 (1.1)	1.6 (0.8)	1.2 (0.3)	3.8 (1.0)	23.0 (3.1)	120 (16)	43.0	2.5	. . .	. . .	6.6
Fangshan	China	774	47 (9)	4.6 (1.0)	1.5 (0.7)	1.4 (0.4)	2.5 (0.9)	24.9 (3.6)	132 (25)	38.4	6.3	. . .	. . .	18.9
Guangzhou Occupational	China	9106	43 (6)	5.2 (1.0)	1.4 (0.7)	1.3 (0.5)	3.3 (1.1)	22.6 (3.3)	113 (15)	44.4	7.9	. . .	. . .	7.6
Hong Kong	Hong Kong	183	79 (7)	5.2 (0.9)	1.6 (1.0)	1.5 (0.5)	3.0 (0.8)	22.0 (3.6)	148 (22)	16.9	10.4	81 (10)	91 (8)	7.3
Huashan	China	1744	53 (12)	4.6 (0.9)	1.4 (0.7)	1.4 (0.4)	2.6 (0.8)	23.3 (3.4)	126 (21)	. . .	10.6	. . .	. . .	8.6
Konan	Japan	1206	52 (16)	4.9 (0.9)	1.1 (0.6)	1.6 (0.4)	2.8 (0.8)	21.9 (3.0)	130 (19)	29.7	12.6	. . .	. . .	3.2
Miyama	Japan	404	59 (9)	5.1 (0.9)	1.2 (0.6)	1.3 (0.3)	3.2 (0.8)	22.3 (3.0)	129 (23)	23.6	2.2	. . .	. . .	4.2
Ohasama	Japan	1869	58 (11)	5.0 (0.9)	1.5 (0.8)	1.4 (0.4)	2.9 (0.8)	23.2 (3.1)	127 (17)	20.1	9.2	. . .	. . .	7.3
Seven Cities Cohorts	China	6050	58 (10)	4.9 (1.3)	1.6 (0.7)	1.5 (0.5)	2.7 (1.3)	22.9 (3.8)	134 (25)	33.9	1.6	. . .	. . .	9.9
Shigaraki Town	Japan	3678	57 (14)	5.0 (0.9)	1.4 (0.7)	1.5 (0.4)	2.9 (0.8)	22.5 (3.1)	132 (20)	28.5	7.1	. . .	. . .	4.8
Singapore Heart	Singapore	2063	41 (13	5.8 (1.1)	1.3 (0.8)	1.0 (0.3)	4.2 (1.0)	23.5 (4.4)	123 (21)	20.8	10.9	. . .	. . .	15.4
Singapore NHS92	Singapore	3223	39 (12)	5.3 (1.0)	1.3 (0.8)	1.3 (0.3)	3.5 (0.9)	23.2 (4.2)	118 (18)	18.0	9.1	. . .	. . .	11.6

TC indicates total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; SBP, systolic blood pressure; WC, waist circumference; ALSA, Australian Longitudinal Study of Aging; ANHF, Australian National Heart Foundation; CISC, Capital Iron and Steel Company; CVDFACTS, The Cardiovascular Disease Risk Factors Two-Townships Study; NHS92, National Health Survey 1992; and EGAT, Electricity Generating Authority of Thailand. Ellipses indicate missing data. Values are mean (SD) unless otherwise specified.

*Obesity was defined as body mass index $\geq$30 kg/m^2 in non-Asians and $\geq$28 kg/m^2 in Asians.

population was affected (Table I in the online-only Data Supplement).

In non-Asians, 27% of individuals (n=7754) had low levels of HDL-C either with or without associated colipid abnormalities. Isolated low HDL-C occurred in half of these individuals (n=4021, 14% of non-Asians; Figure 1B). These estimates were similar in current and not-current smokers (Figure IIa and IIb in the online-only Data Supplement,

Table 2. Baseline Study Characteristics of Contributing Studies From the Obesity in Asia Collaboration

Cohort	Country	n	Age, y	TC, mmol/L	TG, mmol/L	HDL-C, mmol/L	LDL-C, mmol/L	BMI, kg/m^2	SBP, mm Hg	Smoking, %	Diabetes Mellitus, %	WC, cm	Hip Circumference, cm	Obesity, %
AUSDIAB	Australia	10 991	52 (15)	5.6 (1.0)	1.5 (0.8)	1.4 (0.4)	3.5 (0.9)	26.9 (4.9)	129 (19)	15.6	5.1	91 (14)	105 (10)	21.7
China (Zhou)	China	43 209	49 (12)	4.7 (1.0)	1.3 (0.7)	1.4 (0.4)	2.7 (0.9)	23.7 (3.6)	126 (22)	29.0	4.8	79 (10)	94 (8)	11.3
EGAT2	Thailand	2746	43 (5)	6.1 (1.1)	1.6 (0.8)	1.5 (0.4)	3.9 (1.1)	23.8 (3.6)	123 (21)	25.8	4.0	84 (10)	96 (7)	11.4
HK (Lam)	Hong Kong	1499	37 (9)	5.1 (0.9)	1.1 (0.8)	1.4 (0.4)	3.3 (0.9)	23.3 (3.2)	118 (15)	14.5	2.3	78 (9)	93 (6)	7.3
India (Mohan)	India	2422	41 (7)	4.6 (1.1)	1.6 (0.8)	1.0 (0.3)	3.0 (1.1)	23.9 (3.6)	121 (13)	31.7	9.9	87 (10)	90 (7)	11.2
India (Mohan)	India	619	48 (9)	5.3 (1.0)	1.5 (1.0)	1.3 (0.4)	3.3 (0.9)	27.0 (4.6)	119 (15)	4.4	2.4	87 (12)	99 (10)	34.0
India (Mohan)	India	2300	40 (13)	4.6 (1.0)	1.3 (0.7)	1.1 (0.3)	2.9 (0.8)	22.8 (4.0)	119 (18)	18.5	8.4	83 (11)	94 (9)	8.8
India (Mohan)	India	4115	47 (9)	4.8 (1.0)	1.7 (0.7)	1.1 (0.2)	3.0 (0.9)	23.3 (4.9)	119 (20)	20.2	8.5	81 (13)	90 (11)	16.3
India (Lear)	India	299	39 (13)	4.4 (1.0)	1.2 (0.7)	1.4 (0.3)	2.5 (0.9)	24.9 (4.3)	114 (14)	5.7	1.4	81 (11)	99 (9)	16.8
India (Patel)	India	271	50 (14)	4.9 (1.0)	1.0 (0.5)	1.2 (0.3)	3.3 (0.9)	21.0 (3.9)	116 (22)	. . .	7.8	76 (12)	92 (8)	4.8
INTERASIA	Thailand	4876	54 (12)	5.4 (1.2)	1.6 (0.8)	1.2 (0.3)	3.5 (1.1)	24.2 (4.4)	122 (20)	20.9	9.4	82 (12)	94 (9)	17.4
KNHANES	Korea	7944	45 (16)	4.9 (1.0)	1.4 (0.7)	1.3 (0.3)	2.9 (0.9)	23.2 (3.2)	126 (20)	. . .	9.1	80 (9)	93 (7)	7.1
Taiwan	Taiwan	69 624	43 (14)	5.2 (1.0)	1.3 (0.7)	1.3 (0.4)	3.3 (0.8)	23.1 (3.4)	128 (23)	. . .	3.6	77 (10)	94 (6)	7.9

TC indicates total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; SBP, systolic blood pressure; WC, waist circumference; AUSDIAB, Australian Diabetes Obesity and Lifestyle Study; EGAT2, Electricity Generating Authority of Thailand 2; INTERASIA, International Collaborative Study of Cardiovascular Disease in Asia; and KNHANES, Korean National Health and Nutrition Examination Survey. Ellipses indicate missing data. Values are mean (SD) unless specified otherwise.

Table 3. Summary of the Baseline Characteristics of the Overall Study Participants From the Asia Pacific Cohort Studies Collaboration and the Obesity in Asia Collaboration

	Men			Women		
		Mean (SD)			Mean (SD)	
Variable	n	Asian	Non-Asian	n	Asian	Non-Asian
Age, y	108 455	46.7 (12.7)	48.5 (15.6)	111 605	46.4 (13.2)	48.1 (15.2)
Total cholesterol, mmol/L	108 455	5.05 (1.03)	5.56 (1.04)	111 605	5.02 (1.03)	5.59 (1.11)
Triglycerides, mmol/L	108 455	1.48 (0.78)	1.51 (0.81)	111 605	1.24 (0.69)	1.26 (0.70)
HDL-C, mmol/L	108 455	1.24 (0.37)	1.24 (0.32)	111 605	1.43 (0.38)	1.53 (0.38)
LDL-C, mmol/L	108 455	3.13 (0.98)	3.64 (0.94)	111 605	3.05 (0.95)	3.49 (0.98)
Body mass index, kg/m^2	103 789	23.4 (3.31)	26.3 (3.81)	108 480	23.1 (3.76)	25.7 (5.07)
Waist circumference, cm	65 906	82.5 (9.5)	93.8 (11.5)	71 580	74.5 (9.8)	81.4 (13.1)
SBP, mm Hg	76 152	125.9 (19.5)	132.1 (18.2)	76 207	123.5 (22.0)	125.8 (20.4)
DBP, mm Hg	76 171	78.7 (12.0)	79.4 (10.9)	76 209	75.9 (11.9)	72.1 (11.1)
Smoking, %	65 803	50.4	23.3	63 154	6.9	17.5
Diabetes mellitus, %	103 903	5.6	4.4	108 705	4.9	4.6

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; and DBP, diastolic blood pressure.

respectively). Overall, the frequency of high LDL-C was twice as high in Asian as in non-Asian populations (26.1% [95% CI, 25.6–26.6] versus 13.4% [95% CI, 13.3–13.6]; $P<0.001$; Figure 2B), whereas the frequency of elevated triglycerides was comparable between non-Asians and Asians (12.6% [95% CI, 12.2–13.0] versus 11.6% [95% CI, 11.5–11.8], respectively, although the *P* for the regional difference was <0.0001 because of the large sample size).

Table 4 shows the mean phenotypic characteristics of individuals with nonisolated low HDL-C, isolated low HDL-C, and normal levels of HDL-C. Overall, low HDL-C levels were more associated with higher values of body mass index and waist circumference and a higher frequency of diabetes mellitus compared with normal levels of HDL-C, regardless of sex and region. There were no consistent associations between BP and smoking status with HDL-C levels within the sex and region groups.

During a median follow-up of 6.8 years, there were 574 fatal and nonfatal CHD events (42% Asia) and 739 fatal and nonfatal stroke events (76% Asia). Of these, there were 253 ischemic and 186 hemorrhagic strokes (the remainder were unclassified). In adjusted analyses, nonisolated low levels of HDL-C were associated with a nearly 60% higher risk of CHD compared with normal levels of HDL-C (HR, 1.57; 95% CI, 1.31–1.87). This association was observed in all individuals regardless of sex, region, and smoking status (Figure 2). This estimate did not differ materially when either the WHO or EGIR cut points for HDL-C were used (Table IIa and IIb in the online-only Data Supplement). In the subgroup for whom information was available on alcohol consumption at study baseline (yes/no), there was no evidence of interaction in the association between low levels of HDL-C with subsequent CHD (HR, 1.55 [95% CI, 1.18–2.04] in current drinkers versus 1.59 [95% CI, 1.26–2.00] in nondrinkers;

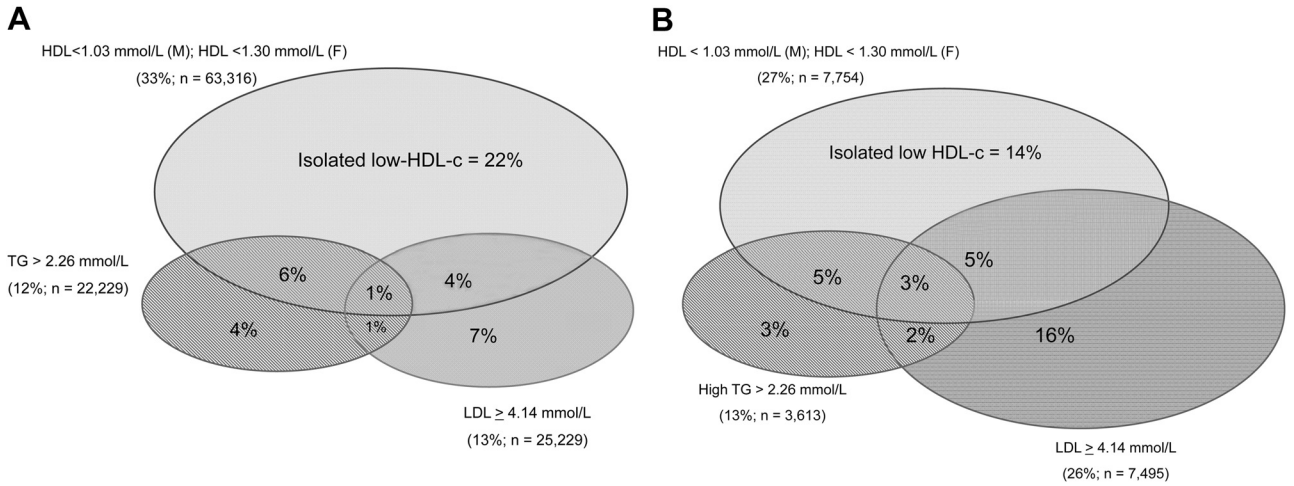

Figure 1. A and **B**, Prevalence of lipid phenotypes in adult Asian populations (**A**; n=191 317) and adult populations from Australia and New Zealand (**B**; n=28 743). HDL indicates high-density lipoprotein; HDL-C, HDL cholesterol; LDL, low-density lipoprotein; and TG, triglycerides.

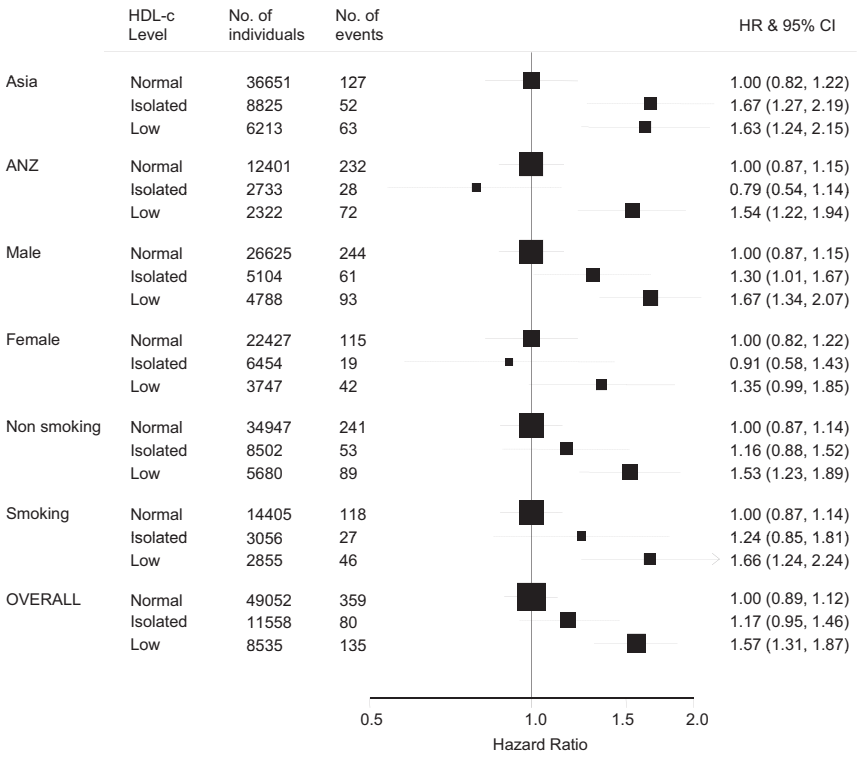

Figure 2. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for coronary heart disease associated with high-density lipoprotein cholesterol levels (HDL-C) by region (Asia vs Australia/New Zealand [ANZ]), sex, and smoking status (current vs not) from studies included in the Asia Pacific Cohort Studies Collaboration. Normal HDL-C means normal levels of HDL-C; isolated, isolated low levels of HDL-C; and low, low levels of HDL-C and high LDL-C and/or high triglycerides. The 3 groups are mutually exclusive. *P* for regional, sex, and smoking interaction=0.016, 0.04, and 0.95, respectively.

P=0.99). For purposes of comparison, the risk of CHD associated with LDL-C level was also determined. In this population, the risk of CHD was nearly 60% higher in those with high levels of LDL-C compared with those with normal levels of LDL-C (HR, 1.58; 95% CI, 1.30–1.93).

There was some evidence that isolated low HDL-C increased the risk of incurring a CHD event compared with normal HDL-C, although the relationship was nonsignificant (HR, 1.17; 95% CI, 0.95–1.46). This estimate did not alter materially when the EGIR cut points were used; however, there was no association when the modified WHO cut points were used (Table II in the online-only Data Supplement), although this may have been a chance finding given the small number of events in those with isolated low HDL-C (n=18). In sensitivity analyses, the relationship between isolated low HDL-C and CHD was particularly apparent in Asian cohorts compared with studies from Australia/New Zealand (HR, 1.67 [95% CI, 1.27–2.19] versus 0.79 [95% CI, 0.54 – 1.14]; *P* for regional interaction=0.016) and in men compared with women (HR, 1.30 [95% CI, 1.01–1.67] versus 0.91 [95% CI, 0.58–1.43]; *P* for sex interaction=0.04). There was no evidence of an interaction with smoking (*P*=0.95) or alcohol (*P*=0.99). In Asians, isolated low HDL-C was as strongly associated with CHD risk as nonisolated low levels of HDL-C (HR, 1.67 [95% CI, 1.27–2.19] versus 1.63 [95% CI, 1.24–2.15], respectively). These results did not differ materially according to how low HDL-C level was defined (Table IIa and IIb in the online-only Data Supplement) or after adjustment for LDL-C and triglycerides (Table III in the online-only Data Supplement).

In adjusted analyses, nonisolated low HDL-C was not associated with risk of stroke compared with those individuals with normal HDL-C (HR, 0.95; 95% CI, 0.78–1.17), both in the overall analysis and within any of the subgroups (Figure 3). This remained unchanged when either the WHO or EGIR cut points for low HDL-C were used (Table IVa and IVb in the online-only Data Supplement). Furthermore, there was no evidence of an interaction between HDL-C level and alcohol consumption (*P*=0.70).

In those with isolated low HDL-C, there was an ≈20% lower risk of stroke compared with those with normal HDL-C both in the overall population and within major subgroups (Figure 3). This remained true regardless of the cut point used to define low HDL-C (Table IVa and IVb in the online-only Data Supplement) and remained unchanged after adjustment for LDL-C and triglycerides (Table III in the online-only Data Supplement).

Discussion

Data from 2 large collaborations of studies with information on nearly 220 000 individuals conducted within populations of the Asia-Pacific region suggest a phenotype of dyslipidemia that is highly prevalent, but not unique, to Asian populations. The most frequent pattern of dyslipidemia among the Asian population (observed in approximately one third) was low HDL-C levels. In two thirds of these individuals, low levels of HDL-C occurred in the absence of any associated colipid abnormality, and this was the most common individual lipid abnormality. In non-Asians, low levels of HDL-C were evident in approximately one quarter of the population, of whom one half had normal levels of LDL-C and triglycerides. Furthermore, the risk of CHD in those individuals expressing the isolated low HDL-C phenotype was 20% higher than in those with normal HDL-C levels. This was particularly evident in Asian populations in whom the risk of CHD associated with isolated low HDL-C was

Table 4. Comparison of the Age- and Study-Adjusted Characteristics of Study Participants According to High-Density Lipoprotein Cholesterol Level by Sex and Ethnicity

	HDL-C Level*					
	Isolated Low HDL-C†		Low HDL-C + High LDL-C and/or TG		Normal HDL-C‡	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Asian men						
SBP, mm Hg	10 263	124.0 (18.7)	6565	127.1 (19.3)	45 783	126.2 (20.0)
DBP, mm Hg	10 262	78.4 (11.8)	6565	80.7 (11.6)	45 780	79.5 (11.9)
BMI, kg/m^2	15 982	24.0 (3.4)	10 029	25.2 (3.2)	64 382	23.0 (3.2)
Waist, cm	11 107	84.3 (9.5)	6614	87.7 (8.6)	38 894	81.1 (9.2)
Smoking, %	8826	49.9	5902	51.8	37 580	50.3
Diabetes mellitus, %	15 962	5.6	10 092	9.9	64 240	4.9
Non-Asian men						
SBP, mm Hg	1877	130.1 (18.1)	1939	134.6 (17.8)	9725	132.1 (18.3)
DBP, mm Hg	1881	78.1 (11.4)	1946	81.5 (11.5)	9737	78.2 (11.7)
BMI, kg/m^2	1858	26.7 (3.9)	1918	28.2 (3.8)	9620	25.8 (3.7)
Waist, cm	1246	94.1 (11.9)	1305	99.5 (10.8)	6740	92.7 (11.1)
Smoking, %	1871	25	1933	29.9	9691	21.7
Diabetes mellitus, %	1881	5.1	1947	6.3	9781	3.9
Asian women						
SBP, mm Hg	17 472	122.3 (21.3)	6827	130.5 (23.2)	36 848	122.8 (21.9)
DBP, mm Hg	17 466	75.5 (11.8)	6826	79.3 (11.9)	36 843	75.5 (12.0)
BMI, kg/m^2	25 732	23.7 (3.9)	9307	25.3 (3.8)	58 615	22.5 (3.5)
Waist, cm	17 521	76.4 (10.0)	5625	81.6 (9.7)	37 738	72.5 (9.0)
Smoking, %	13 485	7.0	5731	8.4	28 939	6.6
Diabetes mellitus, %	25 692	4.8	9321	12.9	58 559	3.7
Non-Asian women						
SBP, mm Hg	2275	122.7 (19.4)	1632	134.1 (21.3)	11 153	125.2 (20.2)
DBP, mm Hg	2275	71.4 (11.9)	1632	75.8 (12.6)	11 167	71.7 (12.1)
BMI, kg/m^2	2238	27.1 (5.9)	1607	28.7 (5.3)	10 981	24.9 (4.6)
Waist, cm	1679	84.6 (14.4)	1145	90.5 (13.4)	7872	79.4 (2.1)
Smoking, %	2268	21.6	1625	25.5	11 106	15.6
Diabetes mellitus, %	2286	3.7	1639	8.2	11 208	2.2

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; SBP, systolic blood pressure; DBP, diastolic blood pressure; and BMI, body mass index.

*Groups are mutually exclusive. For men, low HDL-C is <1.03 mmol/L; for women, <1.30 mmol/L.

†In the absence of a high LDL-C or high TG level.

‡Normal HDL-C with or without high LDL-C and/or TG.

similar to that of individuals exhibiting elevated LDL-C levels.

In comparison, isolated low HDL-C, but not nonisolated low HDL-C, was associated with a reduced risk of stroke, an observation that, to the best of our knowledge, has not been reported previously. A possible explanation for this anomalous finding is that of competing risks; a greater proportion of individuals with the isolated low HDL-C phenotype may have died of CHD, thereby excluding them from those at risk of having a stroke, relative to those with normal HDL-C. In contrast, individuals with normal HDL-C may have had elevated triglycerides or LDL-C and therefore received lipid-lowering medication (in particular fibrates, given that most of the included studies predated the use of statins), which would have reduced the risk of CHD but not stroke.[20]

A key strength of the present analyses, aside from the large sample size, which affords a greater opportunity to investigate specific patterns of lipid abnormalities, is the ability to standardize definitions for dyslipidemia across a large number of studies. Previous studies have been limited in their ability to make such comparisons owing to the lack of uniformity in the cut-point values for low HDL-C. In the present study, the prevalence of low HDL-C was broadly compatible between countries, with approximately one quarter to one third of the overall populations being affected. Singapore and India were exceptions; more than half of the populations were affected, in agreement with earlier studies.[21,22]

Surveys conducted in Asian countries also confirm our finding that low HDL-C is common, affecting between one

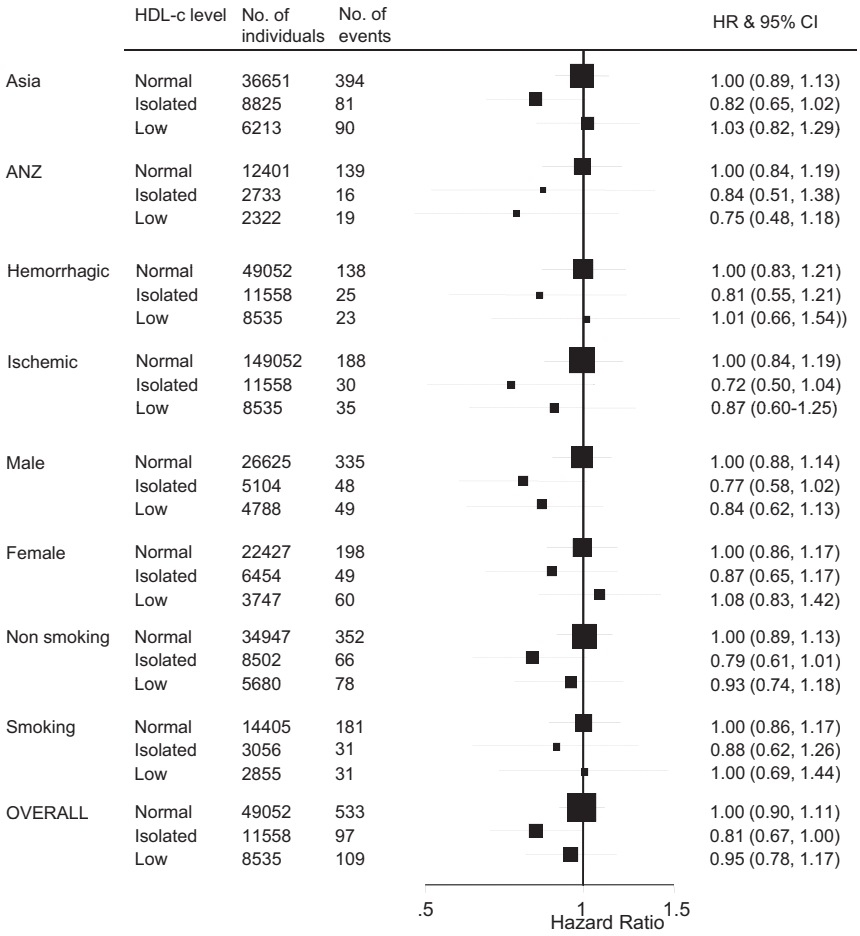

Figure 3. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for stroke associated with high-density lipoprotein cholesterol (HDL-C) levels by region, sex, and smoking status (current vs not) from studies included in the Asia Pacific Cohort Studies Collaboration. ANZ indicates Australia/New Zealand; Normal HDL-C, normal levels of HDL-C; isolated, isolated low levels of HDL-C; and low, low levels of HDL-C and high LDL-C and/or high triglycerides. The 3 groups are mutually exclusive. *P* for regional, sex, and smoking interaction=0.51, 0.51, and 0.88, respectively.

quarter and one half of various populations across Asia. For example, the 2001 Korea National Health and Nutrition Examination Survey of 4639 adults indicated that the prevalence of low HDL-C (defined as <1.03 mmol/L in both sexes) was 35% in men and 18% in women.[23] Because this study used the same HDL-C cut point for men and women rather than the sex-specific values recommended by the NCEP ATP guidelines, it might have considerably underestimated the prevalence of low HDL-C in the female Korean population. Data from Taiwan showed that approximately one quarter of the population in 2002 had low HDL-C defined with sex-specific cut points.[24] In contrast, data from Singapore have indicated that up to one half of the adult population have suboptimal HDL-C levels.[25] The high prevalence of low HDL-C present in these populations may partly explain why migrant studies have shown that South Asians have between 50% and 200% higher CHD rates compared with European populations even after adjustment for conventional risk factors such as smoking, BP, and total cholesterol.[26,27] These results suggest that treatment strategies aiming to increase HDL-C levels might be particularly important in Asia.

The non-Asian populations in this study show a pattern similar to that described for the adult population of the United States. With the use of the National Health and Nutrition Examination Survey (NHANES) 2003–2004 data, the prevalence of low HDL-C was estimated to be 26% and isolated low HDL-C to be 13%,[28] compatible to rates reported for non-Asians in the present study.

In both non-Asian and Asian populations, a low HDL-C level was more prevalent in obese individuals and those with diabetes mellitus. These associations are not unexpected given the clustering of such risk factors in individuals with the metabolic syndrome. Studies have shown that among the nearly 4000 individuals with diabetes mellitus reported in the Pan-European survey, the prevalence of low HDL-C was 50% higher in those with compared with those without diabetes mellitus.[29] Similarly, the greater propensity for low HDL-C in some specific populations (eg, Indians versus other ethnic groups) may be explained in part by their increased susceptibility to central fat accumulation.[30]

Although low HDL-C is associated with several rare genetic diseases, including hypoalphalipoproteinemia, the cause for isolated low HDL-C at the population level remains largely unknown, although factors such as low levels of physical activity, obesity, and avoidance of alcohol are known to be associated with low HDL-C levels. It is therefore possible that variations in diet, alcohol consumption, and physical activity will explain some of the variability between populations. For example, several studies have demonstrated heterogeneity in plasma lipid responses to different levels of dietary fat consumption that may indicate an epigenetic effect.[31,32]

This study has several limitations. First, the ethnic groupings we use are crude and do not take into account the potential variation in genetic differences between Asian populations; we did not have sufficient data to reliably characterize the phenotypes of individuals with isolated low HDL-C by country. Second, given the westernization of many countries across Asia in recent years and the corresponding increase in the prevalence of factors that negatively affect HDL-C levels, such as obesity and low levels of physical activity, the mean population level of HDL-C may have shifted recently to a greater extent in the Asian cohorts. Third, a significant proportion of the included studies are cross-sectional, which precludes examination of the temporal nature of the association between lipids and risk factors. Fourth, there will have been both interstudy and intrastudy measurement errors in the ascertainment of lipid measurements. However, the measurement error is likely to have been random and present across all studies. There may also have been some bias introduced by the different methods used to verify cardiovascular outcomes across the APCSC studies.

Finally, data on apolipoproteins and lipid-lowering therapy were not routinely recorded in the majority of studies included in both the OAC and APCSC, which may have facilitated a more intricate analysis of the data. For example, information on the use of cholesterol-lowering drugs was available in <5% of the entire study population. Statin use is likely to have been uncommon, given that the baseline year of recruitment for these studies ranged from 1966 to 1994. It is possible, however, that LDL-C–lowering therapy, eg, with fibrates or nicotinic acid, which also increases HDL-C,[33] would have been more common in Australia and New Zealand compared with other countries in the Asia-Pacific region. However, data from the pan-European Survey suggest that levels of HDL-C are broadly similar in individuals with and without lipid-lowering therapy.[34]

Conclusions

Isolated low level of HDL-C is a phenotype that appears to be particularly common in Asian populations. Individuals exhibiting this form of lipid abnormality are at increased risk of CHD, but, at the same time, are unlikely to be candidates for lipid-lowering medication because their levels of triglycerides and LDL-C meet targets proposed by current guidelines. These regions will potentially benefit from strategies that can increase levels of HDL-C, such as effective smoking cessation campaigns and initiatives that result in sustained weight loss and increases in physical activity at the population level. Moreover, agents such as niacin and fibrates may be particularly important in Asia. Furthermore, going forward, new drugs such as cholesteryl ester transfer protein inhibitors may be important in cardiovascular prevention in the region.

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Disclosures

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CLINICAL PERSPECTIVE

This study, comprising information from >220 000 individuals from the Asia-Pacific region, describes a novel and potentially important form of dyslipidemia. Low levels of high-density lipoprotein cholesterol (HDL-C) have been independently associated with increased cardiovascular risk. Some earlier observational studies have suggested the existence of such a distinct type of dyslipidemia with low HDL-C occurring in the absence of elevated levels of other lipid fractions, ie, isolated low HDL-C. This phenotype has been postulated to be especially prevalent among Asian populations. Individuals with this form of lipid abnormality are usually not considered to be candidates for lipid-lowering medication because of their comparatively normal levels of total and low-density lipoprotein cholesterol. This study compared the prevalence of isolated low HDL-C in Asian and non-Asian populations and determined whether the risk of coronary heart disease and stroke was elevated in individuals with this form of lipid abnormality. Findings from this study indicated a substantially higher prevalence of isolated low HDL-C among Asians (22.4%) compared with non-Asians (14.5%) that was unlikely to be explained by differences in the background rates of lipid-lowering medication, cigarette smoking, and alcohol use. Both nonisolated low HDL-C and isolated low HDL-C were associated with increased risk of coronary heart disease but not stroke. Compared with non-Asians, the relationship between isolated low HDL-C and subsequent risk of coronary heart disease was stronger in Asians. In this group, it was associated with the same magnitude of coronary risk (≈60%) as low levels of HDL-C combined with other lipid abnormalities.

Supplemental Figures 1a and b

Prevalence of lipid phenotypes in adult Asians who reported being a current cigarette smoker at study baseline (1a; n=29694) or a not-current smoker (1b; n =70769)

Supplemental Figures 2a and b

Prevalence of lipid phenotypes in adult non-Asians who reported being a current cigarette smoker at study baseline (2a; n =5776) or a not-current smoker (2b; n =22718)

Supplemental Table 1. Frequency (%) and 95% confidence intervals of HDL-cholesterol phenotypes by country of study

Country	N (% female)	Mean age (SD)	HDL-cholesterol level*		
			Isolated low HDL-c**	Low HDL-c + High LDL-c and/or TG	Normal HDL-c***
Australia	28447 (52.7)	48.3 (15.4)	14.4 (14.0-14.8)	12.5 (21.1-12.9)	73.1 (72.5-73.6)
China	66800 (51.3)	49.8 (11.6)	20.0 (19.7-20.3)	8.8 (8.6-9.0)	71.2 (70.9-71.5)
Hong Kong	1682 (41.1)	42.0 (15.8)	17.1 (15.3-18.9)	8.2 (6.9-9.5)	74.8 (72.7-76.8)
India	10026 (43.0)	43.7 (10.4)	48.9 (47.9-49.9)	14.9 (14.2-15.6)	36.2 (35.2-37.1)
Singapore	5286 (51.7)	39.7 (12.9)	26.2 (25.1-27.4)	26.9 (25.7-28.1)	46.8 (45.5-48.1)
South Korea	7944 (54.9)	44.7 (15.8)	27.9 (27.0-28.9)	9.4 (8.8-10.1)	62.7 (61.6-63.7)
Taiwan	70084 (52.7)	42.9 (13.6)	22.2 (21.9-22.5)	10.7 (10.5-10.9)	67.1 (66.7-67.4)
Thailand	11012 (41.0)	47.7 (10.1)	18.6 (17.9-19.4)	17.6 (16.9-18.3)	63.8 (62.9-64.7)
Japan	18779 (46.7)	51.5 (10.5)	16.3 (15.8-16.8)	7.7 (7.3-8.1)	76.0 (75.4-76.6)

Supplemental Table 2a. Hazard ratios (95% confidence intervals) for coronary heart disease according to level of high-density lipoprotein cholesterol (HDL-c) defined using the modified World Health Organization (WHO) for HDL-c (<1.0 in men and <0.9 mmol/L in women)

Sub-group	HDL-c level	No. individuals	No. events	HR (95% CI)
Asia	Normal	47661	202	1.00 (0.82-1.22)
	Isolated	1759	13	1.10 (0.64-1.88)
	Low	2269	27	1.20 (0.80-1.80)
ANZ	Normal	16305	300	1.00 (0.87-1.15)
	Isolated	515	5	0.75 (0.31-1.80)
	Low	636	27	2.14 (1.47-3.12)
Male	Normal	33613	345	1.00 (0.86-1.16)
	Isolated	1181	14	0.94 (0.56-1.58)
	Low	1723	39	1.55 (1.12-2.14)
Female	Normal	30353	157	1.00 (0.78-1.29)
	Isolated	1093	4	1.24 (0.47-3.30)
	Low	1182	15	1.81 (1.03-3.19)
Non-smoking	Normal	45344	338	1.00 (0.87-1.15)
	Isolated	1608	10	0.94 (0.51-1.75)
	Low	1877	35	1.61 (1.14-2.28)
Smoking	Normal	18622	164	1.00 (0.82-1.21)
	Isolated	666	8	1.07 (0.54-2.14)
	Low	1028	19	1.60 (1.01-2.55)

OVERALL	Normal	63966	502	1.00 (0.88 – 1.13)
	Isolated	2274	18	0.86 (0.57 – 1.29)
	Low	2905	54	1.02 (0.74 – 1.42)

P value for region interaction = 0.11; for sex interaction = 0.83; for smoking interaction = 0.97.

Supplemental Table 2b. Hazard ratios (95% confidence intervals) for coronary heart disease according to level of high-density lipoprotein cholesterol (HDL-c) defined using the European Group on Insulin Resistance (EGIR) cut-points for HDL-c (<1.0 mmol/L)

Sub-group	HDL-c level	No. individuals	No. events	HR (95% CI)
Asia	Normal	45574	486	1.00 (0.82-1.22)
	Isolated	2882	31	1.75 (1.22-2.51)
	Low	3233	48	1.61 (1.15-2.25)
ANZ	Normal	15452	163	1.00 (0.86-1.16)
	Isolated	933	4	0.67 (0.37-1.20)
	Low	1071	7	1.77 (1.29-2.43)
Male	Normal	30673	368	1.00 (0.87-1.14)
	Isolated	2722	30	1.20 (0.86-1.66)
	Low	3122	34	1.64 (1.27-2.12)
Female	Normal	30353	281	1.00 (0.78-1.29)
	Isolated	1093	5	1.24 (0.47-3.30)
	Low	1182	21	1.81 (1.03-3.19)
Non-smoking	Normal	43821	438	1.00 (0.88-1.13)
	Isolated	2452	22	0.79 (0.52-1.20)
	Low	2556	36	0.95 (0.67-1.34)
Smoking	Normal	17205	211	1.00 (0.86-1.17)
	Isolated	1363	13	0.64 (0.36-1.13)

	Low	1748	19	1.17 (0.73-1.85)
OVERALL	Normal	61026	649	1.00 (0.89 – 1.13)
	Isolated	3815	35	1.20 (0.88-1.64)
	Low	4304	55	1.67 (1.32-2.11)

P value for region interaction = 0.027; for sex interaction = 0.96; for smoking interaction = 0.53.

Supplemental Table 3 Hazard ratios (95% confidence intervals) for coronary heart disease and stroke associated with isolated low high-density lipoprotein cholesterol (HDL-c) before and after adjustment for LDL-cholesterol (LDL-c) and triglycerides (TG)

	Coronary heart disease		Stroke	
	Hazard ratio (95% CI)			
Sub-group	Adjusted for	Adjusted for LDL-c and TG	Current	Adjusted for LDL-c and TG
Asia	1.67 (1.27-2.19)	1.72 (1.31-2.26)	0.82 (0.65-1.02)	0.81 (0.65-1.01)
ANZ	0.79 (0.54-1.14)	0.84 (0.58-1.23)	0.84 (0.51-1.38)	0.83 (0.50-1.36)
Male	1.30 (1.01-1.67)	1.37 (1.06-1.77)	0.77 (0.58-1.02)	0.76 (0.58-1.01)
Female	0.91 (0.58-1.43)	0.97 (0.61-1.54)	0.87 (0.65-1.17)	0.87 (0.65-1.16)
Non-smoking	1.16 (0.88-1.52)	1.23 (0.93-1.62)	0.79 (0.61-1.01)	0.80 (0.63-1.03)
Smoking	1.24 (0.85-1.81)	1.28 (0.87-1.88)	0.88 (0.62-1.26)	0.88 (0.61-1.26)
Overall	1.17 (0.95-1.46)	1.25 (0.99-1.56)	0.95 (0.78-1.17)	0.81 (0.66-0.99)

Supplemental Table 4a. Hazard ratios (95% confidence intervals) for stroke according to level of high-density lipoprotein cholesterol (HDL-c) defined using the modified World Health Organization (WHO) for HDL-c (<1.0 in men and <0.9 mmol/L in women)

Sub-group	HDL-c level	No. individuals	No. events	HR (95% CI)
Asia	Normal	47661	506	1.00 (0.87-1.15)
	Isolated	1759	21	0.88 (0.58-1.34)
	Low	2269	38	1.11 (0.79-1.56)
ANZ	Normal	16305	169	1.00 (0.81-1.24)
	Isolated	515	2	0.77 (0.19-3.08)
	Low	636	3	0.58 (0.19-1.80)
Hemorrhagic	Normal	63966	175	1.00 (0.80-1.25)
	Isolated	2274	4	0.61 (0.23-1.62)
	Low	2905	7	0.93 (0.43-1.99)
Ischemic	Normal	63966	231	1.00 (0.82-1.22)
	Isolated	2274	6	0.69 (0.31-1.54)
	Low	2905	16	1.30 (0.77-2.21)
Male	Normal	33613	345	1.00 (0.85-1.17)
	Isolated	1181	14	1.12 (0.71-1.77)
	Low	1723	39	0.92 (0.59-1.46)
Female	Normal	30353	157	1.00 (0.82-1.22)
	Isolated	1093	4	0.47 (0.20-1.13)
	Low	1182	15	1.15 (0.72-1.81)

Non-smoking	Normal	45344	338	1.00 (0.87-1.16)
	Isolated	1608	10	0.76 (0.44-1.31)
	Low	1877	35	0.93 (0.63-1.38)
Smoking	Normal	18622	164	1.00 (0.84-1.18)
	Isolated	666	8	1.04 (0.56-1.94)
	Low	1028	19	1.24 (0.73-2.13)
OVERALL	Normal	63966	675	1.00 (0.88 – 1.13)
	Isolated	2274	23	0.86 (0.57 – 1.29)
	Low	2905	41	1.02 (0.74 – 1.42)

P value for region interaction = 0.57; for sex interaction = 0.19; for smoking interaction = 0.56.

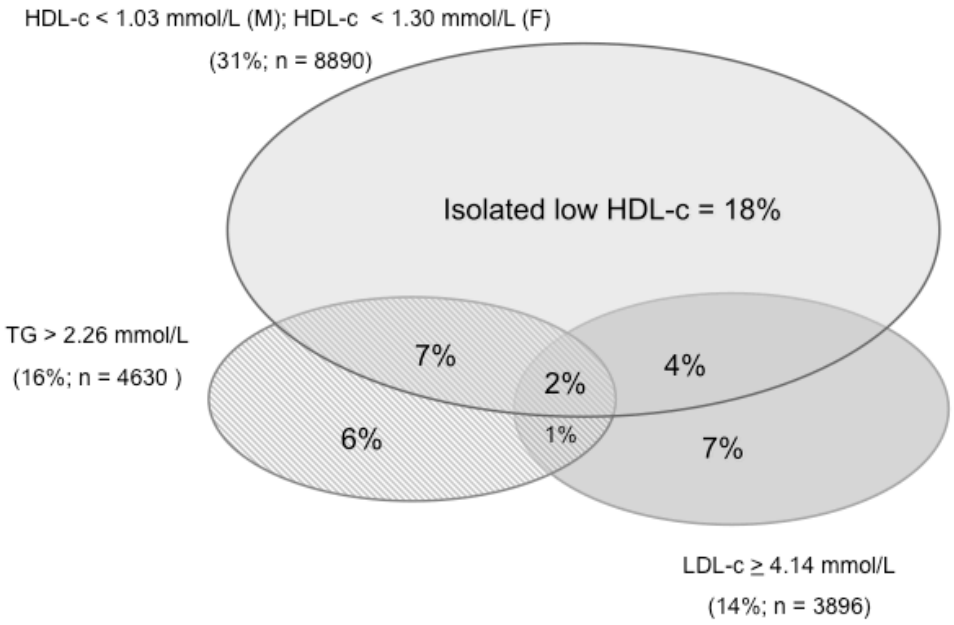
Supplemental Table 4b. Hazard ratios (95% confidence intervals) for stroke according to level of high-density lipoprotein cholesterol (HDL-c) defined using the European Group on Insulin Resistance (EGIR) cut-points for HDL-c (<1.0 mmol/L)

Sub-group	HDL-c level	No. individuals	No. events	HR (95%
Asia	Normal	45574	486	1.00 (0.88-1.
	Isolated	2882	31	0.78 (0.55-1.
	Low	3233	48	1.04 (0.76-1.
ANZ	Normal	15452	163	1.00 (0.81-1.
	Isolated	933	4	0.53 (0.20-1.
	Low	1071	7	0.73 (0.35-1.54)
Hemorrhagic	Normal	61026	171	1.00 (0.81-1.24)
	Isolated	3815	8	0.66 (0.33-1.33)
	Low	4304	7	0.65 (0.30-1.39)
Ischemic	Normal	61026	225	1.00 (0.83-1.20)
	Isolated	3815	11	0.75 (0.42-1.35)
	Low	4304	17	0.98 (0.59-1.64)
Male	Normal	30673	368	1.00 (0.87-1.15)
	Isolated	2722	30	0.81 (0.57-1.17)
	Low	3122	34	0.89 (0.62-1.27)
Female	Normal	30353	281	1.00 (0.82-1.22)
	Isolated	1093	5	0.47 (0.20-1.13)
	Low	1182	21	1.15 (0.72-1.82)

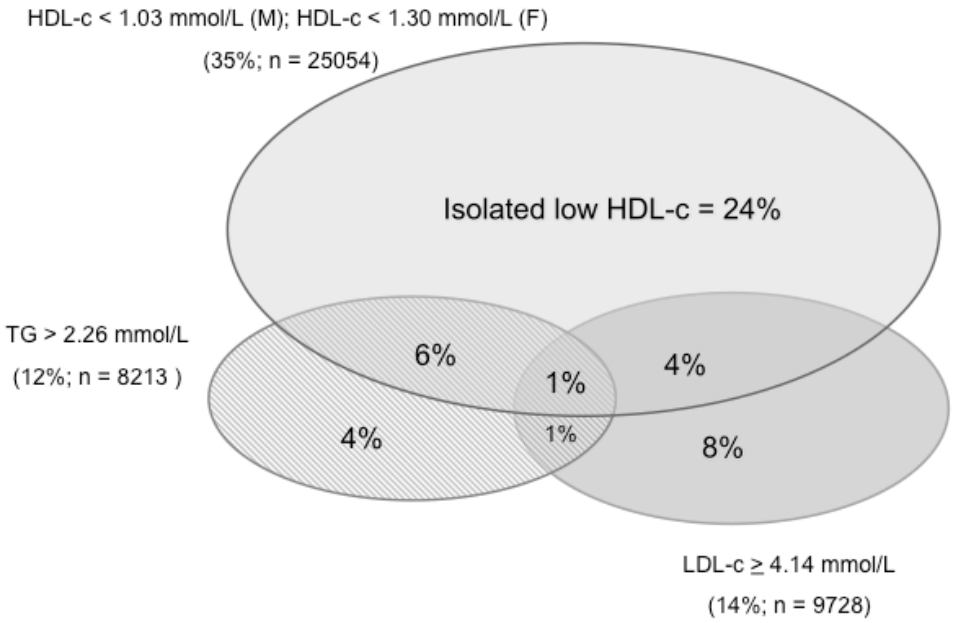
Non-smoking	Normal	43821	438	1.00 (0.88-1.13)
	Isolated	2452	22	0.79 (0.52-1.20)
	Low	2556	36	0.92 (0.65-1.30)
Smoking	Normal	17205	211	1.00 (0.86-1.16)
	Isolated	1363	13	0.66 (0.36-1.16)
	Low	1748	19	1.10 (0.69-1.75)
OVERALL	Normal	61026	649	1.00 (0.89 – 1.12)
	Isolated	3815	35	0.74 (0.53 – 1.03)
	Low	4304	55	0.97 (0.73 – 1.29)

P-value for regional interaction = 0.58; for sex interaction = 0.37; for smoking interaction = 0.73.

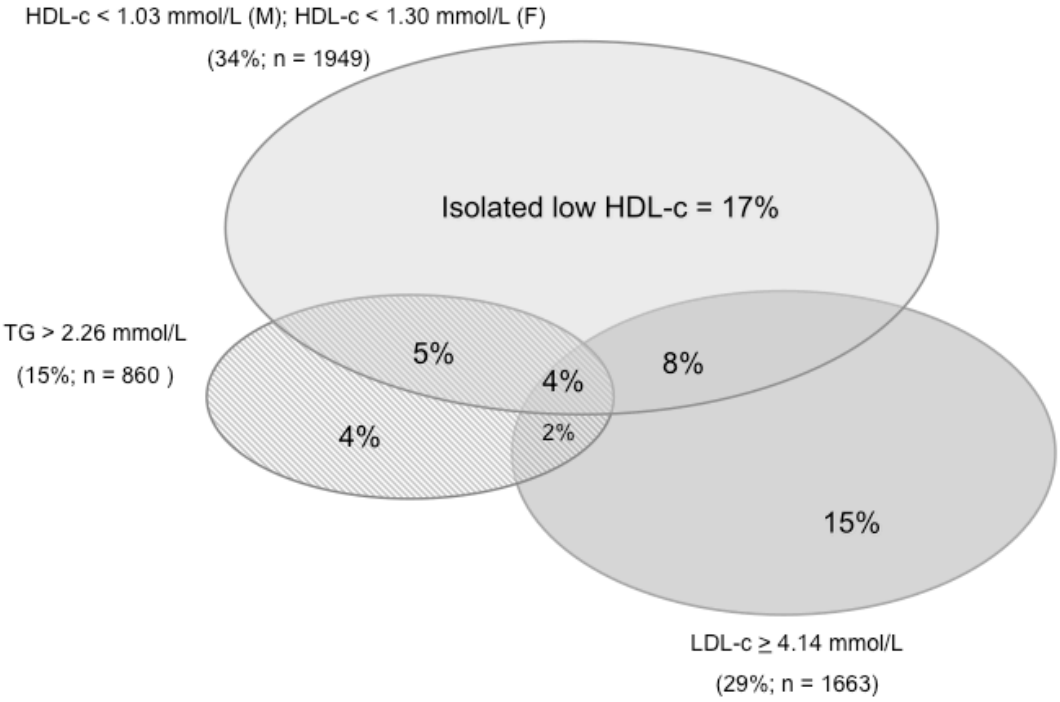
Supplemental Figure 1a



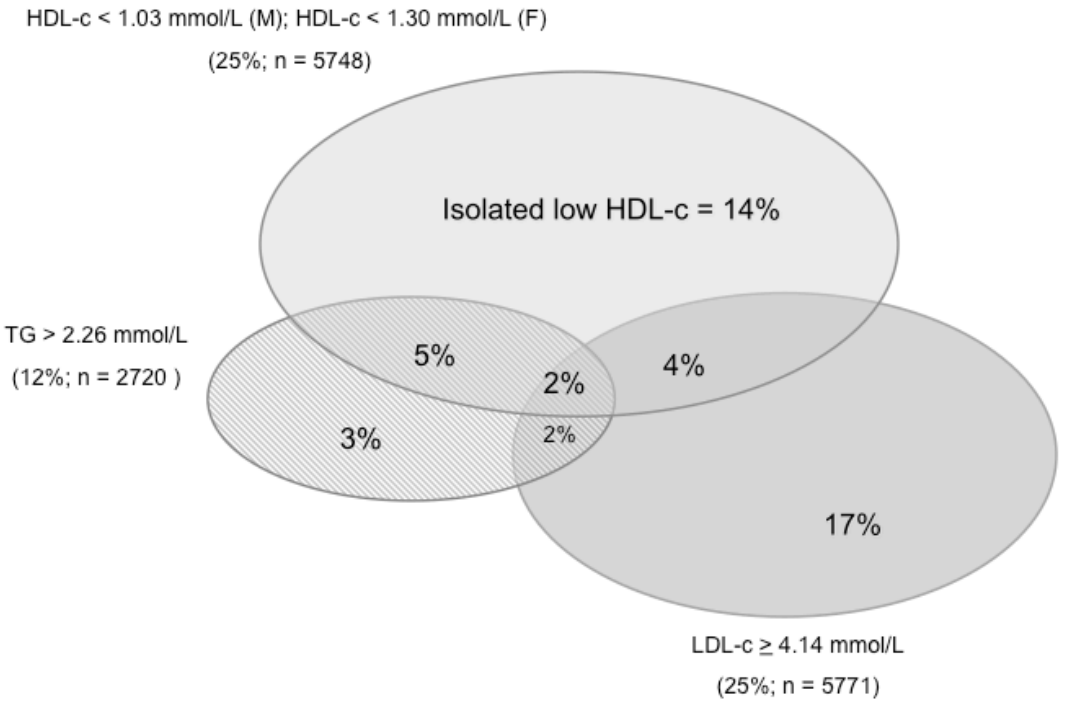
Supplemental Figure 1b



Supplemental Figure 2a



Supplemental Figure 2b



APPENDIX

APCSC Executive Committee

M. Woodward (Chair), R. Huxley, X. Fang, D.F. Gu, Y. Imai, T.H. Lam, W.H. Pan, A. Rodgers, I. Suh, H.C. Kim, H. Ueshima

APCSC Participating Studies and Principal Collaborators

Aito Town: A. Okayama, H. Ueshima; H. Maegawa; Akabane: M. Nakamura, N. Aoki; Anzhen02: Z.S. Wu; Anzhen: C.H. Yao, Z.S. Wu; Australian Longitudinal Study of Aging: M. Luszcz; Australian National Heart Foundation: T.A. Welborn; Beijing Aging: Z. Tang; Beijing Steelworkers: L.S. Liu, J.X. Xie; Blood Donors' Health: R. Norton, S. Ameratunga, S. MacMahon, G. Whitlock; Busselton: M.W. Knuiman; Canberra-Queanbeyan: H. Christensen; Capital Iron and Steel Company: X.G. Wu; CISCH: J. Zhou, X.H. Yu; Civil Service Workers: A. Tamakoshi; CVDFACTS: W.H. Pan; East Beijing: Z.L. Wu, L.Q. Chen, G.L. Shan; Electricity Generating Authority of Thailand: P. Sritara; Fangshan: D.F. Gu, X.F. Duan; Fletcher Challenge: S. MacMahon, R. Norton, G. Whitlock, R. Jackson; Guangzhou: Y.H. Li; Guangzhou Occupational: T.H. Lam, C.Q. Jiang; Hisayama: Y. Kiyohara, H. Arima, M. Iida; Hong Kong: J. Woo, S.C. Ho; Huashan: Z. Hong, M.S. Huang, B. Zhou (deceased); Kinmen: J.L. Fuh; Konan: H. Ueshima, Y. Kita, S.R. Choudhury; KMIC: I. Suh, S.H. Jee, I.S. Kim; Melbourne: G.G. Giles; Miyama: T. Hashimoto, K. Sakata; Newcastle: A. Dobson; Ohasama: Y. Imai, T. Ohkubo, A. Hozawa; Perth: K. Jamrozik, M. Hobbs, R. Broadhurst; Saitama: K. Nakachi; Seven Cities: X.H. Fang, S.C. Li, Q.D. Yang; Shanghai Factory Workers: Z.M.

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OAC Secretariat

R Huxley, F Barzi, I Caterson, T Gill, A Omari, R Stolk, M Woodward

Principal collaborators (and study country) in OAC

J Adam (Indonesia), F Azizi (Iran), C Barba (The Philippines), Z Beifan (Mainland China), C Chunming (Mainland China), S Colagiuri (Tonga), J Cutter (Singapore), C Fong (Singapore), G Giles (Australia), K Huang (Taiwan), E Janus (Hong Kong), J-H Kang (Korea), G Ko (Hong Kong), S Kuriyama (Japan), TH Lam (Hong Kong), S Lear (Canada), S W Oh (Korea), J Patel (India), D Prabhakaran (India), S Reddy (India), J Shaw (Australia), P Suriyawongpaisal (Thailand), T Welborn (Australia), P Zimmet (Australia).

아시아인에서 많은 HDL-C 단독 저하증, 관동맥질환 발생 위험을 증가시킨다

권 준 교수 인하대병원 심장내과

Summary

배경

과거 연구 결과에 의하면, 관동맥질환 발생 위험과 연관되어 HDL-C 단독 저하 이상지혈증이 있는 것으로 나타났으며, 이는 특히 아시아인에서 그 빈도 수가 높은 것으로 알려져 있다.

방법 및 결과

아시아-태평양 지역 37개 연구 자료를 통해, 총 220,060명의 참가자(87% 아시아인)를 대상으로 하였으며, 그 중 HDL-C(HDL-cholesterol) 저하증(남성, HDL <1.03mmol/L; 여성, HDL <1.30mmol/L)을 보인 경우는 아시아인에서 33.1%(95% CI, 32.9–33.3), 비아시아인에서는 27.0%(95% CI, 26.5–27.5)이었다(*P*<0.001). HDL-C 단독 저하증을 보인 경우는 14.5%인 비아시아인(95% CI, 14.1–14.9)에 비하여 아시아인에서 22.4%(95% CI, 22.2–22.5)로 그 빈도가 유의하게 높은 것으로 나타났다(*P*<0.001). 6.8년 추적기간 동안 574명에서 관동맥질환, 그리고 739명에서 뇌졸중이 발생하였다. 모든 사람에서 HDL-C 저하증은 관동맥질환 발생과 역의 상관관계를 보였으며(HR, 1.57; 95% CI, 1.31–1.87), 아시아인에서 HDL-C 단독 저하증은 다른 지질 이상을 동반한 HDL-C 저하증과 마찬가지로 관동맥질환 발생 위험을 높이는 것으로 나타났다[HR, 1.67(95% CI, 1.27–2.19) vs. 1.63(95% CI, 1.24–2.15), respectively]. 반면에, 본 연구 대상에서는 HDL-C 저하증이 뇌졸중 발생 위험을 증가시키지 않는 것으로 나타났다.

결론

HDL-C 단독 저하증은 아시안인에서 많이 볼 수 있는 새로운 이상 지질 표현형으로 관동맥질환 발생 위험을 증가시키는 것으로 나타났다. 향후 이러한 이상지혈증에 대한 더 많은 연구가 필요할 것으로 사료된다.

Commentary

HDL-C 저하증이 LDL-C 수치와 관계없이 관동맥질환 발생의 독립적인 위험인자라는 것은 잘 알려진 사실이다. 더구나 몇몇 연구 결과에서는 LDL-C, 그리고 TG(triglyceride) 수치가 정상치임에도 불구하고 HDL-C 수치가 단독으로 저하된 경우 LDL-C 수치가 상승한 것과 같은 정도의 관동맥질환 발생 위험을 가진 것으로 나타났다. 조사연구 결과, LDL-C나 TG 수치와 관계없이 HDL-C 수치가 저하된 경우는 나라와 인종에 따라 그 빈도가 6-34%로 다양하게 나타났다. 그러나 이러한 HDL-C 저하증에서 HDL-C 수치 상승 치료가 결과적으로 심혈관질환 발생 위험을 줄일 수 있는지에 대한 임상적 근거는 아직 부족하다.

본 연구는 과연 아시아인에서 HDL-C 저하증의 빈도가 높은지 알아보고자 아시아-태평양 지역에서의 2개의 전향적 코호트(Asia Pacific Cohort Studies Collaboration, APCSC) 그리고 횡단적 연구(Obesity in Asia Collaboration, OAC)의 자료들을 이용하여 이 지역에서 아시아인과 비아시아인 분류에 따른 HDL-C 단독 저하증의 빈도를 비교 분석하였으며, 과연 이것이 관동맥질환과 뇌졸중 발생 위험 증가와 독립적인 연관성을 가지고 있는지를 조사하였다. 자료는 중국, 홍콩, 인도, 일본, 한국, 필리핀, 싱가포르, 대만 그리고 태국에서 얻어진 아시아인 자료 그리고 호주와 뉴질랜드에서 얻어진 비아시아인 자료로 분류되었다. 결과적으로, APCSC에서는 총 24개 연구에서 69,145명, 그리고 OAC에서는 13개 연구에서 총 150,915명의 자료가 수집되었으며, 이 중 남성의 87%, 그리고 여성의 86%가 아시아인이었다. 조사 결과 아시아인에서는 33%에서 HDL-C 저하를 보였으며, HDL-C 단독 저하를 보인 경우는 27%나 되었다. 반면에, 비아시아인에서는 27%에서 HDL-C 저하를, 14%에서 HDL-C 단독 저하를 보였다. LDL-C 상승도 아시아인에서 약 2배 높게 나타났으며, 반면 TG 상승은 두 인종 간 유의한 차이를 보이지 않았다. 6.8년 동안의 추적관찰 결과에서 HDL-C 단독 저하증은 HDL-C 비단독 저하증과 마찬가지로 관동맥질환 발생 위험을 높이는 것으로 나타났다. 그러나 HDL-C의 단독 저하증에서는 HDL-C 비단독 저하증과는 달리 뇌졸중 발생 위험을 전혀 증가시키지 않는 것으로 나타났는데, 이러한 결과는 이전에 한 번도 보고된 바 없는 매우 흥미로운 결과이다.

본 연구는 지금까지 진행되어 온 아태 지역에서 이상지혈증의 형태를 관찰해온 연구 결과 중 최대 규모의 연구 결과이다. 이번 연구 결과에서도 과거에 관찰되어 왔던 대로 HDL-C 단독 저하증은 특히 아시아인에서 빈도가 높은 것으로 나타났다. 그동안 HDL-C 단독 저하증은 LDL-C 수치와 TG 수치가 정상범주이기 때문에, 약물치료 대상에서는 제외되어 왔다. 그러나 이번 연구 결과에서 아시아인에서 HDL-C 단독 저하증 역시 HDL-C 비단독 저하증 못지않게 관동맥질환 발생 위험을 증가시키는 것으로 나타났다. 따라서 본 연구 결과는 HDL-C 단독 저하증 환자들에서의 비약물적 또는 약물적 치료를 통한 HDL-C 상승효과 대한 임상적 의의를 제시해준 결과라 할 수 있다.

그러나 이번 연구 결과를 해석하는데 짚고 넘어가야 할 사항이 있다. 그것은 이번 연구 결과에서 아시아인을 국가별로 세분하여 분석해봤을 때, 특히 싱가포르와 인도에서의 HDL-C 저하증의 빈도는 50%로 다른 아시아 국가와 비교해서도 현저히 높다는 것이다. 이는 과거 INTERHEART 연구[1] 결과를 바탕으로 한 분석에서도 나타난 결과이다. 그 당시 타 아시아인에 비해 인도를 포함한 남아시아인에서 HDL-C, LDL-C 수치가 현저히 낮은 것으로 나타났다. 남아시아인이 타 인종에 비하여 현저히 높은 심혈관질환의 발생 위험을 가지고 있는 것은 남아시아인 패러독스(paradox)로도 잘 알려져 있다. Heng DM 등[2]의 보고에 의하면 싱가포르의 심혈관 코호트 연구 결과, 허혈성 심장질환의 발생률은 싱가포르 거주 인도인에서

가장 높았으며, 연령을 보정한 경우 중국인에 비해 남자에서 2.78배, 여자에서 1.97배 더 높은 것으로 나타났다. 물론 타 인종에 비해 남아시아인에서 기존의 일반적인 위험인자(제2형 당뇨병, 고인슐린혈증, 인슐린 저항성, 대사증후군)의 발생 빈도가 높긴 하다. 그러나 이러한 위험인자 만으로는 남아시아인에서의 높은 심혈관질환 발생 빈도를 다 설명할 수 없으며, 본 연구 결과에서도 나타난 남아시아인에서의 현저한 HDL-C 저하증과 같은 이상지혈증과 깊은 관련이 있을 것으로 판단된다. 이와 같이 아시아인 내에서도 남아시아인은 타 아시아인과 달리 심혈관질환 발생위험뿐 아니라, 이상지혈증의 빈도에서도 역시 현저한 차이를 보이고 있다. 따라서 이렇게 임상적으로 그리고 지혈 측정치에서 현저한 차이를 보이는 남아시아인과 다른 아시아인을 하나의 아시아인으로 묶어 분석하는 것이 정작 모든 아시아인에게 적용할 수 있는 효과적인 치료 가이드라인을 결정하는 데 올바른 정보를 줄 것인지 의구심이 든다. 아마도 이를 위해서는 향후 아시아인을 남아시아인과 비남아시아인으로 구분하여 이에 따른 이상지혈증의 빈도와 심혈관질환 발생 위험을 비교분석하는 연구가 더 있어야 할 것으로 사료된다.

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Isolated Low Levels of High-Density Lipoprotein Cholesterol Are Associated With an Increased Risk of Coronary Heart Disease

An Individual Participant Data Meta-Analysis of 23 Studies in the Asia-Pacific Region

Rachel R. Huxley, DPhil; Federica Barzi, PhD; Tai Hing Lam, MD; Sebastien Czernichow, PhD; Xianghua Fang, PhD; Tim Welborn, PhD; Jonathan Shaw, MD; Hirotsugu Ueshima, MD; Paul Zimmet, PhD; Sun Ha Jee, PhD; Jeetesh V. Patel, MD; Ian Caterson, PhD; Vlado Perkovic, PhD; Mark Woodward, PhD; for the Asia Pacific Cohort Studies Collaboration and the Obesity in Asia Collaboration

Background—Previous studies have suggested that there is a novel dyslipidemic profile consisting of isolated low high-density lipoprotein cholesterol (HDL-C) level that is associated with increased risk of coronary heart disease, and that this trait may be especially prevalent in Asian populations.

Methods and Results—Individual participant data from 220 060 participants (87% Asian) in 37 studies from the Asia-Pacific region were included. Low HDL-C (HDL <1.03 mmol/L in men and <1.30 mmol/L in women) was seen among 33.1% (95% confidence interval [CI], 32.9–33.3) of Asians versus 27.0% (95% CI, 26.5–27.5) of non-Asians ($P<0.001$). The prevalence of low HDL-C in the absence of other lipid abnormalities (isolated low HDL-C) was higher in Asians compared with non-Asians: 22.4% (95% CI, 22.2–22.5) versus 14.5% (95% CI, 14.1–14.9), respectively ($P<0.001$). During 6.8 years of follow-up, there were 574 coronary heart disease and 739 stroke events. There was an inverse relationship between low HDL-C with coronary heart disease in all individuals (hazard ratio, 1.57; 95% CI, 1.31–1.87). In Asians, isolated low levels of HDL-C were as strongly associated with coronary heart disease risk as low levels of HDL-C combined with other lipid abnormalities (hazard ratio, 1.67 [95% CI, 1.27–2.19] versus 1.63 [95% CI, 1.24–2.15], respectively). There was no association between low HDL-C and stroke risk in this population (hazard ratio, 0.95 [95% CI, 0.78 to 1.17] with nonisolated low HDL-C and 0.81 [95% CI, 0.67–1.00] with isolated low HDL-C).

Conclusion—Isolated low HDL-C is a novel lipid phenotype that appears to be more prevalent among Asian populations, in whom it is associated with increased coronary risk. Further investigation into this type of dyslipidemia is warranted. **(*Circulation*. 2011;124:2056-2064.)**

Key Words: cardiovascular diseases ■ cholesterol ■ epidemiology

The direct but opposing relationships of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) with coronary heart disease (CHD) risk are well characterized in many populations.[1–3] There is also increasing recognition of the importance of HDL-C in determining coronary risk independently of LDL-C levels.[4,5] Moreover, some studies suggest that isolated low HDL-C, a condition that describes the coexistence of low HDL-C in

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From the George Institute (R.R.H., F.B., S.C., V.P., M.W.) and Boden Institute, Sydney Medical School (I.C.), University of Sydney, Sydney, Australia; Division of Epidemiology and Community Health, University of Minnesota, Minneapolis (R.R.H.); University of Hong Kong, School of Public Health/Department of Community Medicine, Hong Kong (T.H.L.); Department of Nutrition, Ambroise Paré Hospital and University of Versailles Saint Quentin en Yvelines, Boulogne-Billancourt, France (S.C.); Department of Epidemiology and Social Medicine, Xuanwu Hospital, Capital Medical University, Beijing, China (X.F.); Department of Endocrinology and Diabetes, Sir Charles Gairdner Hospital, Nedlands, Western Australia (T.W.); Baker IDI Heart and Diabetes Institute, Melbourne, Victoria, Australia (J.S., P.Z.); Department of Health Science, Shiga University of Medical Science, Shiga, Japan (H.U.); Institute for Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, Korea (S.J.H.); Sandwell Medical Research Unit, Sandwell and West Birmingham Hospitals NHS Trust, West Bromwich, UK (J.V.P.); and Department of Epidemiology, Johns Hopkins University, Baltimore, MD (M.W.).

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Correspondence to Rachel Huxley, DPhil, Division of Epidemiology and Community Health, University of Minnesota School of Public Health, 1300 S Second St, Ste 300, Minneapolis, MN 55454. E-mail rhuxley@umn.edu

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conjunction with normal LDL-C and triglyceride levels, has a coronary risk equivalent to that of elevated LDL-C.[6–8]

Clinical Perspective on p 76

Survey data suggest that the prevalence of low HDL-C, either in isolation or in conjunction with abnormal LDL-C or triglyceride levels, differs substantially between countries and ethnic groups, and published values for the prevalence of isolated low HDL-C range from 6% to 34%.[6,9–11] However, individuals with this lipid phenotype are unlikely to be considered for pharmacotherapy partly because their LDL-C and total cholesterol levels fall within current guidelines, and partly because there is insufficient randomized evidence unequivocally demonstrating that raising HDL-C levels reduces cardiovascular risk.[12]

Here, we determine whether isolated low HDL-C is a form of dyslipidemia that occurs more frequently in Asian populations using data from 2 large-scale collaborations of prospective cohorts and cross-sectional studies from the Asia-Pacific region, namely the Asia Pacific Cohort Studies Collaboration (APCSC) and the Obesity in Asia Collaboration (OAC). We also examine whether isolated low HDL-C is independently associated with increased risk of CHD and stroke and if there is a particular phenotype associated with low HDL-C based on routinely measured clinical characteristics.

Methods

Asia Pacific Cohort Studies Collaboration

Details of APCSC, including study identification, data collection, and event verification, are given elsewhere.[13,14] All studies included in APCSC were conducted prospectively in populations from the Asia-Pacific region, had at least 5000 person-years of follow-up, and recorded age, sex, and blood pressure (BP) at baseline, as well as vital status at the end of the follow-up. Lipid measurements were determined with serum samples, which were obtained while fasting in ≈93% of participants. Information regarding the method of cholesterol analysis was available for ≈70% of all participants, of whom 96% used enzymatic methods. Most studies additionally recorded current smoking status (current/not current) at baseline. BP was measured at rest in the seated position with a standard mercury sphygmomanometer in most studies.

Obesity in Asia Collaboration

Details of OAC, including study identification, data collection, and event verification, are given elsewhere.[15,16] Studies were eligible if they contained information on age, sex, weight, height, waist circumference, hip circumference, fasting plasma glucose, and BP and measures on at least 1 lipid variable (total cholesterol, HDL-C, LDL-C, or triglycerides).

All of the included studies from both the APCSC and OAC were classified as Asian if study members were recruited from mainland China, Hong Kong, India, Japan, Korea, the Philippines, Singapore, South Korea, Taiwan, or Thailand; they were classified as Australia/New Zealand if participants were drawn from Australia or New Zealand. This classification largely represented a split by ethnicity into Asians and non-Asians.

Statistical Methods

Participants without information on lipids were excluded from these analyses. When not measured directly, LDL-C was calculated from the Friedewald formula in samples in which triglyceride levels were <400 mg/dL.[17] National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) guidelines were used to identify people with low values of HDL-C (<1.03 mmol/L in men, <1.30 mmol/L in women), high values of LDL-C (≥4.14 mmol/L), and high values of triglycerides (>2.26 mmol/L).[18] These guidelines were chosen to facilitate comparisons with previous work. Venn diagrams were constructed to illustrate the frequency of different forms of dyslipidemia within Asians and non-Asians. Because cigarette smoking is negatively associated with HDL-C levels, the frequency of lipid abnormalities was also examined by smoking status separately within Asia and Australia/New Zealand.

The outcomes analyzed in this study were fatal or nonfatal CHD (*International Classification of Disease* codes 410, 411, 412, 413, 414, and 798) and stroke (codes 430–438). Fatal CHD and stroke events were recorded in 37 studies from the APCSC using a variety of methods, most often through death registrations or personal contact with subjects or relatives. Nonfatal events were recorded in 8 studies through hospital records or personal contact. The median follow-up was 6.6 years in Asia and 8.3 years in non-Asian countries.

Individuals were divided into 3 mutually exclusive groups according to lipid levels: normal HDL-C, isolated low HDL-C, and nonisolated low HDL-C (ie, low HDL-C combined with elevated LDL-C and/or triglycerides). Differences in the distribution of BP and anthropometry across these groups were assessed with general linear models, and differences in the percentages of smoking and diabetes mellitus were assessed with logistic regression models. All models accounted for the confounding effects of age and study. Hazard ratios (HRs) for CHD and stroke events were calculated with Cox proportional hazard models, with corresponding 95% confidence intervals (CIs) derived with floating absolute risks and taking those with normal HDL-C as the reference group. The continuous relationships between HDL-C and cardiovascular outcomes are described in detail elsewhere.[4] In the main analysis, Cox models were adjusted by age, systolic BP, and current smoking and stratified by study and sex. A sensitivity analysis was performed comparing current smokers with not-current smokers separately within Asia and Australia/New Zealand in models adjusted for age and systolic BP and stratified by study and sex. In a subgroup of the population (n=64 310), information on alcohol consumption at study baseline was available (yes/no); among this group, the models were rerun stratifying by alcohol status. In secondary analyses, we examined the relationships with cardiovascular outcomes when low HDL-C level was defined according to the modified World Health Organization (WHO) guidelines (<1.0 mmol/L in men and <0.9 mmol/L in women) and the European Group for Insulin Resistance (EGIR) guidelines (<1.0 mmol/L).[19]

All analyses were conducted with SAS version 9.1 (SAS Institute, Inc, Cary, NC).

Results

Information was available on 69 145 eligible study participants from 24 studies from the APCSC (Table 1) and 150 915 from 13 studies in the OAC (Table 2). Overall, 87% of men and 86% of women were from Asia. The overall mean levels of cardiovascular risk factors for Asians and non-Asians are summarized in Table 3.

In the Asian cohorts, one third (33%) displayed low levels of HDL-C (n=63 316), and two thirds of these individuals (22% overall) had isolated levels of low HDL-C (Figure 1A). These estimates were comparable in current (Figure Ia in the online-only Data Supplement) and not-current (Figure Ib in the online-only Data Supplement) smokers. High levels of LDL-C either with or without other colipid abnormalities occurred in 13% of the population. When examined by country, the frequency of low HDL-C varied between one quarter and one third of the study population, with the notable exceptions of Singapore and India, where >50% of the

Table 1. Baseline Study Characteristics of Contributing Studies From the Asia Pacific Cohort Studies Collaboration

Cohort	Country	n	Age, y	TC, mmol/L	TG, mmol/L	HDL-C, mmol/L	LDL-C, mmol/L	BMI, kg/m^2	SBP, mm Hg	Smoking, %	Diabetes Mellitus, %	WC, cm	Hip Circumference, cm	Obesity,* %
ALSA	Australia	1121	78 (6)	5.8 (1.1)	1.5 (0.7)	1.3 (0.4)	3.8 (1.0)	25.7 (3.9)	149 (22)	8.3	7.1	. . .	. . .	13.0
ANHF	Australia	8924	43 (13)	5.5 (1.1)	1.4 (0.7)	1.3 (0.4)	3.5 (1.0)	25.3 (4.2)	126 (18)	23.8	1.7	83 (13)	100 (9)	12.2
Busselton	Australia	1585	44 (17)	5.7 (1.2)	1.2 (0.7)	1.5 (0.4)	3.6 (1.1)	24.6 (3.7)	129 (20)	24.0	7.3	. . .	. . .	8.0
Perth	Australia	5826	45 (13)	5.6 (1.1)	1.2 (0.7)	1.4 (0.4)	3.7 (1.0)	25.5 (4.2)	130 (21)	25.4	2.5	. . .	. . .	13.2
Aito town	Japan	893	52 (7)	4.7 (0.8)	1.3 (0.4)	1.4 (0.4)	2.6 (0.8)	22.6 (3.0)	139 (20)	30.8	1.7	. . .	. . .	4.5
Akabane	Japan	1819	54 (8)	5.0 (0.9)	1.2 (0.7)	1.2 (0.3)	3.2 (0.8)	22.5 (3.0)	125 (19)	27.8	2.4	. . .	. . .	4.1
Anzhen02	China	4078	47 (8)	4.7 (0.9)	1.2 (0.7)	1.4 (0.4)	2.7 (0.8)	24.0 (3.3)	122 (18)	20.6	10.7	80 (9)	97 (7)	11.1
Beijing Aging	China	1675	69 (8)	4.4 (1.0)	1.5 (0.8)	1.5 (0.6)	3.0 (1.0)	23.3 (3.9)	141 (25)	30.6	29.4	. . .	. . .	11.4
CISC	China	164	45 (9)	5.0 (0.8)	0.7 (0.6)	1.1 (0.3)	2.8 (1.2)	22.9 (2.7)	123 (20)	73.6		. . .	. . .	4.3
Civil Service Workers	Japan	8910	47 (5)	5.2 (0.9)	1.4 (0.8)	1.4 (0.4)	3.1 (0.8)	22.4 (2.7)	125 (18)	37.8	1.7	. . .	. . .	3.0
CVDFACTS	China	460	45 (16)	4.8 (1.0)	1.2 (0.7)	1.3 (0.4)	3.0 (0.9)	23.2 (3.4)	113 (19)	22.4	3.0	. . .	. . .	8.1
EGAT	Thailand	3390	43 (5)	5.7 (1.1)	1.6 (0.8)	1.2 (0.3)	3.8 (1.0)	23.0 (3.1)	120 (16)	43.0	2.5	. . .	. . .	6.6
Fangshan	China	774	47 (9)	4.6 (1.0)	1.5 (0.7)	1.4 (0.4)	2.5 (0.9)	24.9 (3.6)	132 (25)	38.4	6.3	. . .	. . .	18.9
Guangzhou Occupational	China	9106	43 (6)	5.2 (1.0)	1.4 (0.7)	1.3 (0.5)	3.3 (1.1)	22.6 (3.3)	113 (15)	44.4	7.9	. . .	. . .	7.6
Hong Kong	Hong Kong	183	79 (7)	5.2 (0.9)	1.6 (1.0)	1.5 (0.5)	3.0 (0.8)	22.0 (3.6)	148 (22)	16.9	10.4	81 (10)	91 (8)	7.3
Huashan	China	1744	53 (12)	4.6 (0.9)	1.4 (0.7)	1.4 (0.4)	2.6 (0.8)	23.3 (3.4)	126 (21)	. . .	10.6	. . .	. . .	8.6
Konan	Japan	1206	52 (16)	4.9 (0.9)	1.1 (0.6)	1.6 (0.4)	2.8 (0.8)	21.9 (3.0)	130 (19)	29.7	12.6	. . .	. . .	3.2
Miyama	Japan	404	59 (9)	5.1 (0.9)	1.2 (0.6)	1.3 (0.3)	3.2 (0.8)	22.3 (3.0)	129 (23)	23.6	2.2	. . .	. . .	4.2
Ohasama	Japan	1869	58 (11)	5.0 (0.9)	1.5 (0.8)	1.4 (0.4)	2.9 (0.8)	23.2 (3.1)	127 (17)	20.1	9.2	. . .	. . .	7.3
Seven Cities Cohorts	China	6050	58 (10)	4.9 (1.3)	1.6 (0.7)	1.5 (0.5)	2.7 (1.3)	22.9 (3.8)	134 (25)	33.9	1.6	. . .	. . .	9.9
Shigaraki Town	Japan	3678	57 (14)	5.0 (0.9)	1.4 (0.7)	1.5 (0.4)	2.9 (0.8)	22.5 (3.1)	132 (20)	28.5	7.1	. . .	. . .	4.8
Singapore Heart	Singapore	2063	41 (13	5.8 (1.1)	1.3 (0.8)	1.0 (0.3)	4.2 (1.0)	23.5 (4.4)	123 (21)	20.8	10.9	. . .	. . .	15.4
Singapore NHS92	Singapore	3223	39 (12)	5.3 (1.0)	1.3 (0.8)	1.3 (0.3)	3.5 (0.9)	23.2 (4.2)	118 (18)	18.0	9.1	. . .	. . .	11.6

TC indicates total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; SBP, systolic blood pressure; WC, waist circumference; ALSA, Australian Longitudinal Study of Aging; ANHF, Australian National Heart Foundation; CISC, Capital Iron and Steel Company; CVDFACTS, The Cardiovascular Disease Risk Factors Two-Townships Study; NHS92, National Health Survey 1992; and EGAT, Electricity Generating Authority of Thailand. Ellipses indicate missing data. Values are mean (SD) unless otherwise specified.

*Obesity was defined as body mass index $\geq$30 kg/m^2 in non-Asians and $\geq$28 kg/m^2 in Asians.

population was affected (Table I in the online-only Data Supplement).

In non-Asians, 27% of individuals (n=7754) had low levels of HDL-C either with or without associated colipid abnormalities. Isolated low HDL-C occurred in half of these individuals (n=4021, 14% of non-Asians; Figure 1B). These estimates were similar in current and not-current smokers (Figure IIa and IIb in the online-only Data Supplement,

Table 2. Baseline Study Characteristics of Contributing Studies From the Obesity in Asia Collaboration

Cohort	Country	n	Age, y	TC, mmol/L	TG, mmol/L	HDL-C, mmol/L	LDL-C, mmol/L	BMI, kg/m^2	SBP, mm Hg	Smoking, %	Diabetes Mellitus, %	WC, cm	Hip Circumference, cm	Obesity, %
AUSDIAB	Australia	10 991	52 (15)	5.6 (1.0)	1.5 (0.8)	1.4 (0.4)	3.5 (0.9)	26.9 (4.9)	129 (19)	15.6	5.1	91 (14)	105 (10)	21.7
China (Zhou)	China	43 209	49 (12)	4.7 (1.0)	1.3 (0.7)	1.4 (0.4)	2.7 (0.9)	23.7 (3.6)	126 (22)	29.0	4.8	79 (10)	94 (8)	11.3
EGAT2	Thailand	2746	43 (5)	6.1 (1.1)	1.6 (0.8)	1.5 (0.4)	3.9 (1.1)	23.8 (3.6)	123 (21)	25.8	4.0	84 (10)	96 (7)	11.4
HK (Lam)	Hong Kong	1499	37 (9)	5.1 (0.9)	1.1 (0.8)	1.4 (0.4)	3.3 (0.9)	23.3 (3.2)	118 (15)	14.5	2.3	78 (9)	93 (6)	7.3
India (Mohan)	India	2422	41 (7)	4.6 (1.1)	1.6 (0.8)	1.0 (0.3)	3.0 (1.1)	23.9 (3.6)	121 (13)	31.7	9.9	87 (10)	90 (7)	11.2
India (Mohan)	India	619	48 (9)	5.3 (1.0)	1.5 (1.0)	1.3 (0.4)	3.3 (0.9)	27.0 (4.6)	119 (15)	4.4	2.4	87 (12)	99 (10)	34.0
India (Mohan)	India	2300	40 (13)	4.6 (1.0)	1.3 (0.7)	1.1 (0.3)	2.9 (0.8)	22.8 (4.0)	119 (18)	18.5	8.4	83 (11)	94 (9)	8.8
India (Mohan)	India	4115	47 (9)	4.8 (1.0)	1.7 (0.7)	1.1 (0.2)	3.0 (0.9)	23.3 (4.9)	119 (20)	20.2	8.5	81 (13)	90 (11)	16.3
India (Lear)	India	299	39 (13)	4.4 (1.0)	1.2 (0.7)	1.4 (0.3)	2.5 (0.9)	24.9 (4.3)	114 (14)	5.7	1.4	81 (11)	99 (9)	16.8
India (Patel)	India	271	50 (14)	4.9 (1.0)	1.0 (0.5)	1.2 (0.3)	3.3 (0.9)	21.0 (3.9)	116 (22)	. . .	7.8	76 (12)	92 (8)	4.8
INTERASIA	Thailand	4876	54 (12)	5.4 (1.2)	1.6 (0.8)	1.2 (0.3)	3.5 (1.1)	24.2 (4.4)	122 (20)	20.9	9.4	82 (12)	94 (9)	17.4
KNHANES	Korea	7944	45 (16)	4.9 (1.0)	1.4 (0.7)	1.3 (0.3)	2.9 (0.9)	23.2 (3.2)	126 (20)	. . .	9.1	80 (9)	93 (7)	7.1
Taiwan	Taiwan	69 624	43 (14)	5.2 (1.0)	1.3 (0.7)	1.3 (0.4)	3.3 (0.8)	23.1 (3.4)	128 (23)	. . .	3.6	77 (10)	94 (6)	7.9

TC indicates total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; SBP, systolic blood pressure; WC, waist circumference; AUSDIAB, Australian Diabetes Obesity and Lifestyle Study; EGAT2, Electricity Generating Authority of Thailand 2; INTERASIA, International Collaborative Study of Cardiovascular Disease in Asia; and KNHANES, Korean National Health and Nutrition Examination Survey. Ellipses indicate missing data. Values are mean (SD) unless specified otherwise.

Table 3. Summary of the Baseline Characteristics of the Overall Study Participants From the Asia Pacific Cohort Studies Collaboration and the Obesity in Asia Collaboration

	Men			Women		
		Mean (SD)			Mean (SD)	
Variable	n	Asian	Non-Asian	n	Asian	Non-Asian
Age, y	108 455	46.7 (12.7)	48.5 (15.6)	111 605	46.4 (13.2)	48.1 (15.2)
Total cholesterol, mmol/L	108 455	5.05 (1.03)	5.56 (1.04)	111 605	5.02 (1.03)	5.59 (1.11)
Triglycerides, mmol/L	108 455	1.48 (0.78)	1.51 (0.81)	111 605	1.24 (0.69)	1.26 (0.70)
HDL-C, mmol/L	108 455	1.24 (0.37)	1.24 (0.32)	111 605	1.43 (0.38)	1.53 (0.38)
LDL-C, mmol/L	108 455	3.13 (0.98)	3.64 (0.94)	111 605	3.05 (0.95)	3.49 (0.98)
Body mass index, kg/m^2	103 789	23.4 (3.31)	26.3 (3.81)	108 480	23.1 (3.76)	25.7 (5.07)
Waist circumference, cm	65 906	82.5 (9.5)	93.8 (11.5)	71 580	74.5 (9.8)	81.4 (13.1)
SBP, mm Hg	76 152	125.9 (19.5)	132.1 (18.2)	76 207	123.5 (22.0)	125.8 (20.4)
DBP, mm Hg	76 171	78.7 (12.0)	79.4 (10.9)	76 209	75.9 (11.9)	72.1 (11.1)
Smoking, %	65 803	50.4	23.3	63 154	6.9	17.5
Diabetes mellitus, %	103 903	5.6	4.4	108 705	4.9	4.6

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; and DBP, diastolic blood pressure.

respectively). Overall, the frequency of high LDL-C was twice as high in Asian as in non-Asian populations (26.1% [95% CI, 25.6–26.6] versus 13.4% [95% CI, 13.3–13.6]; $P<0.001$; Figure 2B), whereas the frequency of elevated triglycerides was comparable between non-Asians and Asians (12.6% [95% CI, 12.2–13.0] versus 11.6% [95% CI, 11.5–11.8], respectively, although the *P* for the regional difference was <0.0001 because of the large sample size).

Table 4 shows the mean phenotypic characteristics of individuals with nonisolated low HDL-C, isolated low HDL-C, and normal levels of HDL-C. Overall, low HDL-C levels were more associated with higher values of body mass index and waist circumference and a higher frequency of diabetes mellitus compared with normal levels of HDL-C, regardless of sex and region. There were no consistent associations between BP and smoking status with HDL-C levels within the sex and region groups.

During a median follow-up of 6.8 years, there were 574 fatal and nonfatal CHD events (42% Asia) and 739 fatal and nonfatal stroke events (76% Asia). Of these, there were 253 ischemic and 186 hemorrhagic strokes (the remainder were unclassified). In adjusted analyses, nonisolated low levels of HDL-C were associated with a nearly 60% higher risk of CHD compared with normal levels of HDL-C (HR, 1.57; 95% CI, 1.31–1.87). This association was observed in all individuals regardless of sex, region, and smoking status (Figure 2). This estimate did not differ materially when either the WHO or EGIR cut points for HDL-C were used (Table IIa and IIb in the online-only Data Supplement). In the subgroup for whom information was available on alcohol consumption at study baseline (yes/no), there was no evidence of interaction in the association between low levels of HDL-C with subsequent CHD (HR, 1.55 [95% CI, 1.18–2.04] in current drinkers versus 1.59 [95% CI, 1.26–2.00] in nondrinkers;

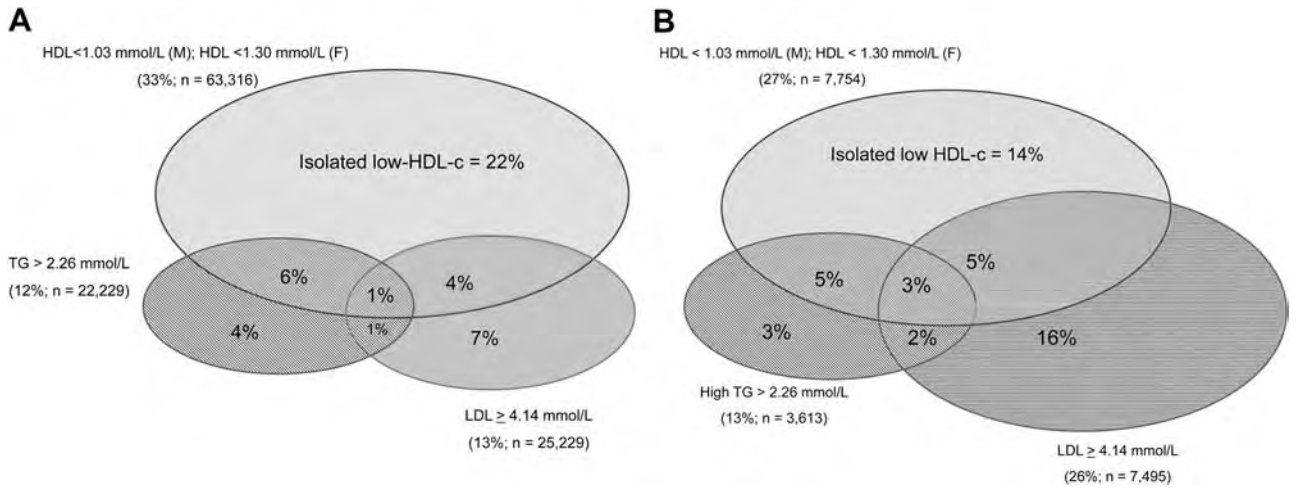

Figure 1. A and **B**, Prevalence of lipid phenotypes in adult Asian populations (**A**; n=191 317) and adult populations from Australia and New Zealand (**B**; n=28 743). HDL indicates high-density lipoprotein; HDL-C, HDL cholesterol; LDL, low-density lipoprotein; and TG, triglycerides.

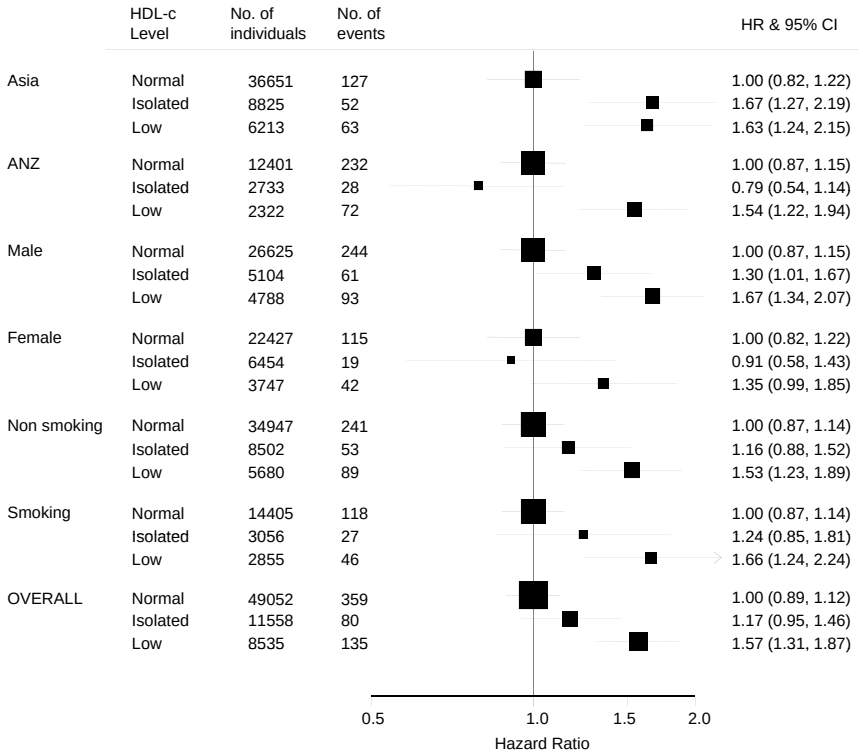

Figure 2. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for coronary heart disease associated with high-density lipoprotein cholesterol levels (HDL-C) by region (Asia vs Australia/New Zealand [ANZ]), sex, and smoking status (current vs not) from studies included in the Asia Pacific Cohort Studies Collaboration. Normal HDL-C means normal levels of HDL-C; isolated, isolated low levels of HDL-C; and low, low levels of HDL-C and high LDL-C and/or high triglycerides. The 3 groups are mutually exclusive. *P* for regional, sex, and smoking interaction=0.016, 0.04, and 0.95, respectively.

P=0.99). For purposes of comparison, the risk of CHD associated with LDL-C level was also determined. In this population, the risk of CHD was nearly 60% higher in those with high levels of LDL-C compared with those with normal levels of LDL-C (HR, 1.58; 95% CI, 1.30–1.93).

There was some evidence that isolated low HDL-C increased the risk of incurring a CHD event compared with normal HDL-C, although the relationship was nonsignificant (HR, 1.17; 95% CI, 0.95–1.46). This estimate did not alter materially when the EGIR cut points were used; however, there was no association when the modified WHO cut points were used (Table II in the online-only Data Supplement), although this may have been a chance finding given the small number of events in those with isolated low HDL-C (n=18). In sensitivity analyses, the relationship between isolated low HDL-C and CHD was particularly apparent in Asian cohorts compared with studies from Australia/New Zealand (HR, 1.67 [95% CI, 1.27–2.19] versus 0.79 [95% CI, 0.54 – 1.14]; *P* for regional interaction=0.016) and in men compared with women (HR, 1.30 [95% CI, 1.01–1.67] versus 0.91 [95% CI, 0.58–1.43]; *P* for sex interaction=0.04). There was no evidence of an interaction with smoking (*P*=0.95) or alcohol (*P*=0.99). In Asians, isolated low HDL-C was as strongly associated with CHD risk as nonisolated low levels of HDL-C (HR, 1.67 [95% CI, 1.27–2.19] versus 1.63 [95% CI, 1.24–2.15], respectively). These results did not differ materially according to how low HDL-C level was defined (Table IIa and IIb in the online-only Data Supplement) or after adjustment for LDL-C and triglycerides (Table III in the online-only Data Supplement).

In adjusted analyses, nonisolated low HDL-C was not associated with risk of stroke compared with those individuals with normal HDL-C (HR, 0.95; 95% CI, 0.78–1.17), both in the overall analysis and within any of the subgroups (Figure 3). This remained unchanged when either the WHO or EGIR cut points for low HDL-C were used (Table IVa and IVb in the online-only Data Supplement). Furthermore, there was no evidence of an interaction between HDL-C level and alcohol consumption (*P*=0.70).

In those with isolated low HDL-C, there was an ≈20% lower risk of stroke compared with those with normal HDL-C both in the overall population and within major subgroups (Figure 3). This remained true regardless of the cut point used to define low HDL-C (Table IVa and IVb in the online-only Data Supplement) and remained unchanged after adjustment for LDL-C and triglycerides (Table III in the online-only Data Supplement).

Discussion

Data from 2 large collaborations of studies with information on nearly 220 000 individuals conducted within populations of the Asia-Pacific region suggest a phenotype of dyslipidemia that is highly prevalent, but not unique, to Asian populations. The most frequent pattern of dyslipidemia among the Asian population (observed in approximately one third) was low HDL-C levels. In two thirds of these individuals, low levels of HDL-C occurred in the absence of any associated colipid abnormality, and this was the most common individual lipid abnormality. In non-Asians, low levels of HDL-C were evident in approximately one quarter of the population, of whom one half had normal levels of LDL-C and triglycerides. Furthermore, the risk of CHD in those individuals expressing the isolated low HDL-C phenotype was 20% higher than in those with normal HDL-C levels. This was particularly evident in Asian populations in whom the risk of CHD associated with isolated low HDL-C was

Table 4. Comparison of the Age- and Study-Adjusted Characteristics of Study Participants According to High-Density Lipoprotein Cholesterol Level by Sex and Ethnicity

	HDL-C Level*					
	Isolated Low HDL-C†		Low HDL-C + High LDL-C and/or TG		Normal HDL-C‡	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Asian men						
SBP, mm Hg	10 263	124.0 (18.7)	6565	127.1 (19.3)	45 783	126.2 (20.0)
DBP, mm Hg	10 262	78.4 (11.8)	6565	80.7 (11.6)	45 780	79.5 (11.9)
BMI, kg/m^2	15 982	24.0 (3.4)	10 029	25.2 (3.2)	64 382	23.0 (3.2)
Waist, cm	11 107	84.3 (9.5)	6614	87.7 (8.6)	38 894	81.1 (9.2)
Smoking, %	8826	49.9	5902	51.8	37 580	50.3
Diabetes mellitus, %	15 962	5.6	10 092	9.9	64 240	4.9
Non-Asian men						
SBP, mm Hg	1877	130.1 (18.1)	1939	134.6 (17.8)	9725	132.1 (18.3)
DBP, mm Hg	1881	78.1 (11.4)	1946	81.5 (11.5)	9737	78.2 (11.7)
BMI, kg/m^2	1858	26.7 (3.9)	1918	28.2 (3.8)	9620	25.8 (3.7)
Waist, cm	1246	94.1 (11.9)	1305	99.5 (10.8)	6740	92.7 (11.1)
Smoking, %	1871	25	1933	29.9	9691	21.7
Diabetes mellitus, %	1881	5.1	1947	6.3	9781	3.9
Asian women						
SBP, mm Hg	17 472	122.3 (21.3)	6827	130.5 (23.2)	36 848	122.8 (21.9)
DBP, mm Hg	17 466	75.5 (11.8)	6826	79.3 (11.9)	36 843	75.5 (12.0)
BMI, kg/m^2	25 732	23.7 (3.9)	9307	25.3 (3.8)	58 615	22.5 (3.5)
Waist, cm	17 521	76.4 (10.0)	5625	81.6 (9.7)	37 738	72.5 (9.0)
Smoking, %	13 485	7.0	5731	8.4	28 939	6.6
Diabetes mellitus, %	25 692	4.8	9321	12.9	58 559	3.7
Non-Asian women						
SBP, mm Hg	2275	122.7 (19.4)	1632	134.1 (21.3)	11 153	125.2 (20.2)
DBP, mm Hg	2275	71.4 (11.9)	1632	75.8 (12.6)	11 167	71.7 (12.1)
BMI, kg/m^2	2238	27.1 (5.9)	1607	28.7 (5.3)	10 981	24.9 (4.6)
Waist, cm	1679	84.6 (14.4)	1145	90.5 (13.4)	7872	79.4 (2.1)
Smoking, %	2268	21.6	1625	25.5	11 106	15.6
Diabetes mellitus, %	2286	3.7	1639	8.2	11 208	2.2

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; SBP, systolic blood pressure; DBP, diastolic blood pressure; and BMI, body mass index.

*Groups are mutually exclusive. For men, low HDL-C is <1.03 mmol/L; for women, <1.30 mmol/L.

†In the absence of a high LDL-C or high TG level.

‡Normal HDL-C with or without high LDL-C and/or TG.

similar to that of individuals exhibiting elevated LDL-C levels.

In comparison, isolated low HDL-C, but not nonisolated low HDL-C, was associated with a reduced risk of stroke, an observation that, to the best of our knowledge, has not been reported previously. A possible explanation for this anomalous finding is that of competing risks; a greater proportion of individuals with the isolated low HDL-C phenotype may have died of CHD, thereby excluding them from those at risk of having a stroke, relative to those with normal HDL-C. In contrast, individuals with normal HDL-C may have had elevated triglycerides or LDL-C and therefore received lipid-lowering medication (in particular fibrates, given that most of the included studies predated the use of statins), which would have reduced the risk of CHD but not stroke.[20]

A key strength of the present analyses, aside from the large sample size, which affords a greater opportunity to investigate specific patterns of lipid abnormalities, is the ability to standardize definitions for dyslipidemia across a large number of studies. Previous studies have been limited in their ability to make such comparisons owing to the lack of uniformity in the cut-point values for low HDL-C. In the present study, the prevalence of low HDL-C was broadly compatible between countries, with approximately one quarter to one third of the overall populations being affected. Singapore and India were exceptions; more than half of the populations were affected, in agreement with earlier studies.[21,22]

Surveys conducted in Asian countries also confirm our finding that low HDL-C is common, affecting between one

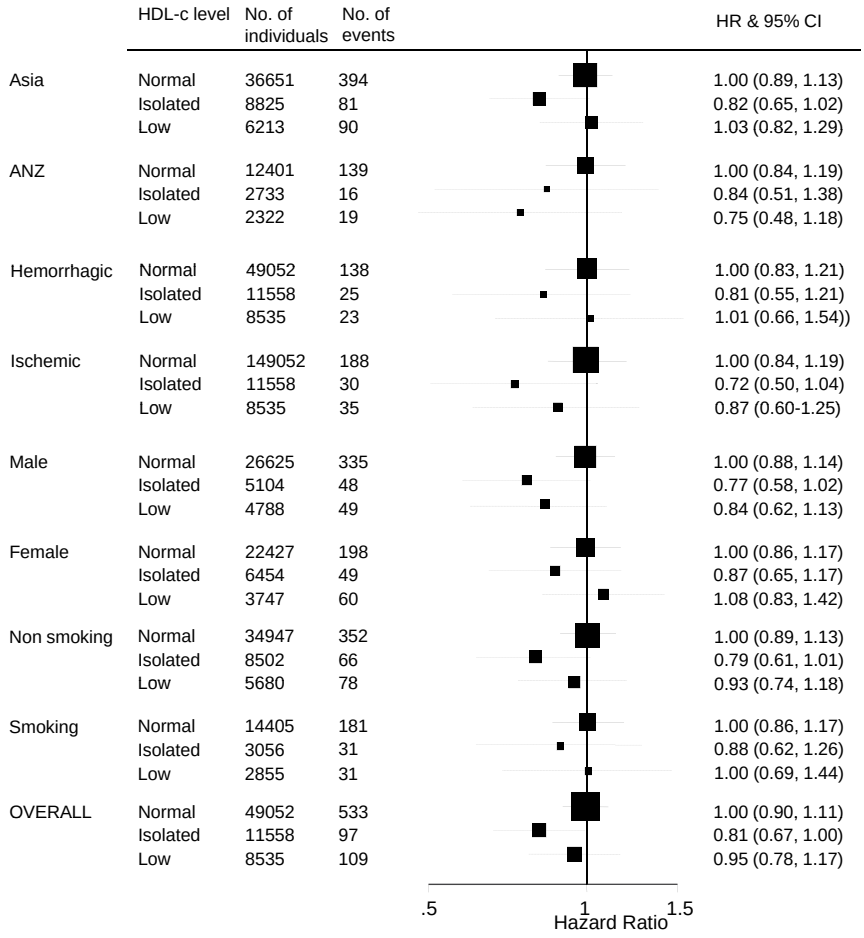

Figure 3. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for stroke associated with high-density lipoprotein cholesterol (HDL-C) levels by region, sex, and smoking status (current vs not) from studies included in the Asia Pacific Cohort Studies Collaboration. ANZ indicates Australia/New Zealand; Normal HDL-C, normal levels of HDL-C; isolated, isolated low levels of HDL-C; and low, low levels of HDL-C and high LDL-C and/or high triglycerides. The 3 groups are mutually exclusive. *P* for regional, sex, and smoking interaction=0.51, 0.51, and 0.88, respectively.

quarter and one half of various populations across Asia. For example, the 2001 Korea National Health and Nutrition Examination Survey of 4639 adults indicated that the prevalence of low HDL-C (defined as <1.03 mmol/L in both sexes) was 35% in men and 18% in women.[23] Because this study used the same HDL-C cut point for men and women rather than the sex-specific values recommended by the NCEP ATP guidelines, it might have considerably underestimated the prevalence of low HDL-C in the female Korean population. Data from Taiwan showed that approximately one quarter of the population in 2002 had low HDL-C defined with sex-specific cut points.[24] In contrast, data from Singapore have indicated that up to one half of the adult population have suboptimal HDL-C levels.[25] The high prevalence of low HDL-C present in these populations may partly explain why migrant studies have shown that South Asians have between 50% and 200% higher CHD rates compared with European populations even after adjustment for conventional risk factors such as smoking, BP, and total cholesterol.[26,27] These results suggest that treatment strategies aiming to increase HDL-C levels might be particularly important in Asia.

The non-Asian populations in this study show a pattern similar to that described for the adult population of the United States. With the use of the National Health and Nutrition Examination Survey (NHANES) 2003–2004 data, the prevalence of low HDL-C was estimated to be 26% and isolated low HDL-C to be 13%,[28] compatible to rates reported for non-Asians in the present study.

In both non-Asian and Asian populations, a low HDL-C level was more prevalent in obese individuals and those with diabetes mellitus. These associations are not unexpected given the clustering of such risk factors in individuals with the metabolic syndrome. Studies have shown that among the nearly 4000 individuals with diabetes mellitus reported in the Pan-European survey, the prevalence of low HDL-C was 50% higher in those with compared with those without diabetes mellitus.[29] Similarly, the greater propensity for low HDL-C in some specific populations (eg, Indians versus other ethnic groups) may be explained in part by their increased susceptibility to central fat accumulation.[30]

Although low HDL-C is associated with several rare genetic diseases, including hypoalphalipoproteinemia, the cause for isolated low HDL-C at the population level remains largely unknown, although factors such as low levels of physical activity, obesity, and avoidance of alcohol are known to be associated with low HDL-C levels. It is therefore possible that variations in diet, alcohol consumption, and physical activity will explain some of the variability between populations. For example, several studies have demonstrated heterogeneity in plasma lipid responses to different levels of dietary fat consumption that may indicate an epigenetic effect.[31,32]

This study has several limitations. First, the ethnic groupings we use are crude and do not take into account the potential variation in genetic differences between Asian populations; we did not have sufficient data to reliably characterize the phenotypes of individuals with isolated low HDL-C by country. Second, given the westernization of many countries across Asia in recent years and the corresponding increase in the prevalence of factors that negatively affect HDL-C levels, such as obesity and low levels of physical activity, the mean population level of HDL-C may have shifted recently to a greater extent in the Asian cohorts. Third, a significant proportion of the included studies are cross-sectional, which precludes examination of the temporal nature of the association between lipids and risk factors. Fourth, there will have been both interstudy and intrastudy measurement errors in the ascertainment of lipid measurements. However, the measurement error is likely to have been random and present across all studies. There may also have been some bias introduced by the different methods used to verify cardiovascular outcomes across the APCSC studies.

Finally, data on apolipoproteins and lipid-lowering therapy were not routinely recorded in the majority of studies included in both the OAC and APCSC, which may have facilitated a more intricate analysis of the data. For example, information on the use of cholesterol-lowering drugs was available in <5% of the entire study population. Statin use is likely to have been uncommon, given that the baseline year of recruitment for these studies ranged from 1966 to 1994. It is possible, however, that LDL-C–lowering therapy, eg, with fibrates or nicotinic acid, which also increases HDL-C,[33] would have been more common in Australia and New Zealand compared with other countries in the Asia-Pacific region. However, data from the pan-European Survey suggest that levels of HDL-C are broadly similar in individuals with and without lipid-lowering therapy.[34]

Conclusions

Isolated low level of HDL-C is a phenotype that appears to be particularly common in Asian populations. Individuals exhibiting this form of lipid abnormality are at increased risk of CHD, but, at the same time, are unlikely to be candidates for lipid-lowering medication because their levels of triglycerides and LDL-C meet targets proposed by current guidelines. These regions will potentially benefit from strategies that can increase levels of HDL-C, such as effective smoking cessation campaigns and initiatives that result in sustained weight loss and increases in physical activity at the population level. Moreover, agents such as niacin and fibrates may be particularly important in Asia. Furthermore, going forward, new drugs such as cholesteryl ester transfer protein inhibitors may be important in cardiovascular prevention in the region.

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Disclosures

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CLINICAL PERSPECTIVE

This study, comprising information from >220 000 individuals from the Asia-Pacific region, describes a novel and potentially important form of dyslipidemia. Low levels of high-density lipoprotein cholesterol (HDL-C) have been independently associated with increased cardiovascular risk. Some earlier observational studies have suggested the existence of such a distinct type of dyslipidemia with low HDL-C occurring in the absence of elevated levels of other lipid fractions, ie, isolated low HDL-C. This phenotype has been postulated to be especially prevalent among Asian populations. Individuals with this form of lipid abnormality are usually not considered to be candidates for lipid-lowering medication because of their comparatively normal levels of total and low-density lipoprotein cholesterol. This study compared the prevalence of isolated low HDL-C in Asian and non-Asian populations and determined whether the risk of coronary heart disease and stroke was elevated in individuals with this form of lipid abnormality. Findings from this study indicated a substantially higher prevalence of isolated low HDL-C among Asians (22.4%) compared with non-Asians (14.5%) that was unlikely to be explained by differences in the background rates of lipid-lowering medication, cigarette smoking, and alcohol use. Both nonisolated low HDL-C and isolated low HDL-C were associated with increased risk of coronary heart disease but not stroke. Compared with non-Asians, the relationship between isolated low HDL-C and subsequent risk of coronary heart disease was stronger in Asians. In this group, it was associated with the same magnitude of coronary risk (≈60%) as low levels of HDL-C combined with other lipid abnormalities.