ORIGINAL RESEARCH

Association of High-Density Lipoprotein-Cholesterol Versus Apolipoprotein A-I With Risk of Coronary Heart Disease: The European Prospective Investigation Into Cancer-Norfolk Prospective Population Study, the Atherosclerosis Risk in Communities Study, and the Women's Health Study

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***Background*—**The contribution of apolipoprotein A-I (apoA-I) to coronary heart disease (CHD) risk stratification over and above high-density lipoprotein cholesterol (HDL-C) is unclear. We studied the associations between plasma levels of HDL-C and apoA-I, either alone or combined, with risk of CHD events and cardiovascular risk factors among apparently healthy men and women.

***Methods and Results*—**HDL-C and apoA-I levels were measured among 17 661 participants of the EPIC (European Prospective Investigation into Cancer)-Norfolk prospective population study. Hazard ratios for CHD events and distributions of risk factors were calculated by quartiles of HDL-C and apoA-I. Results were validated using data from the ARIC (Atherosclerosis Risk in Communities) and WHS (Women's Health Study) cohorts, comprising 15 494 and 27 552 individuals, respectively. In EPIC-Norfolk, both HDL-C and apoA-I quartiles were strongly and inversely associated with CHD risk. Within HDL-C quartiles, higher apoA-I levels were not associated with lower CHD risk; in fact, CHD risk was higher within some HDL-C quartiles. ApoA-I levels were associated with higher levels of CHD risk factors: higher body mass index, HbA1c, non-HDL-C, triglycerides, apolipoprotein B, systolic blood pressure, and C-reactive protein, within fixed HDL-C quartiles. In contrast, HDL-C levels were consistently inversely associated with overall CHD risk and CHD risk factors within apoA-I quartiles ($P<0.001$). These findings were validated in the ARIC and WHS cohorts.

***Conclusions*—**Our findings demonstrate that apoA-I levels do not offer predictive information over and above HDL-C. In fact, within some HDL-C quartiles, higher apoA-I levels were associated with higher risk of CHD events, possibly because of the unexpected higher prevalence of cardiovascular risk factors in association with higher apoA-I levels.

***Clinical Trial Registration*—**URL: https://www.clinicaltrials.gov. Unique identifier: NCT00000479. **(*J Am Heart Assoc*. 2017;6: e006636. DOI: 10.1161/JAHA.117.006636.)**

Key Words: apolipoprotein A-I • cardiovascular disease • coronary heart disease • high-density lipoprotein cholesterol

Prospective epidemiological studies have consistently shown that plasma levels of high-density lipoprotein cholesterol (HDL-C) are inversely associated with coronary heart disease (CHD) risk. However, the biological foundation of this association is controversial. Mendelian randomization studies have shown us that single nucleotide polymorphisms

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Accompanying Tables S1 through S9 are available at http://jaha.ahajournals.org/content/6/8/e006636/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- In 3 large prospective cohort studies, we found that apolipoprotein A-I was unexpectedly associated with increased coronary artery disease risk factors within fixed high-density lipoprotein cholesterol quartiles, and for some quartiles this resulted in increased coronary artery disease risk.

What Are the Clinical Implications?

- Our results indicate that apolipoprotein does not offer predictive information over and above high-density lipoprotein cholesterol levels.

in loci only affecting plasma HDL-C levels do not associate with CHD risk.[1] The inverse association between HDL-C and CHD risk has drawn attention to HDL-C as a pharmacological target to reduce CHD risk. In spite of this, there is currently no evidence in human studies that increasing HDL-C leads to CHD event reduction.[2–4] Combined, these findings give rise to the notion that HDL-C itself might not play a causative role in the protection against atherogenesis and have resulted in a search for parameters that reflect the physical structure or function of HDL as a more relevant predictor of CHD risk. Apolipoprotein A-I (apoA-I), the major constituent of HDL particles, might be such a parameter. Similar associations with CHD risk have been reported for apoA-I as for HDL-C,[5] and antioxidant, anti-inflammatory, antithrombotic, and nitric oxide–promoting properties have been ascribed to apoA-I.[6,7] These findings have driven the development of therapeutic strategies that infuse apoA-I or upregulate apoA-I in the liver that are currently under investigation[8] with varying clinical success.[9–11] Whether apoA-I is a more relevant therapeutic target over HDL-C is heavily debated, however.

Prospective studies comparing the associations of apoA-I and HDL-C with risk of future CHD events have shown conflicting results.[12,13] A possible explanation lies in the intricate relationship between HDL-C and apoA-I levels that is hard to dissect using conventional regression models. Here, we use a new approach by assessing CHD risk based on HDL-C and apoA-I quartiles in a 4×4 fashion. The objective of this study was to assess the association of apoA-I levels with CHD risk and CHD risk factors within fixed HDL-C quartiles, and vice versa, which requires a large study sample. We pursued this objective in the large European Prospective Investigation into Cancer (EPIC) Norfolk cohort, a prospective population study based in the United Kingdom. Results were validated in the ARIC (Atherosclerosis Risk in Communities) cohort and the WHS (Women's Health Study).

Methods

Study Design and Biochemical Analyses

The EPIC-Norfolk study

The EPIC-Norfolk study is a prospective population study of 25 639 male and female residents of Norfolk, United Kingdom, aged between 39 and 79 years. The recruitment process, study design, and population characteristics have been published previously.[14] The study was approved by the Norfolk Local Research Ethics Committee and complies with the declaration of Helsinki. All participants gave written informed consent.

All individuals have been flagged for mortality at the UK Office of National Statistics, with vital status ascertained for the entire cohort. Death certificates were coded by trained nosologists according to the *International Classification of Diseases* 10th revision. In addition, hospitalized participants were identified by using their unique National Health Service number through data linkage with the East Norfolk Health Authority (ENCORE) database, which identifies all hospital contacts throughout England and Wales for residents of Norfolk. Participants were identified as having developed CHD during follow-up if they had a hospital admission and/or died with CHD as the underlying cause during follow-up. CHD was defined as *International Classification of Diseases* 10th revision codes I20 to I25 (which includes myocardial infarction, angina, and other ischemic heart disease). We report results with follow-up to March 31, 2008, after a mean of 12.7±2.3 years. Previous validation studies in this cohort indicate a high specificity of case ascertainment.[15]

Blood samples were drawn at the baseline visit in either fasting or nonfasting state. Samples were processed for assay at the Department of Clinical Biochemistry, University of Cambridge, or stored at −80°C. In the entire population study, serum lipids were analyzed for total cholesterol, HDL-C, and triglyceride on a RA-1000 analyzer (Bayer Diagnostics, Basingstoke, UK). HDL cholesterol levels were measured after precipitation of non-HDL particles with N,N-bis (4-sulfhobutyl)-m-Toluidine-disodium (DSBmT) and peroxidase. Low-density lipoprotein cholesterol levels were calculated with the Friedewald formula.[16] Serum apoA-I and apolipoprotein B (apoB) levels were measured using rate immunonephelometry (Behring Nephelometer BNII, Marburg, Germany) with calibration traceable to the International Federation of Clinical Chemistry primary standards.[17] Researchers and laboratory personnel had no access to identifiable information and could identify samples by number only.

The ARIC Study

The ARIC Study is a population-based prospective cohort study of cardiovascular disease sponsored by the National

Heart, Lung, and Blood Institute. ARIC originally included 15 792 individuals aged 45 to 64 years at baseline (1987–1989), chosen by probability sampling from 4 US communities.[18] Cohort members completed 4 clinic examinations each spread over about 3 years, conducted ≈3 years apart between 1987 and 1998. The data used in this study are from the first visit in 1987–1989. A detailed study protocol is available on the ARIC study website (https://www2.cscc.unc.edu/aric/).

ARIC investigators conduct continuous, comprehensive surveillance for all cardiovascular disease–related hospitalizations and deaths in the 4 communities. CHD was adjudicated on the basis of published criteria.[19] CHD was defined as a definite or probable myocardial infarction, definite coronary death, or coronary revascularization procedure. Those with prevalent CHD were excluded for incident CHD analysis. Follow-up time ended when the participant had a CHD event, died, was lost to follow-up, or survived until December 30, 2009 with a mean follow-up time of 20±3.6 years. Serum lipids and apoA-I levels were measured as previously reported.[20]

The Women's Health Study

The WHS (NCT00000479) is a completed randomized, double-blinded, placebo-controlled trial of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer in women.[21,22] Randomized treatment ended in March 2004, and participants were invited to participate in ongoing observational follow-up. Participants were apparently healthy female healthcare professionals, ages 45 years or older, who were free of self-reported cardiovascular disease and cancer at study entry (1992–1996). At the time of enrollment, women gave written informed consent and completed questionnaires on demographics, anthropometrics, medical history, and lifestyle factors. They were also asked to provide a baseline blood sample; 28 345 women did so, and of these, a total of 27 827 had baseline lipid measurements. We excluded women with missing values for any of the lipid or apolipoprotein measurements (N=275), resulting in 27 552 women for this analysis. The study was approved by the institutional review board of the Brigham and Women's Hospital (Boston, MA).

The end point of incident CHD was defined as nonfatal myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, or coronary death. Information on the occurrence of these end points was ascertained via annual follow-up questionnaires, letters, and telephone calls. Following written informed consent, medical records were obtained and reviewed by a blinded Endpoints Committee for the adjudication of all reported end points based on predefined criteria as previously described.[21,22] We report results with follow-up through 2012, after a mean of 15.8±3.5 years.

HDL-C was measured with a direct homogeneous polyethylene-glycol assay, and apoA-I with an immunoturbidometric assay (DiaSorin, Stillwater, MN). Coefficients of variation for HDL-C and apoA-I were <3%.

Statistical Analysis

We evaluated the distribution of cardiovascular risk factors across quartiles of HDL-C and apoA-I. Metabolic syndrome was defined as previously described.[23] CRP (C-reactive protein) and triglycerides plasma levels showed a skewed distribution and were log-transformed before analysis. *P* values for trend across quartiles (and tertiles for WHS) of HDL-C and apoA-I were assessed in an unadjusted model using the Jonckheere-Terpstra test. Cox proportional hazards models were used to calculate hazard ratios and corresponding 95% CI for CHD risk by quartiles of HDL-C and apoA-I, using the lowest quartile as a reference, and event-free survival per quartile was depicted in Kaplan–Meier curves. Unadjusted regression models were used (model 1), as well as regression models adjusting for sex, age, smoking, body mass index, systolic blood pressure, diabetes mellitus, apoB, log-transformed CRP (model 2), and log-transformed triglycerides (model 3). In addition, we calculated unadjusted hazard ratios and corresponding 95% CIs for combined quartiles of HDL-C and apoA-I. Linear regression analysis was used to assess correlations between HDL-C and apoA-I per HDL-C or apoA-I quartile. Analyses were undertaken using SPSS (version 18.0).

Results

EPIC-Norfolk

A complete data set was available for a total number of 17 661 individuals in the EPIC-Norfolk cohort. This subset did not differ in any of the relevant baseline characteristics from the subset for whom data were missing. A total of 2226 (12.6%) participants experienced a CHD event during follow-up. Baseline characteristics by quartiles of HDL-C and apoA-I are shown in Tables 1 and 2, respectively.

Risk of coronary heart disease across quartiles of HDL-C and apoA-I

Hazard ratios for risk of CHD by HDL-C and apoA-I quartiles are shown in Tables 3 and 4 and Figure 1. Among individuals in the top HDL-C quartile, the hazard ratio for CHD events was 0.34 (95% CI 0.30–0.39) compared with those in the bottom HDL-C quartile (*P* for linear trend <0.001). In a fully adjusted model, the hazard ratio for CHD was 0.69 (95% CI 0.59–0.80) for those in the top versus bottom quartile (*P* for linear trend <0.001).

Table 1. Baseline Characteristics by HDL Cholesterol Quartiles in the EPIC-Norfolk Study

	HDL Cholesterol Quartiles				
	1	2	3	4	*P* Value
N	5031	3595	4444	4591	
HDL cholesterol, mmol/L	1.0±0.1	1.3±0.1	1.5±0.1	2.0±0.3	<0.001
Age, y	59.6±9.1	59.3±9.1	59±9.1	58.8±9.3	<0.001
Male sex	71% (3572)	51% (1834)	35% (1555)	19% (872)	<0.001
Body mass index, kg/m^2	27.3±3.7	26.5±3.67	25.9±3.8	24.9±3.5	<0.001
Diabetes mellitus, % (n)	3.0 (149)	2.1 (75)	1.8 (79)	1.2 (55)	<0.001
HbA1c, %	5.4±1.0	5.3±0.8	5.3±0.8	5.2±0.7	<0.001
Systolic blood pressure, mm Hg	136±18	136±18	134±18	133±19	<0.001
Diastolic blood pressure, mm Hg	83±11	83±11	82±11	81±11	<0.001
Total cholesterol, mmol/L	6.0±1.2	6.2±1.1	6.2±1.1	6.3±1.1	<0.001
LDL cholesterol, mmol/L	4.0±1.0	4.1±1.0	4.0±1.0	3.7±1.0	<0.001
Non-HDL cholesterol, mmol/L	5.0±1.2	4.9±1.1	4.7±1.1	4.2±1.1	<0.001
Triglycerides, mmol/L	2.0 (1.5–2.7)	1.7 (1.2–2.2)	1.4 (1.0–1.9)	1.1 (0.8–1.5)	<0.001
Apolipoprotein A-I, mg/dL	129±22	148±23	161±26	184±30	<0.001
Apolipoprotein B, mg/dL	100±25	99±24	96±24	92±23	<0.001
C-reactive protein, mg/L	2.0 (0.9–4.3)	1.6 (0.8–3.6)	1.6 (0.8–3.5)	1.3 (0.6–2.7)	<0.001
Metabolic syndrome	83% (4176)	70% (2517)	63% (2800)	56% (2571)	<0.001
Alcohol intake, g/day	3.1 (0.8–9.7)	3.4 (0.8–10.5)	4.7 (0.8–10.9)	5.2 (0.9–11.8)	<0.001

Data are shown as mean±SD, percentage (number), or median (interquartile range). *P* for Jonckheere Terpstra test across categories. EPIC indicates European Prospective Investigation into Cancer; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Individuals in the top quartile for apoA-I had a hazard ratio for CHD events of 0.55 (95% CI 0.49–0.62, *P* for linear trend <0.001) using an unadjusted model. In a fully adjusted model the hazard ratio was 0.75 (95% CI 0.66–0.86, *P* for linear trend <0.001).

Table 5 shows the distribution of participants, CHD event rates, and hazard ratio and corresponding 95% CI across HDL-C and apoA-I quartiles. The event-free survival curves per HDL-C and apoA-I quartile are shown in Figure 2. In the majority of study participants (n=9478, 54%), HDL-C quartiles corresponded with apoA-I quartiles. However, for 8183 participants, the HDL-C quartile and apoA-I quartile were discordant.

Compared with study participants in the bottom quartiles for both HDL-C and apoA-I, those in the second, third, and top quartiles for both HDL-C and apoA-I had a hazard ratio (HR) of 0.69 (95% CI 0.59–0.81), HR 0.69 (95% CI 0.59–0.82), and HR 0.57 (95% CI 0.48–0.67), respectively. Those in the lowest HDL-C quartile and the top apoA-I quartile were not at lower CHD risk (HR 0.87, 95% CI 0.54–1.40). By contrast, those in the top HDL-C quartile but the bottom apoA-I quartile were at lower CHD risk (HR 0.47, 95% CI 0.28–0.78), and this hazard ratio was even lower than the participants having both high HDL-C and high apoA-I levels (HR 0.57, 95% CI 0.48–0.67). Within each apoA-I quartile, higher HDL-C levels were associated with lower CHD risk. By contrast, within each HDL-C quartile, we did not find a consistent association between apoA-I and CHD risk. A trend towards increased CHD risk for higher apoA-I levels in the middle HDL-C quartiles was observed, which was significant in the third HDL-C quartile (*P*=0.005).

Distribution of risk factors across quartiles of HDL-C and apoA-I

The distribution of risk factors across HDL-C and apoA-I quartiles is presented in Table 6. Within fixed apoA-I quartiles, HDL-C levels were inversely associated with CHD risk factors (all *P*<0.001). However, the opposite pattern was observed for apoA-I levels within fixed HDL-C quartiles. Here, apoA-I levels were positively associated with age, female sex, body mass index, HbA1c, non-HDL-C, triglycerides, apoB, systolic blood pressure, and CRP (all *P*<0.001). Overall, groups defined by high HDL-C and low apoA-I levels consisted of relatively healthy subjects, compared with subjects defined by low HDL-C and high apoA-I levels, where enrichment for traditional CHD risk factors was observed.

Table 2. Baseline Characteristics by Apolipoprotein A-I Quartiles in the EPIC-Norfolk Study

	Apolipoprotein A-I Quartiles				
	1	2	3	4	*P* Value
N	4325	4514	4403	4419	
HDL cholesterol, mmol/L	1.1±0.3	1.3±0.3	1.5±0.3	1.8±0.4	<0.001
Age, y	58.6±9.2	59.1±9.1	59.3±9.2	59.2	<0.001
Male sex	64% (2768)	56% (2528)	36% (1585)	21% (928)	<0.001
Body mass index, kg/m^2	26.6±3.7	26.4±3.7	26.1±3.9	25.5±3.7	<0.001
Diabetes mellitus, % (n)	2.9 (126)	2.3 (102)	1.8 (77)	1.2 (53)	<0.001
HbA1c, %	5.3±0.8	5.3±0.9	5.3±0.8	5.3±0.8	0.66
Systolic blood pressure, mm Hg	134±18	135±18	135±19	135±19	<0.001
Diastolic blood pressure, mm Hg	82±11	82±11	82±11	82±11	0.90
Total cholesterol, mmol/L	5.9±1.1	6.1±1.1	6.2±1.1	6.4±1.1	<0.001
LDL cholesterol, mmol/L	3.9±1.0	4.0±1.0	4.0±1.0	3.9±1.1	0.50
Non-HDL cholesterol, mmol/L	4.7±1.2	4.8±1.2	4.7±1.2	4.6±1.2	<0.001
Triglycerides, mmol/L	1.7 (1.2–2.4)	1.6 (1.1–2.2)	1.4 (1.0–2.0)	1.3 (0.9–1.8)	<0.001
Apolipoprotein A-I, mg/dL	115±18	145±5	164±6	199±17	<0.001
Apolipoprotein B, mg/dL	88±27	100±23	99±23	99±23	<0.001
C-reactive protein, mg/L	1.9 (0.9–4.4)	1.8 (0.8–3.6)	1.5 (0.8–3.1)	1.5 (0.7–3.3)	<0.001
Metabolic syndrome	71% (3071)	78% (3521)	69% (3038)	55% (2431)	<0.001
Alcohol intake, g/day	3.1 (0.8–9.6)	4.7 (0.8–10.9)	4.1 (0.8–10.9)	5.1 (0.8–11.7)	<0.001

Data are shown as mean±SD, percentage (number), or median (interquartile range). *P* for Jonckheere Terpstra trend test across categories. EPIC indicates European Prospective Investigation into Cancer; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Validation in the ARIC and WHS Study

Atherosclerosis Risk in Communities (ARIC) Study

A full data set was available for 15 494 individuals of the ARIC study. During follow-up, 2993 (19.3%) subjects experienced a CHD event. Baseline characteristics by quartiles of HDL-C and apoA-I are shown in Tables S1 and S2.

Risk of CHD was strongly and inversely associated with HDL-C and apoA-I quartiles in unadjusted and fully adjusted regression analyses (Tables S3 and S4). In a 4×4 analysis by HDL-C and apoA-I quartiles, a small majority (53%, n=8260) was classified in corresponding HDL-C and apoA-I quartiles, whereas 7234 subjects (47%) were not. Within fixed apoA-I quartiles, HDL-C levels were associated with a lower rate of CHD events (Table S5). However, apoA-I levels were not consistently associated with CHD events within fixed HDL-C quartiles, which is in line with the observations in EPIC-Norfolk. Finally, the distribution of risk factors across

Table 3. Risk of CHD Events by HDL Cholesterol Quartiles in the EPIC-Norfolk Study

	HDL Cholesterol Quartiles				
	1	2	3	4	
	<1.1 mmol/L	1.1 to 1.4 mmol/L	1.4 to 1.7 mmol/L	≥1.7 mmol/L	*P* Value
Cases/total	963/5031	479/3595	465/4444	319/4591	
Model 1	1.00	0.67 (0.60–0.74)	0.52 (0.47–0.58)	0.34 (0.30–0.39)	<0.001
Model 2	1.00	0.81 (0.73–0.91)	0.77 (0.69–0.87)	0.61 (0.53–0.71)	<0.001
Model 3	1.00	0.85 (0.76–0.95)	0.83 (0.74–0.94)	0.69 (0.59–0.80)	<0.001

Data are shown as hazard ratios and corresponding 95% CI for the risk of future coronary heart disease events. Hazard ratios were calculated by quartile, using the lowest quartile as reference category. P value is for trend across quartiles. Model 1 indicates an unadjusted regression model. Model 2 is adjusted for sex, age, smoking, body mass index, systolic blood pressure, apolipoprotein B, and C-reactive protein. Model 3 is adjusted for the variables in model 2 and in addition for triglycerides. CHD indicates coronary heart disease; EPIC, European Prospective Investigation into Cancer; HDL, high-density lipoprotein.

Table 4. Risk of CHD Events by Apolipoprotein A-I Quartiles in the EPIC-Norfolk Study

	Apolipoprotein A-I Quartiles				
	1	2	3	4	
	<135 mg/dL	135 to 154 mg/dL	154 to 177 mg/dL	≥177 mg/dL	*P* Value
Cases/total	701/4325	624/4514	494/4403	407/4419	
Model 1	1.00	0.81 (0.73–0.90)	0.66 (0.59–0.74)	0.55 (0.49–0.62)	<0.001
Model 2	1.00	0.77 (0.69–0.86)	0.74 (0.65–0.83)	0.69 (0.61–0.79)	<0.001
Model 3	1.00	0.79 (0.71–0.89)	0.78 (0.69–0.88)	0.75 (0.66–0.86)	<0.001

CHD indicates coronary heart disease; Data are shown as hazard ratios and corresponding 95% CI for the risk of future coronary heart disease events. Hazard ratios were calculated by quartile, using the lowest quartile as reference category. *P* value is for trend across quartiles. Model 1 indicates an unadjusted regression model. Model 2 is adjusted for sex, age, smoking, body mass index, systolic blood pressure, apolipoprotein B, and C-reactive protein. Model 3 is adjusted for the variables in model 2 and in addition for triglycerides. CHD indicates coronary heart disease; EPIC, European Prospective Investigation into Cancer.

HDL-C and apoA-I quartiles is presented in Table S6. There were significant trends across the majority of the HDL-C and apoA-I quartiles for percentage males, body mass index, non-HDL-C, triglycerides, apoB, systolic blood pressure, and prevalence of metabolic syndrome. The characteristics of the individuals at the extremes of the distribution were fundamentally different; the group defined by high HDL-C and low apoA-I levels consisted of relatively healthy subjects compared with the group defined by low HDL-C and high apoA-I levels, where an enrichment of traditional risk factors was observed, similar to the associations observed in EPIC-Norfolk.

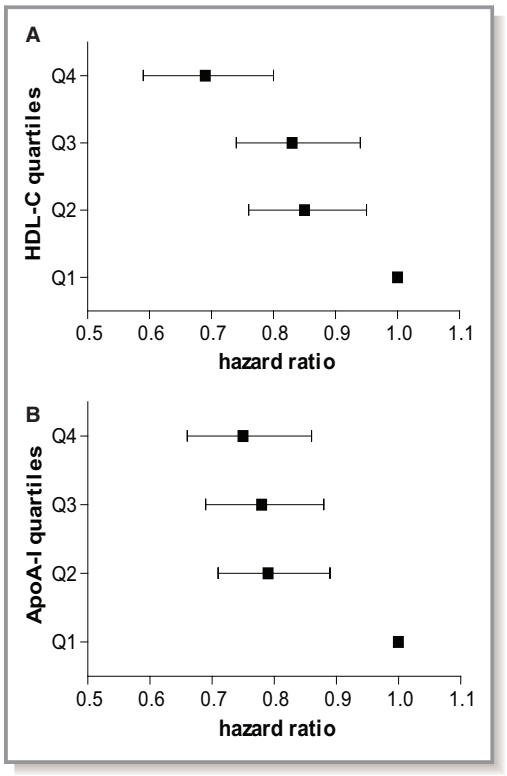

Figure 1. Adjusted hazard ratios for coronary heart disease per HDL-C (A) and apolipoprotein A-I (B) quartile in the EPIC-Norfolk Study. Data are shown as hazard ratios and corresponding 95% CI for the risk of future coronary heart disease events. Hazard ratios were calculated by quartile, using the lowest quartile as reference category, and were adjusted for sex, age, smoking, body mass index, systolic blood pressure, apolipoprotein B, C-reactive protein, and triglyceride levels. ApoA-I indicates apolipoprotein A-I; EPIC, European Prospective Investigation into Cancer; HDL-C, high-density lipoprotein cholesterol.

The Women's Health Study

Of the total 27 552 female participants in the WHS, 1071 (3.9%) experienced a CHD event. Because of the lower CHD event rate, analyses were performed for tertiles of HDL-C and apoA-I. Again, both HDL-C and apoA-I levels were strongly and inversely associated with CHD risk in unadjusted and fully adjusted models (Tables S7 and S8). In a 3×3 analysis by apoA-I and HDL-C tertiles, 18 101 (67%) were classified in corresponding tertiles, in contrast to 9052 (33%) participants who were in different tertiles for HDL-C and apoA-I (Table S9). Within fixed apoA-I tertiles, higher HDL-C levels were consistently associated with lower CHD risk. However, no consistent association for apoA-I and CHD risk was observed, within fixed HDL-C tertiles. In fact, for apoA-I levels there was a trend towards higher CHD risk, within fixed HDL-C tertiles, which was statistically significant for the second HDL-C tertile (*P*=0.002).

Discussion

We present data on the associations between plasma levels of HDL-C and apoA-I, cardiovascular risk factors and risk of CHD in the EPIC-Norfolk cohort. As expected, both HDL-C and apoA-I were strongly and inversely associated with the risk of future CHD. It is noteworthy, however, that these associations were not interchangeable. We found that within each apoA-I quartile, higher plasma HDL-C levels were consistently associated with lower CHD risk. There was, however, no

Table 5. Risk of CHD Events by HDL Cholesterol and Apolipoprotein A-I Quartiles in the EPIC-Norfolk Study

	HDL Cholesterol Quartiles				
	1	2	3	4	*P* Value
ApoA-I quartiles					
1	572/2923	77/615	36/476	16/302	<0.001
	1.00	0.86 (0.67–1.09)	0.61 (0.43–0.85)	0.47 (0.28–0.78)	
2	301/1605	214/1658	97/978	12/273	<0.001
	0.91 (0.79–1.05)	0.69 (0.59–0.81)	0.65 (0.52–0.81)	0.35 (0.19–0.63)	
3	72/397	143/1039	199/1924	80/1043	<0.001
	0.88 (0.68–1.12)	0.75 (0.63–0.91)	0.69 (0.59–0.82)	0.59 (0.46–0.75)	
4	18/97	45/283	133/1066	211/2973	<0.001
	0.87 (0.54–1.40)	0.93 (0.68–1.26)	0.81 (0.67–0.99)	0.57 (0.48–0.67)	
P value	0.41	0.18	0.005	0.35	

Data are shown as number of coronary heart disease events/total number of study participants and unadjusted hazard ratios and corresponding 95% CI. Hazard ratios were calculated using those in the bottom quartiles for both HDL cholesterol and apolipoprotein A-I as reference category. ApoA-I indicates apolipoprotein A-I; CHD, coronary heart disease EPIC, European Prospective Investigation into Cancer; HDL, high-density lipoprotein.

consistent reverse association between apoA-I levels and CHD risk within each HDL-C quartile, and in the EPIC-Norfolk study we even observed a trend towards increased risk in some apoA-I quartiles. This was supported by the unexpected observation that CHD risk factors were positively associated with apoA-I levels within all HDL-C quartiles. In contrast, HDL-C was inversely associated with CHD risk factors within apoA-I quartiles. These findings were externally validated in both the ARIC and WHS studies, and the fact that the observations were consistent in these prospective studies suggests a biologically relevant association.

A number of studies have shown that HDL-C and apoA-I levels are inversely associated with CHD risk. In most subjects, HDL-C and apoA-I levels are closely correlated, and in the EPIC-Norfolk study HDL-C and apoA-I quartiles were concordant in more than half of the participants. This concordance might explain why HDL-C and apoA-I have shown similar association with risk of cardiovascular events in previous studies.[5]

Several studies have addressed the question of the relative contribution and/or superiority of HDL-C and apoA-I levels to CHD risk previously, by comparing their effects in multivariable adjusted regression models. In Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (INTERHEART), the association between apoA-I and CHD risk was stronger than for HDL-C.[24] However, INTERHEART was not a prospective study and did not assess hazard ratios for CHD risk by quartiles of apoA-I and HDL-C. The ERFC (Emerging Risk Factors Collaboration) reported that when apoA-I was added to risk scores containing HDL-C, this led to a slight improvement of cardiovascular disease risk assessment; however, the clinical relevance was questioned.[13] In fact, we reported in a previous article, based on 2349 study participants in a nested case–control set within the EPIC-Norfolk cohort, that the negative association between HDL-C levels and risk of major coronary events was lost upon adjustment for apoA-I and apoB, whereas upon adjustment for HDL-C and apoB the association between apoA-I and risk of major coronary events was retained.[25]

The strong and complex relationships between HDL-C versus apoA-I and other cardiometabolic risk factors make it very difficult to disentangle associations with risk of cardiovascular events, especially when using complex multivariable adjusted regression models. Our current rigorous approach using 4×4 tables to assess these independent associations provides better insight, but can only be performed in very large data sets from prospective cohorts, such as the EPIC-Norfolk, ARIC, and WHS data sets.

In our study, there was no significant association between apoA-I quartiles with the exception of some quartiles where CHD risk was in fact positive rather than inverse. This positive association between CHD risk and apoA-I quartiles has not been reported before. Our results indicate that the predictive value of apoA-I, if anything, does not outperform the predictive value of HDL-C.

The prevalence of CHD risk factors across quartiles of HDL-C and apoA-I confirms our observations. First, we noticed a robust enrichment of risk factors in participants within the lowest HDL-C but highest apoA-I quartile. In other words, subjects with a combined phenotype of low HDL-C and high apoA-I levels are characterized by high levels of triglycerides, apoB, and CRP, and high prevalence of hypertension and metabolic syndrome. Second, we observed that whereas HDL-C quartiles are inversely correlated with all analyzed cardiovascular risk factors, people with the highest apoA-I levels within each HDL-C quartile are characterized by a high

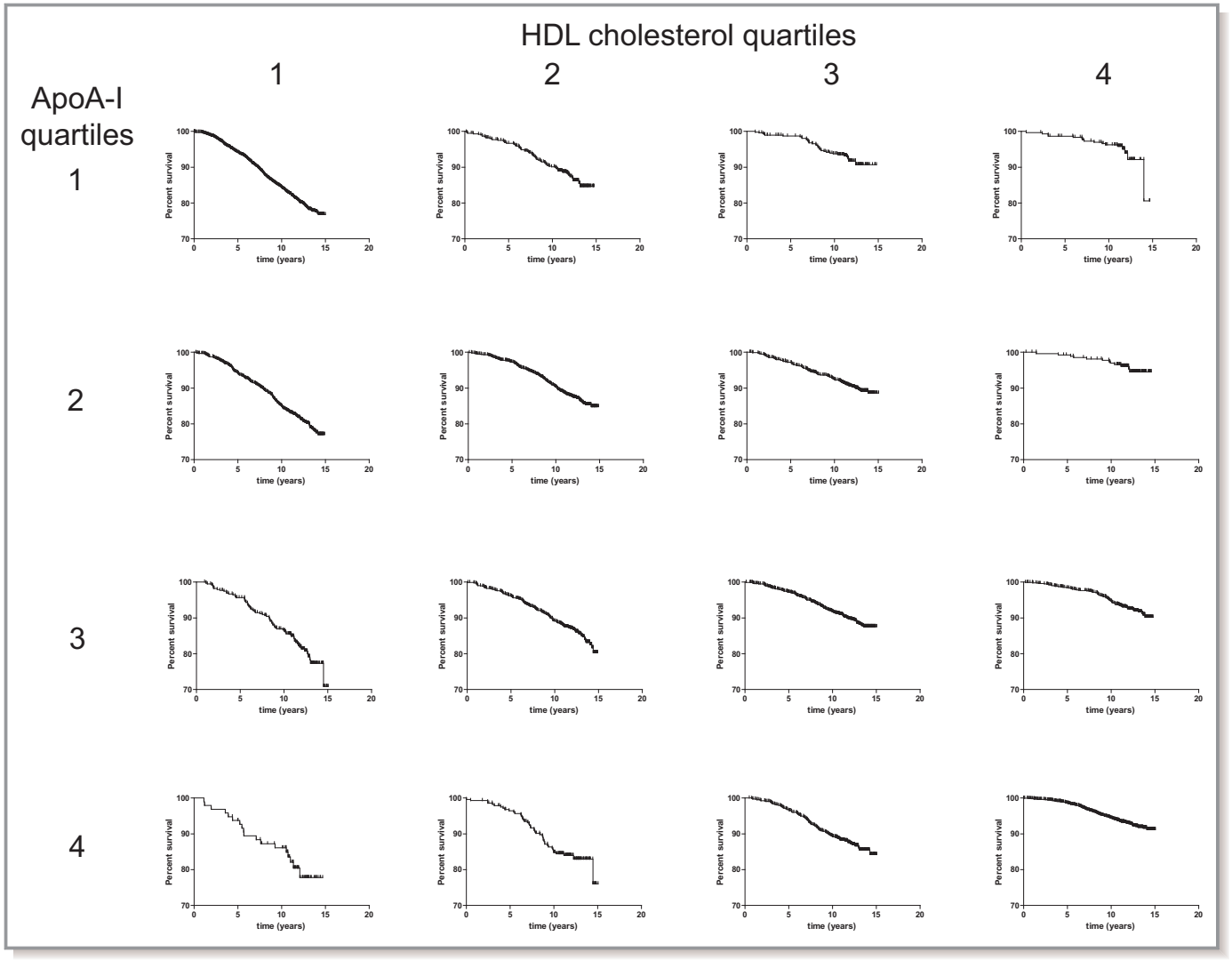

Figure 2. Kaplan–Meier event-free survival curves per HDL cholesterol and apolipoprotein A-I quartile in the EPIC-Norfolk Study. ApoA-I indicates apolipoprotein A-I; EPIC, European Prospective Investigation into Cancer; HDL-C, high-density lipoprotein cholesterol.

prevalence of risk factors; age, body mass index, triglycerides, systolic blood pressure, CRP, prevalence of metabolic syndrome, and percentage males were consistently higher in participants in the top apoA-I quartile compared with those in the lowest quartile, irrespective of the HDL-C quartile. This phenomenon, which we found to be consistent among 3 large prospective studies and within all HDL-C quartiles, has so far not been described in the literature. This unexpected association between established cardiovascular risk factors and apoA-I was possibly not acknowledged to date because it was masked by the very close relationship between apoA-I and HDL-C.

A possible mechanism could be related to the increased rate of metabolic syndrome observed in the high apoA-I quartiles, which has been shown to coincide with high plasma levels of endogenous corticosteroids such as glucocorticoids[26,27] and androgens,[28] which in turn leads to higher levels of apoB and apoA-I.[29] This might imply that individuals in the high HDL-C/high apoA-I quartiles are characterized by overproduction of not only apoB but also apoA-I.

Limitations

Several aspects of this study merit attention when interpreting the results. First, although HDL-C and apoA-I measurements were available in a large set of study participants, these measurements do not inform us about the apolipoprotein content of HDL particles and the intraindividual range of apoA-I molecules per particle.[30] Second, samples in EPIC-Norfolk were not drawn in a fasting state, although the majority of samples in WHS were fasting. The fact that HDL-C and apoA-I are not strongly affected by a meal does not exclude the possibility of spurious associations. Third, CHD events in EPIC Norfolk were based on ICD coding for

Table 6. Baseline Characteristics by HDL-C and apoA-I Quartiles in the EPIC-Norfolk Study

	ApoA-I Quartiles	HDL Cholesterol Quartiles				*P* Value
		1	2	3	4	
Apolipoprotein A-I, mg/dL	1	116±17 (2909)	113±21 (604)	108±20 (456)	111±18 (289)	<0.001
	2	143±5 (1605)	146±6 (1658)	147±5 (978)	147±6 (273)	<0.001
	3	163±6 (397)	163±6 (1039)	165±6 (1924)	167±6 (1043)	<0.001
	4	189±14 (97)	191±13 (282)	192±14 (1061)	202±18 (2863)	<0.001
P value		<0.001	<0.001	<0.001	<0.001	
HDL cholesterol, mmol/L	1	0.93±1.13 (2932)	1.24±0.05 (615)	1.48±0.08 (476)	1.9±0.32 (302)	<0.001
	2	1.03±0.09 (1605)	1.25±0.05 (1658)	1.46±0.08 (978)	1.88±0.23 (273)	<0.001
	3	1.04±0.09 (397)	1.26±0.05 (1039)	1.49±0.08 (1924)	1.86±0.18 (1043)	<0.001
	4	1.03±0.10 (97)	1.26±0.05 (283)	1.52±0.08 (1066)	2.05±0.30 (2973)	<0.001
P value		<0.001	<0.001	<0.001	<0.001	
Age, y	1	59.1±9.1 (2932)	57.5±9.0 (615)	57.6±9.2 (476)	57.4±9.4 (302)	<0.001
	2	60±9.0 (1605)	59±9.0 (1658)	58.1±9.1 (978)	57.2±9.3 (273)	<0.001
	3	60.7±9.0 (397)	60.1±9.1 (1039)	59.1±9.0 (1924)	58.3±9.4 (1043)	<0.001
	4	61.1±8.6 (97)	60.8±8.8 (283)	60.1±9.2 (1066)	59.3±9.3 (2973)	<0.001
P value		<0.001	<0.001	<0.001	<0.001	
Male sex	1	75.5 (2214/2932)	50.6 (311/615)	33.6 (160/476)	22.8 (69/302)	<0.001
	2	67.5 (1083/1605)	57.0 (945/1658)	44.0 (430/978)	22.3 (61/273)	<0.001
	3	52.9 (210/397)	44.7 (464/1039)	34.6 (665/1924)	24.6 (257/1043)	<0.001
	4	46.4 (45/97)	40.6 (115/283)	27.3 (291/775)	15.6 (464/2973)	<0.001
P value		<0.001	<0.001	<0.001	<0.001	
Body mass index, kg/m^2	1	27.1±3.6 (2926)	26.2±3.7 (614)	25.4±3.7 (475)	24.7±3.5 (302)	<0.001
	2	27.3±3.7 (1600)	26.2±3.4 (1657)	25.5±3.5 (977)	25.1±4.0 (273)	<0.001
	3	28±4.2 (396)	27.1±3.9 (1039)	26±3.8 (1923)	24.7±3.3 (1042)	<0.001
	4	28.3±3.8 (97)	27.3±3.9 (283)	26.5±3.8 (1064)	24.9±3.5 (2967)	<0.001
P value		<0.001	<0.001	<0.001	0.28	
HbA1c, %	1	5.4±0.9 (1059)	5.2±0.7 (318)	5.3±0.8 (341)	5.2±0.8 (228)	0.001
	2	5.4±1.0 (615)	5.3±0.8 (476)	5.3±1.0 (238)	5.2±0.8 (140)	<0.001
	3	5.7±1.2 (207)	5.3±0.8 (479)	5.3±0.8 (737)	5.2±0.7 (304)	<0.001
	4	6±1.5 (54)	5.6±0.7 (166)	5.3±0.7 (574)	5.3±0.7 (1499)	<0.001
P value		0.001	<0.001	0.34	0.01	
Non-HDL cholesterol, mmol/L	1	4.9±1.1 (2932)	4.6±1.1 (615)	4.5±1.2 (476)	4±1.0 (302)	<0.001
	2	5.2±1.1 (1605)	4.9±1.1 (1658)	4.4±1.1 (978)	4.1±1.1 (273)	<0.001
	3	5.3±1.2 (397)	5.1±1.1 (1039)	4.7±1.1 (1924)	4.3±1.2 (1043)	<0.001
	4	5.6±1.2 (97)	5.2±1.1 (283)	5±1.1 (1066)	4.3±1.1 (2973)	<0.001
P value		<0.001	<0.001	<0.001	<0.001	
Triglycerides, mmol/L	1	2.0 (1.4–2.7) (2932)	1.4 (1.0–1.9) (615)	1.3 (1.0–1.8) (476)	1.0 (0.8–1.4) (302)	<0.001
	2	2.1 (1.5–2.7) (1605)	1.6 (1.1–2.1) (1658)	1.2 (0.9–1.6) (978)	1.0 (0.8–1.4) (273)	<0.001
	3	2.3 (1.7–2.9) (397)	1.9 (1.4–2.4) (1039)	1.4 (1.0–1.8) (1924)	1.1 (0.8–1.4) (1043)	<0.001
	4	2.4 (1.7–3.1) (97)	2.1 (1.5–2.7) (283)	1.6 (1.2–2.2) (1066)	1.1 (0.9–1.5) (2973)	<0.001
P value		<0.001	<0.001	<0.001	<0.001	

Continued

Table 6. Continued

	ApoA-I Quartiles	HDL Cholesterol Quartiles				*P* Value
		1	2	3	4	
Apolipoprotein B, mg/dL	1	96±25 (2871)	79±23 (577)	66±19 (415)	59±16 (241)	<0.001
	2	106±23 (1601)	101±22 (1653)	94±21 (975)	76±21 (271)	<0.001
	3	109±22 (394)	105±23 (1035)	99±22 (1915)	92±22 (1038)	<0.001
	4	116±23 (95)	109±23 (282)	105±22 (1059)	96±22 (2958)	<0.001
P value		<0.001	<0.001	<0.001	<0.001	
Systolic blood pressure, mm Hg	1	135±18 (2925)	132±17 (613)	131±17 (476)	131±18 (302)	<0.001
	2	138±18 (1601)	136±18 (1658)	132±18 (975)	130±18 (273)	<0.001
	3	139±17 (397)	138±18 (1037)	135±18 (1920)	131±19 (1042)	<0.001
	4	142±18 (97)	140±20 (283)	138±19 (1061)	134±19 (2968)	<0.001
P value		<0.001	<0.001	<0.001	<0.001	
C-reactive protein, mg/L	1	1.8 (0.8–3.8) (2897)	1.1 (0.5–2.4) (595)	0.9 (0.4–1.9) (451)	0.7 (0.3–1.4) (276)	<0.001
	2	2.1 (1.1–4.1) (1587)	1.5 (0.8–3.2) (1635)	1.2 (0.6–2.6) (970)	1.0 (0.5–2.3) (265)	<0.001
	3	2.4 (1.3–4.2) (390)	1.9 (1.0–3.7) (1024)	1.5 (0.8–3.2) (1899)	1.0 (0.5–2.0) (1024)	<0.001
	4	3.2 (1.6–5.7) (96)	2.2 (1.2–4.9) (280)	2.0 (1.0–4.0) (1050)	1.4 (0.7–2.9) (2931)	<0.001
P value		<0.001	<0.001	<0.001	<0.001	
Metabolic syndrome	1	84.0 (2464/2932)	58.9 (362/615)	35.9 (171/476)	26.8 (81/302)	<0.001
	2	82.2 (1319/1605)	77.5 (1285/1658)	77.9 (762/978)	53.1 (145/273)	<0.001
	3	78.6 (312/397)	68.3 (710/1039)	66.1 (1271/1924)	72.2 (753/1043)	0.54
	4	85.6 (83/97)	61.5 (174/283)	56.1 (598/1066)	53.1 (1580/2973)	<0.001
P value		0.02	0.97	0.30	0.07	
Alcohol intake, g/d	1	6.9±10.7 (2830)	7.4 10.4 (539)	7.3±11.4 (464)	8.5±11.4 (297)	0.01
	2	8.3±12.1 (1554)	8.5±13.0 (1616)	9.3±12.5 (947)	9.4±12.9 (268)	0.01
	3	7.5±11.1 (385)	8.6±13.9 (1007)	8.8±13.6 (1874)	9.5±13.8 (1009)	0.002
	4	10±14.7 (90)	8.2±12.9 (276)	8.8±13.3 (1036)	9.8±13.6 (2876)	<0.001
P value		0.003	0.36	0.59	0.10	

For continuous variables, data are shown as mean±SD or in case of skewed distribution, as median (interquartile range). In each cell, the number between parentheses represents the total number of observations on which the summary estimate was based. For categorical variables, data are presented as percentage, and between parentheses number and total. *P* value is for Jonckheere Terpstra trend test across categories. ApoA-I indicates apolipoprotein A-I; EPIC, European Prospective Investigation into Cancer; HDL-C, high-density lipoprotein cholesterol.

hospitalizations and death certificates, and not adjudicated specifically for the purpose of this study, although events were adjudicated by medical record review for WHS and ARIC. The small numbers of participants and CHD events in the extremes of the HDL-C and apoA-I distributions warrant caution when interpreting the hazard ratios for these groups. Lastly, we did not have data on diabetes mellitus duration available and only HbA1C levels were available for 50% of the cohort and we are therefore not fully informed on diabetes mellitus severity or prediabetic conditions. We did adjust for diabetes mellitus status, which was available for all study participants, but cannot rule out that the confounding effect of glucose metabolism might be underestimated in our study.

In conclusion, we show that both HDL-C and apoA-I are inversely correlated with CHD risk. Our findings demonstrate that apoA-I levels do not offer predictive information over and above HDL-C. In fact, within fixed HDL-C quartiles, higher apoA-I levels were associated with a higher prevalence of cardiovascular risk factors. This finding is new and unexpected and was found consistently among the 3 cohorts that were studied. This could be a relevant finding in light of the current development of apoA-I increasing strategies.

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics by HDL cholesterol quartiles in the ARIC study

	HDL cholesterol quartiles				
	1	2	3	4	p-value
N	4148	3619	3879	3848	
HDL cholesterol, mmol/L	0.87±0.12	1.15±0.07	1.41±0.09	1.94±0.34	<0.0001
Age, years	54.4±5.75	54.1±5.78	54.3±5.79	53.9±5.72	0.0003
Male sex % (n)	72 (3002)	52 (1886)	36 (1378)	18 (708)	<0.0001
Body mass index, kg/m^2	29.0±4.85	28.4±5.29	27.7±5.50	25.6±5.13	<0.0001
Diabetes mellitus % (n)	15.6 (647)	10.5 (379)	8.0 (308)	4.6 (178)	<0.0001
HbA1c, %	N/A	N/A	N/A	N/A	N/A
Systolic blood pressure, mmHg	121.7±17.4	121.9±19.2	121.3±19.1	120.0±19.6	<0.0001
Diastolic blood pressure, mmHg	73.9±10.9	74.0±11.2	73.7±11.3	73.0±11.6	<0.0001
Total cholesterol, mmol/L	5.45±1.11	5.60±1.10	5.61±1.11	5.59±1.02	<0.0001
LDL cholesterol, mmol/L	3.66±0.99	3.77±0.99	3.63±1.02	3.19±0.98	<0.0001
Non-HDL cholesterol, mmol/L	4.58±1.10	4.46±1.10	4.21±1.11	3.64±1.04	<0.0001
Triglycerides, mmol/L	1.80 (1.32-2·51)	1.34 (0.99-1.80)	1.12 (0.86-1.48)	0.89 (0.70-1.19)	<0.0001
Apolipoprotein A-I, mg/dL	105.5±18.46	122.9±17.96	137.8±19.90	167.1±28.08	<0.0001
Apolipoprotein B, mg/dL	101.2±29.59	98.3±28.93	92.7±28.31	81.8±25.24	<0.0001
C-reactive protein, mg/L	N/A	N/A	N/A	N/A	N/A
Metabolic syndrome % (n)	72 (2968)	44 (1588)	25 (956)	13 (490)	<0.0001
Alcohol intake, g/day	0 (0-4.31)	0 (0-5.66)	0 (0-6.47)	0 (0-8.63)	<0.0001

Data are shown as mean ± standard deviation, percentage (number), or median (interquartile range). P for Jonckheere Terpstra test across categories. HDL indicates high-density lipoprotein; LDL indicates low-density lipoprotein.

Table S2. Baseline characteristics by apolipoprotein A-I quartiles in the ARIC study

	Apolipoprotein A-I quartiles				
	1	2	3	4	p-value
N	3969	3941	3785	3799	
HDL cholesterol, mmol/L	0.96±0.22	1.18±0.24	1.40±0.28	1.83±0.44	<0.0001
Age, years	54.2±5.76	54.2±5.79	54.1±5.83	54.2±5.68	0.5901
Male sex % (n)	66 (2630)	53 (2094)	38 (1420)	22 (830)	<0.0001
Body mass index, kg/m^2	28.6±5.04	28.1±5.24	27.6±5.44	26.4±5.41	<0.0001
Diabetes mellitus % (n)	12.7 (502)	10.0 (393)	9.4 (357)	6.9 (260)	<0.0001
HbA1c, %	N/A	N/A	N/A	N/A	N/A
Systolic blood pressure, mmHg	120.8±17.87	121.5±18.78	121.2±19.20	121.4±19.46	0.9585
Diastolic blood pressure, mmHg	73.2±10.86	73.9±11.26	73.9±11.50	73.5±11.42	0.4412
Total cholesterol, mmol/L	5.38±1.08	5.51±1.06	5.63±1.11	5.72±1.07	<0.0001
LDL cholesterol, mmol/L	3.64±0.99	3.64±0.97	3.62±1.03	3.34±1.05	<0.0001
Non-HDL cholesterol, mmol/L	4.43±1.09	4.33±1.11	4.24±1.16	3.89±1.16	<0.0001
Triglycerides, mmol/L	1.51 (1.10-2.15)	1.30 (0.94-1.83)	1.15 (0.85-1.64)	1.02 (0.77-1.43)	<0·0001
Apolipoprotein A-I, mg/dL	97.1±11.52	121.1±5.44	140.3±5.96	175.3±21.76	<0.0001
Apolipoprotein B, mg/dL	97.6±28.92	95.4±28.81	93.6±29.38	87.5±28.13	<0.0001
C-reactive protein, mg/L	N/A	N/A	N/A	N/A	N/A
Metabolic syndrome % (n)	57 (2267)	43 (1693)	33 (1241)	21 (801)	<0.0001
Alcohol intake, g/day	0 (0-4.31)	0 (0-5.86)	0 (0-6.47)	0 (0-8.63)	<0.0001

Data are shown as mean ± standard deviation· percentage (number), or median (interquartile range). P for Jonckheere Terpstra trend test across categories. HDL indicates high-density lipoprotein; LDL indicates low-density lipoprotein.

Table S3. Risk of coronary heart disease events by HDL cholesterol quartiles in the ARIC study

	HDL cholesterol quartiles				p-value
	1	2	3	4	
	0.25-1.02 mmol/L	1.03-1.27 mmol/L	1.27-1.57 mmol/L	1.58-4.22 mmol/L	
cases/total	1295/4148	783/3619	607/3879	308/3848	
Model 1	1.00	0.62 (0.57-0.68)	0.43 (0.39-0.47)	0.21 (0.18-0.23)	<0.001
Model 2	1.00	0.70 (0.64-0.77)	0.57 (0.51-0.63)	0.36 (0.32-0.42)	<0.001
Model 3	1.00	0.75 (0.69-0.83)	0.64 (0.58-0.72)	0.44 (0.38-0.51)	<0.001

Table S4. Risk of coronary heart disease events by apolipoprotein A-I quartiles in the ARIC study

	Apolipoprotein A-I quartiles				
	1	2	3	4	p-value
	20-111 mg/dL	112-130 mg/dL	131-151 mg/dL	152-304 mg/dL	
cases/total	1130/3969	859/3941	598/3785	406/3799	
Model 1	1.00	0.71 (0.65-0.77)	0.49 (0.44-0.54)	0.32 (0.29-0.36)	<0.001
Model 2	1.00	0.79 (0.72-0.86)	0.62 (0.56-0.69)	0.51 (0.46-0.58)	<0.001
Model 3	1.00	0.83 (0.75-0.90)	0.68 (0.61-0.75)	0.58 (0.51-0.66)	<0.001

Data are shown as hazard ratios and corresponding 95% confidence intervals for the risk of future coronary heart disease events. Hazard ratios were calculated by quartile, using the lowest quartile as reference category. Model 1 indicates an unadjusted regression model. Model 2 is adjusted for sex, age, smoking, body mass index, systolic blood pressure, and low-density lipoprotein cholesterol (C-reactive protein not available). Model 3 is adjusted for the variables in model 2 and in addition for triglycerides.

Table S5. Risk of coronary heart disease events by HDL cholesterol and apolipoprotein A-I quartiles in the ARIC study

	HDL cholesterol quartiles				p-value
	1	2	3	4	
ApoA-I quartiles					
1	842/2642 1.00	223/998 0.63 (0.54-0.72)	62/302 0.56 (0.43-0.73)	3/27 0.27 (0.09-0.84)	<0.001
2	366/1188 0.94 (0.83-1.06)	304/1393 0.61 (0.54-0.70)	171/1147 0.39 (0.33-0.46)	18/213 0.20 (0.13-0.32)	<0.001
3	78/275 0.86 (0.68-1.08)	210/1023 0.56 (0.48-0.65)	235/1552 0.40 (0.34-0.46)	75/935 0.20 (0.16-0.25)	<0.001
4	9/43 0.63 (0.33-1.22)	46/205 0.63 (0.47-0.85)	139/878 0.43 (0.36-0.51)	212/2673 0.20 (0.17-0.23)	0.006
p-value	0.043	0.257	0.411	0.082	

Data are shown as number of coronary heart disease events / total number of study participants· and hazard ratios and corresponding 95% confidence intervals. Hazard ratios were calculated using those in the bottom quartiles for both HDL cholesterol and apolipoprotein A-I as reference category. HDL indicates high-density lipoprotein; ApoA-I indicates apolipoprotein A-I.

Table S6. Baseline characteristics by HDL-C and apoA-I quartiles in the ARIC study

		HDL cholesterol quartiles				
		1	2	3	4	p-value
	ApoA-I quartiles					
Apolipoprotein A-I, mg/dl	1	94.9±12.15 (2642)	101.3±7.81 (998)	103.8±7.63 (302)	92.8±22.57 (27)	<0.0001
	2	119.5±5.34 (1188)	121.1±5.34 (1393)	122.3±5.32 (1147)	124.2±4.48 (213)	<0.0001
	3	137.9±5.56 (275)	138.9±5.59 (1023)	140.3±5.99 (1552)	142.5±5.70 (935)	<0.0001
	4	164.4±15.21 (43)	160.2±8.75 (205)	165.3±12.29 (878)	179.9±23.24 (2673)	<0.0001
p-value		<0.0001	<0.0001	<0.0001	<0.0001	
HDL cholesterol, mmol/L	1	0.84±0.13 (2642)	1.13±0.06 (998)	1.36±0.08 (302)	1.78±0.20 (27)	<0.0001
	2	0.91±0.10 (1188)	1.14±0.07 (1393)	1.39±0.08 (1147)	1.71±0.15 (213)	<0.0001
	3	0.93±0.11 (275)	1.16±0.06 (1023)	1.41±0.09 (1552)	1.76±0.15 (935)	<0.0001
	4	0.88±0.12 (43)	1.18±0.06 (205)	1.43±0.09 (878)	2.03±0.36 (2673)	<0.0001
p-value		<0.0001	<0.0001	<0.0001	<0.0001	
Age, years	1	54.3±5.72 (2642)	54.0±5.86 (998)	54.2±5.78 (302)	53.3±5.34 (27)	0.1139
	2	54.5±5.76 (1188)	54.2±5.66 (1393)	54.1±5.91 (1147)	52.8±5.89 (213)	0.0011
	3	54.6±5.90 (275)	54.2±5.80 (1023)	54.2±5.78 (1552)	53.6±5.89 (935)	0.0071
	4	52.1±5.50 (43)	54.0±6.06 (205)	54.9±5.65 (878)	54.0±5.64 (2673)	0.0130
p-value		0.5460	0.5426	0.0076	0.0013	
Male sex	1	74.4 (1966/2642)	53.6 (535/998)	40.4 (122/302)	25.9 (7/27)	<0.0001
	2	70.3 (836/1188)	54.9 (765/1393)	38.3 (439/1147)	25.4 (54/213)	<0.0001
	3	66.2 (182/275)	48.7 (498/1023)	35.6 (552/1552)	20.1 (188/935)	<0.0001
	4	41.9 (18/43)	42.9 (88/205)	30.2 (265/878)	17.2 (459/2673)	<0.0001
p-value		<0.0001	0.0015	<0.0001	0.0013	
Body mass index, kg/m^2	1	29.0±4.76 (2641)	27.9±5.42 (996)	27.6±5.67 (302)	24.9±3.59 (27)	<0.0001
	2	28.9±4.83 (1188)	28.4±5.21 (1391)	27.4±5.59 (1147)	25.5±4.41 (212)	<0.0001
	3	29.7±5.38 (275)	28.6±5.24 (1022)	27.7±5.39 (1548)	26.0±5.31 (934)	<0.0001
	4	31.6±5.95 (43)	29.0±5.35 (204)	28.0±5.51 (878)	25.5±5.13 (2673)	<0.0001
p-value		0.1526	0.0001	0.0058	0.0451	
HbA1c, %	1	N/A	N/A	N/A	N/A	N/A
	2	N/A	N/A	N/A	N/A	N/A
	3	N/A	N/A	N/A	N/A	N/A

	4	N/A	N/A	N/A	N/A	N/A
p-value		N/A	N/A	N/A	N/A	
Non-HDL cholesterol, mmol/L	1	4.51±1.07 (2642)	4.32±1.09 (997)	4.12±1.13 (302)	3.72±0.97 (27)	<0.0001
	2	4.66±1.10 (1188)	4.39±1.05 (1393)	4.07±1.07 (1147)	3.54±0.95 (213)	<0.0001
	3	4.79±1.19 (275)	4.62±1.14 (1022)	4.22±1.09 (1552)	3.69±1.05 (935)	<0.0001
	4	5.31±1.67 (43)	4.73±1.17(205)	4.40±1.16 (878)	3.64±1.04 (2672)	<0.0001
p-value		<0.0001	<0.0001	<0.0001	0.5208	
Triglycerides, mmol/L	1	1.74 (1.30-2.39) (2642)	1.20 (0.90-1.60) (998)	1.02 (0.82-1.30) (302)	0.85 (0.56-1.10) (27)	<0.0001
	2	1.81 (1.31-2.55) (1188)	1.30 (0.98-1.73) (1393)	1.04 (0.80-1.37) (1147)	0.84 (0.63-1.04) (213)	<0.0001
	3	2.22 (1.55-3.40) (275)	1.50 (1.12-1.95) (1023)	1.12 (0.87-1.47) (1552)	0.85 (0.67-1.08) (935)	<0.0001
	4	3.42 (1.90-4.91) (43)	1.72 (1.25-2.47) (205)	1.28 (0.97-1.74) (878)	0.91 (0.71-1.22) (2673)	<0.0001
p-value		<0.0001	<0.0001	<0.0001	<0.0001	
Apolipoprotein B, mg/dl	1	99.9±29.1 (2641)	94.3±27.5 (997)	89.6±29.8 (301)	87.3±25.7 (27)	<0.0001
	2	102.7±29.1 (1188)	96.6±28.0 (1393)	89.5±27.8 (1147)	78.9±23.9 (213)	<0.0001
	3	106.1±32.9 (275)	103.5±30.1 (1022)	92.8±27.3 (1552)	80.5±25.0 (934)	<0.0001
	4	112.2±41.9 (43)	104.3±31.2 (204)	97.7±29.6 (877)	82.4±25.4 (2673)	<0.0001
p-value		0.0001	<0.0001	<0.0001	0.0267	
Systolic blood pressure, mmHg	1	120.9±17.1 (2641)	120.7±19.4 (998)	119.8±19.0 (302)	114.3±18.1 (27)	0.0390
	2	122.5±17.7 (1187)	122.2±19.4 (1391)	120.8±19.3 (1146)	115.7±16.6 (213)	<0.0001
	3	124.5±18.3 (275)	122.3±18.7 (1023)	121.0±19.5 (1551)	119.3±19.3 (934)	<0.0001
	4	128.5±16.1 (43)	122.9±19.9 (205)	123.1±18.1 (878)	120.6±19.8 (2673)	<0.0001
p-value		<0.0001	0.0479	0.0005	0.0011	
C-reactive protein, mg/L	1	N/A	N/A	N/A	N/A	N/A
	2	N/A	N/A	N/A	N/A	N/A
	3	N/A	N/A	N/A	N/A	N/A
	4	N/A	N/A	N/A	N/A	N/A
p-value		N/A	N/A	N/A	N/A	
Metabolic syndrome	1	70.0 (1849/2642)	35.7 (356/998)	19.9 (60/302)	7.4 (2/27)	<0.0001
	2	72.3 (858/1187)	42.0 (584/1392)	20.4 (234/1147)	8.0 (17/212)	<0.0001
	3	81.1 (223/275)	51.8 (529/1022)	24.0 (373/1551)	12.4 (116/935)	<0.0001
	4	88.4 (38/43)	58.0 (119/205)	32.9 (289/878)	13.3 (355/2671)	<0.0001
p-value		0.0003	<0.0001	<0.0001	0.0738	
Alcohol intake, g/day	1	0 (0-4.31) (2623)	0 (0-4.31) (992)	0 (0-6.20) (301)	0 (0-5.31) (27)	0.3070

	2	0 (0-5.66) (1183)	0 (0-5.66) (1386)	0 (0-5.93) (1143)	0 (0-7.54) (213)	0.2855
	3	0 (0-5.86) (273)	0 (0-5.66) (1016)	0 (0-7.54) (1543)	0 (0-5.93) (930)	0.5574
	4	0 (0-1.89) (43)	0 (0-8.04) (204)	0 (0-5.66) (872)	0 (0-9.56) (2658)	<0.0001
p-value		0.2109	0.1830	0.9514	<0.0001	

For continuous variables data are shown as mean ± standard deviation or in case of skewed distribution, as median (interquartile range). In each cell the number between parentheses represents the total number of observations on which the summary estimate was based. For categorical variables, data are presented as percentage, and between parentheses number and total. P-value is for Jonckheere Terpstra trend test across categories. HDL indicates high-density lipoprotein; LDL indicates low-density lipoprotein; ApoA-I indicates apolipoprotein A-I.

Table S7. Risk of coronary heart disease events by HDL cholesterol tertiles in WHS

	HDL cholesterol tertiles			p-value
	1	2	3	
	< 44 mg/dL	44 – 55 mg/dL	> 55 mg/dL	
cases/total	514/7487	287/8780	270/11285	
Model 1	1·00	0.45 (0.39-0.53)	0.33 (0.28-0.38)	<0·001
Model 2	1·00	0.50 (0.43-0.58)	0.40 (0.34-0.47)	<0·001
Model 3	1·00	0.56 (0.48-0.66)	0.49 (0.41-0.59)	<0·001
Model 4	1·00	0.58 (0.49-0.68)	0.50 (0.42-0.60)	<0·001

Table S8. Risk of coronary heart disease events by apolipoprotein A-I tertiles in WHS

	Apolipoprotein A-I tertiles			
	1	2	3	p-value
	< 132 mg/dL	132-150 mg/dL	> 150 mg/dL	
cases/total	381/6729	283/7564	407/13259	
Model 1	1·00	0.64 (0.55-0.75)	0.52 (0.45-0.60)	<0·001
Model 2	1·00	0.64 (0.55-0.75)	0.52 (0.44-0.60)	<0·001
Model 3	1·00	0.69 (0.58-0.81)	0.57 (0.49-0.68)	<0·001
Model 4	1.00	0.72 (0.61-0.84)	0.61 (0.52-0.72)	<0·001

Data are shown as hazard ratios and corresponding 95% confidence intervals for the risk of future coronary heart disease events. Hazard ratios were calculated by quartile, using the lowest quartile as reference category. Model 1 indicates an unadjusted regression model. Model 2 is adjusted for age, randomized treatment assignment, hormone use, smoking, body mass index, blood pressure, low-density lipoprotein cholesterol and C-reactive protein. Model 3 is adjusted for the variables in model 2 and in addition for triglycerides. Model 4 is adjusted for the variables in model 3 plus diabetes.

Table S9. Risk of coronary heart disease events by HDL cholesterol and apolipoprotein A-I tertiles in WHS

	HDL cholesterol tertiles			p-value
	1	2	3	
ApoA-I tertiles				
1	336/4940 1.00	42/1584 0.37 (0.27-0.51)	3/205 0.19 (0.06-0.60)	<0·001
2	130/1980 0.95 (0.78-1.16)	117/4032 0.40 (0.33-0.50)	36/1552 0.32 (0.23-0.45)	<0·001
3	48/567 1.23 (0.91-1.6)	128/3164 0.57 (0.46-0.70)	231/9129 0.33 (0.28-0.39)	<0·001
p-value	0.47	0.004	0.47	

Data are shown as number of coronary heart disease events / total number of study participants· and hazard ratios and corresponding 95% confidence intervals. Hazard ratios were calculated using those in the bottom tertiles for both HDL cholesterol and apolipoprotein A-I as reference category. HDL indicates high-density lipoprotein; ApoA-I indicates apolipoprotein A-I.