

Original Article

Association of Serum Lipids and Coronary Heart Disease in Contemporary Observational Studies

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Background—The use of statins increased among US adults with high coronary heart disease (CHD) risk after publication of the 2001 cholesterol treatment guidelines.

Methods and Results—We analyzed the association between lipids and CHD among 9578 Reasons for Geographic and Racial Differences in Stroke (REGARDS) study participants and 346595 Kaiser Permanente Southern California (KPSC) members with baseline lipid measurements in 2003 to 2007. We performed the same analyses among 14590 Atherosclerosis Risk In Communities (ARIC) study participants with lipid measurements in 1987 to 1989. Analyses were restricted to blacks and whites 45 to 64 years of age without CHD who were not taking statins at baseline. Total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured at baseline. Low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and ratios of total to high-density lipoprotein cholesterol and triglycerides to high-density lipoprotein cholesterol were calculated. The prevalence of diabetes mellitus, history of stroke, and antihypertensive medication use increased at higher low-density lipoprotein cholesterol in ARIC but not in REGARDS or KPSC. Over 8.9 years of follow-up, 225 CHD events occurred in REGARDS, 6547 events in KPSC, and 583 events in ARIC. After multivariable adjustment, less favorable lipid levels were associated with higher hazard ratios for CHD in ARIC. These associations were attenuated in REGARDS and KPSC. For example, the hazard ratio associated with the highest versus lowest quartile of low-density lipoprotein cholesterol (≥ 146 versus ≤ 102 mg/dL) was 1.89 (95% confidence interval, 1.42–2.51) in ARIC, 1.25 (95% confidence interval, 0.81–1.92) in REGARDS, and 1.49 (95% confidence interval, 1.38–1.61) in KPSC.

Conclusion—The association between lipids and CHD in contemporary studies may be attenuated by the preferential use of statins by high-risk individuals. (*Circulation*. 2016;133:00-00. DOI: 10.1161/CIRCULATIONAHA.115.011646.)

Key Words: coronary disease ■ epidemiology ■ follow-up studies ■ lipids

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In 2001, the Third Report of the National Cholesterol Education Program, Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) provided guidelines for the diagnosis and treatment of dyslipidemia among US adults.¹ These guidelines recommended that healthcare providers use an individual's low-density lipoprotein cholesterol (LDL-C) level and coronary heart disease (CHD) risk in the decision to initiate statins for primary prevention. In ATP III, statin initiation was recommended for adults with high LDL-C or with low to moderate LDL-C levels but with a high estimated 10-year CHD risk or CHD risk equivalents.¹ The percentage of US adults recommended lipid-lowering therapy by ATP III who were taking statins

increased from 20% in 1999 to 2000 to 38% in 2003 to 2004 and 43% in 2009 to 2010.^{2,3}

Clinical Perspective on p XXX

Given the recommendations for the selective use of statins for primary prevention in ATP III, the group of individuals with high LDL-C who remain untreated may be enriched for adults who have low CHD risk. Therefore, it is possible that the association between LDL-C and incident CHD among adults not taking statins has changed since the publication of ATP III. This might have important implications for the interpretation of epidemiological studies conducted in the era of widespread statin use and for the accuracy of CHD and cardiovascular

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disease risk prediction equations that were derived from data on lipids collected before the publication of ATP III.⁴⁻⁶

The main objective of the present analysis was to determine the association of LDL-C and other serum lipids, including non-high-density lipoprotein cholesterol (non-HDL-C), HDL-C, triglycerides, and ratios of total cholesterol (TC) to HDL-C and triglycerides to HDL-C, with incident CHD after the publication of the ATP III guidelines and the subsequent increase in statin use among US adults. For comparison, we conducted an identical analysis on the association between serum lipids and CHD incidence using data from an era before statin use became common in primary prevention. We hypothesized that the association of LDL-C and other serum lipids with CHD incidence in observational studies would be weaker among untreated adults in the era after publication of the ATP III guidelines as a result of the preferential use of statins by individuals with high LDL-C or low to moderate LDL-C but high CHD risk.

Methods

Study Populations

We used data from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study and Kaiser Permanente Southern California (KPSC) healthcare system to analyze the association between serum lipids and CHD risk for the time period after the publication of the ATP III guidelines. For comparison, we used data from the public-use Atherosclerosis Risk in Communities (ARIC) study data set to analyze the same associations during the period before publication of the ATP III guidelines and the widespread use of statins.

The REGARDS study was designed to investigate reasons underlying the higher rate of stroke mortality among blacks compared with whites and among residents of the southeastern United States compared with other US regions.⁷ CHD events have been identified and adjudicated in an ancillary study.⁸ A total of 30239 black and white men and women ≥ 45 years of age were recruited from all 48 contiguous US states and the District of Columbia between January 1, 2003, and October 31, 2007. KPSC is a healthcare delivery system that provides care for ≈ 3.9 million members in the Southern California region.⁹ The ARIC study was designed to investigate the origin of atherosclerosis in a cohort of black and white men and women 45 to 64 years of age from 4 US communities.¹⁰ A total of 15792 participants were enrolled between 1987 and 1989. The REGARDS and ARIC studies were approved by the Institutional Review boards at the participating centers, and all participants provided written informed consent. The use of KPSC administrative data and electronic health records for the present analysis was approved by the KPSC Institutional Review Board with a waiver for written informed consent. All analyses in KPSC were conducted in compliance with the Health Insurance Portability and Accountability Act regulations.

All REGARDS study participants, black and white KPSC members with a complete lipid panel between January 1, 2003, and October 31, 2007, and ARIC participants in the limited-access public-use data set were assessed for eligibility. A lipid panel that included TC, HDL-C, and triglycerides in 2003 to 2007 was required for KPSC members to match the enrollment period in REGARDS. Additionally, KPSC members were required to have 365 days of continuous healthcare coverage before their first lipid panel. This period was used to assess baseline characteristics. We excluded REGARDS study participants and KPSC members < 45 or ≥ 65 years of age to match the age range of ARIC participants. Further exclusion criteria in REGARDS, KPSC, and ARIC were a history of CHD or the use of lipid-lowering medications at baseline (defined below) and lack of postbaseline participant follow-up to identify the occurrence of CHD events. After these exclusions were applied, 9578 REGARDS study participants, 346595 KPSC members, and 14590 ARIC study participants were included in the present analysis (Figure 1).

Baseline Assessment

The REGARDS and ARIC Studies

As part of the baseline evaluation in the REGARDS and ARIC studies, an interview was conducted, and a blood sample and an ECG were obtained for each participant. Self-reported information collected at baseline in the REGARDS and ARIC studies included age, race, sex, education, annual household income, alcohol consumption, current cigarette smoking, history of stroke, and use of antihypertensive medication. History of CHD at baseline was defined by self-report of a previous diagnosis of myocardial infarction, coronary bypass, or coronary angioplasty (or stenting in REGARDS). Participants with evidence of a previous myocardial infarction on the baseline ECG were also considered to have a history of CHD. Use of lipid-lowering medication was assessed by self-report in the REGARDS study and through the review of pill bottles for all medications that participants reported taken during the 2 weeks before their baseline study visit in ARIC. For REGARDS study participants, use of statins was also assessed through the review of pill bottles for all medications taken during the 2 weeks preceding their baseline study visit. Pill bottle data to identify statin use at baseline are not included in the public-use data set for the ARIC study.

With the use of the blood collected at baseline in REGARDS and ARIC, serum glucose, creatinine, and lipids were measured. Diabetes mellitus was defined as self-reported treatment with oral antidiabetes medications or insulin, fasting (≥ 8 hours) serum glucose ≥ 126 mg/dL, or nonfasting serum glucose ≥ 200 mg/dL.¹¹ For each participant, estimated glomerular filtration rate (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.¹² Baseline serum creatinine levels from ARIC participants were calibrated as previously described.¹³ Reduced eGFR was defined as < 60 mL \cdot min⁻¹ \cdot 1.73 m⁻².¹⁴

KPSC Members

For KPSC members, baseline was defined by the date of their first lipid panel that included TC, HDL-C, and triglycerides between January 1, 2003, and October 31, 2007. Baseline characteristics of KPSC members before the lipid panel were identified from administrative databases and electronic health records. These characteristics included age, sex, race, education, income, alcohol consumption, smoking, diabetes mellitus, reduced eGFR, history of stroke and CHD, and use of antihypertensive medications and lipid-lowering medications (Table I in the online-only Data Supplement).

Serum Lipids Measurements at Baseline

Six serum lipids were analyzed in the present study: LDL-C, non-HDL-C, HDL-C, triglycerides, ratio of TC to HDL-C, and ratio of triglycerides to HDL-C. TC, HDL-C, and fasting triglycerides were measured by colorimetric reflectance spectrophotometry in REGARDS. In ARIC, automated enzymatic methods (Monotest Cholesterol and GPO Triglyceride procedures, Boehringer Mannheim) were implemented with the use of a Cobas-Bio Analyzer (Roche) to measure TC, HDL-C, and fasting triglycerides. TC, HDL-C, and triglycerides were measured by the Kaiser Permanente Regional Laboratory using enzymatic methods. The Friedewald equation was used to calculate LDL-C for individuals with triglycerides < 400 mg/dL in each population.¹⁵ We also calculated values for non-HDL-C (TC minus HDL-C), ratio of TC to HDL-C (TC divided by HDL-C), and ratio of triglycerides to HDL-C (triglycerides divided by HDL-C).

CHD Incidence

Trained personnel in both the REGARDS and ARIC studies used similar approaches to adjudicate incident CHD events.¹⁶ REGARDS participants were contacted by telephone every 6 months, and medical records were retrieved when a heart-related hospitalization was reported by the participant or a proxy respondent. When possible CHD-related deaths were reported, interviews with next of kin or proxies, medical records in the last year of life, death certificates, and autopsy reports were used to determine whether a CHD event was the underlying cause of death. Follow-up of ARIC participants included annual telephone interviews and in-person clinic visits at 3-year

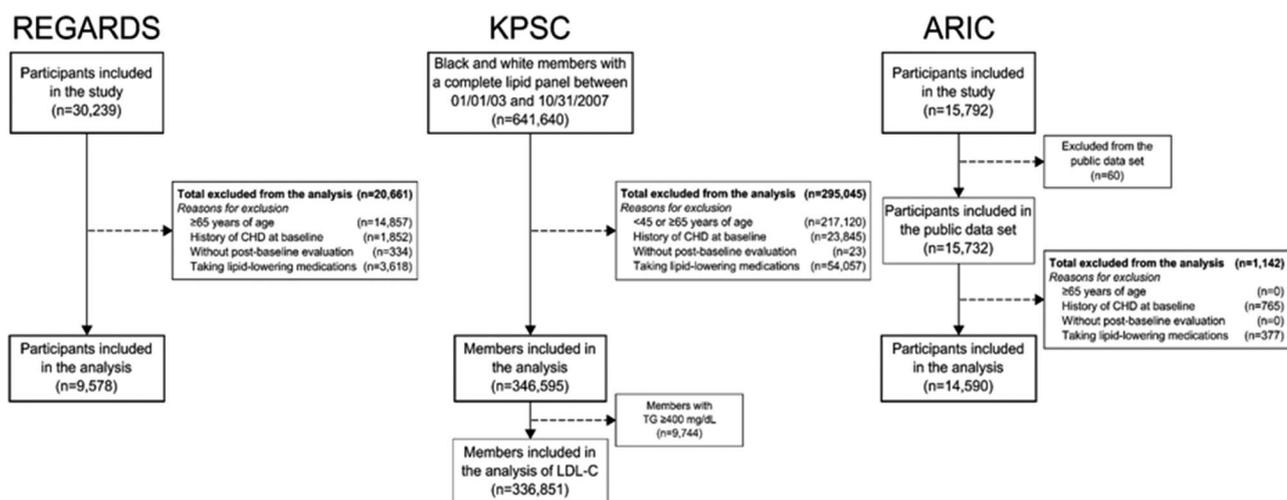


Figure 1. Flowchart of individuals from Reasons for Geographic and Racial Differences in Stroke (REGARDS), Kaiser Permanente Southern California (KPSC), and Atherosclerosis Risk in Communities (ARIC) included in the analysis. CHD indicates coronary heart disease; LDL-C, low-density lipoprotein cholesterol; and TG, triglycerides.

intervals. Additional information on CHD incidence was retrieved from hospital records and death certificates through a community surveillance system. The definition of CHD events from the REGARDS and ARIC studies included definite or probable myocardial infarction or CHD death (death preceded by cardiac symptoms or signs or a history of CHD and with no evidence of noncoronary causes).

Incident CHD events after the baseline lipid panel identified among KPSC members included nonfatal myocardial infarctions, defined by an inpatient stay with a discharge diagnosis code of 410.x according to the *International Classification of Diseases, Ninth Revision* in any position, or CHD deaths, defined by an underlying cause of death identified with *International Classification of Diseases, 10th Revision* codes I20 through I25. KPSC members' deaths were identified from health plan databases, State of California death certificate files, and Social Security Administration death files.

Adjudicated CHD outcomes were available through December 31, 2011, in REGARDS (maximum follow-up, 8.9 years). To match the follow-up time in REGARDS, ARIC participants and KPSC members who remained free of CHD events and alive were censored after 8.9 years of follow-up.

Statistical Analysis

Baseline characteristics of individuals in REGARDS, KPSC, and ARIC included in the present analysis were calculated. For the main analysis, each lipid was divided into 4 levels defined by quartile cut points in the REGARDS study. We chose to use quartiles because few individuals were available in some categories (eg, LDL-C ≥ 160 mg/dL) when clinical cut points were applied. To examine preferential treatment of high-risk individuals with statins after the publication of ATP III, baseline characteristics of individuals in REGARDS, KPSC, and ARIC not taking lipid-lowering medications were calculated by category of LDL-C.

Age-, race-, and sex-adjusted CHD incidence rates were calculated for each lipid category with Poisson regression. Cox proportional hazards models were used to calculate hazard ratios (HRs) for CHD associated with categories of each serum lipid, with the most favorable category used as the reference (eg, lowest LDL-C, highest HDL-C). Three models with progressive adjustment were conducted. The first model included adjustment for age, race, and sex. The second model included the covariates from the first model plus education, household income, alcohol consumption, and current smoking. The third model included variables in the second model plus diabetes mellitus, reduced eGFR, history of stroke, and use of antihypertensive medication. All regression models from REGARDS also included adjustment for region of residence (stroke belt, stroke buckle, and nonbelt regions).⁷ Trends in incidence rates and HRs across categories of each lipid were calculated by modeling the lipid categories as

an ordinal variable. A lower HR for CHD associated with the highest category of LDL-C in contemporary studies may be driven by fewer individuals with very high LDL-C. Therefore, we repeated the analysis for LDL-C after creating a fifth category for individuals with LDL-C ≥ 190 mg/dL. In sensitivity analyses, we calculated HRs for CHD associated with serum lipids as continuous variables and, separately, with categories of lipids defined by quartile cut points derived with ARIC study data.

All analyses in REGARDS and ARIC were conducted with multiple imputation to replace missing data, including covariates and non-fasting LDL-C and triglycerides values. For each lipid analyzed, we imputed 25 data sets using chained equations. Multiple imputation was based on observed values from all the covariates included in the fully adjusted Cox regression models and the outcome.^{17,18} The results were similar in analyses conducted without multiple imputation (data not shown). Analyses in KPSC were conducted with missing indicator variables rather than multiple imputation because of the large number of observations. All analyses were conducted with Stata/I.C. 12.1 (Stata Corp, College Station, TX).

Results

Participant Characteristics

The mean age of individuals included in the present study was 56.7, 53.4, and 54.0 years in REGARDS, KPSC, and ARIC, respectively (Table 1). By design, a high percentage of REGARDS study participants were black. REGARDS participants were more likely to have at least a high school education compared with KPSC members and ARIC study participants. An annual household income $\geq \$25,000$ was more common among REGARDS participants and KPSC members compared with ARIC participants. A smaller percentage of REGARDS participants and KPSC members were currently smoking cigarettes compared with ARIC participants. Antihypertensive treatment was more common in the REGARDS study and among KPSC members. The mean HDL-C and ratio of triglycerides to HDL-C were similar in REGARDS, KPSC, and ARIC. Mean TC, LDL-C, and non-HDL-C were lower for REGARDS participants compared with KPSC members and ARIC participants. Mean ratio of TC to HDL-C was lower in REGARDS participants and KPSC members compared with ARIC participants.

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Table 1. Baseline Characteristics of Individuals From REGARDS, KPSC, and ARIC Included in the Analysis

	REGARDS (n=9578)	KPSC (n=346 595)	ARIC (n=14 590)
Age, mean (SE), y	56.7 (0.05)	53.4 (0.01)	54.0 (0.05)
Men, %	39.3	42.5	43.3
Blacks, %	43.7	20.5	27.6
Region of residence,* %			
Stroke belt (buckle states)	21.4
Stroke belt (nonbuckle states)	36.1
Other contiguous US states	42.5
High school or higher education level, %	92.5	81.1	76.6
Annual household income, %			
<US \$25 000	24.1	2.8	38.5
≥US \$25 000	75.9	91.2	61.5
Unknown	...	6.0	...
Alcohol consumption, %			
None	57.5	45.4	61.4
Moderate	37.8	38.9	30.0
Heavy	4.7		8.3
Unknown	...	15.8	...
Current smoking, %			
Yes	18.7	14.7	26.3
No	81.3	78.8	73.7
Unknown	...	6.5	...
Diabetes mellitus, %	12.7	7.9	11.1
Reduced eGFR, %	2.8	4.8	2.6
History of stroke, %	2.6	1.2	1.4
Taking antihypertensive medication, %	36.7	29.3	23.9
Total cholesterol, mean (SE), mg/dL	202.2 (0.40)	214.1 (0.07)	214.1 (0.35)
LDL-C, mean (SE), mg/dL	123.5 (0.36)	132.9 (0.06)	136.2 (0.34)
Non-HDL-C, mean (SE), mg/dL	148.9 (0.40)	159.9 (0.07)	161.9 (0.37)
HDL-C, mean (SE), mg/dL	53.3 (0.17)	54.2 (0.03)	52.3 (0.14)
TG, mean (SE), mg/dL	126.6 (0.95)	134.8 (0.12)	128.4 (0.72)
Ratio of TC to HDL-C, mean (SE)	4.1 (0.01)	4.2 (0.003)	4.5 (0.01)
Ratio of TG to HDL-C, mean (SE)	2.9 (0.04)	2.9 (0.004)	3.0 (0.03)

ARIC indicates Atherosclerosis Risk in Communities; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; KPSC, Kaiser Permanente Southern California; LDL-C, low-density lipoprotein cholesterol; REGARDS, Reasons for Geographic and Racial Differences in Stroke; TC, total cholesterol; and TG, triglycerides.

*Stroke belt (buckle states) includes coastal North Carolina, South Carolina, and Georgia. Stroke belt (nonbuckle states) includes the remaining parts of the stroke buckle states and Tennessee, Mississippi, Alabama, Louisiana, and Arkansas.

Association Between Baseline Characteristics and LDL-C

At higher LDL-C levels, ARIC participants had a greater burden of cardiovascular risk factors (Table 2). ARIC participants with higher LDL-C were older; were more likely to be men; were more likely to have diabetes mellitus, reduced eGFR, and a history of stroke; and were more likely to be taking antihypertensive medication. In contrast, many of these associations were not present in REGARDS and KPSC. For example, the prevalence of diabetes mellitus and the use of antihypertensive medications were lower at higher LDL-C levels among REGARDS participants and KPSC members.

Lipids and CHD Incidence

Over 8.9 years of follow-up, 225 CHD events occurred in REGARDS, 6547 in KPSC, and 583 in ARIC (Table II in the online-only Data Supplement). With the exception of LDL-C in REGARDS, less favorable lipid levels were associated with a higher age-, race-, and sex-adjusted incidence of CHD in each population (Table 3). LDL-C was not associated with CHD incidence after adjustment for age, race, and sex in REGARDS. For each lipid, the association with CHD incidence was stronger in ARIC compared with REGARDS and KPSC.

Except for LDL-C, HDL-C, and ratio of TC to HDL-C in REGARDS, less favorable lipid levels were associated with a higher multivariable-adjusted HR for CHD in each study

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Table 2. Baseline Characteristics of Individuals From REGARDS, KPSC and ARIC by Category of LDL-C

	Category of LDL-C*				P Value for Trend
	1 (≤ 102 mg/dL)	2 (103–123)	3 (124–145 mg/dL)	4 (≤ 146 mg/dL)	
REGARDS (n=9578)					
Individuals, n	2470	2411	2346	2351	...
Age, mean (SE), y	56.2 (0.11)	56.6 (0.11)	56.8 (0.11)	57.0 (0.11)	<0.001
Blacks, %	45.7	41.8	42.8	44.6	0.64
Men, %	39.8	39.1	39.1	39.2	0.71
Current smoking, %	19.5	18.1	18.3	18.8	0.62
Diabetes mellitus, %	15.6	12.9	10.4	11.5	<0.001
Reduced eGFR, %	3.0	2.4	2.6	3.1	0.79
History of stroke, %	2.6	2.7	2.6	2.6	0.99
Antihypertensive medication, %	39.3	36.9	36.3	34.4	0.002
KPSC (n=336 851)					
Individuals, n	66 101	73 786	82 927	114 037	...
Age, mean (SE), y	52.8 (0.02)	53.2 (0.02)	53.5 (0.02)	53.9 (0.02)	<0.001
Blacks, %	22.9	20.2	19.3	20.3	<0.001
Men, %	40.0	41.1	43.2	44.2	<0.001
Current smoking, %	15.0	13.7	14.3	15.7	0.002
Diabetes mellitus, %	12.2	8.7	6.7	5.9	<0.001
Reduced eGFR, %	4.9	4.3	4.3	4.7	0.28
History of stroke, %	1.5	1.1	1.1	1.1	<0.001
Antihypertensive medication, %	30.6	29.5	29.0	29.0	<0.001
ARIC (n=14 590)					
Individuals, n	2686	2858	3345	5701	...
Age, mean (SE), y	52.7 (0.11)	53.4 (0.11)	54.0 (0.10)	54.8 (0.08)	<0.001
Blacks, %	30.4	27.3	24.8	28.2	0.09
Men, %	36.7	41.2	46.0	45.9	<0.001
Current smoking, %	26.1	25.9	25.8	26.8	0.45
Diabetes mellitus, %	9.2	9.4	11.1	12.8	<0.001
Reduced eGFR, %	1.7	2.3	2.5	3.3	<0.001
History of stroke, %	0.8	1.0	1.6	1.8	<0.001
Antihypertensive medication, %	21.8	22.9	22.3	26.4	<0.001

ARIC indicates Atherosclerosis Risk in Communities; eGFR, estimated glomerular filtration rate; KPSC, Kaiser Permanente Southern California; LDL-C, low-density lipoprotein cholesterol; and REGARDS, Reasons for Geographic and Racial Differences in Stroke.

*Categories of LDL-C were defined on the basis of quartiles from REGARDS participants.

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(Figure 2 and Table III in the online-only Data Supplement). The association between each lipid category and incident CHD was stronger in ARIC compared with REGARDS and KPSC. LDL-C ≥ 190 mg/dL was associated with an increased HR for incident CHD compared with an LDL-C ≤ 102 mg/dL in each study (Table IV in the online-only Data Supplement). The HR for incident CHD associated with LDL-C of 146 to 189 mg/dL was lower in REGARDS (HR, 1.18; 95% confidence interval, 0.78–1.80) and KPSC (HR, 1.38; 95% confidence interval, 1.27–1.49) compared with ARIC (HR, 1.76; 95% confidence interval, 1.30–2.38). A stronger association between each serum lipid and incident CHD was also present among ARIC participants compared with REGARDS participants and KPSC members when serum lipids were analyzed as continuous variables (Table V in the online-only Data Supplement) and with the use of categories defined by ARIC quartile cut points (Table VI in the online-only Data Supplement).

Discussion

In the present study, we contrasted the association of serum lipids with incident CHD using data collected before and after the publication of ATP III and the subsequent increase in the use of statins among US adults. Among participants not taking lipid-lowering medications in the ARIC study, which was conducted before the publication of the ATP III guidelines, less favorable lipid levels were associated with a large increase in risk for CHD. In contrast, the association between less favorable lipid levels and increased CHD risk was weaker among REGARDS study participants and KPSC members not taking lipid-lowering medications, 2 populations studied after publication of the ATP III guidelines. Additionally, ARIC participants with higher LDL-C were more likely to have concomitant CHD risk factors, but these associations were not present for REGARDS participants and KPSC members. These findings suggest that the observed association between

Table 3. Age-, Race-, and Sex-Adjusted Incidence Rates for Associated With Serum Lipids Among Individuals From REGARDS, KPSC, and ARIC (per 1000 Person-Years)

	Category of Serum Lipids*				P Value for Trend
	1	2	3	4	
	IR (95% CI)	IR (95% CI)	IR (95% CI)	IR (95% CI)	
LDL-C, mg/dL	≤102	103–123	124–145	≥146	...
REGARDS	3.65 (2.55–4.75)	3.26 (2.22–4.31)	4.09 (2.93–5.25)	4.11 (2.89–5.33)	0.41
KPSC	2.44 (2.29–2.60)	2.31 (2.17–2.45)	2.45 (2.32–2.59)	3.12 (2.99–3.26)	<0.001
ARIC	3.21 (2.39–4.03)	3.53 (2.69–4.36)	4.57 (3.70–5.45)	6.39 (5.61–7.18)	<0.001
Non-HDL-C, mg/dL	≤122	123–146	147–172	≥173	...
REGARDS	2.90 (1.97–3.83)	3.50 (2.49–4.52)	4.21 (3.07–5.34)	4.55 (3.36–5.75)	0.02
KPSC	2.12 (1.98–2.28)	2.11 (1.98–2.25)	2.46 (2.33–2.60)	3.53 (3.39–3.67)	<0.001
ARIC	2.67 (1.92–3.43)	3.57 (2.77–4.36)	4.35 (3.56–5.15)	6.90 (6.08–7.73)	<0.001
HDL-C, mg/dL	≤41	42–51	52–63	≥64	...
REGARDS	4.73 (3.54–5.92)	3.85 (2.82–4.88)	3.41 (2.34–4.49)	2.83 (1.82–3.84)	0.02
KPSC	4.31 (4.11–4.51)	2.82 (2.69–2.97)	2.16 (2.04–2.29)	1.74 (1.62–1.87)	<0.001
ARIC	8.22 (7.13–9.32)	5.14 (4.27–6.01)	3.53 (2.79–4.26)	2.11 (1.50–2.71)	<0.001
TG, mg/dL	≤77	78–105	106–151	≥152	...
REGARDS	2.18 (1.37–2.99)	3.40 (2.35–4.46)	4.02 (2.90–5.13)	5.67 (4.24–7.11)	<0.001
KPSC	1.71 (1.59–1.83)	2.18 (2.05–2.33)	2.76 (2.62–2.91)	3.82 (3.66–3.98)	<0.001
ARIC	2.77 (2.14–3.41)	3.66 (2.90–4.42)	5.49 (4.61–6.37)	7.79 (6.68–8.91)	<0.001
Ratio of TC to HDL-C	<3.12	3.12–<3.90	3.90–<4.90	≥4.90	...
REGARDS	2.97 (1.97–3.97)	3.12 (2.12–4.11)	3.61 (2.55–4.67)	5.28 (4.00–6.56)	0.004
KPSC	1.72 (1.59–1.86)	1.96 (1.83–2.09)	2.58 (2.44–2.71)	4.23 (4.05–4.41)	<0.001
ARIC	1.94 (1.32–2.56)	2.62 (1.94–3.31)	5.05 (4.20–5.91)	7.94 (6.98–8.89)	<0.001
Ratio of TG to HDL-C	<1.31	1.31–<2.06	2.06–<3.37	≥3.37	...
REGARDS	2.07 (1.20–2.94)	3.52 (2.44–4.60)	3.78 (2.68–4.88)	5.68 (4.26–7.10)	<0.001
KPSC	1.58 (1.47–1.70)	2.15 (2.02–2.29)	2.74 (2.60–2.89)	4.10 (3.93–4.28)	<0.001
ARIC	2.11 (1.52–2.71)	3.65 (2.88–4.42)	5.27 (4.40–6.13)	8.42 (7.28–9.55)	<0.001

CHD definition from REGARDS and ARIC includes definite or probable myocardial infarction or CHD death. CHD definition for KPSC includes nonfatal myocardial infarction (defined by an inpatient stay with a discharge *International Classification of Diseases, Ninth Revision* diagnosis code of 410.x in any position) or CHD death (defined by an underlying cause of death identified by *International Classification of Diseases, 10th Revision* code I20–I25). Analysis from REGARDS includes 225 events from 9578 participants. Analysis from KPSC is limited to 8.9 years of follow-up and includes 6547 events from 346 595 members (6163 events from 336 851 members for the analysis of LDL-C). Analysis from ARIC is limited to 8.9 years of follow-up and includes 583 events from 14 590 participants. All analyses include adjustment for age (mean age, 55 year), race (50% blacks), and sex (50% men). ARIC indicates Atherosclerosis Risk in Communities; CHD, coronary heart disease; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; IR, incidence rate; KPSC, Kaiser Permanente Southern California; LDL-C, low-density lipoprotein cholesterol; REGARDS, Reasons for Geographic and Racial Differences in Stroke; TC, total cholesterol; and TG, triglycerides.

*Categories of serum lipids were defined on the basis of quartiles from REGARDS participants.

serum lipids and CHD in contemporary studies may be attenuated by the preferential use of lipid-lowering medications by high-risk individuals, representing a challenge for observational research on lipids and CHD.

Many previous observational studies have documented strong, graded associations between serum lipids and CHD risk.^{19–23} For example, the Emerging Risk Factors Collaboration, which used participant-level data from 8 observational studies and 44 243 participants, reported that a 33-mg/dL higher LDL-C was associated with a 38% increased risk of CHD (HR, 1.38; 95% confidence interval, 1.09–1.73).²⁴ However, most of the data used in these studies were collected before the widespread use of statins. A series of randomized clinical trials showing a significant reduction in both LDL-C and CHD risk associated with the use of statins were published in the 1990s and early 2000s.^{25–31} As a consequence,

LDL-C became a target for CHD risk reduction therapy, and the use of statins rose substantially.^{2,3}

In 2001, ATP III introduced risk stratification to help guide the initiation of statin therapy, emphasizing a patient's global CHD risk in addition to LDL-C.^{1,32} This recommendation resulted in the preferential use of statin therapy by individuals with high LDL-C or with low to moderate LDL-C but with other CHD risk factors. In a study by Aronow et al,³³ 90.8% of statin users in Medicare and 70.8% of statin users in US commercial health plans had hypertension, diabetes mellitus, chronic kidney disease, CHD, angina, or a history of stroke or transient ischemic attack. In our analysis, there was a marked shift in the distribution of CHD risk factors across categories of LDL-C among individuals not taking lipid-lowering medications from before to after publication of the ATP III guidelines. This shift is consistent with the contemporary

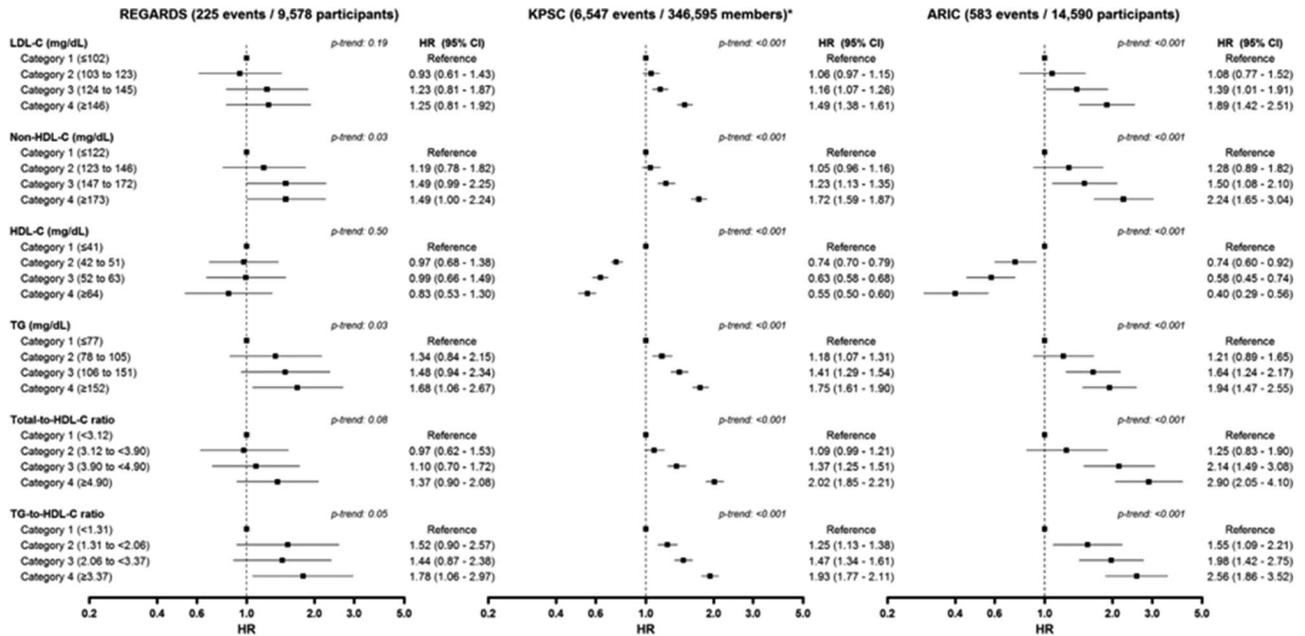


Figure 2. Forest plot of hazard ratios (HRs) for coronary heart disease by lipid categories in Reasons for Geographic and Racial Differences in Stroke (REGARDS), Kaiser Permanente Southern California (KPSC), and Atherosclerosis Risk in Communities (ARIC). All analyses include adjustment by age, race, sex, education and income levels, alcohol consumption, current smoking, diabetes mellitus, reduced estimated glomerular filtration rate, stroke, and use of antihypertensive medications. Analyses from REGARDS also include adjustments for region of residence. Coronary heart disease (CHD) definition from REGARDS and ARIC includes definite or probable myocardial infarction (MI) or CHD death. CHD definition for KPSC includes nonfatal MI (defined by an inpatient stay with a discharge *International Classification of Diseases, Ninth Revision* diagnosis code of 410.x in any position) or CHD death (defined by an underlying cause of death *International Classification of Diseases, 10th Revision* code I20-I25). Analyses in KPSC and ARIC are limited to 8.9 years of follow-up. Categories of serum lipids were defined on the basis of quartiles from REGARDS study participants. CI indicates confidence interval; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; and TG, triglycerides. *A total of 6163 events from 336851 members for the analysis of LDL-C.

use of lipid-lowering medications by individuals with high CHD risk. ARIC study participants with higher levels of LDL-C were more likely to be male; to have diabetes mellitus, reduced eGFR, and a history of stroke; and to use antihypertensive medications. In contrast, among REGARDS study participants and KPSC members, those with higher LDL-C levels were less likely to have diabetes mellitus or to take antihypertensive medication.

Results from the present study should not be interpreted as evidence of a lack of a causal effect of serum lipids on incident CHD. Instead, our results suggest that the ATP III guidelines could have contributed to the attenuation of the association between serum lipids and CHD in contemporary populations. In ATP III, the recommendation to initiate lipid-lowering medications is based on both LDL-C levels and the presence of other CHD risk factors.¹ Preferential initiation of lipid-lowering therapy in individuals with high LDL-C or high burden of CHD risk factors could lead to collider stratification bias in populations after the publication of ATP III when analyses are conducted conditioning on lipid-lowering medication use.³⁴ Adults who are not taking lipid-lowering medication in contemporary populations have lower LDL-C compared with their counterparts before the publication of ATP III. In addition, among adults with high LDL-C in contemporary populations, the average CHD risk will be lower than among individuals with equivalent LDL-C levels in earlier eras. Taken together, these changes can weaken the association between lipids and CHD in contemporary populations. An example

of how ATP III may result in collider stratification bias was provided in a study of the prevalence of diabetes mellitus by LDL-C levels in REGARDS and KPSC versus ARIC (ie, diabetes mellitus was more common at higher LDL-C in ARIC but at lower LDL-C in KPSC and REGARDS). Although we adjusted for known CHD risk factors, unmeasured factors that are associated with lipid-lowering medication use may be present. A collider stratification bias was likely not present in populations before the publication of ATP III because the recommendation to initiate lipid-lowering medication in previous guidelines was based primarily on serum lipid levels.³² Although including individuals taking lipid-lowering medication in the analysis of contemporary populations could avoid collider stratification bias, the results with this approach would also be biased because lipid-lowering therapy modifies both serum lipid levels and CHD incidence. Another possible explanation for the attenuation of the association between serum lipids and incident CHD in contemporary populations is that individuals with high LDL-C who are untreated may be more likely to initiate statins during follow-up compared with individuals before the publication of ATP III. An attenuation in the association between serum lipids and CHD may have important implications for modern studies. For instance, the association of new lipid markers with CHD risk may be obscured. This also might change the role of lipids as potential confounders in the association of other risk factors with CHD risk. Most important, there is a need to evaluate the validity of CHD and cardiovascular disease risk prediction models that

were developed with the use of lipid data collected before ATP III was published.⁶

The present analysis has a number of strengths. ARIC and REGARDS were population-based studies; they included large sample sizes, with the collection of blood samples and a long active follow-up period for CHD events that were rigorously adjudicated with similar approaches in both studies. Results in the contemporary era were replicated with the use of data from KPSC, a large healthcare system with a high degree of generalizability.⁹ The present analysis also has potential and known limitations. We analyzed only a single study from the era before the publication of ATP III. In addition, REGARDS, KPSC, and ARIC had differences in their design and methods for data collection, including the assay used to measure lipids, which may explain differences in results across these studies. We were not able to investigate some relevant cardiovascular risk factors, including C-reactive protein and albuminuria, which could have changed among individuals not taking lipid-lowering medication from before to after publication of the ATP III guidelines, because this information was not available for all 3 populations analyzed. In KPSC, information on fasting status for lipid panels at baseline was not available, and incident CHD events were not adjudicated. Additionally, we did not analyze information on the initiation of statins after baseline.

More than 50 years of research, including both observational studies and randomized trials, demonstrates that serum lipids levels are independent risk factors for CHD and that lipid-lowering medications, mainly statins, reduce this risk.^{19–23,25–31} As a consequence, the use of statins among US adults has increased substantially over the last 15 years. The present analysis suggests that the preferential use of statins for primary prevention in high-risk populations may obscure the association between serum lipids and CHD. Results from the present analysis need to be confirmed in future studies. Until more data become available, caution should be taken in the interpretation of the association between lipids and CHD risk in contemporary observational studies.

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References

- Executive summary of the Third Report of The National Cholesterol Education Program (NCEP): Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
- Mann D, Reynolds K, Smith D, Muntner P. Trends in statin use and low-density lipoprotein cholesterol levels among US adults: impact of the 2001 National Cholesterol Education Program guidelines. *Ann Pharmacother*. 2008;42:1208–1215. doi: 10.1345/aph.1L181.
- Muntner P, Levitan EB, Brown TM, Sharma P, Zhao H, Bittner V, Glasser S, Kilgore M, Yun H, Woolley JM, Farkouh ME, Rosenson RS. Trends in the prevalence, awareness, treatment and control of high low density lipoprotein-cholesterol among United States adults from 1999-2000 through 2009-2010. *Am J Cardiol*. 2013;112:664–670. doi: 10.1016/j.amjcard.2013.04.041.
- D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P; CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA*. 2001;286:180–187.
- D'Agostino RB Sr, Vasani RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117:743–753. doi: 10.1161/CIRCULATIONAHA.107.699579.
- Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC Jr, Sorlie P, Stone NJ, Wilson PW, Jordan HS, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(suppl 2):S49–S73. doi: 10.1161/01.cir.0000437741.48606.98.
- Howard VJ, Cushman M, Pulley L, Gomez CR, Go RC, Prineas RJ, Graham A, Moy CS, Howard G. The reasons for geographic and racial differences in stroke study: objectives and design. *Neuroepidemiology*. 2005;25:135–143. doi: 10.1159/000086678.
- Safford MM, Brown TM, Muntner PM, Durant RW, Glasser S, Halanych JH, Shikany JM, Prineas RJ, Samdarshi T, Bittner VA, Lewis CE, Gamboa C, Cushman M, Howard V, Howard G; REGARDS Investigators. Association of race and sex with risk of incident acute coronary heart disease events. *JAMA*. 2012;308:1768–1774. doi: 10.1001/jama.2012.14306.
- Koebnick C, Langer-Gould AM, Gould MK, Chao CR, Iyer RL, Smith N, Chen W, Jacobsen SJ. Sociodemographic characteristics of members of a large, integrated health care system: comparison with US Census Bureau data. *Perm J*. 2012;16:37–41.
- The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives: the ARIC investigators. *Am J Epidemiol*. 1989;129:687–702.
- Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 1997;20:1183–1197.
- Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
- Manjunath G, Tighiouart H, Ibrahim H, MacLeod B, Salem DN, Griffith JL, Coresh J, Levey AS, Sarnak MJ. Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. *J Am Coll Cardiol*. 2003;41:47–55.
- Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int*. 2013;3:1–150.
- Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499–502.
- Luepker RV, Apple FS, Christenson RH, Crow RS, Fortmann SP, Goff D, Goldberg RJ, Hand MM, Jaffe AS, Julian DG, Levy D, Manolio T, Mendis S, Mensah G, Pajak A, Prineas RJ, Reddy KS, Roger VL, Rosamond WD, Shahar E, Sharrett AR, Sorlie P, Tunstall-Pedoe H; AHA Council on

- Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; National Heart, Lung, and Blood Institute. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. *Circulation*. 2003;108:2543–2549. doi: 10.1161/01.CIR.0000100560.46946.EA.
17. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, Wood AM, Carpenter JR. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:b2393.
 18. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med*. 2011;30:377–399. doi: 10.1002/sim.4067.
 19. Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetière P, Jousilahti P, Keil U, Njølstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM; SCORE Project Group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J*. 2003;24:987–1003.
 20. Dawber TR, Kannel WB, Lyell LP. An approach to longitudinal studies in a community: the Framingham study. *Ann NY Acad Sci*. 1963;107:539–556.
 21. Gaziano JM, Hennekens CH, O'Donnell CJ, Breslow JL, Buring JE. Fasting triglycerides, high-density lipoprotein, and risk of myocardial infarction. *Circulation*. 1997;96:2520–2525.
 22. Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. *Am Heart J*. 1986;111:383–390.
 23. McQueen MJ, Hawken S, Wang X, Ounpuu S, Sniderman A, Probstfield J, Steyn K, Sanderson JE, Hasani M, Volkova E, Kazmi K, Yusuf S; INTERHEART Study Investigators. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. *Lancet*. 2008;372:224–233. doi: 10.1016/S0140-6736(08)61076-4.
 24. Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, Wood AM, Lewington S, Sattar N, Packard CJ, Collins R, Thompson SG, Danesh J. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA*. 2009;302:1993–2000.
 25. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383–1389.
 26. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7–22.
 27. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet*. 2003;361:2005–2016.
 28. Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, Mihaylova B, Simes J, Collins R, Kirby A, Colhoun H, Braunwald E, La Rosa J, Pedersen TR, Tonkin A, Davis B, Sleight P, Franzosi MG, Baigent C, Keech A. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet*. 2015;385:1397–1405.
 29. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ*. 2003;326:1423. doi: 10.1136/bmj.326.7404.1423.
 30. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia: West of Scotland Coronary Prevention Study Group. *N Engl J Med*. 1995;333:1301–1307. doi: 10.1056/NEJM199511163332001.
 31. Taylor F, Ward K, Moore TH, Burke M, Davey Smith G, Casas JP, Ebrahim S. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2011:CD004816. doi: 10.1002/14651858.CD004816.pub4.
 32. Talwalkar PG, Sreenivas CG, Gulati A, Baxi H. Journey in guidelines for lipid management: from Adult Treatment Panel (ATP)-I to ATP-III and what to expect in ATP-IV. *Indian J Endocrinol Metab*. 2013;17:628–635. doi: 10.4103/2230-8210.113753.
 33. Aronow HD, Dutro MP, Kuznik A, Cwengros J. Prevalence of cardiovascular comorbidities and utilization of evidence-based treatment strategies among statin users in a Medicare and commercial health plan. *Curr Med Res Opin*. 2009;25:205–213. doi: 10.1185/03007990802611828.
 34. Cole SR, Platt RW, Schisterman EF, Chu H, Westreich D, Richardson D, Poole C. Illustrating bias due to conditioning on a collider. *Int J Epidemiol*. 2010;39:417–420. doi: 10.1093/ije/dyp334.

CLINICAL PERSPECTIVE

Previous studies have shown that statins are effective in reducing coronary heart disease (CHD) incidence. The proportion of US adults taking statins increased after the publication of the 2001 Adult Treatment Panel III cholesterol treatment guidelines, which recommended statin therapy based on low-density lipoprotein cholesterol (LDL-C) levels and predicted CHD risk. We compared the characteristics of adults not taking lipid-lowering medications by level of LDL-C and the association between serum lipids and CHD using data from populations before (Atherosclerosis Risk In Communities [ARIC]) and after (Kaiser Permanente Southern California [KPSC], and Reasons for Geographic and Racial Differences in Stroke [REGARDS]) the publication of Adult Treatment Panel III. The prevalence of diabetes mellitus, history of stroke, and anti-hypertensive medication use increased at higher levels of LDL-C in ARIC but not in REGARDS or KPSC. These findings were consistent with a preferential use of statins by high-risk individuals or individuals with high LDL-C in the contemporary era. Less favorable levels of each lipid analyzed (LDL-C, high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, triglycerides, and ratios of total to high-density lipoprotein cholesterol and triglycerides to high-density lipoprotein cholesterol) were associated with an increased risk for CHD in ARIC, but these associations were attenuated in REGARDS and KPSC. Results from our study suggest that the preferential use of statins by individuals with high CHD risk in the contemporary era may induce a bias in analyses of the association between serum lipids and CHD. This bias may have important implications for future studies of lipids and CHD risk and for CHD risk prediction.

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