Supplementary Online Content

Zhang Y, Pletcher MJ, Vittinghoff E, et al. Association between cumulative low-density lipoprotein cholesterol exposure during young adulthood and middle age and risk of cardiovascular events. *JAMA Cardiol.* Published online September 22, 2021. doi:10.1001/jamacardio.2021.3508

eFigure 8. Associations Between Cumulative LDL-C, TWA LDL-C, and LDL-C Slope During Young Adulthood and Middle Age With Incident Heart Failure, Stratified by Sex

eFigure 9. Associations Between Cumulative LDL-C, TWA LDL-C, and LDL-C Slope During Young Adulthood and Middle Age With Incident CHD, Stratified by Race

eFigure 10. Associations Between Cumulative LDL-C, TWA LDL-C, and LDL-C Slope During Young Adulthood and Middle Age With Incident Ischemic Stroke, Stratified by Race

eFigure 11. Associations Between Cumulative LDL-C, TWA LDL-C, and LDL-C Slope During Young Adulthood and Middle Age With Incident Heart Failure, Stratified by Race

eFigure 12. Associations Between Cumulative LDL-C, TWA LDL-C, and LDL-C Slope During Young Adulthood and Middle Age With Incident CHD, Among Participants Who Never Used Lipid Lowering Medications

eFigure 13. Associations Between Cumulative LDL-C, TWA LDL-C, and LDL-C Slope During Young Adulthood and Middle Age With Incident Ischemic Stroke, Among Participants Who Never Used Lipid Lowering Medications

eFigure 14. Associations Between Cumulative LDL-C, TWA LDL-C, and LDL-C Slope During Young Adulthood and Middle Age With Incident Heart Failure, Among Participants Who Never Used Lipid Lowering Medications

eFigure 15. Associations Between Cumulative LDL-C During Young Adulthood and Middle Age With Incident CHD, Leaving Out One Study At a Time

eFigure 16. Associations Between TWA LDL-C During Young Adulthood and Middle Age With Incident CHD, Leaving Out One Study At a Time

eFigure 17. Associations Between LDL-C Slope During Young Adulthood and Middle Age With Incident CHD, Leaving Out One Study At a Time

eReferences

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

Study Cohorts

The Atherosclerosis Risk in Communities (ARIC) Study is a prospective cohort study of 15,792 individuals 45 to 64 years of age from 4 US communities (Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland).[1] The baseline visit was carried out during 1987–1989, with 6 subsequent in-person follow-up visits. Of all study participants, 15,345 gave consent for their data to be analyzed.

The Cardiovascular Risk Development in Young Adults (CARDIA) Study is a prospective cohort study of 5,115 individuals 18 to 30 years of age from 4 US communities (Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California).[2] The baseline visit was carried out in 1985-1986, with 8 subsequent in-person follow-up visits at years 2, 5, 7, 10, 15, 20, 25 and 30.

The Framingham Heart Study Offspring Cohort (FHS-O) Study is a prospective cohort study of 5,124 individuals 5 to 70 years of age who were offspring (or offspring's spouses) of the Original Cohort of the Framingham Heart Study.[3] The baseline visit was carried out in 1971, with 8 subsequent in-person follow-up visits.

The Multi-Ethnic Study of Atherosclerosis (MESA) Study is a multicenter prospective cohort study of 6,814 individuals 45 to 84 years of age free of clinical cardiovascular disease (CVD) recruited from 6 US communities (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; northern Manhattan, New York; and St. Paul, Minnesota).[4] The baseline visit was carried out during 2000-2002, with 5 subsequent in-person follow-up visits.

All study protocols were approved by the Institutional Review Boards at participating institutions and all participants provided written informed consent. Ancillary study approvals and data use agreements were also obtained from each parent study. All data were gathered and securely stored at Columbia University for pooling, harmonization, and analysis, as part of the NHLBI Pooled Cohorts Study.[5]

The current analysis was restricted to participants who had ≥2 LDL-C measures at least 2 years apart between 18 to 60 years of age, with at least one of the LDL-C measures during middle age (40 to 60 years; **eFigure 1**). The last study visit between 40 to 60 years of age with an observed LDL-C measure was defined as the index visit (**eFigure 2**). Participants who had an existing CVD prior to the index visit were excluded from the analysis. We further exclude those with missing covariates (e.g., body mass index [BMI], smoking status, blood pressure, etc.). The final sample size comprised 18,288 individuals.

Clinical data collection

Demographic characteristics, LDL-C levels, and other CVD risk factors were measured using standardized protocols in each study.[8-11] Age, race/ethnicity, sex, smoking status, and medication use were self-reported by study participants. The majority of CVD risk factors were ascertained at every study visit using similar standard and validated methods. Data were pooled and harmonized for covariates including race/ethnicity, sex, birth year, BMI, smoking status, high-density lipoprotein cholesterol (HDL-C), systolic blood pressures (SBP), diastolic blood pressure (DBP), diabetes, and use of lipid-lowering and anti-hypertensive medications.

Cumulative LDL-C, TWA LDL-C, and LDL-C slope

The primary exposures of interest were cumulative LDL-C, TWA LDL-C, and LDL-C slope during young adulthood and middle age prior to the index visit. Since most studies were

restricted in age range and did not directly measure LDL-C during both early and later life (for example, participants in ARIC were enrolled after 45 years of age, and therefore, their LDL-C levels before age 45 were not observed), we used a previously developed multiple imputation method to impute LDL-C values from age 18 years for each participant.[6,7] Details of the method have been described previously.[7] Briefly, by pooling data from multiple cohorts which together span the adult life course, we leveraged the risk factor patterns observed in the younger cohorts to impute un-observed young adult exposures in the older cohorts, and vice versa. We used linear mixed-effects modeling to estimate latent trajectories underlying the observed values for each participant, and imputed risk factor levels annually from age 18 years through the end of follow-up for each participant. Imputations were done in the following nested sequence, motivated by prior knowledge of the dominant causal pathways: 1) smoking status: based on age, race, and sex; 2) BMI: based on age, race, sex, and smoking status; 3) diabetes and hypertension status: based on age, race, sex, smoking, and BMI; 4) use of lipid-lowering, anti-diabetes, and anti-hypertensive medications: based on age, race, sex, smoking, BMI, and diabetes or hypertension status; and 5) lipid levels, blood pressure, and glucose level: based on age, race, sex, smoking, BMI, diabetes, and medication use. All imputation models also included adjustment for birth year and cohort. Examples of imputed LDL-C trajectories for 12 randomly selected participants (3 participants per study) are illustrated in **eFigure 2.**

Based on the imputed LDL-C values, we calculated the cumulative LDL-C exposure as the area under the LDL-C vs. age trajectory from age 18 years to the index visit (expressed in “mg/dL-years”). TWA LDL-C was calculated as cumulative LDL-C divided by the total years between age 18 and the index visit. To estimate LDL-C slope for each participant, we fitted a linear mixed-effects model of the imputed LDL-C values prior to the index visit against age, with age modeled as restricted cubic splines with random intercept and slope. The random slope from this model represents the personal slope of LDL-C after removing the overall curve (spline)

common to all participants. The final LDL-C slope for each participant was calculated as the population mean slope plus the individual random slope (**eFigure 2**).

Follow-up and CVD events

All studies prospectively ascertained incident CVD events.[1,2,4,8] The primary outcomes of interest for our analysis were CHD (defined as myocardial infarction or CHD death), ischemic stroke, and HF. Events were ascertained and adjudicated using each cohort's specific protocol, and the details are provided in **eTable 1**. Diagnosis of myocardial infarction generally required at least two of the following: chest pain, electrocardiographic abnormalities consistent with myocardial infarction, and elevated cardiac biomarkers. Diagnosis of stroke generally required a persistent central neurologic deficit lasting >24 hours. Ischemic stroke was defined as atherothrombotic or cardioembolic infarction. Diagnosis of HF generally required heart failure symptoms, or physician diagnosis and medical treatment for HF.

eTable 1. Definitions of Outcomes by Study Cohorts

Cohort	CHD	Ischemic Stroke	HF
ARIC	Defined as MI or fatal CHD; In ARIC, MI was defined based on combinations of chest pain symptoms, ECG changes, and cardiac enzyme levels.	In ARIC, stroke was defined as sudden or rapid onset of neurological symptoms lasting for >24 hours or leading to death, in the absence of evidence for a nonstroke cause. Strokes were further classified into four main types: thrombotic stroke, cardioembolic stroke, subarachnoid hemorrhage, brain hemorrhage. Ischemic strokes were defined as either cardioembolic or thrombotic brain infarctions.	In ARIC, HF was defined as the first HF hospitalization identified with ICD-9/10 codes of 428.x /I50 in any position on the hospital discharge list or a death certificate with death from HF in any position. From 2005 onwards, the classification of HF further included hospitalization for heart failure, as determined by two centrally trained and certified physicians who would review data abstracted from the hospital records (including physical examination signs and symptoms, diagnostic imaging tests, biomarkers, and medication use), and determine likelihood of HF. A physician adjudicator would resolve disagreements.
CARDIA	Defined as MI or fatal CHD; In CARDIA, MI was defined following standard definition (Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third universal definition of myocardial infarction. Circulation. 2012;126:2020-2035.)	In CARDIA, ischemic stroke was defined following standard definition (Adams HP, Jr., Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24(1):35-41; Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the AHA/ASA Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. Stroke. 2009;40(6):2276-2293)	In CARDIA, HF was defined as the HF hospitalization or death from HF. Hospitalization for HF required both a diagnosis of HF made by a physician and under medical treatment for HF. A death was considered to be due to HF if the adjudicated cause was cardiovascular and if an ICD-9 code for HF (428) or cardiomyopathy (425) was noted as a contributory cause.

CHD: coronary heart disease; HF: heart failure; MI: myocardial infarction.

eTable 1 (continued). Definitions of outcomes by study cohorts

Cohort	CHD	Ischemic Stroke	HF
FHS-O	Defined as MI or fatal CHD; In FHS, MI was designated when there were at least two of three findings: 1) symptoms indicative of ischemia; 2) changes in biomarkers of myocardial necrosis; 3) serial changes in the electrocardiograms indicating the evolution of an infarction, including the loss of initial QRS potentials (that is, development of "pathologic" Q-waves of 0.04 second duration or greater).	In FHS, stroke was defined as the sudden onset of a focal neurological deficit of a presumed vascular etiology and lasting more than 24 hours. Ischemic strokes were classified as atherothrombotic brain infarctions or cardioembolic infarctions. Hemorrhagic strokes were classified as intracerebral hemorrhages or subarachnoid hemorrhages.	In FHS, a definite diagnosis of congestive heart failure requires that a minimum of two major or one major and two minor criteria be present concurrently. HF was classified as probable if there was a diagnosis of CHF and from the available records there was no reason to doubt its presence despite incompletely recorded criteria. Major Criteria: 1) Paroxysmal nocturnal dyspnea or orthopnea; 2) Distended neck veins (in other than the supine position); 3) Rales; 4) Increasing heart size by x-ray; 5) Acute pulmonary edema on chest x-ray; 6) Ventricular S(3) gallop; 7) Increased venous pressure > 16 cm H20; 8) Hepatojugular reflux; 9) Pulmonary edema, visceral congestion, cardiomegaly shown on autopsy; 10) Weight loss on CHF Rx: 10 lbs./5days. Minor criteria: 1) Bilateral ankle edema; 2) Night cough; 3) Dyspnea on ordinary exertion; 4) Hepatomegaly; 5) Pleural effusion by x-ray; 6) Decrease in vital capacity by one-third from maximum record; 7) Tachycardia (120 beats per minute or more); 8) Pulmonary vascular engorgement on chest x-ray.
MESA	Defined as MI, resuscitated cardiac arrest, or fatal CHD; In MESA, MI was classified as definite, probable, or absent, based primarily on combinations of symptoms, ECG, and cardiac biomarker levels. In most cases, definite or probable MI required either abnormal cardiac biomarkers (2 times upper limits of normal) regardless of pain or ECG findings; evolving Q waves regardless of pain or biomarker findings; or a combination of chest pain, and ST-T evolution or new LBBB, and biomarker levels 1-2 times upper limits of normal.	In MESA, stroke was defined as a rapid onset of a documented focal neurologic deficit lasting 24 hours or until death, or if < 24 hours, there was a clinically relevant lesion on brain imaging. Patients with focal neurologic deficits secondary to brain trauma, tumor, infection, or other non-vascular cause were excluded. Stroke events were further categorized into one of four types: hemorrhagic, ischemic, other, or undetermined.	In MESA, HF was classified as definite, probable, or absent. Definite or probable HF required heart failure symptoms, such as shortness of breath or edema, as asymptomatic disease is not a MESA endpoint. In addition to symptoms, probable HF required HF diagnosed by a physician and patient receiving medical treatment for HF. Definite HF required one or more other criteria, such as pulmonary edema/congestion by chest X-ray; dilated ventricle or poor LV function by echocardiocardiography or ventriculography; or evidence of left ventricular diastolic dysfunction. We considered participants not meeting any criteria, including just a physician diagnosis of HF without any other evidence, as having no HF.

CHD: coronary heart disease; HF: heart failure; MI: myocardial infarction.

eTable 2. Correlations Between LDL-C Variables				
LDL-C variables	**Pearson correlation coefficient**			
	$LDL\text{-}C_{Cumulative}$	$LDL\text{-}C_{TWA}$	$LDL\text{-}C_{Slope}$	$LDL\text{-}C_{Index\ visit}$
$LDL\text{-}C_{Cumulative}$	1.0			
$LDL\text{-}C_{TWA}$	0.9	1.0		
$LDL\text{-}C_{Slope}$	0.4	0.4	1.0	
$LDL\text{-}C_{Index\ visit}$	0.7	0.7	0.6	1.0

TWA: time-weighted average

eTable 3. Study Observation Period and Number of Events

Study characteristics *	Total	ARIC	CARDIA	FHS-O	MESA
Number of participants	18,288	8,235	3,892	3,827	2,334
Median follow-up (year)	16	18	4	16	8
Number of visits on or before the index date	4.5 ± 2.3	3.1 ± 0.8	7.7 ± 1.6	5.0 ± 2.0	3.0 ± 0.8
Number of events					
CHD	1,165	754	23	333	55
Ischemic stroke	599	388	9	176	26
Heart failure	1,145	846	11	260	28

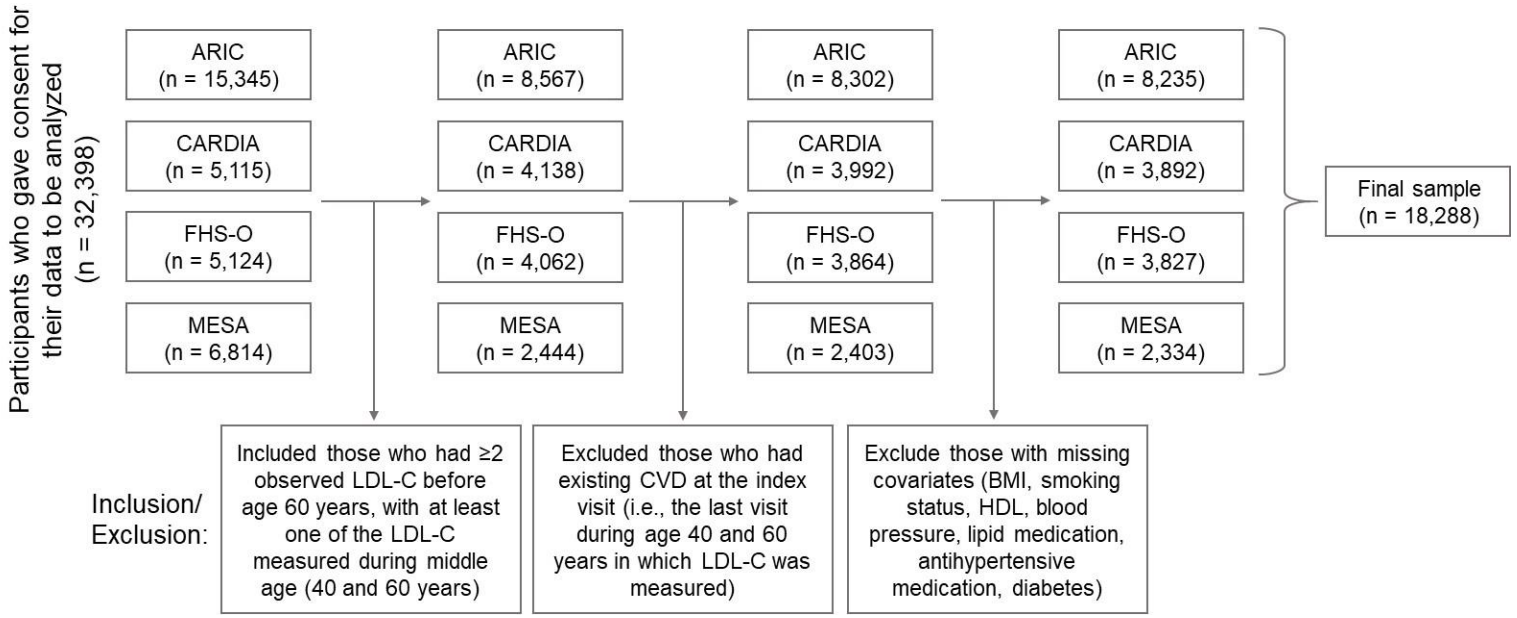
* Values are number or mean ± SD.

eTable 4. Number of Participants and Events by LDL-C Quartiles

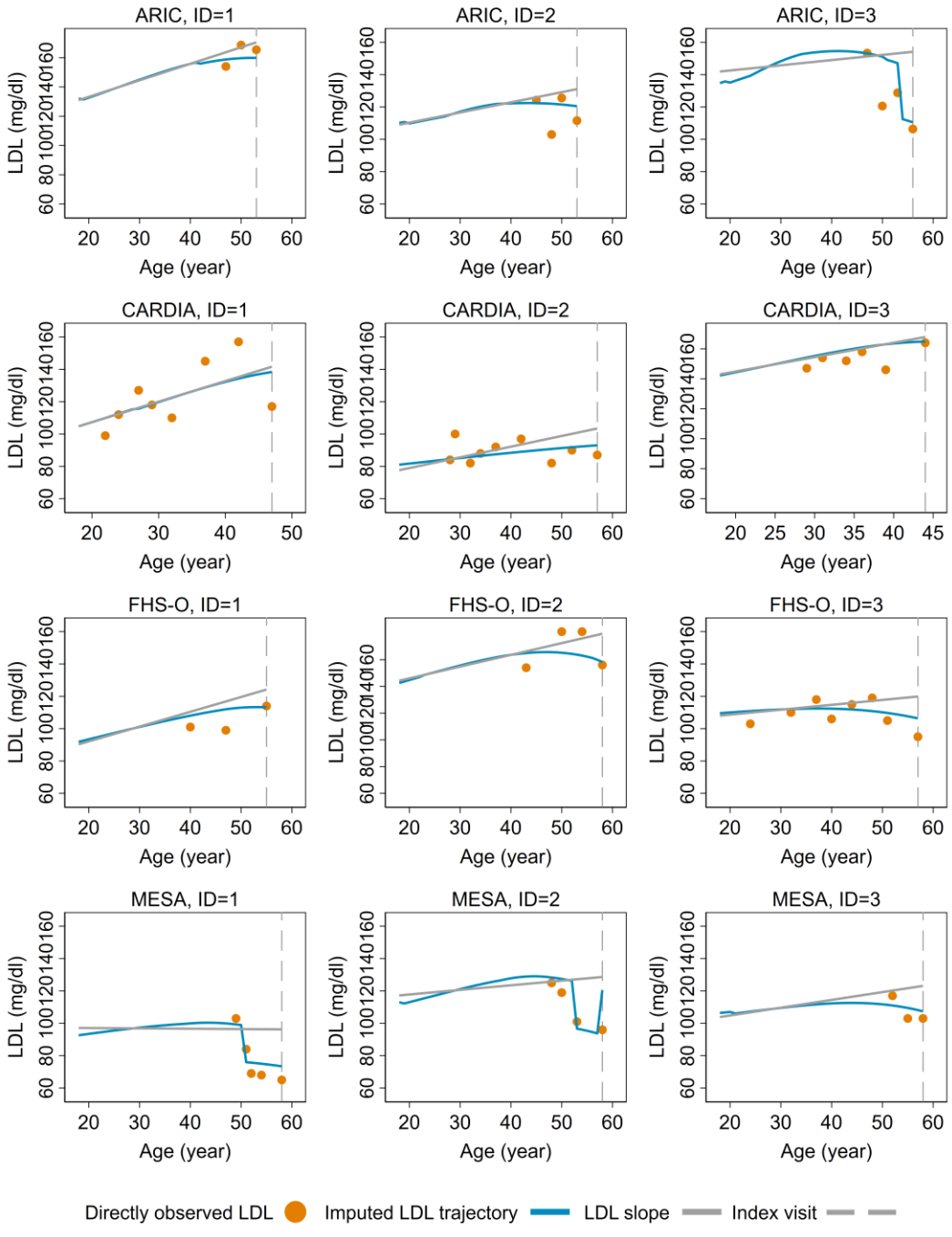
	N of participants	N of events (%) *		
		CHD	Ischemic stroke	HF
LDL-C, Cumulative				
Q1	4,572	104 (2.3%)	69 (1.5%)	139 (3.1%)
Q2	4,572	188 (4.1%)	114 (2.5%)	210 (4.6%)
Q3	4,572	310 (6.8%)	163 (3.6%)	306 (6.7%)
Q4	4,572	564 (12.3%)	253 (5.5%)	490 (10.7%)
LDL-C, TWA				
Q1	4,572	114 (2.5%)	78 (1.7%)	166 (3.6%)
Q2	4,572	184 (4.0%)	118 (2.6%)	221 (4.8%)
Q3	4,572	314 (6.9%)	163 (3.6%)	302 (6.6%)
Q4	4,572	553 (12.1%)	239 (5.2%)	456 (10.0%)
LDL-C, Slope				
Q1	4,572	266 (5.8%)	134 (2.9%)	277 (6.1%)
Q2	4,572	276 (6.0%)	154 (3.4%)	287 (6.3%)
Q3	4,572	279 (6.1%)	145 (3.2%)	286 (6.2%)
Q4	4,572	344 (7.5%)	166 (3.6%)	296 (6.5%)
LDL-C, Index visit				
Q1	4,572	162 (3.5%)	99 (2.2%)	225 (4.8%)
Q2	4,683	228 (4.9%)	128 (2.7%)	250 (5.5%)
Q3	4,506	283 (6.3%)	165 (3.7%)	271 (6.0%)
Q4	4,527	492 (10.9%)	207 (4.6%)	399 (8.8%)

* % represents the number of events among the total number of participants in each LDL-C quartile (row %).
CHD: coronary heart disease; HF: heart failure; TWA: time-weighted average

eFigure 1. Study Flow Chart

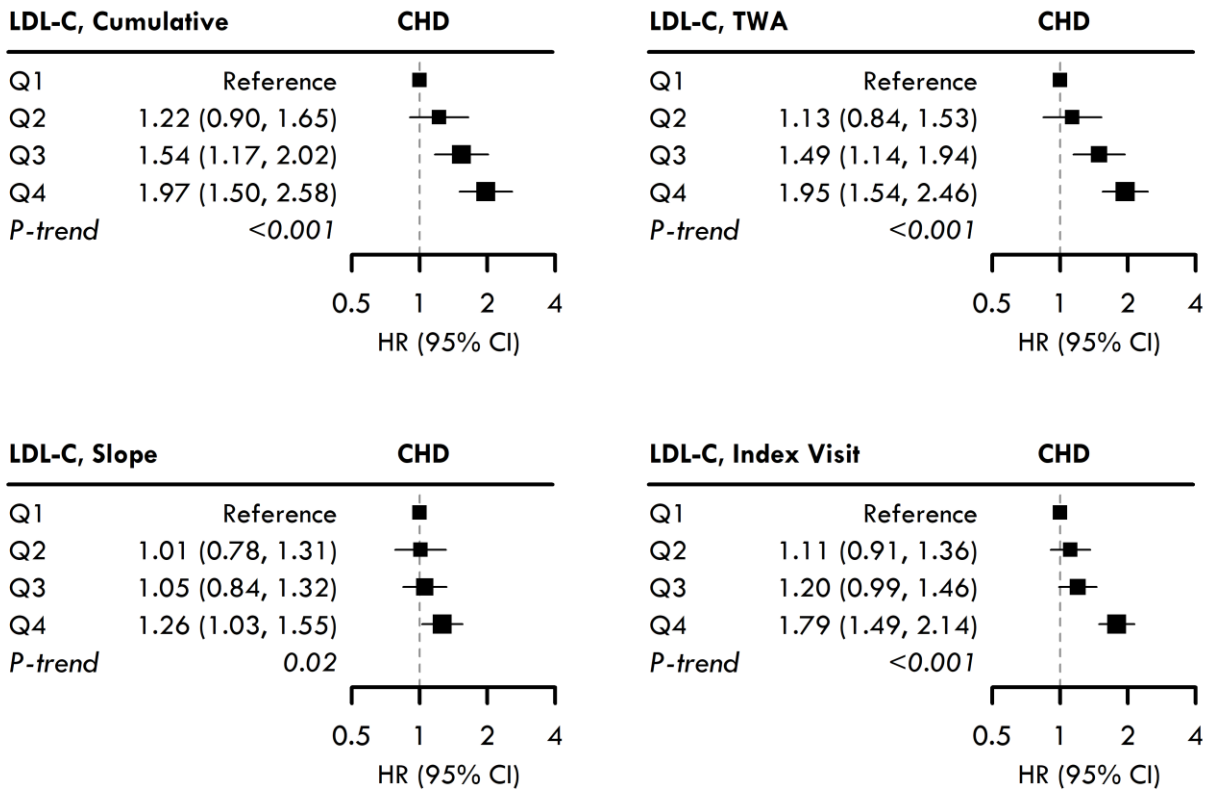


eFigure 2. Example LDL-C Trajectories During Young Adulthood and Middle Age (From Age 18 Years Up to the Index Visit) for 12 Randomly Selected Participants (3 Participants per Study)



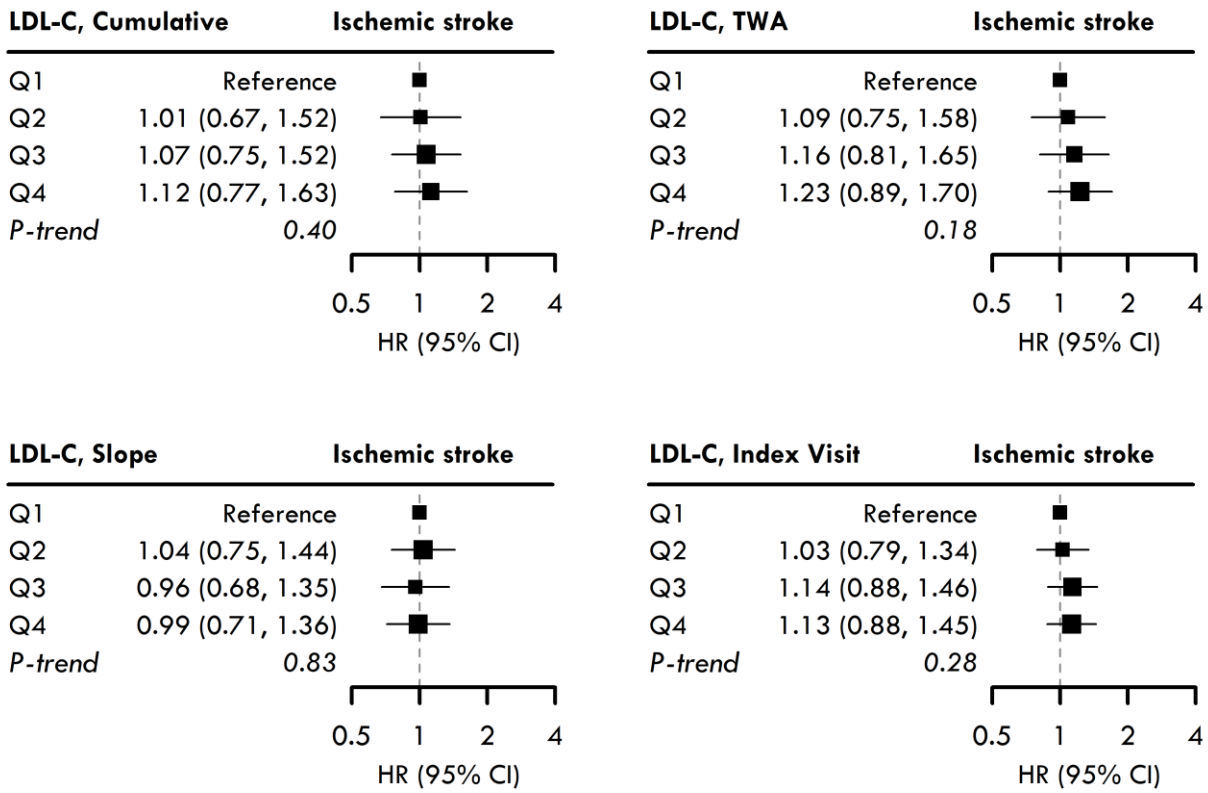
eFigure 3. Associations Between Cumulative LDL-C, TWA LDL-C, and LDL-C Slope During Young Adulthood and Middle Age and LDL-C at the Index Visit With Incident CHD

Models were stratified by study cohort and adjusted for race/ethnicity, sex, birth year, BMI, smoking status, HDL, SBP, DBP, diabetes, and use of lipid-lowering and anti-hypertensive medications.



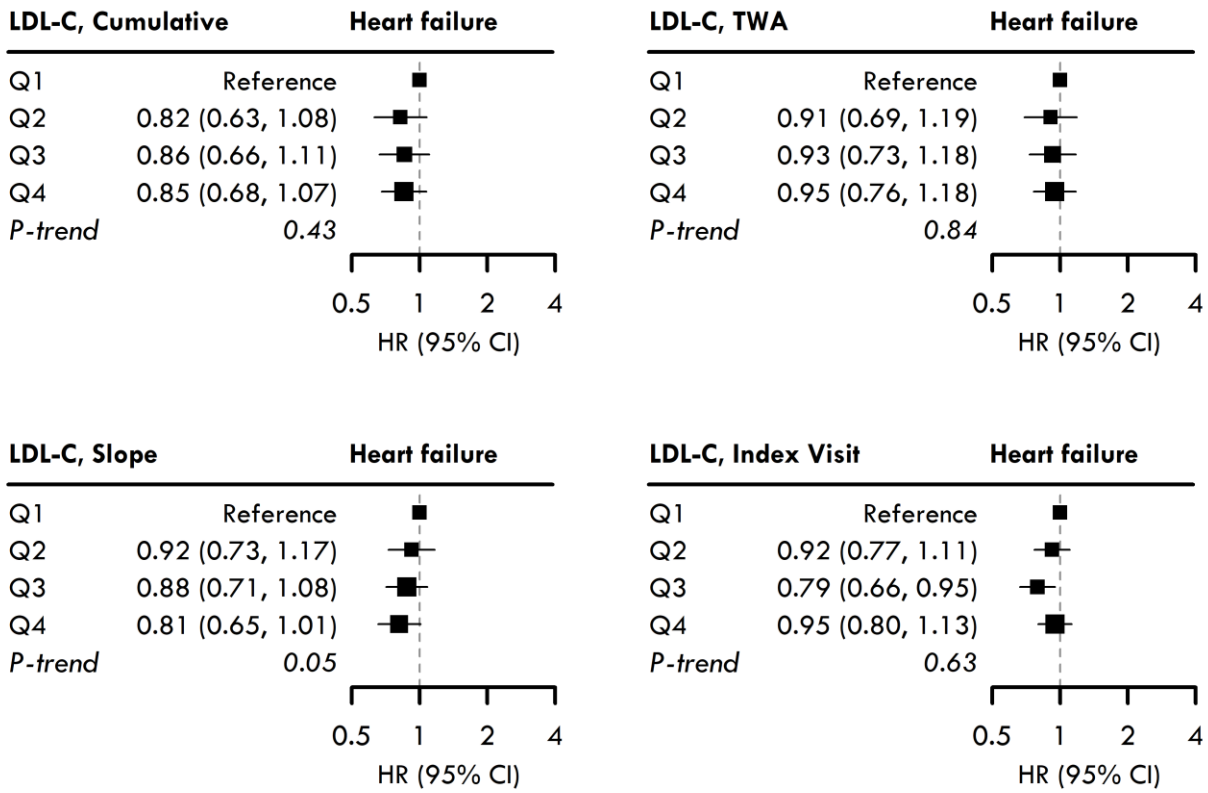
eFigure 4. Associations Between Cumulative LDL-C, TWA LDL-C, and LDL-C Slope During Young Adulthood and Middle Age and LDL-C at the Index Visit With Incident Ischemic Stroke

Models were stratified by study cohort and adjusted for race/ethnicity, sex, birth year, BMI, smoking status, HDL, SBP, DBP, diabetes, and use of lipid-lowering and anti-hypertensive medications.



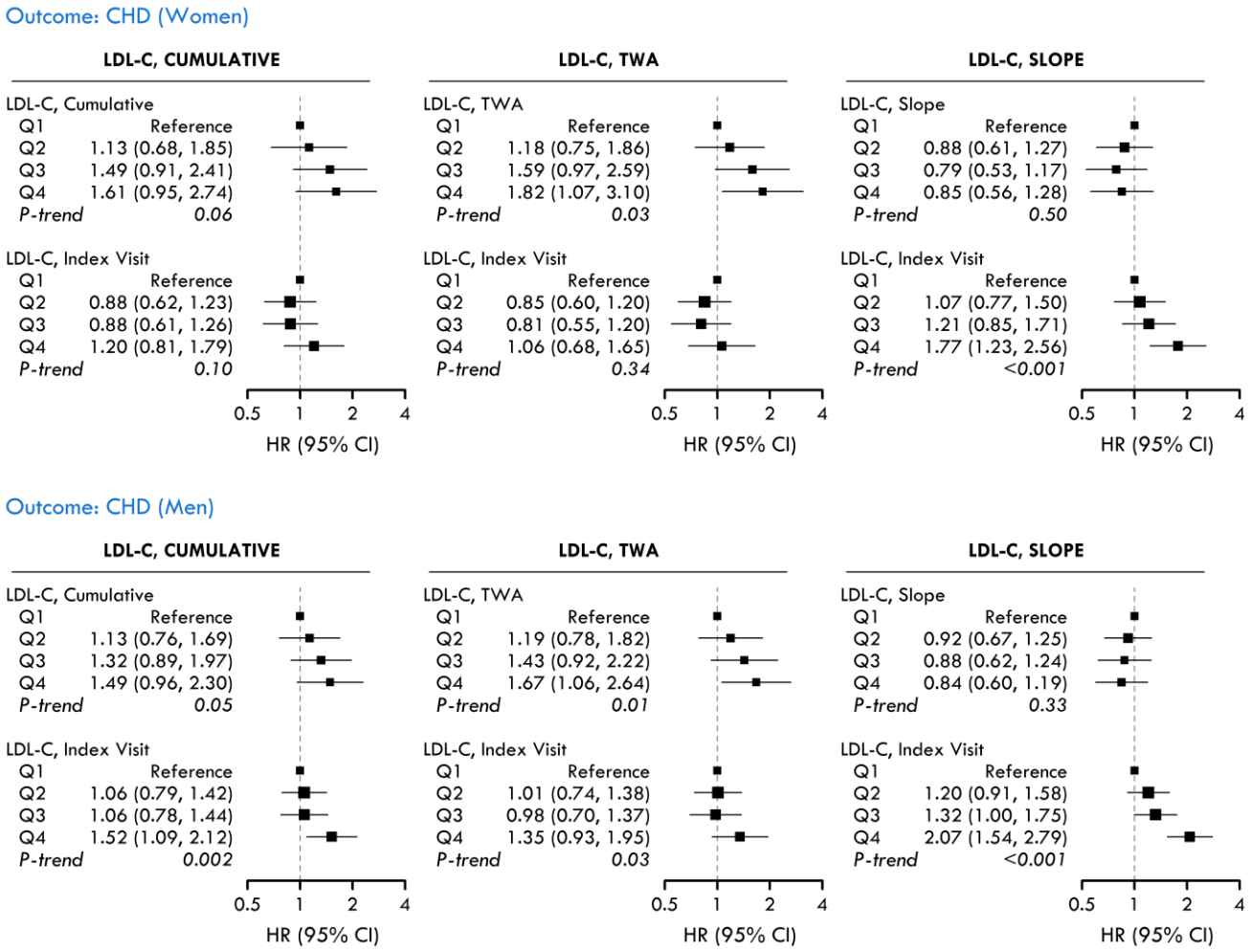
eFigure 5. Associations Between Cumulative LDL-C, TWA LDL-C, and LDL-C Slope During Young Adulthood and Middle Age and LDL-C at the Index Visit With Incident Heart Failure

Models were stratified by study cohort and adjusted for race/ethnicity, sex, birth year, BMI, smoking status, HDL, SBP, DBP, diabetes, and use of lipid-lowering and anti-hypertensive medications.



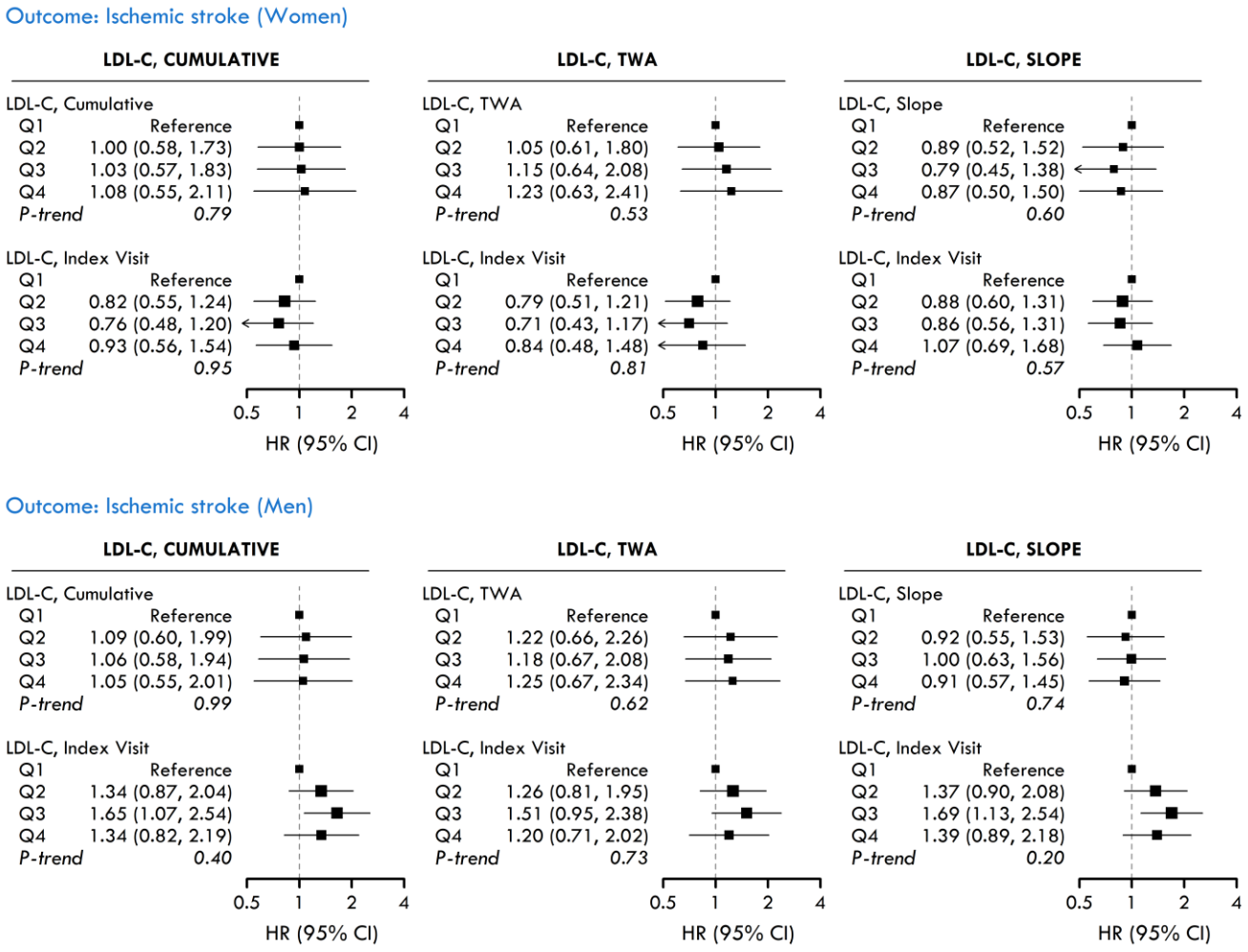
eFigure 6. Associations Between Cumulative LDL-C, TWA LDL-C, and LDL-C Slope During Young Adulthood and Middle Age With Incident CHD, Stratified by Sex

Models were stratified by study cohort and adjusted for race/ethnicity, birth year, BMI, smoking status, HDL, SBP, DBP, diabetes, use of lipid-lowering and anti-hypertensive medications, and LDL-C levels at the index visit.



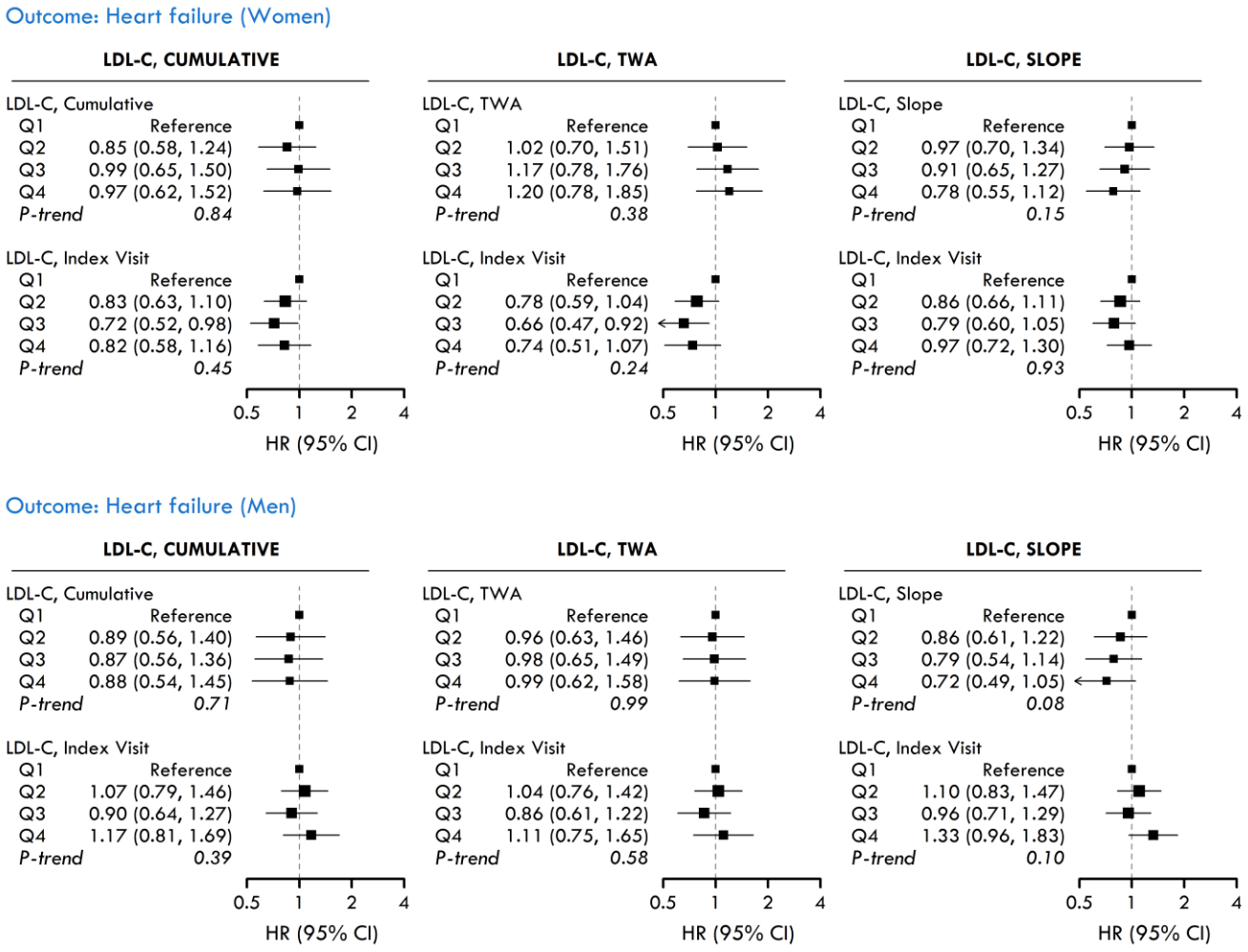
eFigure 7. Associations Between Cumulative LDL-C, TWA LDL-C, and LDL-C Slope During Young Adulthood and Middle Age With Incident Ischemic Stroke, Stratified by Sex

Models were stratified by study cohort and adjusted for race/ethnicity, birth year, BMI, smoking status, HDL, SBP, DBP, diabetes, use of lipid-lowering and anti-hypertensive medications, and LDL-C levels at the index visit.



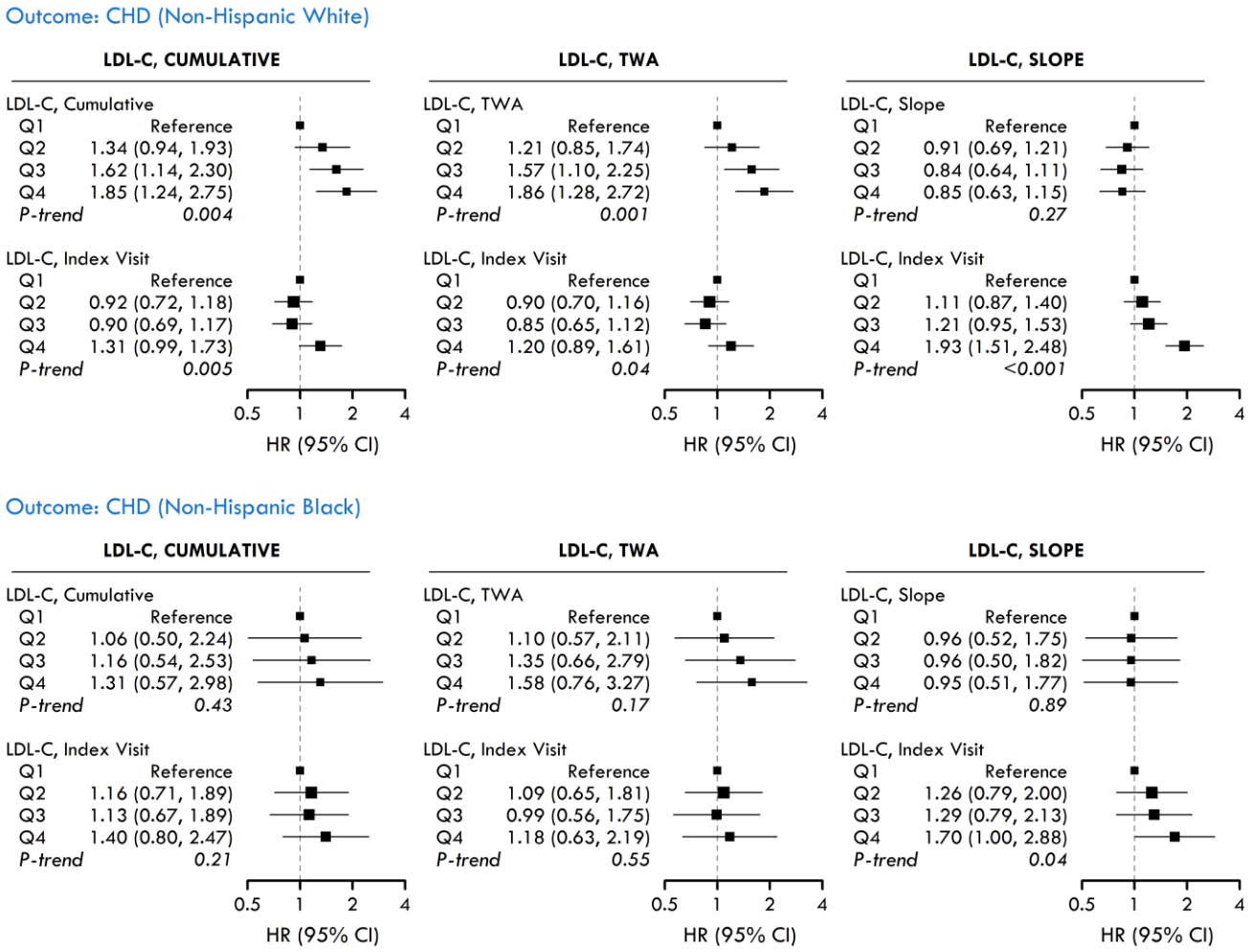
eFigure 8. Associations Between Cumulative LDL-C, TWA LDL-C, and LDL-C Slope During Young Adulthood and Middle Age With Incident Heart Failure, Stratified by Sex

Models were stratified by study cohort and adjusted for race/ethnicity, birth year, BMI, smoking status, HDL, SBP, DBP, diabetes, use of lipid-lowering and anti-hypertensive medications, and LDL-C levels at the index visit.



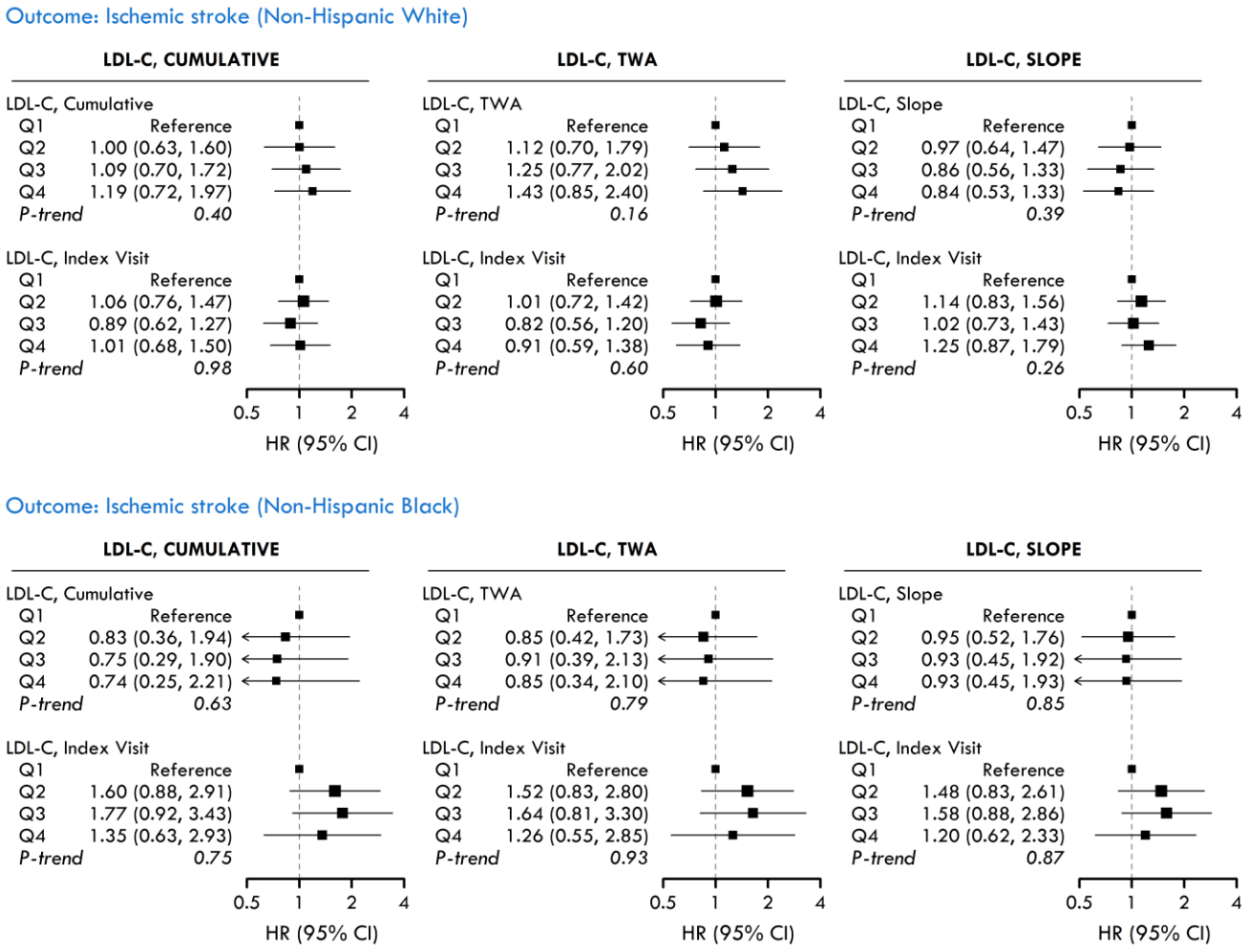
eFigure 9. Associations Between Cumulative LDL-C, TWA LDL-C, and LDL-C Slope During Young Adulthood and Middle Age With Incident CHD, Stratified by Race

Models were stratified by study cohort and adjusted for sex, birth year, BMI, smoking status, HDL, SBP, DBP, diabetes, use of lipid-lowering and anti-hypertensive medications, and LDL-C levels at the index visit.



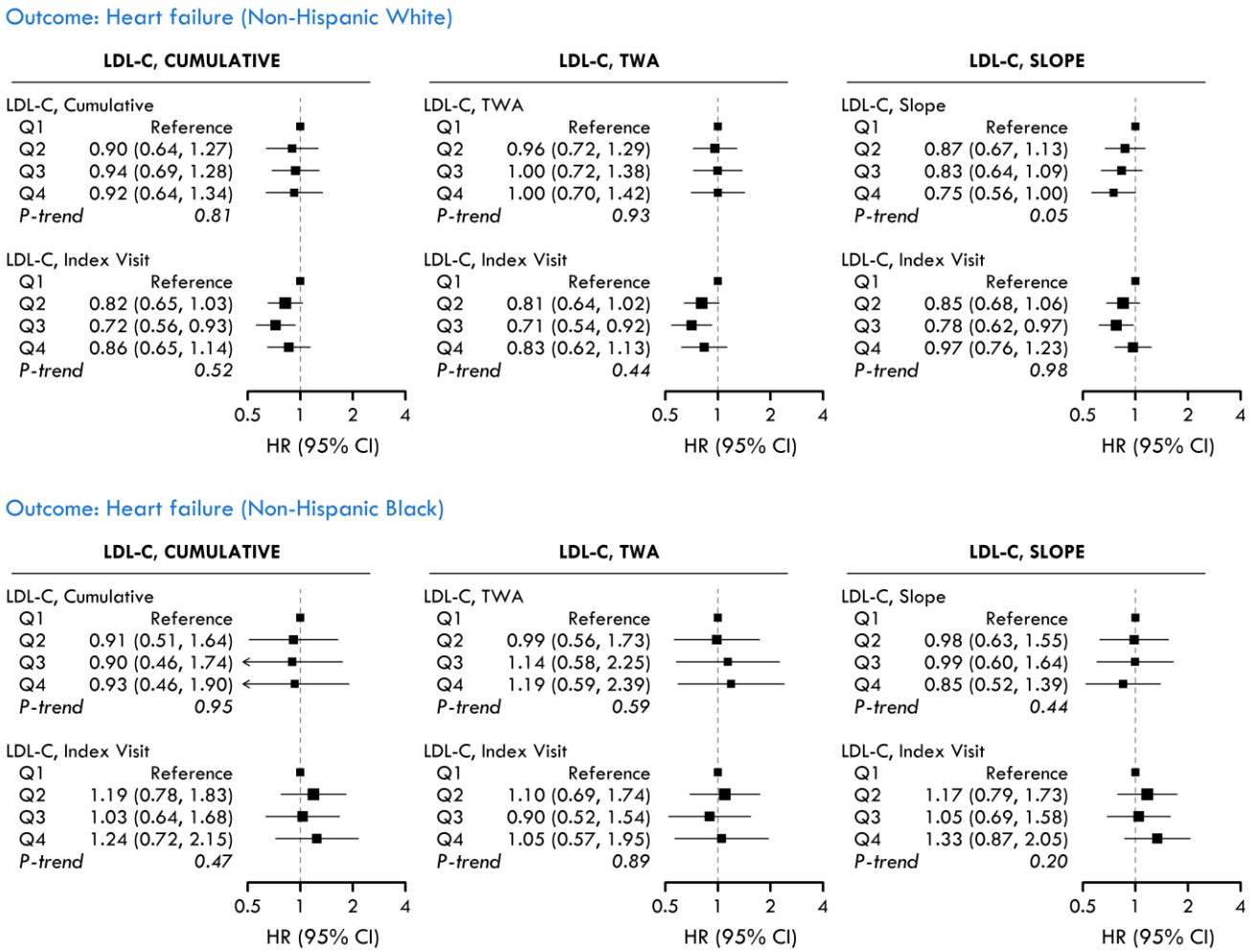
eFigure 10. Associations Between Cumulative LDL-C, TWA LDL-C, and LDL-C Slope During Young Adulthood and Middle Age With Incident Ischemic Stroke, Stratified by Race

Models were stratified by study cohort and adjusted for sex, birth year, BMI, smoking status, HDL, SBP, DBP, diabetes, use of lipid-lowering and anti-hypertensive medications, and LDL-C levels at the index visit.



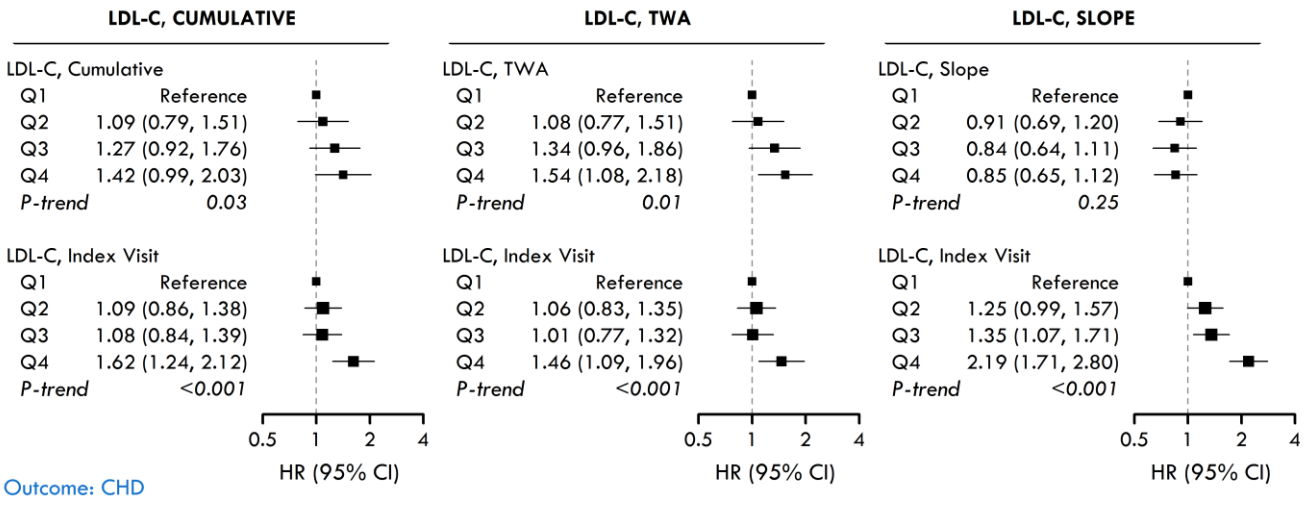
eFigure 11. Associations Between Cumulative LDL-C, TWA LDL-C, and LDL-C Slope During Young Adulthood and Middle Age With Incident Heart Failure, Stratified by Race

Models were stratified by study cohort and adjusted for sex, birth year, BMI, smoking status, HDL, SBP, DBP, diabetes, use of lipid-lowering and anti-hypertensive medications, and LDL-C levels at the index visit.



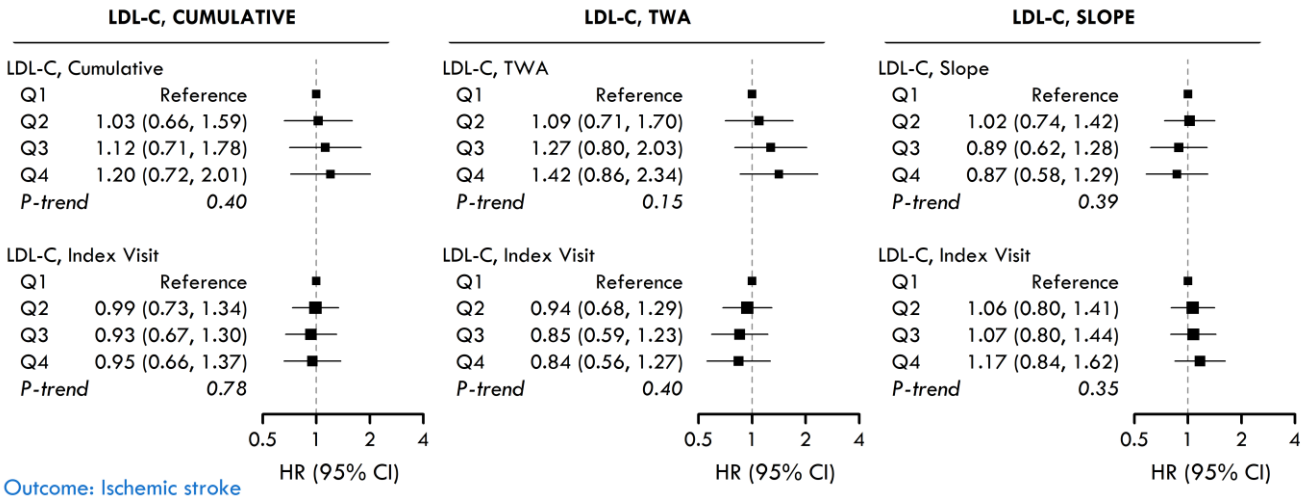
eFigure 12. Associations Between Cumulative LDL-C, TWA LDL-C, and LDL-C Slope During Young Adulthood and Middle Age With Incident CHD, Among Participants Who Never Used Lipid Lowering Medications

Models were stratified by study cohort and adjusted for race/ethnicity, sex, birth year, BMI, smoking status, HDL, SBP, DBP, diabetes, use of anti-hypertensive medications, and LDL-C levels at the index visit.



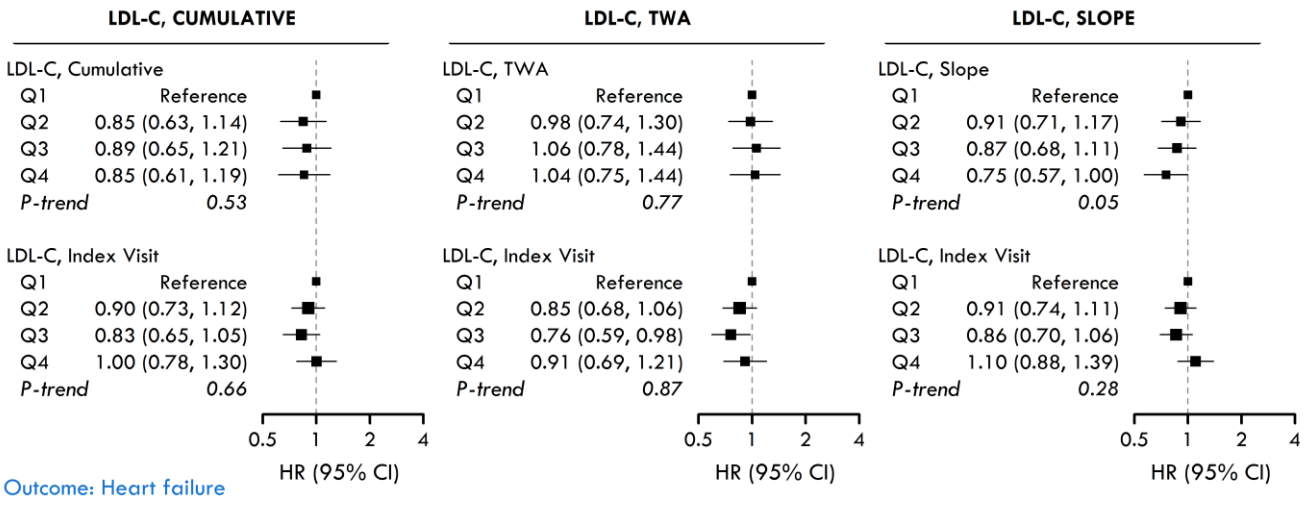
eFigure 13. Associations Between Cumulative LDL-C, TWA LDL-C, and LDL-C Slope During Young Adulthood and Middle Age With Incident Ischemic Stroke, Among Participants Who Never Used Lipid Lowering Medications

Models were stratified by study cohort and adjusted for race/ethnicity, sex, birth year, BMI, smoking status, HDL, SBP, DBP, diabetes, use of anti-hypertensive medications, and LDL-C levels at the index visit.



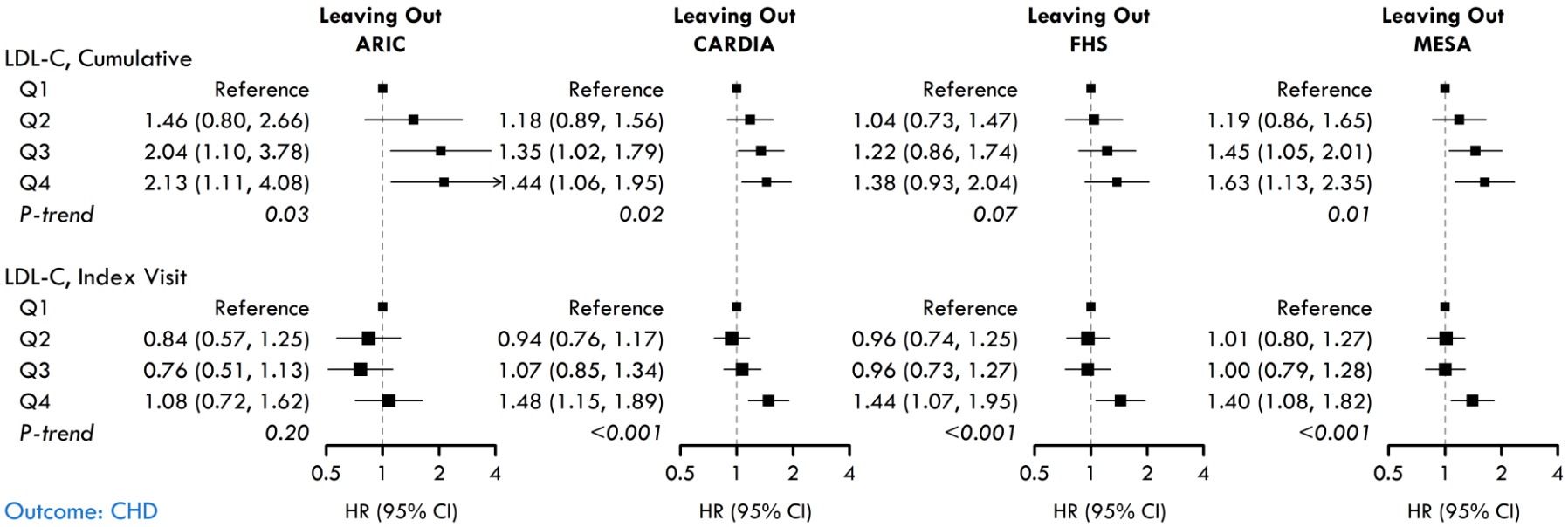
eFigure 14. Associations Between Cumulative LDL-C, TWA LDL-C, and LDL-C Slope During Young Adulthood and Middle Age With Incident Heart Failure, Among Participants Who Never Used Lipid Lowering Medications

Models were stratified by study cohort and adjusted for race/ethnicity, sex, birth year, BMI, smoking status, HDL, SBP, DBP, diabetes, use of anti-hypertensive medications, and LDL-C levels at the index visit.



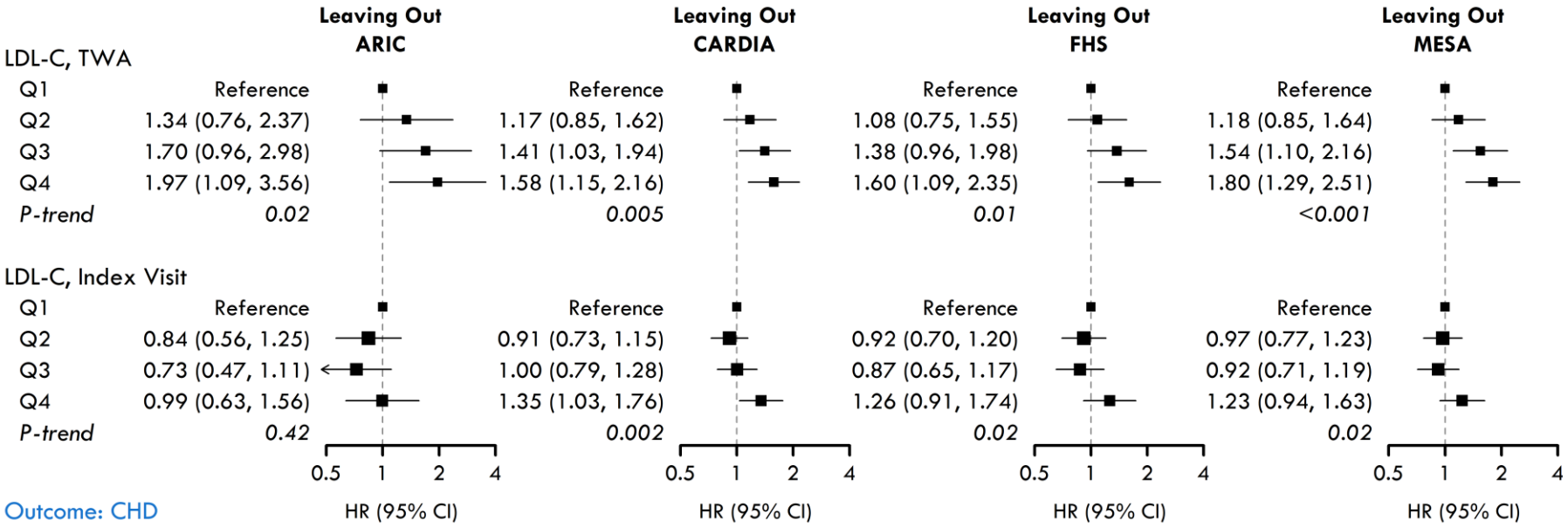
eFigure 15. Associations Between Cumulative LDL-C During Young Adulthood and Middle Age With Incident CHD, Leaving Out One Study At a Time

Models were stratified by study cohort and adjusted for race/ethnicity, sex, birth year, BMI, smoking status, HDL, SBP, DBP, diabetes, use of lipid-lowering and anti-hypertensive medications, and LDL-C levels at the index visit.



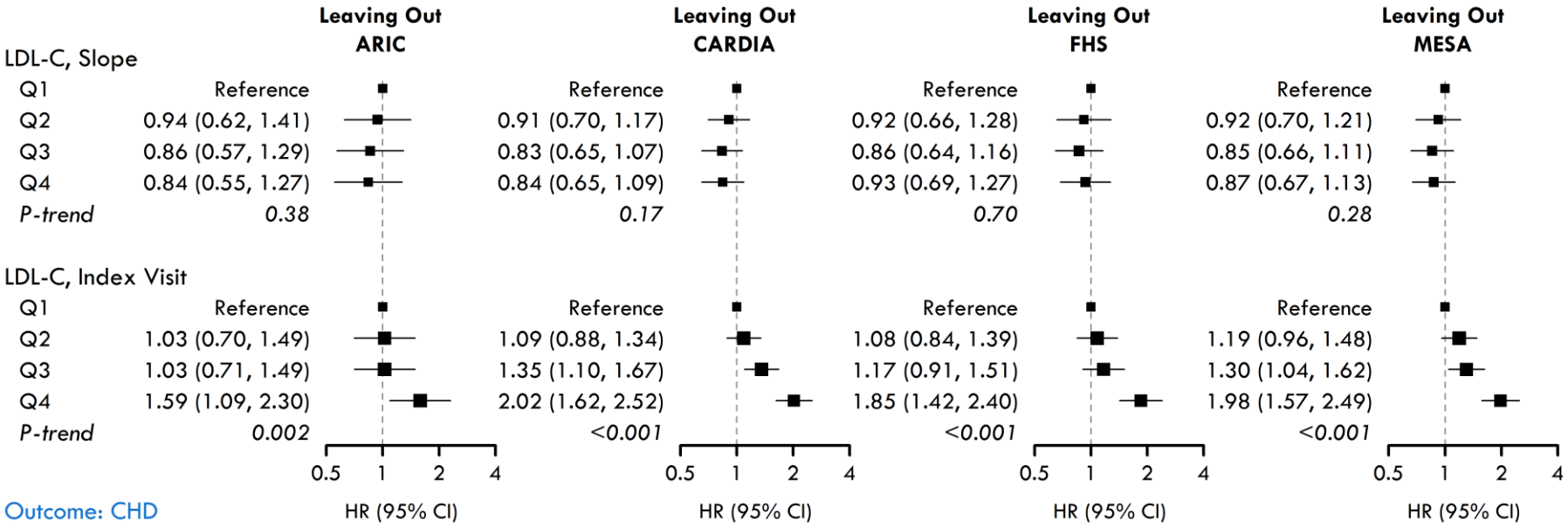
eFigure 16. Associations Between TWA LDL-C During Young Adulthood and Middle Age With Incident CHD, Leaving Out One Study At a Time

Models were stratified by study cohort and adjusted for race/ethnicity, sex, birth year, BMI, smoking status, HDL, SBP, DBP, diabetes, use of lipid-lowering and anti-hypertensive medications, and LDL-C levels at the index visit.



eFigure 17. Associations Between LDL-C Slope During Young Adulthood and Middle Age With Incident CHD, Leaving Out One Study At a Time

Models were stratified by study cohort and adjusted for race/ethnicity, sex, birth year, BMI, smoking status, HDL, SBP, DBP, diabetes, use of lipid-lowering and anti-hypertensive medications, and LDL-C levels at the index visit.



eReferences

1. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. *Am J Epidemiol.* 1989;129(4):687-702.
2. Friedman GD, Cutter GR, Donahue RP, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol.* 1988;41(11):1105-1116.
3. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families. The Framingham offspring study. *Am J Epidemiol.* 1979;110(3):281-290.
4. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol.* 2002;156(9):871-881.
5. Oelsner EC, Balte PP, Cassano PA, et al. Harmonization of respiratory data from 9 US population-based cohorts: the NHLBI pooled cohorts study. *Am J Epidemiol.* 2018;187(11):2265-2278.
6. Pletcher MJ, Vittinghoff E, Thanataveerat A, Bibbins-Domingo K, Moran AE. Young Adult Exposure to Cardiovascular Risk Factors and Risk of Events Later in Life: The Framingham Offspring Study. *PLoS One.* 2016;11(5):e0154288.
7. Zeki Al Hazzouri A, Vittinghoff E, Zhang Y, et al. Use of a pooled cohort to impute cardiovascular disease risk factors across the adult life course. *Int J Epidemiol.* 2018.
8. Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP. The Framingham Offspring Study. Design and preliminary data. *Prev Med.* 1975;4(4):518-525.