Supplementary Table I. Estimated Cox proportional hazard ratios (95% CIs) of incident CHD restricted to myocardial infarction, resuscitated cardiac arrest, or CHD death by quartiles of sdLDL-C, small LDL (NMR), and LDL-C in participants with normal fasting glucose.

CHD risk in normoglycemic, non-diabetic participants (N=3,334)

	LDL-C	**Small LDL-P**	**sdLDL-C**
	(20-284 mg/dL)	(0-2018 nmol/L)	(0.1-214.8 mg/dL)
1	ref	ref	ref
2	0.88 (0.47 - 1.64)	0.66 (0.32 - 1439)	1.16 (0.626 - 2.14)
3	1.30 (0.72 - 2.35)	0.73 (0.34 - 1.55)	1.06 (0.537 - 2.10)
4	1.51 (0.83 - 2.74) *p*=0.18	1.26 (0.54 - 2.91) *p*=0.59	1.92 (0.916 - 4.01) *p*=0.084

Analyses were adjusted for gender, systolic blood pressure, hypertension medication use, age (category), ethnicity, HDL-C, and log triglycerides

LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; small LDL-P = small LDL particle; sdLDL-C = small-dense low density lipoprotein cholesterol

Supplementary Table II. Estimated Cox proportional hazard ratios (95% CIs) of incident CHD by quartiles of sdLDL-C, small LDL (NMR), and LDL-C in a subcohort of MESA participants with **adjustment for lipid lowering medication***

CHD risk in normoglycemic, non-diabetic participants (N=3,334)

	LDL-C	**Small LDL-P**	**sdLDL-C**
	(20-284 mg/dL)	(0-2018 nmol/L)	(0.1-214.8 mg/dL)
1	ref	ref	ref
2	0.84 (0.50 - 1.42)	0.77 (0.44 - 1.34)	1.43 (0.85 - 2.39)
3	1.46 (0.91 - 2.33)	0.87 (0.48 - 1.58)	1.51 (0.88 - 2.60)
4	1.63 (1.01 - 2.63) *p*=0.044	1.31 (0.68 - 2.52) *p*=0.42	2.25 (1.24 - 4.09) *p*=0.0076

CHD risk in participants with impaired fasting glucose or diabetes (N=1,048)

	LDL-C	**Small LDL-P**	**sdLDL-C**
Quartile	(12-315 mg/dL)	(0-2299 nmol/L)	(0.1-172.3 mg/dL)
1	ref	ref	ref
2	0.91 (0.49 - 1.71)	0.90 (0.44 - 1.86)	1.08 (0.57 - 2.04)
3	1.16 (0.63 - 2.16)	0.68 (0.30 - 1.52)	0.76 (0.372 - 1.57)
4	1.19 (0.62 - 2.30)	0.92 (0.41 - 2.07)	1.08 (0.51 - 2.30)

*Analyses were adjusted for gender, systolic blood pressure, hypertension medication use, age (category), ethnicity, HDL-C, log triglycerides, **and lipid lowering medication**

LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; small LDL-P = small LDL particle; sdLDL-C = small-dense low density lipoprotein cholesterol

Materials and Methods

Population

The primary aim of MESA is to investigate clinical and subclinical CHD development and progression. The study design and initial exclusion criteria have been previously described (1), and information about MESA is also available at (www.mesa-nhlbi.org). Briefly, a population of 6,814 men and women without clinical evidence of CHD, between the ages of 45 and 84 years, and composed of 38.6% white, 27.6% black, 11.8% Chinese and 22.0% Hispanic were recruited from six communities in the United States (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; New York, NY; and St. Paul, MN). Institutional Review Board approval was obtained at all MESA sites, and all participants gave informed consent. Recruitment and baseline examinations began in July 2000 and were conducted over a 24-month period.

A number of exclusion criteria were applied for the present analysis. Individuals taking lipid-lowering medication at baseline were excluded (N=1187). In addition, 948 participants of the original MESA 1000, a subcohort of randomly selected individuals enrolled prior to February 2002, were also excluded due to limited sample availability. An additional 292 individuals with probable angina or certain CVD events were additionally excluded (discussed below). The remaining population of 4,387 individuals was representative of the entire MESA cohort with respect to race/ethnicity: 28.7% African American (n=1,257), 12.4% Chinese American (n=546), 22.7% Hispanic (n=996), and 36.2% White (n=1,588) participants. The study population was followed for an 8.5 year study period.

Lipid Measurements

Fasting blood was drawn and serum and EDTA-anticoagulant tubes were collected and stored at -70^{o}C, using a standardized protocol (1). Lipids and glucose were measured at a central laboratory (Collaborative Studies Clinical Laboratory at Fairview-University Medical Center, Minneapolis, MN), using CDC-standardized methods. HDL-C was determined by the cholesterol oxidase method (Roche Diagnostics, Indianapolis, IN), and fasting triglycerides were measured in plasma, using a glycerol-blanked enzymatic method (Trig/GB; Roche Diagnostics, Indianapolis, IN). LDL-C was calculated using the Friedewald equation. Cholesterol within small dense LDL (15.0 nm-20.0 nm) was measured as described previously (2) using a newly developed automated homogenous assay (Denka Seiken Co., Ltd., 3-4-2 Nihonbashi-Kayabacho, Chuo-Ku, Tokyo) and analyzed on a Roche/Hitachi Modular P Chemistry Analyzer, coefficient of variance of 3.2%.

NMR Spectroscopy

Lipoproteins were measured at LipoScience, Inc. (Raleigh, N.C.) by NMR spectroscopy using the LipoProfile-3 algorithm, as described previously (3, 4). Briefly, lipoprotein particle concentrations were measured on plasma specimens frozen at −70 °C. As each lipoprotein particle subclass has a distinct lipid methyl group, concentrations were determined from the

amplitude of their unique NMR signals. The concentrations of small LDL (diameters of 18.0–20.5 nm) are presented in the current analysis with coefficient of variation <8%.

Anthropometric, demographic, and clinical variables

Information regarding age, sex, race/ethnicity, and lifestyle factors was obtained by questionnaires. Height (m), weight (kg), and blood pressure were measured according to standard procedures (1). Hypertension was defined as a mean systolic blood pressure of ≥140 or a diastolic blood pressure of ≥90 mmHg, or the use of antihypertensive medication. Glucose status was defined using the criteria of the American Diabetes Association: NFG, <5.6 mmol/L; IFG, 5.6-6.9 mmol/L; diabetes was defined as those clinically diagnosed or with fasting glucose of ≥7.0 mmol/L.

Classifying Coronary Heart Disease and Exclusion Criteria

Incident CHD was defined as the first occurrence of any of the following: myocardial infarction (n=101), resuscitated cardiac arrest (n=17), CHD death (n=45), or definite angina (n=109). Definite angina was defined as symptoms of typical chest pain and physician diagnosis of angina followed by coronary artery bypass grafting and percutaneous coronary intervention (PTCA), evidence of ischemia by stress tests or resting ECG, or ≥70% obstruction on coronary angiography. In addition, there were 51 cases of 'probable angina,' but only 9 were included as CHD cases in the present analysis. Probable angina cases that were included showed symptoms of typical chest or atypical symptoms and physician diagnosis of angina *followed by* coronary artery bypass grafting. Probable angina cases followed by PTCA were excluded (n=4) as obstruction did not reach 70%. An additional 14 individuals that did not experience angina and underwent PTCA without evidence of obstruction ≥70% were also excluded.

Finally, 250 individuals who experienced CVD events that do not fall under the definition of CHD were excluded from the study. These events included trans-ischemic attack (n=45), stroke (n=94), congestive heart failure (n=73), peripheral vascular disease (n=40), and other revascularization (n=25). Notably, some individuals suffered multiple events.

Statistical Analysis

Statistical analysis was conducted using Stata (version 12.1, Stata Corp, College Station, TX). Baseline characteristics are presented as means (SD) for continuous variables and frequencies (%) for categorical variables. Cox regression were used to test for association between sdLDL-C, sdLDL-particles (sdLDL-P), or LDL-C and the outcomes of CHD stated above, adjusting for sex, systolic blood pressure, hypertension medication use, the standard lipid measures HDL-C and (log-transformed) triglycerides, and stratified by age group and race. Residual analysis suggested nonlinear relationship between martingale residuals and un-transformed LDL-C or sdLDL measures; therefore, quartiles of sdLDL-C, sdLDL-P, and LDL-C were used in the regression. A second Cox regression model was fit to include both quartiles of sdLDL-C (or sdLDL-P) and dichotomized LDL-C (<2.59 mmol/L vs >2.59 mmol/L), adjusting for the same set of covariates. The proportional hazards assumption was examined

using Schoenfeld residuals. The analyses were performed for NFG, and IFG or diabetes individuals separately.

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