

For You Symposium

Lipid and Vascular diseases



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OPEN

Role of Blood Lipids in the Development of Ischemic Stroke and its Subtypes

A Mendelian Randomization Study

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Matthew Traylor, PhD; Hugh S. Markus, DM; Olle Melander, MD, PhD;
Marju Orho-Melander, PhD; on behalf of the Stroke Genetics Network (SiGN)

JAMA | Original Investigation

Association of Triglyceride-Lowering *LPL* Variants and LDL-C-Lowering *LDLR* Variants With Risk of Coronary Heart Disease

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Hindy G et al Stroke 2018; Ference BA et al JAMA 2019

CONCLUSIONS AND RELEVANCE Triglyceride-lowering *LPL* variants and LDL-C-lowering *LDLR* variants were associated with similar lower risk of CHD per unit difference in ApoB. Therefore, the clinical benefit of lowering triglyceride and LDL-C levels may be proportional to the absolute change in ApoB.

JAMA. 2019;321(4):364-373. doi:10.1001/jama.2018.20045

Conflicting opinions among the guidelines



European Heart Journal (2016) 37, 2999–3058
doi:10.1093/euroheartj/ehw272

ESC/EAS GUIDELINES

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)

Authors/Task Force Members: Alberico L. Catapano* (Chairperson) (Italy),

AHA/ASA Guideline

2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

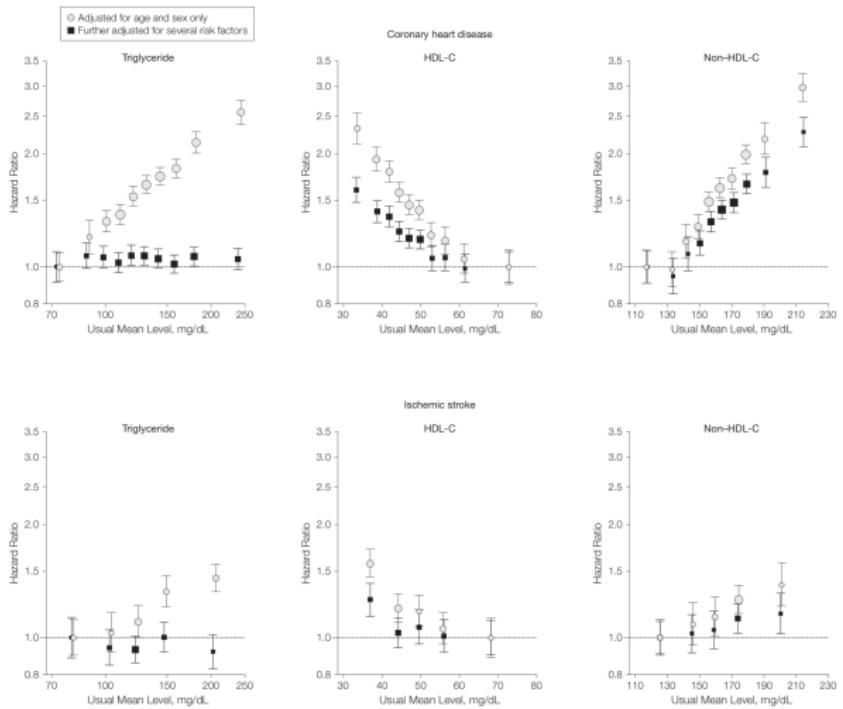
Endorsed by the Society for Academic Emergency Medicine

Stroke 2018 March; European Heart Journal 2016, 2999–3058

Good predictor or Cause of Atherosclerosis ?

- ① LDL-cholesterol
- ② HDL-cholesterol
- ③ Triglyceride

Figure 1. Hazard Ratios for Coronary Heart Disease or Ischemic Stroke Across Quantiles of Usual Triglyceride, HDL-C, and Non-HDL-C Levels



Analyses for coronary heart disease were based on 302 430 participants (involving 12 785 cases) from 68 studies. Analyses for ischemic stroke were based on 173 312 participants (involving 2534 cases) from 32 studies. Regression analyses were stratified, where appropriate, by sex and trial group. Values with further adjustments

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lipoprotein = lipid + apolipoprotein

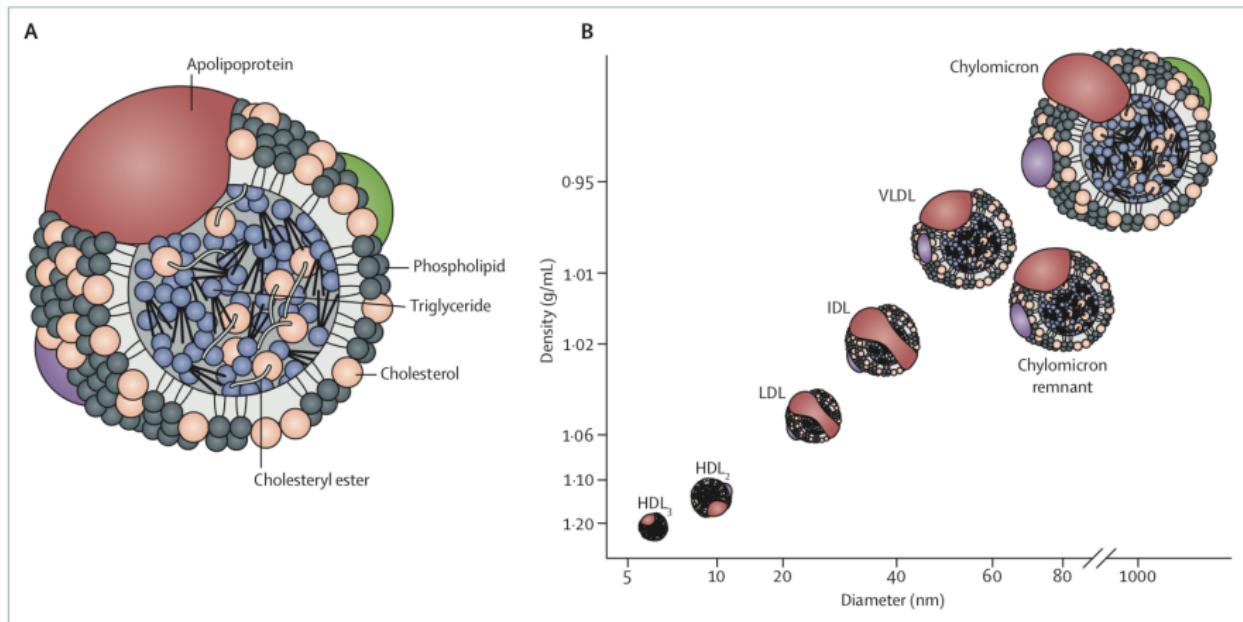


Figure 1: The structural components of lipoproteins (A) and their relation to diameter and density (B)

Adopted from Genest J, Libby P. Lipoprotein Disorders and Cardiovascular Disease. Braunwald's Heart Disease: a textbook of cardiovascular medicine, ninth edition. Elsevier 2012, pp: 975-95. IDL=intermediate-density lipoprotein.

TABLE 400-1 Major Lipoprotein Classes

LIPOPROTEIN	DENSITY, g/mL ^a	SIZE, nm ^b	ELECTROPHORETIC MOBILITY ^c	APOLIPOPROTEINS		OTHER CONSTITUENTS
				MAJOR	OTHER	
Chylomicrons	0.930	75–1200	Origin	ApoB-48	A-I, A-V, C-I, C-II, C-III, E	Retinyl esters
Chylomicron remnants	0.930–1.006	30–80	Slow pre-β	ApoB-48	A-I, A-V, C-I, C-II, C-III, E	Retinyl esters
VLDL	0.930–1.006	30–80	Pre-β	ApoB-100	A-I, A-II, A-V, C-I, C-II, C-III, E	Vitamin E
IDL	1.006–1.019	25–35	Slow pre-β	ApoB-100	C-I, C-II, C-III, E	Vitamin E
LDL	1.019–1.063	18–25	β	ApoB-100		Vitamin E
HDL	1.063–1.210	5–12	α	ApoA-I	A-II, A-IV, A-V, C-III, E	LCAT, CETP, paroxonase
Lp(a)	1.050–1.120	25	Pre-β	ApoB-100	Apo(a)	Oxidized phospholipids

^aThe density of the particle is determined by ultracentrifugation. ^bThe size of the particle is measured using gel electrophoresis. ^cThe electrophoretic mobility of the particle on agarose gel electrophoreses reflects the size and surface charge of the particle, with β being the position of LDL and α being the position of HDL.

Note: All of the lipoprotein classes contain phospholipids, esterified and unesterified cholesterol, and triglycerides to varying degrees.

Abbreviations: CETP, cholesteryl ester transfer protein; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; Lp(a), lipoprotein A; VLDL, very-low-density lipoprotein.

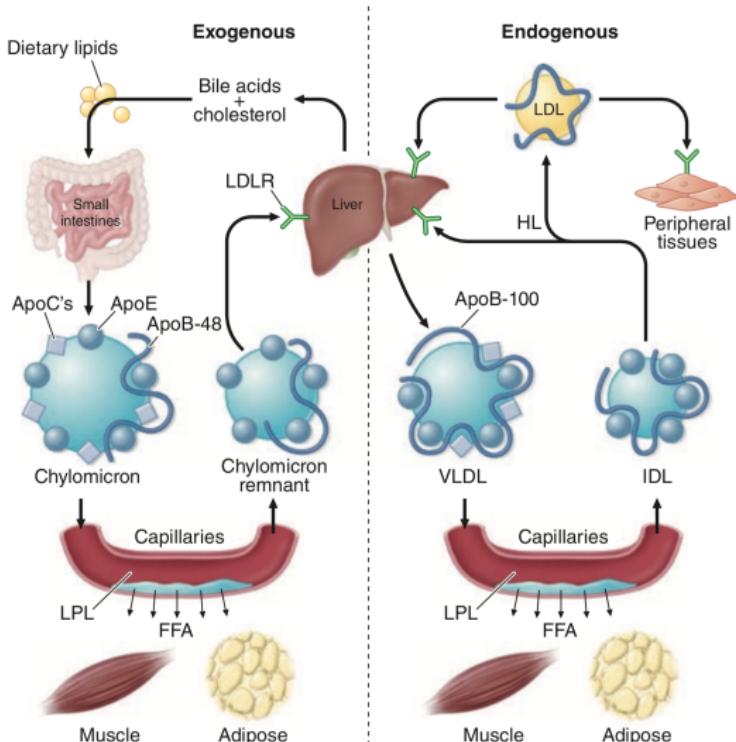
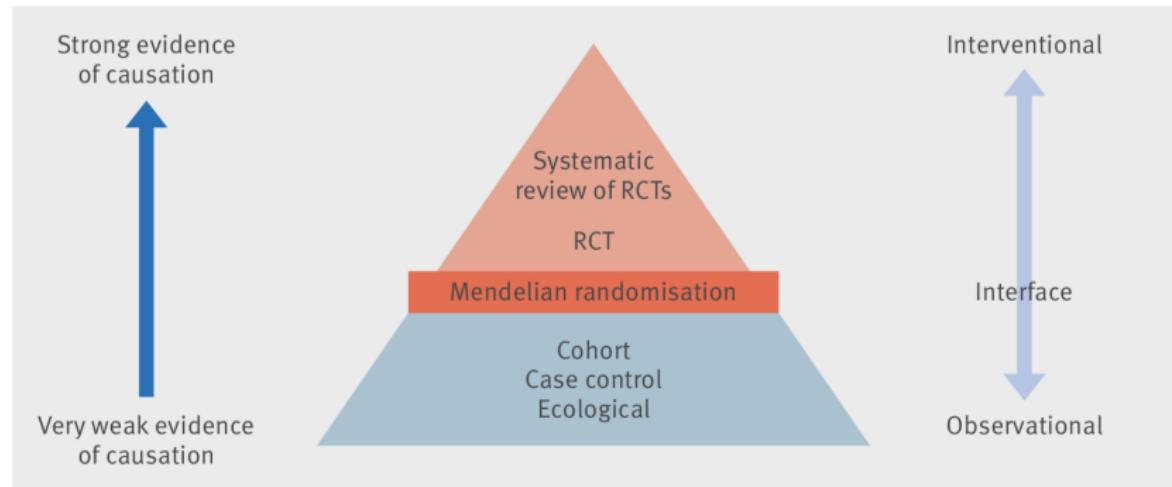


FIGURE 400-2 The exogenous and endogenous lipoprotein metabolic pathways. The exogenous pathway transports dietary lipids to the periphery and the liver. The endogenous pathway transports hepatic lipids to the periphery. FFA, free fatty acid; HL, hepatic lipase; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; LPL, lipoprotein lipase; VLDL, very-low-density lipoprotein.

Mendelian Randomization



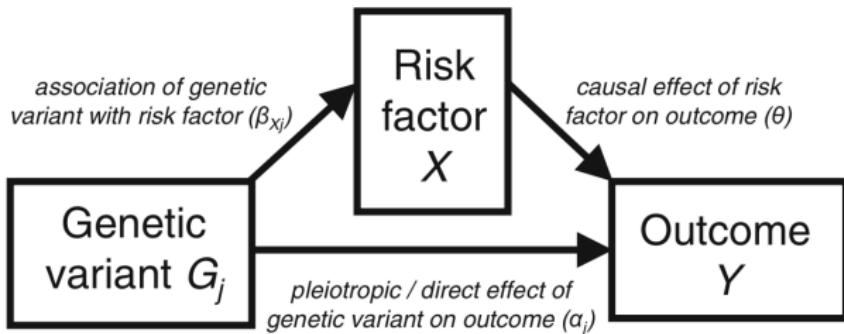
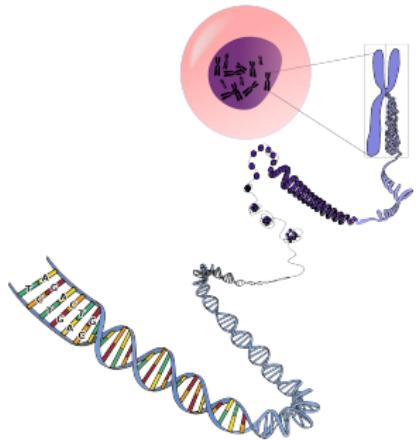


Fig. 1 Decomposing association for genetic variant G_j with the outcome into an indirect (causal) effect via the risk factor and a direct (pleiotropic) effect (see Eq. 1)

Location of DNA variation



- Whole chromosomal and whole genome changes: ~1-6 billion bp
 - Aneuploidy (abnormal number of chromosomes)
 - Aneusomy (fewer or more copies than 2 of a chromosome)
 - Interchromosomal translocations
 - Ring chromosomes
- Microscopic to submicroscopic
 - Segmental aneusomy
 - Chromosomal deletions
 - Chromosomal insertions
 - Chromosomal inversions
 - Intrachromosomal translocations
 - Chromosomal abnormality
 - Fragile sites
- 1 kb to submicroscopic
 - Copy number variants (CNVs)
 - Segmental duplications
 - Inversions, translocations
 - CNV regions
 - Microdeletions
 - Microduplications
- 2 bp to 1,000 bp
 - Microsatellites, minisatellites
 - Insertion-deletions (Indels)
 - Inversions
 - Di-, tri-, tetra-nucleotide repeats
 - Variable number tandem repeats e.g. microsatellites
- Single nucleotide 1 bp
 - Indels
 - SNPs

bp indicates base pairs; SNP single nucleotide polymorphisms.

Cytogenetic
changes



Molecular
genetic
changes

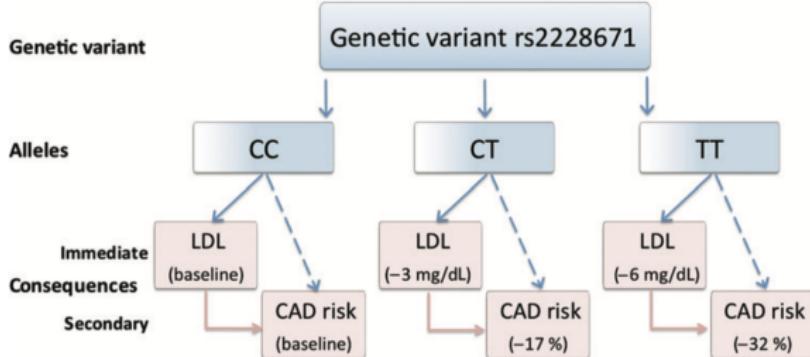
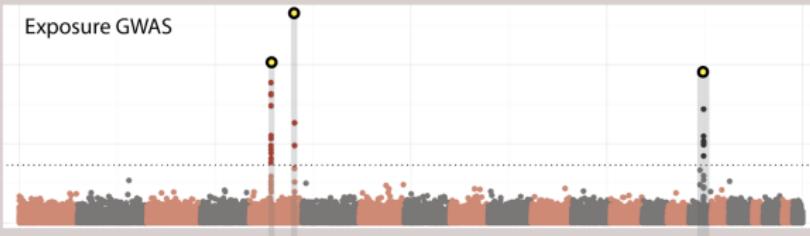
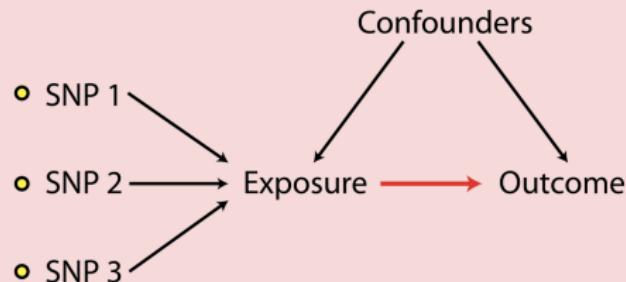


Figure 2 The effects of rs2228671 genotypes in the LDL receptor gene on LDL cholesterol (mg/dL) and coronary artery disease risk (% risk change) are shown as assessed by Linsel-Nitschke *et al.* across different cohorts compromising data from about 9000 individuals.¹⁶ The decrease of LDL serum concentration and the decrease in coronary artery disease risk go in parallel the number of T alleles. Since the gene has no other known functions it can be assumed that the LDL increase is causally involved in coronary artery disease.

Objective: Infer the causal effect of the exposure on the outcome

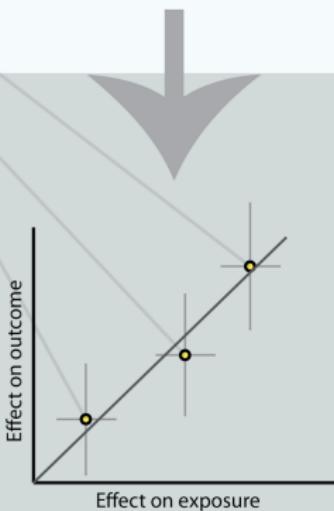


Description

Define instruments: Obtain SNPs that are GWAS significant for the exposure. Ensure that they are independent.

Instruments can be defined from a variety of different sources.

SNP	Exposure GWAS				Outcome GWAS			
	Effect	Effect allele	Other allele	Effect allele frequency	Effect	Effect allele	Other allele	Effect allele frequency
rs123456	0.132	A	G	0.28	0.022	A	G	0.26
rs234567	-0.485	G	T	0.41	-0.056	G	T	0.39
rs345678	0.203	G	C	0.11	0.046	G	C	0.12



Perform analysis: Using the harmonized data, perform Mendelian randomization analyses and related sensitivity analyses.

The slope of the regression line corresponds to the causal effect of the exposure on the outcome

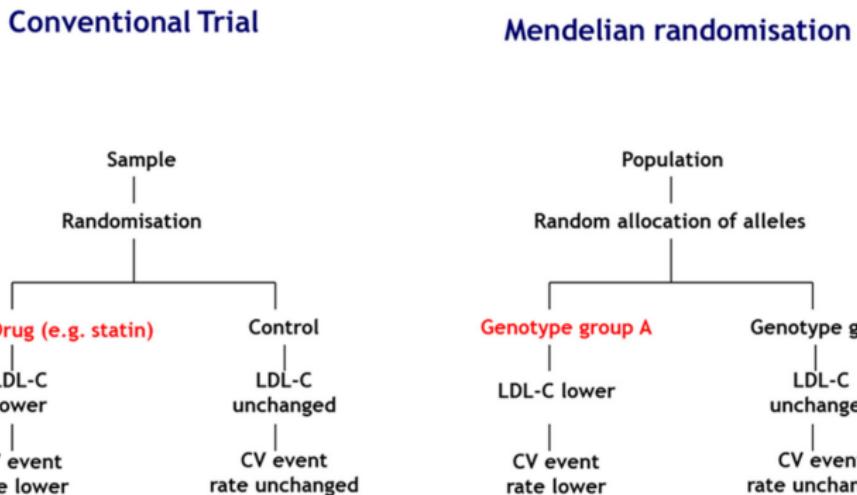
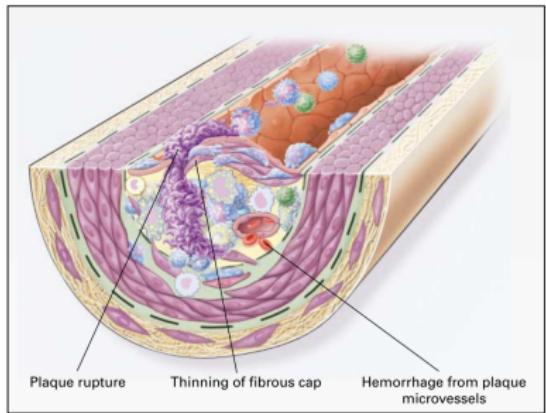


Figure 3 Comparison of a conventional trial with a Mendelian randomisation study. This illustrates the analogy between a conventional randomised controlled trial and a Mendelian randomisation study. CV, cardiovascular.

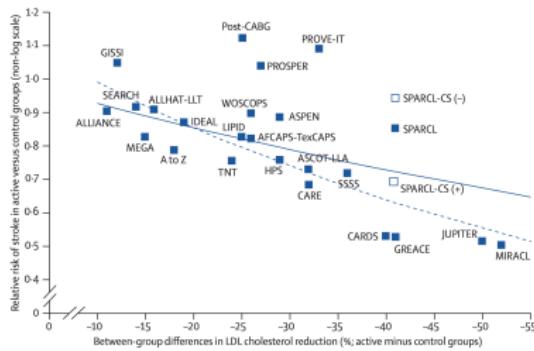
Atherosclerosis: Leading cause of ischemic stroke

- Artery wall thickens as a result of invasion and accumulation of white blood cells with cholesterol fatty substances, calcium and fibrin.
- Intima of medium and large sized systemic arteries are involved.



Ross R. N Engl J Med 1999

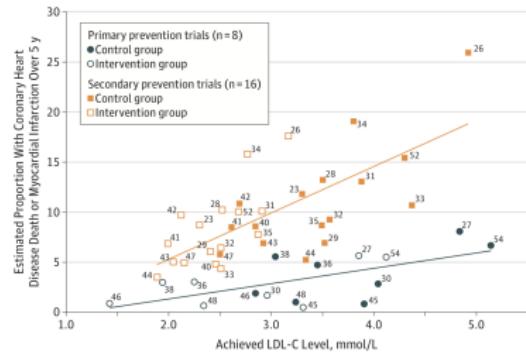
Dose-response relationship in Stroke/IHD and LDL-C



Estimates of relative risk reduction

- 10% LDL reduction: relative risk reduction 7.5% (2.3-12.5) overall
relative risk reduction 13.5% (7.7-18.8) for primary prevention of stroke
- 1 mmol/l (39 mg/dl) LDL reduction: relative risk reduction 21.1% (6.3-33.5) overall
relative risk reduction 35.9% (21.7-47.6) for primary prevention of stroke

Figure 4. Association Between Achieved Low-Density Lipoprotein Cholesterol (LDL-C) and Major Coronary Event Rates From 24 Trials of Established Interventions That Lower LDL-C Predominantly Through Upregulation of LDL Receptor Expression



Amarenco et al. Lancet Neurol 2009;8:453-463; Silverman MG et al. JAMA 2016

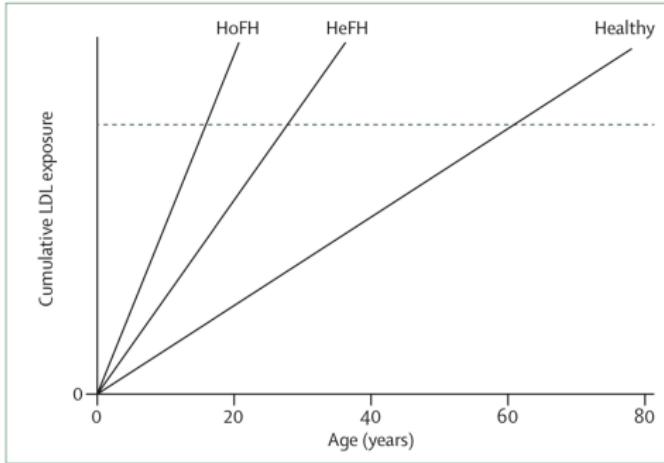


Figure 2: Approximate age of onset of atherosclerotic symptoms for those with homozygous familial hypercholesterolaemia or heterozygous familial hypercholesterolaemia, and those without inherited defects of the LDL-receptor

Adopted from Horton and colleagues.⁶ HoFH=homozygous familial hypercholesterolaemia. HeFH=heterozygous familial hypercholesterolaemia.

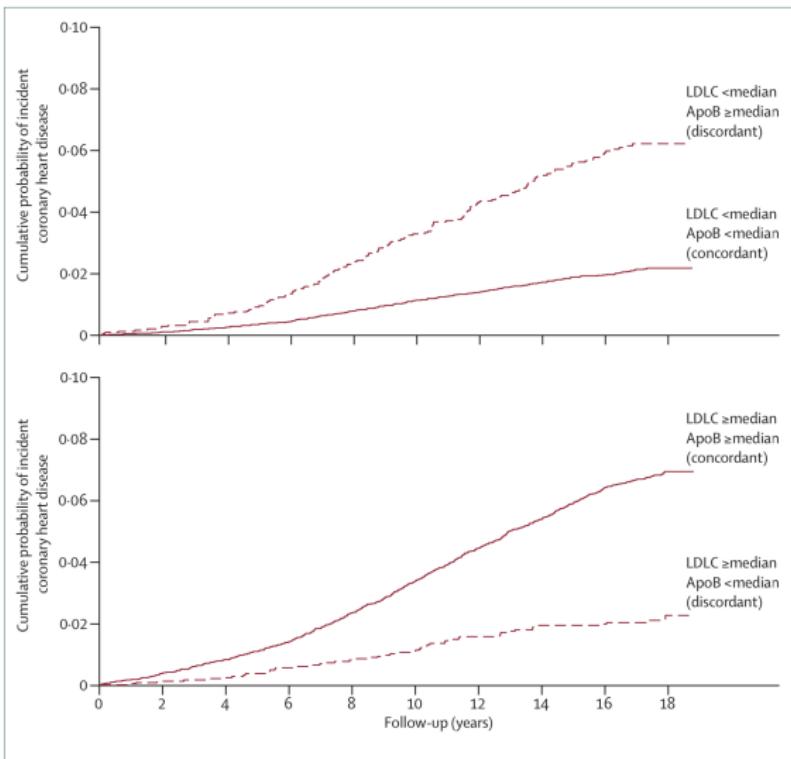


Figure 4: Differential predictive usefulness of the atherogenic lipoproteins LDLC and apolipoprotein B
 Assessed in individuals where there was concordance and discordance between LDLC and apolipoprotein B.
 Adopted from Mora and colleagues.²⁷ LDLC=LDL cholesterol. ApoB=apolipoprotein B.

Ridker PM. Lancet 2014

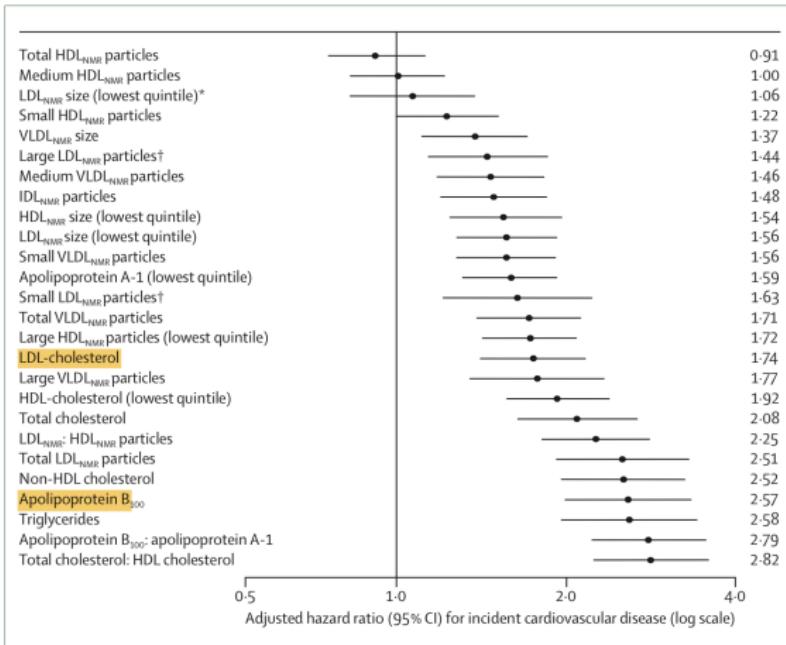


Figure 3: Direct comparison of 26 lipid fractions as predictors of first-ever cardiovascular events in apparently healthy women

Data are shown for the top versus bottom quintile of each lipid fraction, unless otherwise indicated. *Additionally adjusted for total LDL_{NMR} particle concentration. †Additionally adjusted for the other NMR proteins. Adopted from Mora and colleagues.²²

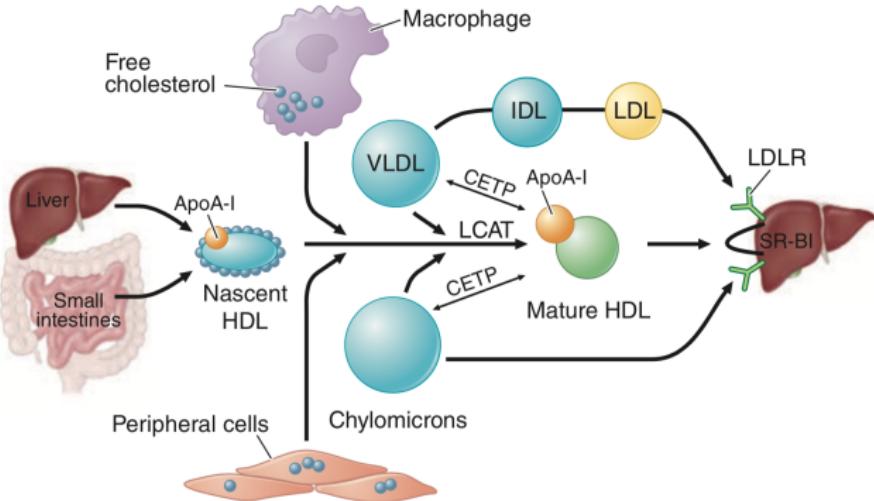


FIGURE 400-3 High-density lipoprotein (HDL) metabolism and reverse cholesterol transport. This pathway transports excess cholesterol from the periphery back to the liver for excretion in the bile. The liver and the intestine produce nascent HDLs. Free cholesterol is acquired from macrophages and other peripheral cells and esterified by lecithin-cholesterol acyltransferase (LCAT), forming mature HDLs. HDL cholesterol can be selectively taken up by the liver via SR-BI (scavenger receptor class BI). Alternatively, HDL cholesteryl ester can be transferred by cholesteryl ester transfer protein (CETP) from HDLs to very-low-density lipoproteins (VLDLs) and chylomicrons, which can then be taken up by the liver. IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor.

RESEARCH

Effect on cardiovascular risk of high density lipoprotein targeted drug treatments niacin, fibrates, and CETP inhibitors: meta-analysis of randomised controlled trials including 117 411 patients OPEN ACCESS

Neither niacin, fibrates, nor CETP inhibitors, three highly effective agents for increasing high density lipoprotein levels, reduced all cause mortality, coronary heart disease mortality, myocardial infarction, or stroke in patients treated with statins.

The statin era

Without background treatment with statins, fibrates were seen to reduce non-fatal myocardial infarction, and niacin to reduce both non-fatal myocardial infarction and stroke. However, in the modern era when treatment with statins is standard, this effect has not been apparent (fig 4). Attempts at risk reduction through these treatments to increase high density lipoprotein levels on top of statin treatment have been unsuccessful so far.

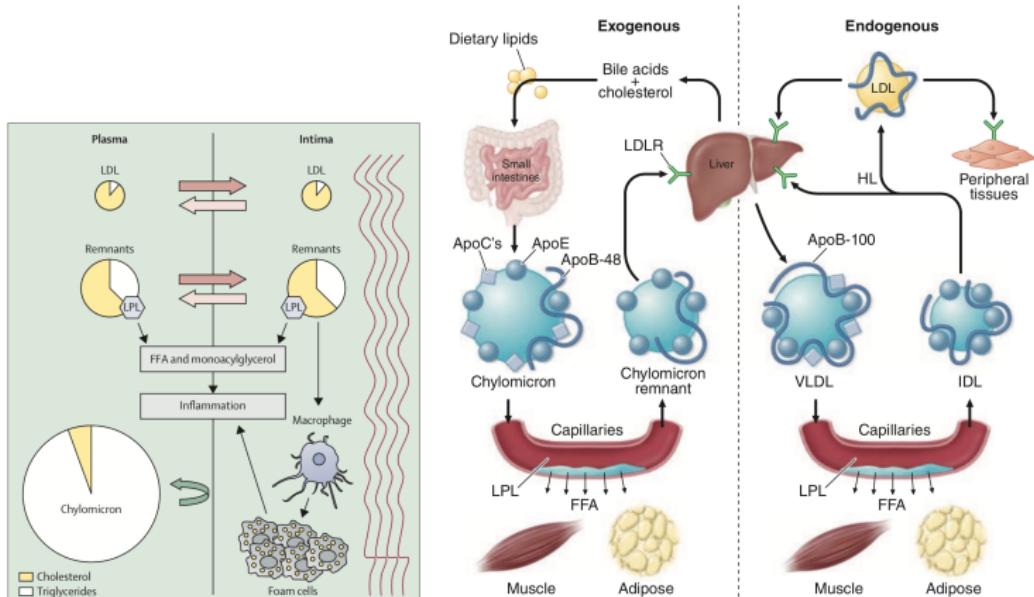


Figure 2: Suggested role of raised plasma triglycerides and remnant cholesterol in intimal low-grade inflammation and development of atherosclerosis
Triglycerides and remnant cholesterol could act through triglyceride hydrolysis and cholesterol accumulation in arterial wall foam cells leading to development of atherosclerosis. FFA=free fatty acids, LPL=lipoprotein lipase.

FIGURE 400-2 The exogenous and endogenous lipoprotein metabolic pathways. The exogenous pathway transports dietary lipids to the periphery and the liver. The endogenous pathway transports hepatic lipids to the periphery. FFA, free fatty acid; HL, hepatic lipase; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; LPL, lipoprotein lipase; VLDL, very-low-density lipoprotein.

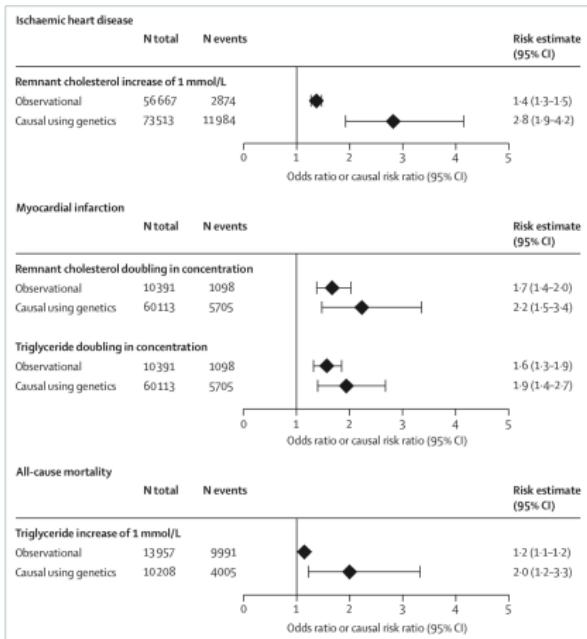


Figure 3: Observational and causal (by use of genetics) associations of raised remnant cholesterol and triglycerides with risk of ischaemic heart disease, myocardial infarction, and all-cause mortality
Top section adapted from Varbo and colleagues.¹⁹ Middle section adapted from Jørgensen and colleagues.¹⁸

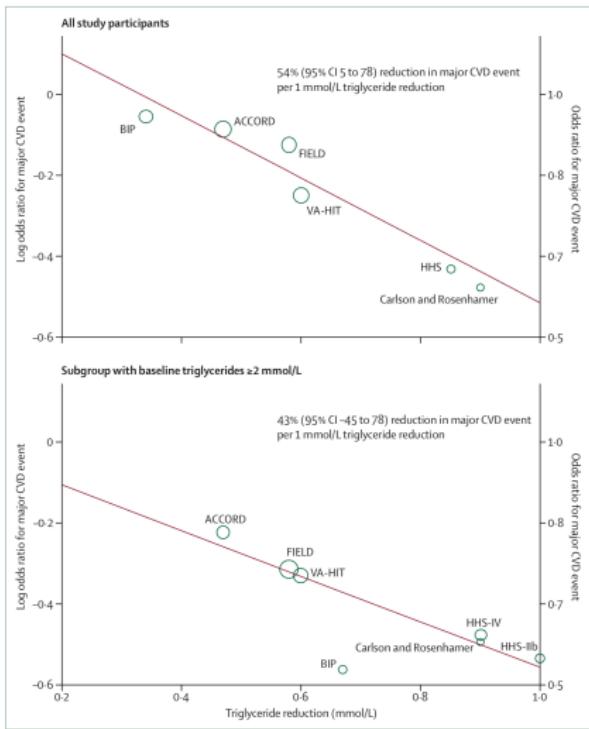


Figure 4: Association estimated by meta-regression between extent of triglyceride-lowering and reduction in risk of a major cardiovascular event in large controlled trials with fibrates

OPEN

Role of Blood Lipids in the Development of Ischemic Stroke and its Subtypes A Mendelian Randomization Study

George Hindy, MD, PhD; Gunnar Engström, MD, PhD; Susanna C. Larsson, PhD;
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Hindy G et al Stroke 2018;

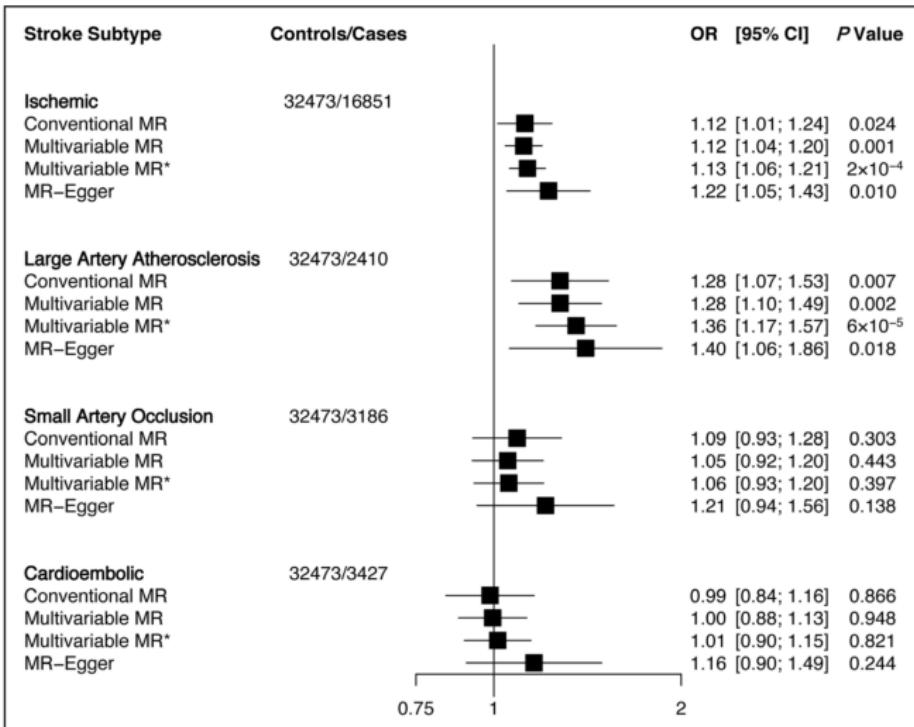


Figure 1. Association of low-density lipoprotein cholesterol with ischemic stroke and subtypes using different Mendelian randomization

Hindry G et al Stroke 2018

JAMA | Original Investigation

Association of Triglyceride-Lowering *LPL* Variants and LDL-C-Lowering *LDLR* Variants With Risk of Coronary Heart Disease

Brian A. Ference, MD, MPhil, MSc; John J. P. Kastelein, MD, PhD; Kausik K. Ray, MD, MPhil; Henry N. Ginsberg, MD; M. John Chapman, PhD, DSc; Chris J. Packard, DSc; Ulrich Laufs, MD, PhD; Clare Oliver-Williams, PhD; Angela M. Wood, PhD; Adam S. Butterworth, PhD; Emanuele Di Angelantonio, MD; John Danesh, DPhil; Stephen J. Nicholls, MBBS, PhD; Deepak L. Bhatt, MD, MPH; Marc S. Sabatine, MD, MPH; Alberico L. Catapano, PhD

Ference BA et al JAMA 2019

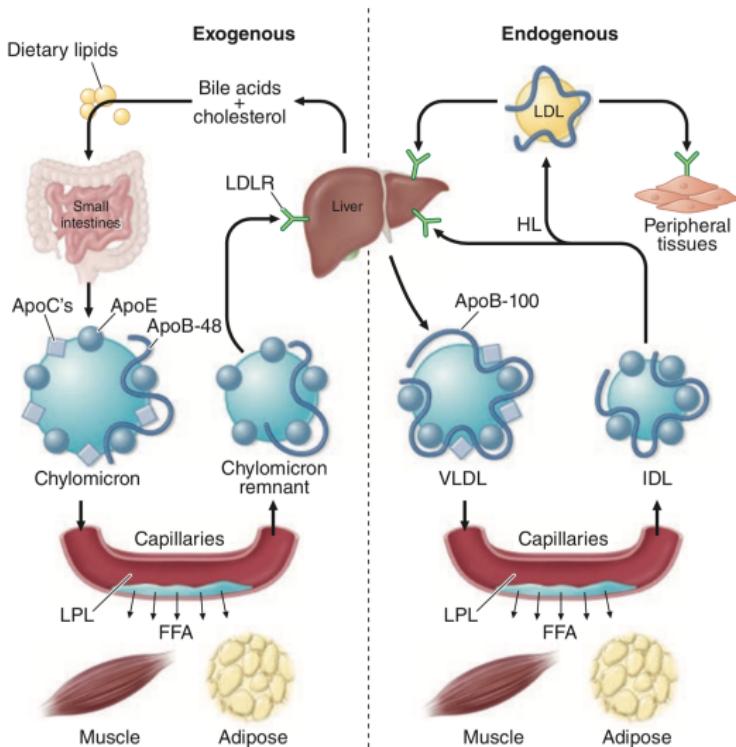
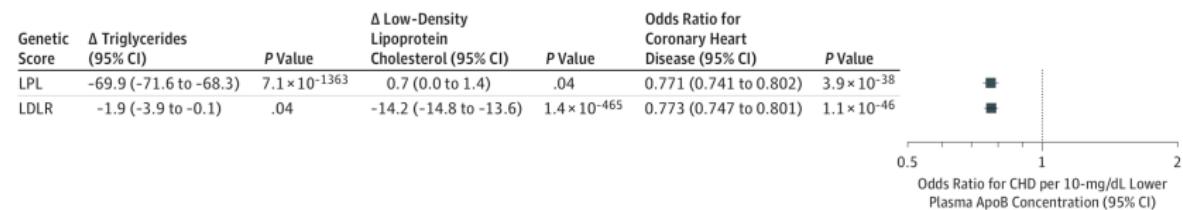


FIGURE 400-2 The exogenous and endogenous lipoprotein metabolic pathways. The exogenous pathway transports dietary lipids to the periphery and the liver. The endogenous pathway transports hepatic lipids to the periphery. FFA, free fatty acid; HL, hepatic lipase; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; LPL, lipoprotein lipase; VLDL, very-low-density lipoprotein.

Methods

- Calculation of genetic score of LPL and LDL-R
- Genetic score - TG/LDL-C/ApoB and CHD (Linear and logistic regression)
- Associations of each score with risk of CHD was scaled for a common 10-mg/dL lower level of ApoB-containing lipoproteins
- The point estimates derived from the individual participant data and the summary data were then combined across studies in a fixed-effect inverse variance-weighted meta-analysis

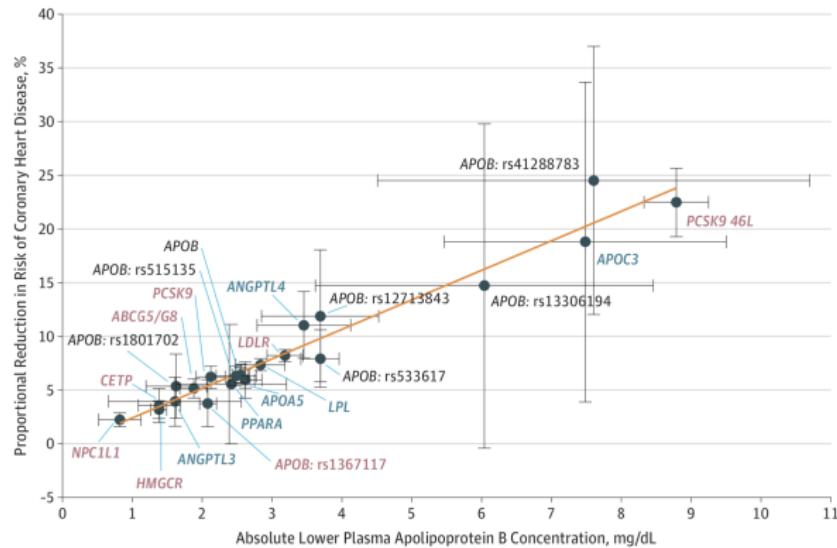
Figure 1. Associations Between the Lipoprotein Lipase (*LPL*) and LDL Receptor Gene (*LDLR*) Genetic Scores With Triglycerides, Low-Density Lipoprotein Cholesterol (LDL-C), and Risk of Coronary Heart Disease (CHD) per 10-mg/dL Lower Concentration of Apolipoprotein B (ApoB)-Containing Lipoproteins



Triglycerides are carried in plasma by ApoB-containing triglyceride-rich lipoproteins while cholesterol is carried predominantly by ApoB-containing low-density lipoproteins. Changes in plasma triglycerides and LDL-C concentration are thus markers of the corresponding changes in the concentration of the ApoB-containing lipoproteins that transport these lipids. Variants in the *LPL* gene that increase *LPL* activity are associated with lower triglycerides and a corresponding lower ApoB concentration, while variants in the *LDLR* gene that increase activity of the LDL receptor are associated with lower LDL-C and a corresponding lower ApoB. The figure shows that for each 10-mg/dL lower plasma ApoB concentration associated with variants in the *LPL* score, there is a corresponding 69.9-mg/dL lower triglyceride level, no change in LDL-C, and a lower risk of CHD (odds ratio, 0.771 [95% CI, 0.741-0.802]). By contrast,

for the same 10-mg/dL lower plasma ApoB concentration associated with variants in the *LDLR* score, there is a corresponding 14.1-mg/dL lower LDL-C level, no change in triglycerides, and a similar lower risk of CHD (odds ratio, 0.773 [95% CI, 0.747-0.801]). Therefore, despite being associated with changes in different lipids, the *LPL* and *LDLR* scores were associated with similar lower risk of CHD for the same lower plasma ApoB concentration. The data presented are for the associations of the *LPL* and *LDLR* genetic scores with risk of CHD per 10-mg/dL decrease in ApoB-containing lipoproteins in all 654 783 participants included in the study. The associations of either score with changes in triglycerides and LDL-C per 10-mg/dL lower level of ApoB-containing lipoproteins are from up to 305 699 participants enrolled in the Global Lipid Genetics Consortium. Boxes represent effect size estimates and lines represent 95% CIs.

Figure 3. Log-Linear Association Between Absolute Differences in Apolipoprotein B (ApoB) and Lower Risk of Coronary Heart Disease (CHD)



The associations of each genetic variant with ApoB concentration is plotted against its unadjusted association with CHD, expressed as a proportional lower risk (calculated as $[1-OR_{CHD}] \times 100$). Variants in the genes that encode the targets of therapies that lower triglycerides through the LPL pathway are marked with blue labels, and variants in the genes that encode the targets of therapies that lower LDL-C through upregulation of the LDL receptor are marked by red labels. Circles represent the associated absolute change in ApoB

and corresponding proportional lower risk of CHD for each variant. The horizontal lines through each circle represent ± 1 standard errors for the associated absolute change in ApoB for each variant; and the vertical line through each circle represents ± 1 standard errors for the associated proportional lower risk of CHD. Associations with CHD were measured in all 654 783 participants included in the study; associations with ApoB were measured in a meta-analysis of 14 studies including up to 84 324 participants.

Table 3. Multivariable Mendelian Randomization Analysis of the Association Between Plasma Triglycerides, LDL-C, and ApoB With the Risk of CHD^a

Analysis	Variables	Odds Ratio for CHD (95% CI)	P Value
Association of 10-mg/dL lower ApoB with risk of CHD	ApoB	0.770 (0.760-0.781)	1.42E-170
Association of 10-mg/dL lower LDL-C with risk of CHD	LDL-C	0.846 (0.833-0.858)	8.16E-77
Association of 50-mg/dL lower triglycerides with risk of CHD	Triglycerides	0.815 (0.785-0.846)	1.37E-18
Association of 10-mg/dL lower LDL-C and 50-mg/dL lower triglycerides with risk of CHD included in same model	LDL-C	0.862 (0.849-0.875)	6.92E-65
	Triglycerides	0.876 (0.850-0.902)	1.36E-14
Association of 10-mg/dL lower LDL-C, 50-mg/dL lower triglycerides, and 10-mg/dL lower ApoB with risk of CHD included in same model	ApoB	0.761 (0.723-0.798)	7.51E-20
	LDL-C	1.010 (0.967-1.055)	.19
	Triglycerides	1.014 (0.965-1.065)	.19

Abbreviations: ApoB, apolipoprotein B; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol.

^a Data presented are derived from a multivariable meta-regression analysis of 186 genetic variants, including the 5 variants included in the *LPL* score, 3 variants included in the *LDLR* score, and 178 variants associated with either triglycerides, LDL-C, or both at genome-wide significance as reported by the Global Lipids Genetics Consortium. Effect sizes for the associated risk of CHD are reported per 10-mg/dL lower ApoB concentration, per 10-mg/dL lower LDL-C level, or per 50-mg/dL lower triglyceride level (because dividing triglyceride concentration by 5 estimates the cholesterol content carried by triglyceride-rich ApoB-containing lipoproteins as estimated by the Friedewald formula). In these analyses, the dependent variable was the effect estimate for risk of CHD in all 654 783 participants included in the study for each variant and the independent variables were the effect estimates for the associated changes in plasma triglycerides, LDL-C, and ApoB, measured in up to 305 699 participants in Global Lipids Genetics Consortium for each variant. The analysis

was weighted by the inverse squared standard error of the associated risk of CHD for each variant and forced to pass through the origin. For example, in multivariable mendelian randomization analyses involving these 186 genetic variants, both triglycerides (odds ratio [OR], 0.876 per 50-mg/dL lower triglycerides) and LDL-C (OR, 0.862 per 10-mg/dL lower LDL-C) were independently associated with a lower risk of CHD at genome-wide level of significance. By contrast, when ApoB was included in the multivariable mendelian randomization analyses, the associations with CHD for both triglycerides (OR, 1.014 per 50-mg/dL lower triglycerides) and LDL-C (OR, 1.010 per 10-mg/dL lower LDL-C) became null, but the association per 10-mg/dL lower ApoB remained unchanged (OR, 0.761 per 10-mg/dL lower ApoB). The unadjusted associations with triglycerides, LDL-C, ApoB, and CHD for each variant included in the analysis are provided in eTable 7 in the *Supplement*. Additional multivariable meta-regression analyses for various combinations of these variants is provided in eTable 8 in the *Supplement*.

Key Points

Question What is the clinical benefit of lowering plasma triglyceride levels compared with lowering low-density lipoprotein cholesterol levels?

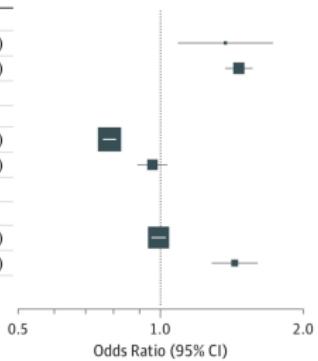
Findings In mendelian randomization analyses involving 654 783 participants, triglyceride-lowering variants in the lipoprotein lipase gene and low-density lipoprotein cholesterol (LDL-C)-lowering variants in the LDL receptor gene were associated with similar lower risk of coronary heart disease per 10-mg/dL lower level of apolipoprotein B (ApoB)-containing lipoproteins (odds ratios of 0.771 and 0.773, respectively).

Meaning The clinical benefit of lower triglyceride levels was similar to the clinical benefit of lower LDL-C levels per unit difference in ApoB and may be related to the absolute reduction in ApoB-containing lipoprotein particles.

Summary

Figure. Comparison of Observational Estimates and Mendelian Randomization Estimates of the Association of Low-Density Lipoprotein (LDL) Cholesterol, High-Density Lipoprotein (HDL) Cholesterol, and Triglycerides With Coronary Heart Disease

Analysis	Source	Odds Ratio (95% CI)
LDL cholesterol		
Observational	ERFC ²	1.37 (1.09-1.73)
Mendelian randomization	Do et al ³	1.46 (1.37-1.56)
Test for heterogeneity: $P = .60$		
HDL cholesterol		
Observational	ERFC ²	0.78 (0.76-0.81)
Mendelian randomization	Do et al ³	0.96 (0.89-1.03)
Test for heterogeneity: $P < .01$		
Triglycerides		
Observational	ERFC ²	0.99 (0.96-1.03)
Mendelian randomization	Do et al ³	1.43 (1.28-1.60)
Test for heterogeneity: $P < .01$		



Observational estimates are derived from the Emerging Risk Factors Collaboration (ERFC).² Mendelian randomization estimates are derived from Do et al³ based on an analysis of 185 genetic variants that alter plasma lipids and mutually adjusted for other lipid fractions (eg HDL cholesterol and triglycerides for LDL cholesterol). A formal test of heterogeneity (Cochran Q test) shows that the observational and mendelian randomization causal estimates are consistent for LDL cholesterol but not so for HDL cholesterol or triglycerides.