Extreme Nonfasting Remnant Cholesterol vs Extreme LDL Cholesterol as Contributors to Cardiovascular Disease and All-Cause Mortality in 90,000 Individuals from the General Population

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BACKGROUND: Increased nonfasting remnant cholesterol, like increased LDL cholesterol, is causally associated with increased risk for ischemic heart disease (IHD). We tested the hypothesis that extreme concentrations of nonfasting remnant and LDL cholesterol are equal contributors to the risk of IHD, myocardial infarction (MI), and all-cause mortality.

METHODS: We compared stepwise increasing concentrations of nonfasting remnant and LDL cholesterol for association with risk of IHD, MI, and all-cause mortality in approximately 90,000 individuals from the Danish general population. During up to 22 years of complete follow-up, 4435 participants developed IHD, 1722 developed MI, and 8121 died.

RESULTS: Compared with participants with nonfasting remnant cholesterol <0.5 mmol/L (19.3 mg/dL), hazard ratios for IHD ranged from 1.3 (95% CI 1.1–1.5) for remnant cholesterol of 0.5–0.99 mmol/L (19.3–38.2 mg/dL) to 2.4 (1.9–2.9) for remnant cholesterol of ≥1.5 mmol/L (58 mg/dL) (P for trend <0.001). Compared with participants with LDL cholesterol <3.0 mmol/L (115.8 mg/dL), hazard ratios for IHD ranged from 1.3 (1.1–1.5) for LDL cholesterol of 3–3.99 mmol/L (115.8–154 mg/dL) to 2.3 (1.9–2.8) for LDL cholesterol of ≥5 mmol/L (193 mg/dL) (P < 0.001). Corresponding hazard ratios for MI ranged from 1.8 (1.4–2.3) to 3.4 (2.5–4.8) for remnant cholesterol (P < 0.001), and from 1.7 (1.4–2.2) to 4.7 (3.5–6.3) for LDL cholesterol (P < 0.001). Nonfasting remnant cholesterol concentrations were associated stepwise with all-cause mortality ranging from hazard ratio 1.0 (0.9–1.1) to 1.6 (1.4–1.9) (P < 0.001). LDL cholesterol concentrations were associated with decreased all-cause mortality risk in a U-shaped pattern, with hazard ratios from 0.8 (0.7–0.8) to 0.9 (0.8–1.0) (P = 0.002). After mutual adjustment, LDL cholesterol best predicted MI, and remnant cholesterol best predicted all-cause mortality.

CONCLUSIONS: Both lipoproteins were associated equally with risk of IHD and MI; however, only nonfasting remnant cholesterol concentrations were associated stepwise with increased all-cause mortality risk.

Increased concentrations of nonfasting remnant cholesterol are thought to be atherogenic in the same way as LDL cholesterol, by transport into and accumulation in the arterial wall (1–3). We recently found genetically increased concentrations of nonfasting remnant cholesterol, like increased LDL cholesterol concentrations, to be causally associated with increased ischemic heart disease (IHD) risk (4,5), independent of low concentrations of HDL cholesterol (4). In another study (6), we found that genetically determined increases in remnant cholesterol concentrations were causally associated with both low-grade inflammation and IHD, whereas genetically determined increases in LDL cholesterol concentrations were causally associated with IHD, but not with low-grade inflammation. These findings suggest that increased LDL cholesterol leads to atherosclerosis without inflammation, whereas an inflammatory component of atherosclerosis is driven by increased remnant cholesterol concentrations. In addition, we previously found associations between increased nonfasting triglycerides and increased risk of IHD, myocardial infarction (MI), and all-cause mortality (7,8). Remnant cholesterol is the
cholesterol content of the triglyceride-rich lipoproteins composed of VLDL and intermediate density lipoprotein (IDL) in the fasting state, and of these 2 lipoproteins together with chylomicron remnants in the nonfasting state; remnant cholesterol concentrations are therefore highly correlated with triglycerides (7, 9). Extreme concentrations of nonfasting remnant and LDL cholesterol may therefore be equally important contributors to risk of IHD, MI, and all-cause mortality in the general population; however, this is presently unknown.

Even after reducing LDL cholesterol below recommended concentrations, there is still a substantial residual risk of cardiovascular disease. There might therefore be a need to look beyond LDL cholesterol reduction to reduce this residual risk, possibly by lowering nonfasting remnant cholesterol concentrations.

In this study, we tested the hypothesis that extreme concentrations of nonfasting remnant and LDL cholesterol are equal contributors to risk of IHD, MI, and all-cause mortality. We examined 97,962 participants from the Copenhagen City Heart Study (CCHS) and the Copenhagen General Population Study (CGPS) combined, with information on nonfasting remnant and LDL cholesterol concentrations. Participants were followed prospectively for up to 22 years without losses to follow-up. They were divided into clinically meaningful groups with increasing concentrations of nonfasting remnant and LDL cholesterol, with similar fractions of participants in top groups, enabling us directly to compare extremely high concentrations of the 2 lipoproteins with respect to risk of IHD, MI, and all-cause mortality.

Methods

The studies were approved by institutional review boards and Danish ethics committees (KF-100.2039/91, KF-01-144/01, H-KF-01-144/01) and were conducted according to the Helsinki Declaration. Informed consent was obtained from participants. All participants were white and of Danish descent.

CCHS

The CCHS is a prospective study of the general Danish population initiated in 1976–78, with follow-up examinations in 1981–83, 1991–94, and 2001–03. Individuals were selected on the basis of the national Danish Civil Registration System to reflect the adult population aged 20–100 years. We included 9558 participants with information on both nonfasting remnant and LDL cholesterol at baseline. LDL and HDL cholesterol were not measured at the first 2 examinations, and therefore the third examination in 1991–94 was used as baseline.

CGPS

The CGPS is a prospective study of the Danish general population initiated in 2003 with ongoing enrollment. Participants have been recruited and examined in the same way as for the CCHS. We included a total of 88,404 participants with information on nonfasting remnant and LDL cholesterol concentrations.

IHD, MI, AND ALL-CAUSE MORTALITY

Information on diagnoses of IHD (WHO International Classification of Diseases, Revision 8 (ICD8): 410–414; Revision 10 (ICD10): I20–I25) and MI (ICD8: 410; ICD10: I21–I22) were collected from 1977 to April 2013 by reviewing all hospital admissions and diagnoses entered in the national Danish Patient Registry and all causes of death entered in the national Danish Causes of Death Registry (7, 10). All-cause mortality was registered in the national Danish Civil Registration System. All individuals in Denmark are assigned a personal identification number at birth by which they can be traced in registers, and therefore follow-up was without losses.

LABORATORY ANALYSES

Nonfasting total cholesterol, triglycerides, and HDL cholesterol were measured by colorimetric assays (Roche and Konelab). LDL cholesterol was calculated with the Friedewald equation when triglycerides were ≤4 mmol/L (354 mg/dL) and otherwise measured directly (Konelab). Nonfasting remnant cholesterol was calculated as nonfasting total cholesterol minus HDL cholesterol minus LDL cholesterol, as previously used (4–7, 10, 11). A fraction of remnant cholesterol was measured directly in 6140 participants from the CGPS enrolled in the study in 2013–14, by use of an automated assay by Denka Seiken measuring the cholesterol content in chylomicron and VLDL remnants specifically, with the aid of enzymes and surfactants.

OTHER COVARIATES

Smokers were current smokers. Hypertension was systolic blood pressure ≥140 mmHg (≥135 mmHg for individuals with diabetes), diastolic blood pressure ≥90 mmHg (≥85 mmHg for individuals with diabetes), and/or use of antihypertensive medication. Physical activity was activity at work and in leisure time and divided into low, moderate, and high physical activity. Alcohol consumption was self-reported as drinks of alcohol per day (1 drink = approximately 12 g alcohol). Lipid-lowering therapy, oral contraceptive therapy, hormone replacement therapy, and menopausal status were self-reported. Body mass index (BMI) was measured weight (kg) divided by measured height squared (m²). Diabetes was self-reported disease, use of antidiabetic medication, nonfasting glucose >11 mmol/L (198 mg/dL), and/or
hospitalization or death due to diabetes (ICD8: 249–250; ICD10: E10, E11, E13, E14).

**STATISTICAL ANALYSIS**

We analyzed data with Stata (version 11.2). Participants were stratified a priori into 4 clinically useful groups according to concentrations of nonfasting remnant cholesterol (<0.5, 0.5–0.99, 1–1.49, and ≥1.50 mmol/L; <19.3, 19.3–38.2, 38.6–57.5, and >58 mg/dL) and LDL cholesterol (<3, 3–3.99, 4–4.99, and ≥5 mmol/L; <115.8, 115.8–154, 154.4–192.6, and >193 mg/dL). For comparison, participants were also divided into percentiles according to concentrations of nonfasting remnant and LDL cholesterol. We aimed at having similar fractions of participants in the top groups of nonfasting remnant and LDL cholesterol. We attempted to have similar numbers of participants in the top groups of nonfasting remnant and LDL cholesterol to allow for direct comparison of extreme concentrations of the 2 lipoproteins for association with risk of IHD, MI, and all-cause mortality.

We estimated the association between calculated remnant cholesterol and directly measured remnant cholesterol with linear regression. \( R^2 \) was estimated from the Spearman correlation coefficient.

In the prospective CCHS and CGPS combined, with use of left truncation and delayed entry, we used Cox proportional hazards regression models with age as time scale to estimate hazard ratios; individuals diagnosed with an endpoint before study entry were excluded, and those dying during follow-up were censored at their death date. Median follow-up time was 5.3 years (range 0–22 years). Multivariable adjustment was for age, sex, smoking, hypertension, physical activity, alcohol consumption, lipid-lowering therapy, time since last meal, time of day for blood sampling, and for women also oral contraceptive use, hormone replacement therapy, and menopausal status. We used data from the CCHS examinations in 1991–94 and 2001–03 as time-dependent covariates for multivariate adjustments. Factors for adjustments were chosen as cardiovascular risk factors and/or treatments that may influence cardiovascular disease risk. Estimates were not adjusted for BMI, diabetes, or HDL cholesterol because increased lipoprotein concentrations may be the explanation for the increased cardiovascular disease risk observed in those with obesity and/or diabetes, and low concentrations of HDL cholesterol are inversely associated with increased remnant cholesterol concentrations because of the lipoprotein metabolism (4); however, estimates incorporating adjustments for these variables were performed as sensitivity analyses. Hazard ratios and CIs were corrected for regression dilution bias by a nonparametric method (12) by use of lipoprotein values from 4400 individuals without lipid-lowering therapy participating in both the 1991–94 and 2001–03 examinations of the CCHS. We computed regression dilution ratios of 0.55, 0.59, and 0.88 for nonfasting remnant cholesterol, LDL cholesterol, and triglycerides, respectively. \( P \) values for trend were estimated by Cuzick extension of a Wilcoxon rank-sum test.

We examined associations of remnant and LDL cholesterol on a continuous scale with risk of IHD, MI, and all-cause mortality using restricted cubic splines with 4 knots and adjusting for age, sex, smoking, hypertension, physical activity, alcohol consumption, lipid-lowering therapy, time since last meal, time of day for blood sampling, and for women also oral contraceptive use, hormone replacement therapy, and menopausal status.

**Results**

Supplemental Table 1, which accompanies the online version of this article at http://www.clinchem.org/content/vol61/issue3, shows characteristics of participants by concentration of nonfasting remnant and LDL cholesterol, respectively. Participants with high concentrations of either remnant or LDL cholesterol were older, more often men, and more often smokers and hypertensive, compared with participants with low concentrations. Online Supplemental Table 2 shows characteristics for men and women separately.

**DISTRIBUTIONS OF NONFASTING REMNANT AND LDL CHOLESTEROL IN THE GENERAL POPULATION**

Nonfasting remnant cholesterol was skewed with a tail toward higher concentrations, whereas LDL cholesterol was distributed normally (Fig. 1). Results for men and women separately showed that a larger fraction of men had high concentrations of nonfasting remnant cholesterol compared with women, whereas the distribution of LDL cholesterol was similar in men and women (see online Supplemental Fig. 1).

**ASSOCIATION OF NONFASTING REMNANT CHOLESTEROL WITH LDL CHOLESTEROL**

Concentrations of nonfasting remnant cholesterol as a function of LDL cholesterol concentrations are shown in online Supplemental Fig. 2. There was no clear linear association between concentrations of the lipoproteins. That is, it was not necessarily the same individuals who had high concentrations of nonfasting remnant cholesterol and LDL cholesterol. Similar results for men and women separately are shown in online Supplemental Fig. 3.

**CALCULATED NONFASTING REMNANT CHOLESTEROL AND DIRECTLY MEASURED REMNANT CHOLESTEROL**

The distribution of calculated nonfasting remnant cholesterol including cholesterol in all remnants, (i.e., chylomicron remnants, VLDL, and IDL) is shown in Fig. 2A. The distribution of directly measured remnant cholesterol...
terol is shown in Fig. 2B for a subset of 6140 participants from the CGPS with information on both types of remnant cholesterol. Concentrations of measured remnant cholesterol were only 13% of the concentrations of calculated remnant cholesterol; however, the 2 types of remnant cholesterol were strongly correlated, with $R^2 = 0.73$ (Fig. 2C).

ASSOCIATIONS OF NONFASTING REMNANT AND LDL CHOLESTEROL WITH TRIGLYCERIDES AND APOLIPOPROTEIN B

The associations between nonfasting remnant and LDL cholesterol with triglycerides and apolipoprotein B concentrations in the general population are shown in Fig. 3. Nonfasting remnant cholesterol concentrations were highly correlated with triglycerides ($R^2 = 0.95$); however, LDL cholesterol concentrations were not correlated with triglycerides to the same extent ($R^2 = 0.14$). In contrast, increasing concentrations of nonfasting remnant and LDL cholesterol were similarly associated with increasing apolipoprotein B concentrations. Online Supplemental Fig. 4 shows associations of nonfasting remnant and LDL cholesterol in quartiles with concentrations of triglycerides and apolipoprotein B, with the same pattern of association as seen in Fig. 3.

CHANGES IN NONFASTING REMNANT AND LDL CHOLESTEROL OVER TIME

Over a time period of 10 years, both nonfasting remnant and LDL cholesterol regressed toward the mean for 4706 participants from the CCHS who participated in both the 1991–94 and 2001–03 examinations and had measurements of remnant and LDL cholesterol at both visits (see online Supplemental Fig. 5).

NONFASTING REMNANT AND LDL CHOLESTEROL AND RISK OF IHD, MI, AND ALL-CAUSE MORTALITY

Associations of nonfasting remnant and LDL cholesterol with risk of IHD, MI, and all-cause mortality were examined prospectively in 97962 participants from the CCHS and CGPS combined (Fig. 4); participants with IHD or MI before lipoprotein measurements and individuals with missing information on covariates were excluded from analyses, leaving 82890 participants.

Participants were divided into clinically useful groups according to concentrations of remnant and LDL cholesterol. When participants having nonfasting remnant cholesterol concentrations $<0.5$ mmol/L (19.3 mg/dL) were used as the comparison group, multivariable adjusted hazard ratios for IHD ranged from 1.3 (95% CI 1.1–1.5) for a remnant cholesterol concentration of 0.5–0.99 mmol/L (19.3–38.2 mg/dL) to 2.4 (1.9–2.9) for remnant cholesterol $\geq 1.5$ mmol/L (58 mg/dL) ($P$ for trend $<0.001$) (Fig. 4A). When participants with LDL cholesterol $<3.0$ mmol/L (115.8 mg/dL) were used as the comparison group, hazard ratios for IHD ranged from 1.3 (1.1–1.5) for a LDL cholesterol concentration of 3–3.99 mmol/L (115.8–154 mg/dL) to 2.3 (1.9–2.8) for LDL cholesterol $\geq 5$ mmol/L (193 mg/dL) ($P < 0.001$) (Fig. 4B). Corresponding hazard ratios for MI ranged from 1.8 (1.4–2.3) to 3.4 (2.5–4.8) for remnant cholesterol ($P < 0.001$), and from 1.7 (1.4–2.2) to 4.7 (3.5–6.3) for LDL cholesterol ($P < 0.001$).

Nonfasting remnant cholesterol concentrations were associated stepwise with all-cause mortality, with hazard ratios ranging from 1.0 (0.9–1.1) for a remnant cholesterol concentration of 0.5–0.99 mmol/L (19.3–38.2 mg/dL) to 1.6 (1.4–1.9) for remnant cholesterol
1.5 mmol/L (58 mg/dL) (P for trend < 0.001), whereas LDL cholesterol concentrations were associated with decreased risk of all-cause mortality in a U-shaped pattern, with hazard ratios from 0.8 (0.7–0.8) to 0.9 (0.8–1.0) (P = 0.002) (Fig. 4, A and B).

When participants were divided into percentiles according to concentrations of nonfasting remnant and LDL cholesterol instead of clinically useful groups, risk estimates were similar (Fig. 4, C and D).

Fig. 4 shows results for all participants. When stratified by sex (see online Supplemental Fig. 6), results were similar for men and women for IHD and MI; however, remnant cholesterol concentrations were associated more strongly with all-cause mortality in women than men.

ADDITIONAL ADJUSTMENT FOR BMI, DIABETES, AND HDL CHOLESTEROL

Analyses in Fig. 4 were purposely not adjusted for BMI or diabetes, because increased lipoproteins associated with these conditions likely are mediators of cardiovascular disease. Also, estimates were not adjusted for HDL cholesterol owing to the inverse association between remnant and HDL cholesterol that results from lipoprotein metabolism (4). When analyses were additionally adjusted for these possible confounders, estimates for nonfasting remnant cholesterol were attenuated somewhat, as expected (Fig. 5).

NONFASTING REMNANT AND LDL CHOLESTEROL ON A CONTINUOUS SCALE AND RISK OF IHD, MI, AND ALL-CAUSE MORTALITY

Associations of concentrations of remnant and LDL cholesterol with risk of IHD, MI, and all-cause mortality, when expressed on a continuous scale and analyzed by use of restricted cubic splines, showed similar patterns of association to those observed by use of categories of the lipoproteins (Fig. 6).

SENSITIVITY ANALYSES

Associations between nonfasting remnant and LDL cholesterol with risk of IHD, MI, and all-cause mortality changed only slightly when additionally adjusted mutually for each other: LDL cholesterol was a stronger predictor of IHD and MI, whereas the opposite was true for all-cause mortality (compare Fig. 4, A and B, with online Supplemental Fig. 7). Results changed only slightly when participants who used lipid-lowering therapy at baseline were excluded from analyses (compare Fig. 4, A and B, with online Supplemental Fig. 8).

When associations between nonfasting remnant and LDL cholesterol with risk of IHD, MI, and all-cause mortality were adjusted further for nonfasting triglycerides, the association between remnant cholesterol and endpoints was attenuated as expected, since triglycerides and remnant cholesterol concentrations are highly correlated (compare Fig. 4, A and B, with online Supplemental Fig. 9). Also, association between extreme concentrations of nonfasting triglycerides and risk of IHD, MI, and all-cause mortality were comparable to associations for extreme concentrations of remnant cholesterol, as expected (see online Supplemental Fig. 10); however, effect...
sizes were larger for remnant cholesterol than for triglycerides.

Discussion

In this very large study of individuals from the general population, risk of IHD and MI were similar for stepwise increasing nonfasting remnant and LDL cholesterol concentrations; however, nonfasting remnant cholesterol concentrations were associated stepwise with increased all-cause mortality risk, whereas LDL cholesterol concentrations were not. The novel aspect of the present study is the direct comparison of remnant cholesterol with LDL cholesterol for prediction of risk of IHD, MI, and all-cause mortality within the same individuals.

We have previously found an observational association between extreme concentrations of nonfasting triglycerides and increased risk of IHD, MI, and all-cause mortality (7, 8) in support of the present results for extreme concentrations of remnant cholesterol. Historically, increased triglycerides have been treated primarily to prevent acute pancreatitis, and there has not been consensus on whether to treat moderately increased triglycerides to prevent cardiovascular disease. Our results provide further support for the use of triglycerides or nonfasting remnant cholesterol as potential targets for treatment. Concentrations of remnant cholesterol are highly correlated with triglycerides; however, because most cells can degrade triglycerides, and none can degrade cholesterol, it is probably the cholesterol content of remnants that accumulates in the arterial intima, causing atherosclerosis.

Non-HDL cholesterol and apolipoprotein B are used as markers of remnants and LDL combined for risk assessment of cardiovascular disease; however, our results indicate that it could be useful to look at remnant and LDL cholesterol separately, particularly when interested in all-cause mortality.

Mechanistically, the explanation for an association between increased nonfasting remnant cholesterol and cardiovascular disease risk could be that remnants enter and get trapped in the intima of the arterial wall (2, 3). Like LDL trapping in the intima, this would lead to intimal accumulation of cholesterol, atherosclerosis, and ultimately cardiovascular disease (9, 13). Remnant cholesterol is the cholesterol content of the triglyceride-rich lipoproteins composed of VLDL and IDL in the fasting state, and of these 2 lipoproteins together with chylomicron remnants in the nonfasting state (7, 9). Increased remnant cholesterol is associated with reduced HDL cholesterol (9, 13, 14); however, as treatment to raise HDL cholesterol has failed to reduce cardiovascular disease (15–18), increased remnant cholesterol may be a more likely causal risk factor. In support of this, we have found in previous studies with a Mendelian randomization design that genetically de-
termined increased nonfasting remnant cholesterol concentrations were associated with increased IHD risk (4, 5), independent of low HDL cholesterol concentrations (4). Furthermore, genetically increased remnant cholesterol was also associated with low-grade inflammation, whereas genetically increased LDL cholesterol was not (6), supporting the concept that in some respects, extremely increased remnant cholesterol may be even more hazardous than extremely increased LDL cholesterol, as demonstrated in the present study for all-cause mortality.

### Fig. 4. Extreme concentrations of nonfasting remnant and LDL cholesterol and risk of IHD, MI, and all-cause mortality.

Risk of IHD, MI, and all-cause mortality for stepwise increasing concentrations of nonfasting remnant cholesterol (A, C) and LDL cholesterol (B, D) in 82890 participants from the CCHS and CGPS combined. Hazard ratios were adjusted for age, sex, smoking, hypertension, physical activity, alcohol consumption, lipid-lowering therapy, time since last meal, time of day for blood sampling, and for women also oral contraceptive use, hormone replacement therapy, and menopausal status. A and B show results for participants divided into clinically useful groups according to concentrations of remnant and LDL cholesterol, and C and D show participants divided by percentiles of remnant and LDL concentrations. To convert cholesterol values from mmol/L to mg/dL, divide by 0.0259.

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<th>Remnant Cholesterol (mmol/L)</th>
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<th>Hazard ratio (95% CI)</th>
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<tr>
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<td>4022</td>
<td>764</td>
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Evidence for increased remnant cholesterol and triglyceride-rich lipoproteins as causal risk factors for cardiovascular disease is emerging (4–6, 9, 19–21); however, there is a lack of information from large randomized trials as to whether reducing remnant cholesterol in individuals with increased concentrations will reduce cardiovascular disease risk. Most trials, including the majority of large statin trials, have excluded participants with increased triglycerides and thereby increased remnant cholesterol concentrations. Therefore, results from these trials cannot tell us whether reducing triglycerides and remnant cholesterol in individuals with increased concentrations will reduce cardiovascular risk, and there is an urgent need for trials examining just that. Fortunately, 2 large-scale randomized clinical intervention trials with n-3 fatty acids in individuals with increased triglycerides have already been initiated: the Reduction of Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT) and Outcomes Study to Assess Statin Residual Risk Reduction With EpaNova in High CV Risk Patients With Hypertriglyceridemia (STRENGTH) trials (22).

The REDUCE-IT trial investigates n-3 fatty acid therapy as add-on to statins and aims to enroll 8000 individuals with increased triglycerides and cardiovascular disease or at high risk thereof. The expected completion date for REDUCE-IT is in 2016. The STRENGTH trial also investigates n-3 fatty acid therapy as an add-on to statins, enrolling 13000 individuals with increased triglycerides...
Favoring a beneficial effect of decreasing triglycerides (and thereby remnant cholesterol) are results from subgroup analyses from fibrate trials in participants with baseline triglyceride concentrations $>2$ mmol/L (177 mg/dL), showing in these participants an effect of decreasing triglycerides on cardiovascular risk: a 0.1-mmol/L (8.9-mg/dL) decrease in triglycerides was associated with a 5% (95% CI 1%–10%) reduction in major coronary events (23). The risk reduction in those with increased triglycerides was significant in the individual studies (24–28), including those investigating fibrates as add-on therapy to statins (29). Also, Carlson and Rosenhamer (24) found that the combination of fibrates and niacin reduced all-cause and IHD mortality by 26% and 36% in patients with previous MI, although the trial was not blinded.

Our finding that LDL cholesterol concentrations were associated with decreased risk of all-cause mortality as well as low HDL cholesterol, and with cardiovascular disease or at high risk thereof. Expected completion date for STRENGTH is in 2019.

Fig. 6. Nonfasting remnant and LDL cholesterol on a continuous scale and risk of IHD, MI, and all-cause mortality. Hazard ratios for endpoints as a function of remnant and LDL cholesterol by use of restricted cubic splines and adjusted as in Fig. 4. To convert cholesterol values from mmol/L to mg/dL, divide by 0.0259.
in a U-shaped pattern might be because we looked at all-cause mortality, and not cardiovascular mortality. Other noncardiovascular common diseases known to be associated with increased mortality such as cancer, severe respiratory diseases, and inflammatory diseases are associated with reduced concentrations of LDL and total cholesterol (30–32).

Remnant cholesterol was determined in nonfasting samples and thus includes cholesterol in all triglyceride-rich lipoproteins, that is, VLDL, IDL, and chylomicron remnants combined. By using nonfasting remnant cholesterol calculated as nonfasting total cholesterol minus HDL cholesterol minus LDL cholesterol, remnant cholesterol can be calculated directly from a standard lipid profile, provided it is taken in the nonfasting state, that is, taken at a random time irrespective of the previous meal, as recommended in Denmark since 2009 (33, 34). Thus, the calculated nonfasting remnant cholesterol as used in this study comes at no extra cost and is easily available. Presently, there is no assay measuring cholesterol in all remnants at the same time, so the only way to get an estimate of the total remnant cholesterol concentration is to calculate it. Reassuringly, we found concentrations of calculated remnant cholesterol to be highly correlated with a fraction of remnant cholesterol measured directly, with $R^2 = 0.73$; $R^2$ for calculated remnant cholesterol with triglycerides was 0.95, suggesting that calculated remnant cholesterol is more reflective of triglyceride concentrations than directly measured remnant cholesterol. How the 2 types of remnant cholesterol compare in estimating risk of cardiovascular disease is presently unknown, and in this study we unfortunately do not yet have enough follow-up for the individuals with directly measured remnant cholesterol to investigate association with endpoints.

Strengths of this study are the large sample size of individuals from the general population without losses to follow-up, and our comparison of extreme concentrations of nonfasting remnant and LDL cholesterol as contributors to cardiovascular disease risk and all-cause mortality in the same individuals. Another strength in our study is lack of bias from population admixture because all participants were white and of Danish descent. A limitation to our study is that we used single measurements of remnant and LDL cholesterol to categorize the participants, presuming that concentrations were constant during follow-up; however, we did correct for regression dilution bias. Also, repeated measurements of adjusted risk factors would probably result in more accurate estimates.

In conclusion, in this large general population study, we found that stepwise increasing concentrations of nonfasting remnant and LDL cholesterol were each associated with increased risk of IHD and MI; however, although nonfasting remnant cholesterol concentrations were associated stepwise with increased all-cause mortality, concentrations of LDL cholesterol were not. Even after reducing LDL cholesterol to recommended concentrations, there is still a substantial residual risk of cardiovascular disease, and our findings, when considered together with previous findings (9, 21), suggest that future intervention studies should not only be focused on lowering LDL cholesterol concentrations, but also on lowering of nonfasting remnant cholesterol in individuals with increased concentrations.

**References**


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Remnants, LDL, and Cardiovascular Disease


