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**FULL RESEARCH PAPER**
*Lipids & atherosclerosis*

# Interplay of HDL cholesterol and apoB and the risk of incident atherosclerotic cardiovascular disease in UK Biobank

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**Aims** Apolipoprotein B (apoB) is the most accurate causal lipid factor associated with increased risk of atherosclerotic cardiovascular disease (ASCVD). While high HDL cholesterol has been considered protective, HDL-C–raising therapies have not shown benefit.

**Objective** To assess whether HDL-C provides independent information from apoB and whether HDL-C modifies the effect of apoB on ASCVD risk.

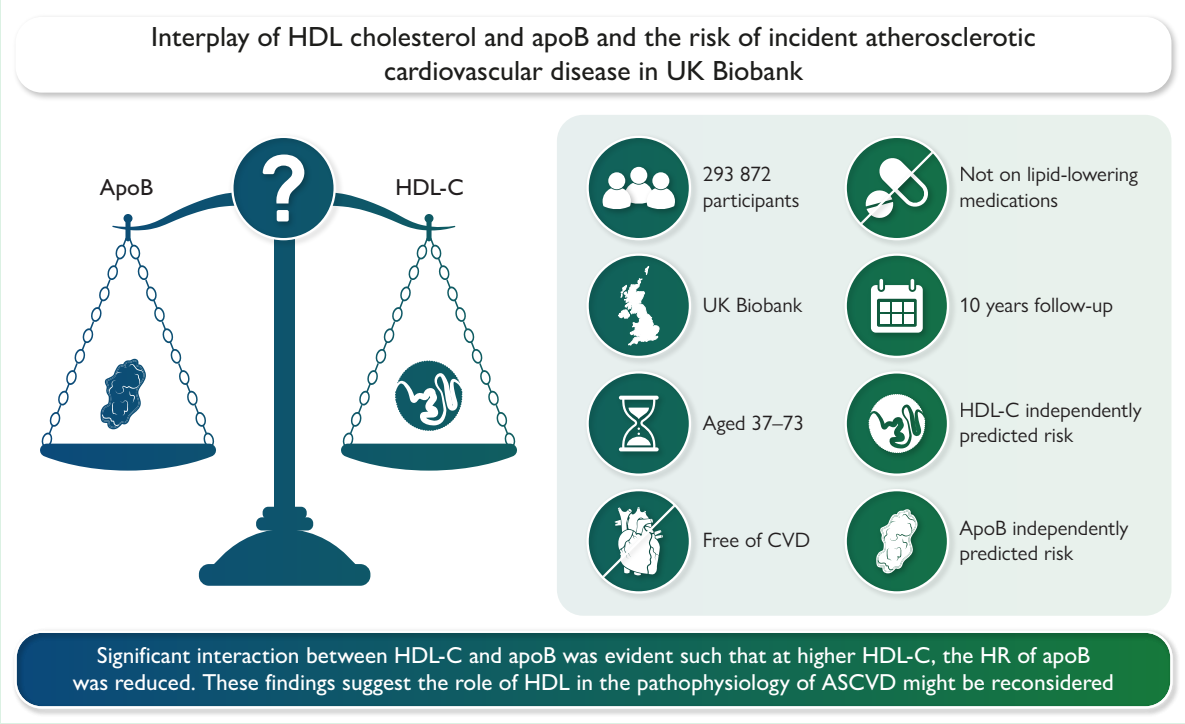
**Methods and results** 293 872 UK Biobank participants aged 37–73, free of CVD, not on lipid-lowering medication, and with complete standard risk factor data were followed for 10 years for incident ASCVD. Cox proportional hazard models, adjusted for standard risk factors, including log-triglycerides, used apoB and HDL-C residuals (regressed on each other) as primary exposures. Interaction between apoB and HDL-C was tested separately. When HDL-C residual was added to a model with apoB, both were significant: hazard ratios (HRs) per 1 SD were 1.16 (95% confidence interval, CI: 1.15–1.18; $P < 0.001$) for apoB and 0.85 (95% CI: 0.84–0.87; $P < 0.001$) for HDL-C residual. Similarly, adding apoB residual to a model with HDL-C yielded HRs of 1.14 (95% CI: 1.12–1.16; $P < 0.001$) for apoB residual and 0.84 (95% CI: 0.82–0.85; $P < 0.001$) for HDL-C. The apoB–HDL-C interaction was significant: HR 0.95 (95% CI: 0.93–0.96; $P < 0.001$), consistent across sexes.

**Conclusion** High HDL-C is associated with lower ASCVD risk, independent of apoB, and it attenuates the effect of high apoB on ASCVD risk. These findings suggest HDL-C's role in primary ASCVD prevention warrants re-evaluation. However, findings from an observational study, such as this, do not establish causation.

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## Graphical Abstract




**Keywords** HDL-C • apoB • Cardiovascular risk

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### Key learning points

- HDL-C is potently predictive of cardiovascular risk.
- However, in contrast to apoB, HDL-C is now widely considered not to play a causal role in atherosclerosis.
- Our study suggests the atherogenic risk associated with apoB may be diminished by HDL-C.
- These results suggest the role of HDL-C in atherogenesis should be rethought.

## Introduction

In 1975, Miller and Miller, in eight subjects, reported an inverse correlation between HDL-C and the mass of cholesterol in the rapidly and slowly exchangeable pools of cholesterol that were in reversible equilibrium with the plasma pool of HDL-C.[1] They assumed the arterial wall would be one of the tissues in the slowly exchangeable pool. They also reported that a group of patients with ischaemic heart disease had a normal LDL-C, but a lower HDL-C.[1] Their observations, as limited as they were, pointed to potential biological linkages between HDL particles, reverse cholesterol transport, and atherosclerosis. Within 2 years, both the Framingham Heart Study[2] and the Tromso Heart Study[3] had reported potent inverse relationships between HDL-C and CAD risk. The methodological rigour of both studies did much to establish the credibility of the relationship. Since then, innumerable studies have confirmed the core epidemiological findings.

However, in contrast to LDL-C[4] and apoB,[5] all attempts to elevate the observed inverse relation between HDL-C and cardiovascular risk from association to causation have failed. Mendelian randomization analyses have not confirmed a causal relation.[6,7] Similarly, pharmacological therapies that raise HDL-C, whether with fibrates or cholesterol ester transfer inhibitors, have not lowered atherosclerotic cardiovascular disease (ASCVD) rates unless apoB was also lowered substantially.[8] Accordingly, interest in HDL-C as an important determinant of cardiovascular risk has plummeted.

Given the failure to establish causality, the inverse relation between HDL-C and ASCVD risk has been attributed to a confounding effect of triglycerides. Based on Mendelian randomization analyses, Boren and Packard and their colleagues calculated that TRL apoB particles are four- to six-fold more atherogenic than LDL particles and concluded that TRL particles are major drivers of ASCVD risk.[9,10] Notably, these results are not adjusted for the levels of HDL-C based on their conclusion that HDL does not play a causal role in atherogenesis. Our studies confirm that, on a per particle basis, TRL particles are more atherogenic than LDL particles.[11,12] However, applying residual discordance analysis, we demonstrate that if the effects on risk of HDL-C and apoB are accounted for, the excess residual risk attributable to the TRL particles, beyond apoB particle number, is small. By contrast, if the effects of triglyceride and apoB are accounted for, the excess residual risk attributable to HDL-C is robust.[11,12] Morze and his colleagues, examining NMR data, also confirm TRL particles are more atherogenic than LDL particles.[13] However, in the great majority of patients, they found

that LDL particles remain the dominant determinant of total apoB particle number and the dominant determinant of ASCVD risk. Nevertheless, the issues are not settled, and opinion remains divided. Accordingly, this report applies discordance analysis to UK Biobank data to investigate the relation of HDL-C to risk that cannot be explained by triglycerides and whether there exists an interaction between apoB and HDL-C that affects ASCVD risk.

# Methods

## Study population

From 502 413 individuals recruited from 2006 to 2010 in the UK Biobank study, aged 37–73, 32 194 with prior CVD, 69 319 on lipid-lowering medication, and 100 503 with incomplete data were removed. An additional 6525 individuals with high TG (≥250 mg/dL) or high LDL-C (≥400 mg/dL) or out-of-range apoB (≥4 g/L or ≤0.2 g/L) were removed. More details can be found in appendix *Figure 1*. A total of 293 872 individuals were analysed including 123 310 males and 170 562 females.

## Outcome

A detailed ASCVD definition can be found in a previously published Supplementary material online, *Table S1*.[11] In brief, we included ICD9, ICD 10, & OPCS4 Codes for ASCVD events. Time to event was defined as the time from recruitment to the first of an ASCVD event, death, or loss to follow-up. End of follow-up was set to 31 October 2022, 31 August 2022, and 31 May 2022 for England, Scotland, and Wales, respectively.

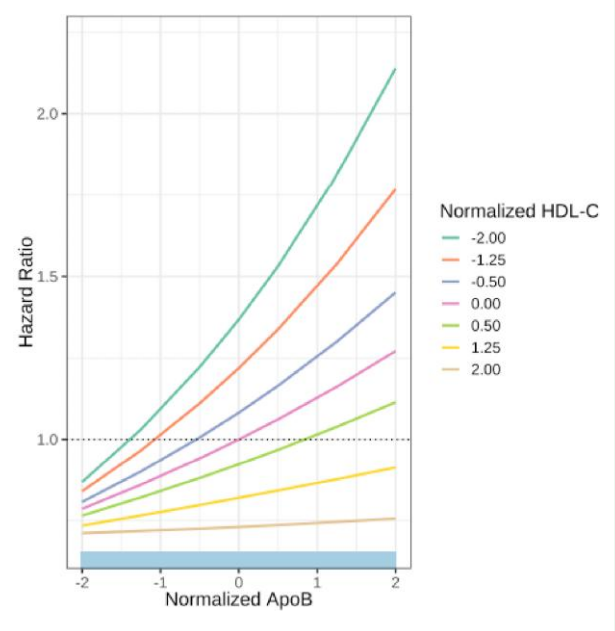



**Figure 1** Hazard ratio for incident ASCVD as a function of apoB modified by levels of HDL-C. Normalized HDL-C is plotted against normalized apoB with the corresponding hazard ratio displayed on the *Y* axis. The relation of apoB to cardiovascular risk is predictably related to the level of HDL-C notwithstanding their minimal shared variance in concentration.

## Exposure measurements

ApoB, HDL-C, and TG measurements were done using Beckman Coulter AU5800 platform and analysed by immuno-turbidimetric, enzyme immuno-inhibition, and enzymatic assays, respectively. Glycated haemoglobin (HbA1c) was measured with Bio-Rad Variant II Turbo analyzer using high-performance liquid chromatography. The systolic blood pressure mean recruitment measurements were used as well as age, sex, body mass index (BMI), smoking status, and medications for blood pressure and diabetes, at recruitment.

## Statistical analysis

Continuous predictor variables are characterized as means and standard deviations and categorical variables as counts and percentages. Correlation between lipid variables was determined using Pearson's correlation coefficient.

To isolate the part of the variable not explained by the other variable, we regressed apoB on HDL-C (residual of apoB) and then HDL-C on apoB (residual of HDL-C). These were used as predictors on Cox proportional hazard regression models with ASCVD as an outcome, adjusting for standard ASCVD risk factors, including age, sex, BMI, systolic and diastolic blood pressure, medication intake, HbA1c, diabetes medication intake, and smoking. Models were further adjusted for log-transformed triglycerides. We then tested the interaction between apoB and HDL-C in adjusted models. All analyses were repeated for men and women separately.

The interaction between apoB and HDL-C was visualized by plotting the hazard of ASCVD as a function of apoB for different levels of HDL-C expressed as *z*-scores (−2, −1.25, −0.50, 0, 0.50, 1.25, 2.0) using the simPH R package.[14] From the same model, we have also estimated the 10-year absolute risk of ASCVD averaging over observed covariate distribution in our sample.

Hazard ratio (HR) estimates and the corresponding 95% confidence intervals (CIs) were expressed per 1 SD. Hypotheses were tested at the two-sided alpha level of.05. Analyses were performed using R version 4.1.0. Analyses of the role of metabolic risk factors in the UK Biobank have been approved by the McGill University Health Center Research Ethics Board.

# Results

The analytic sample included 293 872 individuals with a mean age of 56 and 42% men (*Table 1*). The mean apoB was 1.05 g/L and the mean HDL-C was 1.44 mmol/L, with a correlation of $r = -0.11$, indicating that apoB can explain only ~1% of the variability in HDL-C. ApoB levels were similar in men vs. women (1.04 g/L vs. 1.06 g/L, respectively, $P < 0.001$, *Table 1*), while HDL-C was higher in women vs. men (1.58 mmol/L vs. 1.27 mmol/L, respectively, $P < 0.001$, *Table 1*). The correlations between HDL-C and the other lipid variables are listed in *Table 2*. As anticipated, the correlation between HDL-C and apoB was low (−0.11, $P < 0.001$). The apoB and HDL-C correlations were similar among men and women. Over a median follow-up of 13 years, 8% of individuals experienced their first ASCVD event.

In a multivariable-adjusted Cox model (including log-triglycerides) for time to the first ASCVD event, both apoB and residual of HDL-C regressed on apoB were statistically significant, with HRs per 1 SD of 1.16 (95% CI: 1.15, 1.18; $P < 0.001$) for apoB and 0.85 (95% CI: 0.84, 0.87; $P < 0.001$) for residual of HDL-C (*Table 3*). Consistent with the low correlation between apoB and HDL-C, in the same multivariable-adjusted

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**Table 1 Baseline characteristics**

| | Overall | Female | Male |
|---|---|---|---|
| *n* | 293 872 | 170 562 | 123 310 |
| Age (years) | 56.00 [49.00, 62.00] | 56.00 [49.00, 62.00] | 56.00 [48.00, 62.00] |
| Male (%) | 123 310 (42.0) | | |
| BMI (kg/m$^2$) | 26.26 [23.77, 29.27] | 25.73 [23.18, 29.13] | 26.84 [24.61, 29.41] |
| Ever smoked (%) | 171 823 (58.5) | 93 755 (55.0) | 78 068 (63.3) |
| SBP (mmHg) | 135.00 [123.50, 148.00] | 132.00 [120.50, 146.00] | 138.50 [128.00, 150.50] |
| HbA1C (%) | 5.33 [5.12, 5.55] | 5.34 [5.12, 5.56] | 5.33 [5.11, 5.55] |
| Blood pressure medication (%) | 36 263 (12.3) | 21 100 (12.4) | 15 163 (12.3) |
| Diabetes medication (%) | 2389 (0.8) | 1030 (0.6) | 1359 (1.1) |
| Total cholesterol (mmol/L) | 5.82 [5.16, 6.54] | 5.93 [5.24, 6.66] | 5.69 [5.06, 6.37] |
| HDL-C (mmol/L) | 1.44 [1.21, 1.72] | 1.58 [1.35, 1.84] | 1.27 [1.10, 1.48] |
| TG (mmol/L) | 1.42 [1.01, 2.02] | 1.28 [0.94, 1.80] | 1.63 [1.15, 2.31] |
| LDL-C (mmol/L) | 3.66 [3.15, 4.22] | 3.66 [3.13, 4.24] | 3.66 [3.17, 4.19] |
| ApoB (g/L) | 1.05 [0.90, 1.20] | 1.04 [0.89, 1.20] | 1.06 [0.92, 1.21] |
| Non-HDL-C (mmol/L) | 4.33 [3.69, 5.03] | 4.29 [3.63, 5.01] | 4.38 [3.76, 5.04] |
| ASCVD risk (PCE in %) | 4.78 [2.04, 9.79] | 3.04 [1.30, 6.06] | 8.96 [4.38, 15.10] |
| Incidence ASCVD (%) | 23 942 (8.1) | 9999 (5.9) | 13 943 (11.3) |
| Follow-up (years) | 13.54 [12.7, 14.2] | 13.59 [12.8, 14.2] | 13.46 [12.6, 14.2] |

BMI, body mass index; SBP, systolic blood pressure; HbA1c, glycosylated haemoglobin; ApoB, apolipoprotein B HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; non-HDL-C, total cholesterol-high-density lipoprotein cholesterol; TG, triglyceride; ASCVD, atherosclerotic cardiovascular disease; PCE pooled cohorts equation.

model, but this time including HDL-C and the residual of apoB regressed on HDL-C, the HRs per standard deviation remained similar to the previous model, 1.14 (95% CI: 1.12, 1.16; $P < 0.001$) for residual apoB and 0.84 (95% CI: 0.82, 0.85; $P < 0.001$) for HDL-C (*Table 4*). These results remained consistent in analogous models run separately among men and women. In the full sample, log-triglycerides did not meaningfully alter the effects of apoB and HDL-C and achieved a HR per standard deviation of 1.01 (95% CI: 0.99, 1.02; $P = 0.330$).

We then tested the interaction between apoB and HDL-C, which was statistically significant and came to 0.95 (95% CI: 0.93, 0.96; $P < 0.001$) in the full sample, with consistent results among men and women. To explore this effect further, we plotted the HR of apoB as a function of different levels of HDL-C, presented as a standardized distance from the mean (i.e. z-score). The results are shown in *Figure 1*. We observed that for lower levels of HDL-C, ASCVD risk increases sharply with increasing apoB. Conversely, when HDL-C is high (i.e. above 2 SD from the mean), the effect of changing apoB vanishes, with the HR of ASCVD flat as a function of apoB. This effect was consistent in both men and women. We also explored the relationship on the absolute risk scale for the same standardized distance values of apoB and HDL-C, averaging over the observed covariate distribution in our sample. The results remained directionally consistent (*Table 5*). We note uniformly lower risk for high HDL-C levels at or below 5% for HDL-C at 2 or even 1.25 SD above the mean, regardless of apoB level. Similarly, risk is consistently lower for very low apoB levels. Conversely, the highest risk (> 10%) is observed when apoB is high (2 or 1.25 SD above the mean) and HDL-C is low (2 SD below the mean).

**Table 2 Pearson correlation coefficients for lipids**

| | HDL-C | TG | LDL-C | apoB | Non-HDL-C |
|---|---|---|---|---|---|
| TC | 0.30 | 0.29 | 0.94 | 0.87 | 0.93 |
| | $P < 0.001$ | $P < 0.001$ | $P < 0.001$ | $P < 0.001$ | $P < 0.001$ |
| HDL-C | | −0.44 | 0.01 | −0.11 | −0.08 |
| | | $P < 0.001$ | $P < 0.001$ | $P < 0.001$ | $P < 0.001$ |
| TG | | | 0.34 | 0.39 | 0.47 |
| | | | $P < 0.001$ | $P < 0.001$ | $P < 0.001$ |
| LDL-C | | | | 0.96 | 0.98 |
| | | | | $P < 0.001$ | $P < 0.001$ |
| apoB | | | | | 0.96 |
| | | | | | $P < 0.001$ |

Pearson correlation coefficient between lipids. Note the weak correlation between HDL-C and apoB illustrating they are independent variables so far as their concentration is concerned.
ApoB, apolipoprotein B HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; non-HDL-C, total cholesterol-high-density lipoprotein cholesterol; TG, triglyceride.

## Discussion

In this study, we investigated the interplay of apoB and HDL-C and their association with incident ASCVD. It is known that apoB, LDL-C, and non-HDL-C are independently associated with cardiovascular risk. Using residual discordance analysis with the inclusion of triglycerides, we confirm these findings and demonstrate the relations are not substantially altered by inclusion of triglycerides. HDL-C remains significantly

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**Table 3 Hazard ratios and 95% confidence intervals for incident ASCVD in adjusted Cox proportional hazards models with ApoB and HDL-C residuals**

| Variables | HR (95% CI) | *P* |
|---|---|---|
| ApoB | 1.16 (1.15, 1.18) | <0.001 |
| HDL-C residual | 0.85 (0.84, 0.87) | <0.001 |
| ln TG | 1.01 (0.99, 1.02) | 0.330 |
| SBP | 1.18 (1.16, 1.19) | <0.001 |
| HbA1c | 1.08 (1.07, 1.09) | <0.001 |
| Age | 1.07 (1.06, 1.07) | <0.001 |
| Male | 1.71 (1.66, 1.76) | <0.001 |
| BMI | 1.08 (1.06, 1.09) | <0.001 |
| Blood pressure medication | 1.48 (1.44, 1.53) | <0.001 |
| Diabetes medication | 1.59 (1.44, 1.75) | <0.001 |
| Ever smoked | 1.24 (1.21, 1.28) | <0.001 |

ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; ln TG, natural logarithm transformed triglyceride; BMI, body mass index; SBP, systolic blood pressure; HbA1c, glycolated haemoglobin; ASCVD, atherosclerotic cardiovascular disease; HR, hazard ratio; CI, confidence interval.

**Table 4 Hazard ratios and 95% confidence intervals for incident ASCVD in adjusted Cox proportional hazards models with HDL-C and ApoB residuals**

| Variables | HR (95% CI) | *P* |
|---|---|---|
| HDL-C | 0.84 (0.82, 0.85) | <0.001 |
| ApoB residual | 1.14 (1.12, 1.16) | <0.001 |
| ln TG | 1.01 (0.99, 1.02) | 0.330 |
| SBP | 1.18 (1.16, 1.19) | <0.001 |
| HbA1c | 1.08 (1.07, 1.09) | <0.001 |
| Age | 1.07 (1.06, 1.07) | <0.001 |
| Male | 1.71 (1.66, 1.76) | <0.001 |
| BMI | 1.08 (1.06, 1.09) | <0.001 |
| Blood pressure medication | 1.48 (1.44, 1.53) | <0.001 |
| Diabetes medication | 1.59 (1.44, 1.75) | <0.001 |
| Ever smoked | 1.24 (1.21, 1.28) | <0.001 |

ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; ln TG, natural logarithm transformed triglyceride; BMI, body mass index; SBP, systolic blood pressure; HbA1c, glycolated haemoglobin; ASCVD, atherosclerotic cardiovascular disease; HR, hazard ratio; CI, confidence interval.

**Table 5 Expected 10 years risk of ASCVD from fully adjusted Cox model**

| | ApoB | | | | | | |
|---|---|---|---|---|---|---|---|
| HDL-C | −2.00 | −1.25 | −0.50 | 0.00 | 0.50 | 1.25 | 2 |
| −2.00 | 5.10 | 6.00 | 7.04 | 7.83 | 8.70 | 10.17 | 11.87 |
| −1.25 | 4.91 | 5.62 | 6.41 | 7.00 | 7.64 | 8.71 | 9.90 |
| −0.50 | 4.73 | 5.26 | 5.84 | 6.26 | 6.71 | 7.44 | 8.24 |
| 0.00 | 4.61 | 5.03 | 5.48 | 5.80 | 6.14 | 6.69 | 7.28 |
| 0.05 | 4.50 | 4.81 | 5.14 | 5.38 | 5.62 | 6.01 | 6.43 |
| 1.25 | 4.33 | 4.50 | 4.68 | 4.80 | 4.92 | 5.12 | 5.32 |
| 2.00 | 4.17 | 4.21 | 4.25 | 4.28 | 4.31 | 4.35 | 4.39 |

The numbers in the table are the percent ASCVD risk over 10 years.
ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; ASCVD, atherosclerotic cardiovascular disease.

associated with the risk of new-onset cardiovascular events even when apoB is accounted for, and, conversely, apoB remains significantly associated with cardiovascular risk even when HDL-C is accounted for. Moreover, based on correlation analysis, we observed that their concentrations in plasma appear to be only weakly associated with each other. This reflects weakly shared variance and further points to independent associations with cardiovascular risk.

But are they pathophysiologically independent? Perhaps not. Our novel finding was a statistically significant interaction between HDL-C and apoB, such that at higher levels of HDL-C, the increase in risk associated with a given amount of apoB was significantly reduced. This effect was observed over a full range of concentrations of both HDL-C and apoB, was present in both men and women, and was not altered by the inclusion of triglycerides. Is there evidence from prior research that points to biological mechanisms that might be responsible?

First, it is accepted that the cholesterol within atherosclerotic lesions was not generated within the arterial wall but rather was deposited when apoB particles entered and were trapped within the arterial wall. Moreover, when apoB particle number is reduced by medical therapy, the cholesterol content within the arterial wall tends to be reduced.[15,16] Since the cholesterol cannot be degraded within the arterial wall, any reduction in its content must be due to removal. Two biological processes could be responsible for the removal of this cholesterol from the arterial wall. One would be uptake and removal by macrophages. To the best of our knowledge, there is no evidence for or against this potential mechanism of benefit. Uptake by nascent HDL particles and removal by reverse cholesterol transport is the second possible mechanism. Whether this mechanism to remove cholesterol that has accumulated in the extracellular space within the arterial wall is operative and responsible for the decrease in cholesterol content has not been explicitly demonstrated. Nor has it been demonstrated whether the decrease in cholesterol content within the arterial wall is even amongst the pathophysiological mechanisms responsible for the decrease in the risk of a cardiovascular event following LDL-C/apoB lowering therapy. But a decrease in the cholesterol content, which might lead to a remodelling of the arterial wall that would make it less susceptible to plaque rupture, is a credible pathophysiological hypothesis. Moreover, there is indirect evidence from HDL efflux studies that is consistent with this hypothesis.[17,18]

However, this is not the only possible mechanism of benefit from HDL particles interacting with apoB particles. Binding of apoB particles to proteoglycans has been reported to be inhibited by the exchangeable apoA1 in HDL,[19] and HDL may reduce endothelial transcytosis of apoB.[20] There are, however, multiple other mechanisms, independent of any direct effect on apoB, by which HDL might mitigate the risk of ASCVD. These include anti-inflammatory effects, antioxidant effects, antithrombotic or profibrinolytic effects, and vasoprotective effects.[21–24] If any of these alternate mechanisms are operative, they confound

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our explanation that a beneficial interaction is due to HDL particle-mediated reverse cholesterol transport. They do not confound our general hypothesis that any beneficial interaction between HDL-C and apoB might be produced by some specific property of an HDL particle must be in high correlation with HDL-C. Put the other way around, HDL-C is a surrogate measure, which would have to be highly correlative with the actual active biological factor, if such a factor exists.

While the potent inverse association of HDL-C and cardiovascular risk is unquestionable, the fact that multiple Mendelian randomizations have failed to confirm any causal relation of HDL-C to cardiovascular risk and the failure of pharmaceutical agents, which increase HDL-C, to reduce cardiovascular risk have produced widespread scepticism that HDL-C plays any significant pathophysiological role in mediating cardiovascular risk.

But is this evidence as secure as it seems? Mendelian randomization combines single-nucleotide polymorphisms that relate significantly to the concentration of the marker under study to create an instrumental variable, whose relation to the incidence of the disease under study can be determined. In this instance, instrumental variables were created for HDL-C, and these were related to cardiovascular risk. HDL-C, however, is not a discrete physiological variable. HDL-C is the total mass of cholesterol within HDL particles. However cholesterol is only one constituent of HDL particles, and HDL particles differ substantially in size, cholesterol mass, and apolipoprotein composition- and, therefore, in potential physiologic roles.[25] But it is the HDL particles that enter the arterial wall that might inhibit or heal arterial injury that should have been the targets of the instrumental variables, not the simple sum of the mass of cholesterol within all the HDL particles. It is an HDL particle that would mediate any of the multiple other potential mechanisms of benefit. Accordingly, a conclusion based on an estimate of total HDL-C, which is the simple sum of cholesterol in all the HDL particles, does not necessarily exclude a potential role for an HDL subfraction in the pathophysiology of ASCVD. In this context, it is of interest that while multiple Mendelian randomization studies fail to support a causal role for HDL-C, a limited number of such studies of HDL subfractions do point to a causal link.[26,27] However, any specific HDL particle or particles that might be responsible for any putative beneficial effect must correlate highly with HDL-C. Obviously, more work must be done to test this line of argument.

The second line of argument against HDL having a protective role in reducing ASCVD risk is the failure of the medications, in particular the cholesterol ester transfer protein inhibitors to consistently and significantly reduce cardiovascular risk, notwithstanding substantial increases in HDL-C.[28] We do not dismiss these results, but they share the same limitation as the Mendelian randomization studies of presuming HDL-C to be the relevant variable that relates to ASCVD risk.

Finally, some studies have demonstrated that the relation of HDL-C to risk is U-shaped,[29] that is, risk increases at high concentrations of HDL-C. Interpretation of these observations at the extreme of the HDL-C distribution is difficult given the multiplicity of factors that affect HDL-C concentration. Excessive alcohol intake is one of these.[30] Further work is necessary to disentangle such effects and resolve the question. However, our interpretation of our findings is based on the overall relations between HDL-C and apoB and is not driven by those at the highest levels of HDL-C, which would affect <5% of the overall relation.

As for triglycerides, there is no evidence they play a direct role in atherogenesis, and this analysis adds further support to this contention. However, triglycerides might play an indirect role by lowering HDL-C due to cholesterol ester transfer protein-mediated exchanges of cholesterol ester and triglyceride.[31,32] The decrease in the apoB HR as HDL-C increased, observed in this analysis, should not be interpreted as firm clinical evidence that apoB is not atherogenic or should not be treated when HDL-C is high. First, this is an epidemiological finding from an observational study. We do not challenge the evidence that apoB is a causal factor for ASCVD. However, this observation does raise the possibility that the atherogenic risk associated with apoB might not be constant. Nevertheless, even if the trends observed in this database were reproduced in others, in only a small portion of the population would the level of HDL-C be high enough to significantly impact the atherogenic risk associated with apoB. On the other hand, if this finding were to be biologically valid, this might explain the apparent immunity of some individuals to the clinical consequences of very high levels of LDL-C/apoB. In any case, this would not challenge the practice of lowering LDL-C/apoB in individuals at high ASCVD risk since the benefit of therapy relates to the risk of an event and the level of LDL-C/apoB, not to the causes of the increased risk.[33]

### Limitations

Our study has important limitations. It is based on observational data and is suitable only to demonstrate associations. Furthermore, residual confounding due to the association between HDL-C and multiple metabolic and inflammatory factors cannot be fully eliminated.[34,35] Moreover, any conclusions are limited by the representativeness of the cohort available in the UK Biobank and the fact that a significant portion of the cohort has been excluded from the analysis.

## Conclusion

In this prospective observational study, high HDL-C manifests a protective association to the risk of new onset ASCVD, independent of apoB. Importantly, in the adjusted analyses, the effect of triglycerides is virtually null. HDL-C appears to modify the effect of apoB such that in individuals with high HDL-C, the effect of apoB diminishes. These results suggest that the role and importance of HDL-C in primary prevention of ASCVD should be re-examined.

## Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

## Author contributions

Allan D. Sniderman (Conceptualization, funding acquisition, writing original draft, writing review & editing), Karol Pencina (Methodology, formal analysis), George Thanassoulis (Review & editing), Line Dufresne (Formal analysis), and Michael Pencina (Conceptualization, writing review & editing).

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## Use of AI and AI-assisted technologies statement

AI technology was not used in the generation of this manuscript.

## Data availability

The data analyzed in this study were obtained from the UK Biobank with proper authorization.

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