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FULL RESEARCH PAPER
CVD risk factors

Cardiovascular outcomes in adults with low-density lipoprotein cholesterol levels of ≥4.9 mmol/L: 15-year follow-up of the CoLaus\|PsyCoLaus study

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Aims Guidelines recommend lipid-lowering treatment (LLT) in all adults with LDL cholesterol (LDL-C) ≥4.9 mmol/L independently of a genetic diagnosis or other cardiovascular (CV) risk factors, despite this population being very heterogeneous and limited data available on CV risk. The aim of this study is to assess CV risk in the overall population with LDL-C ≥4.9 vs. <4.9 mmol/L and different subgroups.

Methods and results We analysed 5249 adults without atherosclerotic CV disease (ASCVD) and without LLT at baseline from CoLaus\|PsyCoLaus, a prospective population-based cohort. Atherosclerotic CV disease was our outcome. Among 5249 participants [mean (standard deviation) age 51.7 (10.5) years, 55% female, median follow-up 14.3 years], 291 (5.5%) had LDL-C ≥4.9 mmol/L. Overall, 300 (3.7%) participants experienced a first-time ASCVD, among which 27 (9%) had LDL-C ≥4.9 mmol/L. The adjusted hazard ratio (confidence interval) for first-time ASCVD was 1.64 (1.10–2.44) for LDL-C ≥4.9 vs. <4.9 mmol/L, 1.43 (0.57–3.58) in participants without hypertension, diabetes, or smoking ($n = 2497$), 1.43 (0.80–2.55) in participants without suspicion of familial hypercholesterolaemia ($n = 5101$), and 1.46 (0.93–2.27) following adjustment for a polygenic risk score (data available for $n = 3728$).

Conclusion The study reports an association between LDL-C ≥4.9 mmol/L and ASCVD in a large cohort from Switzerland. However, we found heterogeneity in risk across different subgroups. Furthermore, polygenic risk for coronary artery disease seems to partly account for this association. While further studies are needed to assess the CV risk specifically in healthier subgroups, our results suggest that a more precise risk assessment is needed for individuals with LDL-C ≥4.9 mmol/L.

Lay summary This population-based cohort study assessed the cardiovascular (CV) risk in adults with very high LDL cholesterol (LDL-C) of ≥4.9 mmol/L who have never experienced a CV event and who do not receive lipid-lowering therapy.

- The LDL-C ≥ 4.9 mmol/L is associated with an increased risk for CV disease.
- More data are needed to assess this risk in adults who do not have additional CV risk factors (hypertension, diabetes, and smoking) or who do not have a suspicion of a genetic disease.

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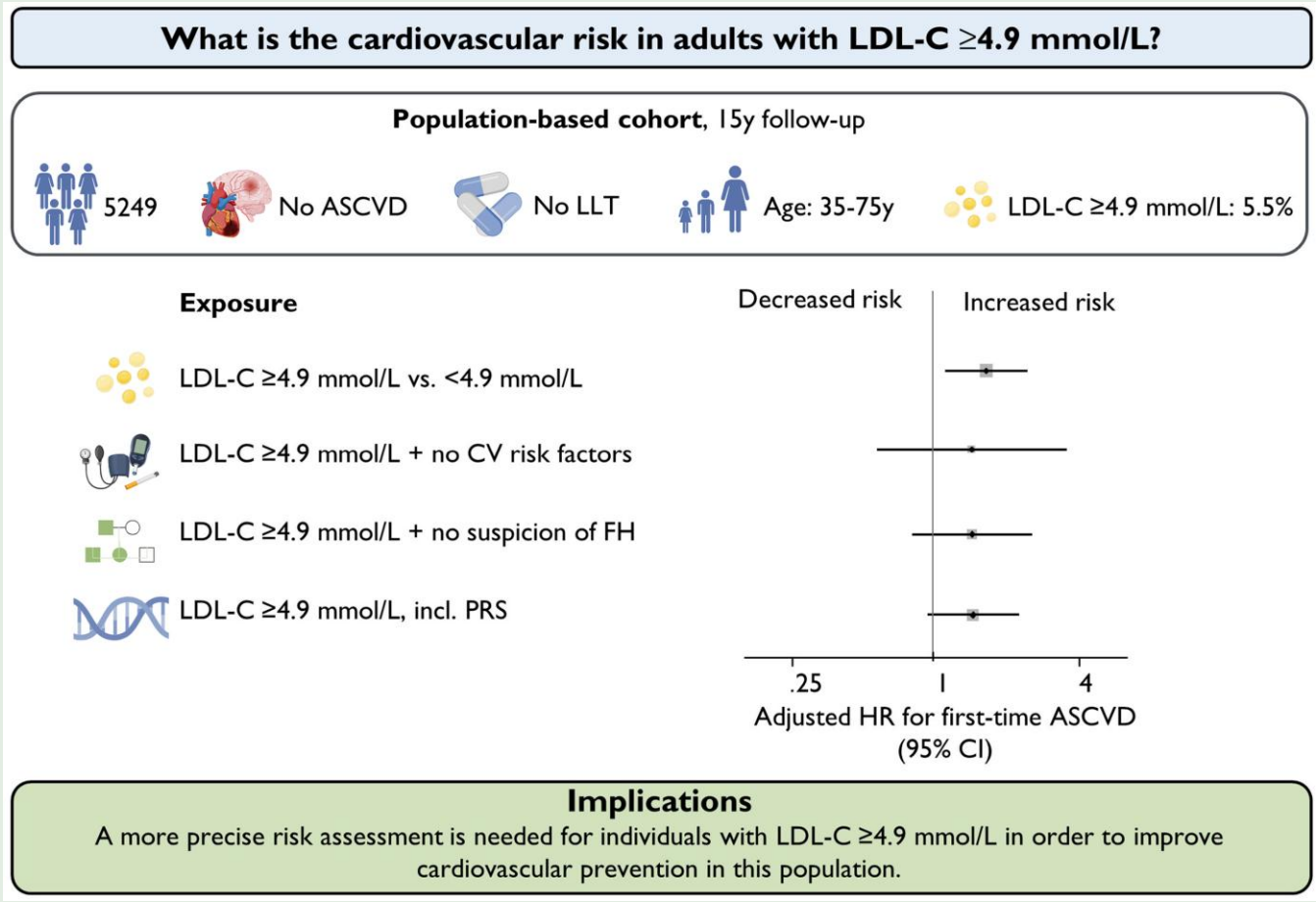
Graphical Abstract



Keywords Hypercholesterolaemia • Familial hypercholesterolaemia • Prospective study • Cardiovascular disease

Introduction

Familial hypercholesterolaemia (FH) is a genetic disease characterized by severely elevated LDL cholesterol (LDL-C) levels and premature atherosclerotic cardiovascular (CV) disease (ASCVD).[1,2] Therefore, individuals with an FH mutation should not be missed when assessed for treatment of hypercholesterolaemia.[1] Unfortunately, testing for FH mutations is not established for widespread use, in part due to high cost, lack of resources, and lack of reimbursement.[2] Consequently, individuals with LDL-C ≥4.9 mmol/L are often referred to as having an FH phenotype.[2,3] However, in a cohort free of coronary artery disease, 5% of the participants had LDL-C ≥4.9 mmol/L, but only 1.9% of those actually were carriers of an FH mutation.[4] This highlights the heterogeneity of the population with LDL-C ≥4.9 mmol/L, which includes individuals not only with FH but also with polygenic increased risk (i.e. without monogenic mutation) and probably other causes of hypercholesterolaemia.[2] Despite FH genotype and phenotype not being equivalent, the newest international guidelines recommend initiating lipid-lowering treatment (LLT) in primary prevention for all persons presenting with LDL-C ≥4.9 mmol/L, independently of the presence of other CV risk factors or a genetic mutation.[5,6] Data on the CV risk in the heterogeneous population with FH phenotype is limited. While the few observational studies that assessed the risk for CV events in persons with FH phenotype showed an increased risk for CV events, they were often limited by methodological issues by pooling treated and untreated individuals and missing time-updated data on LLT and covariates.[3,4,7,8] Consequently, additional studies are needed to further assess the extent of the CV risk in this population.

We therefore used data from a prospective, population-based cohort to assess the CV risk of individuals with LDL-C ≥4.9 vs. <4.9 mmol/L using time-updated data on covariates and LLT (i) in the entire sample population, (ii) in the subgroup with no additional CV risk factors at baseline, and (iii) in the subgroup without suspicion of FH. Furthermore, we included a polygenic risk score (PRS) for ASCVD into our model to account for an individual's genetic background and aimed to assess the CV risk of treated vs. untreated individuals with LDL-C ≥4.9 mmol/L.

Methods

Study design and cohort

We analysed data from CoLaus|PsyCoLaus, which is a population-based cohort that includes a randomly selected sample of inhabitants of Lausanne, Switzerland, recruited between June 2003 and May 2006 (www.colaus-psycolaus.ch). The primary aim of the study was to increase the

understanding of CV disorders and their risk factors in the general population. Inclusion criteria were age of 35–75 years at baseline, living in the city of Lausanne, and written informed consent. No exclusion criteria were applied. In total, 6733 persons were included (54% female). The cohort was followed up at 5 (between April 2009 and September 2012), 10 (between May 2014 and April 2017), and 15 years (between April 2018 and May 2021). Detailed characteristics of the cohort and the recruitment process are described elsewhere.[9]

For this analysis, we excluded persons with missing baseline data on LDL-C or covariates, participants who only had baseline data available, and persons with ASCVD and/or use of statins, ezetimibe, or a combination of both at baseline. We did not exclude participants using other LLT, such as fibrates or omega-3 fatty acids, as these do not significantly influence LDL-C levels and are therefore not recommended as LDL-C-lowering treatment.[5,6] No participants used bile acid sequestrants, bempedoic acid, or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors at baseline.

The Institutional Ethics Committee of the University of Lausanne, which afterwards became the Ethics Commission of Canton Vaud (www.cer-vd.ch) approved the CoLaus|PsyCoLaus Study [project number PB_2018-00038 (239/09)].

Low-density lipoprotein cholesterol measurements

Venous blood samples were collected after overnight fasting. Laboratory analyses took place at Centre hospitalier universitaire Vaudois (CHUV) Clinical Laboratory. The following methods were used to measure lipid levels with maximum inter- and intra-batch coefficients of variability (CoV): total cholesterol by CHOD-PAP (cholesterol oxidase phenol 4-aminoantipyrine peroxidase) with 1.6–1.7% CoV; HDL cholesterol by CHOD-PAP + PEG (polyethylene glycol) + cyclodextrin with 3.6–0.9% CoV; triglycerides by GPO-PAP (glycerol phosphate oxidase) with 2.9–1.5% CoV; and LDL particle size was assessed by polyacrylamide gel electrophoresis (Lipoprint LDL kit®, Quantimetrix Corporation, CA, USA) with 1.5–0.5% CoV.[10] Low-density lipoprotein cholesterol was calculated using the Friedewald formula if triglycerides were <4.6 mmol/L.[9] If triglyceride levels were ≥4.6 and <9.04 mmol/L, we applied the extended Martin–Hopkins equation.[11]

Outcome

Our outcome was prospectively collected, independently adjudicated ASCVD within the 15-year follow-up, which was defined as: (i) acute myocardial infarction, and/or (ii) sudden cardiac death, and/or (iii) symptomatic coronary artery disease ≥50% stenosis and treated by percutaneous coronary intervention or coronary artery bypass graft, and/or (iv) fatal and non-fatal ischaemic stroke including transient ischaemic attack. We did not include peripheral artery disease as an outcome, as it was not assessed in the cohort.[12]

Covariates

Covariates were assessed via self-administered questionnaires, interviews, and physical examinations at baseline and each follow-up visit.[9]

Hypertension was defined as having a systolic blood pressure of ≥140 mmHg and/or a diastolic blood pressure of ≥90 mmHg during the physical examination and/or when participants reported taking antihypertensive medication.[9] We defined diabetes as having a fasting plasma glucose level of ≥7.0 mmol/L and/or the presence of oral hypoglycaemic or insulin treatment.[9] Data on smoking status were self-reported, and being an active smoker was defined as currently smoking ≥1 cigarette per day.[13] Participants were classified as having one of three education levels (low, middle, and high), as described previously.[14,15]

Polygenic risk scores predict a person's genetic predisposition to a certain disease by taking the effect of millions of genetic markers (single-nucleotide polymorphisms) into account.[16] The methods used to compute the PRSs have been described previously.[16] We used the PRS developed by Inouye *et al.* (metaGRS_CAD) as a confounder divided into quintiles,[17] as this PRS has shown the best prediction for ASCVD in the CoLaus|PsyCoLaus cohort.[16]

Medication

Medications were coded using the WHO Anatomical Therapeutic Chemical (ATC) classification system.[18] At baseline and each follow-up visit, participants were asked two questions: '(a) In the past 6 months, have you been taking prescription medications regularly? (Including oral contraceptives and aerosols/sprays for the lungs); (b) In the past 6 months, have you been taking any medications regularly that do not need a prescription, including vitamins, herbal medications, or dietary supplements?'[19]

For this analysis, medications were coded as a binary variable (yes/no). Lipid-lowering treatment was coded as 'yes' if at least one of the following ATC codes was present: C10AA-AD, C10AX, C10BA, or C10BX. Bempedoic acid or PCSK9 inhibitors were not used by study participants. Antihypertensive medication was coded as 'yes' if at least one of the following ATC codes was present: C02, C03, C07, C08, or C09. Diabetes medication was coded as 'yes' if at least one of the following ATC codes was present: A10A or A10B.

Statistical analysis

Descriptive results are shown as the number of participants (percentage), mean ± standard deviation, or as median [interquartile range (IQR)] as appropriate. Bivariate analyses were performed using χ^2, Student's *t*-test, or Mann–Whitney test as appropriate.

We assessed the occurrence of first-time ASCVD in participants with LDL-C ≥4.9 mmol/L vs. <4.9 mmol/L using a Cox proportional hazard model. Using Schoenfeld residuals, we assessed the proportional hazard assumptions (Supplementary material online, *File S2*).[20] Participants were censored when lost to follow-up and additionally when starting LLT (statins, ezetimibe). We censored participants when starting LLT to avoid pooling treated and untreated individuals. We adjusted for sex, education level, age, and time-updated data at each available follow-up for hypertension, active smoking, diabetes, triglycerides, and body mass index by considering these variables as time-varying variables. We structured the data set for time-varying variables as follows. At each available follow-up visit, covariates were updated. The data set was structured with multiple records per participant in long format. A time period was defined as the time between the date of the last available visit and either the date of the next follow-up visit or the date of an event. For each of these time intervals, we considered the values for time-varying variables measured at the beginning of the corresponding period.

Subgroup and sensitivity analysis

We performed the same analysis in the subpopulation without other CV risk factors at baseline (no hypertension, diabetes, and/or active smoking). Although we did adjust for hypertension, diabetes, and smoking status in our primary analysis, we aimed to assess the risk additionally in the subpopulation excluding individuals with hypertension, diabetes, or active smoking at baseline to specifically represent a healthier population, as the decision on whether or not to start LLT is especially challenging in this subgroup of patients. We chose these CV risk factors in accordance with the widely used Swiss Atherosclerosis Association risk calculator [in German: Arbeitsgruppe Lipide und Atherosklerose (AGLA)],[21] SCORE2[22] and SCORE2-OP,[23] respectively.[12] We additionally performed the analysis in the subpopulation of active smokers at baseline, which is the most common risk factor among young patients with acute coronary syndrome in Switzerland.[24]

Second, we performed the analysis in the subpopulation with no suspicion of FH at baseline. We took a pragmatic approach and defined suspicion of FH as having LDL-C ≥4.9 mmol/L and a first-degree relative with premature ASCVD (women <60 years, men <55 years) and/or hypercholesterolaemia (both self-reported), as previously suggested.[1,25] We decided to use this definition, as we did not have all criteria available to apply in the

Dutch Lipid Clinic Network (DLCN) score[26] or the Simon Broome Register algorithm[27] to assess for suspicion of FH (we had no data available on physical examination of participants or of first-degree relatives or on the presence of FH mutation).

Third, we performed the analysis in the subpopulation with available data on PRS for coronary artery disease.[16] We added PRS as a covariate into our model to further examine the associations of LDL-C ≥4.9 mmol/L and ASVCD. Additionally, among those with suspicion of FH, we aimed to compare the risk for ASCVD in participants with a low (<20th percentile) vs. higher PRS (>20th percentile). We used this approach to capture the risk in individuals who were more likely to have a monogenic disease (i.e. FH) vs. those who were not, as it has been suggested that, for complex diseases, persons with a positive family history and a low PRS are more likely to have a monogenic disease.[28]

Fourth, we assessed the occurrence of ASCVD in treated vs. not treated participants with LLT during follow-up among individuals with LDL-C ≥4.9 mmol/L. Participants starting LLT during follow-up were not censored in this analysis.

For all subgroup analyses, we formally tested whether the effect of the exposure on ASCVD risk was modified by including an interaction term between the subgroup and the exposure.

For sensitivity analyses, we used a model for continuous LDL-C and expressed the hazard ratio (HR) per 1 mmol/L increase in LDL-C, performed an analysis using LDL-C divided into quintiles, and, to assess additional risk differences within LDL-C ≥4.9 mmol/L, we compared LDL-C ≥4.9 −<5.5 mmol/L and LDL-C ≥5.5 mmol/L with LDL-C <4.9 mmol/L. Additionally, we considered the exposure to LDL-C levels over time, by creating LDL-C ≥4.9 vs. <4.9 mmol/L at each time point as a binary variable and used it as a time-varying variable in our model.

All statistical analyses were performed using Stata version 16.0 (Stata Corporation, College Station, TX, USA).

Results

Study sample

Of the initial CoLaus|PsyCoLaus study sample of 6733 participants, we included 5249 (78%). The reasons for exclusion are presented in *Figure 1*. Baseline data of included vs. excluded participants due to missing follow-up data are presented in Supplementary material online, *File S1* and *Table S1*.

Baseline characteristics

Baseline characteristics stratified by LDL-C levels are presented in *Table 1*. The mean age was 51.7 years and 54.9% were women. The mean LDL-C was 5.4 mmol/L in participants with LDL-C ≥4.9 vs. 3.2 mmol/L in individuals with LDL-C <4.9 mmol/L. In total, 291 (5.5%) participants had LDL-C ≥4.9 mmol/L. They were older, more likely to have a lower education level, higher triglyceride levels, be active smokers, have hypertension, and have a positive family history for premature CV disease or hypercholesterolaemia. The median follow-up was 14.3 years (IQR 10.5–15.6 years).

Within individuals with LDL-C ≥4.9 mmol/L, 147 (50.5%) had documentation of LLT use at least at one point during the follow-up period (*Table 2*). While they were more likely to be obese, other baseline characteristics did not statistically significantly differ between LLT users and non-users.

Association between assessed exposures and atherosclerotic cardiovascular disease

In total, 300 (5.7%) participants experienced an ASCVD, of whom 27 (9%) had LDL-C ≥4.9 mmol/L at baseline (*Figure 2*). The relative risk

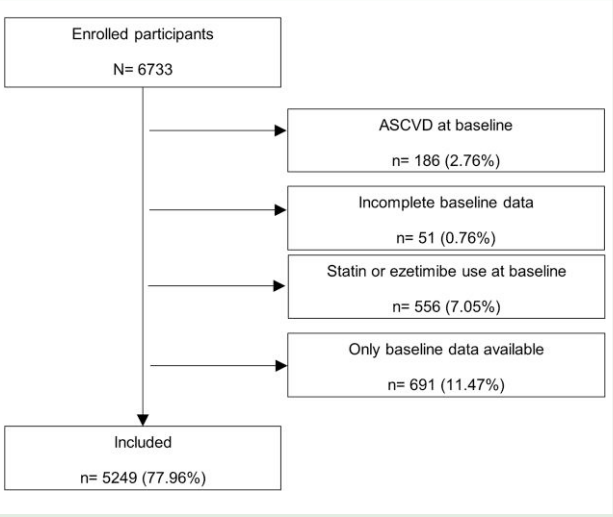


Figure 1 Study flow chart. ASCVD, atherosclerotic cardiovascular disease.

for experiencing an event or being censored of individuals with LDL-C ≥4.9 vs. <4.9 mmol/L is shown in Supplementary material online, *File S1* and *Table S2*. Individuals with LDL-C ≥4.9 mmol/L were more likely to experience an ASCVD compared with participants with LDL-C <4.9 mmol/L [adjusted HR 1.64, 95% confidence interval (CI) 1.10–2.44; *Figure 2*]. This association was less pronounced in participants with no other CV risk factors at baseline (adjusted HR 1.43, 95% CI 0.57–3.58) or no suspicion of FH (adjusted HR 1.43, 95% CI 0.80–2.55; *Figure 2*). Active smokers did not have an increased risk for ASCVD when LDL-C was ≥4.9 vs. <4.9 mmol/L (HR 1.52, 95% CI 0.78–2.93; Supplementary material online, *File S1* and *Table S3*). Among the entire sample for whom the PRS was available ($n = 3728$), the HR for ASCVD attenuated moderately after adding the PRS [HR changed from 1.56, 95% CI 1.0–2.4 (data not shown) to 1.46, 95% CI 0.93–2.27; *Figure 2*]. In individuals with suspicion of FH, having a lower PRS (<20th percentile) and therefore having a higher chance of a monogenic mutation did not lead to a statistically significant increase in risk for ASCVD (HR 2.70, 95% CI 0.62–11.77; Supplementary material online, *File S1* and *Table S3*). Among participants with LDL-C ≥4.9 mmol/L, we did not find a clear association between LLT use in follow-up and ASCVD (adjusted HR 1.15, 95% CI 0.54–2.47; *Figure 2*). Interaction testing across subgroup analyses showed no interactions except when assessing the effect of LLT use among individuals with LDL-C ≥ 4.9 mmol/L at baseline (see Supplementary material online, *File S1* and *Table S4*).

Using a continuous model for LDL-C, we found a statistically significant increase in risk for ASCVD per 1 mmol/L increase in LDL-C (HR 1.23, 95% CI 1.09–1.41; Supplementary material online, *File S1* and *Table S5*). When dividing LDL-C into quintiles, we found a statistically significant increase in risk for ASCVD for the 4th (HR 1.66, 95% CI 1.11–2.47) and 5th quintile (HR 1.76, 95% 1.19–2.61) with a significant *P*-value for the test for trend (Supplementary material online, *File S1* and *Table S5*). Dividing individuals with LDL-C ≥4.9 mmol/L into two additional groups, resulted in a significant increase in risk for ASCVD among those with LDL-C ≥5.5 mmol/L (HR 2.13, 95% CI 1.13–4.03; Supplementary material online, *File S1* and *Table S5*). And finally, when considering LDL-C ≥4.9 vs. <4.9 mmol/L as a time-varying

Table 1 Baseline characteristics stratified by LDL cholesterol level, whole sample

Characteristic	All ($n = 5249$)	LDL-C ≥4.9 mmol/L ($n = 291$)	LDL-C <4.9 mmol/L ($n = 4958$)	*P*-value[a]
Age, years	51.7 ± 10.5	55.2 ± 10.1	51.5 ± 10.5	<0.001
Female sex	2879 (54.9)	149 (51.2)	2730 (55.1)	0.198
Caucasian ethnicity	4797 (91.4)	270 (92.8)	4527 (91.3)	0.383
Education level				
High	1115 (21.2)	42 (14.4)	1073 (21.6)	
Middle	1331 (25.4)	62 (21.3)	1269 (25.6)	
Low	2803 (53.4)	187 (64.3)	2616 (52.8)	<0.001
BMI ≥30 kg/m^2	664 (12.7)	47 (16.2)	617 (12.4)	0.065
LDL-C, mmol/L	3.4 ± 0.9	5.4 ± 0.5	3.2 ± 0.8	<0.001
Triglycerides, mmol/L	1.1 (0.8–1.5)	1.6 (1.2–2.1)	1 (0.8–1.5)	<0.001
Hypertension	1667 (31.8)	122 (41.9)	1545 (31.2)	<0.001
Diabetes	212 (4.0)	15 (5.2)	197 (4.0)	0.320
Active smoking	1401 (26.7)	95 (32.7)	1306 (26.3)	0.018
Positive family history[b]	2337 (44.5)	148 (50.9)	2189 (44.2)	0.025

Results are presented as the number of participants (%), mean ± standard deviation, or median (interquartile range).
BMI, body mass index; LDL-C, LDL cholesterol.
[a]*P*-values were calculated using χ^2, Student's *t*-test, or Mann–Whitney test where appropriate.
[b]First-degree relative with premature cardiovascular disease (women <60 years, men <55 years) and/or hypercholesterolaemia (both self-reported).

Table 2 Baseline characteristics stratified by lipid-lowering treatment use among participants with LDL cholesterol ≥4.9 mmol/L

Characteristic	All ($n = 291$)	LLT in FU ($n = 147$, 50.5%)	No LLT in FU ($n = 144$)	*P*-value[a]
Age, years	55.2 ± 10.1	54.6 ± 9.6	55.9 ± 10.5	0.296
Female sex	149 (51.2)	74 (50.3)	75 (52.1)	0.766
Caucasian ethnicity	270 (92.8)	135 (91.8)	135 (93.8)	0.528
Education level				
High	42 (14.4)	19 (12.9)	23 (16.0)	
Middle	62 (21.3)	37 (25.2)	25 (17.4)	
Low	187 (64.3)	91 (61.9)	96 (66.7)	0.246
BMI ≥30 kg/m^2	47 (16.2)	30 (20.4)	17 (11.8)	0.046
LDL-C, mmol/L	5.2 (5–5.6)	5.3 (5–5.8)	5.2 (5–5.6)	0.367
Triglycerides, mmol/L	1.6 (1.2–2.1)	1.6 (1.2–2.1)	1.6 (1.1–2.0)	0.484
Hypertension	122 (41.9)	66 (44.9)	56 (38.9)	0.299
Diabetes	15 (5.2)	6 (4.1)	9 (6.3)	0.403
Active smoking	95 (32.7)	49 (33.3)	46 (31.9)	0.801
Positive family history[b]	148 (50.9)	81 (55.1)	67 (46.5)	0.144

Results are presented as the number of participants (%), mean ± standard deviation, or median (interquartile range).
BMI, body mass index; FU, follow-up; LDL-C, LDL cholesterol; LLT, lipid-lowering treatment.
[a]*P*-values were calculated using χ^2, Student's *t*-test, or Mann–Whitney test where appropriate.
[b]First-degree relative with premature cardiovascular disease (women <60 years, men <55 years) and/or hypercholesterolaemia (both self-reported).

variable, we observed a slight decrease in the HR to 1.49 (95% CI 1.01–2.20; Supplementary material online, *File S1* and *Table S5*).

Discussion

In this prospective cohort study with 15 years of follow-up, we found that untreated individuals with LDL-C ≥4.9 mmol/L have an increased risk for first-time ASCVD. However, we found heterogeneous strength of this association in the absence of additional CV risk factors, suspicion of FH, and when considering an individual's genetic background through a PRS for coronary artery disease (*Graphical abstract*).

Association between low-density lipoprotein cholesterol ≥4.9 mmol/L and atherosclerotic cardiovascular disease

Our study confirmed an increased risk for ASCVD in primary prevention in individuals with FH phenotype compared with individuals with

Exposure	n with ASCVD[1]/ N total	n with ASCVD[1]/ N with exposure	Adjusted[2] HR (95% CI)	p-value
LDL-C ≥4.9 mmol/L[3]	300/5249	27/291	1.64 (1.10-2.44)	**0.015**
LDL-C ≥4.9 mmol/L, no CV risk factors[3,4]	82/2497	5/100	1.43 (0.57-3.58)	0.450
LDL-C ≥4.9 mmol/L, no suspicion of FH[3,5]	285/5101	12/143	1.43 (0.80-2.55)	0.225
LDL-C ≥4.9 mmol/L, incl. PRS[3]	240/3728	22/216	1.46 (0.93-2.27)	0.096
LLT use in FU among LDL-C ≥4.9 mmol/L[6]	31/291	19/147	1.15 (0.54-2.47)	0.713

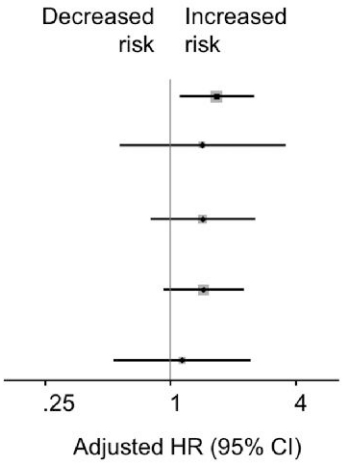


Figure 2 Cox proportional hazard model showing the association between exposures and first-time atherosclerotic cardiovascular disease. ASCVD, atherosclerotic cardiovascular disease; HR, hazard ratio; CI, confidence interval; LDL-C, LDL cholesterol; CV, cardiovascular; FH, familial hypercholesterolaemia; PRS, polygenic risk score; LLT, lipid-lowering treatment; FU, follow-up. (1) Defined as: acute myocardial infarction, sudden cardiac death, symptomatic coronary artery disease ≥50% stenosis and treated by percutaneous coronary intervention or coronary artery bypass graft and fatal and non-fatal ischaemic stroke, including transient ischaemic attack. (2) Adjusted for sex, age, education level, and with time-updated data on: hypertension, diabetes, active smoking, triglycerides, and body mass index. (3) Compared with LDL cholesterol <4.9 mmol/L. (4) No hypertension, diabetes, or active smoking at baseline. (5) First-degree relative with premature cardiovascular disease (women <60 years, men <55 years) and/or hypercholesterolaemia (both self-reported). (6) Compared with no lipid-lowering treatment use.

LDL-C <4.9 mmol/L. To the best of our knowledge, only one other study compared the occurrence of ASCVD in individuals with LDL-C ≥4.9 vs. <4.9 mmol/L in primary prevention, with individuals with FH phenotype showing a higher absolute risk for major adverse CV events.[3] Further studies assessing the CV risk in FH phenotype compared individuals with LDL-C ≥4.9 vs.<3.36 mmol/L[4,8] and individuals with LDL-C >5.95 vs. <2.97 mmol/L.[7] While they all showed an increased risk for CV disease in this population,[4,7,8] they pooled treated and untreated persons and did not have information on time-updated data on CV risk factors and LLT use, possibly enhancing the association. Our results further suggest that FH phenotype may not always have the same ASCVD risk, supporting the concept of heterogeneous risk within individuals with LDL-C ≥4.9 mmol/L. This may partly be influenced by genetic background (polygenic risk, FH) and the presence/absence of other CV risk factors.[29] Not only has a higher CV risk been observed in individuals with monogenic disease vs. polygenic disease even when similar LDL-C levels were present,[30] but even amongst individuals with diagnosed FH variation in the coronary atherosclerotic disease burden has been previously found, with nearly 50% of these persons being free of ASCVD in coronary artery calcium measurements.[31]

Influence of polygenic risk score

Polygenic risk for coronary artery disease seems to be partly responsible for an increase in risk for ASCVD in FH phenotype, as we no longer found an association between LDL-C ≥4.9 mmol/L and ASCVD when considering an individual's genetic background based on a PRS for coronary artery disease. While an individual's PRS not only captures the effects of elevated LDL-C, it further identifies other pathophysiological pathways influencing CV risk and therefore includes valuable information.[32] Unfortunately though, genetic information is not available for widespread use. Therefore, LDL-C levels of ≥4.9 mmol/L can still serve as a useful proxy when PRS and other genetic mutations are unknown.

Lipid-lowering treatment in individuals with low-density lipoprotein cholesterol ≥4.9 mmol/L

In our cohort, 5.5% of individuals had LDL-C ≥4.9 mmol/L. This is in line with a previous study, reporting a prevalence of 5% within a coronary artery disease–free population.[4] Untreated LDL-C ≥4.9 mmol/L lies at the 90% percentile of LDL-C levels in the general population,[33] yet only 1.9% of these individuals actually have an FH mutation.[4] Thus, individuals with LDL-C ≥4.9 mmol/L represent a very heterogeneous group. While persons with FH should receive LLT,[5,6,26,34] at least when other CV risk factors are present, our results suggest that an individual risk assessment rather than a 'one-size-fits-all' approach might be more accurate, when evaluating persons with LDL-C ≥4.9 mmol/L for LLT, especially when individuals are healthier and do not have suspicion of FH.

Within persons with LDL-C ≥4.9 mmol/L, only 50.5% had documentation of LLT use at least at one follow-up visit. Interestingly, treated individuals were younger, had seemingly worse control of CV risk factors, and had a higher risk for ASCVD compared with untreated individuals. Furthermore, interaction testing suggests that the effect of LLT on ASCVD risk may depend on LDL-C levels, as LLT use appears to increase the risk for ASCVD in individuals with LDL-C ≥4.9 mmol/L. Possible explanations are worse control of CV risk factors in follow-up and/or under-dosing of LLT as well as confounding by indication (i.e. patients with more CV risk factors are more likely to be prescribed LLT).[26] The hypothesis of worse control of CV risk factors can be supported by the results from our subgroup analysis of individuals with no other CV risk factors which may suggest that, in cases where other CV risk factors are present, LLT may not be as effective in reducing the risk for ASCVD, unless other risk factors are adequately controlled as well.

In practice, the scarce data on CV risk in this population seem to cause reservations, when assessing individuals with FH phenotype for treatment. To the best of our knowledge, there have been no randomized, placebo-controlled trials on the effect of LLT on ASCVD performed solely in individuals in primary prevention with LDL ≥4.9 mmol/L.[5,35] Additionally, in 2013, it was estimated that in Switzerland only 13% of all persons with FH were officially diagnosed.[26] This may all contribute to a certain hesitancy for LLT initiation. Overall, these data highlight concerns in the treatment of these individuals, which may further support discussions on moving towards a more precision medicine approach, as discussed above. In this regard, recent studies show that personalization of CV risk is a superior approach for the continuation of statin use.[36]

Strengths and limitations

This study has several strengths to consider. We used a large, prospective, population-based cohort with contemporary data, a 15-year follow-up with detailed information on covariates and medication use, and blinded, adjudicated outcomes. Limitations to consider are firstly that LDL-C at baseline was based on a single assessment and calculated only when triglycerides were <9.04 mmol/L. Participants who had triglycerides above that level were excluded ($n = 19$). However, four were LLT users at baseline and would have been excluded for that reason. Among the remaining 15, none had LDL-C ≥4.9 mmol/L in follow-up and none experienced an ASCVD, which lets us assume that this did not greatly influence our results. Second, we did not have all the information available to calculate the DLCN score to better assess the probability of FH as recommended by guidelines[6] and information on family history of ASCVD and hypercholesterolaemia was self-reported. While the report of negative offspring parental CV history has been shown to be relatively reliable, this was not the case for hypercholesterolaemia.[37] Third, although we did have multiple LDL-C measurements over the span of 15 years of follow-up, we only had an LDL-C measurement maximally every 5 years. Fourth, we did not have enough information available to account for dietary factors or physical activity associated with hypercholesterolaemia. This limits our ability to assess the concept of LDL-C burden over time. Fifth, the nature of the observational data limits our ability to draw conclusions on the effect of LLT use among those with LDL-C ≥4.9 mmol/L, especially as we are missing information on adherence to LLT use and dosing of LLT. Sixth, when incorporating the PRS into our model, we were not able to exclude single-nucleotide polymorphisms that may be related to elevated LDL-C, as this would no longer agree with the original score. This might therefore have led to over-adjustment in this subanalysis. And finally, we have relatively wide 95% CI for all our subgroup analysis, indicating that our study lacked the statistical power to detect the well-established association between LDL-C and ASCVD, suggesting however, that the risk in healthier subgroups may differ in magnitude and strength. This highlights the importance of further larger studies assessing the associations in different subgroups.

Conclusions

In this study, we show that individuals with LDL-C ≥4.9 mmol/L overall do have an increased risk for ASCVD compared with individuals with LDL-C <4.9 mmol/L. However, we found heterogeneity in magnitude

and strength of this association in the subgroups with no other CV risk factors or no suspicion of FH and when considering a person's genetic background through a PRS for coronary artery disease, further highlighting heterogeneity in risk among FH phenotype. Further data on CV risk in different subgroups are needed to avoid both possible over- and undertreatment.

Supplementary material

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

Author contribution

Lucy Bolt (Conceptualization, Funding acquisition, Formal analysis, Writing—original draft, Visualization), Stéphanie Baggio (Formal analysis, Writing—review & editing), Julian Teuscher (Formal analysis, Writing—review & editing), Roxane de La Harpe (Data curation, Writing—review & editing), Julien Vaucher (Funding acquisition, Writing—review & editing), Pedro Marques-Vidal (Funding acquisition, Data curation, Writing—review & editing), Drahomir Aujesky (Writing—review & editing), Nicolas Rodondi (Conceptualization, Writing—review & editing, Supervision), and Elisavet Moutzouri (Conceptualization, Writing—review & editing, Supervision)

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Conflict of interest: Co-author P.M.-V. is an editor of *European Journal of Preventive Medicine*.

Declaration of generative AI and AI-assisted technologies in the writing process

No generative AI technology was used to write this manuscript.

Data availability

The data of CoLaus|PsyCoLaus study used in this article cannot be fully shared as they contain potentially sensitive personal information on participants. According to the Ethics Committee for Research of the Canton of Vaud, sharing these data would be a violation of the Swiss legislation with respect to privacy protection. However, coded individual-level data that do not allow researchers to identify participants are available upon request to researchers who meet the criteria for data sharing of the CoLaus|PsyCoLaus Datacenter (CHUV, Lausanne, Switzerland). Any researcher affiliated with a public or private research institution who complies with the CoLaus|PsyCoLaus standards can submit a research application to research.colaus@chuv.ch or research.psycolaus@chuv.ch. Proposals will be evaluated by the Scientific Committee (SC) of the CoLaus|PsyCoLaus study. Detailed instructions for gaining access to the CoLaus|PsyCoLaus data used in this study are available at www.colaus-psycolaus.ch/professionals/how-to-collaborate/.

Previous presentation of information reported in the manuscript

Information reported in this manuscript has been presented as a poster at the Day of Clinical Research, University of Bern, Bern, Switzerland on 17 December 2023 and at the Schweizerische Gesellschaft für Allgemeine Innere Medizin (SGAIM) spring congress in Basel, Switzerland on 30 May 2024.

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