Primary cardiovascular risk prediction by LDL-cholesterol in Caucasian middle-aged and older adults - a joint analysis of three cohorts

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ABSTRACT AND KEYWORDS

Aims

Low density lipoprotein cholesterol (LDL-C) is an established causal driver of atherosclerotic cardiovascular disease (ASCVD), but its performance and age-dependency as a biomarker for incident events and mortality arising from ASCVD is less clear. The aim was to determine the value of LDL-C as a susceptibility/risk biomarker for incident coronary heart disease (CHD), ASCVD and stroke events and deaths, for the age groups <50 and ≥50 years.

Methods and results

The performance of LDL-C was evaluated in three cohorts, FINRISK 2002 (n=7,709), HUSK (n=5,431), and ESTHER (n=4,559), by Cox proportional hazards models, C-statistics and net reclassification index calculations. Additionally, the hazard ratios (HRs) for the three cohorts were pooled by meta-analysis. The most consistent association was observed for CHD (95% confidence interval (CI) for HRs per standard deviation (SD) ranging from 0.99 to 1.37), whereas the results were more modest for ASCVD (0.96-1.18) due to lack of association with stroke (0.77-1.24). The association and discriminatory value of LDL-C with all endpoints in FINRISK 2002 and HUSK were attenuated in subjects 50 years and older (HRs (95% CI) obtained from meta-analysis 1.11 (1.04-1.18) for CHD, 1.15 (1.02-1.29) for CHD death, 1.02 (0.98-1.06) for ASCVD, 1.12 (1.02-1.23) for ASCVD death and 0.97 (0.89-1.05) for stroke).

Conclusion

In middle-aged and older adults, associations between LDL-C and all the studied cardiovascular endpoints were relatively weak, while LDL-C showed stronger association with rare events of pre-mature CHD or ASCVD death among middle-aged adults. The predictive performance of LDL-C also depends on the studied cardiovascular endpoint.

Keywords

LDL, cholesterol, risk, prediction, performance, guideline

INTRODUCTION

According to the European 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias, the SCORE risk assessment system including total cholesterol (TC) should be used to evaluate the 10-year cumulative risk of a first fatal atherosclerotic event, while low-density lipoprotein cholesterol (LDL-C) is recommended to be used as the primary lipid analysis for screening, diagnosis and management of cardiovascular risk.[1] Indeed, LDL-C is an established risk biomarker to identify an increased risk of developing coronary heart disease (CHD) or its complications.[2] The guidelines recommend screening for dyslipidaemias especially in the middle-aged and older population, i.e. in all adult men ≥40 years and in women ≥50 years or post-menopausal, particularly in the presence of other risk factors.[1] In addition, screening is always indicated in subjects with clinical manifestations of atherosclerotic cardiovascular disease (ASCVD), in clinical conditions associated with increased risk for ASCVD, and whenever risk factor screening is considered.[1]

The European guidelines outline that in subjects with low risk, the target for LDL-C is <3.0 mmol/L (115 mg/dL) and for subjects with a moderate risk, the LDL-C goal is set to <2.6 mmol/L (<100 mg/dL).[1] For high and very high-risk subjects both in primary and secondary prevention the LDL-C targets are <1.8 mmol/L (<70 mg/dL) and <1.4 mmol/L (<55 mg/dL), respectively, or >50% LDL-C reduction from baseline with a therapeutic regimen. In the US, the 2018 Cholesterol Clinical Practice Guidelines outline that optimal LDL-C levels are below 2.6 mmol/L (100 mg/dL) and that after age 20 years, the traditional risk factors should be assessed every 4 to 6 years.[3] The basis for risk estimation is the pooled cohort equations (PCE) risk estimator, which incorporates TC, as recommended by the 2019 Guideline on the Primary Prevention of Cardiovascular Disease.[4]

We have previously observed that the prognostic value of LDL-C was weak in subjects with established CHD.[5,6] The large scale SWEDEHEART registry study involving 25,643 first-ever MI patients has also questioned the importance of LDL-C levels achieved at first revisit after myocardial infarction for decisions on continued treatment intensity, based on evidence of weak association with recurrent ASCVD events.[7] Furthermore, in a large Danish cohort study, higher LDL-C was even suggested to be associated with decreased mortality risk in older adults (aged 50+).[8]

Altogether, these observations highlight the need for an in-depth evaluation of LDL-C as a risk marker in primary prevention cohorts, with a particular attention to the influence of age. Hence, we investigated the associations of LDL-C with CHD, CHD death, fatal and non-fatal stroke, ASCVD, and ASCVD death in three independent primary prevention studies from Finland, Norway and Germany and pooled the results thereafter distinctly for the age-groups <50 and ≥50 years with random-effects meta-analyses.

METHODS

Definition of endpoints

For all three cohorts, the definitions of the endpoints were as follows: *Coronary heart disease (CHD):* A) I20–I25, I46, R96 or R98 (ICD-10) or 410–414 or 798 (ICD-9) as cause of death, or I200, I21–I22 (ICD-10) or 410, 4110 (ICD-9) as the main or secondary diagnosis at hospital discharge, or coronary bypass surgery or coronary angioplasty at hospital discharge or identified from the specific country-wide register of invasive cardiac procedures. *CHD death:* death due to CHD. *Stroke:* Stroke (intracerebral haemorrhage, cerebral infarction), excluding subarachnoid haemorrhage: I61, I63, I64 except I63.6 (ICD-10) or 431, 4330A, 4331A, 4339A, 4340A, 4341A, 4349A, 436 (ICD-9) as the cause of death or as the main or secondary diagnosis at hospital discharge. *Atherosclerotic cardiovascular disease (ASCVD) event:* CHD or stroke. *ASCVD death:* death due to ASCVD.

Design of the study cohorts

The National FINRISK Study, including a questionnaire and health examination with blood draw, has been performed every 5 years since 1972 mainly to monitor trends in cardiovascular risk factors in the Finnish population.[9] The FINRISK 2002 study is a stratified random sample of the population aged 25-74 years from specific geographical areas of Finland, as described recently in detail.[9,10] The participants were advised to fast for 4 h or longer and to avoid heavy meals earlier in the day. Serum was separated and the cholesterol measurements were performed immediately.[9] The participants were followed through 31 December 2014, i.e. for up to 13 years.

The Hordaland Health Study (HUSK) is a community-based study conducted in Hordaland County, Western Norway (http://husk.b.uib.no).[11] The present study cohort comprised 7051 men and women born during 1925–1927 or 1950–1951 who participated HUSK in 1997-99, and who had also participated in the Hordaland Homocysteine Study in 1992–1993.[12] The baseline for the current analyses was in 1997-99, when participants underwent a brief health examination and answered self-administered questionnaires. The cohort was then followed for endpoints until 31 December 2009 (the end of follow-up). Non-fasting blood samples were collected at baseline and stored at -80°C until analysis.

In the ESTHER (Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung) study, 9,940 adults aged 50-75 years (median 61 years) with their first residence in the federal state of Saarland, Germany, were recruited at their general practitioners (GPs) office while doing a health check-up (a general health screening examination offered every two years for people older than 35 years in Germany), during years 2000-2002. Furthermore, the participants completed a comprehensive self-administered questionnaire and fasting or non-fasting biological samples (blood, stool, urine) were collected. In addition, comprehensive medical data including results of physical assessment, medical diagnoses and drug prescriptions were obtained from the general practitioner.

The study cohorts are described in more detail in Supplementary Methods.

Statistical analyses

Multivariate Cox proportional hazard regression models with baseline age as time scale were used to determine hazard ratios (HRs) and 95% confidence intervals for the associations of LDL-C with incident events. The HRs for LDL-C were expressed as per one standard deviation increment (SD; 0.9 mmol/L (35 mg/dL) in FINRISK 2002; 0.9 mmol/L (37 mg/dL) in ESTHER; 0.97 mmol/L (37.5 mg/dL) in HUSK). The Cox model was stratified by sex, age at baseline was used as timescale, and the model was adjusted for type 2 diabetes mellitus, current smoking, BMI and lipid-lowering treatment. In sensitivity analyses, lipid-lowering treatment was taken into account by several means, i.e. i) constructing the model only for the

population not on lipid-lowering treatment at baseline, ii) additionally, censoring the follow-up at the time when the lipid-lowering treatment was first taken; and iii) dividing the baseline LDL-C concentrations of the subjects on lipid-lowering treatment by 0.6, consistent with a recent publication[13]. To illustrate the variation of HRs by age in FINRISK 2002, the HRs were estimated for each age ± 10 years. If there were fewer than 10 events in one age group, the result was not illustrated. C-statistics calculations for Cox regression models together with the net reclassification index (NRI) calculations were performed in FINRISK 2002 using the *Hmisc* package. For these analyses, variables and risk category cut-offs were based on the SCORE risk charts recommended by ESC guidelines[1]. For heart failure and stroke, the risk category cut-offs were adjusted by the number of events as compared to fatal ASCVD events. All tests were two-sided and R version 4.0.2 was used for all statistical analyses, except for the meta-analyses.

Additional statistical methods are described in Supplementary Methods.

RESULTS

Concentration of LDL-C in the three cohorts

LDL-C was investigated in three population-based study cohorts, FINRISK 2002, ESTHER and HUSK, from which subjects with prevalent ASCVD were excluded for the present analyses. The baseline characteristics of the cohorts are shown in **Table 1**. The HUSK cohort consists of a middle-aged (46-47 years) and older sub-population (70-72 years). In the ESTHER cohort, all study participants are older adults (50-74 years). For better comparison of results between the cohorts, analyses with the FINRISK 2002 study, which covers a wide age-range from 25 to 74 years, were also performed separately for subjects <50 and ≥50 years of age at baseline. Baseline LDL-C levels of subjects with incident cardiovascular events and with no incident ASCVD as well as full descriptive statistics are shown in **Supplementary Tables S1-S3**.

[TABLE 1]

In an analysis only performed on the FINRISK 2002 data, LDL-C concentrations increased along with age until a plateau was reached at an approximate age of 50 and 60 years among men and women, respectively

(**Supplementary Figure S1**). Women had lower median LDL-C serum concentration than men until they were approximately 65 years old. When baseline LDL-C distribution is visualized in dot plots stratified by study, sex, age-group, and incident ASCVD status, the majority of the populations had LDL-C between 2.5-5.0 mmol/l (**Figure 1**). However, the majority exceeded the ESC guideline LDL-C target for low-risk (3.0 mmol/L, 116 mg/dL). Furthermore, baseline LDL-C concentrations did not seem to differ markedly between subjects with and without subsequent incident ASCVD events during follow-up. The dot plots stratified for all analyzed cardiovascular outcomes are shown in **Supplementary Figures S2-S4**.

[FIGURE 1]

In the older (sub)cohorts (FINRISK 2002, 50-74 years; HUSK, 70-72 years; and ESTHER 50-75 years), the median LDL-C concentrations in subjects without incident ASCVD during follow-up ranged from 3.5 to 4.2 mmol/l (135 – 162 mg/dL) (**Supplementary Tables S1-S3**). Consistently in all studies, the median baseline LDL-C concentrations in subjects with different incident cardiovascular events were either the same or at maximum of 0.2 mmol/l higher as compared to those without incident events during the follow-up. However, in the middle-aged subcohorts (FINRISK 2002, 25-50 years; HUSK, 46-47 years), the median baseline LDL-C concentrations for subjects without incident events ranged between 3.1 – 3.6 mmol/l (120 – 140 mg/dL), and apart from stroke (fatal and non-fatal), the medians for subjects with other incident cardiovascular events were considerably higher, between 3.6 – 4.4 mmol/l (120 – 170 mg/dL) range.

Risk curves analysis in FINRISK 2002 demonstrated that the risk of incident CHD and ASCVD events increased along with LDL-C concentration in subjects aged below 50 years, and the increase was evident especially in subjects with LDL-C above 4 mmol/L (160 mg/dL) (**Figure 2A**). However, the event rate of other endpoints, particularly fatal CHD/ASCVD and stroke did not differ across increasing LDL-C concentrations, but it should be noted that there was small number of events for these endpoints (**Supplementary Table S1**). Furthermore, the risk curves indicated a rather constant event rate for all endpoints in subjects aged 50 years or above, irrespective of LDL-C concentration. In HUSK, for increasing LDL-C levels, the risk for ASCVD events slightly decreased in the old cohort, while a slight increase was

observed in the middle-aged cohort (**Figure 2B**). For all other endpoints, the event rate remained rather stable regardless of baseline LDL-C concentration. The ESTHER cohort included only older study subjects and the curves were rather stable, which were similar to those drawn for the older age groups in FINRISK 2002 and HUSK (**Figure 2C**). The overall results were essentially similar in sensitivity analyses after applying adjusted LDL-C concentrations (divided by 0.6 for those on lipid-lowering treatment at baseline), yet for some endpoints (CHD, ASCVD) a more positive trend for LDL-C and higher risk was observed (**Supplementary Figure S5**).

[FIGURE 2]

Association of LDL-C with cardiovascular events

To assess the associations of LDL-C with cardiovascular endpoints, we estimated hazard ratios (HRs) for each cohort and stratified results by age-group (<50 / ≥50 years) and the age-specific results were pooled by meta-analysis (**Table 2**). For stroke, there was an inverse trend in FINRISK 2002 whereas no association was observed in HUSK or ESTHER. In FINRISK 2002 and HUSK, LDL-C showed strongest association with CHD, and in ESTHER with CHD death. Regarding other endpoints, the associations were positive but variable among the studies.

[TABLE 2]

In the meta-analysis for study participants aged <50 years, LDL-C showed strong associations with CHD death and ASCVD death but the event rate for fatal events was very low, since only 11 and 8 ASCVD deaths were recorded in the middle-aged sub-cohorts of FINRISK 2002 and HUSK, respectively. For CHD and ASCVD there was variability in the positive association between the FINRISK 2002 and HUSK cohorts, and for stroke there was a negative trend in FINRISK 2002 but positive in HUSK. In the meta-analysis for study participants aged ≥50 years, LDL-C was also associated with CHD death and ASCVD death, in addition to CHD. HR point estimates from the three cohorts were very similar but the levels of statistical significance varied. As for the total cohorts, also in the older population, LDL-C showed strongest associations with CHD

in FINRISK 2002 and with CHD death in the ESTHER study. For all endpoints, the HRs were generally attenuated in the older compared to the younger subjects.

Results from sensitivity analyses for the total FINRISK and HUSK cohorts are shown in **Supplementary Tables S4 and S5**, respectively. The strengths of the associations between LDL-C and different outcomes remained practically unchanged after excluding subjects on lipid-lowering treatment at baseline, or after excluding subjects on lipid-lowering treatment at baseline or during the follow-up. For the ESTHER study, another sensitivity analysis was performed: results were also practically unchanged after excluding subjects with non-fasting blood samples (**Supplementary Table S6**). Finally, analysis performed in FINRISK showed that the results were consistent for men and women (**Supplementary Table S7**) and models adjusted additionally with systolic blood pressure and TC did not show markedly different results (**Supplementary Table S8)** than those presented in **Table 2.**

Predictive performance of LDL-C for cardiovascular events according to baseline age

We visualized the potential variation in the strength of the associations between LDL-C and cardiovascular outcomes in FINRISK 2002 according to baseline age (**Figure 3**). For incident CHD and ASCVD events, the HRs were attenuated with increasing age, especially in 40-45 year-old subjects after which the HRs remained more stable. However, plots for CHD deaths and ASCVD deaths need to be interpreted with caution due to the low number of events in young subjects. For stroke, the HRs did not differ according to age.

[FIGURE 3]

The added predictive value of LDL-C on top of a basic ASCVD risk model

In FINRISK 2002, the incremental value of LDL-C, when added to a basic ASCVD risk model which consisted of the variables in the European SCORE risk assessment, incorporating age, sex, current smoking status, systolic blood pressure and TC, was evaluated by 10-year C-statistics and net reclassification index (NRI) analyses. In the full cohort, addition of LDL-C to the basic model did not improve C-statistics clinically significantly for any investigated endpoint (**Table 3**). When TC was omitted from the basic model,

however, for CHD there was an increase from 0.802 to 0.819 in subjects <50 years old (**Supplementary Table S9**).

[TABLE 3]

The categorical NRI was not statistically significantly improved for any of the investigated endpoints, except for CHD in subjects aged <50 years. For continuous NRI, higher reclassifications were observed than for categorical NRIs, and the highest was recorded for CHD in subjects <50 years old (**Table 3, Supplementary Table S8**).

DISCUSSION

Epidemiological studies, Mendelian randomization data, and randomized controlled trials (RCTs) have consistently demonstrated a log-linear relationship between plasma LDL-C levels and the risk of ASCVD.[1,14,15] Due to the consistency across those studies and additional biological and experimental evidence, it has been concluded that LDL-C is causally associated with the risk of ASCVD.[1] In the present study, we evaluated the role of LDL-C as a ASCVD risk biomarker in almost 18,000 subjects without prior ASCVD and showed that the predictive abilities for LDL-C depend on the cardiovascular outcome and the person's age. However, except for an association with fatal ASCVD in subjects younger than 50 years, which needs to be interpreted with caution due to a low number of cases, the associations of LDL-C with incident cardiovascular endpoints were relatively weak in both middle-aged and older individuals.

The present results may appear surprising given the comprehensive literature on the positive relationship of LDL-C with ASCVD. Mendelian randomization have evaluated associations between atherosclerotic phenotypes and genetic variants correlating with serum LDL-C levels, and demonstrated association between LDL-C and atherosclerosis disease burden.[16] However, it should be noted that these kinds of analyses do not reveal the risk prediction performance of a biomarker, which can only be analyzed using study cohorts reflecting real-life situation. Thus, our approach is complementary to the causality demonstrations. In Mendelian randomization studies the genes of interest have been LDL-receptor and *PCSK9* genes that

undoubtedly associate with progression of atherosclerosis. It should be noted that this approach is not LDL-C specific, as it can be applied to all lipid and protein species embedded in the LDL-particles. LDL-particles are known to be carrier particles for hundreds of different lipid species in addition to several distinct cholesteryl esters.[17–20] The relative importance of these species still remain to be studied.

A recent meta-analysis of 244,000 patients from 29 randomized clinical trials (RCTs) showed that LDL-C reduction reduced all key CV endpoints, including MI, stroke, coronary revascularization, and CV death.[21] The analysis looked at patients older and young than 75 years and found consistent benefit from LDL-C reduction in both middle-aged and elderly adults.[21] Similarly to Mendelian randomization studies, simultaneous lowering of cholesterol and a large number of other lipid species does not describe the risk prediction performance of LDL-C. Importantly, RCTs rarely report baseline LDL-C associations with the CVD phenotypes of interest. However, the LIPID[22]and JUPITER[23] trials are examples where statins reduce significantly CVD events but in the placebo arms baseline LDL-C was not associated with CVD death or CVD, respectively.

Cohort studies and RCTs often use different CVD outcomes or their combinations, which may lead to diverse conclusions. It is plausible that different biomarkers should be used to determine risk of premature atherosclerosis or atherosclerotic plaque rupture. Our results suggest that LDL-C is useful for screening early atherosclerosis risk in relatively young individuals, while its importance diminishes in older subjects and more advanced disease stage. Angina pectoris, non-fatal MIs and revascularizations may be considered as atherosclerosis development-related phenotypes, while CVD death as plaque rupture-related phenotype in high risk patients. For example, in 346,686 individuals without baseline CVD or statin use from the UK Biobank, LDL-C was significantly associated with an increased risk of CVD (adjusted HR per 1-SD of 1.20 (95% CI 1.17, 1.23), $p<0.001$) when fatal and non-fatal CVD endpoints were combined.[24] However, the HR for fatal CVD only (SCORE definition) remained non-significant and LDL-C in subjects experiencing fatal CVD had only 2.2% higher median baseline LDL-C levels than those who did not (3.8 mmol/L (146.8 mg/dL) vs. 3.7 mmol/L (143.7 mg/dL)). In the Copenhagen General Population Study, significant HR values for ASCVD were reported particularly for younger indivuals < 50 years, but the HR values remained

significant also in the elderly.[25] However, another report from the same study cohort revealed a U-shaped LDL-C associations with total mortality and a lack of an association between LDL-C and CVD mortality.[26] It was observed that individuals in the general population with a concentration of LDL-C of 3.6 mmol/L (140 mg/dL) live the longest, and the authors concluded that their results will have important clinical and public health implications, if confirmed in more studies.[26] These observational findings are futher supported by RCTs with statin or anti-PCSK9 interventions, in which risk reduction was primarily achieved for non-fatal endpoints.[27–29] Furthermore, our findings are supported by several other studies, some performed already before wide use of cholesterol lowering medications, that have shown that cardiovascular risk prediction by LDL-C or TC for CHD tend to decrease with increasing age.[30–33] Especially the young adulthood may be the most important time to find individuals with potential life-long exposure to high LDL-cholesterol levels and to start preventive measures.

As current guidelines target cholesterol screening especially to the middle-aged and the older population[34], it should be re-evaluated whether it would be more useful to use LDL-C as a screening marker in the younger to middle-aged adult population (i.e., 18-50 years) instead of the older population (≥ 50 years). For example, the current European SCORE risk assessment system is using total cholesterol as one of the key components to predict fatal CVD events. Based on the present results and other recent large-scale studies, research is needed for an updated risk assessment tool specifically designed for older adults, in which total cholesterol is being replaced by other biomarker(s) with a better predictive value for fatal CVD events. Two recently published studies demonstrate that comprehensive control of known CVD risk factors in high-risk patients is suboptimal worldwide.[35,36] In the DA VINCI study, among patients receiving lipid lowering treatment fewer than half of high/very high-risk primary and secondary prevention patients achieved the 2016 European guideline LDL-C goals, with approximately one-fifth achieving the lower 2019 goals.[36] Due to the observations on the prevalent gap between guideline recommended LDL-C goals and their implementation in clinical care, a greater utilization of non-statin trerapy in combination with statins for patients at highest risk was recommended. However, based on the present results as well as those found in the Copenhagen General Population[26] and the UK biobank[24] studies it has become obvious that it would be valuable for the treating physicians to have also other means and targets available for prevention of serious CVD events.

A limitation of our analysis was that fasting before blood samples were drawn for lipid measurement varied both within and between studies. FINRISK 2002 participants were advised to fast for only 4 hours or longer, while in ESTHER only a part of the population had fasted overnight. However, sensitivity analysis in the ESTHER study revealed that the fasting status had no impact on the results. This is in concordance with a previous study that showed that samples taken 3-5 hours after a meal change LDL-C only minimally[37], further implying that non-fasting samples can be used for risk prediction. However, in HUSK, the LDL-C was calculated using the Friedewald equation, including triglycerides, and therefore the results could be affected due to variable fasting more than FINRISK 2002 and ESTHER studies. Another limitation was that the risk association across age could be analyzed in-depth only in FINRISK 2002, since HUSK had two distinct age groups and ESTHER only older participants. Moreover, since in HUSK the younger subpopulation consisted of 46-47 year old subjects, the mean age of the population was considerable higher than the FINRISK 2002 subcohort under 50 years. Further limitation was that the analyses were performed only for a single LDL-C measurement, but this limitation often applies to the real-life estimation of future events and mortality as well. The trajectory of LDL-C could be considered for assessing the risk of the decades-long process of atherosclerosis, which was not the aim of the present study. It should be also noted that most risk calculators utilize TC instead of LDL-C. The strength of this study was the inclusion of three large primary prevention cohorts and extensive sensitivity analyses and analysis of various endpoints.

In conclusion, the present study raises an important point that is often underappreciated, in that the mechanisms that lead to events (e.g. plaque rupture) may very well be different from those which drive the decades long atherogenic process prior to this point, so it is feasible that LDL-C may simultaneously drive the ASCVD process while also poorly predicting CVD events in later life.

AUTHORSHIP

MH and RL contributed to the conception or design of the work. MH, ID, ML, VL, GS, GST, PJ, OKN, HB, BS and RL contributed to the acquisition, analysis, or interpretation of data for the work. MH, RL and BS

drafted the manuscript. ID, ML, VL, GS, GST, PJ, OKN and HB critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

DISCLOSURE

Zora Biosciences Oy holds patent disclosures related for the diagnostic and prognostic use of ceramides and phospholipids in CVD. M.H., M.L., and R.L. are employees and R.L. a shareholder of Zora Biosciences Oy.

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FIGURE LEGENDS

Figure 1. Dot plot of LDL-C distribution in populations defined by study (**A**) FINRISK 2002, **B)** HUSK and **C)** ESTHER study), sex, age-group, and incident ASCVD event status. Red color indicates median LDL-C and 25-75th percentile. The ESC guideline target for LDL-C in low-risk primary prevention subjects (3.0 mmol/L (116 mg/dL) is shown by a dashed line. In FINRISK 2002, two outliers (8.9 and 9.6 mmol/L, no ASCVD) have been removed from the figures for better readability.

Figure 2. Risk curves according to LDL-C concentration in **A)** FINRISK 2002, **B)** HUSK and **C)** ESTHER studies. The LDL-C target for low risk patients (3.0 mmol/L (116 mg/dL) is shown by a dashed line. The lowest and highest 2.5% of the observations have been censored, as for these the confidence intervals were so wide that no reliable conclusions can be drawn. CHD, coronary heart disease; ASCVD, atherosclerotic cardiovascular disease.

Figure 3. Hazard ratios per standard deviation of LDL-C concentration for incident cardiovascular events with increasing age in the FINRISK study. The HRs were calculated for each age shown in the x-axis +/-10 years. If there were fewer than 10 events in the age group, the result was excluded. In the models, baseline age was used as the time scale, sex for stratification, and the models were adjusted for lipid-lowering treatment, prevalent diabetes, current smoking status and BMI. The range of LDL-C standard deviations across different age groups was from 0.86 mmol/L (33 mg/dL) to 0.90 mmol/L (35 mg/dL). CHD, coronary heart disease; ASCVD, atherosclerotic cardiovascular disease.

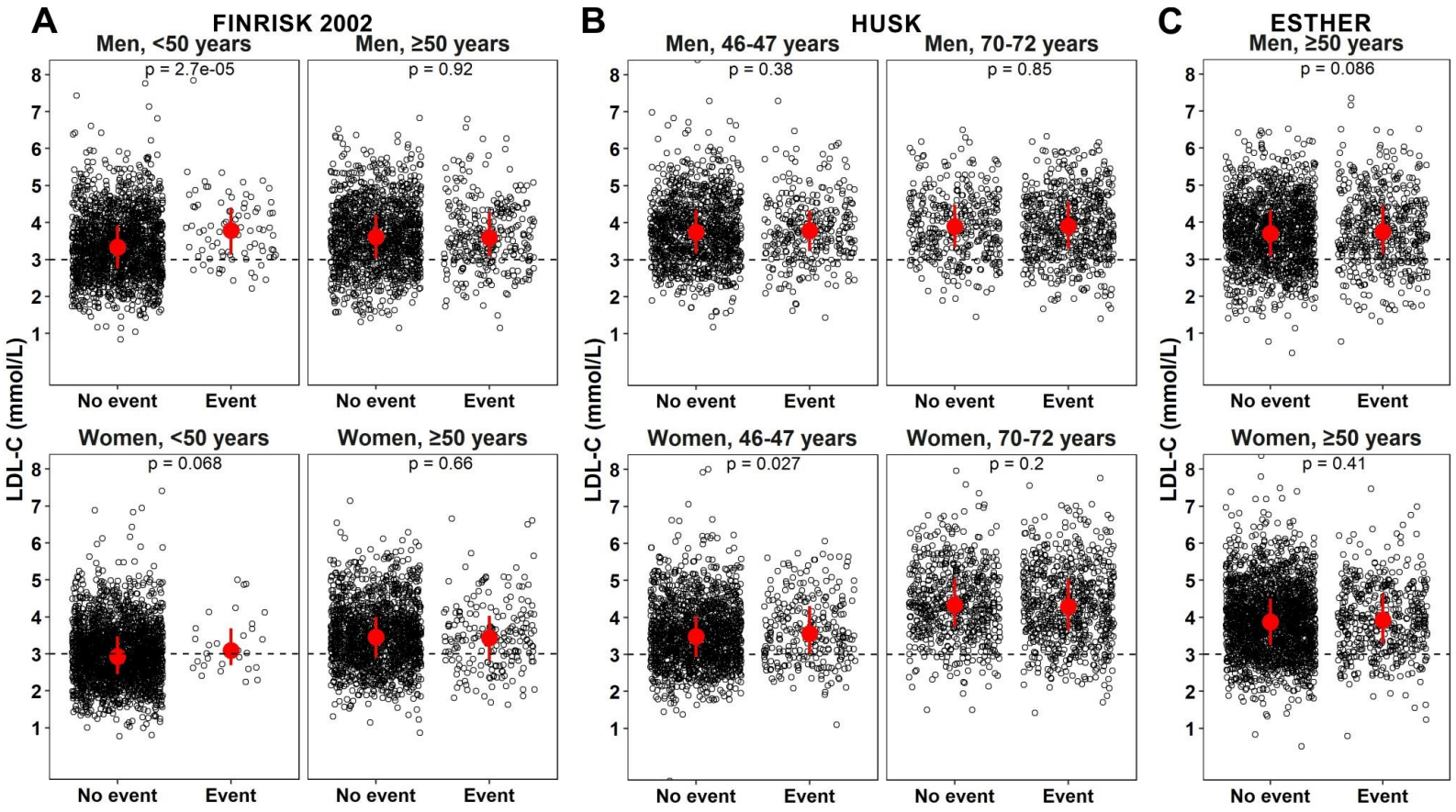
A
FINRISK 2002
Men, <50 years
p = 2.7e-05
Men, ≥50 years
p = 0.92
Women, <50 years
p = 0.068
Women, ≥50 years
p = 0.66
B
HUSK
Men, 46-47 years
p = 0.38
Men, 70-72 years
p = 0.85
Women, 46-47 years
p = 0.027
Women, 70-72 years
p = 0.2
C
ESTHER
Men, ≥50 years
p = 0.086
Women, ≥50 years
p = 0.41
LDL-C (mmol/L)
No event
Event

Figure 1

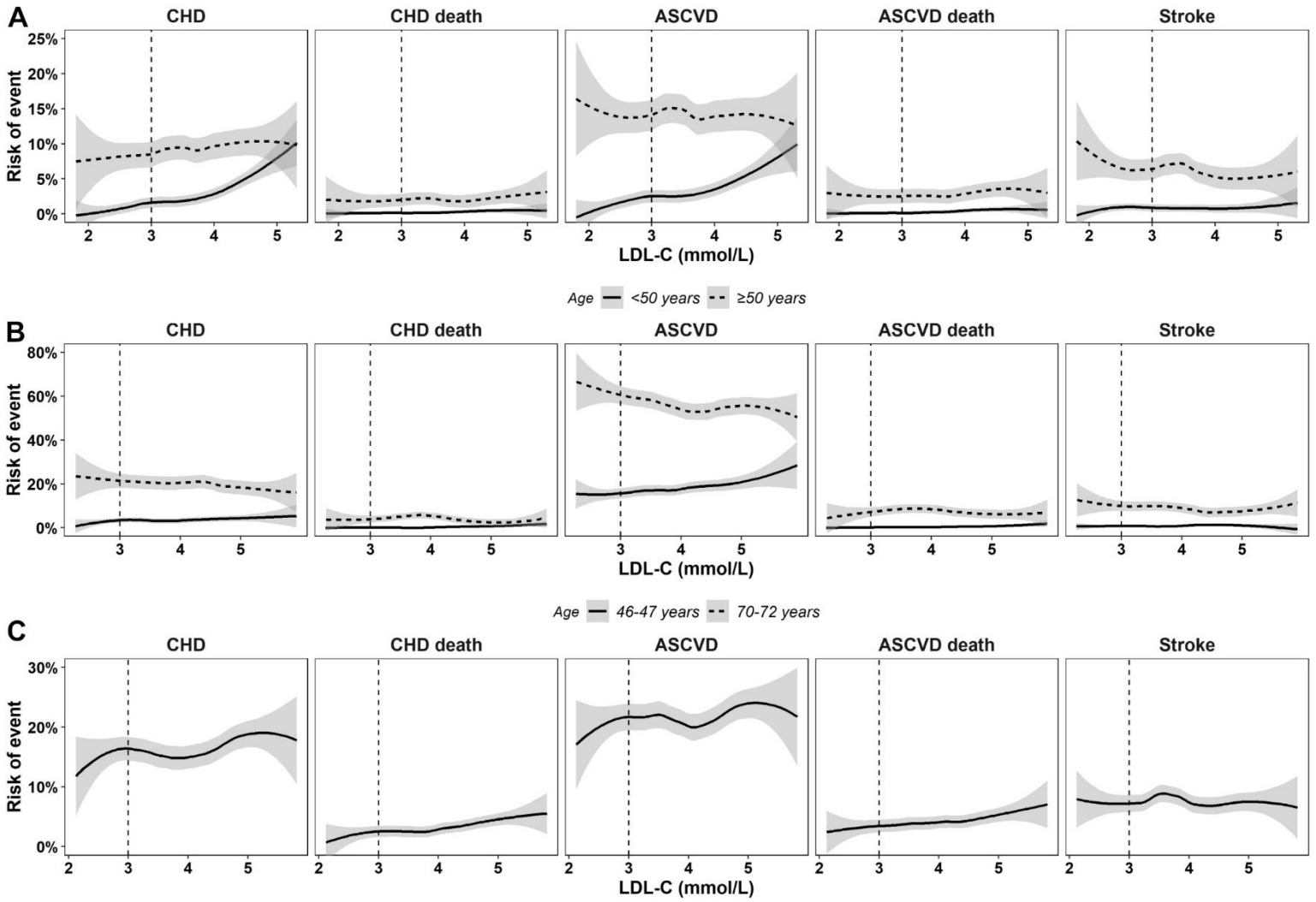
A
CHD
CHD death
ASCVD
ASCVD death
Stroke
Risk of event
25%
20%
15%
10%
5%
0%
2
3
4
5
LDL-C (mmol/L)
Age <50 years ≥50 years
B
CHD
CHD death
ASCVD
ASCVD death
Stroke
Risk of event
80%
60%
40%
20%
0%
3
4
5
LDL-C (mmol/L)
Age 46-47 years 70-72 years
C
CHD
CHD death
ASCVD
ASCVD death
Stroke
Risk of event
30%
20%
10%
0%
2
3
4
5
LDL-C (mmol/L)

Figure 2

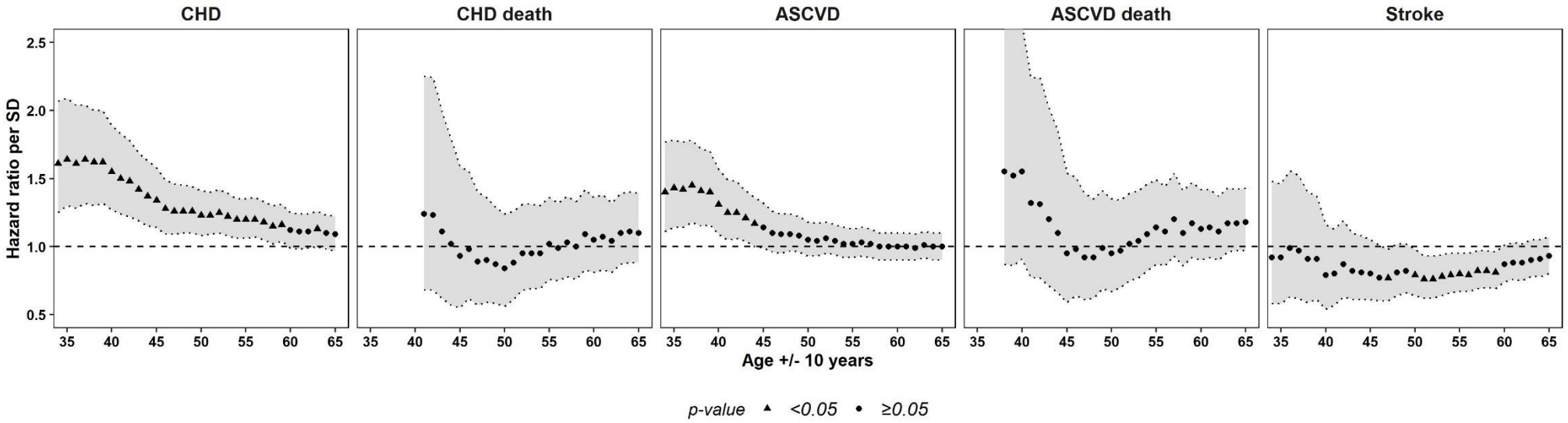
CHD
CHD death
ASCVD
ASCVD death
Stroke
Hazard ratio per SD
2.5
2.0
1.5
1.0
0.5
35
40
45
50
55
60
65
Age +/- 10 years
p-value
<0.05
≥0.05

Figure 3