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Lipid Disorders

The impact of estimated small dense low-density lipoprotein cholesterol on all-cause mortality across the low-density lipoprotein cholesterol spectrum – analysis of longitudinal LIPIDOGRAM studies of Polish primary care patients

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Abstract

Introduction: The small dense low-density lipoprotein cholesterol (sdLDL-C) fraction has been shown to be significantly more atherogenic than large buoyant low-density lipoprotein cholesterol, but its estimation or measurement has not found widespread clinical use. In this study, we aimed to assess the association of sdLDL-C with mortality of Polish primary care patients.
Material and methods: This study analyzed 45,585 patients from Polish nationwide LIPIDOGRAM 2004, 2006, and 2015 cross-sectional studies of primary care patients. Median follow-up was 15.3 years. sdLDL-C was estimated using the method published by Sampson *et al.* Mortality was analyzed in the primary prevention group without major cardiovascular diseases and across low-density lipoprotein cholesterol (LDL-C) quintiles.
Results: Median estimated sdLDL-C was 1.04 mmol/l (IQR: 0.82; 1.31). Multivariable analysis of LIPIDOGRAM2015 subgroup revealed significant negative correlations with statin use, previous myocardial infarction, and high-density lipoprotein cholesterol. sdLDL-C was significantly associated with mortality across all LDL-C quintiles except the first quintile ($p < 0.001$). In the population without major cardiovascular diseases (CVD) of 35,409 patients, elevated sdLDL-C (above the 80th percentile; > 1.38 mmol/l) displayed a significant relationship with increased mortality ($p < 0.001$). In the univariable, spline-based analysis of this subgroup, the relationship between sdLDL-C and mortality was approximately linear, although the multivariable analysis showed a U-shaped curve with the lowest mortality at 1.05 mmol/l.
Conclusions: sdLDL-C appears to be significantly associated with longterm mortality beyond elevated LDL-C and in patients without major CVD. Further research is needed to establish causal relationship with CVD and treatment targets.

Key words: small dense LDL, mortality, survival, sdLDL, sdLDL-C, clinical characteristics.

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is caused by apolipoprotein B100 (ApoB)-containing lipoprotein [1]. Although direct ApoB measurement has been shown to be one of the most reliable markers of ASCVD risk, ApoB-containing lipoprotein particles belong to several fractions, which differ in their biological properties and atherogenic potential [1].

The most significant lipoprotein fraction responsible for ASCVD is the low-density lipoproteins (LDL). Although they do not represent the entirety of ApoB-containing lipoprotein burden, LDL cholesterol (LDL-C) remains both a key component of ASCVD risk and treatment goal assessment [2]. LDL-C can be measured directly or estimated using Friedewald, Sampson-National Institute of Health (Sampson-NIH), or Martin-Hopkins equations [3–5]. To complicate matters further, LDL can be further subdivided into small dense LDL (sdLDL) and large buoyant LDL (lbLDL). sdLDL are significantly more atherogenic than lbLDL [6, 7]. Direct measurement of sdLDL cholesterol (sdLDL-C) is not usually available, but an estimation is possible based on the equation derived by Sampson *et al.* [8].

The size of LDL particles depends on several factors. Several proteins and enzymes are responsible for blood cholesterol homeostasis and variants in their genes affect lipid and lipoprotein metabolism. Among these, the LDL receptor (LDLR) is responsible for hepatic LDL clearance; lipoprotein lipase mediates triglyceride hydrolysis; cholesteryl ester transfer protein exchanges cholesterol esters and triglycerides between ApoB-containing lipoproteins and HDL particles; and microsomal triglyceride transfer protein lipidates ApoB during the formation of nascent VLDL particles. Several apolipoproteins, such as ApoC-II, ApoC-III, and ApoA-V, also participate in these processes [9].

Increased numbers of sdLDL particles are closely related to atherogenic dyslipidemia, characterized by increased triglycerides, very low-density lipoproteins (VLDL), VLDL remnants, and intermediate-density lipoproteins (IDL) as well as low high-density lipoprotein (HDL) cholesterol levels [9].

High-carbohydrate diets promote formation of small dense LDL in at least some patients [10, 11]. Hypertriglyceridemia correlates with sdLDL-C concentration and the mechanism behind this association is mediated by the simultaneous action of CETP and hepatic lipase – CETP transfers cholesterol esters away from LDL lipoproteins and replaces them with triglycerides which are subsequently removed by hepatic lipase [12]. The net result is an sdLDL particle with low lipid content, small size and high density. Insulin resistance appears to promote sdLDL formation because it potentiates hypertriglyceridemia as well as hepatic VLDL production and secretion [12].

In the present study we sought to analyze the relationship between sdLDL-C and clinical characteristics of Polish primary care patients and assess the impact of sdLDL-C on all-cause mortality.

Material and methods

The LIPIDOGRAM 2004, 2006, and 2015 were a series of cross-sectional studies conducted in Poland [13, 14]. In 2004, a total of 675 primary care physicians actively enrolled 17,522 individuals in 444 cities. In 2006, 556 primary care practitioners from 402 Polish cities recruited a total of 15,465 patients, while in 2015, a group of 438 physicians also in primary care practices recruited an additional 13,724 patients [13–15]. Participating physicians were distributed in proportion to the population of each of the voivodeship-level administrative regions. Follow-up data were collected up to December 2021 based on National Health Fund data. Follow-up data were available for 44,620 patients (97.8%, median duration: 15.3 years). Details of each study were published previously [13–15].

lbLDL cholesterol (lbLDL-C) and sdLDL-C levels were computed based on equations published by Sampson et al. sdLDL-C was calculated as the difference between LDL-C and lbLDL-C. The cut-off for elevated sdLDL was set at the 80th percentile, based on the work of Sampson *et al*. [8].

Participants with computed lbLDL-C values below 0.1 mmol/l (n = 5) and sdLDL below 0.25 mmol/l (n = 1) were excluded from further analyses and treated as outliers with negative or implausibly low values to whom sdLDL-C estimation method cannot be reliably applied. Patients were assumed to exhibit elevated sdLDL-C according to the criterion published by Sampson *et al*. – that is, above the 80th percentile [8].

Statistical analysis

Groups with elevated and non-elevated sdLDL-C were compared using standard Welch's t test, Welch's t test of log-transformed values, Wilcoxon rank-sum test, or Fisher's exact test. The normality assumption was assessed by inspecting Q-Q plots.

Univariable and multivariable linear regression analyses were performed to establish which clinical characteristics correlate with sdLDL-C. The multivariable analysis for clinical characteristics was conducted by iteratively removing variables exceeding a variance inflation coefficient threshold of 10 and was applied exclusively to LIPIDOGRAM2015 participants due to data availability [15].

Next, we focused on the primary prevention group. We excluded patients who sustained (1) myocardial infarction (MI) or (2) stroke, had (3) chronic kidney disease (CKD), (4) heart failure (HF), or (5) diagnosed coronary artery disease (CAD), (6) with follow-up less than 1 year, or (7) on fibrate therapy. Separate Kaplan-Meier curves were constructed for low and high sdLDL-C groups. Survival between these groups was compared using the log-rank test.

Restricted cubic spline-based Cox regression was conducted among the primary prevention group. Separate analyses were conducted for sdLDL-C and LDL-C. Multivariable analysis was adjusted for log-transformed HDL cholesterol (HDL-C), age, sex, waist circumference, diabetes mellitus, education level, hypertension, and smoking.

A further Kaplan-Meier analysis was conducted after stratification by LDL-C quintiles in the whole study population. Patients were divided into sdLDL-C quintiles independently of LDL-C quintiles. A Wald linear test for trend for was applied across sdLDL-C quintiles within each LDL-C quintile. To maintain legibility, these Kaplan-Meier curves show combined second, third, and fourth sdLDL-C quintiles, even though they were tested for trend as separate strata.

All statistical analyses were performed in RStudio. Artificial intelligence was used to aid in writing code which was subsequently verified by a human researcher [16, 17].

Results

A total of 45,585 eligible patients were included in the analysis after duplicate removal. The median sdLDL-C was 1.04 mmol/l (IQR: 0.82–1.31). The 80th percentile cut-off of sdLDL-C was 1.38 mmol/l. A histogram of the sdLDL-C distribution is presented in Figure 1. The lbLDL-C distribution is presented in Supplementary Figure S1. Figure 2 demonstrates the relationship between sdLDL-C and lbLDL-C levels in the form of a scatterplot.

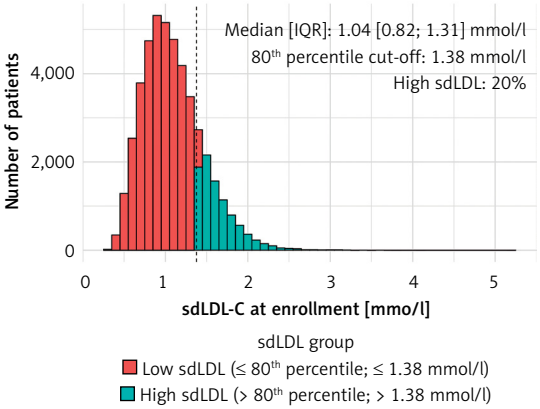

Figure 1. Histogram of small dense low-density lipoprotein cholesterol distribution (sdLDL-C)

Characteristics of participants depending on sdLDL-C levels are presented in Table I. In general, the elevated sdLDL-C group was characterized by higher BMI, waist circumference, fasting glucose as well as increased hypertension, obesity, and smoking prevalence along with a lower prevalence of previous MI (all $p < 0.001$) and no significant difference in statin use ($p = 0.408$).

In the univariable regression analysis, HbA1c, fasting glucose, and metabolic syndrome were strongly correlated with sdLDL-C, while HDL cholesterol (HDL-C), higher education, and female sex were negatively associated with sdLDL-C (Figure 3). Multivariable analysis in the 2015 cohort indicated that factors positively associated with sdLDL-C included smoking, family history of cardiovascular disease, and age, while negative correlations were observed for diabetes, atrial fibrillation, statin use, previous MI, and HDL-C (Figure 4).

In order to further discern the relationship between sdLDL-C and other cardiometabolic factors, we performed a network correlation analysis of patient characteristics (Figure 5). In this analysis, lipid parameters were strongly associated with one another and the non-lipid parameter that was linked to sdLDL-C was BMI.

Next, we compared survival between patients with normal and elevated sdLDL-C within the first 5 years of observation and during the entire observation period in the primary prevention subgroup without major comorbidities (as discussed in the Methods section). The total number of patients included in this analysis was 35,409. Kaplan-Meier curves are presented in Figures 6 and 7. We have found that elevated sdLDL-C was not significantly associated with mortality in the 5-year observation period (log-rank test p-value > 0.05), but the association was significant when evaluated over

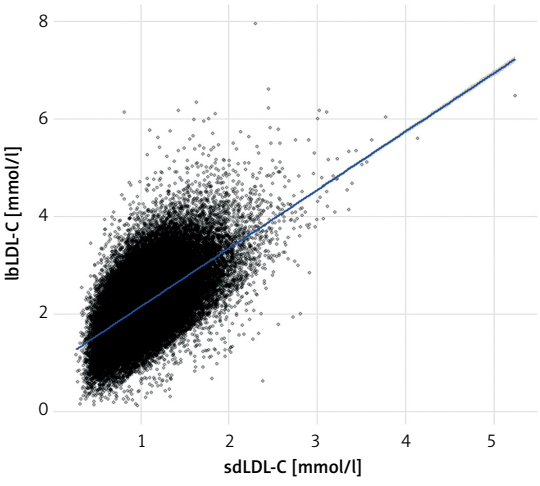

Figure 2. A scatter plot of small dense low-density lipoprotein cholesterol (sdLDL-C) and large buoyant low-density lipoprotein cholesterol (lbLDL-C) concentrations

Table I. Characteristics of participants depending on sdLDL status

Parameter	Total study population	Low sdLDL	High sdLDL	*P*-value
Number of patients	45,585	36,468	9,117	
Age [years]	56.28 ±11.81	56.15 ±12.13	56.78 ±10.43	< 0.001**
Female sex	28140 (61.7%)	22807 (62.5%)	5333 (58.5%)	< 0.001
Higher education	26010 (57.1%)	21143 (58.0%)	4867 (53.4%)	< 0.001
Urban place of residence	25253 (55.4%)	20174 (55.3%)	5079 (55.7%)	0.511
Current smoker	8616 (18.9%)	6500 (17.8%)	2116 (23.2%)	< 0.001
Alcohol consumption	8905 (65.6%)	7071 (64.8%)	1834 (68.5%)	< 0.001
Self-declared physical activity	9165 (30.8%)	7184 (31.0%)	1981 (30.1%)	0.179
BMI [kg/m^2]	27.90 [25.00; 31.20]	27.70 [24.70; 31.00]	28.70 [26.10; 31.70]	< 0.001*
Obesity	24194 (53.1%)	18639 (51.1%)	5555 (60.9%)	< 0.001
Waist circumference [cm]	93.00 [84.00; 102.00]	92.00 [83.00; 100.00]	96.00 [88.00; 103.00]	< 0.001
Systolic blood pressure [mm Hg]	130.00 [120.00; 140.00]	130.00 [120.00; 140.00]	130.00 [120.00; 145.00]	< 0.001*
Diastolic blood pressure [mm Hg]	80.00 [73.00; 87.00]	80.00 [72.00; 85.00]	80.00 [77.00; 90.00]	< 0.001
Hypertension	23499 (51.5%)	18507 (50.7%)	4992 (54.8%)	< 0.001
Glucose	99.00 [90.00; 109.00]	98.00 [90.00; 108.00]	100.00 [92.00; 111.00]	< 0.001*
HbA1c [%]	5.50 [5.20; 5.90]	5.50 [5.20; 5.80]	5.60 [5.30; 5.90]	0.002*
Diabetes	5690 (12.5%)	4571 (12.5%)	1119 (12.3%)	0.512
Metabolic syndrome	17204 (37.7%)	11830 (32.4%)	5374 (58.9%)	< 0.001
Total cholesterol [mmol/l]	5.50 [4.77; 6.28]	5.22 [4.60; 5.83]	6.86 [6.35; 7.45]	< 0.001
LDL-C [mmol/l]	3.28 [2.64; 3.96]	3.03 [2.50; 3.57]	4.45 [3.98; 5.00]	< 0.001
HDL-C [mmol/l]	1.50 [1.25; 1.77]	1.52 [1.27; 1.81]	1.41 [1.21; 1.64]	< 0.001*
Non-HDL cholesterol [mmol/l]	3.94 [3.25; 4.70]	3.67 [3.09; 4.23]	5.39 [5.00; 5.90]	< 0.001
Triglycerides [mmol/l]	1.46 [1.07; 2.02]	1.31 [1.00; 1.73]	2.28 [1.84; 2.90]	< 0.001
sdLDL-C [mmol/l]	1.04 [0.82; 1.31]	0.95 [0.78; 1.14]	1.58 [1.47; 1.76]	< 0.001
Dyslipidemia	22479 (49.3%)	17187 (47.1%)	5292 (58.0%)	< 0.001
Statin treatment	13030 (28.6%)	10456 (28.7%)	2574 (28.2%)	0.414
Fibrate treatment	1594 (3.5%)	1173 (3.2%)	421 (4.6%)	< 0.001
Family history of CVD	4630 (10.2%)	3660 (10.0%)	970 (10.6%)	0.009
Previous myocardial infarction	2706 (5.9%)	2304 (6.3%)	402 (4.4%)	< 0.001
Atrial fibrillation	687 (5.1%)	588 (5.4%)	99 (3.7%)	< 0.001
Chronic kidney disease	382 (2.8%)	299 (2.7%)	83 (3.1%)	0.346

*BMI – body mass index, LDL-C – low-density lipoprotein cholesterol, HDL-C – high-density lipoprotein cholesterol, CVD – cardiovascular disease. Normally distributed variables are provided as mean ± SD, otherwise median [IQR] is provided. Qualitative binary variables were compared with Pearson χ^2 test. Quantitative variables were analyzed with Wilcoxon rank-sum test unless otherwise indicated. *Welch t-test on the corresponding log-transformed variable; **Welch t-test.*

the full observation period (log-rank test *p*-value < 0.0005). The results did not reach statistical significance in the whole population (Supplementary Figure S2). Kaplan-Meier curves for each of the sdLDL-C quintiles assessed separately are presented in Supplementary Figures S3 and S4.

To further analyze the relationship between sdLDL-C and overall mortality, we conducted a spline-based Cox survival analysis in the primary prevention subgroup. This analysis revealed a monotonic and statistically significant relationship between sdLDL-C and hazard ratio (HR)

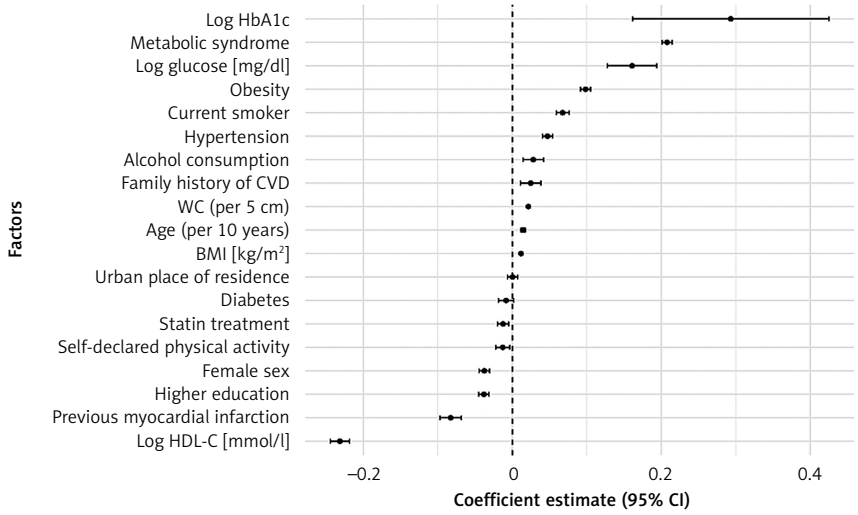

Figure 3. Results of univariable analysis of factors associated with small dense low-density lipoprotein cholesterol (sdLDL-C)

CVD – cardiovascular disease, HDL-C – high-density lipoprotein cholesterol.

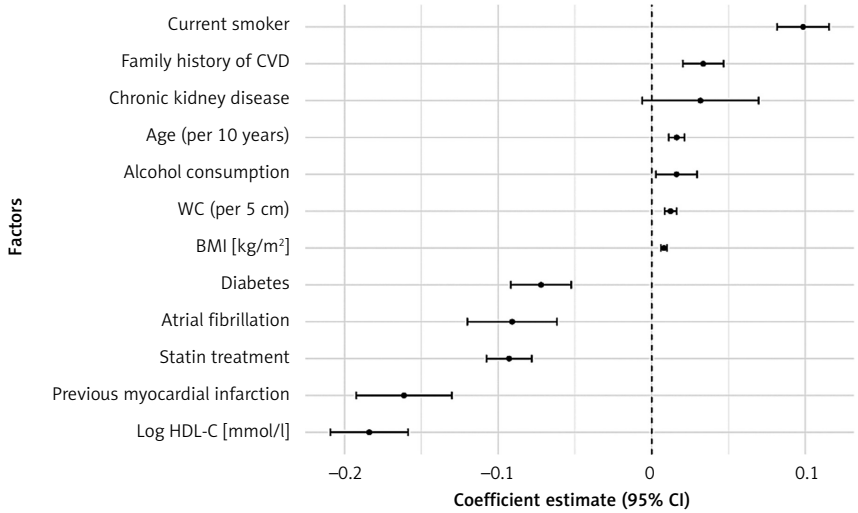

Figure 4. Results of multivariable analysis of factors associated with small dense low-density lipoprotein cholesterol (sdLDL-C) in LIPIDOGRAM 2015 cohort

CVD – cardiovascular disease, BMI – body-mass index, MI – myocardial infarction, HDL-C – high-density.

for all-cause mortality in univariable analysis ($p < 0.001$ in Wald test ANOVA). A U-shaped curve was observed in the multivariable analysis (Figure 8). The results of multivariable analysis for non-sdLDL-C factors are presented in Table II. Unlike sdLDL-C, LDL-C produced a U-shaped HR spline in both the univariable and multivariable analyses (Figure 9, Supplementary Table SI).

To improve our understanding of the prognostic impact of sdLDL-C across a spectrum of total LDL-C, we analyzed the association of sdLDL-C with mortality across LDL-C quintiles (Figure 10). Patients were divided into LDL-C and sdLDL-C quintiles independently. The first quintile of LDL-C did not contain enough patients with high sdLDL-C levels to obtain meaningful conclusions ($n = 8$). Patients with LDL-C values in the second through fifth quintiles had their survival significantly associated with sdLDL-C levels (p for trend < 0.001 across sdLDL-C quintiles). Nevertheless, the fifth quintile of LDL-C contained merely 5 patients in the lowest sdLDL-C quintile, limiting this interpretation (Figure 10).

Discussion

In this study, our principal findings are as follows: (1) in a primary prevention population, sdLDL-C appears to be correlated with long-term survival, (2) given a particular LDL-C level, mortality risk appears to be further related to the level of sdLDL-C.

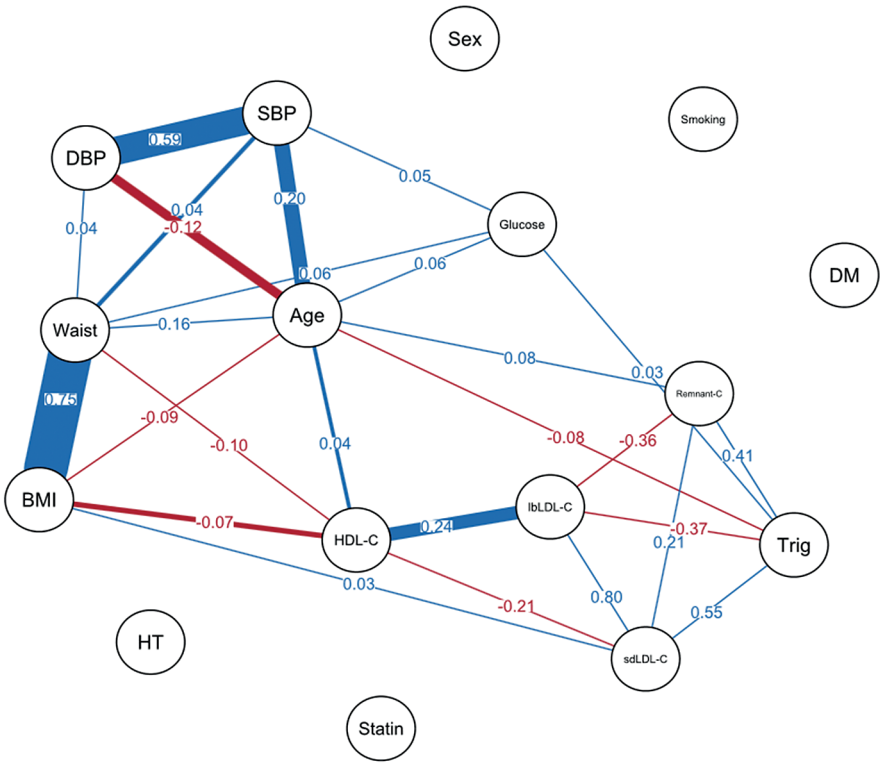

Figure 5. Association network of patient characteristics

BMI – body-mass index, DBP – diastolic blood pressure, DM – diabetes mellitus, HDL-C – high-density lipoprotein, lbLDL-C - large buoyant low-density lipoprotein cholesterol, Remnant-C – non-HDL-C non-LDL-C cholesterol, SBP – systolic blood pressure, sdLDL-C – small dense low-density lipoprotein cholesterol, Trig – blood triglycerides.

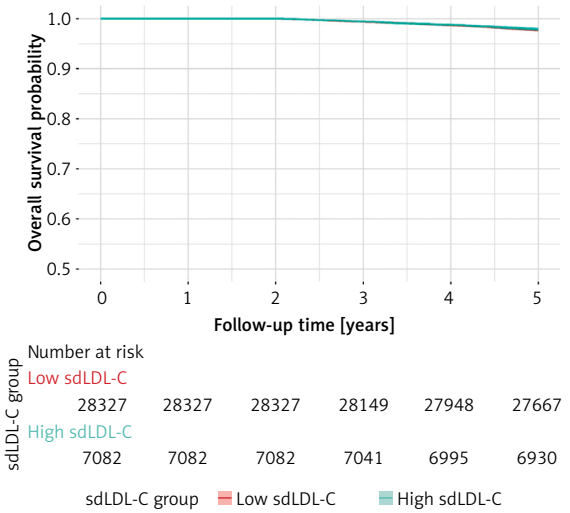

Figure 6. Kaplan-Meier curves for 5-year observation period in primary prevention population (N = 35,409). Red: low sdLDL-group (< 80th percentile). Blue: high sdLDL-group (> 80th percentile). Log rank test p-value = 0.357

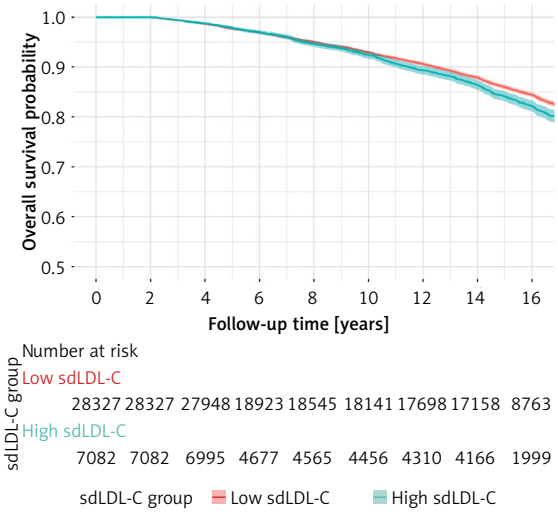

Figure 7. Kaplan-Meier curves for full observation period in primary prevention population (N = 35,409). Low (≤ 80th percentile) small dense low-density lipoprotein cholesterol (sdLDL-C) group (red) had median sdLDL-C levels of 0.96 mmol/l. High (> 80th percentile) sdLDL-C group (blue) had median sdLDL-C levels of 1.58 mmol/l. Log rank test p-value < 0.0005

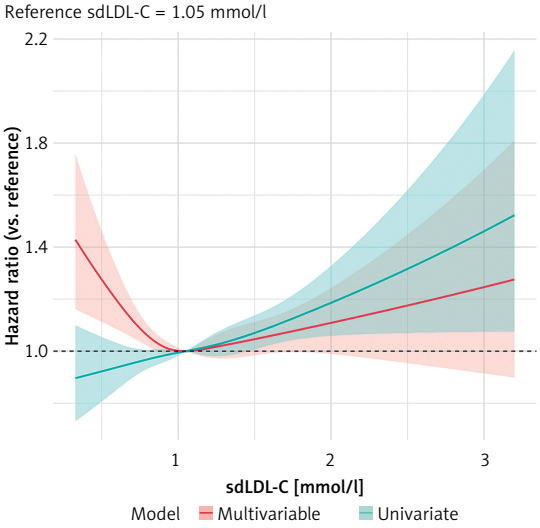

Figure 8. Results of spline-based Cox survival analysis of the impact of small dense low-density lipoprotein (sdLDL-C) on all-cause mortality in primary prevention subgroup (N = 35,409). Shaded areas indicate 95% CI. Multivariable analysis was adjusted for: age, gender, waist circumference, body-mass index, diabetes mellitus, hypertension, log high-density lipoprotein cholesterol, smoking status, and secondary or higher education

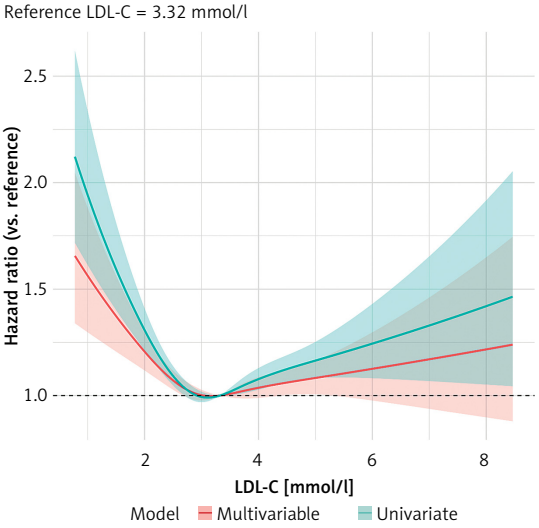

Figure 9. Results of spline-based Cox survival analysis of the impact of small dense low-density lipoprotein (LDL-C) on all-cause mortality in primary prevention subgroup (N = 35,409). Shaded areas indicate 95% CI. Multivariable analysis was adjusted for: age, gender, waist circumference, body-mass index, diabetes mellitus, hypertension, log high-density lipoprotein cholesterol, smoking status, and secondary or higher education

In current clinical practice, LDL-C, total cholesterol, non-HDL-C, and ApoB are used as primary predictors of cardiovascular risk and treatment targets [2]. Lipoprotein(a) has also emerged as an important predictor of cardiovascular risk, despite no approved targeted therapies as of 2026 [18, 19]. sdLDL-C remains a niche predictor not included in major guidelines [20–23], although some national-level guidelines do incorporate it [24]. In particular, ApoB is a leading predictor and a clear indicator of atherogenic particle number regardless of particle composition [2]. Nevertheless, lipoprotein particle number is unlikely to be the sole lipoprotein-related risk factor for atherosclerosis, unless every particle is equally likely to penetrate the endothelium, bind macrophage receptors, and induce inflammation [1].

The increased atherogenic potential of sdLDL was demonstrated in several studies [7, 25]. sdLDL was shown to be more easily oxidized due to its larger relative surface area compared with that of lbLDL [26] and it appears to have a lower affinity for LDLR, possibly reducing its hepatic clearance [27]. sdLDL was also shown to be more easily glycated than lbLDL [28], potentially contributing to its atherogenic potential.

In the prospective Framingham Offspring Study, sdLDL-C was a more significant predictor of atherosclerotic cardiovascular disease than direct LDL-C, total triglycerides, LDL triglycerides, remnant cholesterol, or triglyceriderich lipoprotein cholesterol. However, none of these associations were significant when adjusted for total cholesterol and HDL-C [7]. In the Atherosclerosis Risk

Table II. Results of multivariable Cox analysis with spline-based small dense low-density lipoprotein modelling. The following variables were modeled as binary or linear

Parameter	HR	95% CI		*P*-value
Age	1.10	1.09	1.10	< 0.001
Female gender	0.60	0.56	0.64	< 0.001
Waist circumference	1.01	1.00	1.01	< 0.001
Secondary or higher education	0.79	0.74	0.84	< 0.001
Hypertension	1.15	1.07	1.22	< 0.001
Smoking	2.00	1.86	2.15	< 0.001
Diabetes mellitus	1.79	1.65	1.92	< 0.001
Log HDL-C	0.92	0.80	1.05	0.235

HDL-C – high-density cholesterol.

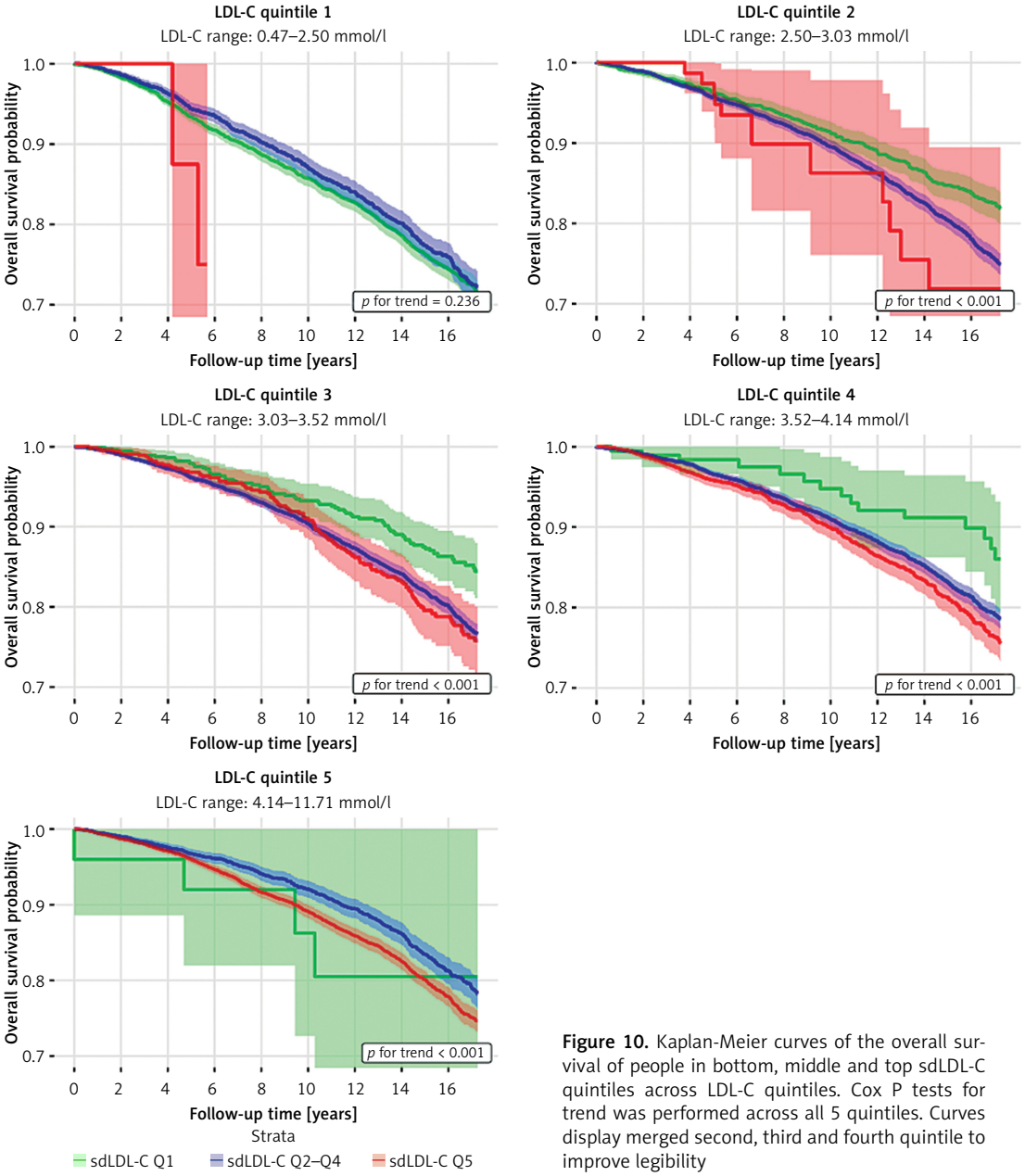

Figure 10. Kaplan-Meier curves of the overall survival of people in bottom, middle and top sdLDL-C quintiles across LDL-C quintiles. Cox P tests for trend was performed across all 5 quintiles. Curves display merged second, third and fourth quintile to improve legibility

in Communities (ARIC) Study of 11,419 patients, sdLDL-C was significantly associated with coronary heart disease in univariable and multivariable analysis that did adjust for total cholesterol, ApoB, and LDL-C [29]. In the Québec Cardiovascular Study, sdLDL-C was elevated in patients who developed coronary artery disease. The highest tertile of sdLDL-C was associated with an increased incidence of ischaemic heart disease within the first 7.3 years of follow-up; however, a similar trend did not reach statistical significance for lbLDL-C [30]. A study by Nishikura *et al.* did not demonstrate a significant correlation between sdLDL-C (as a continuous variable) and survival in a group of 190 patients with stable CAD, although sdLDL-C above the median correlated with worse survival [31]. A study of 271,760 UK Biobank participants found that estimated sdLDL-C was a superior predictor of cardiovascular risk in primary prevention compared to LDL-C [32]. Nevertheless, independent effects of sdLDL-C on coronary artery disease have not been confirmed at the genetic level [33].

Our study clearly indicates that sdLDL-C can serve as a marker for increased risk of death among patients without significant comorbidities, although the direct effects on cause-specific mortality cannot be discerned and the relationship may not exist during shorter term follow-up. Our univariable survival analysis showed a clear relationship between sdLDL-C and mortality. This may be due both to increased atherogenicity of

sdLDL-C and to sdLDL-C being correlated with other risk factors such as high triglycerides, high total LDL-C, high fasting glucose, obesity, or smoking. Multivariable analysis showed a U-shaped relationship between sdLDL-C and mortality, which may be explained in several ways. One possibility is reverse causality, where low sdLDL-C is itself a sign of health issues not included in our study design once some cardiometabolic risk factors are accounted for. Another is collider bias, where the covariates are combined consequences of several underlying factors and conditioning on them creates false associations. Therefore, overadjustment of the multivariable models cannot be excluded.

Of note, most of our analyses did not show a clear relationship between statin use and sdLDL-C. This is surprising given the previously published data, which show that sdLDL-C levels drop in patients receiving statins [34, 35]. Nevertheless, multivariable analysis of LIPIDOGRAM 2015 participants has shown a correlation with statin use. It is possible that in the unadjusted analyses the effect of statin therapy on sdLDL-C is attenuated by the fact that patients with elevated LDL-C or sdLDL-C and with cardiovascular risk factors are more likely to receive statin therapy, which may reduce their sdLDL-C down to levels comparable with those found in the lower-risk patients. Unfortunately, the influence of lipid-lowering therapy on sdLDL-C may introduce reverse causation and significantly reduce apparent survival of the low sdLDL-C group when patients with severe cardiovascular comorbidities are included in the analysis (Supplementary Figures S2 and S3).

Our study utilizes sdLDL-C measured indirectly, based on the Sampson equation [8]. Despite reasonable concordance with direct measurements in the original paper (R^2 = 0.745, slope = 0.73), it remains possible that our population deviates enough to make this equation largely inadequate. The equation used is not derived from strict physicochemical factors but is instead related to complex lipoprotein pathophysiology. LDL-C is frequently calculated instead of being directly measured and this is a well-established method with a long history of clinical use, although direct LDL assays are increasingly common in diagnostic laboratories [36, 37]. Unfortunately, the use of any indirect, equation-based estimation in statistical analysis runs the risk of misattributing the effects to the equation estimate rather than the underlying variables themselves – in our case, direct relationships with sdLDL-C or with triglycerides and LDL-C cannot be fully distinguished.

Based on our results, sdLDL-C estimation may benefit patients with elevated LDL-C and primary prevention patients without major cardiovascular diseases as a means to identify elevated mortality risk. Our data did not provide sufficient evidence for association between sdLDL-C and mortality in patients with diagnosed cardiovascular disease and low LDL-C. It must be noted that contemporary lipid-lowering targets have led to a large, although still insufficient, proportion of patients achieving low LDL-C [38, 39]. As far as sdLDL-C thresholds for different risk categories are concerned, our research did not support definite thresholds for increased or reduced risk and the risk appeared to increase gradually with sdLDL-C. Nevertheless, it may be possible to identify high risk patients in the highest sdLDL-C quintile (> 1.38 mmol/l) and "reduced risk" patients in the lowest sdLDL-C quintile (< 0.78 mmol/l) at least in Polish population.

The strengths of our study include a population representative of Polish primary care settings, and to our knowledge the longest median follow-up among all major sdLDL-C-focused studies. The limitations include a lack of cause-specific mortality data and major cardiovascular disease event data and a lack of direct measurements of sdLDL-C levels. An additional limitation is the fact that our data is strictly observational. This means that the causal nature of the observed associations is uncertain and insufficient to establish the optimum clinical approach for managing patients with elevated sdLDL-C (lipid lowering therapy, lifestyle changes, intensification of other preventive measures etc.). Moreover, our study utilized a one-time measurement of sdLDL-C at study initiation; it is very likely that sdLDL-C levels varied during the follow-up due to initiation of lipid-lowering therapy or changes in insulin resistance. Also, our population is exclusively European and further studies in diverse populations are necessary to validate our observations.

In conclusion, sdLDL-C may serve as a marker associated with cardiovascular disease and overall mortality in primary prevention populations and beyond information provided by LDL-C levels. Further research is needed to understand its clinical usefulness and the causal nature of its impact on major cardiovascular events.

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Ethical approval

The studies were approved by the Bioethical Committee of the Polish Chamber of Physicians (no. 51/2004/U) – years 2004 and 2006 – and Bioethical Commission of the District Medical Chamber in Częstochowa on 02/12/2015 (No K.B.Cz.–0018/2015) – year 2015. All studies conformed to the principles outlined in the Declaration of Helsinki.

Conflict of interest

JJ and MB have received an unrestricted educational grant from Valeant and served as consultants/speaker for Valeant. G.Y.H.L. reports institutional consultancy, advisory, and speaker roles for BMS/Pfizer, Boehringer Ingelheim, Anthos, Boston Scientific, Huawei (No fees were received personally).

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