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Material and methods
In approximately 2,000 NATPOL participants, serum TG was measured, and serum RC and sdLDL-C were calculated and compared between women and men, across age groups, and in relation to overweight/obesity and plasma glucose. RC/sdLDL-C levels were also compared in the serum TG intervals: <100, 100–149 and 150–499 mg/dL, and their percentile distribution was analyzed.

Results
Serum TG, RC and sdLDL-C were higher in overweight / obese participants and in those with prediabetes. In subjects with serum TG <100, 100–149 and 150–499 mg/dL, RC and sdLDL-C levels were successively higher, with values adopted as cut-offs for high ASCVD risk observed in both intervals >100 mg/dL. Participants with serum RC and sdLDL-C above these cutoffs had higher TG. Serum TG of 100 mg/dL and 150 mg/dL were the 55.9th and 88.2nd percentile, respectively, serum RC of 24 mg/dL was the 73.8th percentile, and serum sdLDL-C of 30 mg/dL (adopted cut-offs) was the 38th percentile of the distribution results.

Conclusions
We found an association between serum RC and sdLDL-C, and TG levels >100 mg/dL indicating that serum TG levels of 100–150 mg/dL already represent a state of possible TRL remnants and sdLDL accumulation. Calculated serum RC/sdLDL-C may be considered a useful supplement to the lipid profile.

Serum triglycerides, remnant cholesterol and small dense low-density lipoprotein cholesterol levels – lessons from the NATPOL 2011 survey

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Introduction

Triglyceride (**TG**)-rich lipoproteins (TRL) include chylomicrons (CM), very-low-density lipoproteins (VLDL), and the end products of their metabolism, remnants. The association of TRL with atherogenesis and the risk for atherosclerotic cardiovascular disease **(**ASCVD**)** is well established [1,2]. Direct atherogenic effects are exerted by TRL remnants and small dense LDL **(**sdLDL**)** produced in increased amounts in hypertriglyceridemia [3–9].

CM, secreted by enterocytes, in the blood, are deprived of TG by lipoprotein lipase **(**LPL) and enriched in cholesteryl esters from HDL and LDL by cholesteryl ester transfer protein (CETP), and they acquire apolipoprotein E (apoE). The resulting CM remnants are cleared by the liver [3,4]. VLDL are secreted by hepatocytes in two molecular forms: a larger, TG-richer VLDL1 and a smaller VLDL2, with equal proportions when plasma TG is below 100 mg/dL, whereas in hypertriglyceridemia, the VLDL1 fraction predominates. VLDL remnants formed after TG removal, unlike CM remnants, are not cleared by the liver but are mainly converted to LDL, with VLDL1 being considered the main precursor of sdLDL **[**3,4].

The structural and functional properties of TRL remnant particles, including small size and enrichment in cholesteryl esters and apoE, predispose them to participate in atherogenesis. They easily enter the arterial intima through transcytosis and are trapped by proteoglycans in the subendothelial space. Remnant particles are engulfed by vascular macrophages by

binding to the LDL receptors and LDL receptor related protein 1 (LRP-1) via apoE to form foam cells. Additionally, macrophage LPL mediates remnant TG hydrolysis with the release of free fatty acids that trigger the inflammatory response [3–7].

Small dense LDL particles, contrary to large buoyant LDL (lbLDL), are characterized by **a** reduced affinity for the LDL receptor, longer blood residence time, greater susceptibility to oxidation, penetration into the arterial intima, and binding to subendothelial proteoglycans. Oxidized sdLDL particles are taken up by macrophages via scavenger receptors [9,10].

Many studies, including the PESA (Progression of Early Subclinical Atherosclerosis) study, showing an association between vascular inflammation and plasma TG ≥ 150 mg/dL [11], have demonstrated that hypertriglyceridemia is a risk factor for ASCVD. In 2021, the European Atherosclerosis Society (EAS) proposed a consensus classification of plasma TG concentrations, considering TG <100 mg/dL as optimal, and higher values as borderline, moderate, severe, and very severe (extreme) hypertriglyceridemia, with TG levels of 100–150 mg/dL, 150–500 mg/dL, 500–880 mg/dL, and >880 mg/dL, respectively. This classification is based on the relationship between plasma TG levels and TRL accumulation and the associated ASCVD risk [3]. This recommendation is part of the 2024 Guidelines of the Polish Society of Laboratory Diagnostics and the Polish Lipid Association on laboratory diagnostics of lipid metabolism disorders [12].

However, plasma TG levels reflect TRL metabolism indirectly and approximately. Measurements of plasma remnant or remnant-like particles (RLPs) using ultracentrifugation, electrophoresis, or immunoseparation techniques are available [4] but are not recommended for clinical practice. Plasma remnant cholesterol (RC) can be easily measured using a direct enzymatic assay or calculated as the difference between total cholesterol and

the sum of HDL and LDL cholesterol, or between non-HDL and LDL cholesterol concentrations [2,4]. However, so far, these measurements and calculations are only for scientific purposes and have not been recommended for clinical practice.

Similarly, **s**dLDL content in plasma is widely measured for scientific purposes using ultracentrifugation and other techniques but is not quantified in diagnostic practice. In 2021, Sampson et al. developed an equation enabling the calculation of plasma sdLDL cholesterol based on the results of a standard lipid profile [13].

In the current study, we evaluated the distribution of serum TG, RC**,** and sdLDL-C levels and their relationships in the NATPOL 2011 survey participants.

Materials and methods

Study population

The NATPOL 2011 (Arterial Hypertension and Other CVD Risk Factors in Poland) survey was a cross-sectional observational study conducted between January and August 2011 to assess the prevalence and control of CVD risk factors. The study cohort was a sample of Polish men and women aged 18–79 [14]. Subjects who declared the use of lipid-lowering treatment were excluded from this analysis. The NATPOL 2011 survey design conformed to the ethical guidelines of the 1975 Declaration of Helsinki and were approved by the Bioethics Committee of the Medical University of Gdańsk, Poland. Prior to enrolment, each participant gave informed consent.

Measurements

Blood samples were collected at the patient's home after 10–12 h of fasting. Frozen serum and plasma samples were transported to the central laboratory, where tests were

performed. Serum total cholesterol (TC) was measured by an enzymatic method based on cholesterol esterase and cholesterol oxidase reactions; HDL-C by using Accelerator Selective Detergent (Abbott Laboratories). TG by an enzymatic method with glycerol kinase and glycerol-3-phosphate oxidase. Plasma glucose was measured by the hexokinase/glucose-6-phosphate dehydrogenase method. All tests were performed on the Architect c8000 clinical chemistry analyzer (Abbott Laboratories). Serum LDL-C was calculated using the Friedewald formula: LDL-C [mg/dL] = TC – HDL-C – TG/5 [mg/dL]. When serum TG exceeded 400 mg/dL, the direct LDL-C assay was applied instead of calculation.

Serum RC was calculated as the difference: TC – HDL-C – LDL-C. Small dense LDL cholesterol (sdLDL-C) wascalculated as the difference between serum LDL-C and lbLDL-C [13]:

lbLDL-C = 1.43 × LDL-C – 0.14 × (ln TG × LDL-C) – 8.9 [mg/dL]

sdLDL-C = LDL-C – lbLDL-C [mg/dL]

Serum TG was measured in 2,099 survey participants (998 men and 1,101 women); LDL-C, sdLDL-C, lbLDL-C, and RC were determined in 2,073 participants (975 men and 1,098 women); and plasma glucose was measured in 2,088 participants (993 men and 1,095 women).

The serum TG, RC, and sdLDL-C levels were compared between women and men, across age groups, and in relation to body mass index (BMI), visceral obesity, and fasting plasma glucose (FPG). The distribution of serum RC, LDL-C, lbLDL-C, and sdLDL-C levels was compared among subgroups of survey participants with optimal serum TG, borderline, and moderate hypertriglyceridemia, in line with the 2021 EAS consensus statement [3]. No cases of severe (500–880 mg/dL) or very severe (>880 mg/dL) hypertriglyceridemia were found in the survey cohort. Based on clinical trial reports, serum RC of 24 mg/dL and sdLDL-C of 30 mg/dL were adopted as cut-off values for increased ASCVD risk [4,15–20]. Serum TG distribution was

analyzed in participants with RC and sdLDL-C levels below and above the adopted cut-off values. The percentile distribution of serum TG, RC, LDL-C, and sdLDL-C was also analyzed.

Statistical analysis

Statistical analyses were conducted utilizing R software, version 4.4.2 (R Core Team). Continuous variables were reported as means accompanied by 95% confidence intervals (CIs), calculated based on the t-distribution. All subgroups analyzed were defined a priori. To evaluate the statistical significance of differences between subgroup means, the criterion of non-overlapping 95% confidence intervals was employed. It is important to note that this approach is more conservative compared to a formal hypothesis test at a significance level of $\alpha = 0.05$. Missing data were addressed through complete-case analysis, whereby observations with missing values for the variables of interest were excluded. The analysis did not adjust for multiple comparisons, and the complex survey design was not taken into account.

Results

In the survey cohort, we observed a similar distribution of serum TG, RC, and sdLDL-C, with minor differences mainly between age groups (Tab. 1). In the entire cohort, and independently in men and women, serum TG, RC, and sdLDL-C were higher in those with overweight/obesity compared with BMI <25 kg/m², and in those with rather than without visceral obesity. Serum TG and RC in all BMI categories, and serum sdLDL-C in subjects with BMI >30 kg/m², were higher in men than in women. In the entire cohort, and independently in men and women, serum TG was higher in subjects with impaired fasting glucose (IFG) and plasma glucose indicative of diabetes, compared with those with normal fasting glucose

(NFG), while serum RC and sdLDL-C were higher in subjects with IFG than in those with NFG (Tab. 1).

In the subgroups with serum TG <100 mg/dL, 100–149 mg/dL, 150–499 mg/dL, serum RC was consecutively and significantly higher (Tab. 2). In subsequent serum TG groups, the concentrations of LDL-C and sdLDL-C were higher, while serum lbLDL-C did not differ significantly (Tab. 2). Additionally, at these serum TG intervals, the mean sdLDL-C levels were 24.7%, 31%, and 37.2% of the mean serum LDL-C, respectively. Of note, in both analyzed TG intervals above 100 mg/dL, the study participants had serum RC and sdLDL-C levels of ≥24 mg/dL and ≥30 mg/dL, respectively (Tab. 2, Fig. 1). On the other hand, survey participants with serum RC ≥24 mg/dL and sdLDL-C ≥30 mg/dL had higher TG levels compared with participants with levels below these cut-off values (Tab. 3).

Percentile distribution analysis showed that the median values of serum TG, RC, LDL-C, and sdLDL-C were 95 mg/dL, 19 mg/dL, 122 mg/dL, and 33.5 mg/dL, respectively. Serum TG values of 100 mg/dL and 150 mg/dL corresponded to the 55.9th and 88.2nd percentiles, respectively; serum RC of 24 mg/dL was at the 73.8th percentile, serum LDL-C of 100 mg/dL was at the 26.1st percentile, and serum sdLDL-C of 30 mg/dL was at the 38th percentile (Tab. 4).

Discussion

TRL remnants, together with LDL and lipoprotein (a) [Lp(a)], belong to the atherogenic lipoproteins directly involved in all stages of atherogenesis. Therefore, their elevated plasma levels should be considered separate risk factors, also because the treatment of these forms of dyslipidemia differs [21,22].

For many years, plasma/serum TG was considered a measure of TRL and their remnants'

content in the blood. In principle, this rule is correct. Recently, this relationship has been described more accurately – the EAS proposed shifting optimal TG levels to <100 mg/dL and defined higher levels as progressive degrees of hypertriglyceridemia, linking serum TG levels with TRL accumulation and the associated ASCVD risk [3,12].

However, serum TG levels are an indirect and not always accurate measure of TRL remnant formation and content in plasma. TRL metabolism, mediated mainly by LPL and hepatic lipase (HL)**,** is affected by many factors, including the regulation of the synthesis and activity of LPL, leading to inter-individual variability [23]. Therefore, serum TG alone may be insufficient in this context. An extreme example is familial chylomicronemia – the accumulation of CM and very high plasma TG due to a lack of LPL functionality without increased ASCVD risk in affected patients [24].

Therefore, plasma/serum RC and sdLDL-C determined together with TG levels may help to more accurately assess TRL-related ASCVD risk and the indications for TG-lowering treatment. Some TRL remnants or remnant-like particles (RLP) determination methods are available to clinical laboratories [4,6]. Calculation of plasma/serum RC and sdLDL-C is considered a convenient tool because dedicated formulas use the results of a standard lipid profile [4,13]. We used these formulas in our study.

We analyzed the relationship between serum RC and sdLDL-C and TG levels based on their distribution in approximately 2,000 NATPOL 2011 participants, representative of the Polish population aged 18–79. We found that serum TG, RC, and sdLDL-C were higher in older age groups**,** in subjects with overweight/obesity, including visceral obesity, and in subjects with IFG (prediabetes) compared to survey participants in the 18–39 age group, with BMI <25 kg/m^2, without visceral obesity, and with NFG, respectively. Furthermore, serum TG, RC, and sdLDL-C were higher in men than in women (Tab. 1). The relationship between TRL

metabolism and serum TG levels with age is well established and explained [25,26]. Also, in many studies involving subjects with metabolic syndrome, hypertriglyceridemia with a parallel increase in serum RC and sdLDL-C has been observed, which is consistent with our findings [27–31].

In the categories of serum TG proposed by EAS, RC levels increased gradually and differed significantly between subjects with optimal serum TG, borderline, and moderate hypertriglyceridemia. Of note, subjects with borderline hypertriglyceridemia had serum RC close to the adopted cut-off value for increased ASCVD risk (24 mg/dL) (Fig. 1, Tab. 2). The equation used in our study to calculate serum RC as the transformed Fredrickson formula closely relates RC and TG levels, with a regression equation close to RC = 0.2 × TG [mg/dL] and a correlation coefficient of 0.999 found. To keep this calculation accurate, it is recommended to use LDL-C levels measured directly (at least in subjects with hypertriglyceridemia, as in our study) or obtained using the Martin-Hopkins or Sampson NIH equation in this formula [4,5,32–35]. The relationship, together with the distribution of RC levels in participants with borderline hypertriglyceridemia, indicates that serum RC close to or higher than 24 mg/dL can be expected within this TG level interval. Furthermore, there are data showing that at concentrations >20 mg/dL, directly measured serum RC may be higher than the calculated one [32].

Serum sdLDL-C also increased and differed significantly between successive TG level categories, exceeding, in borderline hypertriglyceridemia, the adopted cut-off value, with a mean of 40.65 mg/dL (Tab. 2, Fig. 1 and 2). Increases in serum sdLDL-C across successive TG concentration intervals were the main cause of increased serum LDL-C because serum lbLDL-C did not differ between these intervals. Across the serum TG intervals, the mean sdLDL-C levels increased both in absolute values and relatively, as a percentage of mean serum LDL-C

(Tab. 2). These findings support the role of sdLDL as a second link, beyond TRL remnants, between increased serum TG with TRL accumulation and ASCVD risk.

On the other hand, in survey participants, serum RC ≥24 mg/dL and sdLDL-C ≥30 mg/dL were associated with higher TG levels compared to serum RC and sdLDL-C below these cut-offs. TG levels in subjects with serum RC ≥24 mg/dL and sdLDL-C ≥30 mg/dL were within moderate and borderline/moderate hypertriglyceridemia, respectively (Tab. 3). Our two-way analysis confirmed the association of serum RC and sdLDL-C with TG levels and the correctness of the triglyceridemia classification proposed by the EAS [3]. Such data shed new light on atherogenic dyslipidemia, previously defined by high serum TG and low HDL-C, and currently by increased non-HDL-C reflecting TRL remnants accumulation [36].

Dyslipidemia is the most common modifiable risk factor for ASCVD. The NATPOL 2011 survey revealed hypercholesterolemia (LDL-C >115 mg/dL) in 57,8% of the Polish population aged 18–79 [37]. A similar incidence of hypercholesterolemia has also been observed in other countries [38]. In our present study, percentile-distribution analysis showed that serum TG levels >100 mg/dL and >150 mg/dL were found in 44.1% and 11.8% of participants, respectively (in Poland this corresponds to approx. 14 million and 4 million people, respectively). Serum RC >24 mg/dL was found in 26.2% (in Poland, approx. 9 million people); and serum sdLDL-C >30 mg/dL was found in 62% of participants. Of note, this frequency was close to the frequency of LDL-C >115 mg/dL – in Poland, approx. 20 million people. These numbers clearly indicate the importance of the TRL-related ASCVD risk.

To the best of our knowledge, the present study it **is** the first analysis of the distribution of RC and sdLDL-C in the cohort representative of the Polish population. Standardized preanalytical procedures and centralized laboratory testing ensured high-quality measurements.

The time elapsed since the survey was completed may be considered a limitation of our study. The motivation for this study was the 2021 EAS consensus statement [3[. Taking into account the increasing prevalence of CVD risk factors such as obesity, diabetes, and metabolic syndrome, we may assume that the epidemiological situation, even with the described distribution of RC and sdLDL in the population, might be worse today [39,40].

Conclusion

Our results confirm the association between serum RC and sdLDL-C levels with TG, showing it at triglyceridemia already exceeding 100 mg/dL. These findings should draw attention to borderline hypertriglyceridemia (100–150 mg/dL), until recently considered normal, as a possible state of TRL remnant and/or sdLDL accumulation. Calculation of serum RC and sdLDL-C, although still under discussion, is a convenient tool to identify patients with increased plasma content of these atherogenic particles. Taking this further, it could provide a basis for personalized assessment of serum TG in the context of ASCVD risk. Supplementing the standard lipid profile with these calculations could allow for a more comprehensive assessment of dyslipidemia-related residual ASCVD risk. However, further research is required to evaluate the diagnostic characteristics of RC and sdLDL-C.

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Conflict of interest

No declared.

References

1. Nordestgaard BG. Triglyceride-Rich Lipoproteins and Atherosclerotic Cardiovascular Disease New Insights From Epidemiology, Genetics, and Biology. Circ Res. 2016; 118: 547-563.
2. Xu D, Xie L, Cheng C et al. Triglyceride-rich lipoproteins and cardiovascular diseases. Front Endocrinol 2024; 15: 1409653.
3. Ginsberg HN, Packard CJ, Chapman MJ et al. Triglyceride-rich lipoproteins and their remnants: metabolic insights, role in atherosclerotic cardiovascular disease, and emerging therapeutic strategies - a consensus statement from the European Atherosclerosis Society. Eur Heart J 2021; 42: 4791-4806.
4. Durana EK, Pradhanb AD. Triglyceride-Rich Lipoprotein Remnants and Cardiovascular Disease. Clin Chem 2021; 67: 183-197.
5. Balling M, Afzal S, Varbo A et al. Remnant Cholesterol: Quantification, Concentrations by Sex and Age, and Risk of Ischemic Heart Disease. Clin Chem 2025; 71: 451-462.
6. Zhao Y, Zhuang Z, Li Y et al. Elevated blood remnant cholesterol and triglycerides are causally related to the risks of cardiometabolic multimorbidity. Nature Com 2024; 15: 2451.
7. Baratta F, Cocomello N, Coronati M et al. Cholesterol Remnants, Triglyceride-Rich ipoproteins and Cardiovascular Risk. Int J Mol Sci 2023; 24: 4268.

8. Duran EK, Aday AW, Cook NR et al. Triglyceride-Rich Lipoprotein Cholesterol, Small Dense LDL Cholesterol, and Incident Cardiovascular Disease. JACC 2020; 75: 1 2 2 - 3 5.
9. Krauss RM. Small Dense LDL Particles: Clinically Relevant? Cur Opin Lipidol 2022; 33: 160-166.
10. Vekic J, Zeljkovic A, Cicero AFG, Janez A et al. Atherosclerosis Development and Progression: The Role of Atherogenic Small, Dense LDL. Medicina 2022; 58: 299.
11. Raposeiras-Roubin S, Rossello X, Oliva B et al. Triglycerides and residual atherosclerotic risk. J Am Coll Cardiol 2021; 77: 3031–3041.
12. Solnica B, Sygitowicz G, Sitkiewicz D et al. 2024 Guidelines of the Polish Society of Laboratory Diagnostics and the Polish Lipid Association on laboratory diagnostics of lipid metabolism disorders. Arch Med Sci 2024; 20: 357-374.
13. Sampson M, Wolska A, Warnick R et al. New Equation Based on the Standard Lipid Panel for Calculating Small Dense Low-Density Lipoprotein-Cholesterol and Its Use as a Risk-Enhancer Test. Clin Chem 2021; 67:987-997.
14. Zdrojewski T, Rutkowski M, Bandosz P et al. Prevalence and control of cardiovascular risk factors in Poland. Assumptions and objectives of the NATPOL 2011 Survey. Kardiol Pol 2013; 71:381-392.
15. Quispe R, Martin SS, Michos ED et al. Remnant cholesterol predicts cardiovascular disease beyond LDL and ApoB: a primary prevention study. Eur Heart J. 2021; 42: 4324–4332.
16. Varbo A, Freiberg JJ, Nordestgaard BG. Remnant Cholesterol and Myocardial Infarction in Normal Weight, Overweight, and Obese Individuals from the Copenhagen General Population Study. Clin Chem 2018; 64: 1219-230.

17. Doi T, Langsted A, Nordestgaard BG. Elevated Remnant Cholesterol Reclassifies Risk of Ischemic Heart Disease and Myocardial Infarction. J Am Coll Cardiol. 2022; 79: 2383–2397.

18. Ikezaki H, Lim E, Cupples LA et al. Small Dense Low-Density Lipoprotein Cholesterol Is the Most Atherogenic Lipoprotein Parameter in the Prospective Framingham Offspring Study. J Am Heart Assoc. 2021;10: e019140.

19. Inyaku M, Tanaka M, Sato T et al. Calculated Small Dense Low-Density Lipoprotein Cholesterol Level is A Predominant Predictor for New Onset of Ischemic Heart Disease. J Atheroscler Thromb 2024; 31: 232-248.

20. Koba S, Satoh N, Ito Y et al. Impact of Direct Measurement of Small Dense Low-Density Lipoprotein Cholesterol for Long-Term Secondary Prevention in Patients with Stable Coronary Artery Disease. Clin Chem 2024; 70: 957–966.

21. Toth PP, Banach M. It is time to address the contribution of cholesterol in all apoB-containing lipoproteins to atherosclerotic cardiovascular disease. Eur Heart J Open. 2024;4: oeae057.

22. Makover ME, Surma S, Banach M et al. Eliminating atherosclerotic cardiovascular disease residual risk. Eur Heart J. 2023; 44: 4731-4733.

23. Wu SA, Kersten S, Qi L. Lipoprotein Lipase and Its Regulators: An Unfolding Story. Trends Endocrinol Metab. 2021; 32: 48–61.

24. Moulin P, Dufour R, Averna c M et al. Identification and diagnosis of patients with familial chylomicronaemia syndrome (FCS): Expert panel recommendations and proposal of an “FCS score”. Atherosclerosis 2018; 275: 265e272.

25. Spitler KM, Davies BSJ. Aging and plasma triglyceride metabolism. J Lipid Res 2020; 61: 1161-1167.

26. Feng L, Nian S, Tong Z et al. Age-related trends in lipid levels: a large-scale cross-sectional study of the general Chinese population. BMJ Open 2020;10: e034226.
27. ZhangID F, Zhang Y, Zhang J et al. Small dense low density lipoprotein predominance in patients with type 2 diabetes mellitus using Mendelian randomization. PLoS ONE 2024;19: e0298070.
28. **Li** B. Liu Y, Zhou X, Chen L et al. Remnant cholesterol is more positively related to diabetes, prediabetes, and insulin resistance than conventional lipid parameters and lipid ratios: A multicenter, large sample survey. J Diabetes 2024; 16: e13592.
29. Hirano T. Hypertriglyceridemia contributes significantly to high prevalence of small dense LDL-cholesterol in patients with type 2 diabetes, even when LDL-C targets are achieved. Diabetol Int 2023; 14: 288-293.
30. Srisawasdi P, Vanavanan S, Rochanawutanon M et al. Small-dense LDL/large-buoyant LDL ratio associates with the metabolic syndrome. Clin Biochem 2015; 48: 495-502.
31. Hirano T, Satoh N, Ito Y. Specific Increase in Small Dense Low-Density Lipoprotein-Cholesterol Levels beyond Triglycerides in Patients with Diabetes: Implications for Cardiovascular Risk of MAFLD. J Atheroscler Thromb 2024; 31: 36.
32. Wadstrom BN, Pedersen KM, Wulf AB et al. Elevated remnant cholesterol in atherosclerotic cardiovascular disease in diabetes: a population-based prospective cohort study. Eur Heart J 2023; 44(Suppl 2).
33. Langlois MR, Nordestgaard BG, Langsted A et al for the European Atherosclerosis Society (EAS) and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM).Joint Consensus Initiative Quantifying atherogenic lipoproteins for lipid-lowering strategies: consensus-based recommendations from EAS and EFLM. Clin Chem Lab Med 2019; aop.

34. Grant JK, Kaufman HW, Martin SS. Extensive Evidence Supports the Martin–Hopkins Equation as the LDL-C Calculation of Choice. Clin Chem 2024; 70: 392_–398.
35. Sampson M, Wolska A, Meeusen JW et al. The Sampson-NIH Equation Is the Preferred Calculation Method for LDL-C. Clini Chem 2024; 70: 399–402.
36. Raja V, Aguiar C, Alsayed N et al. Non-HDL-cholesterol in dyslipidemia: Review of the state-of-the-art literature and outlook. Atherosclerosis 2023; 383: 117312.
37. Zdrojewski T, Solnica B, Cybulska B et al. Prevalence of lipid abnormalities in land. The NATPOL 2011 survey. Kardiol Pol 2016; 74: 213-23.
38. NCD Risk Factor Collaboration (NCD-RisC). Repositioning of the global epicenter of non-optimal cholesterol. Nature 2020; 582(7810): 73-77.
39. Chen Y, Gue Y, Banach M et al. LIPIDOGRAM Investigators. Phenotypes of Polish primary care patients using hierarchical clustering: Exploring the risk of mortality in the LIPIDOGEN2015 study cohort. Eur J Clin Invest. 2024; 54: e14261.
40. Osadnik T, Nowak D, Osadnik K et al. LIPIDOGRAM Investigators. Association of body mass index and long-term mortality in patients from nationwide LIPIDOGRAM 2004-2015 cohort studies: no obesity paradox? Cardiovasc Diabetol. 2023; 22: 323.

Figure legends

Figure 1. Mean (95% CI) serum remnant cholesterol (RC) and small dense LDL cholesterol (sdLDL-C) across triglyceride level intervals according to the EAS [3]

Figure 2. Relationship between serum small dense LDL cholesterol (sdLDL-C) and triglyceride levels. Serum sdLDL-C above 30 mg/dL was observed in borderline and moderate hypertriglyceridemia according to the EAS [3]

Table 1. Serum of triglycerides, remnant cholesterol and small dense LDL cholesterol levels in the survey subjects

Groups	Triglycerides: N, mean (95% CI) [mg/dL]			Remnant Cholesterol: N, mean (95% CI) [mg/dL]			small dense LDL Cholesterol: N, mean (95% CI)) [mg/dL]		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
The entire cohort	998 120.70 (115.43, 125.97)	1101 96.95 (94.32, 99.58)	2099 108.24 (105.34, 111.14)	975 22.30 (21.66, 22.94)	1098 19.19 (18.72, 19.65)	2073 20.65 (20.26, 21.04)	975 36.90 (36.12, 37.69)	1098 34.06 (33.40, 34.72)	2073 35.40 (34.89, 35.91)
Age groups									
18–39	411 116.58 (108.83, 124.33)	471 85.17 (81.94, 88.39)	882 99.80 (95.68, 103.93)	400 21.45 (20.48, 22.42)	471 17.04 (16.40, 17.69)	871 19.07 (18.48, 19.65)	400 33.82 (32.71, 34.93)	471 29.46 (28.66, 30.27)	871 31.46 (30.78, 32.15)
40–59	365 130.27 (119.99, 140.56)	350 100.67 (95.30, 106.03)	715 115.78 (109.82, 121.74)	355 23.56 (22.45, 24.67)	348 19.64 (18.83, 20.46)	703 21.62 (20.91, 22.33)	355 40.75 (39.38, 42.12)	348 36.97 (35.79, 38.15)	703 38.88 (37.96, 39.79)
60–79	222 112.60 (104.35, 120.85)	280 112.12 (106.98, 117.26)	502 112.33 (107.71, 116.96)	220 21.81 (20.55, 23.08)	279 22.23 (21.27, 23.20)	499 22.05 (21.28, 22.82)	220 36.30 (34.69, 37.92)	279 38.21 (36.82, 39.59)	499 37.37 (36.32, 38.42)
Body Mass Index (BMI)									
<25 kg/m^2	345 99.39 (92.69, 106.09)	569 86.76 (83.71, 89.80)	914 91.53 (88.35, 94.70)	342 19.27 (18.32, 20.22)	569 17.35 (16.74, 17.96)	911 18.07 (17.55, 18.59)	342 32.82 (31.68, 33.96)	569 31.42 (30.57, 32.27)	911 31.95 (31.26, 32.63)
25-29 kg/m^2	425 125.76 (118.20, 133.31)	324 106.45 (100.64, 112.26)	749 117.41 (112.40, 122.41)	412 23.04 (22.07, 24.00)	321 20.61 (19.77, 21.44)	733 21.97 (21.31, 22.63)	412 38.44 (37.20, 39.67)	321 36.78 (35.52, 38.04)	733 37.71 (36.82, 38.60)
≥30 kg/m^2	222 144.86 (129.90, 159.83)	200 110.60 (104.75, 116.45)	422 128.63 (120.15, 137.10)	215 25.80 (24.33, 27.28)	200 22.13 (20.96, 23.30)	415 24.03 (23.07, 25.00)	215 40.60 (38.84, 42.36)	200 37.11 (35.57, 38.65)	415 38.92 (37.73, 40.10)
Visceral obesity									
yes	590 135.88 (128.31, 143.45)	653 105.22 (101.58, 108.86)	1243 119.77 (115.62, 123.93)	573 24.81 (23.93, 25.69)	650 20.71 (20.10, 21.31)	1223 22.63 (22.09, 23.17)	573 39.90 (38.85, 40.95)	650 36.27 (35.41, 37.12)	1223 37.97 (37.30, 38.65)
no	408 98.75 (92.51, 104.99)	444 84.39 (81.00, 87.77)	852 91.26 (87.77, 94.76)	402 18.72 (17.94, 19.50)	444 16.88 (16.20, 17.55)	846 17.75 (17.24, 18.27)	402 32.63 (31.57, 33.69)	444 30.69 (29.73, 31.65)	846 31.61 (30.90, 32.33)
Cardiovascular disease									

yes	96 130.11 (110.58, 149.65)	98 105.83 (97.14, 114.51)	194 117.85 (107.19, 128.50)	93 23.39 (21.10, 25.68)	97 20.62 (19.26, 21.97)	190 21.97 (20.65, 23.29)	93 34.10 (31.68, 36.52)	97 35.32 (33.31, 37.33)	190 34.72 (33.17, 36.28)
no	902 119.70 (114.24, 125.15)	1003 96.08 (93.32, 98.84)	1905 107.26 (104.26, 110.27)	882 22.18 (21.52, 22.85)	1001 19.05 (18.55, 19.54)	1883 20.52 (20.10, 20.93)	882 37.20 (36.37, 38.03)	1001 33.94 (33.24, 34.64)	1883 35.47 (34.92, 36.01)
Fasting plasma glucose									
NFG (<100 mg/dL)	721 112.57 (107.55, 117.59)	927 93.71 (90.92, 96.51)	1648 101.96 (99.23, 104.70)	708 21.28 (20.60, 21.97)	925 18.56 (18.07, 19.05)	1633 19.74 (19.33, 20.15)	708 35.90 (35.01, 36.80)	925 33.36 (32.65, 34.08)	1633 34.47 (33.90, 35.03)
IFG (100–125 mg/dL)	217 138.06 (126.12, 150.00)	146 114.23 (106.76, 121.71)	363 128.48 (120.67, 136.28)	213 25.88 (24.22, 27.54)	145 22.48 (21.14, 23.81)	358 24.50 (23.37, 25.63)	213 40.73 (38.95, 42.52)	145 38.45 (36.62, 40.27)	358 39.81 (38.52, 41.10)
Indicative of Diabetes (≥126 mg/dL)	55 162.73 (112.87, 212.59)	22 121.32 (97.75, 144.89)	77 150.90 (114.79, 187.00)	49 22.16 (19.96, 24.37)	22 24.32 (19.58, 29.06)	71 22.83 (20.77, 24.89)	49 35.62 (32.24, 39.00)	22 35.33 (30.06, 40.59)	71 35.53 (32.75, 38.30)

Table 2. Distribution of serum remnant cholesterol (RC), low-density lipoprotein cholesterol (LDL-C), small dense LDL cholesterol (sdLDL-C) and large buoyant LDL cholesterol (lbLDL-C) among subjects with optimal triglyceridemia, borderline and moderate hypertriglyceridemia (EAS 2021)[3]

Fasting serum triglycerides	Remnant Cholesterol: N, mean (95% CI) [mg/dL]			LDL Cholesterol: N, mean (95% CI) [mg/dL]			sdLDL Cholesterol: N, mean (95% CI) [mg/dL]			lbLDL Cholesterol: N, mean (95% CI) [mg/dL]		
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
<100 mg/dL *optimal*	484 14.95 (14.67, 15.24)	669 14.32 (14.07, 14.56)	1153 14.58 (14.40, 14.77)	484 116.43 (113.58, 119.28)	669 118.33 (115.99, 120.67)	1153 117.53 (115.73, 119.34)	484 29.14 (28.47, 29.82)	669 28.65 (28.11, 29.20)	1153 28.86 (28.43, 29.28)	484 87.29 (85.02, 89.56)	669 89.68 (87.79, 91.57)	1153 88.67 (87.22, 90.13)
100–149 mg/dL *borderline hypertriglyceridemia*	338 24.51 (24.21, 24.81)	353 24.20 (23.90, 24.50)	691 24.35 (24.14, 24.57)	338 131.00 (127.24, 134.77)	353 130.94 (127.09, 134.80)	691 130.97 (128.28, 133.66)	338 40.79 (39.81, 41.76)	353 40.53 (39.54, 41.51)	691 40.65 (39.96, 41.35)	338 90.22 (87.39, 93.05)	353 90.41 (87.51, 93.32)	691 90.32 (88.29, 92.34)
150–499 mg/dL *moderate hypertriglyceridemia*	153 40.65 (39.18 42.13)	76 38.75 (37.01, 40.49)	229 40.02 (38.88,,4 1.16)	153 141.42 (135.3, 147.48)	76 139.58 (130.45, 148.71)	229 140.81 (135.79, 145.83)	153 52.88 (50.87, 54.90)	76 51.66 (48.66, 54.66)	229 52.48 (50.82, 54.14)	153 88.54 (84.32, 92.76)	76 87.92 (81.62, 94.22)	229 88.33 (84.85, 91.82)

Table 3. Serum TG in participants with remnant cholesterol (RC) and small dense LDL cholesterol (sdLDL-C) levels below and above 24 mg/dL and 30 mg/dL, respectively

Serum Triglycerides			
Serum RC 24–69 mg/dL			
	Male	Female	Total
N	355	265	620
Mean (95% CI)	162.52 (157.61, 167.44)	149.91 (145.63, 154.19)	157.13 (153.75, 160.51)
RC <24 mg/dL			
N	620	833	1453
Mean (95% CI)	82.13 (80.56, 83.71)	82.13 (80.56, 83.71)	78.76 (77.36, 80.15)
Serum sdLDL-C 30–111 mg/dL			
N	648	636	1284
Mean (95% CI)	129.67 (125.81, 133.52)	114.51 (111.51, 117.51)	122.16 (119.68, 124.64)
Serum sdLDL-C <30 mg/dL			
N	326	462	788
Mean (95% CI)	74.62 (71.94, 77.29	74.62 (71.94, 77.29)	70.35 (68.29, 72.41)

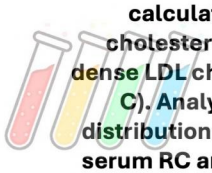
Table 4. Percentile distribution of serum triglyceride (TG), remnant cholesterol (RC), low-density lipoprotein cholesterol (LDL-C), and small dense LDL cholesterol (sdLDL-C) levels in the entire survey cohort

Percentile	Serum TG	Serum RC	Serum LDL-C	Serum sdLDL-C
5th	49	10	73	19.69
10th	57	11	83	21.97
25th	72	14	99	26.69
25.1st			100	
38th				30
50th (Median)	95	19	122	33.50
55.9th	100			
73.8th		24		
75th	125	25	146	42.13
88.2nd	150			
90th	160	31	169	51.23
95th	206	38	187	56.76

Population

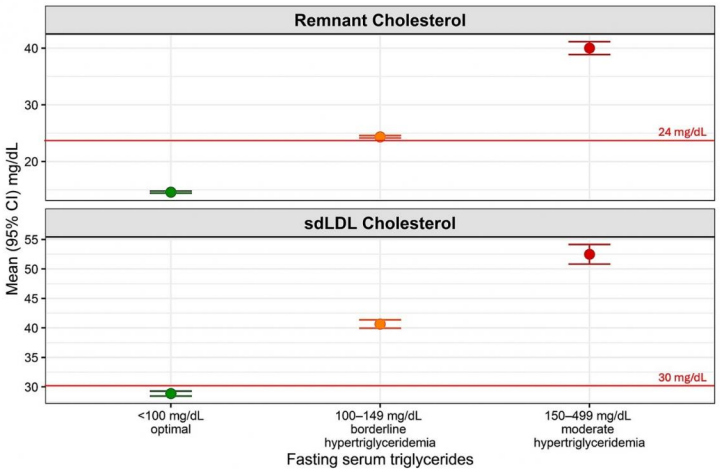
2,099 NATPOL 2011 participants aged 18-79 years – a cohort representative of the Polish population

Measurements & Analyses



Standard lipid profile, calculated remnant cholesterol (RC) & small dense LDL cholesterol (sdLDL-C). Analysis of results distribution & comparison of serum RC and sdLDL-C, with adopted cutoffs for high ASCVD risk of 24 mg/dLand 30 mg/dL, respectively, across TG level intervals.

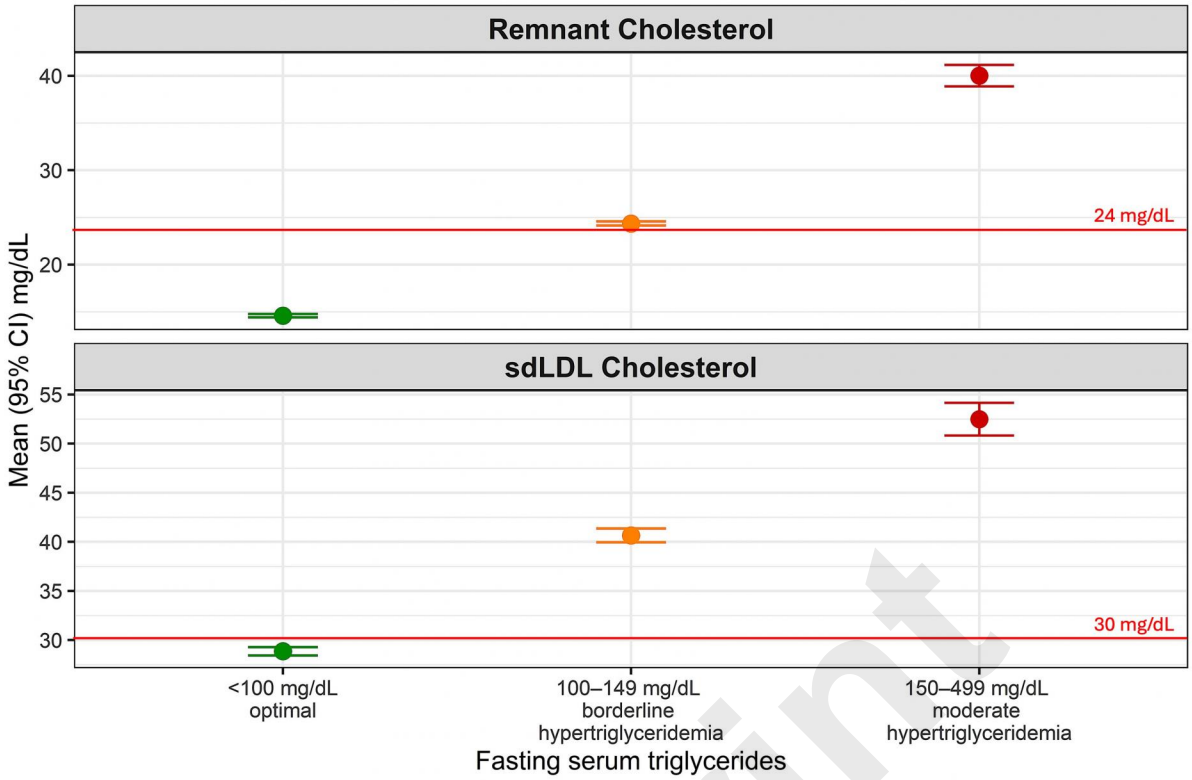
Main findings

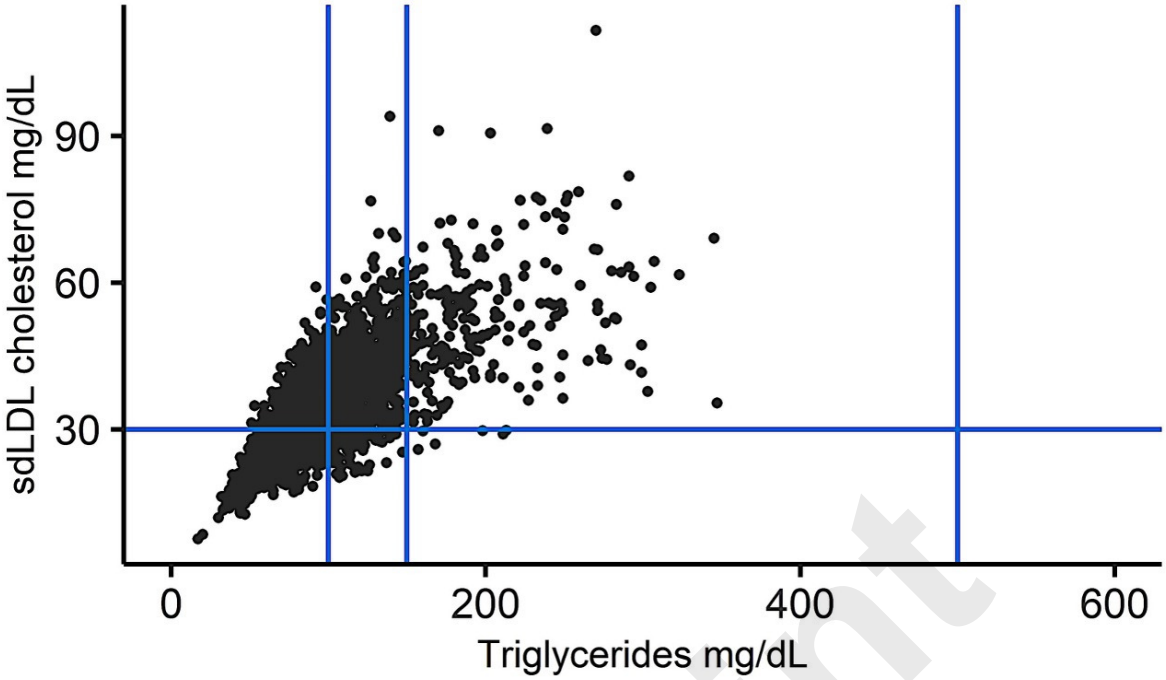


Conclusions

We found an association between serum RC and sdLDL-C, and TG levels >100 mg/dL indicating that serum TG levels of 100–150 mg/dL already represent a state of possible TRL remnants and sdLDL accumulation. The frequency of these disturbances is high – serum TG, RC and sdLDL-C ≥100, ≥24 and ≥30 mg/dL, were observed in 44.1%, 26.2% and 62% of the cohort, respectively.

Key message: Watch out for serum TG levels >100 mg/dL!


Remnant Cholesterol
40
30
20
24 mg/dL
sdLDL Cholesterol
55
50
45
40
35
30
30 mg/dL
Mean (95% CI) mg/dL
<100 mg/dL
optimal
100–149 mg/dL
borderline
hypertriglyceridemia
150–499 mg/dL
moderate
hypertriglyceridemia
Fasting serum triglycerides


sdLDL cholesterol mg/dL
90
60
30
0
200
400
600
Triglycerides mg/dL