

ORIGINAL ARTICLE

Impact of Lipoprotein (a) on the Quantification of LDL-Cholesterol

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SUMMARY

Background: Accurate LDL-C measurement is essential for cardiovascular risk management. The established methods to determine LDL-C also include Lp(a)-C and potentially distort the actual LDL-C value. The need for Lp(a)-adjusted LDL-C remains debated. Our study aimed to evaluate the impact of Lp(a) on the determination of LDL-C.

Methods: We included 3,923 datasets from two cohorts. LDL-C was determined by beta-quantification (LDL-C_{UC}), the reference method recommended by the Lipid Research Clinics, and according to Friedewald (LDL-C_{FW}), Martin/Hopkins (LDL-C_{MH}), and Sampson (LDL-C_{SN}). Correction of LDL-C was performed as follows: corrected LDL-C* = crude LDL-C - (Lp(a) × 0.23 + 1.00). Passing-Bablok regression and Spearman correlation were used for intermethod comparisons.

Results: Above 10 mg/dL Lp(a) had a significant effect on LDL-C_{UC}. The effect increased with increasing concentrations of Lp(a) levels and, in relative terms, was most pronounced at lower LDL-C values. For Lp(a) > 58 mg/dL, the actual LDL-C_{UC} was overestimated by ≥ 10%, which was considered clinically relevant. Similar overestimations were observed with the Friedewald, Martin/Hopkins, and Sampson formulas, with Friedewald showing the smallest deviation from LDL-C regardless of Lp(a)-correction. Artificial intelligence models showed that it was not possible to raise the suspicion of elevated Lp(a) from the conventional lipid profile.

Conclusions: The influence of Lp(a) on the determination of LDL-C may lead to clinically significant overestimations of the actual LDL-C. Therefore, we recommend using Lp(a)-corrected LDL-C when 1) the Lp(a) concentration is high, 2) the LDL-C concentration is low, and 3) the LDL-C-lowering treatment is less effective than expected.

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Supplementary Data

Table S1. Study population characteristics.

Characteristic	Overall study		LURIC study		PCSK9i study	
samples (n)	3,923		3,245		678	
age (year) ¹	62.6 (56 - 71)		62.8 (56 - 71)		61.7 (54 - 70)	
men/women (%) ²	2,647/1,276	(67.5/32.5)	2,258/987	69.6/30.4	391/287	57.6/42.4
BMI ³	27.6 (4)	27 (25 - 30)	27.5 (4)	27 (25 - 30)	28.2 (5) ⁴	28 (25 - 31) ⁴
TG (mg/dL) ³	159.3 (77)	142 (104 - 195)	161.3 (75)	145 (108 - 196)	149.9 (84)	129 (88 - 188)
TC (mg/dL) ³	192.6 (48)	189 (161 - 219)	191.8 (39)	189 (165 - 216)	195.9 (79)	186 (136 - 245)
HDL-C (mg/dL) ³	40.6 (12)	39 (32 - 47)	39.0 (11)	37 (32 - 45)	48.2 (16)	46 (37 - 57)
non-HDL-C (mg/dL) ³	152.0 (47)	149 (123 - 178)	152.8 (37)	150 (126 - 176)	147.7 (80)	137 (84 - 197)
VLDL-C _{UC} (mg/dL) ³	30.9 (23)	25 (18 - 37)	28.3 (14)	25 (19 - 35)	34.7 (34)	25 (13 - 46)
LDL-C _{UC} (mg/dL) ³	116.9 (41)	114 (91 - 140)	117.6 (34)	115 (95 - 138)	113.0 (66)	101 (62 - 151)
LDL-C _{FW} (mg/dL) ³	120.2 (44)	117 (94 - 144)	120.9 (34)	118 (97 - 142)	117.7 (75)	105 (61 - 167)
LDL-C _{SN} (mg/dL) ³	123.3 (43)	120 (97 - 146)	123.8 (34)	121 (100 - 145)	120.3 (74)	109 (64 - 169)
LDL-C _{MH} (mg/dL) ³	124.4 (43)	121 (99 - 148)	124.9 (33)	122 (102 - 146)	121.3 (74)	111 (65 - 167)
Lp(a) (mg/dL) ³	32.5 (39)	17 (7 - 44)	29.3 (35)	16 (7 - 38)	47.3 (53)	25 (8 - 72)

¹ Median and 25th and 75th percentiles in brackets.² Absolute numbers on the left, percentages on the right.³ Means and standard deviations in brackets on the left, medians and 25th and 75th percentiles on the right.⁴ Only 514 of 678 BMI values available in the PCSK9 study.

BMI - body mass index, TG - triglycerides, TC - total cholesterol, HDL-C - high-density lipoprotein cholesterol, LDL-C - low-density lipoprotein cholesterol, Non-HDL-C - non-high-density lipoprotein cholesterol, VLDL-C_{UC} - Very low-density lipoprotein cholesterol measured by ultracentrifugation, LDL-C_{UC} - LDL-C measured by beta-quantification, LDL-C_{FW} - LDL-C estimated with Friedewald equation, LDL-C_{SN} - LDL-C estimated with Sampson equation, LDL-C_{MH} - LDL-C estimated with Martin/Hopkins equation, Lp(a) - lipoprotein(a), UC - ultracentrifugation, SD - standard deviation. Only samples with TG less than 500 mg/dL included.

Table S2. Mean and median differences between estimated LDL-C and LDL-C_{UC} at increasing triglycerides (mg/dL).

Mean differences					
	TG < 500 mg/dL	TG < 150 mg/dL	TG 150 - 300 mg/dL	TG 300 - 500 mg/dL	TG > 500 mg/dL
n	5,783	3,719	1,779	240	76
LDL-C _{FW}	0.04 (0.41) *	-0.006 (0.32)	0.104 (0.44) *	0.191 (0.95) *	-0.13 (0.93) *
	1.55 (15.85) *	-0.23 (12.37)	4.02 (17.01) *	7.39 (36.74) *	- 5.03 (35.96) *
LDL-C _{MH}	0.11 (0.44) *	-0.014 (0.32) *	0.284 (0.43) *	0.740 (0.89) *	1.02 (0.82) *
	4.25 (17.01) *	-0.54 (12.37) *	10.98 (16.63) *	28.62 (34.42) *	39.44 (31.71) *
LDL-C _{MH} extended	0.12 (0.46) *	-0.016 (0.32) *	0.282 (0.43) *	0.702 (0.88) *	1.00 (0.80) *
	4.64 (17.79) *	-0.62 (12.37) *	10.90 (16.63) *	27.15 (34.03) *	38.67 (30.94) *
LDL-C _{SN}	0.11 (0.40) *	0.035 (0.32) *	0.214 (0.43) *	0.391 (0.82) *	0.42 (0.71) *
	4.25 (15.47) *	1.35 (12.37) *	8.28 (16.63) *	15.12 (31.71) *	16.24 (27.46) *

Table S2. Mean and median differences between estimated LDL-C and LDL-C_{UC} at increasing triglycerides (mg/dL) (continued).

Median differences					
	TG < 500 mg/dL	TG < 150 mg/dL	TG 150 - 300 mg/dL	TG 300 - 500 mg/dL	TG > 500 mg/dL
n	5,783	3,719	1,779	240	76
LDL-C _{FW}	-0.04 (-0.17, 0.13) *	-0.06 (-0.17, 0.07)	0.03 (-0.15, 0.24) *	-0.03 (-0.31, 0.42) *	-0.33 (-0.65, 0.00) *
	-1.55 (-6.57, 5.03) *	-2.32 (-6.57, 2.71)	1.16 (-5.80, 9.28) *	-1.16 (-11.99, 16.24) *	-12.76 (-25.14, 0.00) *
LDL-C _{MH}	0.02 (-0.14, 0.23) *	-0.07 (-0.18, 0.08) *	0.20 (0.04, 0.42) *	0.54 (0.25, 0.89) *	0.77 (0.53, 1.31) *
	0.77 (-5.41, 8.89) *	-2.71 (-6.96, 3.09) *	7.74 (1.55, 16.24) *	20.88 (9.67, 34.42) *	29.78 (20.50, 50.66) *
LDL-C _{MH extended}	0.02 (-0.14, 0.24) *	-0.07 (-0.19, 0.07) *	0.20 (0.04, 0.41) *	0.51 (0.22, 0.86) *	0.80 (0.54, 1.33) *
	0.77 (-5.41, 9.28) *	-2.71 (7.35, 2.71) *	7.73 (1.55, 15.85) *	19.72 (8.51, 33.26) *	30.94 (20.88, 51.43) *
LDL-C _{SN}	0.02 (-0.11, 0.20) *	-0.02 (-0.13, 0.12) *	0.13 (-0.03, 0.34) *	0.20 (-0.07, 0.57) *	0.19 (-0.03, 0.65) *
	0.77 (-4.25, 7.73) *	-0.77 (-5.03, 4.64) *	5.03 (-1.16, 13.15) *	7.73 (-2.71, 22.04) *	7.35 (-1.16, 25.14) *

The cells contain mean (standard deviations) and median differences (25th and 75th percentiles) between the respective calculated LDL-C and the LDL-C_{UC}. Top and bottom lines contain mmol/L and mg/dL, respectively. Asterisks mark significant differences ($p < 0.05$) between estimated LDL-Cs LDL-C_{UC}. For abbreviations see legend of Table 1.

Table S3. Correlations of LDL-C_{FW}, LDL-C_{MH}, and LDL-C_{SN} with LDL-C_{UC} and LDL-C_{UC}*.

Slope and intercepts of regression lines according to Passing Bablok (95% CI)			
	Lp(a) < 30 mg/dL	Lp(a) 30 - 50 mg/dL	Lp(a) > 50 mg/dL
n	2,616	429	876
LDL-C _{FW} - LDL-C _{UC}	1.06 (1.044 - 1.068)	1.04 (1.017, 1.065)	1.05 (1.034 - 1.067)
	-6.6 (-8.0, -5.3)	-5.0 (-7.7, -2.2)	-6.1 (-8.2, -4.0)
LDL-C _{SN} - LDL-C _{UC}	1.04 (1.028 - 1.051)	1.04 (1.011, 1.059)	1.05 (1.030 - 1.065)
	-1.7 (-3.2, -0.3)	-1.5 (-3.9, 1.8)	-3.0 (-5.2, -0.8)
LDL-C _{MH} - LDL-C _{UC}	1.01 (1.000 - 1.028)	1.01 (0.986, 1.038)	1.03 (1.007 - 1.047)
	2.0 (0.4 - 3.7)	2.3 (-0.7, 5.5)	-0.4 (-2.9, 2.0)
LDL-C _{FW} - LDL-C _{UC} *	1.06 (1.047 - 1.072)	1.04 (1.020 - 1.069)	1.04 (1.016 - 1.060)
	-3.2 (-4.6, -1.8)	5.3 (2.8, 7.7)	17.1 (15.4, 19.5)
LDL-C _{SN} - LDL-C _{UC} *	1.04 (1.030 - 1.055)	1.04 (1.012, 1.061)	1.03 (1.013 - 1.056)
	1.8 (0.5, 3.2)	9.2 (6.3, 11.6)	20.3 (18.2, 22.6)
LDL-C _{MH} - LDL-C _{UC} *	1.02 (1.003 - 1.032)	1.01 (0.988 - 1.042)	1.03 (1.007 - 1.047)
	5.6 (3.8, 7.3)	11.9 (9.3, 14.7)	22.7 (20.4, 25.0)

Table S3. Correlations of LDL-C_{FW}, LDL-C_{MH}, and LDL-C_{SN} with LDL-C_{UC} and LDL-C_{UC}* (continued).

Spearman rank correlation coefficient (95%)			
	Lp(a) < 30 mg/dL	Lp(a) 30 - 50 mg/dL	Lp(a) > 50 mg/dL
n	2616	429	876
LDL-C _{FW} - LDL-C _{UC}	0.90 (0.893 - 0.907)	0.94 (0.930 - 0.951)	0.94 (0.926 - 0.943) *
LDL-C _{SN} - LDL-C _{UC}	0.90 (0.891 - 0.906)	0.94 (0.929 - 0.951)	0.93 (0.924 - 0.941) *
LDL-C _{MH} - LDL-C _{UC}	0.88 (0.873 - 0.890)	0.93 (0.917 - 0.942)	0.92 (0.909 - 0.929) *
LDL-C _{FW} - LDL-C _{UC} *	0.90 (0.892 - 0.907)	0.94 (0.931 - 0.952)	0.90 (0.890 - 0.914) *
LDL-C _{SN} - LDL-C _{UC} *	0.90 (0.890 - 0.905)	0.94 (0.930 - 0.952)	0.90 (0.888 - 0.913) *
LDL-C _{MH} - LDL-C _{UC} *	0.88 (0.873 - 0.890)	0.93 (0.918 - 0.943)	0.89 (0.875 - 0.903) *

Slopes and intercepts of the regressions lines were calculated according to Passing and Bablok and the rank correlation coefficients according to Spearman, each is shown with 95%CI. The comparison is based on the crude LDL-C_{UC} (LDL-C_{UC}), shown in the upper blocks, and on the corrected LDL-C_{UC} (corrected LDL-C = LDL-C - 0.23*Lp(a) + 1.00; LDL-C_{UC}*), shown in the lower blocks. The Passing and Bablok slopes are each listed on the upper line and the intercepts on the lower line. Significant differences between LDL-C_{UC} and LDL-C_{UC}* within each equation/parameter are marked with an asterisk (p < 0.05). LDL-C_{UC} - crude LDL-C_{UC}, LDL-C_{UC}* - LDL-C_{UC} corrected for Lp(a)-C. For the remaining abbreviations see legend of Table 1.

Table S4. Relation between Lp(a), LDL-C_{UC} and LDL-C_{UC}* according to increasing relative differences between LDL-C_{UC} and LDL-C_{UC}*.

Relative difference	Lp(a) mean (mg/dL)	LDL-C _{UC} mean (mg/dL)	LDL-C _{UC} * mean (mg/dL)
0 - 5%	9	124	121
5 - 10%	30	112	105
10 - 20%	65	114	98
20 - 30%	104	103	78
30 - 40%	133	91	60

A total of 3,921 data from the LURIC and PCSK9i study were examined. The relative differences were calculated according to the formula: (LDL-C_{UC} - LDL-C_{UC}*) / LDL-C_{UC}. Columns 2, 3 and 4 show the means of the Lp(a), LDL-C_{UC} and LDL-C_{UC}* for the corresponding range of differences in mg/dL. LDL-C_{UC}* = LDL-C_{UC} - (Lp(a)*0.23+1.00). For abbreviations see legend of Table 1.

Table S5. Percentage distribution of samples with relative differences ≥ 10% between LDL-C_{UC} and LDL-C_{UC}* according to LDL-C_{UC}.

LDL-C _{UC}	n	n (%)	mean LDL-C _{UC}	mean LDL-C _{UC} *	median Lp(a)	≥ 10% deviation
0 - 50	162	4.16	36.75	27.61	15.5	61.0%
50 - 75	356	9.14	64.38	56.65	12.5	32.9%
75 - 100	841	21.59	88.90	81.17	16.0	27.1%
100 - 125	1,109	28.47	112.03	104.28	15.6	23.9%
125 - 150	877	22.52	136.64	127.55	18.0	22.0%
150 - 175	455	11.68	160.50	150.95	20.0	19.3%
175 - 200	133	3.41	185.61	175.05	22.0	17.3%
200 - 225	57	1.46	208.93	199.36	23.1	12.3%
225 - 250	32	0.82	235.25	222.72	33.0	15.6%

Based on 3,895 data sets from the LURIC and PCSK9i studies, the relative deviation of LDL-C_{UC}* from LDL-C_{UC} according to LDL-C_{UC} strata are listed. The number of samples is given in absolute (column 2) and relative (column 3) terms. Column 7 indicates the relative proportion of samples the LDL-C_{UC}* of which form differs from LDL-C_{UC} form by ≥ 10% (related the number of samples in the respective stratum). Different shades of grey indicate the extent of the deviation: light grey up to 20%, medium grey up to 30%, and dark grey above 30%. Deviations above 10% are marked in red. LDL-C_{UC}* - Lp(a)-corrected LDL-C_{UC}. For remaining abbreviations see legend of Table 1.

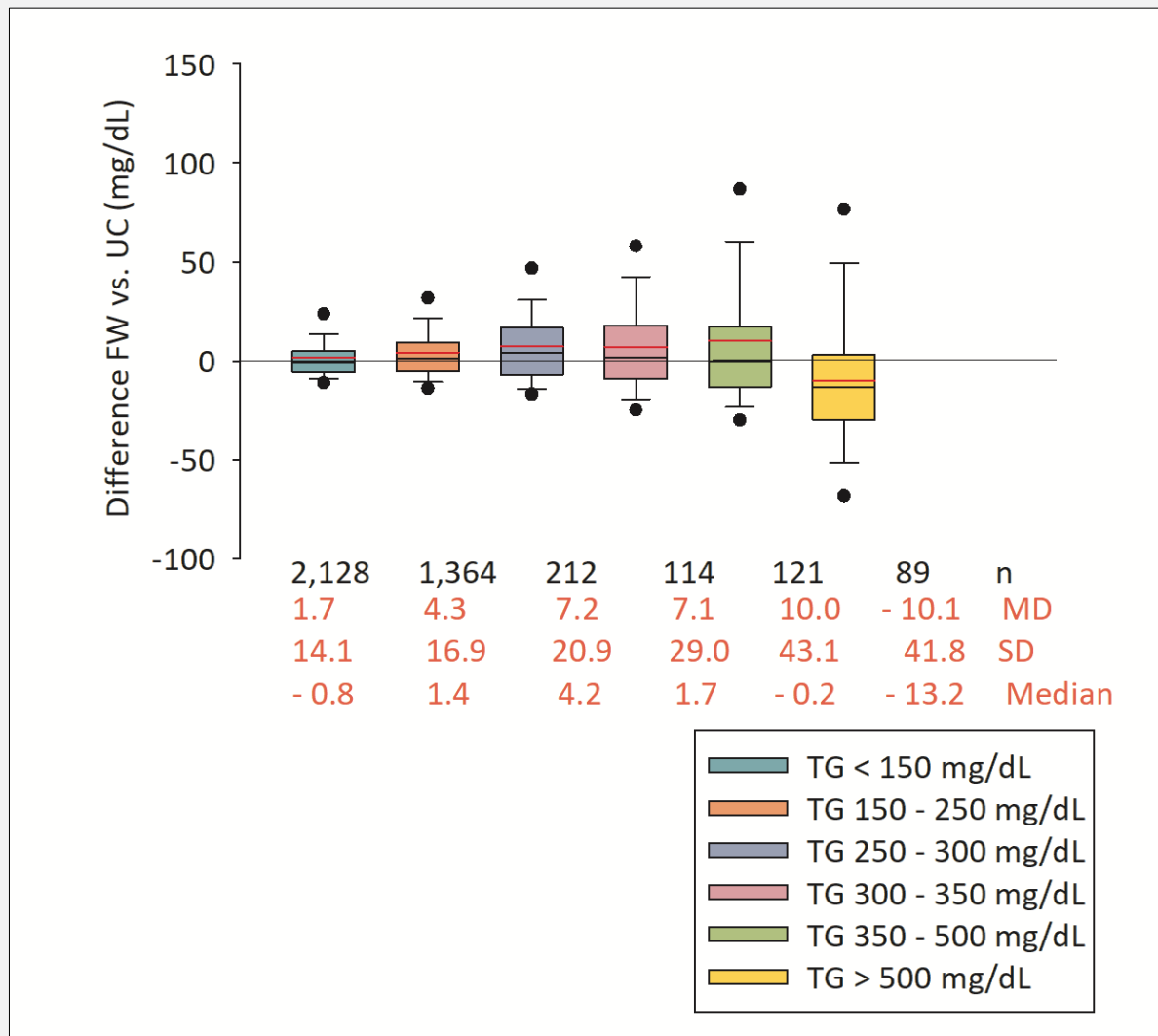


Figure S1. Effect of increasing triglyceride concentrations on the accuracy of LDL-C_{FW} in 4,014 samples from two studies.

Mean differences (MD) were calculated from the differences between LDL-C_{FW} and LDL-C_{UC} and presented as boxplots. The red center lines indicate means, the black lines medians. The boxes contain the 25th to 75th percentiles of datasets. The black whiskers mark the 10th and 90th percentiles. The black dots mark the 5th and 95th percentiles. Data was divided into five subgroups according to triglycerides. Statistically significant differences are indicated by asterisks. The numbers (n) of data sets, mean differences (MD) with corresponding standard deviations, and the median differences are shown at the bottom of the diagram.

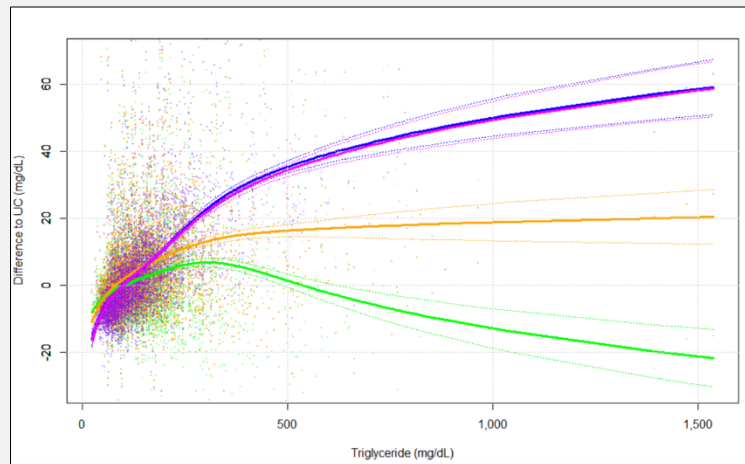


Figure S2. Differences of four equations for the calculation of LDL-C to LDL-C obtained by beta quantification (LDL-C_{UC}).

The difference was calculated as the LDL-C estimated with the formulas minus LDL-C_{UC} value. The four formulas are color-coded: green - FW, orange - SN, blue - MH, pink - MHe.

TG - triglycerides, LDL-C - low-density lipoprotein cholesterol, FW - Friedewald equation, SN - Sampson equation, MH - Martin/Hopkins equation, MHe - extended Martin/Hopkins, UC - β -quantification.

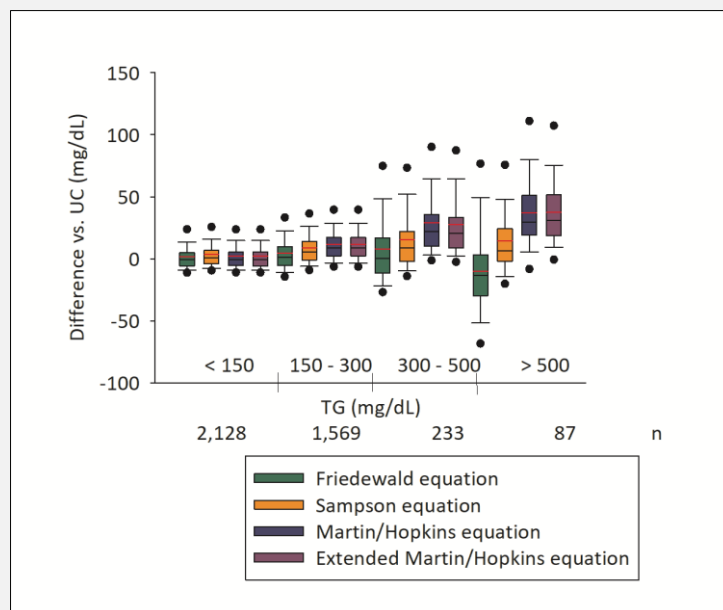


Figure S3. Effect of increasing triglycerides on the accuracy of LDL-C_{FW} (Friedewald equation), LDL-C_{SN} (Sampson equation), LDL-C_{MH} (Martin/Hopkins equation), and extended LDL-C_{MH} (Martin/Hopkins equation).

The means of the differences between formula-derived LDL-C and LDL-C_{UC} (beta quantification) are shown as boxplots in mg/dL. Red center lines represent means, black lines medians. The black boxes span from the 25th to 75th percentiles. The black whiskers mark the 10th and 90th percentiles. The black dots mark the 5th and 95th percentiles. Samples were divided into four strata according to TGs as indicated. Significant differences were observed between the LDL-C formulas and LDL-C_{UC} across all TG strata, with the only exception for LDL-C_{FW} compared to the LDL-C_{UC} at TG < 150 mg/dL. The number (n) of datasets is listed below the diagram. TG - triglycerides, MD - mean difference.

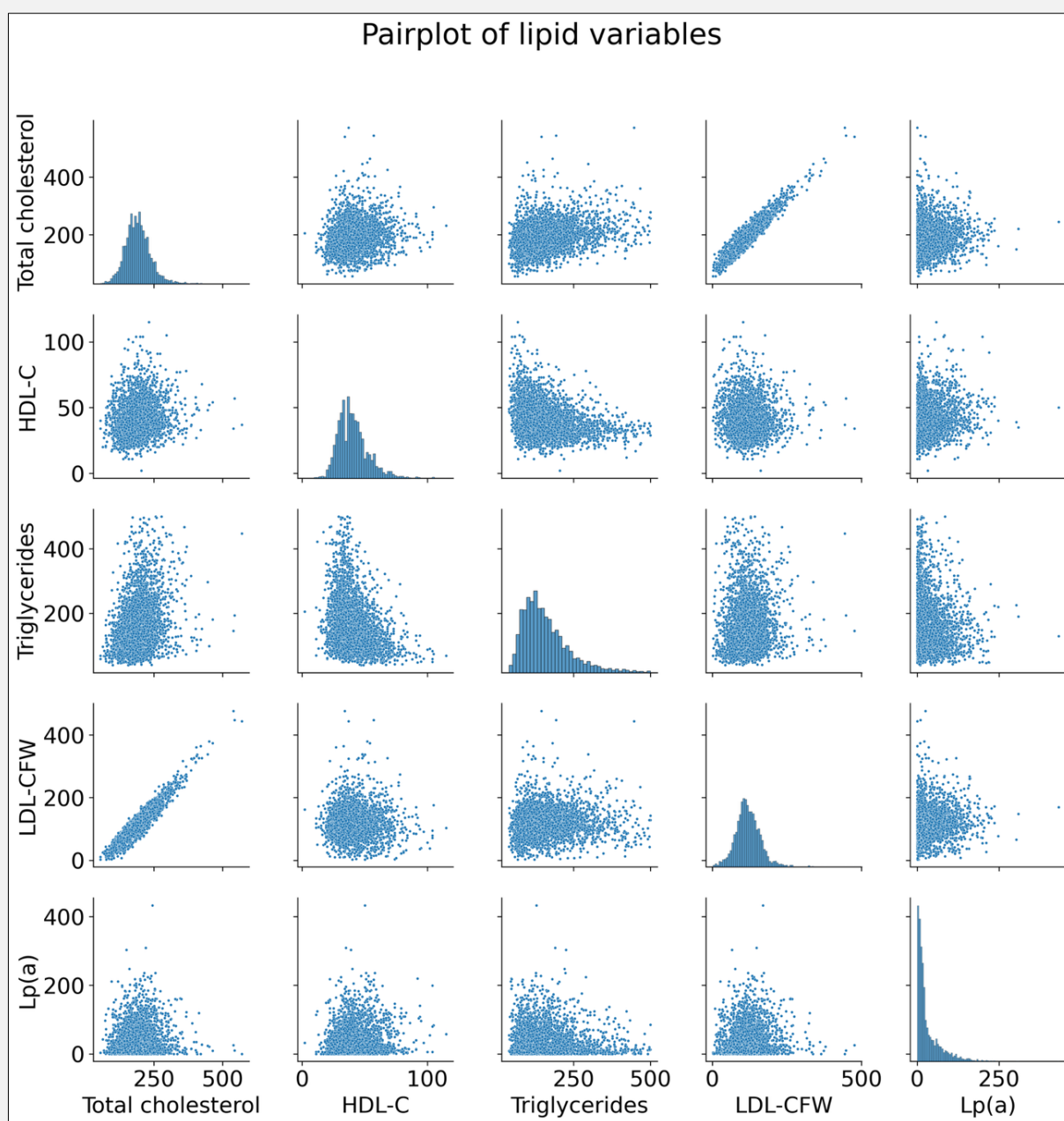


Figure S4. Correlation analysis between lipid variables using scatter plots and histograms.

Each row refers to a variable, which is related to itself (in a histogram) and four other variables (in a scatter plot). First row - total cholesterol, 2nd row - HDL-C, 3rd row - triglycerides, 4th row - LDL-C_{FW}, and 5th row - Lp(a).

HDL-C - high density lipoprotein cholesterol, LDL-C FW - low density lipoprotein determined by Friedewald equations.

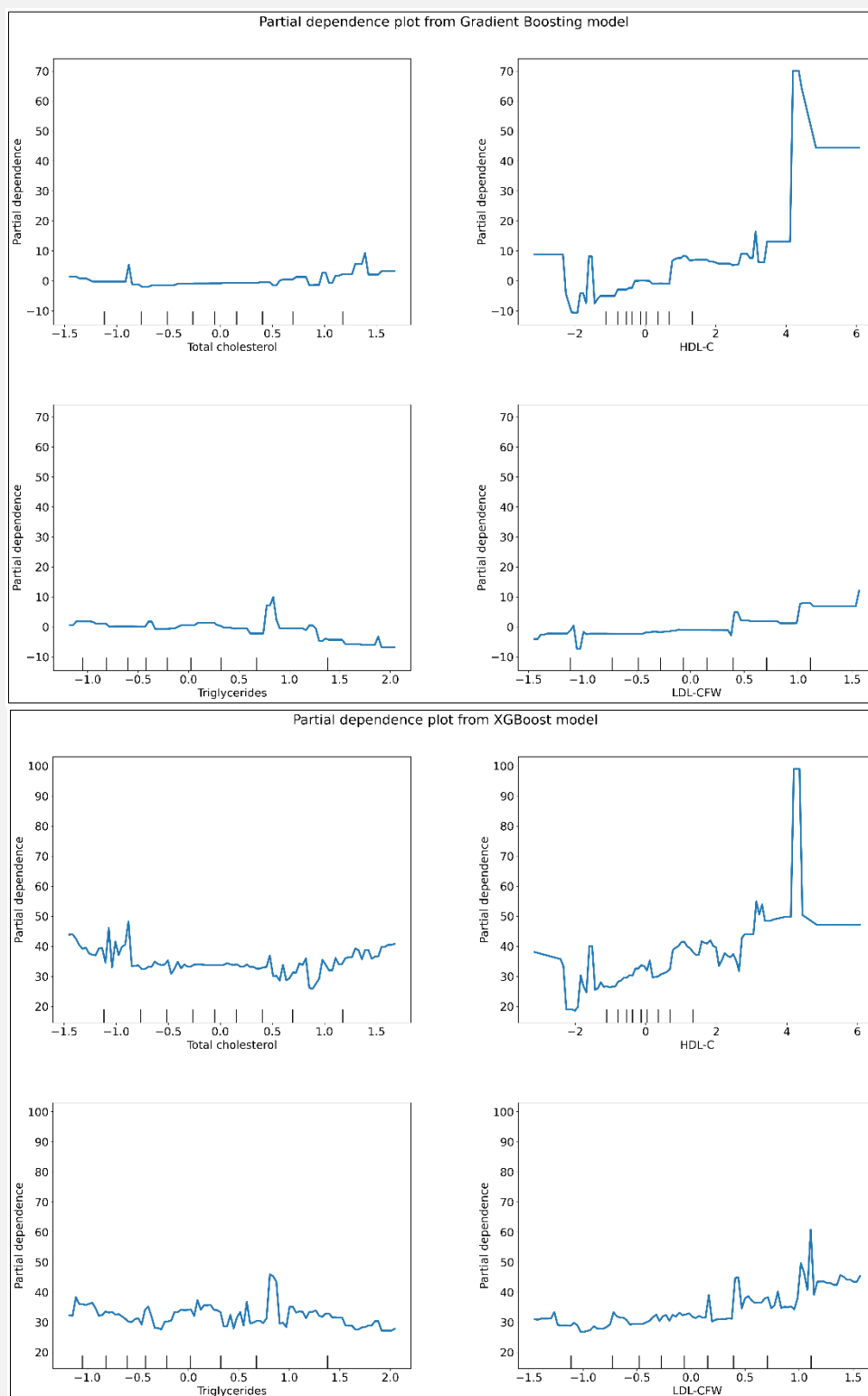


Figure S5. Partial dependence plots for gradient boosting (left panel) and for XGBoost (right panel).

First row, left - total cholesterol, first row, central - HDL-C, first row, right - LDL-C_{FW}. The partial dependence is plotted on the x-axis and the corresponding variable on the y-axis.

HDL-C - high density lipoprotein cholesterol, LDL-C FW - low density lipoprotein determined by Friedewald equations.