Received: 25 July 2023 | Revised: 19 October 2023 | Accepted: 28 October 2023

DOI: 10.1111/jcpe.13902

ORIGINAL ARTICLE

Journal of Clinical Periodontology WILEY

Serum lipoprotein subfractions are associated with the periodontal status: Results from the population-based cohort SHIP-TREND

Marius Kapp[1] | Birte Holtfreter[1] | Thomas Kocher[1] | Nele Friedrich[2] | Christiane Pink[3] | Henry Völzke[4,5] | Matthias Nauck[2]

[1]Department of Restorative Dentistry, Periodontology, Endodontology, and Preventive and Pediatric Dentistry, Dental School, University Medicine Greifswald, Greifswald, Germany

[2]Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Greifswald, Germany

[3]Department of Orthodontics, Dental School, University Medicine Greifswald, Greifswald, Germany

[4]German Centre for Cardiovascular Research (DZHK), Partner Site Greifswald, Greifswald, Germany

[5]Institute for Community Medicine, SHIP/Clinical-Epidemiological Research, University Medicine Greifswald, Greifswald, Germany

Correspondence
Birte Holtfreter, Department of Restorative Dentistry, Periodontology, Endodontology, Preventive and Pediatric Dentistry, University Medicine Greifswald, Fleischmannstraße 42, 17475 Greifswald, Germany.
Email: birte.holtfreter@med.uni-greifswald.de

Funding information
German Federal State of Mecklenburg-West Pomerania

Abstract

Aim: To investigate the medium-term associations of serum protein subfractions derived from proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy with periodontitis and tooth loss.

Materials and Methods: A total of 3031 participants of the cohort Study of Health in Pomerania (SHIP-TREND) were included. In addition to conventional serum testing, serum lipoprotein contents and subfractions were analysed by ^{1}H-NMR spectroscopy. Confounder-adjusted associations of lipoprotein variables with periodontitis and the number of missing teeth variables were analysed using mixed-effects models with random intercepts for time across individuals, accounting for multiple testing.

Results: While only spurious associations between lipoprotein levels from conventional blood tests were found—that is, triglycerides were associated with mean clinical attachment level (CAL) and low-density lipoprotein cholesterol/high-density lipoprotein cholesterol (LDL-C/HDL-C) ratio with the number of missing teeth - several associations emerged from serum lipoprotein subfractions derived from ^{1}H-NMR analysis. Specifically, elevated LDL triglycerides were associated with higher levels of mean probing depth (PD), mean CALs, and increased odds of having <20 teeth. HDL-4 cholesterol levels were inversely associated with mean PD. Systemic inflammation (C-reactive protein) might mediate the effects of LDL and HDL triglyceride contents on periodontitis severity.

Conclusions: Several associations between serum lipoprotein subfractions and periodontitis were observed. As the underlying biochemical mechanisms remain unclear, further research is needed.

KEYWORDS
cohort study, epidemiology, lipoprotein profile, periodontitis, tooth loss

Clinical Relevance

Scientific rationale for study: To date, no cohort data on the associations of serum protein subtractions with periodontitis and the number of missing teeth is available.

Principal findings: Using 7-year follow-up data from a population-based cohort study, consistent associations of serum lipoprotein subfractions, mainly LDL triglyceride contents, with periodontitis were observed. Systemic inflammation could be a possible pathway.
Practical implications: Taking our findings into account in nutritional counselling might have beneficial effects on periodontitis prevention and treatment in the general population in a broader perspective.

1 | INTRODUCTION

Serum lipoproteins are macromolecular assemblies that facilitate the circulation of insoluble metabolites throughout the cardiovascular system. Lipoproteins are composed of an inner covalent core of triglycerides and cholesterol esters and an outer polar layer of apolipoproteins and phospholipids (Feingold, 2000). Depending on their molecular composition and size, lipoproteins are divided into different classes. The entirety of all lipoprotein subclasses is referred to as an individual's lipid profile (Feingold, 2000).

Altered lipid profiles are a pervasive burden. With a prevalence of 39% pathologically elevated serum lipid levels among adults worldwide, 2.6 million deaths (4.5% of total mortality rate) are attributable to it every year (World Health Organization, 2023). Dyslipidaemia is involved in pathological pathways of various inflammatory diseases such as atherosclerosis (Rader & Daugherty, 2008), peripheral artery disease (Firnhaber & Powell, 2019; Tendera et al., 2011) and pancreatitis (Yang & McNabb-Baltar, 2020), possibly partly mediated by their effects on systemic chronic inflammation (Esteve et al., 2005).

Periodontitis is characterized by a destructive inflammatory host response to colonization of the periodontium by pathogenic bacteria (Papapanou et al., 2018), leading to loss of connective tissue and the supporting bone (Holtfreter et al., 2010; Kinane et al., 2015). If left untreated, periodontitis can lead to tooth loss and eventually edentulism (Ramseier et al., 2017). In East Germany, 44.9% of 35- to 44-year-olds and 63.9% of 65- to 74-year-olds had moderate or severe periodontitis in 2015 (Schutzhold et al., 2015), whereas globally more than 1 billion people were affected by severe periodontitis in 2019 (Jain et al., 2023). Periodontitis is therefore considered one of the most common global burdens (Disease et al., 2018; Eke et al., 2015; Listl et al., 2015).

Although the aetiology of periodontitis is complex, pre-existing low-grade systemic inflammation was identified as an accelerator of periodontal destruction (Josey & Merchant, 2016). Various risk factors for periodontitis, such as smoking, low physical activity, obesity and unbalanced diet, increase serum levels of inflammatory mediators (Bonaccio et al., 2017; Bruunsgaard, 2005; Yanbaeva et al., 2007), thereby affecting the onset and progression of periodontitis (Pink et al., 2015). Thus, it can be hypothesized that systemic inflammation may link dyslipidaemia with periodontitis.

The current evidence for an association between serum lipid levels and periodontitis is very inconsistent and weak. Only a few cross-sectional studies have reported associations between serum lipid profiles and periodontitis in a population-based setting (Izumi et al., 2009; Kim & Nam, 2020; Lee et al., 2018). Other studies have reported associations only in specific subgroups (Saxlin et al., 2008) or no significant associations at all (Korhonen et al., 2011). However, apart from two case–control studies (Cutler et al., 1999; Losche et al., 2000), all other studies were cross-sectional in design, so none of them could make a statement on causality.

Conventional lipid profiling is performed using a blood lipid panel testing. But this method provides only a limited characterization of the lipoprotein subclasses, which might explain the inconsistent and insignificant results in previous studies (Emeasoba, 2022). In contrast, proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy has provided a broader and more precise insight into lipoprotein composition and content in other research areas (Wurtz et al., 2017). ^{1}H-NMR spectroscopy allows recording specific interaction of nuclei in a sample with an applied electromagnetic field. Advantages of ^{1}H-NMR analysis include its high reproducibility and its capability of non-destructive characterization, allowing examination of various analytes in a single sample (Teo et al., 2015). Therefore, a more distinct profiling technique could also be useful in interpreting possible associations between lipoprotein subclasses and periodontitis.

To this end, we analysed associations of highly resolved lipoprotein particle measurements obtained by ^{1}H-NMR spectroscopy with periodontitis and tooth loss using 7-year follow-up data from the population-based Study of Health in Pomerania (SHIP-TREND). In addition to evaluating whether systemic inflammation links the lipoprotein profile with periodontitis, we also analysed the effects on high-sensitivity C-reactive protein (CRP).

2 | MATERIALS AND METHODS

2.1 | Study design and sample

SHIP-TREND is a population-based cohort study conducted in Western Pomerania, Germany. A random sample of 10,000 adults aged 20–79 years was drawn from the central resident's registration office of the federal state of Mecklenburg/Western Pomerania. The sample was stratified by age, sex and place of residence. The sample size reduced to 8826 individuals after exclusion of migrated ($n = 851$) and deceased individuals ($n = 323$). Incomplete/unreliable response ($n = 1039$) and refusal to participate ($n = 3367$) further reduced the sample size to 4420 participants (response 50.1%). Baseline

TABLE 1 Baseline characteristics of the total study population, supplemented with 7-year follow-up values for periodontal variables.

	N	Total (N = 3030[a])
Follow-up time, years	3030	7.4 ± 0.7 7.3 (7.0; 7.5)
Age, years	3030	48.1 ± 14.4 47 (37; 59)
Male sex, yes	3030	1438 (47.5%)
School education	3030	
<10 years		464 (15.3%)
10 years		1696 (56.0%)
>10 years		870 (28.7%)
Household equivalence income, €	3030	1416.3 ± 739.4 1275.0 (894.9; 1803.1)
Smoking status	3030	
Never smoker		1101 (36.3%)
Former smoker		1058 (34.9%)
Current smoker		871 (28.8%)
Food frequency score pattern	3030	
Unfavourable		2120 (70.0%)
Intermediate		524 (17.3%)
Recommendable		386 (12.7%)
Waist circumference, cm	3030	89.0 ± 14.0 88.0 (78.5; 98.5)
Known diabetes mellitus, yes	3030	177 (5.8%)
HbA1c, %	3030	5.2 ± 0.7 5.2 (4.8; 5.5)
Alcohol, g/day	3030	8.7 ± 13.1 3.9 (1.0; 11.1)
Physically inactive, yes	3030	904 (29.8%)
Dental visits within last 12 months, yes	3030	2697 (89.0%)
Low-density lipoprotein cholesterol, mmol/L	3030	3.43 ± 0.95 3.38 (2.76; 3.99)
High-density lipoprotein cholesterol, mmol/L	3030	1.45 ± 0.37 1.41 (1.17; 1.68)
Triglycerides, mmol/L	3030	1.55 ± 1.15 1.29 (0.90; 1.86)
Cholesterol, mmol/L	3030	5.52 ± 1.12 5.50 (4.70; 6.20)
LDL-C/HDL-C ratio	3030	2.54 ± 0.99 2.40 (1.81; 3.13)
NMR device	3030	
Bruker AVANCE NEO 600 MHz NMR		1261 (41.6%)
Bruker AVANCE III 600 MHz NMR		917 (30.3%)
Bruker AVANCE II 600 MHz NMR		852 (28.1%)
Baseline periodontal status and C-reactive protein		
Mean PD, mm	2975	2.55 ± 0.68 2.38 (2.13; 2.75)
Mean CAL, mm	2859	2.30 ± 1.60 1.92 (1.20; 3.06)
CDC/AAP case definition	2804	
No or mild periodontitis		1431 (51.0%)
Moderate periodontitis		952 (34.0%)
Severe periodontitis		421 (15.0%)
Number of missing teeth	3030	5.7 ± 6.5 3 (1; 8)
C-reactive protein, mg/L	2941	2.36 ± 3.86 1.19 (0.61; 2.68)
7-year periodontal status and C-reactive protein		
Mean PD, mm	1891	2.38 ± 0.53 2.25 (2.07; 2.57)
Mean CAL, mm	1808	2.20 ± 1.25 1.84 (1.41; 2.61)
CDC/AAP case definition	1783	
No or mild periodontitis		1064 (59.7%)
Moderate periodontitis		550 (30.8%)
Severe periodontitis		169 (9.5%)
Number of missing teeth	2021	6.40 ± 7.44 4 (1; 8)
C-reactive protein, mg/L	2021	2.34 ± 4.61 1.17 (0.59; 2.51)

[a]Participants taking lipid-lowering medication were excluded. Data are presented as mean ± standard deviation and median (25%; 75% quantiles) or number (percentage).

Abbreviations: AAP, American Academy of Periodontology; CAL, clinical attachment level; CDC, Centers for Disease Control and Prevention; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; N, number; NMR, nuclear magnetic resonance; PD, probing depth; SD, standard deviation.

examinations were conducted between 2008 and 2012. The first follow-up (SHIP-TREND-1) was conducted between 2014 and 2018 on 2507 participants. A flow-chart of the study population is shown in Figure A2.

Our reporting followed the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies (von Elm et al., 2014). Detailed information on the periodontal examination, calibration data, laboratory measurements, ^{1}H-NMR profiling and covariates is provided in Appendix S1.

2.2 | Statistical analysis

Outcome variables comprised mean PD, mean CAL, the Centers for Disease Control and Prevention (CDC)/American Academy of Periodontology (AAP) case definition and the number of missing teeth. Means with standard deviations (SD) and/or medians with 25% and 75% quantiles were reported for continuous variables. Relative frequency distributions were computed for categorical variables.

Matrix	Analyte	N	SD
Total plasma	Triglycerides	4867	85.9
	Cholesterol	4867	48.4
	Apo−B	4867	26.7
VLDL	Triglycerides	4867	65.1
	Cholesterol	4853	16.4
	Phospholipids	4867	15
	Apo−B	4863	5.4
IDL	Triglycerides	4746	15.1
	Cholesterol	4848	8.2
	Phospholipids	4864	5
	Apo−B	4866	2.6
LDL	Triglycerides	4867	7.6
	Cholesterol	4866	37.8
	Phospholipids	4867	18.5
	Apo−B	4867	23.5
HDL	Triglycerides	4867	4.7
	Cholesterol	4867	14.9
	Phospholipids	4867	21
	Apo−A1	4867	30.7
	Apo−A2	4867	6.1
VLDL−1	Triglycerides	4835	37.9
	Cholesterol	4671	6.8
VLDL−2	Triglycerides	4863	13.9
	Cholesterol	4744	3.3
VLDL−3	Triglycerides	4855	10.5
	Cholesterol	4758	3.4
VLDL−4	Triglycerides	4865	5.5
	Cholesterol	4824	3.5
VLDL−5	Triglycerides	4862	0.9
	Cholesterol	4693	0.7
LDL−1	Triglycerides	4864	2.8
	Cholesterol	4858	8.1
	Apo−B	4863	4.1
LDL−2	Triglycerides	4863	1
	Cholesterol	4842	7.3
	Apo−B	4854	3.6
LDL−3	Triglycerides	4862	0.9
	Cholesterol	4808	8.6
	Apo−B	4839	4.5
LDL−4	Triglycerides	4856	1.4
	Cholesterol	4801	9.6
	Apo−B	4813	5.9
LDL−5	Triglycerides	4862	1.6
	Cholesterol	4856	9.9
	Apo−B	4860	6.8
LDL−6	Triglycerides	4867	2.2
	Cholesterol	4864	11.2
	Apo−B	4866	9.3
HDL−1	Triglycerides	4863	2.2
	Cholesterol	4860	9
	Apo−A1	4864	15.9
	Apo−A2	4867	1.7
HDL−2	Triglycerides	4866	0.9
	Cholesterol	4865	3.1
	Apo−A1	4867	6.2
	Apo−A2	4867	1.4
HDL−3	Triglycerides	4866	1
	Cholesterol	4865	3.1
	Apo−A1	4867	7.6
	Apo−A2	4865	1.9
HDL−4	Triglycerides	4867	1.4
	Cholesterol	4866	4.5
	Apo−A1	4867	13.6
	Apo−A2	4867	4.3

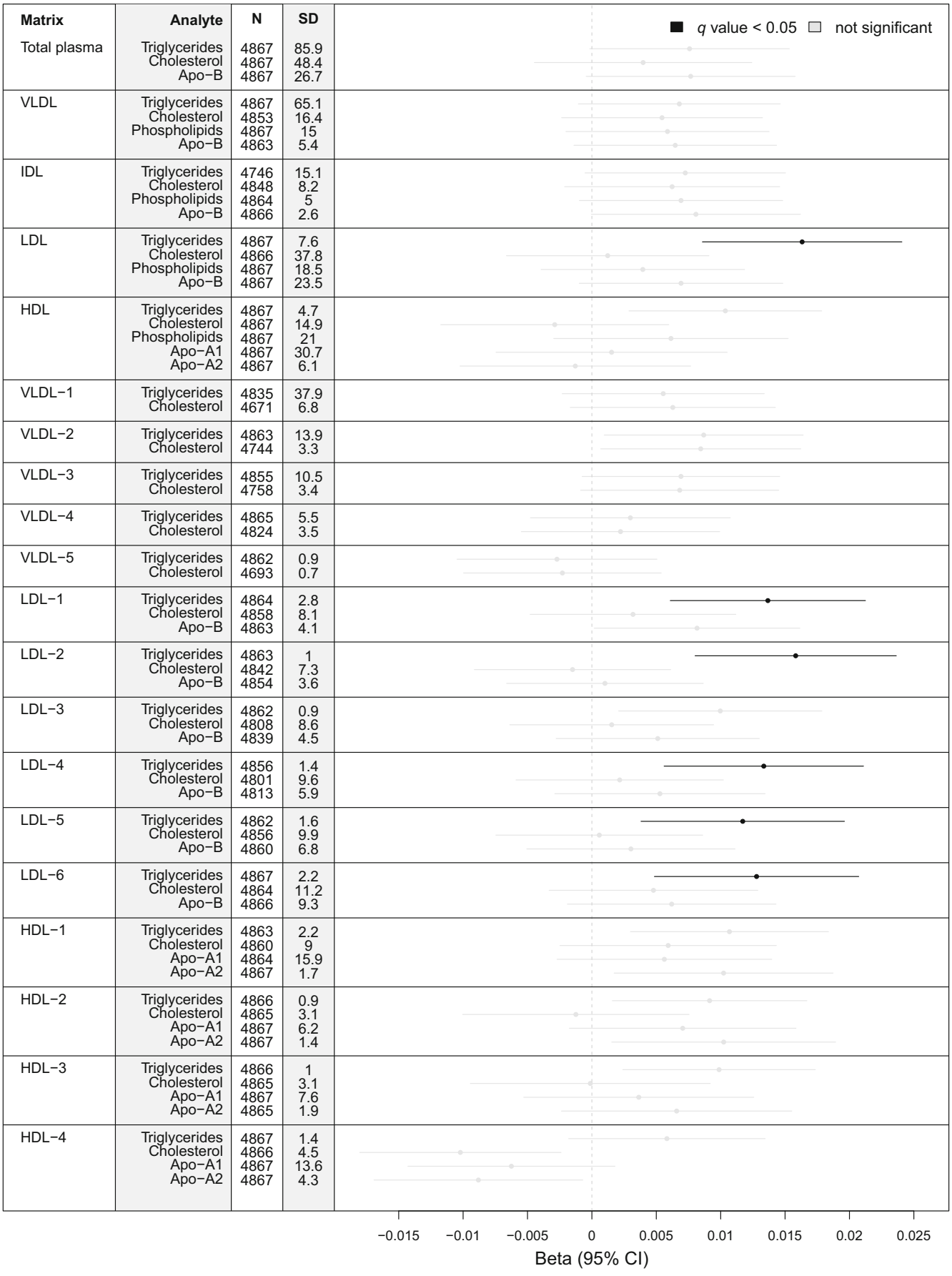

FIGURE 1 Legend on next page.

Generally, we fitted mixed-effects models with random intercepts for time across individuals (Singer & Willett, 2003). Mixed models can incorporate all available data and handle missing data flexibly. Models were adapted by sequentially fitting the fixed (i.e., find optimal parameterizations for all variables) and the random part (i.e., define the covariance structure of random effects) (Kwok et al., 2008). Specifically, time-varying levels of outcome variables were modelled as dependent variables. The confounders were selected on the basis of prior clinical knowledge and checked by directed acyclic graphs. Thus, the fixed-factors part of all models included baseline levels of exposure variables (per 1 SD increase; calculated from baseline levels), age, sex, school education, household equivalence income, smoking status, alcohol, known diabetes mellitus, haemoglobin A1c (HbA1c), physical activity, waist circumference, dental visits within the last 12 months and the ^{1}H-NMR device. Non-linear associations with the outcome variables were checked for all continuous variables, but only confirmed for age; thus, age was modelled via restricted cubic splines with three knots. For mean PD, mean CAL and CRP (all distributions were skewed), we fitted generalized linear mixed models via penalized quasi-likelihood; beta coefficients with 95% confidence intervals (CIs) are reported. For the CDC/AAP case definition, ordinal logistic mixed models were estimated; odds ratios (ORs) with 95% CIs are reported. For the number of missing teeth, negative binomial mixed-effects models were estimated; incidence rate ratios (IRRs) with 95% CIs are reported.

To account for multiple testing when evaluating associations of lipoprotein particle measurements obtained by ^{1}H-NMR spectroscopy with outcome variables (separately for each of the outcome variables), we adjusted the *p*-values from regression models by controlling the false discovery rate (FDR) at 5% using the Benjamini–Hochberg procedure. Using the *q*-values, significant associations ($q < 0.05$) are marked black in the respective plots. To additionally summarize the results for the four outcomes, heat plots of *q*-values (colours from blue to red) are constructed. For standard lipoprotein levels from conventional blood tests, no screening approach was pursued; thus, *p*-values were not corrected for multiple testing.

In sensitivity analyses, follow-up-only analyses were conducted for mean PD, mean CAL and the CDC/AAP case definition and are graphically reported in Figures A12–A14. For mean probing depth (PD) and mean clinical attachment level (CAL; skewed distributions), we fitted generalized linear models with gamma distribution and log link. Effect estimates are presented as exp(β) with the corresponding 95% CIs and interpreted as a percent change of the outcome (Manning et al., 2005). For the CDC/AAP case definition, ordinal logistic regression models were estimated, and ORs with 95% CIs are reported. Incident tooth loss (any tooth loss; yes/no; between baseline and follow-up) was analysed using logistic regression models, reporting ORs and 95% CIs (Figure A15). For each outcome variable separately, *p*-values were adjusted for multiple testing, as described above.

Whenever *p*-values are reported, a two-sided $p < .05$ is considered statistically significant. All analyses were performed using Stata/SE version 17.0 (StataCorp., 2021) and R 4.1.2 (R Core Team, 2023).

3 | RESULTS

3.1 | Baseline and follow-up characteristics

Top panel of Table 1 shows the basic characteristics of the study population at baseline. Participants were followed for an average of 7.4 years. At baseline, the mean age was 48.1 years (SD 14.4), and 47.5% were male. The mean serum levels of LDL-C, HDL-C, triglycerides and cholesterol were 3.43 ± 0.95 mol/L, 1.45 ± 0.37 mol/L, 1.55 ± 1.15 mol/L and 5.52 ± 1.12 mol/L, respectively. For baseline levels of all lipoprotein particles, see Table A1.

The bottom panel describes the periodontal status of participants at baseline and at the 7-year follow-up. Mean PD and mean CAL were 2.55 ± 0.68 mm and 2.30 ± 1.60 mm, respectively, at baseline, and 2.38 ± 0.53 and 2.20 ± 1.25 mm, respectively, at follow-up. The mean number of missing teeth in participants was higher (6.4 ± 7.5) during follow-up than at baseline (5.7 ± 6.6).

3.2 | Associations of plasma lipoprotein particles and contents with periodontitis outcomes

We graphically presented effect estimates (with 95% CIs) for the whole range of lipoprotein particles and contents with mean PD (Figure 1), mean CAL (Figure 2), CDC/AAP case definition (Figure 3) and the number of missing teeth (Figure 4). We also generated models for the effects of total blood lipid levels on the four outcome variables (Figure 5). In short, higher levels of LDL, LDL-1, LDL-2 and

FIGURE 1 Associations of the whole range of lipoprotein particle measures obtained by ^{1}H-NMR spectroscopy with mean probing depth, excluding participants taking lipid-lowering medication (ATC Code C10). Depicted are beta coefficients with 95% confidence intervals (CI) from linear mixed-effects regression models for effects of lipoprotein subclasses (per 1 standard deviation [SD] increase) on the mean probing depth. The first column of each block contains the matrix (e.g., the specific particle), the second column contains the analyte determined (e.g. the cholesterol content), the third column contains the number of participants included (with and without repeated measurements) and the fourth column contains the SD of the lipoprotein particle measures at baseline. Significant associations (controlling the false discovery rate at 5%) are indicated in black. Models were adjusted for age, sex, school education, smoking status, known diabetes mellitus, HbA1c, physical inactivity, waist circumference, alcohol intake, household equivalence income, food frequency score pattern, dental visits and nuclear magnetic resonance device type. Apo, apolipoprotein; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; *N*, number of observations; VLDL, very-low-density lipoprotein.

Matrix	Analyte	N	SD
Total plasma	Triglycerides	4668	86.2
	Cholesterol	4668	48.2
	Apo−B	4668	26.7
VLDL	Triglycerides	4668	65.2
	Cholesterol	4655	16.5
	Phospholipids	4668	15
	Apo−B	4664	5.4
IDL	Triglycerides	4548	15.1
	Cholesterol	4649	8.2
	Phospholipids	4665	5
	Apo−B	4667	2.6
LDL	Triglycerides	4668	7.6
	Cholesterol	4667	37.6
	Phospholipids	4668	18.4
	Apo−B	4668	23.4
HDL	Triglycerides	4668	4.7
	Cholesterol	4668	14.9
	Phospholipids	4668	21.1
	Apo−A1	4668	30.8
	Apo−A2	4668	6.1
VLDL−1	Triglycerides	4636	38
	Cholesterol	4477	6.8
VLDL−2	Triglycerides	4664	13.9
	Cholesterol	4549	3.3
VLDL−3	Triglycerides	4656	10.6
	Cholesterol	4565	3.4
VLDL−4	Triglycerides	4666	5.5
	Cholesterol	4627	3.5
VLDL−5	Triglycerides	4663	0.9
	Cholesterol	4501	0.7
LDL−1	Triglycerides	4666	2.8
	Cholesterol	4659	8
	Apo−B	4665	4.1
LDL−2	Triglycerides	4664	1
	Cholesterol	4645	7.2
	Apo−B	4657	3.6
LDL−3	Triglycerides	4663	0.9
	Cholesterol	4614	8.5
	Apo−B	4643	4.5
LDL−4	Triglycerides	4657	1.4
	Cholesterol	4605	9.6
	Apo−B	4615	5.9
LDL−5	Triglycerides	4663	1.6
	Cholesterol	4657	9.9
	Apo−B	4661	6.8
LDL−6	Triglycerides	4668	2.2
	Cholesterol	4665	11.3
	Apo−B	4667	9.4
HDL−1	Triglycerides	4664	2.2
	Cholesterol	4662	9
	Apo−A1	4665	16
	Apo−A2	4668	1.7
HDL−2	Triglycerides	4667	0.9
	Cholesterol	4666	3.1
	Apo−A1	4668	6.2
	Apo−A2	4668	1.4
HDL−3	Triglycerides	4667	1
	Cholesterol	4666	3.1
	Apo−A1	4668	7.6
	Apo−A2	4666	1.9
HDL−4	Triglycerides	4668	1.4
	Cholesterol	4667	4.5
	Apo−A1	4668	13.6
	Apo−A2	4668	4.3

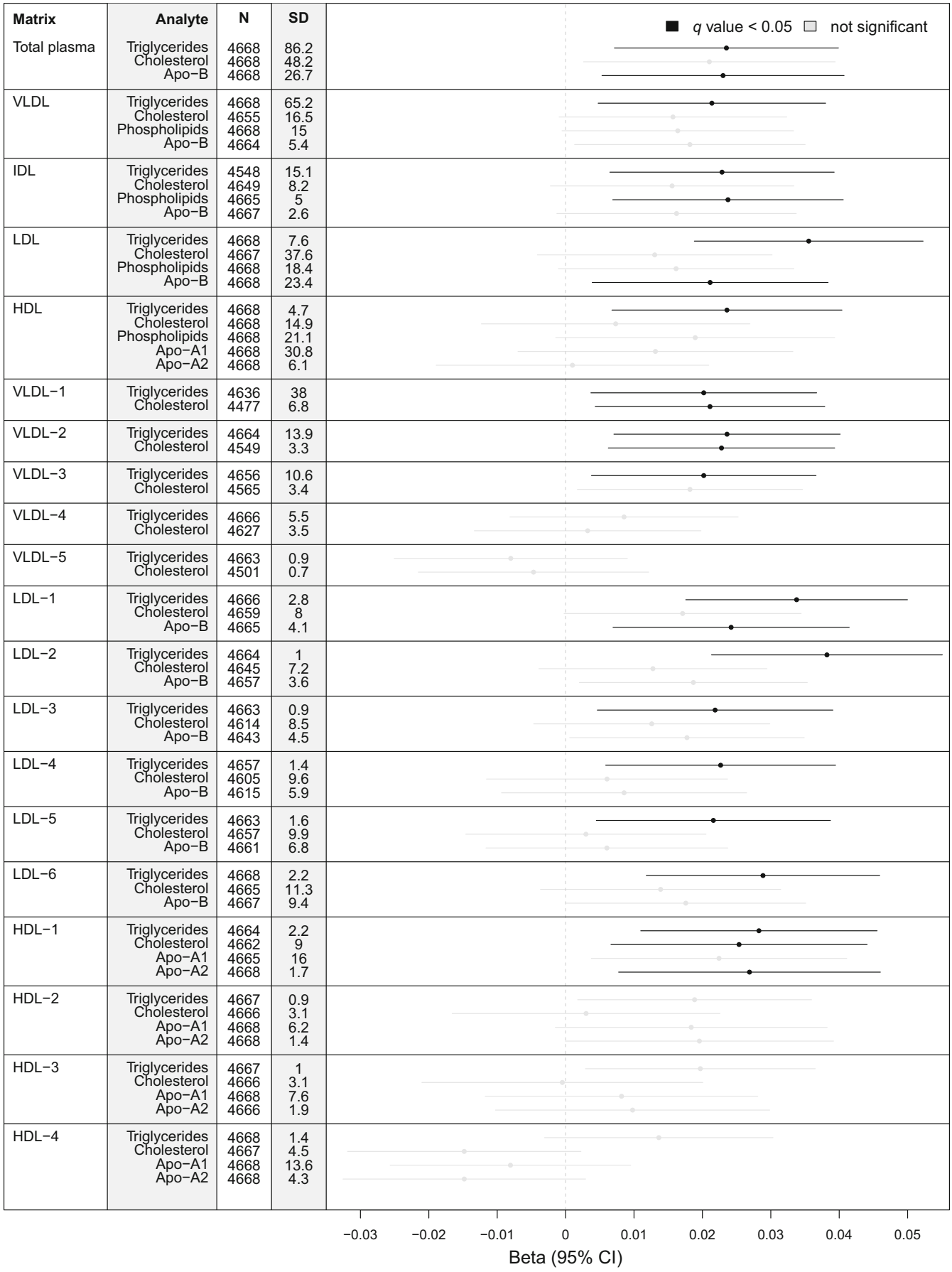

FIGURE 2 Legend on next page.

LDL-4 triglycerides were consistently associated with higher levels of all three periodontitis outcomes over the entire time period (Figure A3).

Specifically, elevated levels of LDL triglycerides (LDL-1/-2/-4/-6 triglycerides) as well as HDL and HDL-1 triglycerides were associated with higher values of mean PD. For example, for persons with a measured LDL triglyceride value higher by 7.6 mg/dL (equalling 1 SD), the mean PD was 0.016 mm higher. For HDL triglycerides (SD = 4.7 mg/dL), HDL-1 triglycerides (SD = 2.2 mg/dL), LDL-4 triglycerides (SD = 1.4 mg/dL) and LDL-6 triglycerides (SD = 2.2 mg/dL), the effects were comparable, with mean PD differing by 0.010–0.013 mm. In contrast, for persons with a measured HDL-4 cholesterol value higher by 4.5 mg/dL (equalling 1 SD), the mean PD was 0.0113 mm lower.

Associations for mean CAL were numerous and versatile. Except for VDLD-4/5 and HDL-2/3/4, higher levels of triglyceride contents were associated with higher levels of mean CAL. For instance, for persons with a VLDL (very-low-density lipoprotein) triglyceride value higher by 65.2 mg/dL (equalling 1 SD), the mean CAL was 0.021 mm higher. For persons with a measured LDL triglyceride value higher by 7.6 mg/dL (equalling 1 SD), the mean CAL was 0.036 mm higher; effect sizes were comparable for LDL-1 and LDL-2 triglycerides. In addition, higher levels of cholesterol contents in total plasma, VLDL-1 and VLDL-2, as well as higher levels of Apo-B contents in LDL-1 and Apo-A1/A2 contents in HDL-1, were associated with increased levels of mean CAL.

For the CDC/AAP case definition, ORs reflect the changes in odds of having a higher periodontitis classification (moderate or severe) for a 1 SD increase in the lipoprotein subclass. Higher levels of triglyceride contents in LDL, LDL-1, LDL-2 and LDL-4 were associated with increased odds of having higher levels of the CDC/AAP case definition.

Modelling the number of missing teeth revealed no significant hits. However, effect estimates for all lipoprotein particles were consistent in direction with those from periodontitis variables.

For total blood lipid levels, effect estimates were generally consistent in direction, albeit predominantly not statistically significant, showing risk associations for triglycerides, cholesterol, LDL-C and LDL-C/HDL-C ratio, but protective associations for HDL-C. Significant associations were found for triglycerides with mean CAL (Figure 5b) and for LDL-C/HDL-C ratio with the number of missing teeth (Figure 5d).

Several sensitivity analyses were performed. First, the number of healthy caries-free surfaces (Figure A4) revealed no significant associations with any of the 64 lipoprotein particle measures. Second, all analyses were repeated, including individuals taking lipid-lowering medication at baseline (Tables A2 and A3; Figures A5–A11). Accordingly, regression models were additionally adjusted for the intake of lipid-lowering medication. Overall, the results were consistent, essentially confirming the associations of triglyceride and cholesterol contents in different matrices with periodontal outcomes. In addition, HDL-3 triglyceride content was positively associated with moderate/severe periodontitis (Figure A7). The number of missing teeth (Figure A8) and the number of healthy caries-free surfaces (Figure A11) did not show significant associations with any of the lipoprotein particle measures. Third, follow-up-only analyses of periodontitis variables (Figures A12–A14) and analyses of incident tooth loss (Figure A15) were conducted. Basically, associations with triglyceride contents of LDL, LDL-1 and LDL-2 were confirmed. An increase of LDL triglyceride by 7.1 mg/dL was associated with a 2% increase in mean PD or a 4% increase in mean CAL.

3.3 | Associations of plasma lipoprotein particles and contents with CRP

To evaluate a potential mediation of effects via systemic inflammation, we investigated associations of lipoprotein particle measures with the CRP levels (Figure 6). Noticeably, higher levels of LDL and HDL triglyceride contents, as well as VLDL-4, VLDL-5, LDL-1, LDL-2, LDL-3, LDL-4, LDL-5, LDL-6, HDL-1, HDL-2 and HDL-3 triglyceride contents, were associated with higher CRP levels, while HDL-4 contents of cholesterol, Apo-A1 and Apo-A2 were inversely associated with CRP levels.

4 | DISCUSSION

This is the first cohort study with comprehensive 7-year follow-up data to report consistent associations of specific lipoprotein particles and contents determined by ^{1}H-NMR spectroscopy with periodontitis outcomes, while conventional lipid profiling revealed few significant hits. Specifically, triglyceride contents of LDL and LDL particles were positively associated with periodontitis (using mean PD, mean CAL

FIGURE 2 Associations of the whole range of lipoprotein particle measures obtained by ^{1}H-NMR spectroscopy with mean clinical attachment levels, excluding participants taking lipid-lowering medication (ATC Code C10). Depicted are beta coefficients with 95% confidence intervals (CI) from linear mixed-effects regression models for effects of lipoprotein subclasses (per 1 standard deviation [SD] increase) on the mean clinical attachment levels. The first column of each block contains the matrix (e.g., the specific particle), the second column contains the analyte determined, (e.g., the cholesterol content), the third column contains the number of participants included (with and without repeated measurements) and the fourth column contains the SD of the lipoprotein particle measures at baseline. Significant associations (controlling the false discovery rate at 5%) are indicated in black. Models were adjusted for age, sex, school education, smoking status, known diabetes mellitus, HbA1c, physical inactivity, waist circumference, alcohol intake, household equivalence income, food frequency score pattern, dental visits and nuclear magnetic resonance device type. Apo, apolipoprotein; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; *N*, number of observations; VLDL, very-low-density lipoprotein.

Matrix	Analyte	N	SD
Total plasma	Triglycerides	4588	86.5
	Cholesterol	4588	48.5
	Apo–B	4588	26.8
VLDL	Triglycerides	4588	65.8
	Cholesterol	4576	16.6
	Phospholipids	4588	15.2
	Apo–B	4584	5.5
IDL	Triglycerides	4471	15.1
	Cholesterol	4569	8.2
	Phospholipids	4585	5
	Apo–B	4587	2.7
LDL	Triglycerides	4588	7.7
	Cholesterol	4587	37.9
	Phospholipids	4588	18.5
	Apo–B	4588	23.6
HDL	Triglycerides	4588	4.7
	Cholesterol	4588	14.9
	Phospholipids	4588	21.1
	Apo–A1	4588	30.8
	Apo–A2	4588	6.2
VLDL–1	Triglycerides	4556	38.1
	Cholesterol	4401	6.8
VLDL–2	Triglycerides	4584	14.1
	Cholesterol	4472	3.4
VLDL–3	Triglycerides	4576	10.7
	Cholesterol	4488	3.4
VLDL–4	Triglycerides	4586	5.6
	Cholesterol	4550	3.5
VLDL–5	Triglycerides	4583	1
	Cholesterol	4426	0.7
LDL–1	Triglycerides	4586	2.8
	Cholesterol	4579	8.1
	Apo–B	4585	4.1
LDL–2	Triglycerides	4584	1
	Cholesterol	4565	7.3
	Apo–B	4577	3.6
LDL–3	Triglycerides	4583	0.9
	Cholesterol	4535	8.6
	Apo–B	4564	4.5
LDL–4	Triglycerides	4577	1.4
	Cholesterol	4527	9.7
	Apo–B	4536	6
LDL–5	Triglycerides	4583	1.6
	Cholesterol	4577	10
	Apo–B	4581	6.9
LDL–6	Triglycerides	4588	2.2
	Cholesterol	4585	11.4
	Apo–B	4587	9.4
HDL–1	Triglycerides	4584	2.2
	Cholesterol	4582	9
	Apo–A1	4585	15.9
	Apo–A2	4588	1.7
HDL–2	Triglycerides	4587	0.9
	Cholesterol	4586	3.1
	Apo–A1	4588	6.2
	Apo–A2	4588	1.4
HDL–3	Triglycerides	4587	1
	Cholesterol	4586	3.1
	Apo–A1	4588	7.7
	Apo–A2	4586	1.9
HDL–4	Triglycerides	4588	1.4
	Cholesterol	4587	4.5
	Apo–A1	4588	13.6
	Apo–A2	4588	4.3

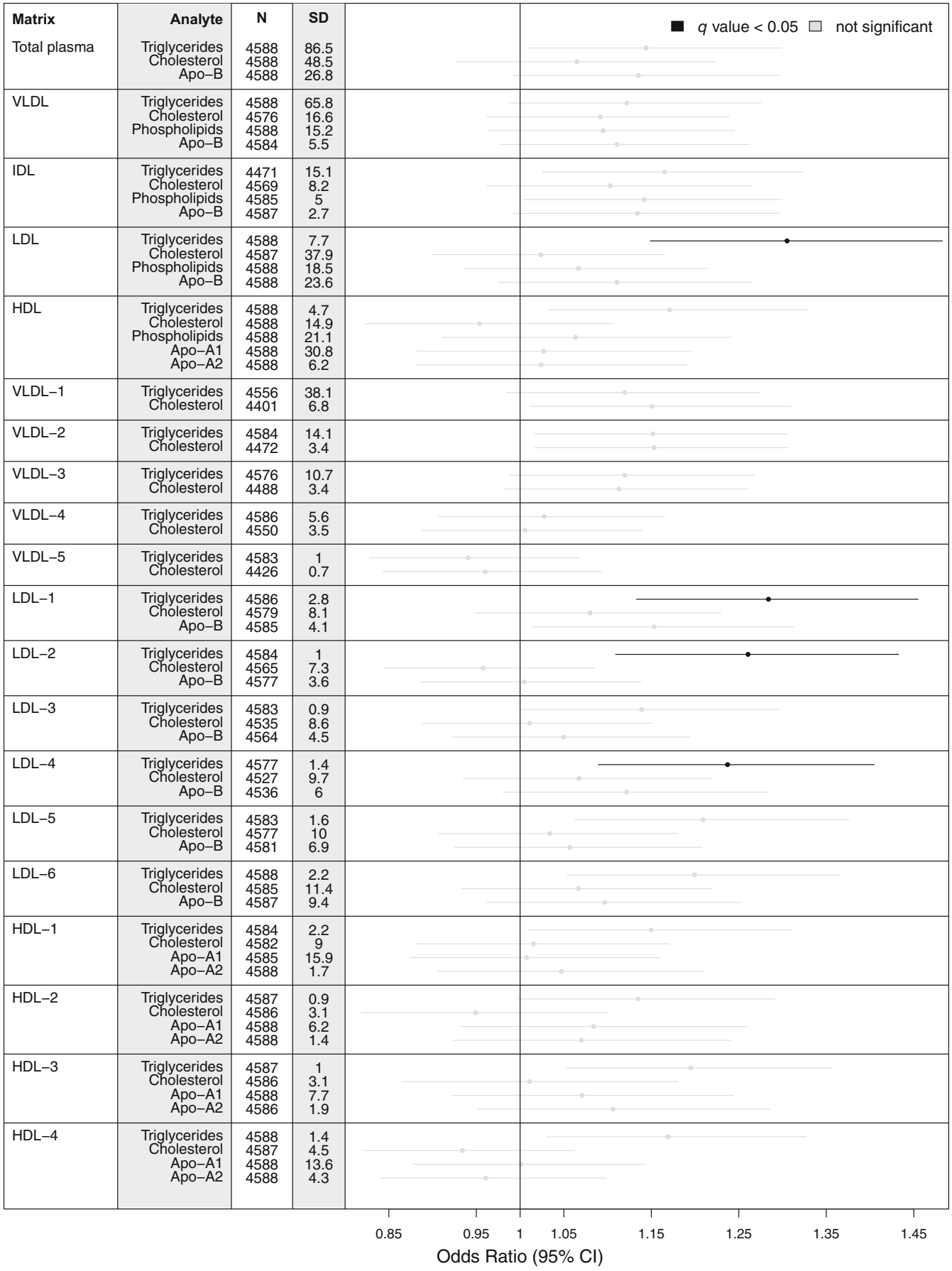

FIGURE 3 Legend on next page.

and the CDC/AAP case definition) and the number of missing teeth. In terms of mid-term effects on mean CAL, cholesterol contents of small dense VLDL particles and HDL-1 particles were noticeably associated with higher levels. Mediation via systemic inflammation seemed plausible, as triglyceride contents of LDL, HDL and the respective particles were associated with higher CRP levels.

Using conventional lipid profiling, previous studies had reported inconsistent associations between pathological blood lipid compositions and periodontitis. Two case–control studies found an association between elevated triglyceride levels and periodontal markers (Cutler et al., 1999; Losche et al., 2000). Kim and Nam (2020) found that the expression level of periodontal disease was 1499-fold higher in individuals with elevated triglyceride levels than in individuals with regular triglyceride profile, when they analysed 14,068 individuals of the Korea National Health and Nutrition Examination Survey (KNHANES). When Lee et al. examined 18,210 individuals of the same cohort, high total cholesterol, high total triglycerides and low HDL cholesterol were associated with periodontitis (Lee et al., 2013). However, pre-hypercholesterolemia, as a state of initially elevated total cholesterol, did not show any association with periodontitis. Other studies have limited validity because of small sample sizes (Izumi et al., 2009; Mikami et al., 2021) or restricted sample compositions (Izumi et al., 2009), or they assessed the CPI or CPITN (Kim & Nam, 2020; Lee et al., 2013), which is likely to overestimate or underestimate periodontal disease severity (Kingman & Albandar, 2002). Interestingly, only one study adjusted for lipid-lowering medication (Saxlin et al., 2008). Therefore, well-designed clinical and epidemiological surveys are urgently needed.

In contrast to the above studies, a cross-sectional study by Saxlin et al. (2008) found no significant association between the lipid profile and the presence of periodontal pockets in a population of 1297 non-smoking, normal-weight Finns under 50 years of age. These findings are consistent with our results, as we also found no significant associations of total serum lipid levels with periodontitis variables (Figure 5). Inconsistencies in previous studies may be due to the fact that undifferentiated measurements were evaluated: while conventional blood testing measures the amount of LDL, HDL, cholesterol and triglycerides in serum or plasma, it does not provide information on lipoprotein contents and subfractions. However, lipid metabolism is complex and lipid subfractions have diverse functions (Movva & Rader, 2009). While HDL-2, for example, plays a pivotal role in the reverse cholesterol transport pathway, other HDL subfractions are a crucial part of anti-inflammatory pathways due to their capability to bind free radicals and to inhibit the production of pro-inflammatory cytokines. Because of these differentiated functions, profiling for subfractions has been well established in other medical disciplines such as cardiovascular risk assessment (Harangi et al., 2009; Masuch et al., 2018). In a similar way, the lack of information on lipoprotein contents and subfractions could lead to a blind spot in the assessment of periodontal risk factors. In our study, ^{1}H-NMR profiling revealed that HDL-1 cholesterol and HDL-4 cholesterol may have inverse effects on periodontitis (Figures 1–4). While HDL-1 cholesterol was associated with increased levels of mean CAL, HDL-4 cholesterol levels showed an inverse association with mean PD in terms of a potentially protective effect. Therefore, ^{1}H-NMR analysis may be crucial for further research into the interplay between lipid subfractions and periodontitis.

Regardless of the lipoprotein subfraction (IDL, LDL, HDL, VDL 1–4, LDL 1–6, HDL-1), triglyceride contents were most consistently associated with increased levels of periodontitis, supporting the assumption that increased triglyceride levels may exacerbate periodontitis. Specifically, a 1 SD increase (7.6 mg/dL) in triglyceride contents of LDL was associated with ∼0.03 mm higher mean CAL levels. Although this effect seems rather moderate, it is similar in magnitude to the annual progression rates of mean CAL (0.02 mm/year) (Gatke et al., 2012). However, since previous studies had assumed that hypertriglyceridaemia peaks in middle age for men and increases throughout lifetime for women (Park et al., 2023), these effects may accumulate over time and be of greater clinical relevance in ageing societies.

Another way to address the question of whether elevated serum triglyceride levels are a clinically relevant risk factor for periodontitis is to examine the effects of statin use on periodontitis. Statin therapy lowers LDL cholesterol levels on average by 1.07 mmol/L after 1 year (Cholesterol Treatment Trialists et al., 2010), and, in turn, a reduction of 1 mmol/L would reduce risk for major vascular events and all-cause mortality by 10% and 20%, respectively (Cholesterol Treatment Trialists et al., 2010). In the SHIP-TREND participants with a measured total blood LDL-C value higher by 1.1 mmol/L (see Figure 5), the mean CAL was 0.01 mm higher, which is half the annual rate of progression (Gatke et al., 2012). Thus, reducing blood LDL-C levels might also have beneficial effects on the periodontal status. Indeed, statin use was found to be associated with a reduced risk for 5-year

FIGURE 3 Associations of the whole range of lipoprotein particle measures obtained by ^{1}H-NMR spectroscopy with the Centers for Disease Control and Prevention/American Academy of Periodontology (CDC/AAP) case definition, excluding participants taking lipid-lowering medication (ATC Code C10). Depicted are odds ratios with 95% confidence intervals (CI) from ordinal logistic mixed-effects regression models for effects of lipoprotein subclasses (per 1 standard deviation [SD] increase) on the CDC/AAP case definition. The first column of each block contains the matrix (e.g., the specific particle), the second column contains the analyte determined (e.g., the cholesterol content), the third column contains the number of participants included (with and without repeated measurements) and the fourth column contains the SD of the lipoprotein particle measures at baseline. Significant associations (controlling the false discovery rate at 5%) are indicated in black. Models were adjusted for age, sex, school education, smoking status, known diabetes mellitus, HbA1c, physical inactivity, waist circumference, alcohol intake, household equivalence income, food frequency score pattern, dental visits and nuclear magnetic resonance device type. Apo, apolipoprotein; CAL, clinical attachment level; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; *N*, number of observations; PD, probing depth; VLDL, very-low-density lipoprotein.

Matrix	Analyte	N	SD
Total plasma	Triglycerides	5051	86.1
	Cholesterol	5051	48.4
	Apo−B	5051	26.7
VLDL	Triglycerides	5051	65.4
	Cholesterol	5036	16.4
	Phospholipids	5051	15.1
	Apo−B	5047	5.4
IDL	Triglycerides	4926	15.1
	Cholesterol	5030	8.1
	Phospholipids	5048	5
	Apo−B	5050	2.6
LDL	Triglycerides	5051	7.6
	Cholesterol	5050	37.8
	Phospholipids	5051	18.5
	Apo−B	5051	23.5
HDL	Triglycerides	5051	4.7
	Cholesterol	5051	15
	Phospholipids	5051	21.1
	Apo−A1	5051	30.7
	Apo−A2	5051	6.2
VLDL−1	Triglycerides	5017	38.1
	Cholesterol	4850	6.8
VLDL−2	Triglycerides	5047	13.9
	Cholesterol	4928	3.3
VLDL−3	Triglycerides	5039	10.5
	Cholesterol	4940	3.4
VLDL−4	Triglycerides	5049	5.5
	Cholesterol	5006	3.5
VLDL−5	Triglycerides	5045	0.9
	Cholesterol	4870	0.7
LDL−1	Triglycerides	5048	2.8
	Cholesterol	5042	8.1
	Apo−B	5047	4.1
LDL−2	Triglycerides	5047	1
	Cholesterol	5024	7.3
	Apo−B	5036	3.6
LDL−3	Triglycerides	5046	0.9
	Cholesterol	4988	8.6
	Apo−B	5022	4.5
LDL−4	Triglycerides	5040	1.4
	Cholesterol	4983	9.6
	Apo−B	4997	5.9
LDL−5	Triglycerides	5046	1.6
	Cholesterol	5040	9.9
	Apo−B	5044	6.8
LDL−6	Triglycerides	5051	2.2
	Cholesterol	5047	11.3
	Apo−B	5050	9.4
HDL−1	Triglycerides	5047	2.2
	Cholesterol	5044	9
	Apo−A1	5048	15.9
	Apo−A2	5051	1.7
HDL−2	Triglycerides	5050	0.9
	Cholesterol	5049	3.1
	Apo−A1	5051	6.2
	Apo−A2	5051	1.4
HDL−3	Triglycerides	5049	1
	Cholesterol	5049	3.1
	Apo−A1	5051	7.6
	Apo−A2	5049	1.9
HDL−4	Triglycerides	5051	1.4
	Cholesterol	5050	4.5
	Apo−A1	5051	13.7
	Apo−A2	5051	4.3

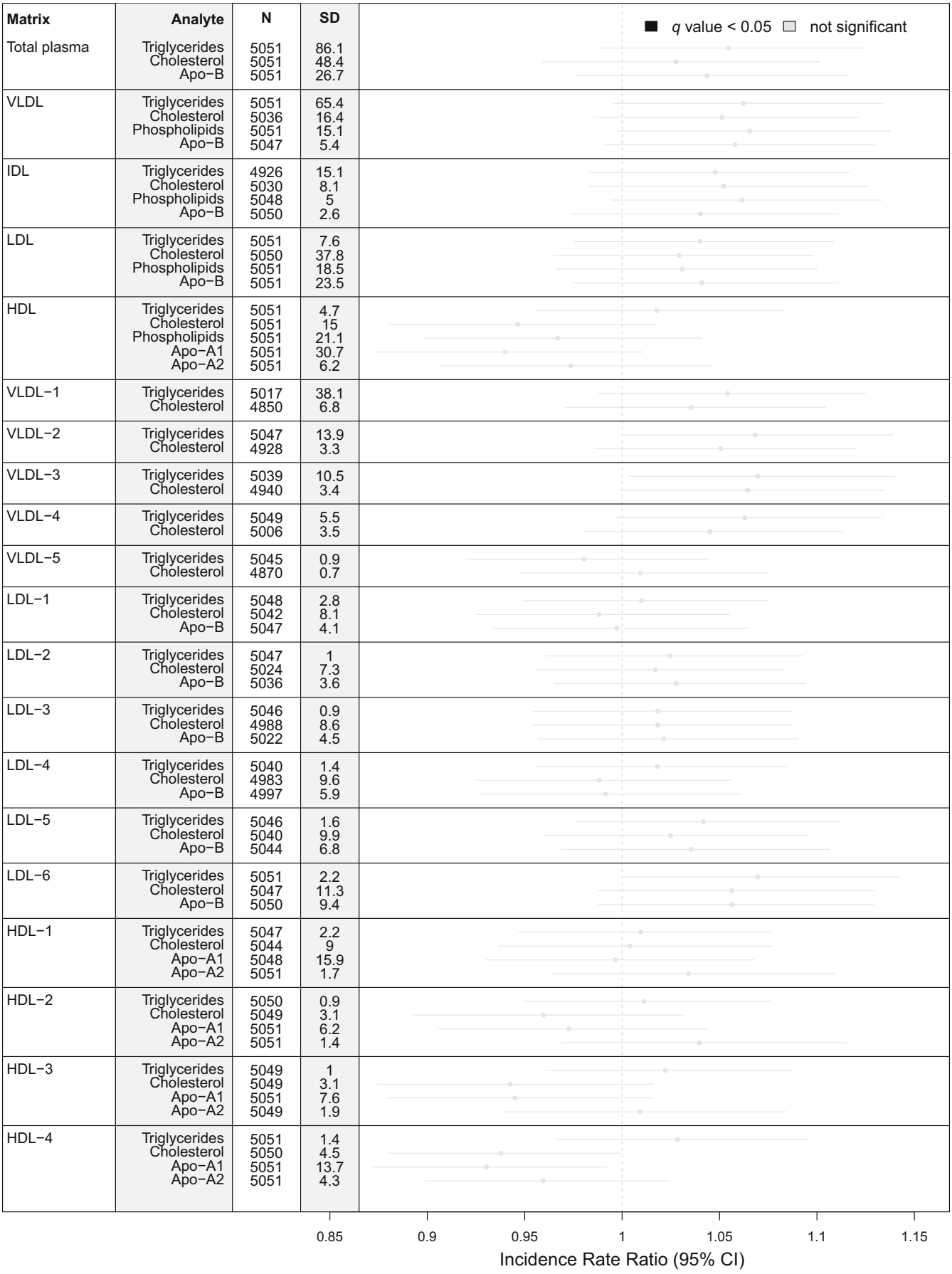

FIGURE 4 Legend on next page.

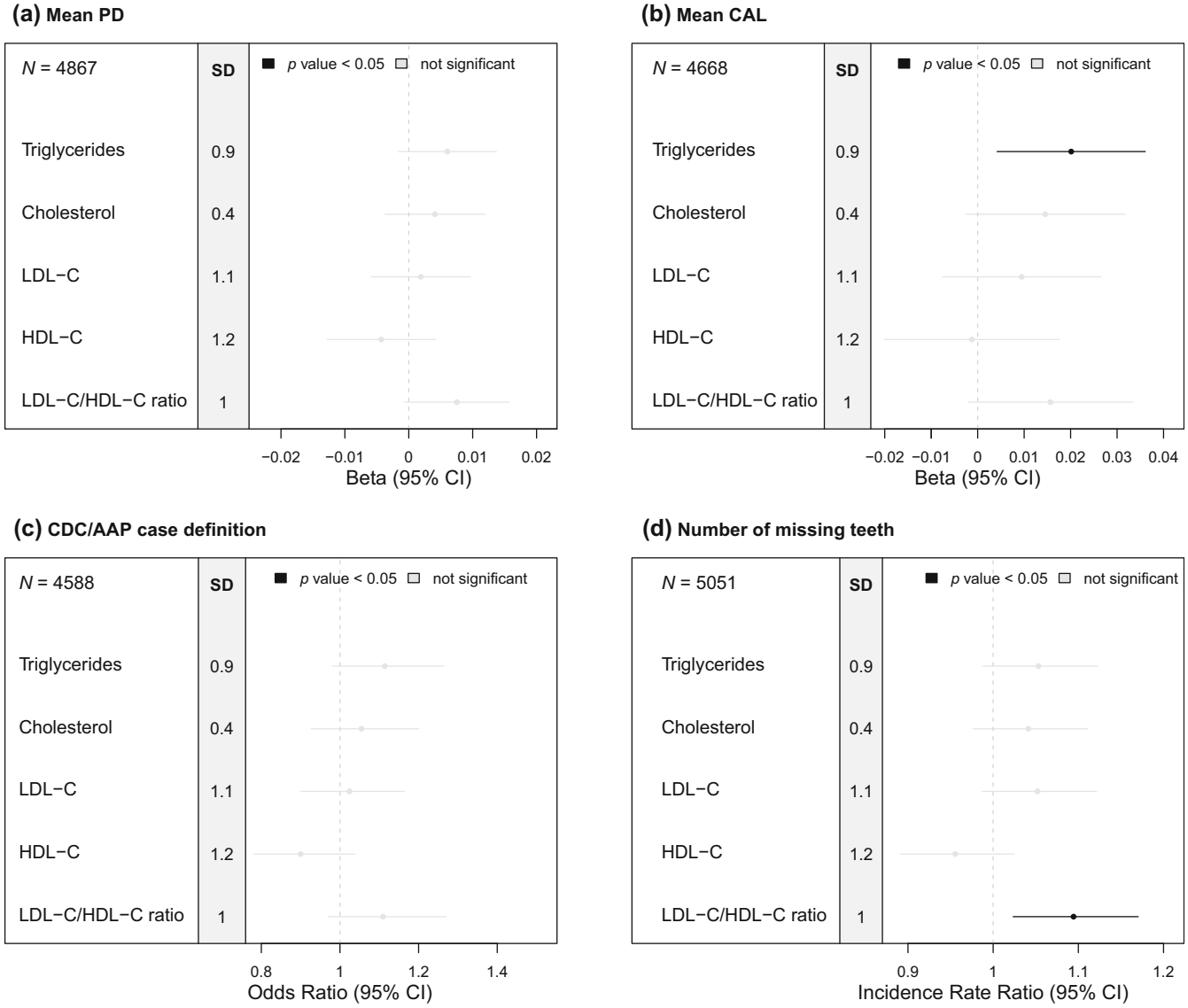

FIGURE 5 Associations of plasma lipid levels (measured in mmol/L) with (a) mean probing depth (PD), (b) mean clinical attachment level (CAL), (c) Centers for Disease Control and Prevention/American Academy of Periodontology (CDC/AAP) case definition, and (d) the number of missing teeth, excluding participants taking lipid-lowering medication (ATC Code C10). Depicted are betas, odds ratios or incidence rate ratios with 95% confidence intervals (CI) from linear, ordinal logistic or negative binomial mixed-effects regression models for effects of blood lipids (per 1 standard deviation [SD]) increase]. Significant associations are indicated in black. Models were adjusted for age, sex, school education, smoking status, known diabetes mellitus, HbA1c, physical inactivity, waist circumference, alcohol intake, household equivalence income, food frequency score pattern, dental visits and nuclear magnetic resonance device type. AAP, American Academy of Periodontology; CDC, Centers for Disease Control and Prevention; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; *N*, number of observations.

FIGURE 4 Associations of the whole range of lipoprotein particle measures obtained by ^{1}H-NMR spectroscopy with the number of missing teeth, excluding participants taking lipid-lowering medication (ATC Code C10). Depicted are incidence rate ratios with 95% confidence intervals (CI) from negative binomial mixed-effects regression models for effects of lipoprotein subclasses (per 1 standard deviation SD] increase) on the number of missing teeth. The first column of each block contains the matrix (e.g., the specific particle), the second column contains the analyte determined (e.g., the cholesterol content), the third column contains the number of participants included (with and without repeated measurements) and the fourth column contains the SD of the lipoprotein particle measures at baseline. Significant associations (controlling the false discovery rate at 5%) are indicated in black. Models were adjusted for age, sex, school education, smoking status, known diabetes mellitus, HbA1c, physical inactivity, waist circumference, alcohol intake, household equivalence income, food frequency score pattern, dental visits and nuclear magnetic resonance device type. Apo, apolipoprotein; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; *N*, number of observations; VLDL, very-low-density lipoprotein.

Matrix	Analyte	N	SD
Total plasma	Triglycerides	5127	86.5
	Cholesterol	5127	48.5
	Apo–B	5127	26.8
VLDL	Triglycerides	5127	65.8
	Cholesterol	5111	16.6
	Phospholipids	5127	15.2
	Apo–B	5123	5.5
IDL	Triglycerides	5003	15.1
	Cholesterol	5105	8.2
	Phospholipids	5124	5
	Apo–B	5126	2.7
LDL	Triglycerides	5127	7.7
	Cholesterol	5126	37.9
	Phospholipids	5127	18.5
	Apo–B	5127	23.6
HDL	Triglycerides	5127	4.7
	Cholesterol	5127	14.9
	Phospholipids	5127	21.1
	Apo–A1	5127	30.8
	Apo–A2	5127	6.2
VLDL–1	Triglycerides	5095	38.1
	Cholesterol	4928	6.8
VLDL–2	Triglycerides	5123	14.1
	Cholesterol	5005	3.4
VLDL–3	Triglycerides	5115	10.7
	Cholesterol	5016	3.4
VLDL–4	Triglycerides	5125	5.6
	Cholesterol	5082	3.5
VLDL–5	Triglycerides	5121	1
	Cholesterol	4946	0.7
LDL–1	Triglycerides	5124	2.8
	Cholesterol	5115	8.1
	Apo–B	5121	4.1
LDL–2	Triglycerides	5123	1
	Cholesterol	5097	7.3
	Apo–B	5109	3.6
LDL–3	Triglycerides	5122	0.9
	Cholesterol	5063	8.6
	Apo–B	5097	4.5
LDL–4	Triglycerides	5115	1.4
	Cholesterol	5058	9.7
	Apo–B	5073	6
LDL–5	Triglycerides	5122	1.6
	Cholesterol	5116	10
	Apo–B	5120	6.9
LDL–6	Triglycerides	5127	2.2
	Cholesterol	5122	11.4
	Apo–B	5126	9.4
HDL–1	Triglycerides	5123	2.2
	Cholesterol	5120	9
	Apo–A1	5124	15.9
	Apo–A2	5127	1.7
HDL–2	Triglycerides	5126	0.9
	Cholesterol	5125	3.1
	Apo–A1	5127	6.2
	Apo–A2	5127	1.4
HDL–3	Triglycerides	5125	1
	Cholesterol	5125	3.1
	Apo–A1	5127	7.7
	Apo–A2	5125	1.9
HDL–4	Triglycerides	5127	1.4
	Cholesterol	5126	4.5
	Apo–A1	5127	13.6
	Apo–A2	5127	4.3

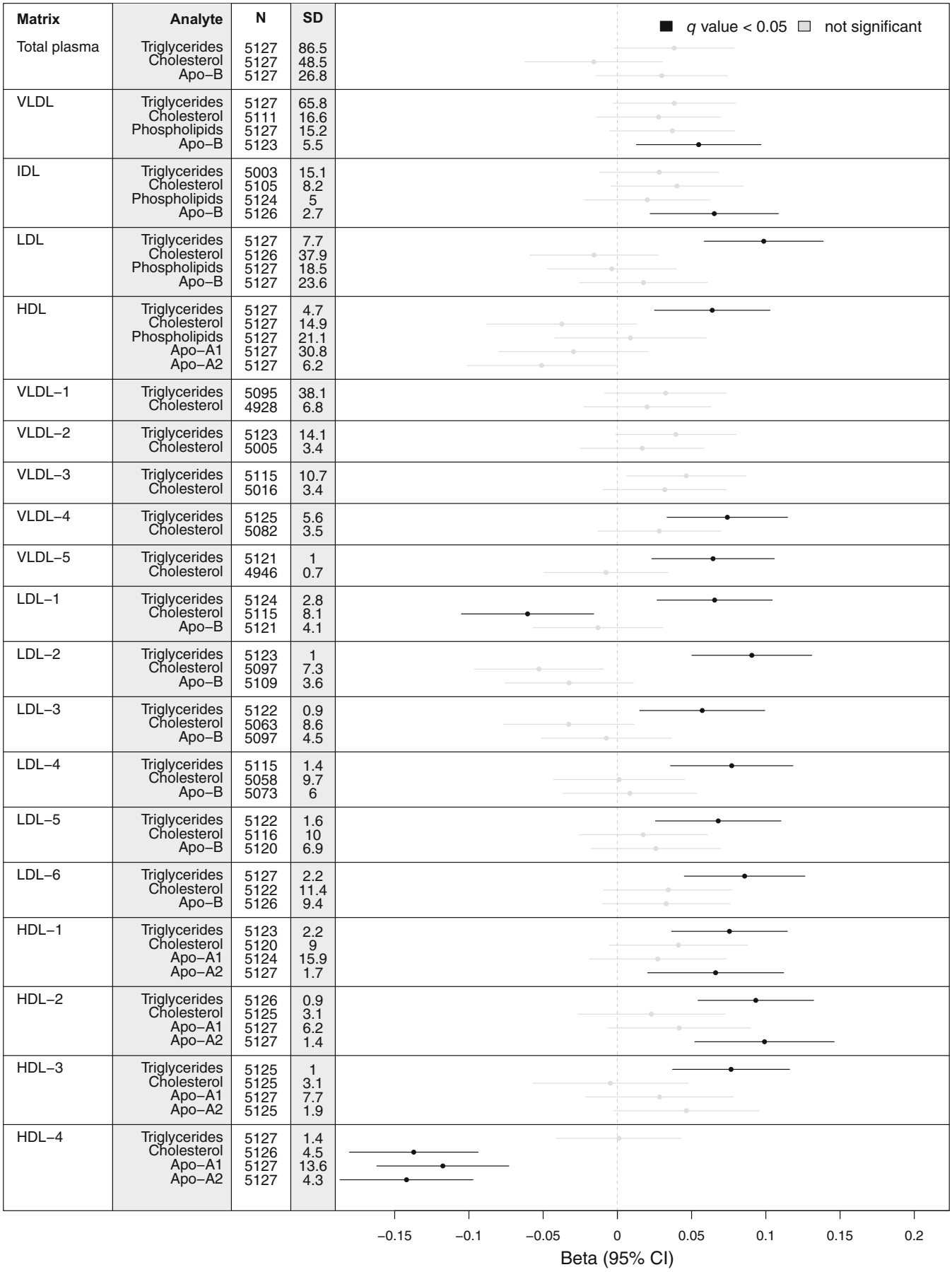

FIGURE 6 Legend on next page.

tooth loss (Meisel et al., 2014). In addition, a recent meta-analysis based on observational studies found a more favourable periodontal profile in patients taking statins (Di Spirito et al., 2021). Thus, further research is needed to clarify the role of statins and especially of triglyceride-lowering effects of statin therapy on periodontitis.

In this study, LDL triglyceride contents were consistently associated with periodontitis and the number of missing teeth. As lifestyle habits such as unfavourable nutrition, obesity, alcohol and diabetes may confound the association between triglyceride levels (Akinkugbe et al., 2015) and periodontitis (Lindhe, 2008), we comprehensively adjusted for these factors. However, the interplay between serum triglyceride contents and periodontal inflammation remains complex. In this study, mediation via systemic inflammation seemed plausible, as triglyceride contents of LDL, HDL and the respective particles were associated with higher CRP levels. In agreement, a recent review based on results from the Copenhagen City study reported that triglyceride-rich lipoproteins caused systemic low-grade inflammation (Ganda, 2023). In line with increased chronic inflammation, it has been argued that systemic inflammation alters the microenvironment in the periodontal pocket, favouring a shift to a dysbiotic microbiome (Van Dyke et al., 2020). Cutler et al. hypothesized that elevated serum triglycerides induce increased expression of interleukin-1β, a pro-inflammatory cytokine, by polymorphonuclear neutrophils (Cutler et al., 1999). This pathway is known to trigger further inflammatory responses and facilitate destruction of the periodontal tissue (Cheng et al., 2020). Hypertriglyceridaemia has also been linked to decreased secretion of adiponectin (Kanda et al., 2006). This protein hormone regulates different metabolic processes and plays a protective role in systemic inflammatory diseases and particularly in periodontitis pathogenesis where it binds lipopolysaccharides (LPSs) and thereby inhibits the inflammatory cascade (Wang et al., 2021). In summary, it seems reasonable to assume that regulation of the triglyceride profile plays a role in periodontitis pathology.

In this study, higher levels of HDL-4 cholesterol were associated with lower levels of mean PD, a measure of acute periodontitis severity. This aligns with analyses of the 2012–2014 KNHANES data including 7178 Koreans aged 19 years or older (Kwon et al., 2011), where individuals with low HDL-cholesterol levels had significantly higher odds for periodontitis (OR = 1.34; 95% CI: 1.14–1.56). Even though a direct comparison of results for HDL-4 cholesterol and total HDL-cholesterol values is invalid, the underlying biological mechanisms might be similar. HDL-cholesterol is a primary vehicle for the removal of unesterified cholesterol from extrahepatic cells. HDL-cholesterol binds and esterifies free cholesterol, which is known to have pro-inflammatory effects on the organism (Tall & Yvan-Charvet, 2015), and cholesterol from other lipoproteins before delivering them to the liver (Barter, 2004). HDL-cholesterol is also known to bind and dispose endotoxic LPSs. LPSs are a crucial component of the inflammation pathway, also contributing to loss of periodontal tissue (Mahanonda & Pichyangkul, 2007). When LPS is bound by HDL-cholesterol, it is no longer able to interact with toll-like receptors and initiate macrophage infiltration (Feingold & Grunfeld, 2011). These mechanisms apply to HDL-cholesterol and subgroups. While the strength of the protective influence of the individual HDL-cholesterol subgroup is a subject of recent research (Martin et al., 2015), it can be assumed that the underlying mechanism partly explains our findings with respect to HDL-4 cholesterol.

Several strengths of our study deserve consideration. First, the prospective study design with 7 years of follow-up and large sample size allowed robust estimation of the effects of serum lipids and the lipoprotein profile on pre-defined periodontitis variables. Second, this is the first study to analyse the effects of the complex lipoprotein profile, which was assessed by ^{1}H-NMR spectroscopy, on periodontitis. This sophisticated technique allows the characterization of lipid profiles more accurately by providing information on lipid subcategories and contents. This information helps in finding possible explanations for the observed relations from a molecular perspective. Third, all models were comprehensively adjusted, allowing also for non-linear associations of continuous variables, thereby minimizing the chance of residual confounding.

Limitations of our study include the following. First, as the examined cohort is a locally drawn sample, it is predominantly white Caucasian. Generalizability to other ethnic groups is therefore limited. Second, the half-mouth protocol for PD and CAL measurements imposes certain limitations; in particular, the prevalence of moderate or severe periodontitis according to the CDC/AAP case definition may be underestimated. However, the assumed inaccuracy appears to be less pronounced for mean PD/CAL (Susin et al., 2005). In general, epidemiological measures of associations are usually biased with unknown direction and magnitude (Akinkugbe et al., 2015) but the aberration between partial- and full-mouth protocol might fall within the 95% CI of the full-mouth OR when investigating risk factors for periodontitis (Alawaji et al., 2022). Therefore, the specific impact on epidemiological measures of association for mean PD and mean CAL may be negligible. Third, we cannot exclude reverse causality, as the

FIGURE 6 Associations of the whole range of lipoprotein particle measures obtained by ^{1}H-NMR spectroscopy with C-reactive protein levels, excluding participants taking lipid-lowering medication (ATC Code C10). Depicted are beta coefficients with 95% confidence intervals (CI) from linear mixed-effects regression models for effects of lipoprotein subclasses (per 1 standard deviation [SD] increase) on the mean probing depth. The first column of each block contains the matrix (e.g., the specific particle), the second column contains the analyte determined (e.g., the cholesterol content), the third column contains the number of participants included (with and without repeated measurements), and the fourth column contains the SD of the lipoprotein particle measures at baseline. Significant associations (controlling the false discovery rate at 5%) are indicated in black. Models were adjusted for age, sex, school education, smoking status, known diabetes mellitus, HbA1c, physical inactivity, waist circumference, alcohol intake, household equivalence income, food frequency score pattern, dental visits and nuclear magnetic resonance device type. Apo, apolipoprotein; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; *N*, number of observations; VLDL, very-low-density lipoprotein.

temporal aspect could not be separated from the cross-sectional aspect of the analysis used.

Finally, by excluding an exposure–time interaction because of sample size restrictions (Gelman et al., 2020), we were only able to evaluate associations of baseline exposure status with baseline and follow-up levels of periodontitis variables. It might be acknowledged that change score, ANCOVA or follow-up-only models provide potentially suitable alternatives (Glymour, 2022; Tennant et al., 2022). However, there are a few arguments favouring mixed-effects models in this specific situation: (i) Because of the higher number of observations included, mixed-effects models (which can also handle missing data) are more powerful. (ii) Both change score analysis and ANCOVA are affected by doubled measurement error of the outcome status (at baseline and follow-up). (iii) Less precision can be expected for the analysis of change (Chambless et al., 2002), as within-person variance of the dependent variable is twice as large for change as for baseline levels. (iv) Since CAL is a cumulative quantity (like, e.g. intima media thickness), it is more likely to show a signal in the cross-section than in longitudinal section (Chambless et al., 2002). These arguments support the decision to analyse data in the cross-section without interaction terms in mixed-effects models. However, we additionally present results from follow-up-only models (they circumvent the problem doubled measurement error) for periodontitis variables and from logistic models analysing incident tooth loss in the Appendix S1.

5 | CONCLUSIONS

This is the first large-scale cohort study to demonstrate that analysis of ^{1}H-NMR lipoprotein particle data provides a more detailed insight into the associations between lipoproteins and periodontitis and tooth loss than total blood levels alone. Specifically, LDL and LDL subfraction triglyceride contents were consistently associated with periodontitis severity and tooth loss. In addition, higher levels of HDL-4 cholesterol were associated with lower levels of mean PD. Systemic inflammation potentially mediates the effects of triglyceride contents of LDL, HDL and their respective particles on periodontitis. Future well-designed, large-scale clinical and epidemiological studies on this issue may elucidate and/or confirm cause–effect relationships between specific lipoprotein particles and periodontitis and clarify the underlying biochemical mechanisms.

AUTHOR CONTRIBUTIONS

Marius Kapp, Birte Holtfreter, Thomas Kocher, Nele Friedrich and Matthias Nauck substantially contributed to the conception or design of the work. Marius Kapp, Birte Holtfreter, Thomas Kocher, Nele Friedrich, Christiane Pink, Henry Völzke and Matthias Nauck contributed to the acquisition, analysis or interpretation of data. Marius Kapp, Birte Holtfreter and Thomas Kocher drafted the manuscript. Nele Friedrich, Christiane Pink, Henry Völzke and Matthias Nauck revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript and are accountable for all aspects of the work.

ACKNOWLEDGEMENT

Open Access funding enabled and organized by Projekt DEAL.

FUNDING INFORMATION

SHIP is part of the Community Medicine Research Network of the University Medicine Greifswald, which is supported by the German Federal State of Mecklenburg-West Pomerania.

CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest associated with this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Forschungsverbund Community Medicine Greifswald. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from https://transfer.ship-med.uni-greifswald.de/FAIRequest/ with the permission of Forschungsverbund Community Medicine Greifswald.

ETHICS STATEMENT

SHIP-TREND was positively evaluated by the ethics committee of the University of Greifswald (SHIP-TREND-0: BB 39/08a; SHIP-TREND-1: BB 174/15). All participants were informed about the study protocol and signed the informed consent and privacy statement.

ORCID

Marius Kapp https://orcid.org/0009-0000-9585-6124
Birte Holtfreter https://orcid.org/0000-0002-6541-3127
Thomas Kocher https://orcid.org/0000-0001-9605-2822
Nele Friedrich https://orcid.org/0000-0002-1017-7622
Christiane Pink https://orcid.org/0000-0001-5950-2716
Henry Völzke https://orcid.org/0000-0001-7003-399X
Matthias Nauck https://orcid.org/0000-0002-6678-7964

REFERENCES

Akinkugbe, A. A., Saraiya, V. M., Preisser, J. S., Offenbacher, S., & Beck, J. D. (2015). Bias in estimating the cross-sectional smoking, alcohol, obesity and diabetes associations with moderate-severe periodontitis in the atherosclerosis risk in communities study: Comparison of full versus partial-mouth estimates. *Journal of Clinical Periodontology*, *42*(7), 609–621. https://doi.org/10.1111/jcpe.12425

Alawaji, Y. N., Mostafa, N., Carvalho, R. M., Alshammari, A., & Aleksejuniene, J. (2022). Accuracy and precision of using partial-mouth recordings to study the prevalence, extent and risk associations of untreated periodontitis. *Saudi Dental Journal*, *34*(2), 142–149. https://doi.org/10.1016/j.sdentj.2021.12.005

Barter, P. (2004). Metabolic abnormalities: High-density lipoproteins. *Endocrinology and Metabolism Clinics of North America*, *33*(2), 393. https://doi.org/10.1016/j.ecl.2004.03.006

Bonaccio, M., Pounis, G., Cerletti, C., Donati, M. B., Iacoviello, L., de Gaetano, G., & Investigators, M.-S. S. (2017). Mediterranean diet, dietary polyphenols and low grade inflammation: Results from the MOLI-SANI study. *British Journal of Clinical Pharmacology*, *83*(1), 107–113. https://doi.org/10.1111/bcp.12924

Bruunsgaard, H. (2005). Physical activity and modulation of systemic low-level inflammation. *Journal of Leukocyte Biology*, *78*(4), 819–835. https://doi.org/10.1189/jlb.0505247

Chambless, L. E., Folsom, A. R., Davis, V., Sharrett, R., Heiss, G., Sorlie, P., Szklo, M., Howard, G., & Evans, G. W. (2002). Risk factors for progression of common carotid atherosclerosis: The Atherosclerosis Risk in Communities Study, 1987-1998. *American Journal of Epidemiology*, *155*(1), 38–47. https://doi.org/10.1093/aje/155.1.38

Cheng, R., Wu, Z., Li, M., Shao, M., & Hu, T. (2020). Interleukin-1beta is a potential therapeutic target for periodontitis: A narrative review. *International Journal of Oral Science*, *12*(1), 2. https://doi.org/10.1038/s41368-019-0068-8

Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent, C., Blackwell, L., Emberson, J., Holland, L. E., Reith, C., Bhala, N., Peto, R., Barnes, E. H., Keech, A., Simes, J., & Collins, R. (2010). Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*, *376*(9753), 1670–1681. https://doi.org/10.1016/S0140-6736(10)61350-5

Cutler, C. W., Shinedling, E. A., Nunn, M., Jotwani, R., Kim, B. O., Nares, S., & Iacopino, A. M. (1999). Association between periodontitis and hyperlipidemia: Cause or effect? *Journal of Periodontology*, *70*(12), 1429–1434. https://doi.org/10.1902/jop.1999.70.12.1429

Di Spirito, F., Schiavo, L., Pilone, V., Lanza, A., Sbordone, L., & D'Ambrosio, F. (2021). Periodontal and peri-implant diseases and systemically administered statins: A systematic review. *Dentistry Journal*, *9*(9), 100. https://doi.org/10.3390/dj9090100

Disease, G. B. D., Injury, I., & Prevalence, C. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet*, *392*(10159), 1789–1858. https://doi.org/10.1016/S0140-6736(18)32279-7

Eke, P. I., Dye, B. A., Wei, L., Slade, G. D., Thornton-Evans, G. O., Borgnakke, W. S., Taylor, G. W., Page, R. C., Beck, J. D., & Genco, R. J. (2015). Update on Prevalence of periodontitis in adults in the United States: NHANES 2009 to 2012. *Journal of Periodontology*, *86*(5), 611–622. https://doi.org/10.1902/jop.2015.140520

Emeasoba, E. (2022). Clinical relevance of nuclear magnetic resonance LipoProfile. *Frontiers in Nuclear Medicine*, *2*, 960522.

Esteve, E., Ricart, W., & Fernandez-Real, J. M. (2005). Dyslipidemia and inflammation: An evolutionary conserved mechanism. *Clinical Nutrition*, *24*(1), 16–31. https://doi.org/10.1016/j.clnu.2004.08.004

Feingold, K. R. (2000). Introduction to lipids and lipoproteins. In K. R. Feingold, B. Anawalt, M. R. Blackman, A. Boyce, G. Chrousos, E. Corpas, W. W. de Herder, K. Dhatariya, K. Dungan, J. Hofland, S. Kalra, G. Kaltsas, N. Kapoor, C. Koch, P. Kopp, M. Korbonits, C. S. Kovacs, W. Kuohung, B. Laferrere, … D. P. Wilson (Eds.), *Endotext*. South Dartmouth (MA): MDText.com, Inc.

Feingold, K. R., & Grunfeld, C. (2011). The role of HDL in innate immunity. *Journal of Lipid Research*, *52*(1), 1–3. https://doi.org/10.1194/jlr.E012138

Firnhaber, J. M., & Powell, C. S. (2019). Lower extremity peripheral artery disease: Diagnosis and treatment. *American Family Physician*, *99*(6), 362–369.

Ganda, O. P. (2023). Triglyceride-rich lipoproteins, remnant-cholesterol, and atherosclerotic cardiovascular disease. *Current Opinion in Lipidology*, *34*(3), 105–113. https://doi.org/10.1097/Mol.0000000000000875

Gatke, D., Holtfreter, B., Biffar, R., & Kocher, T. (2012). Five-year change of periodontal diseases in the Study of Health in Pomerania (SHIP). *Journal of Clinical Periodontology*, *39*(4), 357–367. https://doi.org/10.1111/j.1600-051X.2011.01849.x

Gelman, A., Hill, J., & Vehtari, A. (2020). *Regression and other stories*. Cambridge University Press.

Glymour, M. M. (2022). Modelling change in a causal framework. *International Journal of Epidemiology*, *51*(5), 1615–1621. https://doi.org/10.1093/ije/dyac151

Harangi, M., Seres, I., Harangi, J., & Paragh, G. (2009). Benefits and difficulties in measuring HDL subfractions and human paraoxonase-1 activity during statin treatment. *Cardiovascular Drugs and Therapy*, *23*(6), 501–510. https://doi.org/10.1007/s10557-009-6205-4

Holtfreter, B., Kocher, T., Hoffmann, T., Desvarieux, M., & Micheelis, W. (2010). Prevalence of periodontal disease and treatment demands based on a German dental survey (DMS IV). *Journal of Clinical Periodontology*, *37*(3), 211–219. https://doi.org/10.1111/j.1600-051X.2009.01517.x

Izumi, A., Yoshihara, A., Hirotomi, T., & Miyazaki, H. (2009). The relationship between serum lipids and periodontitis in elderly non-smokers. *Journal of Periodontology*, *80*(5), 740–748. https://doi.org/10.1902/jop.2009.080584

Jain, N., Dutt, U., Radenkov, I., & Jain, S. (2023). WHO's global oral health status report 2022: Actions, discussion and implementation. *Oral Diseases*. Epub ahead of print. https://doi.org/10.1111/odi.14516

Josey, M. J., & Merchant, A. T. (2016). Low-grade systemic inflammation may increase the risk of periodontitis. *The Journal of Evidence-Based Dental Practice*, *16*(4), 251–253. https://doi.org/10.1016/j.jebdp.2016.11.002

Kanda, H., Tateya, S., Tamori, Y., Kotani, K., Hiasa, K. I., Kitazawa, R., … Kasuga, M. (2006). MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity. *Journal of Clinical Investigation*, *116*(6), 1494–1505. https://doi.org/10.1172/Jci26498

Kim, S. R., & Nam, S. H. (2020). Association between periodontal disease and levels of triglyceride and total cholesterol among Korean adults. *Healthcare*, *8*(3), 337. https://doi.org/10.3390/healthcare8030337

Kinane, D. F., Berglundh, T., & Lindhe, J. (2015). Pathogenesis of periodontitis. In *Clinical periodontology and implant dentistry*. John Wiley & Sons.

Kingman, A., & Albandar, J. M. (2002). Methodological aspects of epidemiological studies of periodontal diseases. *Periodontology*, *2000*(29), 11–30. https://doi.org/10.1034/j.1600-0757.2002.290102.x

Korhonen, S., Saxlin, T., Suominen, L., Jula, A., Knuuttila, M., & Ylostalo, P. (2011). Serum cholesterol ratios and periodontal infection: Results of the Health 2000 Survey. *Journal of Clinical Periodontology*, *38*(9), 787–794. https://doi.org/10.1111/j.1600-051X.2011.01758.x

Kwok, O. M., Underhill, A. T., Berry, J. W., Luo, W., Elliott, T. R., & Yoon, M. (2008). Analyzing longitudinal data with multilevel models: An example with individuals living with lower extremity intra-articular fractures. *Rehabilitation Psychology*, *53*(3), 370–386. https://doi.org/10.1037/a0012765

Kwon, Y. E., Ha, J. E., Paik, D. I., Jin, B. H., & Bae, K. H. (2011). The relationship between periodontitis and metabolic syndrome among a Korean nationally representative sample of adults. *Journal of Clinical Periodontology*, *38*(9), 781–786. https://doi.org/10.1111/j.1600-051X.2011.01756.x

Lee, J. B., Yi, H. Y., & Bae, K. H. (2013). The association between periodontitis and dyslipidemia based on the Fourth Korea National Health and Nutrition Examination Survey. *Journal of Clinical Periodontology*, *40*(5), 437–442. https://doi.org/10.1111/jcpe.12095

Lee, S., Im, A., Burm, E., & Ha, M. (2018). Association between periodontitis and blood lipid levels in a Korean population. *Journal of Periodontology*, *89*(1), 28–35. https://doi.org/10.1902/jop.2017.170111

Lindhe, J. (2008). *Clinical periodontology and implant dentistry*. Wiley Blackwell.

Listl, S., Galloway, J., Mossey, P. A., & Marcenes, W. (2015). Global economic impact of dental diseases. *Journal of Dental Research*, *94*(10), 1355–1361. https://doi.org/10.1177/0022034515602879

Losche, W., Karapetow, F., Pohl, A., Pohl, C., & Kocher, T. (2000). Plasma lipid and blood glucose levels in patients with destructive periodontal disease. *Journal of Clinical Periodontology*, *27*(8), 537–541. https://doi.org/10.1034/j.1600-051x.2000.027008537.x

Mahanonda, R., & Pichyangkul, S. (2007). Toll-like receptors and their role in periodontal health and disease. *Periodontology*, *2000*(43), 41–55. https://doi.org/10.1111/j.1600-0757.2006.00179.x

Manning, W. G., Basu, A., & Mullahy, J. (2005). Generalized modeling approaches to risk adjustment of skewed outcomes data. *Journal of Health Economics*, *24*(3), 465–488. https://doi.org/10.1016/j.jhealeco.2004.09.011

Martin, S. S., Khokhar, A. A., May, H. T., Kulkarni, K. R., Blaha, M. J., Joshi, P. H., … LIC. (2015). HDL cholesterol subclasses, myocardial infarction, and mortality in secondary prevention: The lipoprotein investigators collaborative. *European Heart Journal*, *36*(1), 22–30. https://doi.org/10.1093/eurheartj/ehu264

Masuch, A., Pietzner, M., Bahls, M., Budde, K., Kastenmuller, G., Zylla, S., … Friedrich, N. (2018). Metabolomic profiling implicates adiponectin as mediator of a favorable lipoprotein profile associated with NT-proBNP. *Cardiovascular Diabetology*, *17*(1), 120. https://doi.org/10.1186/s12933-018-0765-1

Meisel, P., Kroemer, H. K., Nauck, M., Holtfreter, B., & Kocher, T. (2014). Tooth loss, periodontitis, and statins in a population-based follow-up study. *Journal of Periodontology*, *85*(6), e160–e168. https://doi.org/10.1902/jop.2013.130456

Mikami, R., Mizutani, K., Matsuyama, Y., Matsuura, T., Kido, D., Takeda, K., Takemura, S., Nakagawa, K., Mukaiyama, Y., Suda, T., Yasuda, T., Ohta, S., Takaya, N., Fujiwara, T., Izumi, Y., & Iwata, T. (2021). Association between periodontal inflammation and serum lipid profile in a healthy population: A cross-sectional study. *Journal of Periodontal Research*, *56*(6), 1037–1045. https://doi.org/10.1111/jre.12917

Movva, R., & Rader, D. J. (2009). Laboratory assessment of HDL heterogeneity and function. *Annales de Biologie Clinique*, *67*(1), 7–21. https://doi.org/10.1684/abc.2008.0284

Papapanou, P. N., Sanz, M., Buduneli, N., Dietrich, T., Feres, M., Fine, D. H., Flemmig, T. F., Garcia, R., Giannobile, W. V., Graziani, F., Greenwell, H., Herrera, D., Kao, R. T., Kebschull, M., Kinane, D. F., Kirkwood, K. L., Kocher, T., Kornman, K. S., Kumar, P. S., … Tonetti, M. S. (2018). Periodontitis: Consensus report of workgroup 2 of the 2017 world workshop on the classification of periodontal and peri-implant diseases and conditions. *Journal of Clinical Periodontology*, *45*(Suppl 20), S162–S170. https://doi.org/10.1111/jcpe.12946

Park, K. Y., Hong, S., Kim, K. S., Han, K., & Park, C. Y. (2023). Trends in prevalence of hypertriglyceridemia and related factors in Korean adults: A serial cross-sectional study. *Journal of Lipid and Atherosclerosis*, *12*(2), 201–212. https://doi.org/10.12997/jla.2023.12.2.201

Pink, C., Kocher, T., Meisel, P., Dorr, M., Markus, M. R., Jablonowski, L., … Holtfreter, B. (2015). Longitudinal effects of systemic inflammation markers on periodontitis. *Journal of Clinical Periodontology*, *42*(11), 988–997. https://doi.org/10.1111/jcpe.12473

R Core Team. (2023). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing https://www.R-project.org/

Rader, D. J., & Daugherty, A. (2008). Translating molecular discoveries into new therapies for atherosclerosis. *Nature*, *451*(7181), 904–913. https://doi.org/10.1038/nature06796

Ramseier, C. A., Anerud, A., Dulac, M., Lulic, M., Cullinan, M. P., Seymour, G. J., Faddy, M. J., Bürgin, W., Schätzle, M., & Lang, N. P. (2017). Natural history of periodontitis: Disease progression and tooth loss over 40 years. *Journal of Clinical Periodontology*, *44*(12), 1182–1191. https://doi.org/10.1111/jcpe.12782

Saxlin, T., Suominen-Taipale, L., Kattainen, A., Marniemi, J., Knuuttila, M., & Ylostalo, P. (2008). Association between serum lipid levels and periodontal infection. *Journal of Clinical Periodontology*, *35*(12), 1040–1047. https://doi.org/10.1111/j.1600-051X.2008.01331.x

Schutzhold, S., Kocher, T., Biffar, R., Hoffmann, T., Schmidt, C. O., Micheelis, W., … Holtfreter, B. (2015). Changes in prevalence of periodontitis in two German population-based studies. *Journal of Clinical Periodontology*, *42*(2), 121–130. https://doi.org/10.1111/jcpe.12352

Singer, J. D., & Willett, J. B. (2003). Treating TIME more flexibly. In *Applied longitudinal data analysis-modeling change and event occurrence* (pp. 138–188). Oxford University Press, Inc.

StataCorp. (2021). *Stata statistical software: Release 17*. StataCorp LLC.

Susin, C., Kingman, A., & Albandar, J. M. (2005). Effect of partial recording protocols on estimates of prevalence of periodontal disease. *Journal of Periodontology*, *76*(2), 262–267. https://doi.org/10.1902/jop.2005.76.2.262

Tall, A. R., & Yvan-Charvet, L. (2015). Cholesterol, inflammation and innate immunity. *Nature Reviews Immunology*, *15*(2), 104–116. https://doi.org/10.1038/nri3793

Tendera, M., Aboyans, V., Bartelink, M. L., Baumgartner, I., Clement, D., Collet, J. P., … Guidelines, E. C. P. (2011). ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: The Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). *European Heart Journal*, *32*(22), 2851–2906. https://doi.org/10.1093/eurheartj/ehr211

Tennant, P. W. G., Arnold, K. F., Ellison, G. T. H., & Gilthorpe, M. S. (2022). Analyses of 'change scores' do not estimate causal effects in observational data. *International Journal of Epidemiology*, *51*(5), 1604–1615. https://doi.org/10.1093/ije/dyab050

Teo, C. C., Chong, W. P. K., Tan, E., Basri, N. B., Low, Z. J., & Ho, Y. S. (2015). Advances in sample preparation and analytical techniques for lipidomics study of clinical samples. *Trends in Analytical Chemistry*, *66*, 1–18.

Van Dyke, T. E., Bartold, P. M., & Reynolds, E. C. (2020). The nexus between periodontal inflammation and dysbiosis. *Frontiers in Immunology*, *11*, 511. https://doi.org/10.3389/fimmu.2020.00511

von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gotzsche, P. C., Vandenbroucke, J. P., & Initiative, S. (2014). The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. *International Journal of Surgery*, *12*(12), 1495–1499. https://doi.org/10.1016/j.ijsu.2014.07.013

Wang, Z. D., Chen, Z. H., Fang, F. C., & Qiu, W. (2021). The role of adiponectin in periodontitis: Current state and future prospects. *Biomedicine & Pharmacotherapy*, *137*, 111358. https://doi.org/10.1016/j.biopha.2021.111358

World Health Organization. (2023). Indicator Metadata Registry List - Raised Cholesterol. https://www.who.int/data/gho/indicator-metadata-registry/imr-details/3236

Wurtz, P., Kangas, A. J., Soininen, P., Lawlor, D. A., Smith, G. D., & Ala-Korpela, M. (2017). Quantitative serum nuclear magnetic resonance metabolomics in large-scale epidemiology: A primer on-Omic technologies. *American Journal of Epidemiology*, *186*(9), 1084–1096. https://doi.org/10.1093/aje/kwx016

Yanbaeva, D. G., Dentener, M. A., Creutzberg, E. C., Wesseling, G., & Wouters, E. F. M. (2007). Systemic effects of smoking. *Chest*, *131*(5), 1557–1566. https://doi.org/10.1378/chest.06-2179

Yang, A. L., & McNabb-Baltar, J. (2020). Hypertriglyceridemia and acute pancreatitis. *Pancreatology*, *20*(5), 795–800. https://doi.org/10.1016/j.pan.2020.06.005

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Kapp, M., Holtfreter, B., Kocher, T., Friedrich, N., Pink, C., Völzke, H., & Nauck, M. (2024). Serum lipoprotein subfractions are associated with the periodontal status: Results from the population-based cohort SHIP-TREND. *Journal of Clinical Periodontology*, *51*(4), 390–405. https://doi.org/10.1111/jcpe.13902