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ORIGINAL RESEARCH

A Chemokine Profile Linked to Both Triglyceride-Rich Lipoproteins and Lipoprotein(a), But Not LDL, Is Associated With Cardiovascular Disease

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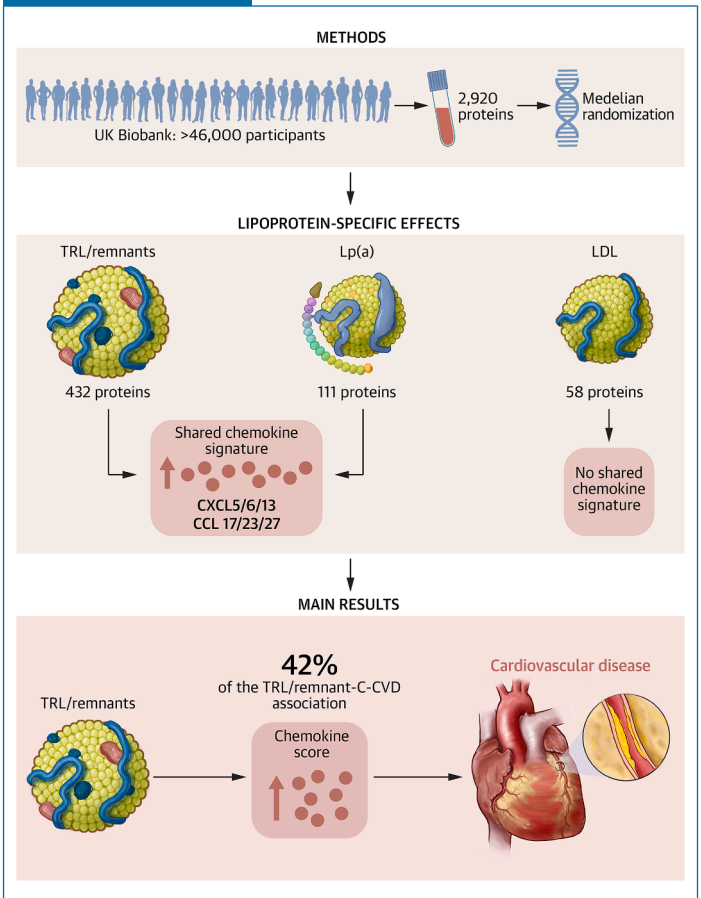
VISUAL ABSTRACT



Björnson E, et al. JACC Basic Transl Sci. 2026;11(11):101736.

HIGHLIGHTS

- **Chemokine-rich inflammatory pathways may underlie cardiovascular risk conveyed by triglyceride-rich lipoproteins (TRL) and lipoprotein(a) [Lp(a)], beyond low-density lipoprotein cholesterol.**
- **Circulating proteomic and Mendelian randomization data implicate TRLs and Lp(a) as causal drivers of systemic chemokine activation.**
- **TRL- and Lp(a)-driven chemokine activation may enhance cardiovascular risk stratification beyond traditional lipid measures.**
- **Future work should integrate lipidomics, plaque imaging, and orthogonal proteomics to define mechanisms and therapeutic targets.**

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ABBREVIATIONS AND ACRONYMS

apoB = apolipoprotein B

CCL = C-C motif chemokine ligand

CHD = coronary heart disease

CVD = cardiovascular disease

CXCL = C-X-C motif chemokine ligand

IL = interleukin

GO = gene ontology

MESA = multi-ethnic study of atherosclerosis

MR = Mendelian randomization

pQTL = protein quantitative trait loci

SNP = single nucleotide polymorphism

TG = triglyceride

TRL/remnant-C = triglyceride-rich lipoprotein/remnant cholesterol

SUMMARY

Triglyceride-rich lipoproteins (TRL) and lipoprotein(a) [Lp(a)] demonstrate heightened per-particle atherogenicity compared with low-density lipoproteins (LDL), yet mechanistic underpinnings remain unclear. Using Mendelian randomization in >46,000 UK Biobank participants, we linked genetically determined variation in TRL/remnants, LDL, and Lp(a) to 2,920 plasma proteins and found causal associations with 432, 58, and 111 proteins, respectively. Notably, TRL/remnants and Lp(a) both impacted chemokine-signaling and leukocyte-chemotaxis pathways, distinct from LDL's effect on lipid metabolism. A specific chemokine signature linked to both TRL and Lp(a) accounted for around 40% (with wide confidence limits) of the TRL/remnant cholesterol: cardiovascular disease (CVD) association. However, a more general causal relationship between plasma chemokine concentrations and CVD risk independent of a TRL/Lp(a) effect was not supported by quantitative trait loci analysis. These results are compatible with a model in which TRL/Lp(a)-driven chemokine activation contributes meaningfully to CVD risk.
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Atherosclerosis initiation and progression involves focal accumulation of cholesterol at susceptible sites in the artery wall.[1] Three apolipoprotein B (apoB)-containing lipoproteins, low-density lipoproteins (LDL), triglyceride-rich lipoproteins and their remnants (TRL/remnants), and lipoprotein(a) [Lp(a)], that transport this lipid in the bloodstream have been identified as independent causal agents for atherosclerotic cardiovascular disease (CVD).[2-4] Intrinsic to the formation of artery wall plaque is a maladaptive inflammatory response at sites of lipoprotein infiltration.[1,5,6] This response entails a complex interplay between lipoproteins, cellular and extracellular components of the artery wall, and circulating blood leukocytes which are recruited to, and become incorporated in, the growing lesion.[1,7,8]

Plasma triglyceride, a measure of the abundance of TRL, exhibits modest but significant associations with classic biomarkers of chronic systemic inflammation such as C-reactive protein (CRP)[9] and blood white cell count.[10] Recent analyses have shown that genetically determined increases in TRL/remnant levels are related to elevated CRP, white cell count, and neutrophil count.[11] In contrast, LDL and Lp(a) do not appear to be causally associated with these inflammatory biomarkers.[12-14] However, in vitro evidence has emerged to indicate that Lp(a) can generate pro-inflammatory changes in blood monocytes and cultured macrophages, and its relationship to wider aspects of inflammation deserves further exploration.[4,15,16] This is especially pertinent in light of recent reports that both TRL/remnants and Lp(a) on a per-particle basis are several-fold more atherogenic than LDL.[11,17-19] The question remains whether this is attributable, at least in part, to effects of these lipoproteins on inflammatory pathways.

Through the availability of proteomic data in large patient-based studies, it is now possible to develop comprehensive maps of the association of plasma proteins with each of the 3 major apoB-containing lipoprotein classes.[20] This initial study provided strong support for the hypothesis that the greater per-particle atherogenicity of TRL and Lp(a) is partly explained by their downstream effects on systemic inflammatory pathways. Here, we use Mendelian randomization (MR) analyses to discern the

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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potentially causal (genetically determined) effects of TRL/remnants, LDL, and Lp(a) on specific inflammation-linked plasma proteins with a particular focus on cytokines. Our findings of a common, likely causal effect of TRL/remnants and Lp(a) on circulating chemokine profiles, not shared by LDL, raise fundamental questions as to the etiological role of TRL/remnants and Lp(a) in atherogenesis.

METHODS

STUDY GROUP. The study was conducted in the UK Biobank study group, which comprised over 502,000 UK residents of mainly European ancestry.[21]

ETHICAL APPROVAL. This research was conducted using the open-access UK Biobank resource under application number [82018]. In accordance with UK Biobank governance, all participants provided written informed consent, and the study complies with the ethical standards of the UK Biobank Ethics and Governance Council. The present analysis of de-identified UK Biobank data was therefore exempt from additional institutional research ethics board review.

BIOCHEMICAL AND PROTEOMIC ANALYSES. Details of the measurements of plasma lipids and lipoproteins are provided on the UK Biobank data showcase website (https://biobank.ctsu.ox.ac.uk). LDL-C was measured directly (Beckman Coulter). TRL/remnant cholesterol (TRL/remnant-C) was derived by subtracting direct LDL-C and high-density lipoprotein cholesterol from total plasma cholesterol. Lp(a) concentration was measured by immunoturbidimetry using the Randox assay (Data Field 30,790). The assay range was 3.8 to 189 nmol/L (values outside the working range were classified as "not available"). Complete plasma lipid profiles were available for 341,502 individuals. CRP was available for 468,483 individuals. Plasma concentrations of 2,920 proteins were measured using Olink technology (Olink Explore panel) in 53,029 individuals, of which 46,799 were randomly selected as representative of the whole biobank. Genetic analyses were conducted on the latter group of individuals. Observational analyses (using measured lipoprotein levels) were conducted using the subgroup of 43,141 individuals not on lipid-lowering therapy at recruitment.

GENETIC INSTRUMENTS AND MR. To assess the causal effects of TRL/remnants, LDL, and Lp(a) on plasma proteins, we performed MR analyses using genetic variants associated with the 3 individual lipoprotein classes. The genetic instruments—single nucleotide polymorphism (SNP) set 1 specific for TRL/remnants, SNP set 2 specific for LDL, and SNP set 3 specific for Lp(a)—were derived as previously described,[11,17] and their properties are detailed in Supplemental Figure 1. Using SNP sets 1 to 3, we performed inverse-variance weighted MR regression to estimate effect sizes (beta coefficients) for each of the 2,920 proteins across the 3 lipoprotein classes.

PROTEOMIC PATHWAY ANALYSIS. To explore biological pathways enriched among proteins significantly affected by TRL/remnants, LDL, and Lp(a), we conducted over-representation analyses (https://maayanlab.cloud/Enrichr/) using Gene Ontology Biological Processes. Pathways were considered significant at a Benjamini-Hochberg false discovery rate of <0.05.

CHEMOKINE SCORE. To generate an integrating metric of the chemokine profile for each individual, we derived a series of chemokine scores. Chemokine score 1 was an unweighted sum of the concentrations of those chemokines most strongly linked to TRL/remnants; chemokine score 2 was a weighted sum of all chemokine concentrations using as weighting factors the beta coefficients derived by MR with SNP set 1 (TRL/remnant associated effect sizes); chemokine score 3 was a weighted sum of all chemokine concentrations using as weighting factors beta coefficients derived with SNP set 3 (Lp[a] associated effect sizes).

STATISTICAL ANALYSES. All statistical evaluations were performed using R statistical software (version 4.3.0; R Core Team 2023).

MENDELIAN RANDOMIZATION. Analyses were carried out using the *MendelianRandomization* package. MR-estimates refer to the percent increase in the circulating protein level for a given TRL/Lp(a)/LDL concentration increase; depending on the analysis, this was per standardized increment in cholesterol (mmol/L), per standardized increment in Lp(a) in nmol/L, or per 10 mg/dL apoB.

MEDIATION ANALYSIS. An analysis to test the extent to which variation in inflammatory biomarkers and chemokine scores accounted for the association of TRL/remnant-C with CVD risk was conducted using the *mediation* package in R. The analysis was performed in a group of 43,141 individuals in the UK Biobank who had proteomic data and were not on lipid-lowering therapy. A causal interpretation of this mediation analysis assumes a pathway from the exposure (TRL/remnants) through the mediator (chemokine score or interleukin concentration) to the outcome (CHD events), with no reverse causality, no unmeasured confounding of the

exposure-mediator, exposure-outcome, or mediator-outcome relationships conditional on the included covariates, and no mediator-outcome confounder affected by the exposure. The potential influence of other nonlipid risk factors was assessed by including these as covariates in the mediation models. The results are presented as percent (%) mediation with 95% CIs.

PROTEIN QUANTITATIVE TRAIT LOCI ANALYSIS. A protein quantitative trait loci (pQTL) approach was used to test the nature of the relationship of selected circulating chemokines to CVD risk. Loci that were associated with plasma chemokine concentrations and with risk of CHD were identified by GWAS. These sets of variants were then pruned and tested in MR models with CHD events as the outcome. Models were unadjusted, adjusted for TRL-C and Lp(a) levels (since some of the loci were in genes affecting the levels of these lipoproteins), or cropped to remove variants that affected TRL or Lp(a).

RISK PREDICTION MODELS AND REGRESSION MODELS. Cox proportional hazards models were fitted using the *survival* package in R, and HRs are presented per 1 SD increase with 95% CIs unless otherwise stated. "Explained variance" was assessed using linear regression models. All statistical tests were 2-sided, and a value of $P < 0.05$ was considered statistically significant unless otherwise stated. For the MR analyses, P values were adjusted for multiple testing using the Bonferroni correction.

RESULTS

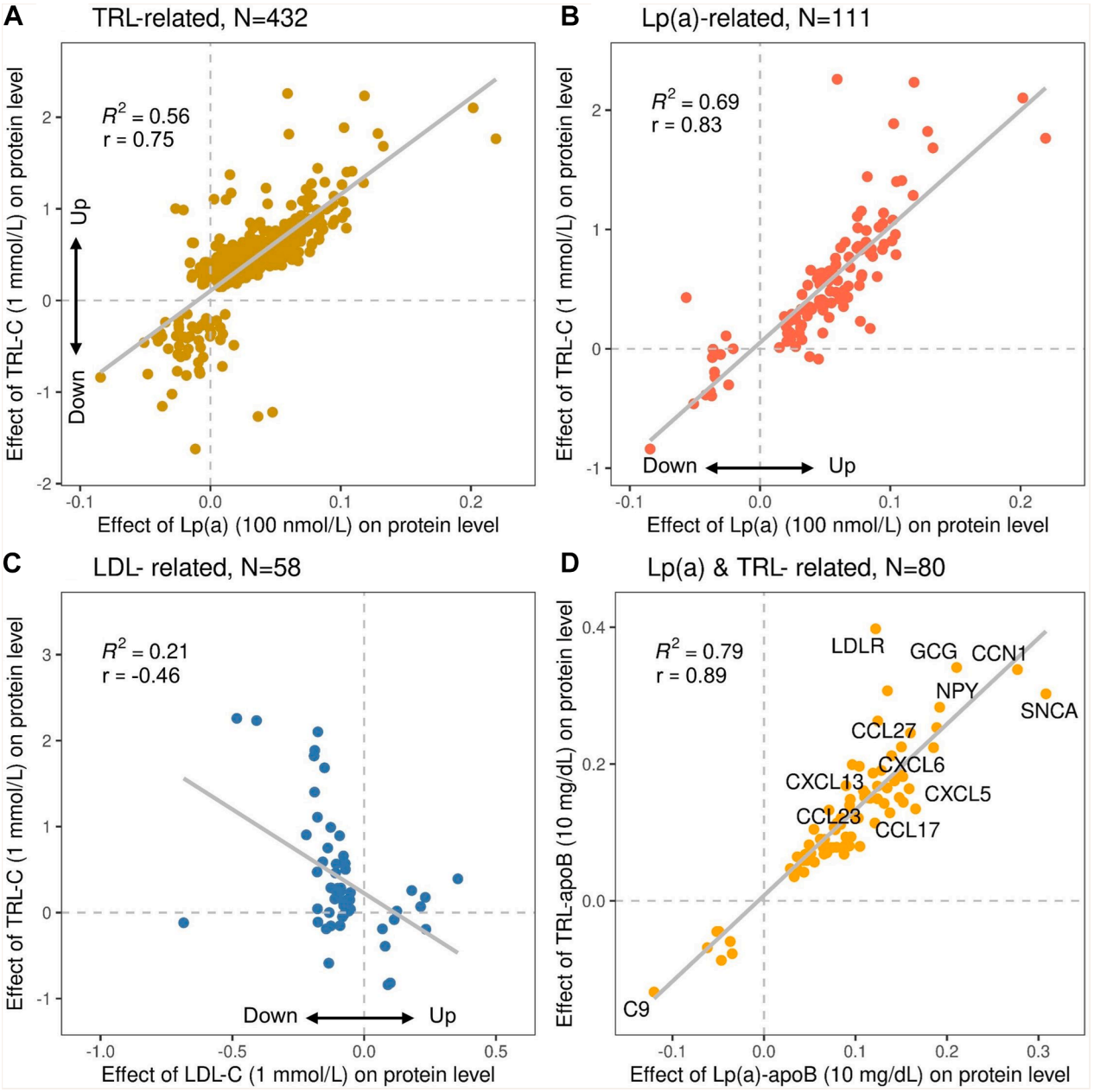
The UK Biobank cohort comprises 502,460 men and women with a mean age of 56.5 ± 8.0 years at enrolment. Plasma levels of the 3 major apoB-containing lipoproteins were partially interrelated. TRL/remnant-C (associated strongly with triglyceride (TG); r = 0.77, $P < 0.001$) correlated moderately with LDL-C (r = 0.60, $P < 0.001$) but not with Lp(a). Lp(a) correlated weakly with LDL-C (r = 0.06, $P < 0.001$) because the cholesterol in Lp(a) is included in the measurement of direct LDL-C. A total of 2,920 plasma proteins were measured using Olink technology, and the genetic analyses described in the present study were conducted in the group of 46,799 individuals randomly selected for proteomic profiling.

CAUSAL ASSOCIATIONS OF TRL/remnant-C, LDL-C AND LP(a) WITH PLASMA PROTEINS. Potentially causal (genetically determined) relationships of TRL/remnant-C, LDL-C, and Lp(a) with plasma proteins were evaluated using SNP sets 1, 2, and 3, respectively.[11,17] For each of the 2,920 proteins, the increase or decrease in plasma concentration (effect size) per genetically determined increase in TRL/remnant-C (in mmol/L), in LDL-C (in mmol/L) and in Lp(a) (in nmol/L) was estimated by MR analysis (See Supplemental Figure 2 for examples and Supplemental Figure 3 for relative effect sizes for all proteins). After Bonferroni adjustment for multiple comparisons, 432 of the 2,920 proteins exhibited significant associations with genetically determined variation in TRL/remnant-C (**Figure 1A**, y-axis), and 111 of the 2,920 proteins showed significant relationships with genetically determined variation in Lp(a) (**Figure 1B**, x-axis). Genetically determined variation in LDL-C was significantly associated with a much smaller number (N = 58) of proteins (**Figure 1C**, x-axis). Supplemental Table 1 gives the effect sizes for the top 20 proteins affected by each lipoprotein class.

GENETICALLY DETERMINED VARIATION IN TRL/remnants AND LP(a), BUT NOT IN LDL, AFFECTS A COMMON SET OF INFLAMMATION-LINKED PLASMA PROTEINS. Many of the proteins associated with TRL/remnants were also associated with Lp(a) (**Figures 1A and 1B**). **Figure 1A** shows that the 432 proteins identified as significantly associated with TRL/remnant-C (using SNP set 1) had effect sizes that correlated in direction and magnitude with the effect sizes seen for Lp(a) (using SNP set 3) with r = 0.75. (Note this plot presents protein effect sizes for genetically determined increase in Lp(a) whether or not the association achieved Bonferroni-adjusted significance). Likewise, for the 111 proteins associated significantly with Lp(a) (identified using SNP set 3), there was a strong correlation of effect size with TRL/remnant-C effect sizes (**Figure 1B**, $r^2 = 0.69$). A group of 80 proteins was significantly affected by both TRL/remnants and Lp(a), and their effect sizes were highly correlated ($r^2 = 0.79$). Indeed, when expressed per unit increase in apoB (equivalent to "per-particle" since each lipoprotein particle contains 1 apoB), the effect sizes were almost the same, with a slope of 1.25 for the regression line (**Figure 1D**). Contrary to expectations, the proteins causally associated with LDL were mostly distinct from those related to TRL/remnants and Lp(a) (**Figure 1C**) (see also Supplemental Table 1).

Thus, genetically determined variation in TRL/remnants and Lp(a) appears to generate a common plasma proteome "signature," with a concordant increase or decrease in the concentration of the proteins. Further, the quantitative impact of a TRL/remnant particle appears to be about the same as that of an Lp(a) particle.

FIGURE 1 **Comparison of Effect Sizes for Proteins Significantly Associated With Genetically Determined Variation in Triglyceride-Rich Lipoprotein (TRL), Low-Density Lipoprotein Cholesterol (LDL), and Lipoprotein(a) (Lp[a])**



(A) Of the 2,920 proteins in the Olink Explore panel, 432 showed a significant association with TRL/remnant-cholesterol (TRL remnant-C) in Mendelian randomization analysis using single nucleotide polymorphism (SNP) Set 1. Panel (A) presents on the y-axis those proteins (each dot is 1 protein) that were significantly upregulated (UP arrow: having a positive effect size) or downregulated (DOWN arrow: having a negative effect size) for a standardized 1 mmol/L genetically determined increase in TRL/remnant-C. The corresponding effect sizes for each of the 432 proteins obtained using SNP set 3 specific for Lp[a] are shown on the x-axis, whether they were significant or not. (B) Repeats the information in (A) for the 111 proteins significantly associated with Lp(a) using SNP set 3. The y-axis presents the effect sizes for TRL/remnant-C, again whether they were significant or not. (C) The x-axis presents the same information for the 58 proteins significantly associated with LDL-cholesterol using SNP set 2 and their corresponding effect sizes for TRL/remnant-C (SNP set 1). (D) Compares the effect sizes for the 80 proteins that were significantly associated with *both* TRL and Lp(a). Here, the effect sizes are expressed per 10 mg/dL of TRL-apoB or per 10 mg/dL of Lp(a)-apolipoprotein B (apoB). Since each particle type contains 1 apoB, this is a direct comparison of the quantitative effect on each protein of a TRL particle vs an Lp(a) particle. The effect sizes are remarkably similar on a per-particle basis. The slope of the line was 1.25. Explained variance (R^2) and Pearson's r are displayed.

BIOLOGICAL PROCESSES LINKED TO TRL/remnants, LDL AND LP(a) PROTEOME SIGNATURES. The proteins in the proteome signatures of TRL/remnants and Lp(a) were categorized by biological process in a gene-ontology (GO) analysis (**Figure 2**). For the proteins apparently upregulated by TRL/remnants (N = 380) and Lp(a) (N = 96) (ie exhibiting a positive change per unit increase in the lipoprotein), the processes identified as most significant were linked to "antimicrobial humoral response," "chemokine-mediated signaling pathway," "cellular response to chemokine," and "granulocyte chemotaxis" (**Figure 2**, upper). There was a strong concordance in the biological processes identified for the TRL/remnants and Lp(a) proteome signatures, as might be expected from the substantial overlap in individual proteins and effect sizes (**Figure 1D**).

The 52 proteins apparently downregulated (negative effect size) by a genetically determined TRL/remnant increase were categorized as being linked to "HDL remodelling" and lipid metabolism processes. Only a small number of proteins (N = 14) were downregulated by a genetically determined Lp(a) increase, and these were assigned to a variety of processes including collagen metabolism.

Biological processes associated with the 58 proteins causally linked to an increase in LDL were distinct and related mainly to lipid transport and cell sterol metabolism (Supplemental Table 2).

IDENTIFICATION OF A CHEMOKINE PROFILE LINKED TO TRL/remnants AND LP(a), BUT NOT LDL. The GO analysis revealed that the biological processes most strongly affected by genetic determinants of TRL/remnants and Lp(a) involved chemokines and other cell-signaling proteins. Accordingly, we re-examined the possible causal effects of variation in these lipoproteins on all chemokines measured in the Olink Explore panel (listed in Supplemental Tables 3 and 4). **Figures 3A and 3B** show that TRL/remnants and Lp(a) had common effects on both C-X-C and C-C motif chemokines. Not only were the effect sizes for TRL/remnants and Lp(a) highly correlated, but the potential impact on the plasma concentration of the chemokines was substantial. An increase in TRL-apoB of 10 mg/dL (about a 1.5 mmol/L increase in plasma triglyceride, a 0.68 mmol/L increase in TRL/remnant-C) was associated with a 10% to 30% increment in the plasma level of a number of chemokines (**Figures 3A and 3B**, Supplemental Table 4). The same was true of Lp(a), with similar effect sizes per 10 mg/dL increment in Lp(a)-apoB (about a 180 nmol/L increase in total Lp[a]) (**Figures 3A and 3B**, Supplemental Table 4). In contrast to these observations of a close link between TRL, Lp(a) and chemokines, there was no comparable association of LDL with the chemokine profile (or interleukins) (**Figures 3C and 3D**, Supplemental Table 4).

The relationships seen in the UK Biobank were also observed in an independent cohort—the multi-ethnic study of atherosclerosis (MESA)—as reported elsewhere,[20] and summarized in Supplemental Figure 4. There was good agreement between the MESA and UK Biobank cohorts in effect sizes for the association of observed TRL-C and Lp(a) levels with chemokine concentrations.

Given the previous focus on the interleukin (IL)-1β/IL-6 axis, it was noteworthy that, compared with chemokines, the plasma level of these cytokines was much less affected by TRL/remnants (**Figures 3E and 3F**); TRL/remnant-C explained up to 13.4% of the variance for the chemokines listed in **Table 1** compared with ≤ 1.5% for IL-1β and IL-6. Further, after Bonferroni adjustment, none of IL-1β, IL-6, or tumor necrosis factor (TNF)-related proteins had a significant causal association with TRL/remnants. Likewise, there was no detectable association of Lp(a) with these cytokines.

DERIVATION OF CHEMOKINE SCORES. To provide an integrated view of the chemokine profile, a series of chemokine scores was created (**Table 1**). The simplest, chemokine score 1, was for each individual the sum of the concentrations of chemokines identified as most affected by TRL/remnants (namely C-X-C motif chemokine ligand [CXCL]5/6/13 and C-C motif chemokine ligand [CCL]17/23/27 with >20% effect per 10 mg/dL TRL-apoB, Supplemental Table 4). The second, chemokine score 2, was a weighted sum in which, for each individual, the concentrations of all chemokines were added together after giving each chemokine a weighting factor based on the effect size for TRL/remnants (beta coefficient determined by MR using SNP set 1) on that chemokine (thus, if a chemokine had a high plasma concentration but a small effect size, its contribution to the overall sum was reduced proportionately). This weighting reprofiled an individual's chemokine pattern to reflect the impact of TRL/remnants. The third, chemokine score 3, was created using as weighting factors beta coefficients determined using SNP Set 3, that is, a solely Lp(a)-based weighting. The 3 scores were highly correlated, as seen in Supplemental Figure 5.

Chemokine score was strongly associated with TRL/remnant-C (and plasma TG) in the study group (Supplemental Figure 6A), and this relationship appeared to be similar across tertiles of age. TRL/remnant-C explained about 12% of the variance in

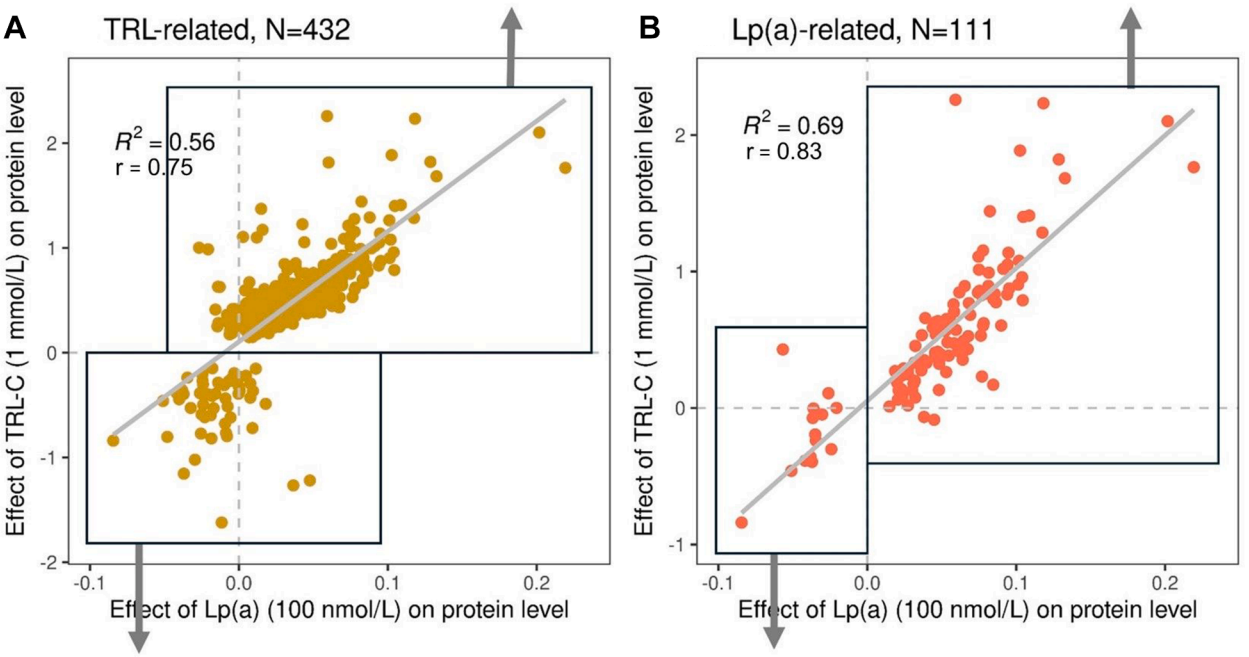
FIGURE 2 Gene Ontology Classification of Proteins Identified as Causally Associated With Triglyceride-Rich Lipoprotein (TRL)/remnants and Lipoprotein(a) (Lp[a])

Upregulated by TRL (N=380)

Pathway	Adjusted p-value
Antimicrobial Humoral response mediated by antimicrobial peptide	1.4E-18
Antimicrobial Humoral response	2.8E-18
Chemokine-mediated signalling pathway	5.1E-14
Granulocyte chemotaxis	7.0E-14
Cellular response to chemokine	1.3E-13

Upregulated by Lp(a) (N=96)

Pathway	Adjusted p-value
Antimicrobial Humoral response	1.2E-7
Antimicrobial Humoral response mediated by antimicrobial peptide	1.2E-7
Granulocyte chemotaxis	2.8E-7
Inflammatory response	1.4E-5
Neutrophil chemotaxis	4.3E-4



Downregulated by TRL (N=52)

Pathway	Adjusted p-value
HDL particle remodelling	4.7E-9
Cholesterol homeostasis	1.1E-5
Sterol homeostasis	1.1E-5
Negative regulation of multicellular organismal processes	2.7E-5
Cholesterol efflux	3.8E-5

Downregulated by Lp(a) (N=14)

Pathway	Adjusted p-value
Collagen catabolic process	0.032
Acylglycerol metabolic process	0.032
Lipid catabolic process	0.032
Triglyceride metabolic process	0.034
Positive regulation of endothelial ell proliferation	0.038

The 432 proteins significantly associated with TRL/remnant-cholesterol (TRL/remnant-C) (A) and the 111 proteins significantly associated with Lp(a). (B) This image was subjected to gene ontology analysis to identify the biological processes/pathways most likely to be linked to their presence in plasma. For each lipoprotein, the analysis was performed separately for proteins upregulated (positive effect size; top) and downregulated (negative effect size; bottom) for a genetically determined standard increase in TRL/remnant-C or Lp(a) mass. Adjusted values of *P*, obtained using the Bonferroni post hoc test, give an indication of the probability that the process identified maps on to the protein profile entered into the analysis. For each set of proteins, the 5 most significant processes are given. Note, there are 111 Lp(a)-related proteins, however the LPA protein itself is not indcluded in the above pathway-analyses.

FIGURE 3 **Magnitude of Effect of Triglyceride-Rich Lipoprotein (TRL), Low-Density Lipoprotein Cholesterol (LDL), and Lipoprotein(a) (Lp[a]) on Plasma Cytokine Profile**

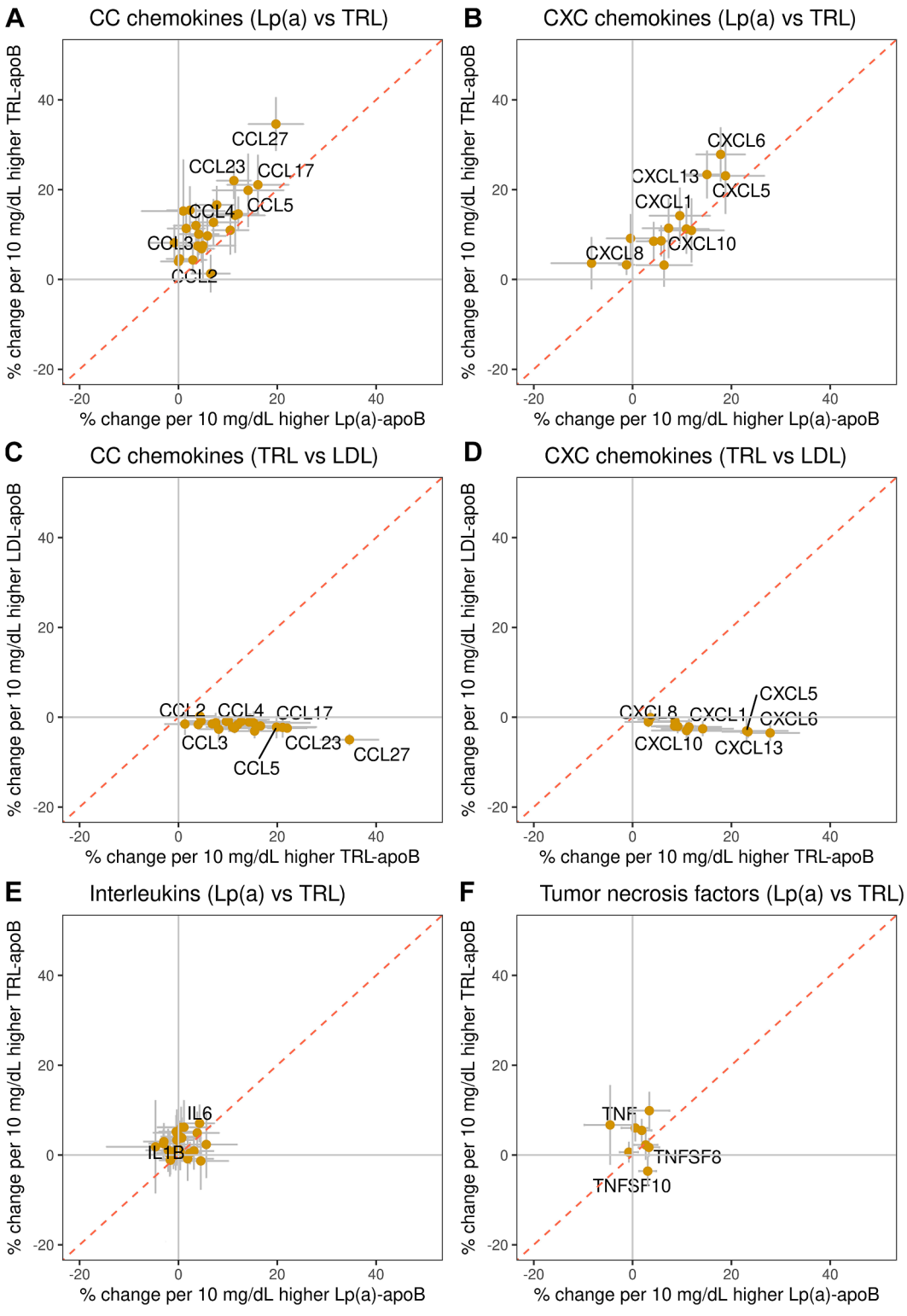


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TABLE 1 Impact of TRL/remnant-C on Plasma Concentrations of Cytokines and Chemokine Scores

Cytokine/Inflammatory Biomarker	Variance Explained By TRL-Cholesterol
IL-1β pathway	
IL-1β	0.69%[b]
IL-6	1.5%
CRP	0.31%
Chemokine profile	
CXCL5	2.0%
CXCL6	5.9%
CXCL13	4.2%
CCL17	5.0%
CCL23	9.9%
CCL27	13.4%
Chemokine score 1[a]	12.0%
Chemokine score 2	12.1%
Chemokine score 2 +age, sex, BMI	17.4%

[a]Chemokine score 1 was a simple addition of the concentrations of CXCL5/6/13 and CCL17/23/27. Chemokine score 2 was a weighted sum of all chemokines, with the weighting factors being proportionate to the beta coefficients for each chemokine derived using the TRL-specific SNPs (SNP set 1). [b]TRL/remnant-cholesterol was significantly associated with all biomarkers ($P < 0.001$).

BMI = body mass index; CCL = C-C motif chemokine ligand; CXCL = C-X-C motif chemokine ligand; CRP = C-reactive protein; IL = interleukin.

TABLE 2 Chemokines as Mediators of TRL/remnant-C Association With Cardiovascular Disease

Models/Variables[a]	TRL/remnant-C Association With CVD Percent Mediation	*P* Value
IL-1β pathway		
IL-1β	2.7 (0-9)	0.0740
IL-6	13 (7.5-32)	<0.0001
CRP	5 (2.3-12)	<0.0001
Models with individual chemokines		
CXCL5	4.2 (0-14)	0.15
CXCL6	3.0 (0-16)	0.50
CXCL13	32 (17-79)	<0.0001
CCL17	19 (9-50)	<0.0001
CCL23	15 (2.8-45)	0.016
CCL27	12 (0-40)	0.13
Models with chemokine profile scores[b]		
Chemokine score 1 (sum of CXCL5/6/13 & CCL17/23/27)	31 (13-82)	<0.0001
Chemokine score 2	42 (24-95)	<0.0001
Chemokine score 3	33 (18-81)	<0.0001
Chemokine score 2 plus IL-6	43 (25-98)	<0.0001

Data presented as percent mediation with 95% CI. [a]All models include age, sex, BMI, LDL-C, and Lp(a) as covariates. [b]Chemokine score 1 was a simple addition of the concentrations of the noted chemokines; Chemokine scores 2 and 3 were a weighted sum of all chemokines with the weights being proportionate to the beta coefficients for each chemokine derived using either the TRL-specific SNPs (SNP set 1) (score 2) or the Lp(a) specific SNPs (SNP set 3) (score 3).

CCL = C-C motif chemokine ligand; CCXL = C-X-C motif chemokine ligand; CRP = C-reactive protein; IL = interleukin.

chemokine scores 1 and 2; adding age, sex, and BMI increased this to 17.4% (Table 1). In contrast, the impact of TRL/remnant-C on CRP was less pronounced, explaining <0.5% of the variance (Table 1, Supplemental Figure 6B). Accordingly, a 1 mmol/L increase in TRL/remnant-C was associated with relatively small changes (0.18-0.34 SD) in IL-1β, IL-6 and CRP but much greater changes (1.08-1.13 SD) in chemokine scores (Supplemental Figure 6).

TRL/remnant-ASSOCIATED CHEMOKINE PROFILE AND CVD RISK. The chemokine scores were significant predictors of CVD risk (Supplemental Table 5) with hazard ratios of 1.2 to 1.3 per 1 SD increase. In comparison, IL-1β, IL-6, and CRP gave hazard ratios of around 1.1 to 1.2 per 1 SD increase. These biomarkers of inflammation were tested in mediation analyses to see if they explained a proportion of the CVD risk linked to elevated TRL/remnant-C concentrations. The proportion, of course, is a function of the causal influence of TRL/remnants on the inflammatory biomarker and the strength of the association of the biomarker with CVD risk. IL-6 explained about 13% of the association of TRL/remnant-C with risk, whereas CRP accounted for 5% (Table 2). Individual chemokines gave mediation results of 3% to 32%, whereas the chemokine scores were found to explain 31% to 42% of the association of TRL/remnant-C with CVD risk. Chemokine score 2, as the most comprehensive index of the TRL/remnant-related chemokine profile, gave the highest mediation result at 42%. Chemokine scores 1 and 3, on the other hand, with no intrinsic association to TRL/remnants (being either a simple sum of the concentrations of selected chemokines, or a weighted sum using beta coefficients as weighting factors based on SNPs at the *LPA* locus),

FIGURE 3 Continued

For all cytokines included in the Olink Explore panel, Mendelian randomization effect sizes (percent change in protein concentration) per genetically determined 10 mg/dL increase in TRL-apolipoprotein B (apoB), LDL-apoB, or Lp(a)-apoB were estimated. Note: to provide a comprehensive picture, this analysis included proteins regardless of whether they achieved Bonferroni-adjusted significance or not. (A and B) Present effect sizes for chemokines divided into those with a C-C and a C-X-C motif. The effect size for each chemokine is compared for a 10 mg/dL increase in TRL-apoB (using SNP set 1; y-axis) and a 10 mg/dL increase in Lp(a)-apoB (using SNP set 3; x-axis). (C and D) present the same information this time for effect sizes related to a 10 mg/dL increase in LDL-apoB (y-axis) vs effect size associated with a 10 mg/dL increase in TRL-apoB (x-axis). (E and F) Compare effect sizes (percent change in protein concentration per 10 mg/dL TRL-apoB or Lp(a)-apoB increase) for other cytokines, including interleukins (E) and tumor necrosis factor (TNF)-related cytokines (F). Explained variance (R2) and Pearson's r are displayed.

gave slightly lower mediation results (**Table 2**). Including IL-6 in the model with chemokine score 2 did not lead to an additive effect in the mediation analysis (**Table 2**). Further models were constructed to test if the degree of mediation was influenced by other risk factors for CVD. As shown in Supplemental Table 6, adjustment for nonlipid variables (blood pressure, hemoglobin A1c, and smoking) did not materially alter the strength of the association.

To test if the mediation results for chemokines were attributable to a general causal relationship between the circulating concentrations of these proteins and CVD risk, we performed a pQTL analysis for those chemokines most strongly related to TRL/Lp(a) concentrations in **Table 2** - CXCL5, 6, 13, and CCL17, 23, 27. Variants affecting the levels of these chemokines were identified (including TRL- and Lp[a]-linked SNPs) and assessed for association with CVD (Supplemental Table 7). Although there was evidence of an association, though not statistically significant, for CXCL13 and CCL27 with CVD in unadjusted models, once adjusted for TRL and Lp(a) levels, or following cropping of variants linked to these lipoproteins, there appeared to be no significant relationship between chemokine concentrations and CVD risk. We interpret these pQTL findings as indicating that the mediation estimates in Supplemental Table 6 reflect TRL/Lp(a)-driven activation of chemokine pathways which leads to increased circulating levels of these proteins rather than the existence of a generic causal effect of circulating chemokines (proportional to their plasma concentration) on CVD risk.

DISCUSSION

The present study explored whether potentially causal effects of apoB-containing lipoproteins on the plasma proteome provided insight into the differences in atherogenicity of TRL/remnant, LDL and Lp(a) particles. The major finding was unexpected and informative. Both TRL/remnants and Lp(a) had significant effects on chemokine concentrations that LDL did not, and the altered chemokine profile appeared to explain a substantial proportion of the association of TRL/remnants with cardiovascular disease. These observations have important implications for our understanding of the role of TRL and Lp(a) in atherogenesis.

Our approach in this investigation was to use the power of genetic analyses to detect potentially causal relationships and so obviate possible confounding of any associations between lipoproteins and the plasma proteomic profile that would occur if specific plasma proteins affected the levels of apoB-containing lipoproteins (reverse causality). We explored using separate SNP sets as genetic instruments the effects of TRL/remnants, LDL and Lp(a) on >2,900 proteins representing a wide range of biological processes with the expectation that patterns in the proteomic profiles would give insight as to why the atherogenicity of TRL/remnant and Lp(a) particles was higher than that of LDL. The hypothesis that TRL/remnants would exhibit a heightened version of the effects of LDL and that Lp(a) would be linked to atherothrombotic pathways was not borne out by the data. The finding that TRL/remnants affected apparently causally a large number of proteins, many of which were shared with Lp(a) but not LDL, was remarkable. In the GO analysis, both TRL/remnants and Lp(a) associated proteins were linked to pathways of cell signaling, leukocyte migration, and the response to the presence of foreign material or damaged tissue. Genetically determined increase in LDL, in contrast, was associated with a different proteome pattern with increases in proteins linked to cell sterol metabolism and lipid transport. LDL appeared unrelated to biomarkers of inflammation in line with previous reports.[13,14] In an investigation related to the present study,[20] we explored the association of the plasma proteome with measured plasma concentrations of the 3 apoB-containing lipoproteins. Again, TRL and Lp(a) plasma concentrations exhibited significant associations with a common set of inflammation-linked proteins that were distinct from those associated with LDL. This concordance between genetic and observational (measured concentration) approaches provides a high degree of confidence in the findings. Further, we were able to validate the key relationships observed between plasma lipids and circulating proteins in the UK Biobank in an independent cohort.[20]

Focusing on the proteins we found to be affected by genetic variation in both TRL/remnants and Lp(a), it was observed that the effect sizes correlated strongly; that is, if TRL/remnants had a large effect on a protein, so did Lp(a). Indeed, the magnitude of the effect of a TRL/remnant particle (ie, per apoB increment) on these plasma proteins was very similar to that of an Lp(a) particle, which is surprising given the structural differences between the lipoproteins. At present, we can only speculate as to the properties of TRL and Lp(a) that are responsible for their similar effects on inflammatory proteins. Both particles have apoB as the main structural protein integrated into the phospholipid surface monolayer, whereas apo(a) is found only in Lp(a). Probably, the best candidates are minor and oxidized lipid components that

conceivably could exchange between the particles.[22] Oxidized lipids have been reported to be present in TRL and enriched in individuals with diabetes and metabolic syndrome,[23-25] whereas Lp(a) is well known on a per-particle basis to have a high content of oxidized lipids.[23,24] A study into the mechanism whereby Lp(a) induced CXCL8 (IL-8) expression in cultured macrophages identified the kringle IV domain of apo(a) as critical for the transport of oxidized phospholipids, and enzymatic removal of this lipid blunted the ability of Lp(a) to promote release of the chemokine.[16] The recent study by Dzobo et al[15] reported that, in addition, Lp(a) contains lysophosphatidic acid and diacylglycerols, both of which have been shown to have pro-inflammatory actions. Lysophosphatidic acid, in particular, has been reported to stimulate the synthesis of chemokines as well as other cytokines, and induce chemokinesis of leukocytes.[26] These minor lipid products could be produced on Lp(a) since the lipoprotein carries enzymes capable of generating them from precursors. TRL, as it undergoes lipolysis, will also contain substantial amounts of partially hydrolyzed lipids derived from triglyceride (diacylglycerols, monoacylglycerols) and phospholipid (lysophospholipids).[27] These molecules may transfer to other lipoproteins including Lp(a). In light of the findings in this and other recent studies, it is clear that building on what has been established already,[22] further quantitation and experimentation are needed to determine how minor lipids are generated and move between lipoprotein species in the circulation.

Of the proteins affected by both TRL/remnants and Lp(a) it was the chemokines that stood out as the most abundantly represented cognate protein group. Specific chemokines were influenced strongly by both TRL and Lp(a), again with a concordance in magnitude of effect size. Further, TRL/remnants were found to be significant determinants of the plasma levels of a number of chemokines, including CXCL5, CXCL6, CXCL13, and CCL27, accounting for a substantial proportion of their variance. Other cytokine classes were much less affected by TRL/remnants. In the present study, IL-1β, IL-6, and CRP correlated with measured TRL/remnant-C levels, as has been shown previously,[9] but the magnitude of the effect sizes in MR analysis of TRL/remnants on these biomarkers was much smaller than for chemokines, and associations did not reach Bonferroni-adjusted significance.

Chemokines are secreted by stromal cells and leukocytes and have important functions in tissue homeostasis and immune responses.[28] In inflammation, they promote blood leukocyte migration towards sites of tissue damage in response to microbial invasion or the presence of damage-associated molecular pattern signals.[29,30] Chemokines are also central orchestrators of vascular inflammation and are abundantly expressed in human atherosclerotic plaques, where they are released by endothelial cells, smooth muscle cells, and resident and infiltrating leukocytes.[31,32] The chemokine profile changes with lesion progression and clinical phenotype. In early lesion development, chemokines promoting innate leukocyte recruitment, particularly monocytes, are prominent.[1,5,33] These include the CCL2-CCR2 (CC receptor 2) axis and related inflammatory C-C chemokines such as CCL3, which amplifies early macrophage accumulation and local cytokine production. With disease progression, additional chemokines become more dominant, including CCL5, which promotes monocyte and T cell recruitment, and the dendritic cell-derived CCL17, which influences T-cell differentiation and function.[28,31,32]

Many chemokines important in atherosclerosis are detectable in the circulation. Our study identified a number significantly associated with TRL/remnants—CXCL1, CXCL5, CXCL6, CXCL13, CCL17, CCL23, CCL27—that are implicated in different chronic inflammatory pathways involved in atherogenesis.[31,32] For example, the CXCR2 ligands CXCL1/3/5/6/8 are key mediators of endothelial activation and early recruitment of myeloid cells, particularly neutrophils, thereby promoting lesion progression, plaque destabilization, and thrombo-inflammatory responses.[32] Notably, these chemokines and others are typically induced in an NFκB-dependent manner by pro-inflammatory cytokines (IL-1β, TNF), but also by oxidized lipids.[34,35] On the other hand, other chemokines reflect adaptive immune mechanisms that sustain the atherosclerotic disease process. CXCR3 ligands such as CXCL9 support the recruitment of Th1 cells and cytotoxic T cells, which have been implicated in the immune activation of plaques, whereas CCL17 is central in the homeostasis of regulatory T cells, which mediate atheroprotection.[36] CCL17 has been demonstrated to promote atherosclerosis by suppressing regulatory T cells.[31,37] Moreover, the CXCR5 ligand CXCL13 is a key chemokine in B cell activation/migration and the organization of tertiary lymphoid organs that have been found in the adventitia surrounding atherosclerotic plaques.[38] Although the exact function of arterial tertiary lymphoid organs in atherogenesis is still unclear, B cells are prominent modulators of disease, and CXCL13 has been implicated in atherosclerosis.[39-41]

We hypothesize that a number of these chemokine-related pathways are activated or enhanced by the

chronic stimulatory effects of TRL/remnants and Lp(a). As noted above, both particle types carry oxidized lipids and a number of minor lipids that have the potential to promote chemokine synthesis.[34,35,42] Our observation that the association of TRL/remnant-C with increased chemokine score was as evident in individuals in their mid-40s as in those in their 60s prompts speculation that the TRL/remnant effect might be a contributing factor throughout lesion development. That is, elevated TRL/remnants may, by chronically stimulating chemokine secretion, exaggerate the artery wall's response to retention of lipoproteins and so promote the initiation of atherosclerotic plaques and later augment the recruitment of leukocytes to the growing lesion. Lp(a) at high concentration appears to have the potential to generate the same chronic overstimulation of chemokine release as TRL/remnants. However, on a patient basis, the relative impact of TRL/remnants and Lp(a) on chemokine levels is likely to differ. The frequency of elevated TRL levels in the UK Biobank cohort (as an example study group) is high; about 80% of individuals have a plasma TG between 1.0 (an optimal level) and 2.5 mmol/L. A 1.5 mmol/L increment in plasma TG (10 mg/dL TRL-apoB) is sufficient to cause a substantial perturbation in the chemokine profile that could be of pathological significance. Lp(a), on the other hand, is low in most people; the median in the UK Biobank is 21 nmol/L. A 180 nmol/L increment in Lp(a) mass (again about a 10 mg/dL increase in Lp[a]-apoB) would be present in only about 7% of the patients.[4] Thus, stimulation of the chemokine pathway might be expected to contribute less to the overall association of Lp(a) with CVD. Other plasma proteins beyond the chemokine group were associated with genetically determined variation in TRL and Lp(a). A number of these are cell-signaling factors (such as neuropeptide Y) and may also contribute to the maladaptive response. They have functions that are possibly involved in remodeling of the artery wall architecture and so could be plausibly involved in atherogenesis.[20]

The present work provides strong support for the proposition that TRL/remnants causally influence plasma chemokine concentrations, in some cases substantially. The observation that the TRL-associated chemokine profile predicted CVD risk prompted us to consider that a component of the TRL effect on CVD was through the chemokine axis. Mediation analysis suggested that chemokine signaling pathways as reflected in the chemokine scores may explain approximately 40% of the association of TRL/remnant-C with CVD. These mediation estimates, derived using observed rather than genetic data, are best viewed as measures of explained variance that are consistent with a substantial contribution from chemokine pathways to the TRL-CVD relationship, but not definitive proof of causality. Although our pQTL analysis of likely chemokine candidates did not indicate the existence of a generic causal relationship between their circulating levels and CVD, variants or deficiencies in specific chemokine genes have been reported to alter plasma chemokine concentrations and CVD risk.[43-45] This includes CXCL5, CXCL12 and CCL17, chemokines that we show here are responsive to TRL. To explain these seemingly discordant observations, we postulate that locality and context are key. That is, in a TRL-chemokine-atherosclerosis causal chain, it is the stimulation of chemokines in specific cellular environments (such as the subendothelial space of the artery wall as described previously) that is of importance in atherogenesis, and plasma chemokine levels can reflect this activity.

Our findings can be set in the broad context of previous extensive investigations of the relationship between apoB-containing lipoproteins, inflammation, and atherosclerosis.[1,43,46-49] The focus to date has largely been on the IL-1β/IL-6/CRP axis, with CRP and IL-6 as biomarkers of the activity of this pathway being risk factors for CVD. This pathway appears to play an important role in atherosclerosis since a specific IL-1β antagonist, canakinumab, has been shown to substantially reduce CVD events in individuals with elevated CRP levels.[50] The connection of the IL-1β/IL-6 pathway to apoB-containing lipoproteins, however, seems to be weak at least in statistical terms (as shown again in the present study and in Wadstrom et al[49]). In contrast, the relationship between TRL and chemokines is considerably stronger, consistent with a more direct mechanistic connection.

A major strength of the present study lies in the fact that investigation of the TRL/Lp(a)-chemokine relationship was based on genetic analyses, which obviates potential confounding and issues of reverse causality. The main limitation is that it was conducted in a single population of predominantly white European ancestry since only the UK Biobank has the essential data elements of comprehensive genetic profiling and proteomic analysis. To provide a measure of validation for the main findings, we compared effect sizes for the association of observed TRL/remnants and Lp(a) concentrations on chemokines (determined using the same Olink technology) in the MESA study. There was a high degree of concordance between the 2 cohorts. We were unable to test the relationship between chemokine scores and outcome independently, so the generalizability of our findings

to study groups with different genetic backgrounds and those with established CVD or on lipid-lowering drugs remains an open question. Other limitations were methodological constraints in that the Olink technology generates normalized concentrations rather than absolute levels, and there are a number of possibly important chemokines not included in the Explore panel. Finally, it should be noted that circulating chemokine concentrations may not necessarily reflect the local chemokine levels in atherosclerotic plaques. Thus, the potential involvement of chemokines in LDL-driven pathways of atherogenesis cannot be excluded.

The findings of the present work raise mechanistic questions that could be addressed in further basic and translational experimentation. For example, the approach taken to elucidate the proinflammatory effects of minor lipids transported on Lp(a) could be replicated for TRL. In this context, it is notable that Reilly et al[51] have reported recently that freshly isolated lymphocytes from individuals with elevated plasma TG levels exhibit a pro-inflammatory phenotype with increased expression of genes linked to inflammation pathways. This, alongside the observations of the effects of Lp(a) on peripheral blood monocytes, indicates that high TRL and high Lp(a) may chronically program blood leukocyte populations toward a proinflammatory state. If, as has been observed, this leads to extravasation (the basis of which needs further exploration), then this may help explain the recruitment of blood leukocytes to growing atherosclerotic lesions. At the cellular level, it is important to elucidate which specific pathways are activated by TRL and Lp(a) to stimulate chemokine release. Alongside these mechanistic studies, further clinical investigations are needed to support the proposed causal chain. A major question is whether perturbing the concentration and composition of TRL and Lp(a) using diet or drugs leads to reduced levels of key chemokines involved in atherogenesis.

In conclusion, this study revealed that TRL/remnant particles have a profound influence on the plasma chemokine profile that is likely to be of significance in the aetiology of atherosclerotic cardiovascular disease. This effect appears to be shared by Lp(a) but not LDL. The impact of TRL/remnants on chemokine-related pathways is quantitatively greater than on other cytokines such as IL-6. These observations have significant implications for our understanding of the role of TRL/remnants and possibly also Lp(a) in atherogenesis. They offer new routes of investigation at the translational and clinical level, and a means of identifying potential targets for intervention.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This study demonstrates that TRL and Lp(a), but not LDL, causally converge on a shared chemokine profile. In mediation analyses based on measured plasma concentrations, this chemokine profile was estimated to explain around 40% (with wide confidence limits) of the association of TRL/remnant-C with CVD. This finding is consistent with specific chemokine signaling pathways contributing substantially to the TRL/remnant—CVD relationship, although it does not establish causality.
A quantitative trait loci analysis indicated that there was no generic chemokine—CVD effect independent of TRL and Lp(a). TRL (measured as plasma TG) appears to have a substantial effect on the chemokine profile; a 1.5 mmol/L increase in plasma triglyceride drives a 10% to 30% rise in the circulating concentration of specific chemokines. This previously unrecognized connection establishes a biological mechanism to explain in part why TRL particles and possibly Lp(a) are more atherogenic than LDL.

TRANSLATIONAL OUTLOOK: Chemokine pathway antagonism represents a novel, mechanistically targeted approach to attenuate TRL and Lp(a) atherogenicity independent of lipid regulation. Future trials of antisense therapies targeting apoC-III and ANGPTL3 should test whether chemokine suppression mediates cardioprotection. Chemokine profiling may enable risk stratification beyond traditional lipid biomarkers, informing precision interventions in dyslipidemia.

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APPENDIX For supplemental tables, please see the online version of this paper.