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ORIGINAL RESEARCH

TNFR Pathway-Related Proteins and Recurrent Coronary Artery Disease Events

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ABSTRACT

BACKGROUND Despite optimization with lifestyle modifications and medications, complications of coronary artery disease (CAD) remain the leading cause of adult mortality worldwide.

OBJECTIVES This study aimed to identify proteins and pathways linked to recurrent CAD events to better understand residual risk.

METHODS We used data from 1,009 participants in the UK Biobank with baseline Olink plasma proteomic measures and CAD. Cox proportional hazards regression modeled the association between proteins measured and recurrent CAD events in follow-up.

RESULTS Participants had a mean age of 62.51 years (SD 5.94) at enrollment; 183 (18.14%) were females and 656 (65.01%) had recurrent CAD events over 11.40 (IQR: 8.00-14.69) years of follow-up. Among 1,463 proteins tested, 102 proteins were independently associated with recurrent CAD events. Molecular functions were significantly enriched for tumor necrosis factor receptor (TNFR) activity by 100-fold ($P = 6.37 \times 10^{-10}$). Of the 16 proteins related to TNF annotated by the Gene Ontology database, tumor necrosis factor-alpha had a risk estimate of 1.36 (95% CI: 1.17-1.57; $P = 6.38 \times 10^{-5}$), TNFR1 (*TNFRSF1A*) had a risk estimate of 1.73 (95% CI: 1.43-2.09; $P = 1.23 \times 10^{-8}$), and TNFR2 (*TNFRSF1B*) had a risk estimate of 1.27 (95% CI: 1.13-1.44; $P = 9.15 \times 10^{-5}$) for recurrent CAD events.

CONCLUSIONS Although TNFR1 and TNFR2 were initially thought to have opposing roles in cardiac remodeling postmyocardial infarction, this study highlights the complex interaction between these pathways and the need to identify specific inflammation-related targets to therapeutic strategies. (JACC Adv. 2026;5:102687) © 2026 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

DAVID = Database for Annotation, Visualization, and Integrated Discovery

GO = Gene Ontology

HDL = high-density lipoprotein

KEGG = Kyoto Encyclopedia of Genes and Genomes

MI = myocardial infarction

PPP = Pharma Proteomics Project

TNF = tumor necrosis factor

TNFR = tumor necrosis factor receptor

TNFRSF = tumor necrosis factor receptor superfamily

UKB = UK Biobank

Despite advances in prevention and treatment options, cardiovascular disease driven by coronary artery disease (CAD) has emerged as the leading cause of mortality and morbidity in the world in the 21st century.[1] Clinical practice guidelines continue to emphasize primary and secondary prevention of CAD through targeting modifiable risk factors, with an emphasis on lipid modification, blood pressure lowering, and glucose control.[2-4] Despite optimization of these factors with lifestyle modifications and medications, the residual risk of recurrent CAD remains alarmingly high, with incidence dramatically increasing over extended follow-up periods.[5-7] Recurrent CAD risk prediction models have demonstrated only a modest added benefit from inclusion of conventional biomarkers including N-terminal pro-brain natriuretic peptide,[8] C-reactive protein,[9] and troponin T,[10] highlighting an area of unmet need.

The ongoing search for novel biomarkers that enhance risk stratification and mechanistic clarity has begun to increasingly leverage novel multiplexed scalable platforms. Proteomics platforms enable broad-based scans to identify disease-relevant biomarkers. For example, utilization of these powerful technological approaches has improved predictive power for primary CAD,[11,12] but there have only been limited assessments among those with CAD already manifested. A recent study modeling recurrent CAD events found that comprehensive clinical, lifestyle, sociodemographic, and genetic risk factors together accounted for $< 20\%$ of the risk for CAD recurrence, suggesting the presence of yet unknown risk factors.[13] The progression of CAD to recurrence involves numerous changes, including oxidative stress, endothelial cell dysfunction, and both proinflammatory and antiinflammatory mechanisms.[14] Many of these cellular changes may manifest in circulating plasma proteins.[15]

In this study, we investigated the plasma proteomic profiles of 1,009 participants from the UK Biobank (UKB) with CAD to identify associations with recurrent CAD events. We characterized the proteomic profiles in subgroups and enriched pathways associated with recurrent CAD events to better understand drivers and mechanisms underlying recurrent CAD events.

METHODS

STUDY POPULATION. The UKB is a prospective cohort study with genetic and clinical data collected on approximately 500,000 individuals between the ages of 40 and 69 years at the time of recruitment.[16] The data were linked to the National Health Service records from 2006 to 2022, permitting identification of prevalent clinical conditions and incident events. Analyses in the UKB were approved by the Northwest Multicentre Research Ethics Committee (11/NW/0382) and secondary use scope (application #7089) by the Massachusetts General Hospital Institutional Review Board in accordance with the Declaration of Helsinki under IRB #2021P002228.

Based on physician diagnoses or procedural codes, 10,688 participants had CAD before UKB enrollment (Supplemental Figure 1). We then excluded 322 participants with unavailable genotype information and 2,067 individuals with incomplete covariates measurements. An additional 7,270 individuals did not have proteomic profiling at baseline and were excluded. The final analytical cohort included 1,009 individuals.

OUTCOME MEASURE. Prevalent CAD was defined with previously used diagnoses codes for a CAD event identified in the hospital episode statistics inpatient master table that entails information on inpatient episodes of care, including diagnoses, admissions and discharge, operations, and procedures described in UKB (Supplemental Table 1). Specifically, diagnostic and procedural codes for a CAD event included myocardial infarction (MI), percutaneous coronary intervention, coronary artery bypass graft, or the death register indicating MI and related sequelae as either a primary or secondary cause of death in the UKB. The primary outcome of a recurrent CAD event in the UKB was defined as previously described,[13] which briefly was the first CAD event that occurred after UKB recruitment irrespective of the number of CAD events before recruitment. The recurrent CAD event had to occur at least 28 days after the most recent CAD event before recruitment as previously described to differentiate independent incidences from combined attributions of diagnoses and procedures within a single episode or hospitalization.

VARIABLES. Other standard cardiovascular risk factors used in this analysis were selected based on previously described cardiovascular risk prediction models,[13] including age at enrollment, age at first CAD event, sex, cigarette smoking, diabetes diagnosis, body mass index, systolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein (HDL) cholesterol, statin prescription, and the first 10 components of genetic ancestry. Both the age at UKB enrollment and the age at first CAD event were used in the analysis. Sex was derived from biological classification as male or female. Racial background was derived from fixed self-reported categories, including African, Bangladeshi, British, Caribbean, Chinese, Indian, Irish, Pakistani, White and Asian, White and Black African, White and Black Caribbean, other Asian, other Black, other White, other mixed, or other/unknown. Given small sample sizes of some groups, categories were consolidated into broader categories of African, Asian, European, and other for analysis. Current cigarette smoking was defined as lifetime smoking of at least 100 cigarettes and currently without cessation. Body mass index was measured using Tanita BC-418MA body composition analyzer. Blood pressure was measured by the UKB staff at the time of enrollment. All laboratory values for total and HDL cholesterol were derived from a nonfasting sample collection assayed within 24 hours. Statin prescription was defined as a prescription written at the time of enrollment. Diabetes mellitus was defined as glycated A1c ≥6.5% or prior physician diagnosis.[17]

PROTEOMICS DATA PROCESSING. Proteomics data were collected from a random set of individuals enrolled in the UKB Pharma Proteomics Project (UKB-PPP) as previously described.[18] Briefly, the UKB-PPP includes 54,306 participants: 46,673 (85.9%) were randomly selected from baseline, 6,385 (11.8%) were preselected by consortium members based on characteristics of interest such as disease status or genetic ancestry, and 1,268 (2.3%) were selected for participation in multiple visits of the COVID-19 case-control imaging study. Nonfasting baseline plasma samples were collected from these 52,749 UKB participants using the Olink Explore 1,536 platform with Olink Proximity Extension Assay technology. Exclusion criteria for individuals were high rate of missingness (>10% missing protein measurements) and those with excess relatedness (second-degree relatives or closer). The remaining missing values were imputed using the "miceforest" (Python package) with 10-fold cross-validation to impute the residual absent protein readings in the quality-controlled Olink proteomics data set. Although performing imputation, we evaluated factors that can potentially affect protein measurements such as protein batch, the study center, and first 10 principal components of genetic ancestry. Our evaluation indicated a negligible impact on protein levels arising from these factors, with the weakest Pearson correlation between protein levels and residuals being 0.93.

STATISTICAL TESTING. Cox proportional hazards regression models were run to assess the association between proteins measured and recurrent CAD events in a population of patients with CAD. Multivariable models were constructed, testing the association of each protein individually with recurrent CAD events. Consistent with prior studies, covariates included standard cardiovascular risk factors, and all *P* values reported were two-sided. *P* values were corrected using the corresponding Bonferroni *P* value for multiple testing of proteins. Significant proteins were annotated with Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), and UniProt associated terms and enrichment analysis was performed using the Database for Annotation, Visualization, and Integrated Discovery (DAVID) tool in the background of Olink proteins.[19] Briefly, users upload a prioritized protein list of interest and background list of all proteins assayed by the platform to identify enrichment. The tool then retrieves annotation lists from biological databases such as GO, KEGG, and UniProt to provide annotations for each protein representing molecular functions, cellular components, and biological processes. The tool also performs protein-term enrichment analysis to identify which annotations within these databases are significantly over-represented in the input protein list compared to the background. GO terms represent the most widely accepted functional annotation scheme in biological research and form the foundation of the DAVID annotation tool.[20] This information can then be extracted from the tool and used to standardize representations of protein-pathway relationships.

Kaplan-Meier survival plots were constructed to evaluate time to recurrent CAD event in those with significant enriched proteins in the 4th quartile vs lower concentrations and compared using the log-rank test. Cox proportional hazards regression models were run to assess the association between proteins measured and recurrent CAD events in a population of patients with CAD. A total of 1,463 separate multivariable models were constructed, with each model testing the association of a single protein with recurrent CAD events. All models were adjusted for covariates that included standard cardiovascular risk factors consistent with prior studies, and all *P* values reported were two-sided. Models

TABLE 1 Demographics of the UK Biobank Cohort by Recurrent CAD Status

	Total (N = 1,009)	Without Recurrent CAD (n = 353)	With Risk Recurrent CAD (n = 656)	*P* Value
Age at enrollment in years mean (SD)	62.51 (5.94)	62.41 (5.80)	62.56 (6.01)	0.688
Age at primary event in years mean (SD)	57.69 (6.53)	57.90 (6.53)	57.58 (6.54)	0.460
Female sex	183 (18.14)	75 (21.25)	108 (16.46)	0.073
Race				0.684
African (%)	5 (0.50)	3 (0.85)	2 (0.30)	
Asian (%)	22 (2.18)	6 (1.70)	16 (2.44)	
European (%)	969 (96.04)	342 (96.88)	627 (95.58)	
Other (%)	13 (1.29)	2 (0.57)	11 (1.68)	
Current smoker (%)	129 (12.78)	35 (9.92)	94 (14.33)	0.158
Body mass index, mean (SD)	29.38 (4.60)	29.09 (4.61)	29.53 (4.59)	0.150
Systolic blood pressure in mm Hg mean (SD)	138.95 (20.58)	140.60 (20.39)	138.06 (20.64)	0.061
Statin prescribed (%)	935 (92.67)	316 (89.52)	619 (94.36)	0.007
Diabetes (%)	193 (19.13)	55 (15.58)	138 (21.04)	0.044
Total cholesterol in mg/dL mean (SD)	167.72 (38.12)	169.66 (40.13)	166.67 (36.98)	0.246
High-density lipoprotein cholesterol in mg/dL, mean (SD)	44.65 (10.84)	45.84 (11.69)	44.01 (10.31)	0.014
Low-density lipoprotein cholesterol in mg/dL, mean (SD)	101.08 (27.78)	102.10 (29.10)	100.53 (27.06)	0.402

CAD = coronary artery disease.

were additionally adjusted for established CAD-related biomarkers to assess whether the identified proteins provided additional contributions beyond these known markers in their association with recurrent CAD. All statistical analyses were performed using R (version 4.2.2, R Foundation for Statistical Computing).

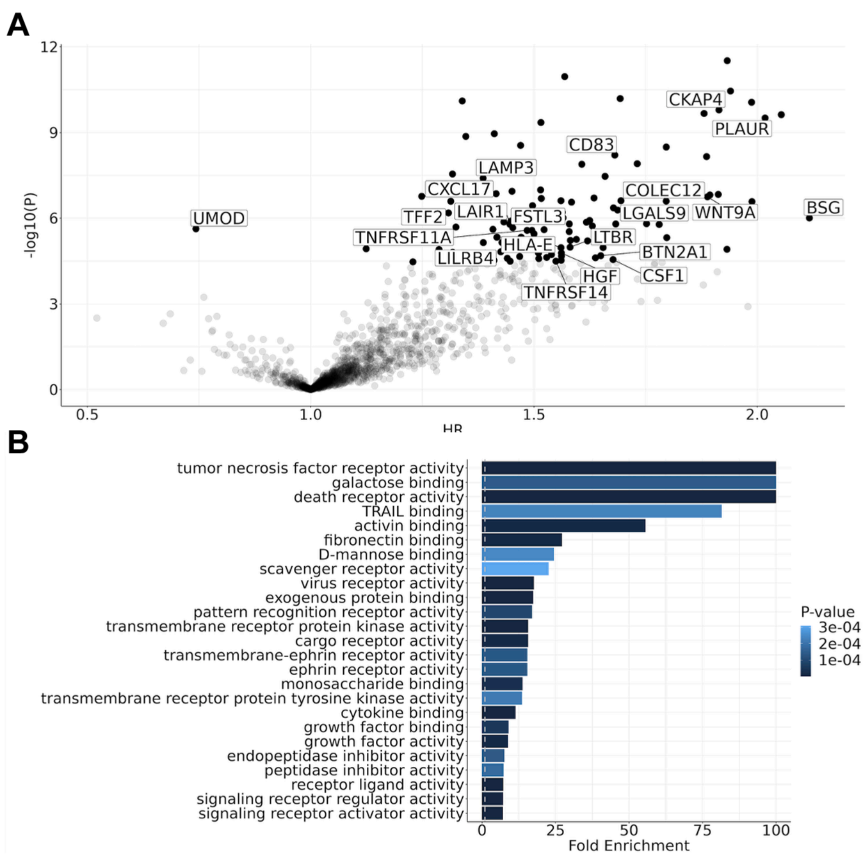
RESULTS

BASELINE CHARACTERISTICS. We included 1,009 participants from the UKB who had CAD at enrollment (Supplemental Figure 1). Participants had a mean age of 62.51 years (SD 5.94) at enrollment; 183 (18.14%) were females, and 656 (65.01%) had recurrent CAD events over 11.40 (IQR: 8.00-14.69) years follow-up (Table 1). Those with vs without recurrent CAD events in follow-up had a higher rate of statin prescriptions (94.36% vs 89.52%, $P = 0.007$), a greater prevalence of diabetes (94.36% vs 89.52%, $P = 0.007$), and lower HDL cholesterol levels (44.01 mg/dL vs 45.84 mg/dL, $P = 0.014$). The remaining features stratified by recurrent CAD status were comparable within each cohort. Of the 52,705 UKB participants with 1,463 protein measurements, 42 proteins were imputed due to missing values.

ENRICHMENT ANALYSIS HIGHLIGHTS THE ROLE OF TNF-RELATED PATHWAYS IN RECURRENT CAD. Among the 1,463 proteins tested, 482 proteins at nominal significance ($P < 0.05$) and 102 proteins at experiment wide significance (Bonferroni $P < 3.42 \times 10^{-5}$) were associated with recurrent CAD events after adjusting for standard cardiovascular risk factors (Figure 1A, Supplemental Table 2). Of the 102 Bonferroni-corrected proteins associated with recurrent CAD events, 29 (28.43%) were classified as cardiometabolic proteins by Olink annotations (Supplemental Figure 2). Enrichment analysis of significant proteins using GO terms revealed that molecular functions were significantly enriched for tumor necrosis factor (TNF) receptor (TNFR) activity by 100-fold ($P = 6.37 \times 10^{-10}$) and death receptor activity by 100-fold ($P = 9.30 \times 10^{-14}$) (Figure 1B, Supplemental Figure 3). Annotation with GO terms for biological processes showed significant enrichment for the TNF-mediated signaling pathway ($P = 2.04 \times 10^{-7}$) (Supplemental Figure 4). GO terms for cellular compartments showed significant proteins were enriched in the endolysosome lumen ($P = 2.36 \times 10^{-4}$) (Supplemental Figure 5).

To further investigate the role of TNF and related proteins annotated by signaling pathways, proteins were classified based on their primary involvement with TNFR1, TNFR2, both, or neither of these pathways and plotted alongside pathway annotations using the DAVID annotation tool (Figure 2, Supplemental Figure 5). GO term biological process identified 13 significantly enriched proteins in the apoptotic pathway, 16 significantly enriched proteins in the TNF-mediated signaling pathway, and 8 significantly enriched proteins in the canonical NF-κB pathway associated with an increased risk of

FIGURE 1 **Risk of Recurrent Coronary Artery Disease Linked to UKB Proteins by Gene Ontology**

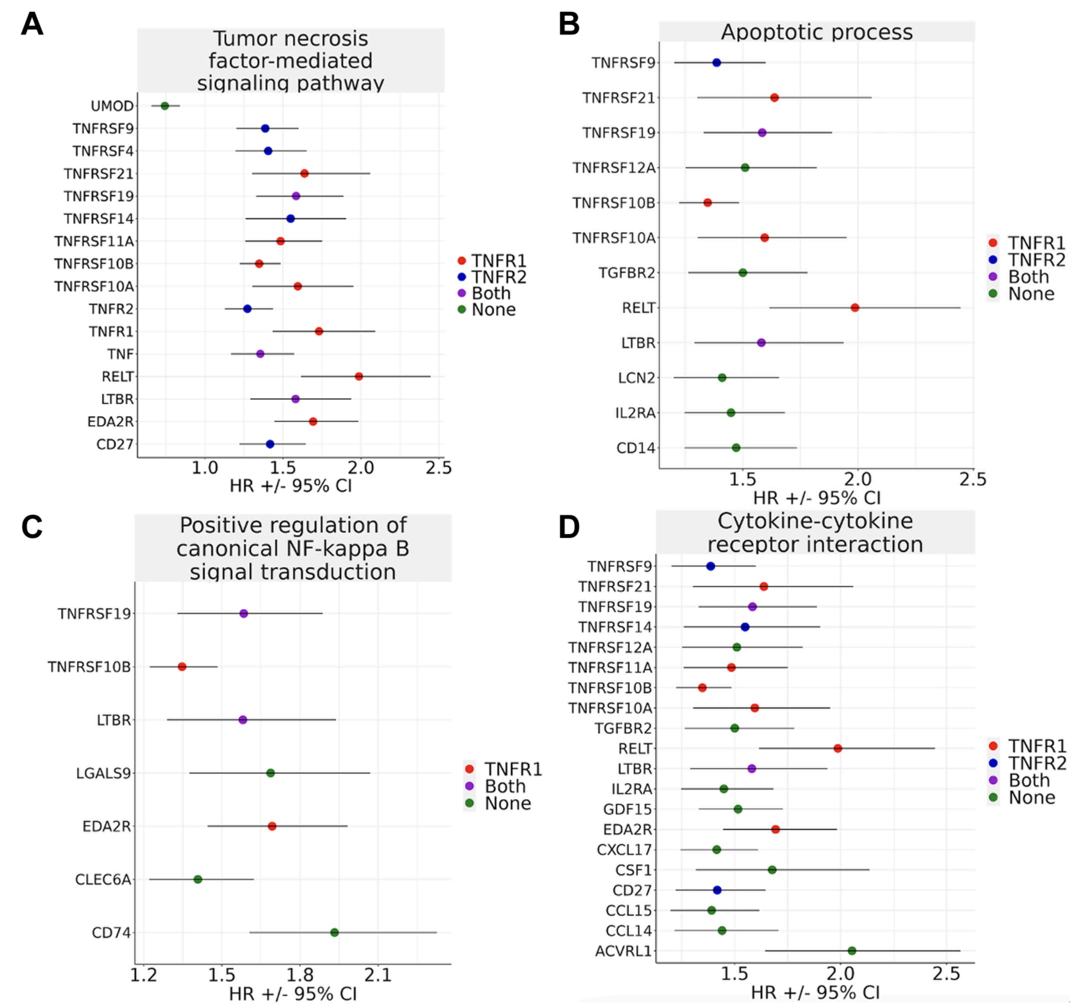


(A) Volcano plot of HRs and corresponding 95% CIs are based on Cox proportional hazards regression models with covariates of age at UKB enrollment, age at first CAD event, sex, smoking status, diabetes diagnosis, body mass index, systolic blood pressure, LDL cholesterol, HDL cholesterol, statin prescription, and the first 10 principal components of genetic ancestry. All *P* values were Bonferroni corrected for 1,463 measured proteins. DAVID annotation was utilized to provide Gene Ontology enrichment analysis of significant proteins by the top (B) molecular function. TNFRSF = tumor necrosis factor receptor superfamily.

recurrent CAD events (Figures 2A to 2C). There was a similar finding when using KEGG pathway annotations, where TNF-alpha and TNF-related proteins were further implicated in cytokine-cytokine receptor interactions that occur in both apoptosis and canonical NF-κB signaling (Figure 2B). Within these clusters, TNF-alpha exhibited a risk estimate of 1.36 (95% CI: 1.17-1.57; $P = 6.38 \times 10^{-5}$) for recurrent CAD events. TNFR1 (tumor necrosis factor receptor superfamily [*TNFRSF]1A*) had an HR of 1.73 (95% CI: 1.43-2.09; $P = 1.23 \times 10^{-8}$) for developing recurrent CAD.

Enriched proteins related to TNFR1, including receptor expressed in lymphoid tissues (HR: 1.99; 95% CI: 1.61-2.45; $P = 8.71 \times 10^{-11}$), TNFRSF21 (HR: 1.64; 95% CI: 1.30-1.44; $P = 2.43 \times 10^{-5}$), and TNFRSF11A (HR: 1.48; 95% CI: 1.26-1.75; $P = 2.66 \times 10^{-6}$) were also strongly associated with recurrent CAD events. TNFR2 (*TNFRSF1B*) had an HR of 1.27 (95% CI: 1.13-1.44; $P = 9.15 \times 10^{-5}$) for developing recurrent CAD. Enriched proteins related to TNFR2, including TNFRSF14 (HR: 1.55; 95% CI: 1.26-1.90; $P = 3.19 \times 10^{-5}$) and TNFRSF9 (HR: 1.27; 95% CI: 1.20-1.60; $P = 7.12 \times 10^{-6}$) had a modest association with recurrent CAD events. Enriched proteins involved in both TNFR1 and TNFR2 pathways, including lymphotoxin beta receptor (LTBR) (HR: 1.58; 95% CI: 1.29-1.94; $P = 1.03 \times 10^{-5}$) and TNFRSF19 (HR: 1.58; 95% CI: 1.33-1.89; $P = 2.74 \times 10^{-7}$) were also associated with recurrent CAD events. A similar strength of association for all TNFR-related proteins was observed when the median follow-up time of

FIGURE 2 Proteins Significantly Associated With Recurrent Coronary Artery Disease Events Annotated Using DAVID



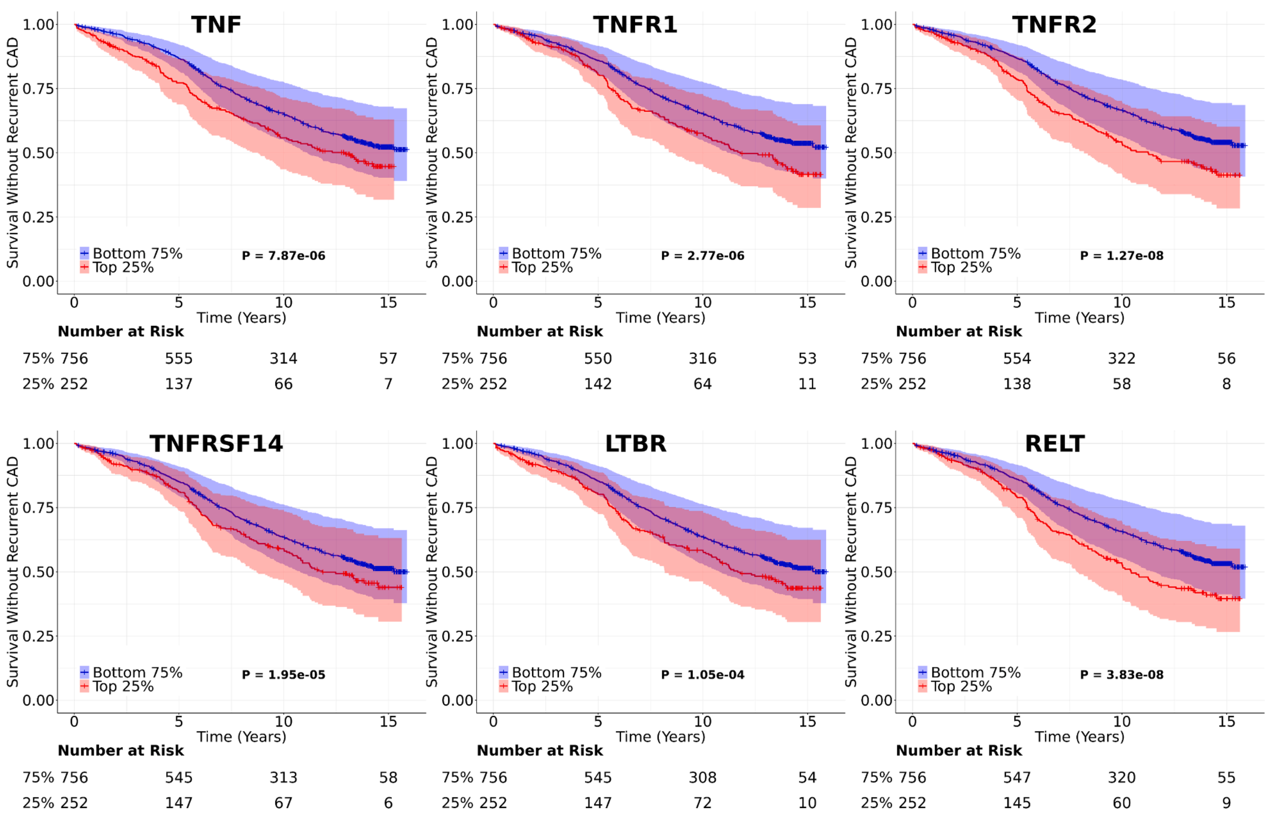
Annotations were performed by (A, B, C) biological processes in the Gene Ontology database and (D) KEGG functional pathways. HRs and corresponding 95% CIs are based on Cox proportional hazards regression models with covariates of age at UKB enrollment, age at first CAD event, sex, smoking status, diabetes diagnosis, body mass index, systolic blood pressure, LDL cholesterol, HDL cholesterol, statin prescription, and the first 10 principal components of genetic ancestry. Proteins were colored by involvement in TNFR1 as red, TNFR2 as blue, both pathways as purple, and neither of these 2 pathways in green. LTBR = lymphotoxin beta receptor; RELT = receptor expressed in lymphoid tissues; TNF = tumor necrosis factor; TNFR = tumor necrosis factor receptor; other abbreviations as in Figure 1.

11.40 years was limited to 3, 5, and 10 years (Supplemental Figure 6). A comprehensive list of annotated proteins with enriched UP-related terms is provided in Supplemental Figure 7 for sequencing features and Supplemental Figure 8 for biological processes.

TNFR1 AND TNFR2 PATHWAYS REMAIN ASSOCIATED WITH RECURRENT CAD ACROSS SUBGROUPS. In exploratory analyses, we created survival plots for TNF-alpha and enriched TNF-related proteins, specifically those involved in TNFR1, TNFR2, or both pathways, that had the strongest association with recurrent CAD events. Participants with elevated TNFR-related proteins had lower recurrence-free survival, with log-rank P values demonstrating significantly different survival curves between individuals in the top 25% of protein level compared to those in the bottom 75% of protein level (log-rank $P < 0.05$) (Figure 3).

We performed regression modeling of these significant TNF-related proteins in relation to recurrent

FIGURE 3 **Kaplan-Meier Curves by TNF-Related Protein Quartiles for Coronary Artery Disease Recurrence**

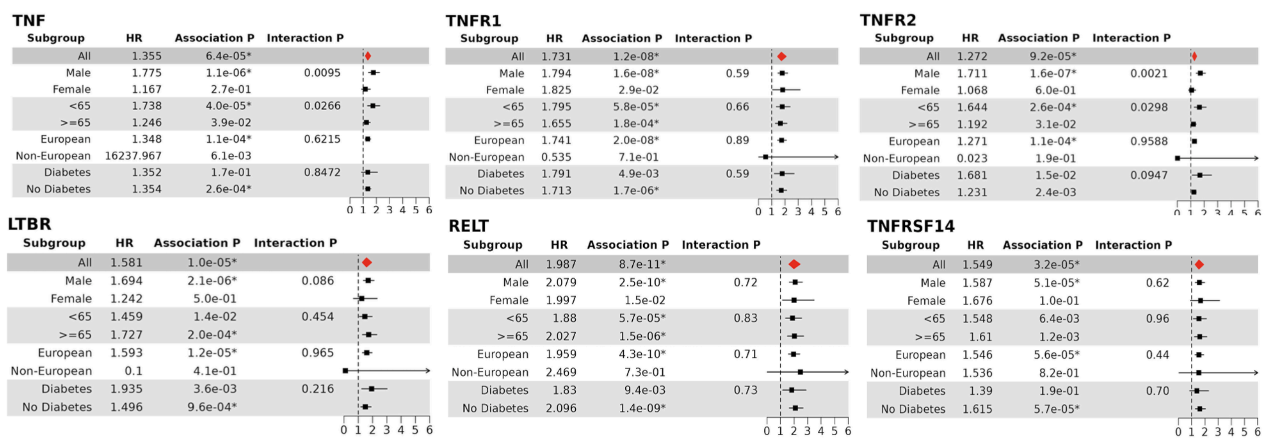


Kaplan-Meier curves showing recurrence-free survival for coronary artery disease (CAD) events during follow-up stratified by concentration of significantly enriched TNF-related proteins. Participants with protein concentrations in the highest quartile (Q4; red) were compared to those with lower concentrations (Q1-Q3; blue) using the log-rank test. CAD = coronary artery disease; other abbreviations as in **Figures 1 and 2**.

CAD stratified by clinical subgroups to assess consistency of the observed associations across varying patient characteristics (**Figure 4**, Supplemental Table 3). Formal interaction testing between age dichotomized at age 65 years, and TNF pathway proteins revealed significant age-dependent differences in risk associations for specific pathway members. When stratifying by age using a dichotomous threshold, TNF-alpha demonstrated significantly stronger associations with recurrent CAD events in younger patients (HR: 1.74) compared to older patients (HR: 1.25; *P* interaction = 0.027). Similarly, TNFR2 showed differential effects across age strata, with a HR of 1.64 in younger patients vs 1.19 in older patients (*P* interaction = 0.030). In contrast, TNFR1 exhibited similar associations across both age groups (HR: 1.66 in younger vs 1.80 in older patients; *P* interaction = 0.660), suggesting its prognostic may be consistent across ages. To further characterize the effect of TNF-related proteins on recurrent CAD risk over the whole life course, time-varying models demonstrated a modestly higher risk conferred by elevated TNF-related proteins at younger ages compared to older ages but significant effects remained across ages assessed similar to other well-established biomarkers (Supplemental Figure 9). There was also a higher risk of recurrent CAD events in males compared to females for TNF-alpha (1.78 vs 1.17, *P* interaction = 0.010) and TNFR2 (1.71 vs 1.07, *P* interaction = 0.002), but not TNFR1 (1.79 vs 1.83, *P* interaction = 0.590). Otherwise, the risk of recurrent CAD related to other TNF-related proteins remained similarly elevated among subgroups stratified by age, sex, race, and the presence of diabetes as shown in the **Central Illustration**.

When comparing the prognostic value of TNF-related proteins to that of established cardiovascular risk factors, we found that the HRs associated with TNF-related proteins were of comparable or greater magnitude, even after adjusting for all

FIGURE 4 **TNF-Related Proteins Linked to Recurrent Coronary Artery Disease Events Across Defined Clinical Subgroups**



HRs and corresponding 95% CIs are based on Cox proportional hazards regression models with covariates of age at UKB enrollment, age at first CAD event, sex, smoking status, diabetes diagnosis, body mass index, systolic blood pressure, LDL cholesterol, HDL cholesterol, statin prescription, and the first 10 principal components of genetic ancestry. Subgroup analyses were performed by splitting cohorts based on presence or absence of clinical grouping. An interaction *P* value was calculated to identify significant interactions between clinical subgroups and proteins influencing recurrent CAD risk. Abbreviations as in Figure 3.

traditional risk factors (Supplemental Table 4). Among the conventional risk factors evaluated, statin use demonstrated the highest HR at 1.48 (95% CI: 1.05-2.09; $P = 0.026$). Notably, TNFR1 exhibited an even greater HR of 1.73 (95% CI: 1.43-2.09; $P < 0.0001$) following multivariable adjustment. To evaluate the independence of our findings from established CAD-related biomarkers, we further adjusted models for both standard cardiovascular risk factors and well-established cardiac and inflammatory markers, including N-terminal pro-brain natriuretic peptide, interleukin-6, cystatin C, C-reactive protein, B-type natriuretic peptide, and troponin (Supplemental Figure 9). The HRs for the identified proteins remained robust after these adjustments, demonstrating their independent potential value.

DISCUSSION

In this study of 1,009 UKB participants with baseline CAD, we identified 102 proteins significantly associated with recurrent CAD events after adjustment for common cardiovascular risk factors. The identified proteins were significantly enriched for TNFR activity, cytokine-cytokine receptor interaction, and canonical NF-κB activation pathways. We demonstrate that the enriched TNFR proteins are positively associated with recurrent CAD events and span across both TNFR1 and TNFR2 pathways. These positive associations remained consistent across clinical subgroups of race and diabetes but suggest a potential effect modification related to age and sex for specific TNFR proteins.

Recurrent CAD event rates vary widely in the literature, depending on the duration of follow-up. At 3 years, Spironolactone trial reported event rates of 7.9% in the treatment group and 8.3% in the comparison group.[21] By 5 years, the Cholesterol and Recurrent Events (CARE) trial demonstrated increasing recurrent event rates of 10.2% in the pravastatin group and 13.2% in the placebo group.[6] A 2017 study using the UKB identified 6,440 individuals with baseline CAD and of those, 3,733 experienced a recurrent event during the follow-up period at approximately 58%.[7] Similarly, our analysis identified 656 participants (65.01%) with recurrent CAD events over a median follow-up of 11.40 years (IQR: 8.00-14.69), which may reflect partial preselection of UKB-PPP participants based on specific characteristics of interest. Restricting follow-up to 7, 5, or 3 years did not significantly alter the HRs associated with TNFR-related proteins.

Although the TNFR1 pathway has been associated with detrimental cardiac remodeling post-MI and the TNFR2 pathway with promoting cardiac recovery,[22] this study revealed that elevated TNFR1 and TNFR2 correlate with an increased risk of recurrent CAD events, consistent with the growing body of evidence that both proteins confer increased cardiovascular

CENTRAL ILLUSTRATION **TNF-Pathway Protein Associations With Recurrent Coronary Artery Disease Risk Across Clinical Subgroups**

UK Biobank Study

Prospective, observational study

- 1,256 participants with CAD at baseline
- 817 participants (65.05%) with recurrent CAD events

	TNFR1		TNFR2		TNFR1 & TNFR2	
	Hazard Ratio	Association *P*-Value	Hazard Ratio	Association *P*-Value	Hazard Ratio	Association *P*-Value
Overall Association	**1.35**	**6.4×10^{-5}**	**1.73**	**1.2×10^{-8}**	**1.27**	**9.2×10^{-5}**
Male	1.78	1.1×10^{-6}	1.79	1.6×10^{-8}	1.71	1.6×10^{-7}
Female	1.17	2.7×10^{-1}	1.83	2.9×10^{-2}	1.07	6.0×10^{-1}
<65	1.74	4.0×10^{-5}	1.80	5.8×10^{-5}	1.64	2.6×10^{-4}
≥65	1.25	3.9×10^{-2}	1.66	1.8×10^{-4}	1.19	3.1×10^{-2}
European	1.35	1.1×10^{-4}	1.74	2.0×10^{-8}	1.27	1.1×10^{-4}
Non-European	1.01	1.0×10^{0}	3.33	6.4×10^{-2}	1.85	4.2×10^{-1}
Diabetes	1.25	1.7×10^{-1}	1.79	4.9×10^{-3}	1.68	1.5×10^{-2}
No Diabetes	1.35	2.6×10^{-4}	1.71	1.7×10^{-6}	1.23	2.4×10^{-3}

Elevated TNFR1, TNFR2, and proteins associated with both pathways correlated with an increased risk of recurrent CAD events. Further research is needed to test whether perturbing each pathway will ameliorate residual CAD risk.

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Associations between TNFR1, TNFR2, and TNF-α protein levels and risk of recurrent coronary artery disease (CAD) events in the UK Biobank. Prospective observational analysis of 1,009 participants with established CAD at baseline, of whom 656 (65.0%) experienced recurrent CAD events. HRs and association *P* values for TNFR1, TNFR2, and TNF-α are shown overall and stratified by sex, age group, ancestry, and diabetes status. CAD = coronary artery disease; TNFR = tumor necrosis factor receptor.

risk in humans.[23] TNFR1 and TNFR2 can both be activated by TNF-alpha, released in large amounts from ischemia and hypoxia-activated cardiomyocytes following acute MI.[24] TNFR1 activation is known to promote apoptosis of certain cell types through the assembly of large signaling complexes, such as canonical activation, which collectively contribute to adverse cardiac remodeling.[25,26] In contrast, the role of TNFR2 remains less clearly defined, as studies have demonstrated cardioprotective effects in both animal models[22,27] and human tissue, where TNFR2 activation promoted cell cycle entry associated with cardiac repair processes.[28,29] TNFR2 is hypothesized to enhance cardiac remodeling by activating cell survival pathways primarily through noncanonical NF-κB pathways, which mostly results in cell survival and proliferation.[30,31] However, other studies have identified adverse effects of TNFR2 on creating an inflammatory reaction and adverse ventricular remodeling in patients that experienced MI.[23,32] Recent research has also uncovered overlap between TNFR1 and TNFR2 signaling on cardiovascular risk, as both pathways share downstream signal proteins such LTBR and TNFRS19, which were also associated with recurrent CAD events in our study. These proteins activate the noncanonical NF-κB pathway that was enriched in this study,[33] but the resulting effects depend on which of the 500 genes it transcriptionally regulates.[34] Correspondingly, vascular smooth muscles cells can be signaled to survive, proliferate, and migrate to the areas of endothelial cell death causing increased intimal thickening and progression of atherosclerosis.[35,36] Our study indicated that both TNFR1 and TNFR2 signaling are associated with increased risk of recurrent CAD events, underscoring the complex interaction between these 2 signaling pathways and the need to identify specific inflammation-related targets within these pathways to improve therapeutic strategies.

Cellular assays have demonstrated that TNFR2 signaling is dependent on the structure of TNFR2 itself. Vascular endothelial cells exhibit activation of NF-κB reporter genes when TNFR1 or TNF receptor associated factor 2 binding sites of TNFR2 are expressed, but not when the constitutively active form of a TNFR2 domain Etk-SK is expressed alone.[37] Although certain forms of TNFR2, including those with TRAF binding sites, can activate the NF-κB reporter gene, this study did not show an association between TNF receptor associated factor 2 and recurrent CAD events. This suggests that another subtype of TNFR2 may be responsible for triggering NF-κB activation. These findings emphasize the critical importance of elucidating TNFR2 structures and other associated structural proteins identified in this study to better understand its dual function in apoptotic mechanisms.

Emerging evidence highlights the clinical relevance of soluble TNF-related proteins in CAD, linking them to inflammation, cardiovascular events, and disease progression.[38] In a study of humans with stable coronary heart disease, increased concentrations of both soluble TNFR1 and TNFR2 were associated with increased risks of cardiovascular events and mortality.[39] Although a cohort study adjusting for estimated glomerular filtration rate attenuated the association between TNFR1 and 2 with cardiovascular mortality,[40] revascularization of cardiac lesions have also been shown to reduce serum concentrations of both TNF-alpha and serum levels of TNFR1, suggesting a functional relationship between soluble TNF-related proteins and inflammatory signaling.[41] This functional relationship is further supported by studies of inflammatory diseases at both the cellular[42] and patient levels.[43] Our study identified associations not only with TNFR1 and TNFR2 but also with additional TNFR-related proteins, including TNFSF14. Soluble TNFSF14, that enters serum after proteolytic processing at the membrane, has previously been associated with repeat cardiovascular events in patients with stable CAD.[44] Our study expands on this work by identifying an additional association between LTBR, a ligand of TNFSF14,[44] and recurrent CAD events, highlighting the potential functional role of this pathway in CAD progression. In addition, we demonstrate that the HRs associated with the 16 TNF-related proteins were comparable to, or exceeded, those of traditional cardiovascular risk factors. These findings suggest that TNF-related proteins provide independent prognostic information beyond that captured by traditional risk factors.

The failure of anti-TNF therapy in heart failure trials underscores the complexity of translating TNF biology into clinical cardiovascular therapeutics. Several critical evidence gaps must be addressed before future trials of TNF-modifying therapies can be considered for cardiovascular risk reduction. First, cardiovascular safety data from existing randomized control trials of anti-TNF therapy for rheumatologic conditions could be systematically analyzed to prioritize patient populations and disease contexts where TNF modification may be beneficial vs harmful.[45,46] Second, biomarker-guided approaches are needed to identify patients most likely to benefit from TNF pathway modulation based on their specific inflammatory profile. Finally, the optimal timing, duration, and degree of TNF pathway inhibition required for cardiovascular benefit without compromising other important functions remains undefined.[45] These evidence gaps represent important priorities for future translational research advancing TNF-modifying therapies for cardiovascular risk reduction.

Further work is needed to identify which patient demographics are most likely to benefit from therapies targeting parts of the TNFR pathway. For example, sex-specific differences in TNF-alpha biology are well-established in the literature and may have important implications for cardiovascular risk stratification. Prior studies have demonstrated that males with atherosclerotic disease maintain higher circulating TNF-alpha concentrations compared to females, a disparity that persists even after accounting for sex hormone levels.[46] In vitro studies have also shown that human neutrophils from males release more TNF-alpha than females on similar lipopolysaccharide stimulation.[47] The molecular basis for this sex dimorphism has been previously attributed to differential regulation of adenylyl cyclase signaling pathways between males and females.[48] Our study similarly demonstrates that the association of TNF and recurrent CAD events is modified by sex, with males being at greater risk for recurrent CAD. These sex-specific effects suggest that males with established CAD may represent a particularly responsive population for TNF-targeted therapeutic interventions and highlight the potential value of sex-stratified assessments in future clinical trials. In addition, we found TNF and TNFR2 had significant interaction terms in age groups, where elevated levels in younger individuals confer a higher risk for recurrent CAD events. This age-related susceptibility is supported by previous findings, such as the Northern Manhattan Stroke Study, which found that associations between TNF-related proteins and carotid stenosis were more prominent in relatively younger individuals.[49] Similarly, mouse studies have shown that administering TNF-alpha treatment in young animals induces endothelial dysfunction, oxidative stress, and increased apoptosis in carotid and coronary arteries.[50] A similar phenomenon is well-documented for genetic risk, in which polygenic risk scores have significantly greater predictive power in younger adults while traditional risk factors have more dominant effects in older individuals.[51] Circulating biomarkers may have greater effects on cardiovascular risk earlier in the lifespan, when other risk factors, such as smoking, become more pronounced.

A comprehensive proteomic assessment of recurrent CAD events prioritized 102 proteins, with a notable enrichment of TNF-related proteins, associated with recurrent CAD events. Elevated TNFR1, TNFR2, and proteins associated with both pathways correlated with an increased risk of recurrent CAD events. Although TNFR1 and TNFR2 were initially thought to have opposing roles in cardiac remodeling post-MI, this study provides evidence of the complex interaction between these signaling pathways and highlights the need to identify specific inflammation-related targets to improve therapeutic strategies.

STUDY LIMITATIONS. Our study should be interpreted in the context of several limitations. First, majority of study participants were of European descent, a known limitation of the UKB that compromises the generalizability of this study to diverse ancestries. We performed several subgroup analyses to assess for effect modification without significant differences in risk estimates. Second, plasma proteins of low abundance as well as cellular processes not reflected in plasma proteomics are not suitably assessed through the present technology. Third, this study did not account for medications that influence TNFR levels, as the UKB may not have comprehensively recorded all such medications. Fourth, we used the Olink technology from a single cohort. Nevertheless, our observations aligned with several experimental models assessing the role of TNFR-related proteins on atherosclerosis. Further investigation from randomized control trials of anti-TNF therapy, such as for rheumatologic conditions,[52,53] should additionally consider the cardiovascular side effects before TNF-modifying therapy can be considered for cardiovascular risk.[45]

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