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Qida He, Mengtong Sun, Yu Wang, Jiazhen Yao & Yueping Shen

Adherence to the EAT-Lancet Diet, plasma proteomics, and risk of venous thromboembolism: a large-scale prospective cohort study

Qida He [1,3#], Mengtong Sun [3#], Yu Wang [3], Jiazhen Yao [4], Yueping Shen [1,2*]

[1] Department of Oncology, The Third Affiliated Hospital of Soochow University, 185 Juqian Street, Changzhou 213003, China.

[2] Department of Epidemiology and Biostatistics, School of Public Health, Suzhou Medical College of Soochow University, Suzhou 215000, China

[3] Department of Infectious Diseases and Public Health, Tat Chee Avenue, Kowloon, City University of Hong Kong, Hong Kong SAR 999077, China

[4] School of Public Health, Southeast University, 87 Dingjiaqiao, Nanjing 210009, China.

*Corresponding author (shenyueping@suda.edu.cn)
#Equal contributors

Abstract

Background: The EAT Lancet diet is increasingly recognized for its simultaneous benefits to human and planetary health. Its key components are known to exert anti-inflammatory and antiplatelet effects; however, the potential association between adherence to the EAT-Lancet diet and incident venous thromboembolism (VTE), as well as the underlying biological mechanisms, remains unclear.

Methods: This prospective study involved 201,695 UK Biobank participants who were free of VTE at baseline, and integrated large-scale Olink plasma proteomics to identify diet-related molecular signatures. Adherence to the EAT-Lancet diet was quantified using two validated indices. Cox models were employed to evaluate associations between EAT-Lancet diet, plasma proteins, and incident VTE (including deep vein thrombosis [DVT] and pulmonary embolism [PE]). Mediation analyses quantified the role of plasma proteins.

Results: During a median follow-up of 13.77 years, participants in the highest adherence group of the Stubbendorff index showed lower risks of VTE (HR=0.809, 95% CI: 0.750-0.874), DVT (HR=0.856, 95% CI: 0.781-0.938), and PE (HR=0.754, 95% CI: 0.678-0.838). Consistent protective associations were observed with the Knuppel index. Mediation analyses identified 94 shared

plasma protein mediators, with mediation proportions ranging from -4.77% to 8.45% of the association, among which FABP4, LEP, and ENPP6 were the top-ranked mediators. The overall proteomic signature mediated 59.19% (95% CI: 27.02%-92.15%) and 40.10% (95% CI: 14.53%-65.96%) of the associations between the Stubbendorff and Knuppel index and incident VTE, respectively.

Conclusions: Higher adherence to the EAT-Lancet diet is significantly associated with a reduced risk of incident VTE, DVT, and PE, with plasma proteins potentially mediating this effect.

Keywords: EAT-Lancet Diet; Venous Thromboembolism; Deep Vein Thrombosis; Pulmonary Embolism; Plasma Proteomics

Background

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), represent the third most common cardiovascular disease globally, following myocardial infarction and stroke (1, 2). Despite significant advancements in anticoagulant therapy, VTE remains associated with high recurrence rates, mortality, and enduring complications, notably post-thrombotic syndrome in survivors (3, 4). While previous studies have well established that advanced age, surgery, immobilization, malignancy, and genetic susceptibility are major risk factors for VTE (5, 6), our understanding of modifiable lifestyle factors in primary VTE prevention, as well as the mechanisms linking environmental exposures to VTE pathogenesis, remains relatively limited.

Dietary modification is an easy yet high-impact intervention with broad health benefits. Prior research has demonstrated that the intake of ultra-processed foods is associated with an elevated risk of VTE (7), whereas adherence to a healthy plant-based diet (8), the Dietary Approaches to Stop Hypertension (DASH) diet (9) and anti-inflammatory diet index (AIDI) (10) is inversely associated with VTE risk. Unlike these dietary patterns, which prioritize human health

alone, the EAT-Lancet Commission proposed the planetary health reference diet in 2019. This framework aims to simultaneously support human well-being and ecological sustainability, addressing the substantial environmental footprint associated with modern agricultural systems (11). Characterized primarily by plant-based foods, this dietary plan emphasizes the consumption of whole grains, vegetables, fruits, nuts, and unsaturated fats, while substantially curtailing the consumption of added sugars, processed meats, and red meat (11). Unlike rigid vegetarian regimens, the EAT-Lancet diet allows for modest amounts of animal-derived products and focuses on diverse plant consumption, ensuring it remains adaptable to various cultural contexts and local food supplies.

Prior epidemiological investigations have shown that following the EAT-Lancet guidelines correlates with a reduced risk of all-cause mortality (12), cardiovascular diseases (13), and type 2 diabetes (14, 15). However, the potential link between EAT-Lancet diet adherence and the incidence of VTE and its subtypes remains largely unexplored. Given that VTE pathogenesis is rooted in oxidative stress and inflammation (16), and that key components of the EAT-Lancet diet exhibit anti-inflammatory and antiplatelet

aggregation properties (17, 18), it is reasonable to hypothesize that high compliance with these dietary recommendations could lead to a decreased risk of incident VTE. Furthermore, the biological mechanisms underlying this potential association remain poorly understood. Plasma proteins are sensitive to environmental exposures and play pivotal roles in pathophysiological processes driving VTE (6, 19). Investigating how EAT-Lancet diet adherence modulates plasma protein profiles may provide insights into potential molecular pathways linking this dietary pattern to VTE risk and may help identify candidate biomarkers for risk stratification and future investigation.

To address these knowledge gaps, this study aims to: (1) evaluate the longitudinal association between EAT-Lancet diet adherence and the risk of incident VTE and its subtypes; (2) utilize large-scale plasma proteomics data to systematically identify potential protein biomarkers related to EAT-Lancet diet and/or incident VTE; and (3) quantify mediating role of proteins in the diet-VTE association.

Methods

Study design and participants

Participants in this study were included from the UK Biobank, a

prospective cohort study designed to investigate diverse health-related results. A detailed description of the study rationale and design is available in previous literature (20). In summary, the baseline survey conducted between 2006 and 2010 involved over half a million UK residents aged 40 to 69.

In this study, we excluded participants without at least one valid 24-h dietary assessment (N=291,197), those lost to follow-up (N=568), those with implausible energy intake (≥18 MJ/day for women and ≥20 MJ/day for men; N=3,159), and those with the history of VTE at baseline (N=5,317). The final analytic sample for the primary analyses comprised 201,695 participants. For the mediation analysis evaluating the role of plasma proteins in the relationship between the EAT-Lancet diet and incident VTE, participants without available biomarker data were excluded (N = 183,703), resulting in a sample size of 17,992 (Additional file 1: Fig. S1). A schematic timeline of the study design is provided in Additional file 1: Fig. S2.

Assessment of EAT-Lancet diet index

To evaluate dietary consumption, we used the Oxford WebQ, an online, self-reported instrument designed to capture 24-hour

dietary recall data (21). Validation studies have previously confirmed the accuracy of this tool, showing that it yields nutrient and food group estimates comparable to those obtained via interviewer-led recalls (22). Data collection occurred between 2009 and 2012, during which participants completed the questionnaire on up to five separate occasions, separated by intervals of 1 to 5 months. The distribution of participants contributing 1 to 5 dietary assessments is shown in Additional file 1: Table S1. To mitigate the impact of day-to-day fluctuations in eating habits, we computed the mean intake for individuals who provided data at multiple time points (23).

To quantify alignment with the EAT-Lancet Commission's guidelines, we applied the scoring protocols from Knuppel et al. (24) and Stubbendorff et al (25). The Stubbendorff score (range: 0-42) assigns 0 to 3 points to 14 food items. Points are awarded for higher intake of seven healthy components (vegetables, fruits, whole grains, legumes, nuts, fish, and unsaturated oils) and lower consumption of seven restricted components (red/processed meats, poultry, eggs, dairy, potatoes, and sugar). The Knuppel score (range: 0-14) assesses these same categories using a binary scale, granting one point for each recommendation met. Full definitions

are available in Additional file 1: Tables S2-S4.

Measurement of OLINK proteomics

Proteomic data were derived from baseline samples (2006-2010). We employed the Olink Explore platform, which encompasses approximately 2,923 unique assays (UK Biobank category 1838) (26). Following rigorous quality control and normalization procedures conducted by Olink facilities, data were provided as Normalized Protein Expression (NPX) values for every subject. The NPX unit serves as a log2-transformed metric for relative protein abundance. Detailed documentation regarding the QC workflow is available elsewhere (26).

After excluding participants who had more than 49.9% missing values and proteins with more than 10% missing values, retaining 45,175 out of 53,014 participants and 2,916 out of 2,923 proteins. The retained proteins included 731 from the cardiometabolic panel, 728 from the inflammation panel, 728 from the neurology panel, and 730 from the oncology panel. For proteins with less than 10% missing data, the k-nearest neighbors algorithm was employed to perform missing value imputation (27). The specifics of the proteomic data could be seen in Additional file 1: Table S5.

Ascertainment of Outcome

The primary study outcome was incident VTE, which includes both DVT and PE; these subtypes were also examined as secondary outcomes. Cases were identified from UK Biobank 'First Occurrence' fields, a resource that aggregates health information from multiple channels, including death registries, primary care logs, inpatient records, and self-reported data. VTE occurrences were defined according to the ICD (10th Revision), using codes I80-I82 (for DVT) and I26 (for PE) (28). The observation period for each participant started on the date of the last diet questionnaire completion until the earliest of the following events: a VTE diagnosis, death, or the administrative censoring date of December 31, 2024. Additional file 1: Table S6 details the specific ICD codes used.

Assessment of covariates

The covariates for this study included sociodemographic factors (age, sex, ethnicity, education level, and Townsend Deprivation Index [TDI]) and lifestyle characteristics (body mass index [BMI], smoking status, alcohol consumption, physical activity, and total energy intake). Medical history covariates included diabetes,

hypertension, cancer, hyperlipidemia, and aspirin use (see details in Additional file 2: Supplementary Methods (29-32)). To maximize data utilization, missing values were imputed with multiple imputations with chained equations (see details in Additional file 2: Supplementary Methods (33, 34)).

Statistical analysis

We investigated the relationship between EAT-Lancet diet compliance and VTE occurrence by employing the multivariable Cox proportional hazards models. We constructed three hierarchical models: Model 1 (unadjusted); Model 2 (adjusted for age, sex, ethnicity); and Model 3 (fully adjusted for education, TDI, BMI, smoking and alcohol habits, physical activity, aspirin use, and pre-existing conditions including diabetes, hypertension, hyperlipidemia, and cancer). Restricted cubic splines were applied to visualize non-linear trends (35).

Multivariable linear regression models (fully adjusted) were employed to evaluate the relationships between individual plasma proteins and the EAT-Lancet index. For the prospective analysis of plasma proteins and incident VTE risk, Cox models (fully adjusted) were utilized for each protein. Following this, Elastic Net

regression analysis was implemented to select representative proteomic biomarkers from the pool of proteins significantly associated with EAT-Lancet diet. Elastic net models were fitted separately for the Stubbendorff index and the Knuppel index using the glmnet method implemented in the 'caret' package. This regularization technique, which combines Lasso and Ridge penalties, was chosen to minimize overfitting and handle collinearity (36). We utilized 10-fold cross-validation to determine the optimal tuning parameters. Specifically, the optimal combination of α (predefined grid from 0.1 to 1.0 in increments of 0.1) and λ was selected according to the minimum cross-validated root mean squared error (RMSE). The final selected values were α = 0.1 and λ = 0.2287 for the Stubbendorff index model, and α = 0.1 and λ = 0.07383 for the Knuppel index model. The combined proteomic score was computed as the weighted aggregate of the proteins identified by Elastic Net. Finally, to explore whether the proteomic signature (or specific proteins) acted as a mediator in the association between the EAT-Lancet diet and incident VTE, we performed mediation analyses based on a hypothesized causal framework (37). Specifically, individual proteins as well as proteomic signature were each evaluated separately as mediators in single-mediator models. The mediation proportion was

determined by dividing the indirect effect by the total effect. The CIs were estimated via quasi Bayesian Monte Carlo method with 1000 simulations (38). Furthermore, to explore the biological significance of the identified proteins, KEGG (Kyoto Encyclopedia of Genes and Genomes) functional enrichment analyses were performed.

To test result robustness, a set of sensitivity and subgroup analyses were performed, including excluding participants who completed only one occasion dietary recall, excluding incident VTE cases that occurred within the first two years, conducting a complete-case analysis by excluding participants with missing data, and assessing the associations between individual dietary components and VTE risk. Furthermore, we also examined effect modification by adding cross-product terms of EAT-Lancet diet indices with age, sex, socioeconomic status, and smoking status to the models, followed by corresponding stratified analyses. Given that several of the top mediating proteins are well-established adiposity-related proteins, we performed additional sensitivity analyses by further adjusting for waist circumference when evaluating the associations between the EAT-Lancet diet scores and VTE risk (39, 40). We also repeated the mediation analyses for the top candidate proteins after further

adjustment for waist circumference.

Statistical processing was performed in SAS 9.4 and R 4.5.1. For specific modeling tasks, we executed mediation analyses with the 'mediation' package and Elastic Net regression via the 'glmnet' and 'caret' package. A two-sided *P*-value of less than 0.05 indicated statistical significance for the relationships between the EAT-Lancet diet and VTE. To address multiple testing in proteomic studies, we considered a Benjamini-Hochberg FDR threshold of 0.05 as significant.

Results

Baseline characteristics

A total of 201,695 individuals were analyzed. Participants were classified into four groups using quartiles of the Stubbendorff EAT-Lancet index. The mean age of the overall population was 56.04±7.95 years, 55.09% were females, and 95.73% were White. Table 1 summarizes that participants with elevated EAT-Lancet dietary scores exhibited a lower BMI and were less likely to be current smokers or daily alcohol consumers. They had higher levels of physical activity, lower total energy intake, and a higher rate of college education. Regarding health conditions, a lower prevalence

of hypertension, hyperlipidemia, diabetes, and malignant tumors was noted in the high-adherence group compared to the lowest quartile. Consistency in these baseline characteristics was confirmed through stratification by the Knuppel EAT-Lancet index (Additional file 1: Table S7).

Associations between EAT-Lancet diet index and risk of VTE

We observed linear associations of the Stubbendorff and Knuppel indices with incident VTE, DVT, and PE (Figure 1) (*P* for nonlinearity > 0.05 for all). During a median (IQR) follow-up of 13.77 (13.36-14.58) years, we found that higher quartiles of the Stubbendorff EAT-Lancet index (Quartile 2-Quartile 4) correlated with lower risks of VTE, with respective HRs (95% CIs) of 0.868 (0.809-0.932), 0.863 (0.806-0.925) and 0.809 (0.750-0.874) compared with the lowest quartile in the model 3 (Table 2). The corresponding HRs (95% CIs) of higher adherence groups versus the lowest group of the Stubbendorff EAT-Lancet index for DVT were 0.891 (0.811-0.978), 0.873 (0.790-0.964) and 0.856 (0.781-0.938), and for PE were 0.855 (0.779-0.940), 0.824 (0.748-0.908) and 0.754 (0.678-0.838). Consistent findings were also obtained when analyzing the Knuppel EAT-Lancet diet index (Additional file 1: Table S8).

Associations of the EAT-Lancet diet index with proteins

Following FDR correction, the proteomic analysis identified significant correlations between plasma proteins and the EAT-Lancet diet indices (Additional file 1: Tables S9-S10). Specifically, the Stubbendorff index was associated with 1584 proteins (236 positive and 1348 negative), while the Knuppel index showed associations with 847 proteins (206 positive and 641 negative), with 738 proteins (148 positive and 590 negative) shared between the two indices (Figure 2; Figure 3A-B).Notable proteins displaying consistent positive associations with both dietary indices included key metabolic regulators such as adiponectin (ADIPOQ), lipoprotein lipase (LPL), and ghrelin (GHRL), as well as a distinct cluster of pancreatic digestive enzymes including pancreatic lipase (PNLIP), amylase (AMY1A/1B/1C), and chymotrypsin C (CTRC). In contrast, proteins demonstrating consistent inverse associations were largely characterized by pro-inflammatory and thrombotic markers. These included key cytokines and adipokines such as interleukin-6 (IL6), tumor necrosis factor (TNF), and leptin (LEP), alongside hemostasis and matrix-remodeling proteins such as fibrinogen alpha chain (FGA), plasminogen (PLG), and matrix metalloproteinases (MMP9). Separately, Elastic Net regression

selected 359 and 274 proteins to construct the Stubbendorff and Knuppel proteomic signature scores, respectively (Additional file 1: Tables S11-S12).

Mediation analysis of plasma proteins

In the subset of participants with available Olink proteomic data, 553 incident VTE events were documented during a median follow-up of 13.76 years (IQR, 13.34-14.59). A total of 435 plasma proteins exhibited a significant correlation with incident VTE after FDR correction (Additional file 1: Table S13). Specifically, 253 and 168 proteins were simultaneously associated with the Stubbendorff and Knuppel indices, respectively, and incident VTE (Figure 3C and Figure 3D). Among these proteins, 190 and 116 of them exhibited significant mediation effects (Additional file 1: Tables S14-S15). There were 94 shared mediators for VTE between the two EAT-Lancet indices. The mediation proportions (95% CIs) of the shared mediators ranged from -4.77% (-9.30%, -0.71%) to 8.45% (3.55%, 13.63%), among which fatty acid-binding protein 4 (FABP4), leptin (LEP), and ectonucleotide pyrophosphatase/phosphodiesterase 6 (ENPP6) were identified as the top-ranked mediators. Figure 4 shows the mediation proportions of mediators between the two indices and VTE. In addition, the overall proteomic signature

scores mediated 59.19% (95% CI: 27.02% to 92.15%) and 40.10% (95% CI: 14.53% to 65.96%) of the associations between the Stubbendorff and Knuppel indices and incident VTE, respectively (Additional file 1: Table S16). Using KEGG methods, the significant mediators were mainly enriched into such pathways as Cytokine-cytokine receptor interaction, Viral protein interaction with cytokine and cytokine receptor, and Rheumatoid arthritis, which were consistently observed across the indices (Additional file 1: Tables S17-S18).

Sensitivity and subgroup analyses

The inverse associations between the EAT-Lancet indices and the risk of incident VTE remained robust across a series of sensitivity analyses. These included excluding participants who completed the only one occasion dietary recall (Additional file 1: Table S19), excluding cases that occurred within the first 2 years of follow-up (Additional file 1: Table S20), conducting a complete-case analysis by excluding participants with missing data (Additional file 1: Table S21), and additionally adjusted for waist circumference (Additional file 1: Table S22). Analyses of individual dietary components generally supported the main findings, with specific components such as fruits and vegetables showing significant protective effects

against VTE (Additional file 1: Tables S23-S24). Furthermore, we evaluated potential effect modifiers by stratifying participants according to age, sex, Townsend deprivation index, and smoking status. No significant interactions were observed, and the protective associations remained consistent across these subgroups (Additional file 1: Tables S25-S27). In additional sensitivity analyses adjusting for waist circumference, the mediating proportions of FABP4, LEP, and ENPP6 remained statistically significant for both the Stubbendorff and Knuppel EAT-Lancet diet scores, although some estimates were slightly attenuated (Additional file 1: Table S28).

Discussion

In this prospective cohort, we demonstrated that higher adherence to the EAT-Lancet diet as quantified by two distinct indices shows an inverse correlation with the risk of VTE, DVT, and PE. Additionally, we characterized a specific profile of plasma proteins associated with dietary adherence that is enriched in inflammatory, coagulation, and metabolic pathways. Notably, the overall proteomic signature mediated 59.19% and 40.10% of the relationships between the Stubbendorff and Knuppel EAT-Lancet indices and incident VTE, respectively.

The observed protective effect of the EAT-Lancet diet on VTE aligns with and extends prior research on dietary patterns and cardiovascular health. Previous epidemiological investigations have consistently shown that higher adherence to the EAT-Lancet diet is associated with reduced risks of cardiovascular diseases (41), and type 2 diabetes (14). For instance, a longitudinal cohort investigation from ARIC study showed that individuals with the highest adherence to the EAT-Lancet reference diet had a 13% lower risk of total cardiovascular diseases (HR: 0.87; 95% CI: 0.79 - 0.96).(42). These conditions share common pathophysiological pathways with VTE, including inflammation, oxidative stress, and metabolic dysfunction (43). Our study is the first to demonstrate the protective role of the EAT-Lancet diet against VTE. Unlike exclusively health-focused patterns including the DASH and anti-inflammatory diets, the EAT-Lancet diet uniquely integrates human health with environmental sustainability (44). Moreover, its allowance of moderate animal-source foods enhances cultural adaptability and long-term adherence compared to strict vegetarian diets (30), potentially making it a more practical dietary pattern for population-level VTE prevention.

The proteomic findings provide important insights into the biological mechanisms underlying this association. We found 253 proteins were concurrently associated with the Stubbendorff index and the risk of incident VTE, while 168 shared proteins were linked to the Knuppel index and VTE incidence. The larger number of shared proteins identified for the Stubbendorff index may largely reflect differences in score construction, particularly its wider multilevel scoring range compared with the binary Knuppel index. The overall pattern was highly consistent across both indices, suggesting that the association between the EAT-Lancet diet and VTE is linked to coordinated changes in inflammatory and immune-related proteomic pathways rather than to isolated biomarkers.

Pathway enrichment analyses further supported this interpretation. The most consistently enriched pathways across both dietary indices were cytokine-cytokine receptor interaction, viral protein interaction with cytokine and cytokine receptor, and rheumatoid arthritis. Rather than indicating disease-specific mechanisms per se, these pathway annotations collectively point to a broader network of immune and inflammatory signaling. In particular, the cytokine-cytokine receptor interaction pathway highlights the potential relevance of immunothrombotic processes, through which

chronic low-grade inflammation may promote endothelial activation, platelet reactivity, coagulation factor expression, and impaired fibrinolytic balance, all of which are central to VTE development (45, 46).

The top mediating proteins also converged on this inflammatory-metabolic axis. FABP4 and LEP, which showed relatively strong mediation effects for both dietary indices, are closely linked to adiposity-related inflammation and vascular dysfunction. FABP4, an adipokine released from adipocytes and macrophages, has been implicated in endothelial dysfunction and vascular inflammatory responses (47, 48). The EAT-Lancet diet's emphasis on unsaturated plant oils and restriction of processed meats likely downregulates FABP4 expression, mitigating vascular injury. LEP, a marker of adiposity and direct pro-thrombotic factor, upregulates plasminogen activator inhibitor-1 (PAI-1) and enhances platelet aggregation (49). Furthermore, LEP and FABP4 have previously been identified as BMI-related proteins in patients with established VTE, but the corresponding BMI-related proteomic signature did not materially mediate the obesity paradox for recurrent VTE or death (50). Our findings supplement previous evidence by suggesting that these proteins may mediate the association

between EAT-Lancet diet adherence and incident VTE, and that their role may extend beyond adiposity alone to broader metabolic and inflammatory pathways. ENPP6 may represent a more exploratory signal, potentially linking nutrient-related metabolic processes, including choline metabolism, to vascular or coagulation pathways (51). We also identified overall proteomic signatures closely associated with the EAT-Lancet diet. This underscores that the EAT-Lancet diet acts through cumulative remodeling of the metabolic and inflammatory milieu, rather than a single pathway.

The findings have potential translational relevance for VTE prevention. Given the high recurrence rate and long-term complications of VTE, identifying modifiable lifestyle factors remains an important public health priority (52). From a public health perspective, our observational findings suggest that greater adherence to the EAT-Lancet diet may be associated with a lower risk of VTE. Additionally, the identified proteins may offer insight into biological pathways underlying this association and may serve as candidates for future biomarker research. However, whether plasma proteomics can meaningfully predict future VTE risk remains an evolving and controversial question. Although previous studies suggest that circulating proteins may carry predictive

information for incident VTE, the current evidence remains largely limited to biomarker discovery and association, and robust validation of predictive performance and clinical utility is still lacking (53-55). Therefore, the predictive implications of these proteomic findings should be interpreted cautiously. In the present study, the proteomic analysis was designed primarily to explore potential biological mechanisms rather than to develop or validate a clinical prediction model. Independent external validation and future researches is needed before recommending this diet as a clinical intervention or considering these proteins for clinical risk stratification.

The primary strengths of this study include its prospective design, the large sample size from the UK Biobank, and the integration of high-throughput Olink proteomics, which allowed for a comprehensive exploration of molecular pathways. The use of two different EAT-Lancet diet scores further reinforces the robustness of our findings. However, some limitations must be acknowledged. First, as an observational study, residual confounding cannot be excluded. Although we adjusted for a wide range of covariates available in the UK Biobank, some established VTE risk factors were not fully captured. In addition, participants were not

necessarily new adopters of the dietary pattern at baseline, individuals susceptible to VTE may already have experienced an event before dietary assessment, and dietary adherence may have changed during follow-up. Accordingly, the findings should be interpreted as associative rather than causal. Further independent external validation is needed before clinical or public health implementation. Second, dietary consumption and some covariates were evaluated using 24-hour recalls and self-reported questionnaires, which, despite being validated, may be subject to recall bias and measurement error; however, we mitigated this by averaging multiple assessments where available. Third, plasma proteins were measured only at baseline. Accordingly, the mediation findings should be interpreted as exploratory. Finally, participants in our study were predominantly white, healthier, and had a higher socioeconomic status than the general population in the UK (56). Therefore, these findings may not be fully generalizable to the wider population.

Conclusions

This study suggests that higher adherence to the EAT-Lancet dietary pattern is associated with a lower risk of incident VTE, DVT, and PE. Plasma proteins may partly mediate these

associations. These findings provide insight into potential biological mechanisms linking the EAT-Lancet dietary pattern to VTE risk.

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Abbreviations

Abbreviation	Full Term
VTE	Venous thromboembolism
DVT	Deep vein thrombosis
PE	Pulmonary embolism
ADIPOQ	Adiponectin
AMY1A/1B/1C	Amylase
CTRC	Chymotrypsin C
ENPP6	Ectonucleotide pyrophosphatase/phosphodiesterase 6
FABP4	Fatty acid-binding protein 4
FGA	Fibrinogen alpha chain
GHRL	Ghrelin
IL6	Interleukin-6
LEP	Leptin
LPL	Lipoprotein lipase
MMP9	Matrix metalloproteinases
NPX	Normalized Protein Expression
PAI-1	Plasminogen activator inhibitor-1
PLG	Plasminogen
PNLIP	Pancreatic lipase
TNF	Tumor necrosis factor
AIDI	Anti-inflammatory diet index
BMI	Body mass index
CI	Confidence Interval
DASH	Dietary Approaches to Stop Hypertension

FDR	False discovery rate
HR	Hazard Ratio
ICD	International Classification of Diseases
KEGG	Kyoto Encyclopedia of Genes and Genomes
TDI	Townsend Deprivation Index

Additional file 1: Table S1. Distribution of repeated 24-hour dietary assessments in the study. **Table S2.** Details of food components in the EAT-Lancet reference diet. **Table S3.** Scoring criteria for the Stubbendorff EAT-Lancet index. **Table S4.** Scoring criteria for the Knuppel EAT-Lancet index. **Table S5.** Detailed information of 2,916 proteins in the UK Biobank. **Table S6.** Definition of clinical outcomes. **Table S7.** Baseline characteristics of participants according to Knuppel EAT-Lancet index categories. **Table S8.** Associations between the Knuppel EAT-Lancet diet index and risks of VTE. **Table S9.** Multivariable-adjusted linear regression models for the associations of Stubbendorff index with proteins. **Table S10.** Multivariable-adjusted linear regression models for the associations of Knuppel index with proteins. **Table S11.** The coefficient of Elastic Net-identified proteins that significantly associated with Stubbendorff index. **Table S12.** The

coefficient of Elastic Net-identified proteins that significantly associated with Knuppel index. **Table S13.** Multivariable-adjusted regression models for the associations of 435 plasma proteins with Venous Thromboembolism. **Table S14.** Associations of Stubbendorff EAT-Lancet diet index with Venous thromboembolism mediated by proteins. **Table S15.** Associations of Knuppel EAT-Lancet diet index with Venous thromboembolism mediated by proteins. **Table S16.** Associations of EAT-Lancet diet index with Venous thromboembolism mediated by proteomic signature scores. **Table S17.** Details of significant KEGG pathways enrichment analyses for Stubbendorff EAT-Lancet diet -associated proteins. **Table S18.** Details of significant KEGG pathways enrichment analyses for Knuppel EAT-Lancet diet -associated proteins. **Table S19.** Sensitivity analysis of associations between EAT-Lancet diet index and risks of VTE excluding participants who completed the 24-hour dietary recall only once. **Table S20.** Sensitivity analysis of associations between EAT-Lancet diet index and risks of VTE excluding cases diagnosed within the first two years of follow-up. **Table S21.** Sensitivity analysis of associations between EAT-Lancet diet index and risks of VTE excluding participants with missing data. **Table S22.** Sensitivity analysis of the associations between the EAT-Lancet diet index and risks of VTE with additional

adjustment for waist circumference. **Table S23.** Associations between individual food components of Stubbendorff EAT-Lancet diet index and risks of VTE. **Table S24.** Associations between individual food components of Knuppel EAT-Lancet diet index and risks of VTE. **Table S25.** Subgroup analyses for the association between EAT-Lancet diet index and risks of VTE. **Table S26.** Subgroup analyses for the association between EAT-Lancet diet index and risks of DVT. **Table S27.** Subgroup analyses for the association between EAT-Lancet diet index and risks of PE. **Table S28.** Sensitivity analysis of mediation by top plasma proteins in the associations between EAT-Lancet diet index and venous thromboembolism after additional adjustment for waist circumference. **Table S29.** STROBE checklist for cohort studies. **Fig. S1.** Flowchart of the study design. **Fig. S2.** Schematic timeline of the study.

Additional file 2. Supplementary methods.

Declarations

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Consent for Publication

Not applicable.

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Data Availability

Access to the UK Biobank data used in this study is available through application to the UK Biobank in accordance with their established access procedure (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access).

Authors' Contributions

QDH contributed to the conception and design of the study, drafted and revised the manuscript, and was responsible for the integrity and accuracy of the data analyses. MTS conceived and designed the study, contributed to result interpretation, and drafted the manuscript. YW conceived and designed the study and contributed to result interpretation. JZY contributed to result interpretation. YPS contributed to result interpretation and had full access to all the data used in this study. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Ethics Approval and Consent to Participate

The UK Biobank received ethics approval from the UK National Health Service's National Research Ethics Service (ref. 11/NW/0382). Informed consent was obtained from all participants prior to their enrollment in the UK Biobank project.

Table 1. Baseline characteristics of participants according to Stubbendorff Eat-Lancet diet index categories.

		Categories of the Stubbendorff EAT-Lancet diet score			
	Overall (n=201,695)	Quartile 1 (<22) (n=44,965)	Quartile 2 (22-24) (n=56,064)	Quartile 3 (24-27) (n=53,684)	Quartile 4 (□27) (n=46,982)
Age (mean [SD])	56.04 ± 7.95	55.60 ± 8.06	56.13 ± 7.96	56.23 ± 7.90	56.14 ± 7.85
Sex (n, %)					
Female	111,119 (55.09)	20,924 (46.53)	29,398 (52.44)	30,843 (57.45)	29,954 (63.76)
Male	90,576 (44.91)	24,041 (53.47)	26,666 (47.56)	22,841 (42.55)	17,028 (36.24)
Ethnicity (n, %)					
White	193,083 (95.73)	43,408 (96.54)	53,971 (96.27)	51,390 (95.73)	44,314 (94.32)
Others	8,612 (4.27)	1,557 (3.46)	2,093 (3.73)	2,294 (4.27)	2,668 (5.68)
Body mass index (kg/m^2) (mean [SD])	26.91 ± 4.62	27.57 ± 4.71	27.22 ± 4.63	26.79 ± 4.57	26.05 ± 4.44
Physical activity (n, %)					
Low	36,610 (18.15)	9,756 (21.70)	10,649 (18.99)	9,288 (17.30)	6,917 (14.72)
Moderate	85,958 (42.62)	18,941 (42.12)	24,304 (43.35)	22,914 (42.68)	19,799 (42.14)
High	79,127 (39.23)	16,268 (36.18)	21,111 (37.66)	21,482 (40.02)	20,266 (43.14)
Drinking (n, %)					
Daily or almost daily	46,149 (22.88)	11,010 (24.49)	12,888 (22.99)	12,192 (22.71)	10,059 (21.41)
Three or four times a week	50,584 (25.08)	10,764 (23.94)	14,117 (25.18)	13,731 (25.58)	11,972 (25.48)
Once or twice a week	50,380 (24.98)	11,141 (24.78)	14,133 (25.21)	13,597 (25.33)	11,509 (24.50)
One to three times a month	22,177 (11.00)	5,052 (11.24)	6,092 (10.87)	5,825 (10.85)	5,208 (11.09)
Special occasions only	19,876 (9.85)	4,335 (9.64)	5,504 (9.82)	5,113 (9.52)	4,924 (10.48)
Never	12,529 (6.21)	2,663 (5.92)	3,330 (5.94)	3,226 (6.01)	3,310 (7.05)
Smoking (n, %)					
Never	114,393 (56.72)	24,218 (53.86)	31,601 (56.37)	30,976 (57.70)	27,598 (58.74)

Previous	71,522 (35.46)	15,664 (34.84)	19,963 (35.61)	19,132 (35.64)	16,763 (35.68)
Current	15,780 (7.82)	5,083 (11.30)	4,500 (8.03)	3,576 (6.66)	2,621 (5.58)
Townsend deprivation index (mean [SD])	-1.58 ± 2.87	-1.53 ± 2.91	-1.66 ± 2.83	-1.64 ± 2.84	-1.47 ± 2.91
Education (n, %)					
≥College	86,329 (42.80)	15,781 (35.10)	22,577 (40.27)	24,044 (44.79)	23,927 (50.93)
<College	115,366 (57.20)	29,184 (64.90)	33,487 (59.73)	29,640 (55.21)	23,055 (49.07)
Total energy intake (kcal/day) (mean [SD])	2,047.62 ± 568.69	2,067.61 ± 600.07	2,040.18 ± 575.08	2,034.70 ± 555.44	2,022.12 ± 544.03
History of aspirin use (n, %)	24,133 (11.97)	5,586 (12.42)	6,939 (12.38)	6,338 (11.81)	5,270 (11.22)
History of hypertension (n, %)	48,756 (24.17)	11,670 (25.95)	14,022 (25.01)	12,706 (23.67)	10,358 (22.05)
History of diabetes (n, %)	8,343 (4.14)	1,828 (4.07)	2,323 (4.14)	2,201 (4.10)	1,894 (4.03)
History of hyperlipidemia (n, %)	22,218 (11.02)	5,349 (11.90)	6,304 (11.24)	5,816 (10.83)	4,749 (10.11)
History of malignant tumor (n, %)	14,217 (7.05)	3,237 (7.20)	3,980 (7.10)	3,758 (7.00)	3,242 (6.90)

Abbreviations: SD, standard deviation.

Table 2. Associations between the Stubbendorff EAT-Lancet diet index and risks of VTE.

	Cases/Total	HR (95 % CI)		
		Model 1	Model 2	Model 3
Venous thromboembolism				
Quartile 1 (<22)	1566/44965	Reference (1.000)	Reference (1.000)	Reference (1.000)
Quartile 2 (22-24)	1665/56064	0.847 (0.791, 0.908)	0.838 (0.782, 0.898)	0.868 (0.809, 0.932)
Quartile 3 (24-27)	1554/53684	0.823 (0.767, 0.883)	0.820 (0.764, 0.880)	0.863 (0.806, 0.925)
Quartile 4 (≥27)	1199/46982	0.724 (0.671, 0.780)	0.739 (0.685, 0.797)	0.809 (0.750, 0.874)
P-trend		<0.001	<0.001	<0.001
Continuous (per 1 score increase)	5984/201695	0.973 (0.966, 0.979)	0.974 (0.968, 0.981)	0.983 (0.976, 0.989)
Deep vein thrombosis				
Quartile 1 (<22)	890/44965	Reference (1.000)	Reference (1.000)	Reference (1.000)
Quartile 2 (22-24)	936/56064	0.839 (0.766, 0.920)	0.836 (0.763, 0.917)	0.891 (0.811, 0.978)
Quartile 3 (24-27)	903/53684	0.844 (0.769, 0.925)	0.851 (0.775, 0.934)	0.873 (0.790, 0.964)
Quartile 4 (≥27)	732/46982	0.780 (0.707, 0.860)	0.809 (0.733, 0.893)	0.856 (0.781, 0.938)
P-trend		<0.001		0.005
Continuous (per 1 score increase)	3461/201695	0.978 (0.970, 0.987)	0.982 (0.973, 0.990)	0.989 (0.980, 0.997)
Pulmonary embolism				
Quartile 1 (<22)	856/44965	Reference (1.000)	Reference (1.000)	Reference (1.000)
Quartile 2 (22-24)	899/56064	0.838 (0.763, 0.920)	0.823 (0.750, 0.904)	0.855 (0.779, 0.940)
Quartile 3 (24-27)	802/53684	0.777 (0.706, 0.856)	0.767 (0.696, 0.845)	0.824 (0.748, 0.908)
Quartile 4 (≥27)	604/46982	0.667 (0.601, 0.740)	0.673 (0.606, 0.748)	0.754 (0.678, 0.838)
P-trend		<0.001	<0.001	0.003
Continuous (per 1 score increase)	3161/201695	0.966 (0.958, 0.975)	0.966 (0.958, 0.975)	0.977 (0.968, 0.986)

HR, Hazard ratio; CI, Confidence interval.

Model 1: unadjusted.

Model 2: adjusted for age, sex, and ethnicity.

Model 3: adjusted for Model 2 plus Townsend deprivation index, education level, BMI, smoking status, alcohol intake frequency, physical activity, total energy intake, history of aspirin use, diabetes, hypertension, hyperlipidemia and malignancy.

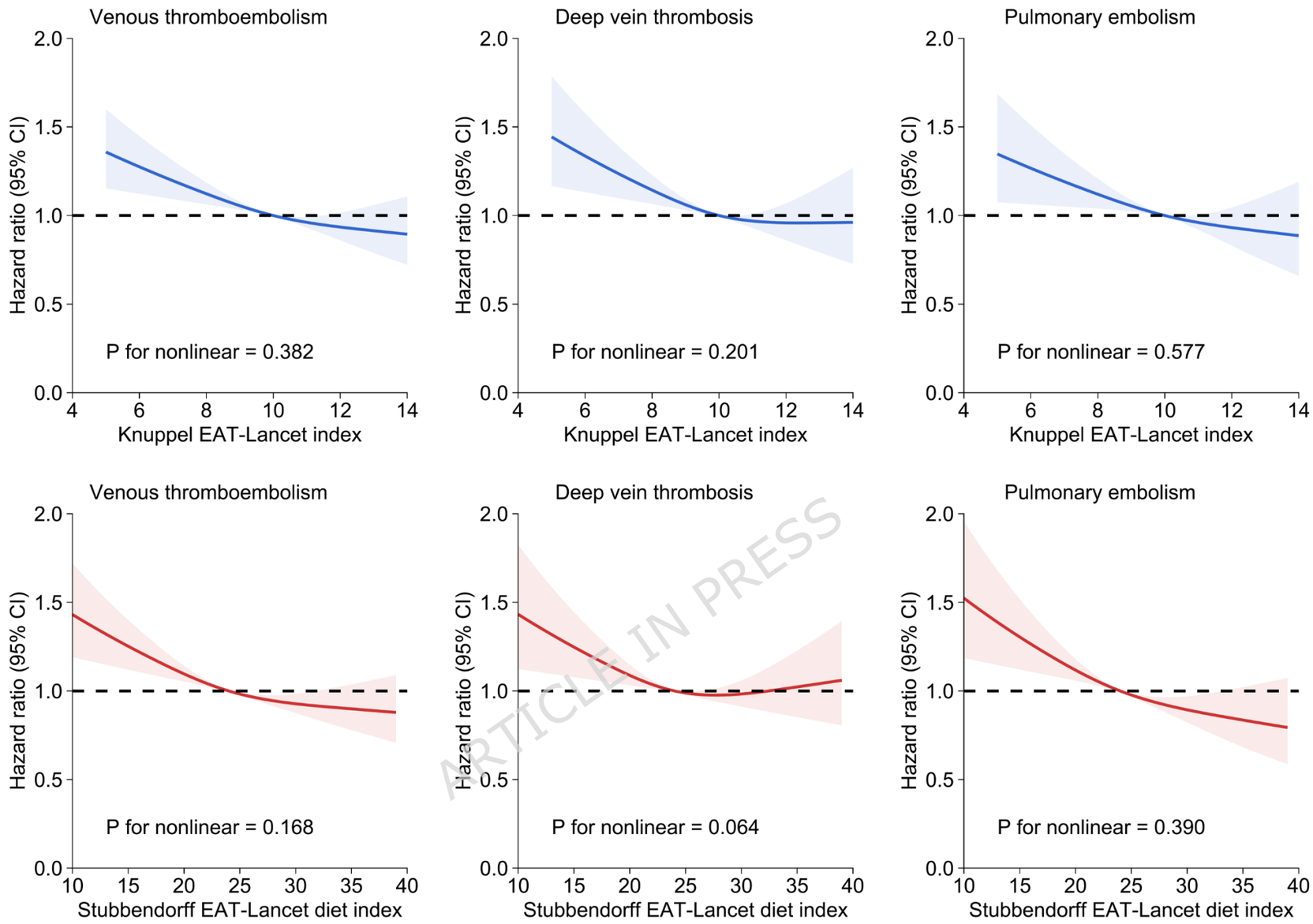

Figure 1. Dose-response relationships between EAT-Lancet diet indices and risk of venous thromboembolism and its subtypes. Restricted cubic spline (RCS) analyses illustrating the association between the Stubbendorff EAT-Lancet diet index and the Knuppel EAT-Lancet index with the hazard ratio (HR) for Venous Thromboembolism (VTE), Deep Vein Thrombosis (DVT), and Pulmonary Embolism (PE). The top row of plots displays the results for the Knuppel EAT-Lancet index, while the bottom row displays the results for the Stubbendorff EAT-Lancet diet index. The solid lines represent the estimated HR, and the shaded areas represent the 95% Confidence Interval (CI).

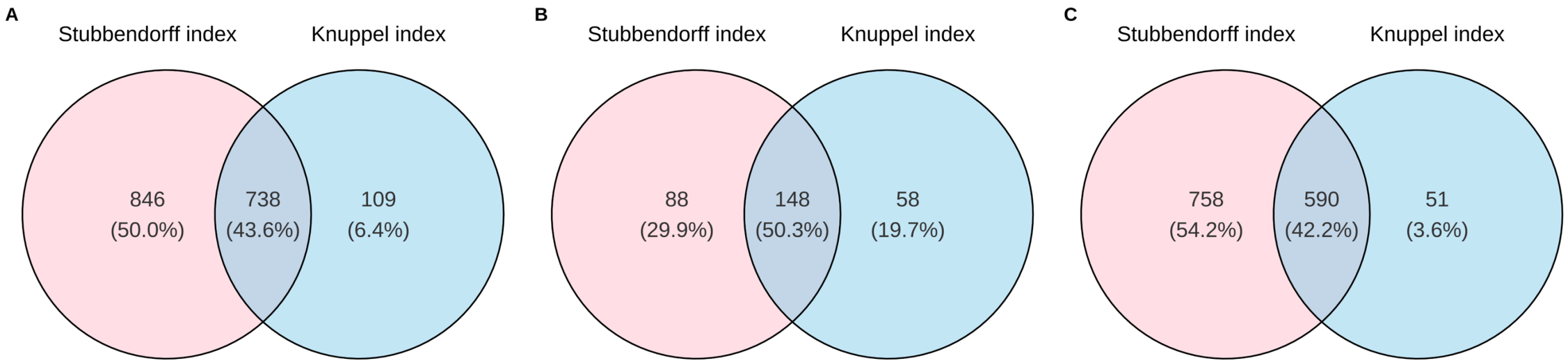

Figure 2. Venn diagrams illustrate the overlap of plasma proteins associated with the Stubbendorff and Knuppel indices. (A) all significant associations combined, (B) positive associations, and (C) negative associations.

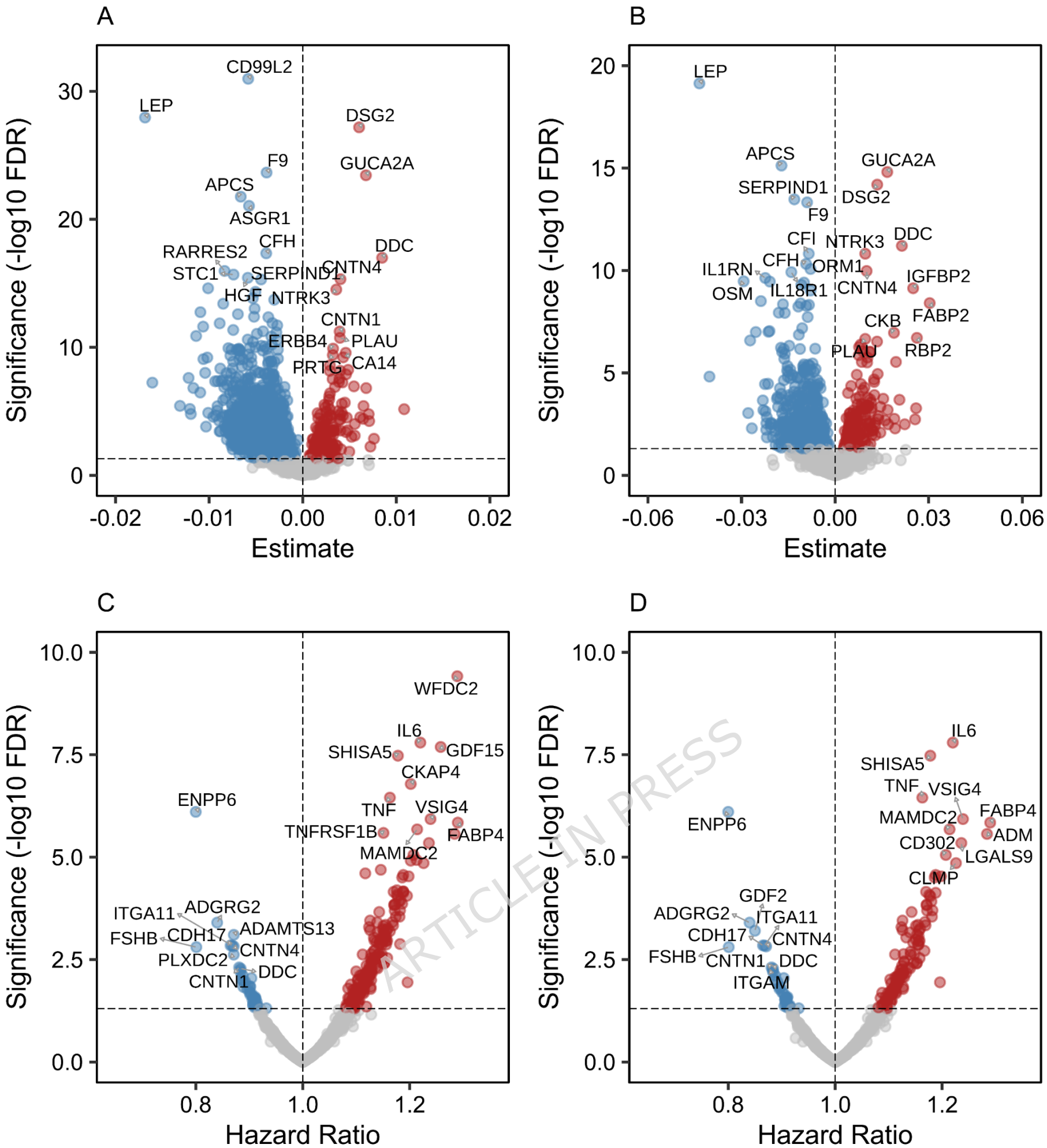

Figure 3. Volcano plots depicting the associations of plasma proteins with EAT-Lancet diet indices and incident VTE. Associations between plasma proteins and the Stubbendorff (A) or Knuppel (B) index. Hazard ratios calculated by Cox model for the risk of incident VTE associated with proteins identified in the Stubbendorff (C) and Knuppel (D) analyses. All model adjusted for age, sex, ethnicity, Townsend deprivation index, education level, BMI, smoking status, alcohol intake frequency, physical activity, total energy intake, history of aspirin use, diabetes, hypertension, hyperlipidemia and malignancy.

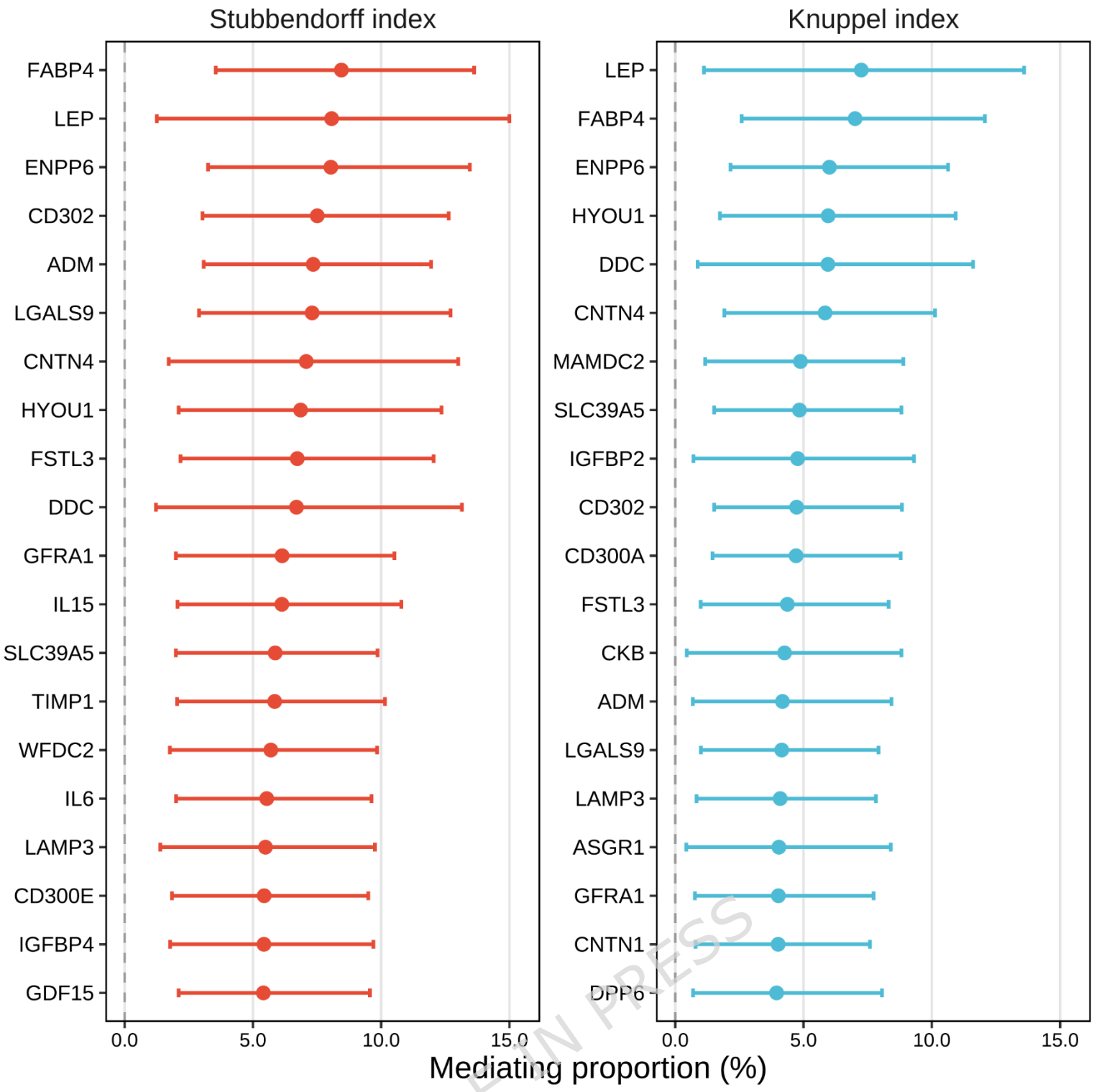

Figure 4. Mediation analysis of the top 20 significant proteins linking EAT-Lancet diet adherence to VTE risk. All model adjusted for age, sex, ethnicity, Townsend deprivation index, education level, BMI, smoking status, alcohol intake frequency, physical activity, total energy intake, history of aspirin use, diabetes, hypertension, hyperlipidemia and malignancy.