ORIGINAL RESEARCH

Dietary Pattern Specific Protein Biomarkers for Cardiovascular Disease: A Cross-Sectional Study in 2 Independent Cohorts

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Background—Mechanisms related to the influence of diet on the development of cardiovascular disease are not entirely understood, and protein biomarkers may help to understand these pathways. Studies of biomarkers identified with multiplex proteomic methods and dietary patterns are largely lacking.

Methods and Results—Dietary patterns were generated through principal component analysis in 2 population-based Swedish cohorts, the EpiHealth (EpiHealth study; n=20 817 men and women) and the SMCC (Swedish Mammography Cohort Clinical [n=4650 women]). A set of 184 protein cardiovascular disease biomarkers were measured with 2 high-throughput, multiplex immunoassays. Discovery and replication multivariable linear regression analyses were used to investigate the associations between the principal component analysis–generated dietary patterns and the cardiovascular disease–associated protein biomarkers, first in the EpiHealth (n=2240) and then in the Swedish Mammography Cohort Clinical. Four main dietary patterns were identified in the EpiHealth, and 3 patterns were identified in the Swedish Mammography Cohort Clinical. The *healthy* and the *Western/traditional* patterns were found in both cohorts. In the EpiHealth, 57 protein biomarkers were associated with 3 of the dietary patterns, and 41 of these associations were replicated in the Swedish Mammography Cohort Clinical, with effect estimates ranging from 0.057 to 0.083 (*P*-value range, 5.0×10^{-2}–1.4×10^{-9}) for each SD increase in the relative protein concentration. Independent associations were established between dietary patterns and the 21 protein biomarkers. Two proteins, myeloperoxidase and resistin, were associated with both the *healthy* and the *light meal* pattern but in opposite directions.

Conclusions—We have discovered and replicated independent associations between dietary patterns and 21 biomarkers linked to cardiovascular disease, which have a role in the pathways related to inflammation, endothelial and immune function, cell adhesion, and metabolism. **(*J Am Heart Assoc*. 2019;8:e011860. DOI: 10.1161/JAHA.118.011860.)**

Key Words: cardiovascular disease • dietary patterns • EpiHealth study • inflammation • proteomics • Swedish Mammography Cohort Clinical

The role of diet in the prevention of cardiovascular disease (CVD) is indisputable, and unhealthy dietary components, including low consumption of vegetables and whole grains, are important risk factors for the total global burden of disease.[1] Healthy dietary patterns emphasized in CVD prevention, including the recommendations of the American Heart Association,[2] are also characterized by a high consumption of fruits, nuts, cereals, fish, low-fat fermented dairy products, and vegetable oils, as opposed to a low consumption of unhealthy foods, such as meats and foods high in saturated fat and sugars.[3,4] A recent study reported that suboptimal intakes of dietary components were responsible for 45% of the estimated total cardiometabolic deaths in the United States in 2012,[5] although disease pathway mechanisms are not thoroughly understood. Hence, we need to identify new biomarkers to improve the understanding of the mechanisms underlying the

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Accompanying Tables S1 through S5 and Figures S1, S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011860

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Clinical Perspective

What Is New?

- We studied cross-sectional associations between principal component derived dietary patterns and cardiovascular-specific protein biomarkers in 2 independent cohorts.
- We were able to discover and replicate independent associations between healthy and Western-type dietary patterns and 21 protein biomarkers.
- The identified proteins have different roles in pathways related to inflammation, endothelial and immune function, cell adhesion, and metabolism.

What Are the Clinical Implications?

- Early detection at the nonsymptomatic stages of cardiovascular disease is the key to providing a better outcome for the preventive interventions.
- The identification of the proteins associated with dietary patterns in the present study may help to understand the mechanisms related to diet and development of cardiovascular disease.

association between dietary intake and CVD development. Novel proteomic technologies have made it possible to measure a large number of protein biomarkers simultaneously. In nutritional research, this may translate into identifying pathways that could be modified by diet and relevant for the study of diet-disease relationships.[6] Nutritional epidemiological studies that use protein biomarkers are largely lacking. Early detection at the nonsymptomatic stages of CVD is the key to providing a better outcome for the preventive interventions. Detailed understanding through using modern omics techniques may be important for formulation and adherence to dietary guidelines.[7,8]

There are several suggested mechanisms through which a healthy diet may reduce the risk of CVD (eg, through pathways of oxidative stress, inflammation, and immune dysfunction).[9–11] Furthermore, a recent study reported that the benefit of a Mediterranean diet on CVD risk reduction could mainly be explained through inflammatory biomarkers.[12]

We aimed to investigate whether dietary patterns would associate with circulating levels of CVD protein biomarkers, measured through 2 proteomic panels (hereinafter referred to as CVD2 and CVD3) in the EpiHealth (EpiHealth study) and the SMCC (Swedish Mammography Cohort Clinical). Thereby, we aim to identify novel associations with protein biomarkers linked to the development of CVD.

Methods

This study is based on cross-sectional data from the EpiHealth and the SMCC. Our data contain information classified as sensitive according to the European Union's General Data Protection Regulation and are, therefore, not accessible through an open repository. Data are available to any researcher after ethical approval and approval from the steering committees of the Swedish Infrastructure for Medical Population-Based Life-Course and Environmental Research (http://simpler4health.se/) and EpiHealth (https://www.epihealth.se/)

EpiHealth: Discovery Cohort

The objectives of the EpiHealth have previously been described.[13] The assessment of diet, background, and lifestyle characteristics, including history of diabetes mellitus, myocardial infarction, and stroke, was done via web-based questionnaires that were completed 1 to 3 months before the clinical examination. The collection and analysis of data have been approved by the regional ethical review board at Uppsala University (Uppsala, Sweden). All participants gave their written consent to participate.

Study sample

The study sample was drawn on June 16, 2016, from the core database. A total of 20 817 individuals had complete dietary information and were included in the analysis to generate the dietary patterns. The proteome analyses were conducted in a random subsample (n=2500) from the Uppsala part of the EpiHealth. Valid proteomic data were obtained from 2360 and 2467 individuals using the Olink Multiplex CVD2 and CVD3 assay panels, respectively. When the 2 proteomic data files were combined with the questionnaire data, the sample comprised 2281 individuals with complete data on diet and protein biomarkers. After exclusion of individuals with missing data on covariates, the final analysis data set consisted of 2240 individuals (1124 men and 1116 women).

Dietary assessment and food groupings

Diet was assessed in a food frequency questionnaire called MiniMealQ, including 75 to 126 common Swedish foods, dishes, and beverages, covering diet during the past few months.[14] The dietary items were reported using 8 or 5 predefined frequency levels, depending on the food. The 8-level frequency scale ranged from 1 to 2 times per week to ≥5 times per day for intake of bread and dairy products. The 5-level frequency scale ranged from 1 to 3 times per month to >7 times per week and collected information on intake of fruits, vegetables, bakery products, and different dishes. Information about alcohol consumption was collected using a 6-level ordinal scale, ranging from never to ≥4 times per week. All frequencies were transformed into consumption frequencies per day. Altogether, 35 food groups, based on

similarities in nutrients and culinary use, were formed from the frequencies per day.

Covariate information

Level of education was collected with 6 different categories that were transformed into a 4-level variable (≤9 years, 10–12 years, >12 years, and other). Information on smoking habits was collected using several questions that were combined under a categorical variable coded as present, former, and never smoker. Information on physical activity at leisure time during the past few months was collected using a 5-grade scale (ranging from low to high/strenuous). At the clinical examination, body fat percentage was measured using bioimpedance (Tanita, Tokyo, Japan). Height and weight were measured, and the body mass index (BMI; kg/m^2) was derived. On the basis of the BMI, participants were categorized into normal weight (≤24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30.0 kg/m^2). Blood pressure was recorded twice in the sitting position by an automatic device (Omron, Kyoto, Japan).

The SMCC: Replication Cohort

Study sample

SMCC is a clinical subcohort of the SMC and is part of the national research infrastructure of the Swedish Infrastructure for Medical Population-Based Life-Course and Environmental Research. Between November 2003 and October 2009, a random sample of individuals living in the city of Uppsala were invited to undergo dual-energy X-ray absorptiometry (Lunar Prodigy; Lunar Corp, Madison, WI) measurements between 1 and 3 months after the questionnaire was completed. Participants also provided blood and urine samples, and height and weight measurements were taken. Blood pressure was also measured in a subsample (n=2235). The participants arrived in 5 phases, and information on diet and lifestyle factors was collected in 3 similar questionnaires. The participation rate was 65%, and the subcohort consisted of 5022 women. The present study sample contains 4560 individuals after the following exclusions: 16 individuals lacked questionnaire information; 39 individuals had energy intakes that were deemed as implausible (±3 SDs from the mean value of the ln-transformed energy intake); and 134 individuals had missing information on ≥10 food groups.[15] Protein analyses were performed in 5012 SMCC participants, and valid proteomic data were obtained from 4882 and 5004 individuals from the CVD2 and CVD3 assay panels, respectively. When the 2 proteomic data sets were merged with the dietary data, the combined study sample size was 4561 individuals. One individual was excluded because of being the only one having "other" as the educational level. The study was approved by the regional ethical review boards at Uppsala University and Karolinska Institutet (Stockholm, Sweden).

Dietary assessment and food groupings

Diet was assessed using food frequency questionnaires, which included ≈100 food items. Participants indicated how often, on average, they had consumed each food item during the past year and chose from 8 predefined frequency categories, ranging from "never/seldom" to "≥3 times per day." Frequently consumed foods, such as dairy products and bread, were additionally reported as number of servings per day. Energy and nutrient intakes were estimated by multiplying the consumption frequency of each food item with the energy content of age-specific portion sizes. Energy and nutrient values were obtained from the Swedish food composition database at the National Food Agency. Nutrient intakes were adjusted for total energy intake using the residual method.[16] The consumption frequency per day of the different food items was collapsed into 33 food groups, based on the similarities in nutrients and culinary use and to match the food grouping in EpiHealth. The 3 food frequency questionnaires were similar but contained slightly different numbers of food items, but they were harmonized into the same number of food groups.

Covariate information

Covariate information obtained from the questionnaires included educational level (≤9, 10–12, or >12 years), cohabiting status, use of postmenopausal estrogen therapy, smoking habits, body weight and height, and leisure time physical activity during the past year, with 5 predefined levels, ranging from 1 h/wk to >5 h/wk. BMI (kg/m^2) was categorized as in the EpiHealth. *International Classification of Diseases, Eighth Revision*, *Ninth Revision*, and *Tenth Revision* (*ICD-8*, *ICD-9*, and *ICD-10*, respectively), diagnosis codes were obtained from the Swedish National Patient Registry, were used to calculate the Charlson Comorbidity Index,[17] and were used to derive history of diabetes mellitus, acute myocardial infarction, and stroke. The fat mass was approximated as total body fat percentage from the dual-energy X-ray absorptiometry measurements. The clinical biomarkers included as covariates were alanine aminotransferase, which is an approximate liver function test; cystatin C, as a proxy for kidney function; CRP (C-reactive protein), as a marker for inflammation; and total vitamin D (25-OH vitamin D).

Proteomic profiling in both cohorts

Blood samples were drawn at the clinical examination, from the antecubital vein in a supine position, after a minimum of 6 hours of fasting in the EpiHealth and after overnight fasting in the SMCC; thereafter, the blood samples were cool centrifuged and subsequently frozen at −80°C until

analysis. Analysis of 184 protein biomarkers was done using 2 high-throughput, multiplex, immunoassays: the Olink Proseek Multiplex CVD 2 and 3 (Olink Bioscience, Uppsala, Sweden). All protein names and abbreviations are found in Table S1. Each panel enables simultaneous analysis of 92 protein biomarkers across 90 samples and 6 controls. The analyses were performed at SciLifeLab, Uppsala University. Each assay uses a proximity extension assay (PEA) technology, in which 92 oligonucleotide-labeled antibody probe pairs are allowed to bind to their respective target present in the sample. PEA uses pairs of antibodies equipped with DNA reporter molecules, producing DNA amplicons, which are subsequently quantified using a Fluidigm BioMark HD real-time polymerase chain reaction platform. The method has acceptable reproducibility and repeatability, with mean intra-assay and interassay coefficients of variation of ≈8% and 12%, respectively.[18] Because only correctly matched antibody pairs produce a signal, the PEA technique has an accuracy advantage over conventional multiplex immunoassays. The polymerase chain reaction platform provides normalized protein expression values on a log2 scale. Protein values below the limit of detection were imputed as limit of detection/2. Protein values were standardized to a distribution, with a mean of 0 and an SD of 1. According to the manufacturer's recommendation, biomarkers with >15% and 25% of the samples below limit of detection in the EpiHealth and SMCC, respectively (Table S2), were excluded.

Statistical analysis

Dietary pattern development

Dietary patterns were computed through principal component analysis (PCA) using the consumption frequency per day of 35 and 33 food groups of the entire EpiHealth sample (n=20 817) and SMCC (n=4650), respectively. The number of food groups that overlapped between the 2 cohorts was 31. We tested the suitability of the data for PCA with the Kaiser-Meyer-Olkin measure of sampling adequacy and the Bartlett's test of sphericity. The Kaiser-Meyer-Olkin value was 0.75 in the EpiHealth and 0.71 in the SMCC, and Bartlett's test of sphericity was statistically significant ($P<0.001$) in both cohorts, thus indicating suitability. The PCA components were retained on the basis of the Scree plot (Figure S1), eigenvalues (>1.5), and interpretability of the components. The retained components were varimax rotated to become orthogonal (uncorrelated factors). The dietary patterns were interpreted and named on the basis of the component's loadings, and each participant was assigned a score for each dietary pattern. The dietary scores were standardized (mean=0, and SD=1) to be comparable and used in multivariable linear regression analysis with every protein biomarker as the dependent variable (mean=0, and SD=1).

Discovery and replication of dietary pattern–protein biomarker associations

In EpiHealth, the discovery analysis was performed to test the association between the dietary patterns and the protein biomarkers using multivariable linear regression analysis. The analyses were adjusted for age (continuous), leisure time physical activity (categorical), educational attainment (categorical), smoking status (never, former, or current), and sex. This minimally adjusted model allows for associations between diet and protein biomarkers, mediated through body fatness, to be retained for further testing in the replication cohort. To account for multiple testing, a corrected *P* value was estimated using the 5% false discovery rate, according to Benjamini and Hochberg using the multproc command in Stata.[19] This was done for each dietary pattern separately. Because of the strong correlation between many of the assessed protein biomarkers, we chose this procedure rather than the more conservative Bonferroni method, which assumes independent tests. All the dietary pattern–protein associations discovered in EpiHealth were replicated in the SMCC using a nominal *P* value of 0.05. Applying a nominal *P* value in the replication phase has been shown to be conservative enough, and the risk of false-positive findings in the replication stage (validation false discovery rate) was calculated to be low, ≤0.1% for each dietary pattern.[20] A dietary pattern–protein association discovered in EpiHealth was considered to be replicated in the SMCC if the association was directionally similar, with the same type of dietary pattern, or directionally opposing, with an opposite dietary pattern (healthy or unhealthy). The replication model (model 1) included the same variables as in the EpiHealth data, except for sex, and protein chip number (categorical) to account for any storage or analytical drifts between the chips and the questionnaire (3-level categorical variable) to account for the different questionnaires. The additional multivariable models applied in the SMCC data included the following covariates: model 2=model 1+total energy intake; model 3=model 2+ln(phosphorylated alanine aminotransferase) and ln(plasma-cystatin C); model 4=model 3+Charlson weighted comorbidity index; model 5=model 4+% fat mass; and model 6=model 5+ln(plasma CRP) and total serum 25-hydroxyvitamin D (D_2 and D_3). All variables were modeled as continuous variables. Missing data for the covariates in the SMCC were imputed using the "mi" command in Stata, using a chained multiple imputation, creating 20 separate data sets. The linear regression analysis was then run on all separate data sets, but the final results are the combined estimates from each analysis. Leisure time physical activity was missing in 13% and smoking status was

missing in 5% of the total participants; other covariates were missing in <3% of the participants. To produce robust estimates and minimize bias in the multiple imputation, BMI (continuous), cohabiting status (binary), and estrogen use (binary) were included in addition to the model variables, including both exposure (dietary patterns) and outcome (relative protein concentrations). In sensitivity analysis, we stratified the minimally adjusted discovery analyses on BMI category and sex in EpiHealth; in the SMCC, model 1 was stratified on BMI category. All analyses were performed using Stata, version 15.0 (Stata Corp, College Station, TX).

Results

Dietary Patterns

In the EpiHealth study, 4 dietary patterns, explaining 27% of the variance of the dietary data, were identified (Table 1). The *healthy pattern* was characterized by high loadings of typically healthy food items, such as vegetables and fruits, fish, and nuts/seeds. The *dairy and sandwich pattern* was characterized by high loadings from hot and cold cereals, fiber-rich breads, meats, nuts and seeds, cheese, egg, milk, and fermented milk. The *Western/traditional pattern* loaded high on unhealthy food items, such as fast foods, white bread, sweets, sodas, and cordials. The *fast food and alcohol pattern* was characterized by fried potatoes, fast food, coffee, eggs, poultry, savory snacks, high-fat dairy products, and alcoholic beverages. In the SMCC, 3 dietary patterns were identified (Table 1), explaining 21% of the variance of the dietary data. The *Western/traditional pattern* and the *healthy pattern* in the SMCC had several similar characteristics as in the EpiHealth. The *light meal pattern* loaded high in cereals, crisp breads, milk and fermented milk, coffee, pancakes and waffles, sugar, honey, and marmalades as well as sweet bakery products, and also was considered an unhealthy pattern. There were overlaps between the *Western/traditional pattern* in EpiHealth with both the *Western/traditional pattern* and the *light meal pattern* in the SMCC.

Background Characteristics

In Table 2, background characteristics of participants in both the EpiHealth and the SMCC are presented, stratified according to the tertiles of their respective *healthy pattern*. Clinical and dietary characteristics did not differ much between the tertiles of the healthy dietary patterns. The number of participants with a history of diabetes mellitus, myocardial infarction, or stroke was low, and the lowest numbers were found in the highest tertiles of the healthy dietary pattern. Healthy food items, such as vegetables and fruits as well as fish, were more frequently consumed; and participants tended to be leaner, to have a higher physical activity level, and to have a higher educational level, and they were less often current smokers in the highest tertiles of the healthy dietary patterns. Energy intake levels were the greatest in the highest tertiles of the healthy patterns. The participants were younger in EpiHealth (mean age, 61 years; and SD, 8.4 years) than in the SMCC (mean age, 67 years; and SD, 6.7 years). More women than men were classified in the highest tertiles of the *healthy pattern* in the EpiHealth.

Discovery and Replication of Dietary Pattern–Protein Biomarker Associations

In the discovery phase of the study, 57 different proteins (Table S3) were associated with any of the dietary patterns in EpiHealth, using the false discovery rate correction for multiple tests. The *healthy pattern* was associated with 5 proteins, the *dairy and sandwich pattern* did not associate with any proteins, and the *Western/traditional* and the *fast food and alcohol patterns* associated with 44 and 10 proteins, respectively. Two of the proteins were associated with two dietary patterns: SLAM family member 5 (CD84) and insulin-like growth factor–binding protein 1. In total, 41 dietary pattern–proteins associations were replicated in the SMCC, with β estimates in the range from −0.057 to 0.083 (P between 5.0×10^{-2} and 1.4×10^{-9}; Table S4 and Figure 1). All five *healthy pattern*–protein associations discovered in EpiHealth were replicated in the SMCC (spondin-2, follistatin, SLAM family member 5, matrix metalloproteinase-7, and paraoxonase 3). Of the 44 *Western/traditional* pattern–protein associations discovered in EpiHealth, 36 were replicated in the SMCC. Only 4 of the *fast food and alcohol pattern*–protein associations discovered in the EpiHealth cohort were replicated in the SMCC (brother of CDO, V-set and immunoglobulin domain–containing protein 2, contactin-1, and insulin-like growth factor–binding protein 1).

In the multivariable linear regression analysis after the initial replication (model 1), 21 dietary pattern–protein associations remained in the SMCC, even after all the potential confounder adjustments (models 2–6), as shown in Table 3. Of the replicated associations, 5 were observed with the *Western/traditional pattern*, 7 with the *healthy pattern,* and 11 with the *light meal pattern*. Two proteins associated with the dietary patterns, myeloperoxidase and resistin, were replicated in association with the *healthy* and the *light meal* pattern in opposite directions. The sensitivity analyses confirmed that the associations between the dietary patterns and the 21 replicated proteins were

Table 1. Component Loadings for the Dietary Patterns Generated Through PCA in the EpiHealth and the SMCC

	EpiHealth				SMCC		
	Healthy	Dairy and Sandwich	Western/ Traditional	Fast Food/Alcohol	Western/ Traditional	Healthy	Light Meal
Vegetables, legumes	0.4555*	0.0163	−0.0450	0.0169	0.1125	0.4090*	−0.0720
Fruits, berries	0.2425*	0.1211	0.1387	−0.1533	−0.0023	0.4420*	0.0589
Nuts, seeds	0.2476*	0.2063*	−0.1013	−0.0699	−0.0627	0.3805*	−0.0872
Boiled potatoes	−0.0967	0.0938	0.2758*	−0.0209	0.1166	0.0498	0.3201*
Fried potatoes, French fries	0.0047	−0.0819	0.2464*	0.2309*	0.3192*	−0.1036	0.0688
Cereals	0.0368	0.4078*	0.0154	−0.0549	−0.0757	0.3576*	0.2335*
Rice, pasta	0.2602*	−0.1453	0.1879*	0.0567	0.1542*	0.0830	−0.1161
Crisp bread	−0.0329	0.3456*	0.0541	−0.0079	−0.0119	0.1218	0.2633*
Whole meal bread	−0.0194	0.3458*	0.0654	0.0055	−0.0810	0.2119*	0.1046
White bread	−0.1247	0.0330	0.2109*	0.1004	0.1657*	−0.2034	0.0636
Meat	−0.0502	0.2304*	0.0778	0.3456*	0.3560*	0.0000	0.0064
Offals, black pudding	−0.0753	0.0999	0.2021*	−0.0377	0.2270*	−0.0026	0.0605
Poultry	0.2478*	−0.0428	−0.0436	0.2868*	0.1299	0.1811*	−0.1880
Fatty fish	0.3033*	0.0460	−0.0310	0.0331	0.1526*	0.1987*	−0.0648
Lean fish, shellfish	0.2481*	0.0473	0.0707	0.0343	0.3229*	0.1110	−0.0817
Eggs	0.0892	0.2732*	−0.1636	0.2145*	0.1886*	0.0933	−0.0622
Milk	−0.1100	0.1633*	0.1599*	−0.0476	−0.0051	0.0305	0.3488*
Fermented milk	0.0447	0.3923*	−0.0492	0.0163	−0.0704	0.1849*	0.1796*
Cheese	−0.0204	0.3421*	0.0387	0.1007	−0.0161	0.1493	0.1240
High-fat dairy products	0.1426	−0.0324	0.0491	0.3013*	0.2832*	0.0729	−0.0008
Dressings, mayonnaise	−0.1171	−0.005	0.0553	−0.0775	0.1718*	0.1563*	−0.1921
Soda and cordials	−0.0845	0.0047	0.1985*	0.0552	0.1322	−0.1551	0.0871
Wine, spirits	0.1009	−0.045	−0.1301	0.2309*	0.1276	0.0377	−0.3583
Light beer					0.0993	0.0193	0.0753
Coffee	−0.0199	0.0485	−0.0803	0.3360*	0.0077	0.0120	0.2651*
Tea	0.1199	0.0195	0.1178	−0.3107	0.0167	0.1181	−0.1524
Pancakes, waffles	−0.0490	0.0285	0.3679*	−0.0622	0.1852*	−0.0882	0.2448*
Pizza, ketchup	0.0637	−0.1249	0.2839*	0.2726*	0.3241*	−0.0878	0.0418
Sugar, honey, jam, and marmalade	…	…	…	…	0.1079	−0.0300	0.1978*
Ice cream	0.0859	−0.0198	0.2177*	0.0463	0.1748*	0.0178	0.0317
Sweet bakery products	−0.0250	0.0588	0.3823*	−0.0970	0.1864*	0.0021	0.3154*
Candy, chocolate	0.1457	−0.0652	0.2466*	0.0474	0.1938*	0.0222	−0.0037
Chips, popcorn	0.0703	−0.1397	0.1458	0.2254*	0.1823*	−0.0763	−0.1669
Vegetarian dishes	0.2627*	−0.0614	0.0545	−0.3133	…	…	…
Salads	0.3270*	0.0092	−0.0758	−0.0424	…	…	…
Sandwiches	0.0732	−0.0473	0.1720*	0.0244	…	…	…
Soups	0.2080*	0.0463	0.1467	−0.1767	…	…	…
Proportion of variance, %	8	7	7	5	8	7	6
Eigenvalues	2.6	2.6	2.4	1.8	3.0	2.1	1.7

Cereals include oatmeal porridge, other porridges and gruels, breakfast cereals, and husks. Wine and spirits were only captured by one question in the EpiHealth on frequency of consumption. In the EpiHealth, dressings and mayonnaise were only represented by vinaigrette dressing, and pizza and ketchup also included ready-to-eat hamburgers. EpiHealth indicates EpiHealth study; PCA, principal component analysis; SMCC, Swedish Mammography Cohort Clinical.
*Loadings >0.15 were considered important for the respective dietary pattern.

Table 2. Background Characteristics of Study Participants With Valid Diet and Proteomics Data, Stratified by Tertiles of the *Healthy Pattern* in EpiHealth and SMCC

	EpiHealth						SMCC		
	Men			Women			Women		
Tertiles of the *Healthy Pattern*	Low	Middle	High	Low	Middle	High	Low	Middle	High
No. of individuals	484	387	277	277	373	483	1510	1520	1530
Age, y	63 (8)	60 (9)	60 (9)	63 (8)	61 (9)	61 (8)	68 (6.8)	67 (6.7)	67 (6.4)
HDL cholesterol, mmol/L	1.3 (0.3)	1.3 (0.3)	1.4 (0.3)	1.6 (0.4)	1.7 (0.4)	1.7 (0.4)	1.6 (0.4)	1.6 (0.4)	1.6 (0.4)
LDL cholesterol, mmol/L	3.8 (1.0)	3.9 (1.0)	3.9 (0.9)	4.0 (0.9)	4.0 (1.0)	4.0 (1.0)	3.6 (0.9)	3.5 (0.9)	3.5 (0.9)
BMI, kg/m^2	27 (3)	27 (3)	26 (3)	27 (4)	26 (4)	26 (4)	26 (4)	26 (4)	25 (4)
Body fat percentage, %	26 (5)	25 (5)	24 (5)	37 (7)	36 (6)	35 (6)	39 (7)	38 (7)	36 (7)
Total vitamin D, nmol/L	…	…	…	…	…	…	57 (18)	59 (17)	60 (19)
Cystatin C, mg/L	…	…	…	…	…	…	0.98 (0.33)	0.93 (0.22)	0.88 (0.19)
ALAT, μkat/L	…	…	…	…	…	…	0.24 (0.28)	0.23 (0.13)	0.23 (0.13)
Systolic blood pressure, mm Hg	139 (17)	136 (16)	137 (19)	136 (18)	134 (18)	131 (19)	134 (19)	133 (19)	133 (19)
Diastolic blood pressure, mm Hg	85 (10)	85 (9)	85 (10)	83 (9)	83 (9)	81 (9)	77 (9)	78 (9)	78 (9)
History of diabetes mellitus, %*	5.8	7.0	2.5	1.5	1.9	2.5	2.9	2.0	1.7
History of MI, %*	3.3	4.2	2.9	0.7	1.0	0.2	2.4	2.1	1.1
History of stroke, %*	2.5	1.3	1.8	0.4	0.5	0.2	3.6	2.7	2.1
High leisure time physical activity level, %†	31	35	44	29	26	31	23	27	31
≥12 y of schooling, %	28	45	58	30	42	57	25	40	49
Current smokers, %	9	7	4	17	6	5	15	8	5
Vegetables and fruit‡	1.8 (0.8)	2.8 (0.9)	4.0 (1.3)	2.3 (1.0)	3.1 (1.0)	4.4 (1.2)	4.0 (1.6)	6.3 (1.8)	9.5 (3.7)
Fish‡	0.2 (0.1)	0.3 (0.1)	0.4 (0.2)	0.2 (0.1)	0.3 (0.1)	0.4 (0.2)	0.5 (0.3)	0.7 (0.4)	0.9 (0.5)
Meat‡	1.2 (0.9)	1.2 (0.8)	1.2 (0.8)	1.0 (0.8)	1.1 (0.8)	1.0 (0.8)	0.9 (0.6)	1.0 (0.6)	1.1 (0.7)
White bread‡	0.5 (0.7)	0.4 (0.6)	0.3 (0.4)	0.4 (0.7)	0.3 (0.5)	0.2 (0.3)	0.9 (1.25)	0.5 (0.83)	0.4 (0.7)
Soda‡	0.6 (0.9)	0.3 (0.5)	0.3 (0.6)	0.3 (0.6)	0.2 (0.5)	0.1 (0.3)	0.3 (0.8)	0.2 (0.5)	0.1 (0.3)
Chips, popcorn, and cheese doodles‡	0.04 (0.06)	0.04 (0.06)	0.05 (0.1)	0.02 (0.04)	0.03 (0.06)	0.04 (0.08)	0.03 (0.08)	0.02 (0.05)	0.03 (0.06)
Alcoholic beverages‡	0.2 (0.2)	0.2 (0.2)	0.3 (0.2)	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)	0.2 (0.3)	0.3 (0.3)	0.3 (0.4)
Energy intake, kcal/d	1814 (616)	1955 (548)	2281 (725)	1356 (509)	1579 (519)	1824 (587)	1487 (380)	1733 (380)	2171 (479)
Fiber, g/d	20 (5)	21 (5)	23 (6)	17 (5)	19 (5)	21 (5)	19 (6)	25 (6)	35 (10)
PUFA, g/d	11 (3)	12 (3)	13 (3)	10 (2)	11 (3)	12 (3)	7 (2)	9 (2)	11 (4)

Data are given as mean (SD). ALAT indicates alanine aminotransferase; BMI, body mass index; EpiHealth, EpiHealth study; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; PUFA, polyunsaturated fatty acid; SMCC, Swedish Mammography Cohort Clinical.

*Self-reported data in the EpiHealth and in the SMCC were extracted from the patient register and *International Classification of Diseases, Tenth Revision* (*ICD 10*), codes E10 to E14 (diabetes mellitus), I21 and I22 (MI), and I60 to I67 (stroke).

†High physical activity, participants with activity levels 4 and 5.

‡Servings per day.

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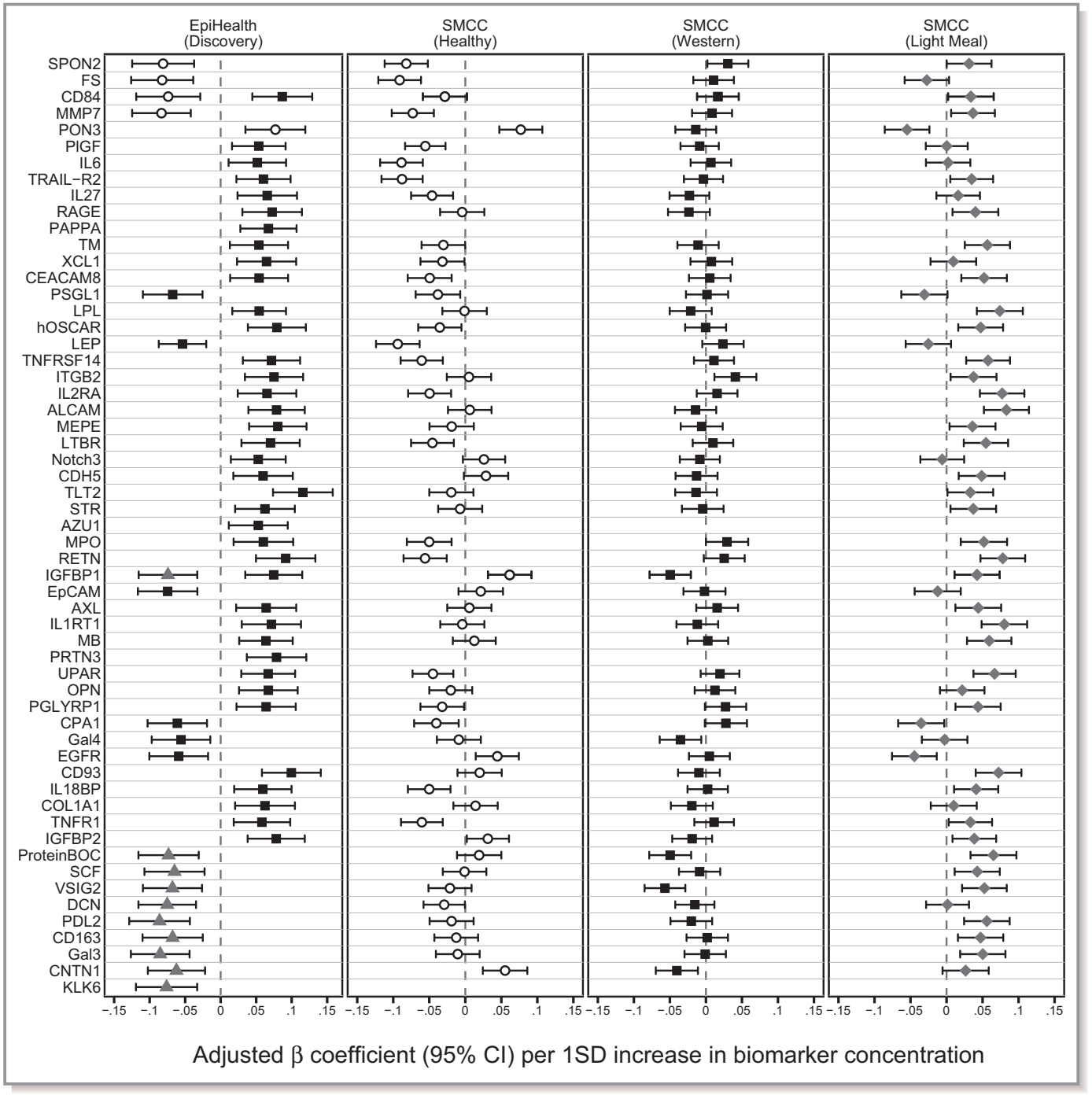

Figure 1. β Estimates and corresponding 95% CIs for the discovery and replication linear regression analyses between dietary patterns and protein biomarkers and in the EpiHealth study (EpiHealth; panel 1, discovery) and Swedish Mammography Cohort Clinical (SMCC; panel 2, *healthy*; panel 3, *Western*; panel 4, *light meal*). The discovery analysis in the EpiHealth was adjusted for age, physical activity, educational level, smoking status, and sex. The replication analysis in the SMCC was adjusted for age, physical activity, educational level, smoking status, chip number, and phase. In panel 1, β estimates are depicted with -○- for the *healthy pattern*, -■- for the *Western/traditional pattern,* and -▲- for the *fast food and alcohol pattern*. The complete name of the abbreviated proteins in this figure are found in Table S1.

independent of sex and BMI category (data not shown) in EpiHealth and of BMI category (data not shown) in the SMCC. The magnitude of the effect estimates was similar in the stratified analyses but with lower precision compared with the overall results. The effect estimates and 95% CIs from the analyses stratified on sex in EpiHealth are presented in Figure 2. The correlation matrix of the validated proteins is depicted in Figure S2.

Table 3. Fully Adjusted β Estimates and *P* Values for the Linear Association Between Dietary Patterns and Proteins That Were Replicated in the SMCC

	EpiHealth		SMCC					
			Western/Traditional		Healthy		Light Meal	
Protein	β Estimate	*P* Value	β Estimate	*P* Value	β Estimate	*P* Value	β Estimate	*P* Value
	Healthy							
Spondin-2	−0.081	2.80e-04	. . .	. . .	−0.056	1.4e-03	. . .	. . .
Follistatin	−0.082	2.30e-04	. . .	. . .	−0.087	3.0e-06	. . .	. . .
MMP-7	−0.083	7.80e-05	. . .	. . .	−0.059	1.4e-03	. . .	. . .
Paraoxonase 3	0.077	3.50e-04	. . .	. . .	0.046	1.0e-02	. . .	. . .
	Western/traditional							
Gal-4	−0.056	8.00e-03	−0.039	2.0e-02	. . .	. . .	. . .	. . .
TRAIL-R2	0.060	2.00e-03	. . .	. . .	−0.039	1.6e-02	. . .	. . .
Myeloperoxidase	0.060	5.00e-03	. . .	. . .	−0.061	2.2e-03	0.046	9.0e-03
Resistin	0.092	1.80e-05	. . .	. . .	−0.044	1.6e-02	0.058	2.7e-04
IL1RT1	0.071	7.90e-04	. . .	. . .	. . .	. . .	0.063	2.8e-04
UPAR	0.067	5.40e-04	. . .	. . .	. . .	. . .	0.041	4.1e-03
TM	0.054	9.90e-03	. . .	. . .	. . .	. . .	0.038	1.7e-02
CEACAM8	0.054	9.30e-03	. . .	. . .	. . .	. . .	0.046	6.7e-03
LPL	0.054	5.00e-03	. . .	. . .	. . .	. . .	0.064	2.1e-04
IL2RA	0.065	1.90e-03	. . .	. . .	. . .	. . .	0.054	5.0e-04
ALCAM	0.079	1.00e-04	. . .	. . .	. . .	. . .	0.067	6.6e-05
CPA-1	−0.061	4.20e-03	. . .	. . .	. . .	. . .	−0.036	4.3e-02
EGFR	−0.059	5.10e-03	. . .	. . .	. . .	. . .	−0.044	9.6e-03
	Fast food and alcohol							
Protein BOC	−0.073	7.20e-04	−0.072	3.2e-05	. . .	. . .	. . .	. . .
VSIG2	−0.068	1.40e-03	−0.071	1.4e-05	. . .	. . .	. . .	. . .
Contactin-1	−0.062	2.50e-03	−0.057	1.0e-03	. . .	. . .	. . .	. . .
IGFBP-1	−0.074	4.30e-04	−0.077	5.5e-07	. . .	. . .	. . .	. . .

Also presented are the β estimates and *P* values from the discovery analysis in the EpiHealth cohort. The Western/traditional pattern in the EpiHealth shares common characteristics with both the Western/traditional and the light meal pattern in the SMCC. The discovery analysis in the EpiHealth was adjusted for age, physical activity, educational level, smoking status, and sex. The fully multivariable adjusted model (model 6) in SMCC includes age, physical activity, educational level, smoking status, chip number, phase, total energy intake, alanine aminotransferase, cystatin C, Charlson weighted comorbidity index, fat mass (percentage), CRP (C-reactive protein), and total vitamin D (D_2 and D_3). Both dietary patterns and protein biomarkers were standardized to a distribution with a mean=0 and SD=1. EpiHealth, EpiHealth study; IGFBP-1, insulin-like growth factor–binding protein 1; MMP, matrix metalloproteinase; protein BOC, brother of CDO; SMCC, Swedish Mammography Cohort Clinical; VSIG, V-set and immunoglobulin domain–containing protein. All protein names and abbreviations are found in Table S1.

Discussion

Principal Findings

By using well-powered data from 2 population-based cohort studies in Sweden, we provide compelling evidence of associations between the actual dietary patterns and 21 CVD-related protein biomarkers. Two of the protein biomarkers, myeloperoxidase[21] and resistin,[22] were inversely associated with the *healthy pattern* but positively associated with the *light meal pattern* (unhealthy diet), indicating contrary effects of respective dietary pattern. Although the association between dietary patterns and every individual protein biomarker was not statistically strong, the sum of its actions may have clinical impact in the long-term development of CVD. The reported associations between dietary patterns and protein biomarkers were independent of markers of adiposity and age as well as other risk factors for CVD, implying novel discovery of pathways. The history of CVD and diabetes mellitus was low in both cohorts, and these diseases were taken into account in the analysis by the inclusion of the Charlson Comorbidity Index. The biomarker proteins in the CVD2 and CVD3 panels were chosen because of their previous reported association with CVD. The 21 replicated

proteins were correlated to a varying degree (Figure S2), which may indicate activation of common underlying pathways. In the EpiHealth discovery analysis, the *dairy and sandwich pattern* did not associate with any protein, which may indicate that this pattern is related to noncardiovascular or no disease processes.

Pathways and Associations With CVD

The identified proteins have been reported to have different roles in the development of CVD through pathways related to, for example, inflammation, oxidative stress, endothelial and immune responses, cell adhesion, and metabolism. Information about the functions and biological processes of the 21 protein biomarkers is described in Table S5. Furthermore, several of the protein biomarkers that were associated with the dietary patterns have previously been associated with cardiometabolic disease outcomes, thus suggesting a causal link between dietary patterns in a population and disease, as discussed below. Both myeloperoxidase and resistin have been reported to be associated with CVD development in different population settings.[22–24]

The *healthy pattern* was inversely associated with spondin-2, FS (Follistatin), matrix metalloproteinase-7, and TRAIL-R2 (TNF-related apoptosis inducing ligand receptor 2) protein biomarkers. These *healthy pattern* associated proteins have been shown to have a role in the inflammatory response. For example, matrix metalloproteinase-7 is part of the cascade reactions after atherosclerotic tissue destruction, is upregulated during inflammation, and has previously been associated with incident CVD.[25] TRAIL-R2 was an independent predictor of long-term all-cause mortality in patients with acute myocardial infarction.[26] The *healthy pattern* also was positively associated with paraoxonase 3. Paraoxonase 3 is 1 of 3 paraoxonases, and their role has been implicated in the atherosclerotic process, reduction in atherogenesis, and adiposity in animal models[27] as well as development of type 2 diabetes mellitus in humans.[28]

The *Western/traditional pattern* was inversely associated with concentrations of Gal-4 (Galectin-4), brother of CDO, V-set and immunoglobulin domain–containing protein 2, contactin-1, and insulin-like growth factor–binding protein 1. These dietary pattern associated proteins are involved in pathways of inflammation, cell adhesion, and metabolic processes. Altered expression of Gal-4, among 4 other proteins from the CVD3 panel, was associated with later development of aortic valve stenosis[29] and incident type 2 diabetes mellitus.[28] There is not much evidence about the potential role of either brother of CDO[30] or V-set and immunoglobulin domain–containing protein 2.[31] In the FHS (Framingham Heart Study), contactin-1 was inversely associated with all-cause mortality, whereas insulin-like growth factor–binding protein 1 and resistin were associated

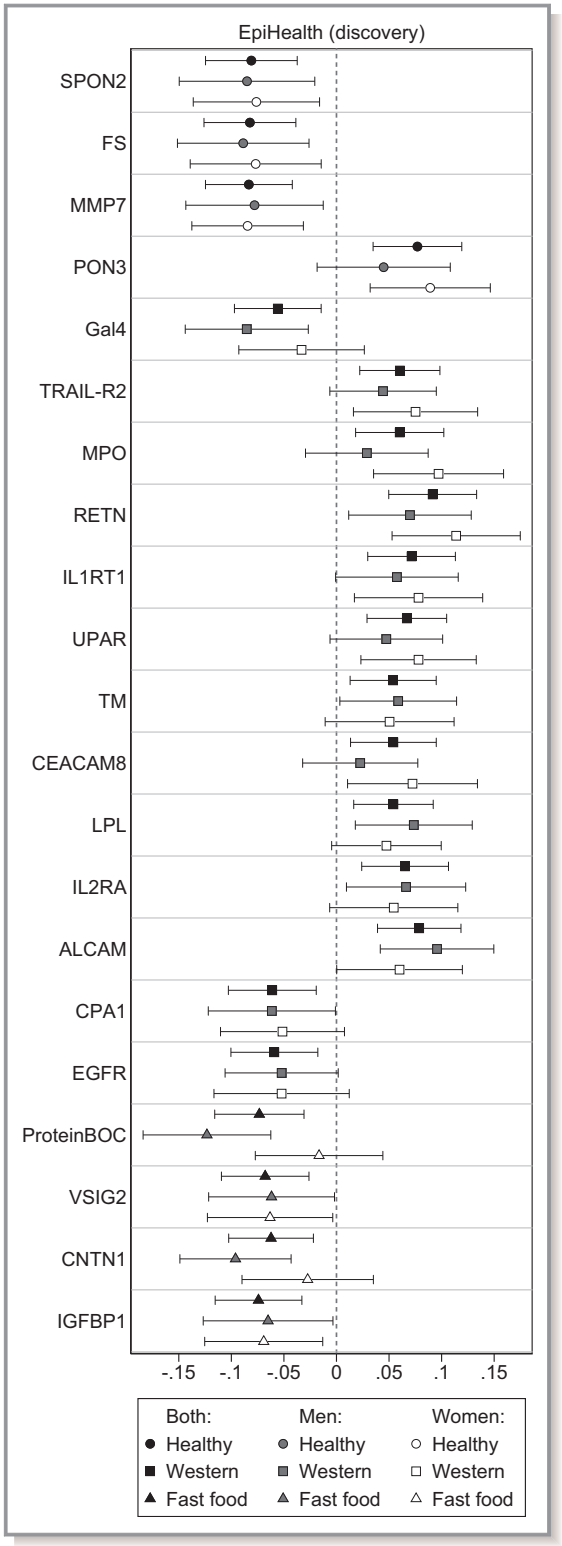

Figure 2. The β estimates and corresponding 95% CIs from the discovery analysis stratified on sex in the EpiHealth (EpiHealth study). The complete name of the abbreviated proteins in this figure are found in Table S1.

positively with the incidence of heart failure as well as all-cause and CVD mortality.[32]

The *light meal pattern* was associated positively with TM (Thrombomodulin), CEACAM-8 (Carcinoembryonic antigen-related cell adhesion molecule 8), LPL (Lipoprotein lipase), IL2RA (Interleukin-2 receptor subunit alpha), ALCAM (CD166 antigen), IL1R-T1 (Interleukin-1 receptor type 1), and UPAR (Urokinase plasminogen activator surface receptor), in addition to myeloperoxidase and resistin. Lower levels of TM, together with other biomarkers of endothelial dysfunction, have been associated with a healthier diet.[33] CEACAM8[34] and IL2RA[35] have been involved in the immune responses, and LPL plays a critical role in lipid metabolism and its transport.[36] Higher circulating serum levels of ALCAM have been observed in patients with type 2 diabetes mellitus,[37] and IL1R-T1 is 1 of the 2 isoforms of the interleukin-1 receptor, which regulates interleukin-1 activity. Interleukin-1, a proinflammatory cytokine, has been linked to type 2 diabetes mellitus.[38] Expression of UPAR also reflects increased inflammation and has been presented as a new emerging biomarker for CVD and critical illness.[39] CPA1 (Carboxypeptidase A1) and EGFR (Epidermal growth factor receptor) were both inversely associated with the *light meal pattern* and have an important role in metabolism and cell adhesion. EGFR deficiency in myeloid cells has been reported to reduce early and late stages of atherosclerosis development.[40] UPAR, TRAIL-R2, and FST protein biomarkers, measured with the same PEA proteomic method as in the present study, were associated with heart failure incidence[41]; and TRAIL-R2 predicted major cardiovascular events in type 2 diabetic patients.[42]

Dietary Patterns

Overall diet is complex and contains many nutrients and bioactive components, such as antioxidants, polyphenols, and phytosterols, which have the potential to reduce vascular damage and prevent CVD in numerous ways, including alleviating inflammatory, oxidative, and immune responses.[10] PCA-derived dietary patterns reflect the usual and actual dietary patterns within a population, and all food groups contribute with component loadings in each dietary pattern. The food groups with the highest component loadings will be considered important. Component loadings can be seen as correlations between the food group and the dietary pattern; consequently, different dietary patterns in a population will reflect patterns on a continuous scale from a healthy to a more unhealthy diet. This is in contrast to the index derived dietary patterns, which aim to classify individuals into relative adherence categories of healthy dietary patterns, such as the Mediterranean diet,[43] or separate food groups and do not take the full complexity of the food matrix into account.[44] Both the *Western/traditional* and the *healthy patterns*, identified in the EpiHealth and the SMCC, respectively, shared common characteristics, but also differences, which relate to differences in diet data between the 2 cohorts. For example, the generation of the dietary patterns used 35 and 33 food groups in the EpiHealth and the SMCC, respectively, and 31 of these food groups overlapped between the studies. The *light meal pattern* in the SMCC also overlapped with the *Western/traditional* pattern in EpiHealth. However, the healthy and unhealthy patterns in this study are in agreement with the dietary patterns identified in previous studies in population-based Swedish cohorts[45,46] as well as in the mother study of SMCC.[15,47] Although dietary patterns identified in a population depend on the diet data and the collapsing of food groups, the use of data reduction techniques, such as PCA, renders major dietary patterns that are fairly stable across populations. We are aware of only one previous study on plasma proteins and dietary patterns.[48] In this study, dietary patterns and ethnicity were associated with high-abundance plasma protein groups of 54 proteins involved in inflammation and lipid metabolism.[48] The plasma proteins included in the previous study had little overlap with the proteins in the present study.

Strengths and Limitations

The strengths of the study include the study size and careful characterization of study participants in both the EpiHealth and SMCC. Furthermore, proteins were measured in a multiplex proteomic assay using a PEA technique, which is both specific and sensitive and requires a low sample volume.[18] Although we adjusted for important covariates, including education, physical activity, smoking, and comorbidities, including CVD, as well as other covariates, there may be an influence of residual or unmeasured confounding. In EpiHealth, the proportion of participants with a university degree was high, which may theoretically have skewed the overall dietary patterns. However, we were able to identify similar dietary patterns in the SMCC too. In fact, the *healthy pattern* in the SMCC was correlated with the healthy patterns identified in SMC, 10 to 20 years earlier, including the baseline 1987 data (r=0.41) as well as the 1997 data (r=0.51),[15] implying long-term stability of the broader dietary pattern among these women. Furthermore, dietary patterns identified herein shared characteristics with patterns identified in other population-based cohorts in Sweden. It would have been ideal to have generated the dietary patterns in a combined data set of the 2 cohorts. However, because the dietary assessment method differs substantially between the 2 cohorts, this was not deemed suitable. Nonetheless, the diet data were collected using valid methods both in EpiHealth[49] and the SMCC. The cross-sectional nature of the study is a limitation. However, the results add to the growing body of omics studies aiming to establish biomarkers,

this time on a functional scale, which is relevant in the pathophysiological features of CVD and pathways activated by dietary components. Dietary exposure is difficult to measure, which is connected to random and systematic measurement errors in the diet report; however, random errors are reduced by incremental study sizes. Systematic error in the diet report probably influences all the dietary patterns in the present study and most unlikely influences interpretation of the overall results. Both men and women were included in the discovery analysis, but the replication analysis was done only in women, which could be viewed as a drawback because men were not included in the replication; however, having a replication cohort is a major strength of the study design. The sensitivity analysis confirmed similar associations between dietary patterns and proteins in both men and women in the EpiHealth study.

Conclusions

We have discovered and replicated independent associations between a posteriori dietary patterns and 21 CVD protein biomarkers involved in inflammation, oxidative stress, endothelial function and immune responses, cell adhesion, and metabolism. The results of the present study should be confirmed in other settings.

Author Contributions

Warensjö Lemming and Michaëlsson designed the research. All authors were involved in conducting the research. Warensjö Lemming and Stattin performed the data management and statistical analysis. Warensjö Lemming drafted the article. All authors participated in the interpretation of data and in finalizing the article. Warensjö Lemming had the primary responsibility for the final content. All authors read and approved the final article.

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Disclosures

None.

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Supplemental Material

Table S1. The protein biomarkers included in the CVD2 and CVD3 assay panels are depicted.

CVD 2		**CVD 3**	
Name	**Abbreviation**	**Name**	**Abbreviation**
Angiotensin-converting enzyme 2	ACE2	CD166 antigen	ALCAM
A disintegrin and metalloproteinase with thrombospondin motifs 13	ADAM-TS13	Aminopeptidase N	AP-N
ADM	ADM	Tyrosine-protein kinase receptor UFO	AXL
Agouti-related protein	AGRP	Azurocidin	AZU1
Protein AMBP	AMBP	Bleomycin hydrolase	BLM hydrolase
Angiopoietin-1	ANG-1	Caspase-3	CASP-3
Bone morphogenetic protein 6	BMP-6	C-C motif chemokine 15	CCL15
Natriuretic peptides B	BNP	C-C motif chemikine 22	CCL22
Carbonic anhydrase 5A, mitochondrial	CA5A	C-C motif chemokine 24	CCL24
C-C motif chemokine 17	CCL17	Scavenger receptor cysteine-rich type 1 protein M130	CD163
C-C motif chemokine 3	CCL3	Complement component C1q receptor	CD93
T-cell surface glycoprotein CD4	CD4	Cadherin-5	CDH5
CD40 ligand	CD40-L	Chitinase-3-like protein 1	CHI3L1
SLAM family member 5	CD84	Chitotriosidase-1	CHIT1
Carcinoembryonic antigenrelated cell adhesion molecule 8	CEACAM8	Contactin-1	CNTN1
Chymotrypsin C	CTRC	Collagen alpha-1(I) chain	COL1A1
Cathepsin L1	CTSL1	Carboxypeptidase A1	CPA1
C-X-C motif chemokine 1	CXCL1	Carboxypeptidase B	CPB1
Decorin	DCN	Cystatin-B	CSTB
2,4-dienoyl-CoA reductase, mitochondrial	DECR1	Cathepsin D	CTSD
Dickkopf-related protein 1	Dkk-1	Cathepsin Z	CTSZ
Fatty acid-binding protein, intestinal	FABP2	C-X-C motif chemokine 16	CXCL16
Fibroblast growth factor 21	FGF-21	Protein delta homolog 1	DLK-1
Fibroblast growth factor 23	FGF-23	Epidermal growth factor receptor	EGFR
Follistatin	FS	Epithelial cell adhesion molecule	Ep-CAM
Galectin-9	Gal-9	Ephrin type-B receptor 4	EPHB4

Growth/differentiation factor 2	GDF-2	Fatty acid-binding protein, adipocyte	FABP4
Growth hormone	GH	Tumor necrosis factor receptor superfamily member 6	FAS
Gastric intrinsic factor	GIF	Galectin-3	Gal-3
Lactoylglutathione lyase	GLO1	Galectin-4	Gal-4
Gastrotropin	GT	Growth/differentiation factor 15	GDF-15
Proheparin-binding EGF-like growth factor	HB-EGF	Granulins	GRN
Heme oxygenase 1	HO-1	Intercellular adhesion molecule 2	ICAM-2
Osteoclast-associated immunoglobulin-like receptor	hOSCAR	Insulin-like growth factor-binding protein 1	IGFBP-1
Heat shock 27 kDa protein	HSP 27	Insulin-like Growth Factor-Binding Protein 2	IGFBP-2
Alpha-L-iduronidase	IDUA	Insulin-like growth factor-binding protein 7	IGFBP-7
Low affinity immunoglobulin gamma Fc region receptor II-b	IgG Fc receptor II-b	Interleukin-17 receptor A	IL-17RA
Pro-interleukin-16	IL16	Interleukin-18-binding protein	IL-18BP
Interleukin-17D	IL-17D	Interleukin-1 receptor type 1	IL-1RT1
Interleukin-18	IL-18	Interleukin-1 receptor type 2	IL-1RT2
Interleukin-1 receptor antagonist protein	IL-1ra	Interleukin-2 receptor subunit alpha	IL2-RA
Interleukin-1 receptor-like 2	IL1RL2	Interleukin-6 receptor subunit alpha	IL-6RA
Interleukin-27	IL-27	Integrin beta-2	ITGB2
Interleukin-4 receptor subunit alpha	IL-4RA	Junctional adhesion molecule A	JAM-A
Interleukin-6	IL-6	Kallikrein-6	KLK6
Melusin	ITGB1BP2	Low-density lipoprotein receptor	LDL receptor
Kidney injury molecule 1	KIM-1	Lymphotoxin-beta receptor	LTBR
Leptin	LEP	Myoglobin	MB
Lectin-like oxidized LDL receptor 1	LOX-1	Monocyte chemotactic protein 1	MCP-1
Lipoprotein lipase	LPL	Matrix extracellular phosphoglycoprotein	MEPE
Macrophage receptor MARCO	MARCO	Matrix metalloproteinase-2	MMP-2
Tyrosine-protein kinase Mer	MERTK	Matrix metalloproteinase-3	MMP-3
Matrix metalloproteinase-12	MMP-12	Matrix metalloproteinase-9	MMP-9
Matrix metalloproteinase-7	MMP-7	Myeloperoxidase	MPO

NF-kappa-B essential modulator	NEMO	Neurogenic locus notch homolog protein 3	Notch 3
Pappalysin-1	PAPPA	Osteoprotegerin	OPG
Proteinase-activated receptor 1	PAR-1	Osteopontin	OPN
Platelet-derived growth factor subunit B	PDGF subunit B	Plasminogen activator inhibitor 1	PAI
Programmed cell death 1 ligand 2	PD-L2	Proprotein convertase subtilisin/kexin type 9	PCSK9
Polymeric immunoglobulin receptor	PIgR	Platelet-derived growth factor subunit A	PDGF subunit A
Placenta growth factor	PlGF	Platelet endothelial cell adhesion molecule	PECAM-1
Prolargin	PRELP	Peptidoglycan recognition protein 1	PGLYRP1
Brother of CDO	Protein BOC or BOC	Elafin	PI3
Serine protease 27	PRSS27	Perlecan	PLC
Prostasin	PRSS8	Paraoxonase (PON 3)	PON3
P-selectin glycoprotein ligand 1	PSGL-1	Myeloblastin	PRTN3
Pentraxin-related protein PTX3	PTX3	Pulmonary surfactant-associated protein D	PSP-D
Receptor for advanced glycosylation end products	RAGE	Retinoic acid receptor responder protein 2	RARRES2
Renin	REN	Resistin	RETN
Stem cell factor	SCF	Secretoglobin family 3A member 2	SCGB3A2
Serpin A12	SERPINA12	E-selectin	SELE
SLAM family member 7	SLAMF7	P-selectin	SELP
Superoxide dismutase [Mn], mitochondrial	SOD2	Tyrosine-protein phosphatase non-receptor type substrate 1	SHPS-1
Sortilin	SORT1	Spondin-1	SPON1
Spondin-2	SPON2	ST2 protein	ST2
Proto-oncogene tyrosine-protein kinase Src	SRC	Trefoil factor 3	TFF3
Serine/threonine-protein kinase 4	STK4	Tissue factor pathway inhibitor	TFPI
Tissue factor	TF	Metalloproteinase inhibitor 4	TIMP4
Protein-glutamine gamma-glutamyltransferase 2	TGM2	Trem-like transcript 2 protein	TLT-2
Thrombospondin-2	THBS2	Tumor necrosis factor receptor 1	TNF-R1
Thrombopoietin	THPO	Tumor necrosis factor receptor 2	TNF-R2

Angiopoietin-1 receptor	TIE2	Tumor necrosis factor receptor superfamily member 10C	TNFRSF10C
Thrombomodulin	TM	Tumor necrosis factor receptor superfamily member 14	TNFRSF14
Tumor necrosis factor receptor superfamily member 10A	TNFRSF10A	Tumor necrosis factor ligand superfamily member 13B	TNFSF13B
Tumor necrosis factor receptor superfamily member 11A	TNFRSF11A	Tissue-type plasminogen activator	t-PA
Tumor necrosis factor receptor superfamily member 13B	TNFRSF13B	Transferrin receptor protein 1	TR
TNF-related apoptosis-inducing ligand receptor 2	TRAIL-R2	Tartrate-resistant acid phosphatase type 5	TR-AP
Vascular endothelial growth factor D	VEGF-D	Urokinase-type plasminogen activator	uPA
V-set and immunoglobulin domain-containing protein 2	VSIG2	Urokinase plasminogen activator surface receptor	U-PAR
Lymphotactin	XCL1	von Willebrand factor	vWF

Table S2. Protein biomarkers excluded in quality control in the CVD2 and CVD3 panels are shown. Proteins were excluded if more than 15 % of the samples were below the limit of detection (LOD) in EpiHealth or more than 25 % of samples below LOD in SMCC.

EpiHealth		**SMCC**	
CVD2	**CVD 3**	**CVD2**	**CVD 3**
BNP	NT-ProBNP	ITGB1BP2	AZU1
CA5A		CA5A	PI3
SLAMF7		BNP	KLK6
IgGFcreceptorIIb		IL4RA	EPHB4
		PARP1	PSPD
		PAPPA	MMP9
			PRTN3
			SPON1
			CCL22

SMCC Swedish Mammography Cohort Clinical. Abbreviations of proteins are explained in Table S1.

Table S3. Adjusted *β*-estimates and *P*-values for the discovery analysis in Epihealth between dietary patterns and all protein biomarkers. Both dietary patterns and protein biomarkers were standardized to a distribution with a mean=0 and SD=1.

	Healthy		Dairy and sandwich		Western/ Traditional		Fast food and alcohol	
Protein	*β*-estimate	*P*-value	*β*-estimate	*P*-value	*β*-estimate	*P*-value	*β*-estimate	*P*-value
BMP6	-0.055	1.70E-02	0.009	7.00E-01	0.053	1.40E-02	-0.014	5.40E-01
ANG1	-0.049	3.20E-02	0.013	5.60E-01	-0.003	8.80E-01	-0.019	3.80E-01
ADM	-0.057	5.30E-03	-0.010	6.00E-01	0.020	3.00E-01	0.031	1.10E-01
CD40L	-0.023	3.20E-01	-0.011	6.30E-01	0.016	4.70E-01	0.022	3.20E-01
PlGF	-0.040	5.20E-02	0.016	4.20E-01	0.054	5.20E-03	-0.010	6.00E-01
ADAMTS13	0.009	6.90E-01	0.028	2.00E-01	-0.025	2.40E-01	-0.024	2.60E-01
ProteinBOC	0.021	3.60E-01	0.029	1.80E-01	0.016	4.40E-01	-0.073	7.20E-04
IL4RA	-0.001	9.80E-01	0.031	1.70E-01	0.014	5.10E-01	-0.064	3.50E-03
SRC	-0.011	6.50E-01	-0.033	1.50E-01	0.031	1.50E-01	-0.006	7.90E-01
IL1ra	-0.066	3.20E-03	-0.019	3.90E-01	-0.013	5.20E-01	0.013	5.60E-01
IL6	-0.062	5.10E-03	-0.029	1.80E-01	0.052	1.20E-02	0.000	9.90E-01
TNFRSF10A	-0.021	3.40E-01	-0.012	5.80E-01	0.011	6.10E-01	-0.024	2.60E-01
STK4	-0.015	5.30E-01	-0.027	2.30E-01	0.043	4.60E-02	-0.026	2.50E-01
IDTA	-0.045	5.10E-02	-0.017	4.50E-01	0.008	7.20E-01	-0.026	2.30E-01
TNFRSF11A	-0.047	3.30E-02	0.037	8.60E-02	0.028	1.70E-01	-0.050	2.00E-02
PAR1	-0.004	8.50E-01	0.013	5.50E-01	0.047	2.70E-02	-0.052	1.60E-02
TRAIL-R2	-0.039	5.80E-02	0.017	4.00E-01	0.060	2.00E-03	-0.030	1.30E-01
PRSS27	-0.001	9.80E-01	0.011	6.10E-01	0.020	3.60E-01	-0.036	1.10E-01
TIE2	0.008	7.10E-01	0.037	9.70E-02	-0.012	5.80E-01	-0.053	1.60E-02
TF	0.005	8.30E-01	0.044	4.20E-02	0.008	7.00E-01	-0.031	1.40E-01
IL1RL2	0.012	6.10E-01	-0.022	3.30E-01	0.028	1.80E-01	-0.042	5.40E-02
PDGFsTbTnitB	-0.042	6.90E-02	0.020	3.80E-01	0.017	4.20E-01	-0.008	7.10E-01
IL27	-0.032	1.60E-01	0.041	6.90E-02	0.066	2.10E-03	-0.063	4.00E-03
IL17D	-0.037	8.30E-02	-0.002	9.30E-01	0.038	5.60E-02	-0.020	3.20E-01
CXCL1	-0.030	1.90E-01	-0.008	7.10E-01	0.005	8.00E-01	-0.012	5.90E-01

LOX1	-0.046	3.80E-02	0.006	7.60E-01	0.021	3.20E-01	-0.039	6.70E-02
Gal9	-0.049	2.20E-02	-0.011	5.90E-01	0.023	2.60E-01	-0.012	5.60E-01
GIF	0.020	3.80E-01	-0.016	4.70E-01	-0.034	1.20E-01	-0.043	5.20E-02
SCF	-0.003	8.90E-01	0.031	1.60E-01	0.050	1.70E-02	-0.065	2.60E-03
IL18	-0.043	4.90E-02	-0.002	9.40E-01	0.031	1.30E-01	-0.023	2.70E-01
FGF21	-0.044	5.20E-02	-0.073	8.60E-04	0.004	8.40E-01	0.017	4.30E-01
PIgR	-0.045	3.70E-02	0.000	1.00E+00	-0.015	4.50E-01	-0.006	7.80E-01
RAGE	0.031	1.80E-01	0.036	1.10E-01	0.072	7.10E-04	-0.042	5.40E-02
SOD2	-0.014	5.40E-01	0.000	9.90E-01	0.025	2.40E-01	-0.038	8.30E-02
CTRC	0.034	1.40E-01	0.018	4.20E-01	-0.040	6.60E-02	-0.022	3.30E-01
FGF23	-0.021	3.50E-01	0.021	3.40E-01	0.035	9.10E-02	0.007	7.60E-01
SPON2	-0.081	2.80E-04	-0.019	3.90E-01	0.027	1.90E-01	-0.056	9.10E-03
GH	0.009	6.70E-01	0.026	1.70E-01	-0.019	3.10E-01	0.005	7.90E-01
FS	-0.082	2.30E-04	0.006	7.90E-01	0.049	1.90E-02	0.005	8.30E-01
GLO1	-0.030	1.90E-01	0.022	3.30E-01	0.019	3.70E-01	-0.005	8.00E-01
CD84	-0.074	1.30E-03	0.010	6.50E-01	0.087	5.70E-05	-0.044	5.00E-02
PAPPA	-0.050	2.10E-02	0.030	1.60E-01	0.067	8.80E-04	-0.040	5.50E-02
SERPINA12	-0.022	3.50E-01	0.002	9.20E-01	-0.042	5.10E-02	-0.036	1.10E-01
REN	-0.051	2.10E-02	-0.008	7.20E-01	-0.022	3.00E-01	-0.025	2.30E-01
DECR1	-0.010	6.70E-01	-0.011	6.20E-01	0.008	7.30E-01	-0.017	4.50E-01
MERTK	-0.043	4.70E-02	-0.009	6.60E-01	0.024	2.50E-01	0.008	7.10E-01
TIM	-0.041	5.30E-02	0.000	1.00E+00	-0.047	1.80E-02	0.049	1.50E-02
THBS2	-0.049	3.30E-02	-0.038	9.00E-02	-0.002	9.40E-01	-0.024	2.70E-01
TM	-0.017	4.40E-01	0.031	1.60E-01	0.054	9.90E-03	-0.061	4.50E-03
VSIG2	-0.001	9.50E-01	0.008	7.00E-01	-0.005	8.20E-01	-0.068	1.40E-03
AMBP	-0.047	3.50E-02	0.017	4.50E-01	0.011	6.00E-01	0.013	5.40E-01
PRELP	-0.042	3.60E-02	0.025	2.00E-01	0.044	2.00E-02	-0.005	8.00E-01
HO1	0.020	3.80E-01	-0.007	7.60E-01	-0.029	1.60E-01	0.057	7.90E-03
XCL1	-0.027	2.30E-01	-0.026	2.50E-01	0.065	2.30E-03	-0.034	1.20E-01
IL16	-0.018	4.20E-01	0.002	9.20E-01	0.028	1.80E-01	-0.030	1.70E-01

SORT1	-0.038	8.30E-02	0.011	6.10E-01	-0.016	4.50E-01	-0.015	4.80E-01
CEACAM8	-0.026	2.40E-01	0.050	2.20E-02	0.054	9.30E-03	-0.051	1.70E-02
PTX3	-0.016	4.80E-01	0.006	8.10E-01	0.018	4.10E-01	-0.002	9.40E-01
PSGL1	0.029	2.10E-01	-0.003	9.10E-01	-0.068	1.60E-03	0.032	1.40E-01
CCL17	-0.045	4.90E-02	0.006	7.80E-01	0.005	8.10E-01	-0.050	2.10E-02
CCL3	-0.016	4.80E-01	-0.030	1.80E-01	0.000	1.00E+00	0.009	7.00E-01
MMP7	-0.083	7.80E-05	-0.018	3.70E-01	-0.025	2.00E-01	-0.035	8.90E-02
ITGB1BP2	-0.023	3.10E-01	-0.040	7.90E-02	0.026	2.30E-01	-0.003	9.00E-01
DCN	-0.028	2.00E-01	0.010	6.30E-01	0.014	4.90E-01	-0.075	2.80E-04
Dkk1	-0.051	2.50E-02	0.031	1.60E-01	0.028	1.80E-01	-0.043	4.90E-02
LPL	0.008	7.00E-01	0.016	4.30E-01	0.054	5.00E-03	-0.054	6.70E-03
PRSS8	-0.036	8.20E-02	-0.044	2.80E-02	0.026	1.80E-01	-0.014	4.90E-01
AGRP	-0.023	3.20E-01	0.003	9.00E-01	0.048	2.40E-02	-0.010	6.60E-01
HBEGF	-0.049	3.10E-02	0.017	4.40E-01	0.053	1.40E-02	-0.050	2.20E-02
GDF2	0.013	5.30E-01	0.022	2.90E-01	-0.016	4.10E-01	-0.038	6.30E-02
FABP2	0.020	3.90E-01	0.032	1.60E-01	-0.037	9.20E-02	-0.038	8.50E-02
THPO	-0.017	4.70E-01	0.015	5.10E-01	-0.010	6.30E-01	-0.008	7.20E-01
MARCO	-0.041	6.80E-02	-0.011	6.30E-01	-0.029	1.70E-01	-0.035	1.00E-01
GT	0.026	2.60E-01	0.034	1.30E-01	-0.029	1.80E-01	-0.009	6.90E-01
MMP12	-0.029	1.60E-01	-0.015	4.60E-01	0.003	8.90E-01	-0.043	3.30E-02
ACE2	-0.042	5.20E-02	0.033	1.10E-01	-0.027	1.70E-01	0.030	1.50E-01
PDL2	-0.007	7.70E-01	0.027	2.20E-01	0.036	8.70E-02	-0.086	8.00E-05
CTSL1	0.038	9.20E-02	0.061	5.40E-03	0.009	6.80E-01	-0.039	7.30E-02
hOSCAR	-0.048	3.00E-02	0.020	3.50E-01	0.079	1.50E-04	-0.036	8.90E-02
TNFRSF13B	0.002	9.30E-01	-0.006	7.80E-01	0.047	2.80E-02	-0.061	5.30E-03
TGM2	0.033	1.50E-01	0.037	1.00E-01	0.027	2.10E-01	0.009	6.80E-01
LEP	-0.027	1.40E-01	-0.023	2.00E-01	-0.054	1.70E-03	0.023	1.90E-01
HSP27	-0.018	4.40E-01	-0.002	9.20E-01	0.028	1.90E-01	-0.010	6.70E-01
CD4	-0.028	2.20E-01	0.034	1.20E-01	0.034	1.10E-01	-0.010	6.30E-01
NEMO	-0.013	5.60E-01	-0.029	2.00E-01	0.037	8.70E-02	-0.032	1.50E-01

VEGFD	0.030	1.80E-01	-0.008	7.10E-01	-0.018	3.80E-01	-0.019	3.70E-01
PARP1	-0.029	2.10E-01	0.005	8.20E-01	0.010	6.50E-01	-0.017	4.50E-01
HAOX1	-0.035	1.20E-01	-0.014	5.20E-01	-0.046	3.10E-02	0.044	4.50E-02
TNFRSF14	-0.021	3.50E-01	-0.003	8.80E-01	0.072	5.10E-04	-0.048	2.40E-02
LDLreceptor	-0.050	2.60E-02	0.005	8.40E-01	0.022	3.00E-01	0.008	7.30E-01
ITGB2	0.003	9.00E-01	0.037	8.80E-02	0.075	3.30E-04	-0.038	7.90E-02
IL17RA	0.024	3.00E-01	-0.042	6.40E-02	-0.008	7.00E-01	-0.011	6.30E-01
TNFR2	-0.014	5.10E-01	-0.016	4.60E-01	0.030	1.50E-01	-0.042	4.70E-02
MMP9	-0.053	1.70E-02	0.020	3.50E-01	0.007	7.50E-01	-0.006	7.80E-01
EPHB4	-0.010	6.60E-01	0.005	8.20E-01	0.053	1.30E-02	-0.041	6.60E-02
IL2RA	-0.014	5.20E-01	-0.006	8.00E-01	0.065	1.90E-03	-0.027	2.10E-01
OPG	-0.020	3.40E-01	0.028	1.60E-01	0.023	2.40E-01	-0.016	4.10E-01
ALCAM	0.021	3.40E-01	0.048	2.40E-02	0.079	1.00E-04	-0.046	2.70E-02
TFF3	-0.013	5.60E-01	0.019	3.90E-01	0.008	7.10E-01	-0.031	1.50E-01
SELP	-0.014	5.20E-01	0.012	5.70E-01	0.015	4.80E-01	-0.013	5.50E-01
CSTB	0.006	7.90E-01	0.010	6.50E-01	0.012	5.50E-01	-0.017	4.10E-01
MCP1	-0.024	2.80E-01	-0.013	5.60E-01	0.044	3.50E-02	0.012	5.80E-01
CD163	0.018	4.40E-01	-0.008	7.10E-01	0.010	6.50E-01	-0.068	1.80E-03
Gal3	0.026	2.30E-01	0.013	5.40E-01	0.015	4.70E-01	-0.085	5.50E-05
GRN	0.007	7.70E-01	0.001	9.70E-01	-0.026	2.30E-01	-0.007	7.70E-01
MEPE	-0.014	5.30E-01	0.027	2.20E-01	0.080	9.70E-05	-0.026	2.20E-01
BLMhydrolase	-0.007	7.50E-01	0.024	2.90E-01	0.019	3.80E-01	-0.002	9.50E-01
PLC	-0.008	7.00E-01	0.015	4.90E-01	0.051	1.30E-02	-0.030	1.60E-01
LTBR	-0.038	8.90E-02	-0.014	5.20E-01	0.070	7.90E-04	-0.008	7.10E-01
Notch3	0.023	2.80E-01	0.022	2.80E-01	0.053	7.20E-03	-0.029	1.60E-01
TIMP4	0.014	5.20E-01	-0.007	7.30E-01	0.022	2.80E-01	-0.008	6.90E-01
CNTN1	0.051	1.60E-02	0.060	4.00E-03	0.005	8.20E-01	-0.062	2.50E-03
CDH5	0.029	2.00E-01	0.036	1.10E-01	0.060	5.20E-03	-0.045	3.90E-02
TLT2	-0.024	3.10E-01	0.033	1.40E-01	0.116	7.50E-08	-0.035	1.20E-01
FABP4	-0.003	9.00E-01	-0.003	8.90E-01	-0.032	9.00E-02	0.014	4.50E-01

TFPI	-0.002	9.20E-01	0.022	3.20E-01	0.010	6.30E-01	0.020	3.60E-01
PAI	-0.043	5.80E-02	0.019	4.00E-01	-0.026	2.20E-01	0.032	1.50E-01
CCL24	0.016	4.80E-01	-0.006	7.90E-01	0.006	7.70E-01	0.030	1.70E-01
TR	-0.003	8.90E-01	0.033	1.40E-01	0.062	3.60E-03	-0.062	4.80E-03
TNFRSF10C	-0.035	1.20E-01	0.052	1.90E-02	0.049	2.00E-02	-0.021	3.40E-01
SGDF15	-0.012	5.20E-01	-0.018	3.10E-01	0.014	4.30E-01	-0.021	2.50E-01
SELE	-0.035	1.20E-01	0.005	8.10E-01	-0.010	6.30E-01	-0.001	9.70E-01
AZU1	-0.050	2.70E-02	0.018	4.30E-01	0.053	1.20E-02	-0.022	3.10E-01
DLK1	0.046	4.30E-02	0.041	6.10E-02	0.045	3.20E-02	-0.055	1.10E-02
SPON1	0.003	8.70E-01	0.028	1.90E-01	0.026	2.10E-01	-0.013	5.50E-01
MPO	-0.047	3.80E-02	0.037	1.00E-01	0.060	5.00E-03	-0.045	4.20E-02
CXCL16	0.001	9.80E-01	-0.002	9.30E-01	0.000	9.80E-01	-0.021	3.40E-01
IL6RA	-0.002	9.30E-01	-0.004	8.70E-01	-0.013	5.30E-01	0.010	6.50E-01
RETN	-0.037	1.10E-01	0.039	8.00E-02	0.092	1.80E-05	-0.010	6.40E-01
IGFBP1	0.003	8.80E-01	0.003	8.80E-01	0.075	2.60E-04	-0.074	4.30E-04
CHIT1	-0.009	7.00E-01	-0.015	4.90E-01	0.033	1.20E-01	-0.013	5.50E-01
TRAP	-0.021	3.50E-01	-0.015	4.80E-01	-0.029	1.60E-01	0.031	1.50E-01
CCL22	-0.016	4.70E-01	0.032	1.40E-01	-0.023	2.70E-01	0.023	2.90E-01
PSPD	-0.011	6.20E-01	0.011	6.20E-01	0.034	1.10E-01	0.010	6.50E-01
PI3	-0.022	3.30E-01	0.011	6.10E-01	0.052	1.50E-02	-0.028	2.10E-01
EpCAM	0.027	2.30E-01	0.036	1.10E-01	-0.075	4.90E-04	0.036	1.00E-01
APN	0.023	3.20E-01	0.034	1.30E-01	-0.012	5.70E-01	-0.003	9.00E-01
AXL	0.007	7.50E-01	0.008	7.10E-01	0.064	3.00E-03	-0.036	1.10E-01
IL1RT1	0.000	1.00E+00	0.020	3.60E-01	0.071	7.90E-04	-0.044	4.50E-02
MMP2	0.036	1.10E-01	0.025	2.50E-01	0.029	1.70E-01	-0.024	2.70E-01
FAS	0.010	6.40E-01	0.007	7.50E-01	0.004	8.40E-01	-0.017	4.20E-01
MB	0.022	2.90E-01	0.017	4.00E-01	0.064	9.10E-04	-0.057	4.00E-03
TNFSF13B	-0.034	1.20E-01	0.007	7.30E-01	0.043	3.60E-02	0.004	8.40E-01
PRTN3	-0.054	1.90E-02	0.001	9.50E-01	0.079	2.30E-04	-0.018	4.20E-01
PCSK9	-0.047	3.60E-02	-0.040	7.00E-02	0.010	6.40E-01	-0.038	8.10E-02

UPAR	-0.030	1.50E-01	0.001	9.70E-01	0.067	5.40E-04	-0.017	3.80E-01
OPN	-0.049	2.90E-02	0.000	9.90E-01	0.067	1.40E-03	0.006	7.90E-01
CTSD	-0.055	1.60E-02	-0.040	7.50E-02	0.004	8.40E-01	0.047	3.10E-02
PGLYRP1	-0.040	8.20E-02	0.020	3.60E-01	0.064	2.60E-03	-0.023	2.90E-01
CPA1	0.016	4.80E-01	-0.005	8.20E-01	-0.061	4.20E-03	0.003	8.90E-01
JAMA	0.005	8.10E-01	-0.019	3.90E-01	0.006	7.70E-01	-0.006	7.80E-01
Gal4	0.038	9.00E-02	0.033	1.30E-01	-0.056	8.00E-03	-0.058	7.10E-03
IL1RT2	0.030	1.90E-01	0.049	2.80E-02	-0.008	7.10E-01	0.056	1.00E-02
SHPS1	0.024	3.00E-01	0.018	4.20E-01	0.051	1.70E-02	0.004	8.40E-01
CCL15	-0.021	3.60E-01	-0.024	2.70E-01	-0.023	2.70E-01	-0.010	6.40E-01
CASP3	0.008	7.30E-01	-0.016	4.90E-01	0.016	4.60E-01	0.003	9.00E-01
uPA	0.059	9.50E-03	0.024	2.70E-01	0.039	6.90E-02	-0.046	3.50E-02
CPB1	0.014	5.30E-01	-0.015	4.90E-01	-0.047	2.80E-02	0.018	4.20E-01
CHI3L1	-0.046	3.20E-02	-0.048	2.30E-02	0.004	8.50E-01	-0.018	3.80E-01
ST2	0.022	3.00E-01	-0.010	6.40E-01	-0.010	6.10E-01	-0.010	6.40E-01
tPA	-0.024	2.60E-01	-0.023	2.60E-01	-0.031	1.20E-01	0.030	1.50E-01
SCGB3A2	0.020	3.60E-01	-0.005	8.30E-01	-0.031	1.20E-01	0.009	6.80E-01
EGFR	0.056	1.20E-02	0.049	2.50E-02	-0.059	5.10E-03	0.034	1.10E-01
IGFBP7	0.017	4.50E-01	0.002	9.10E-01	0.029	1.70E-01	-0.008	7.10E-01
CD93	0.028	2.10E-01	0.050	2.50E-02	0.100	2.60E-06	-0.054	1.30E-02
IL18BP	-0.006	7.90E-01	-0.018	4.10E-01	0.059	3.90E-03	-0.042	4.60E-02
COL1A1	0.022	3.40E-01	0.011	6.20E-01	0.062	3.70E-03	0.000	9.90E-01
PON3	0.077	3.50E-04	0.019	3.60E-01	-0.019	3.40E-01	0.057	6.40E-03
CTSZ	-0.062	5.20E-03	-0.018	4.00E-01	0.043	3.90E-02	-0.005	8.20E-01
MMP3	0.017	3.40E-01	-0.014	4.30E-01	0.006	7.10E-01	-0.028	1.00E-01
RARRES2	-0.046	3.30E-02	-0.014	5.20E-01	0.016	4.30E-01	0.045	3.00E-02
ICAM2	0.003	9.00E-01	0.019	4.10E-01	0.047	3.00E-02	-0.008	7.20E-01
KLK6	0.019	4.10E-01	0.015	4.90E-01	0.045	3.60E-02	-0.076	5.40E-04
PDGFsubunitA	-0.039	8.90E-02	0.025	2.70E-01	0.014	5.10E-01	-0.008	7.10E-01
TNFR1	-0.023	2.90E-01	0.003	8.80E-01	0.058	4.20E-03	-0.037	7.30E-02

IGFBP2	-0.007	7.50E-01	0.027	2.10E-01	0.078	1.40E-04	-0.009	6.60E-01
vWF	0.009	6.80E-01	-0.002	9.20E-01	-0.006	7.90E-01	-0.017	4.30E-01
PECAM1	-0.003	9.10E-01	0.014	5.30E-01	0.005	8.30E-01	-0.027	2.20E-01
CCL16	-0.055	1.10E-02	0.000	9.90E-01	-0.025	2.20E-01	0.029	1.70E-01

Analysis was adjusted for age, physical activity, educational level, smoking status and sex.

Table S4. Adjusted *β*-estimates and *P*-values for the significant discovery analyses in Epihealth and all the replication analyses in SMCC between dietary patterns and protein biomarkers. Both dietary patterns and protein biomarkers were standardized to a distribution with a mean= 0 and SD=1. Color legends are found below the table.

			Epihealth			**SMCC**					
			Healthy pattern			**Western/traditional**		**Healthy**		**Light meal**	
Protein	Abbreviation	CVD Panel	*β*-estimate	*P*-value		*β*-estimate	*P*-value	*β*-estimate	*P*-value	*β*-estimate	*P*-value
Spondin-2	SPON2	2	-0.081	2.80E-04		0.030	3.60E-02	-0.082	9.00E-08	0.031	4.90E-02
Follistatin	FS	2	-0.082	2.30E-04		0.011	4.60E-01	-0.091	1.80E-09	-0.027	8.20E-02
SLAM family member 5	CD84	2	-0.074	1.30E-03		0.017	2.60E-01	-0.028	7.00E-02	0.034	3.70E-02
Matrix metalloproteinase-7	MMP7	2	-0.083	7.80E-05		0.009	5.50E-01	-0.073	1.10E-06	0.037	1.80E-02
Paraoxonase 3	PON3	3	0.077	3.50E-04		-0.014	3.30E-01	0.077	4.30E-07	-0.055	5.40E-04
			Western/traditional			**Western/traditional**		**Healthy**		**Light meal**	
		CVD Panel	*β*-estimate	*P*-value		*β*-estimate	*P*-value	*β*-estimate	*P*-value	*β*-estimate	*P*-value
Placenta growth factor	PlGF	2	0.054	5.20E-03		-0.009	5.20E-01	-0.056	1.00E-04	0.000	9.80E-01
Interleukin-6	IL6	2	0.052	1.20E-02		0.007	6.30E-01	-0.089	4.80E-09	0.002	8.90E-01
TNF-related apoptosis-inducing ligand receptor 2	TRAIL-R2	2	0.060	2.00E-03		-0.003	8.10E-01	-0.088	1.90E-09	0.035	2.10E-02
Interleukin-27	IL27	2	0.066	2.10E-03		-0.023	1.00E-01	-0.046	1.90E-03	0.016	2.90E-01
Receptor for advanced glycosylation end products	RAGE	2	0.072	7.10E-04		-0.024	1.10E-01	-0.004	7.80E-01	0.040	1.30E-02
SLAM family member 5	CD84	2	0.087	5.70E-05		0.017	2.60E-01	-0.028	7.00E-02	0.034	3.70E-02
Pappalysin-1	PAPPA	2	0.067	8.80E-04							
Thrombomodulin	TM	2	0.054	9.90E-03		-0.011	4.60E-01	-0.030	4.90E-02	0.057	3.90E-04
Lymphotactin	XCL1	2	0.065	2.30E-03		0.008	6.10E-01	-0.032	4.20E-02	0.009	5.60E-01
Carcinoembryonic antigenrelated cell adhesion molecule 8	CEACAM8	2	0.054	9.30E-03		0.005	7.20E-01	-0.049	1.50E-03	0.052	1.20E-03
P-selectin glycoprotein ligand 1	PSGL1	2	-0.068	1.60E-03		0.002	9.20E-01	-0.038	1.60E-02	-0.031	6.00E-02
Lipoprotein lipase	LPL	2	0.054	5.00E-03		-0.021	1.60E-01	-0.001	9.50E-01	0.074	5.60E-06

Osteoclast-associated immunoglobulin-like receptor	hOSCAR	2	0.079	1.50E-04	0.000	9.80E-01	-0.035	2.10E-02	0.047	2.80E-03
Leptin	LEP	2	-0.054	1.70E-03	0.024	1.10E-01	-0.094	1.40E-09	-0.025	1.20E-01
Tumor necrosis factor receptor superfamily member 14	TNFRSF14	3	0.072	5.10E-04	0.011	4.30E-01	-0.060	5.30E-05	0.058	2.00E-04
Integrin beta-2	ITGB2	3	0.075	3.30E-04	0.041	5.80E-03	0.005	7.40E-01	0.037	2.10E-02
Interleukin-2 receptor subunit alpha	IL2RA	3	0.065	1.90E-03	0.015	2.80E-01	-0.050	1.10E-03	0.077	9.80E-07
CD166 antigen	ALCAM	3	0.079	1.00E-04	-0.014	3.30E-01	0.006	6.90E-01	0.083	2.00E-07
Matrix extracellular phosphoglycoprotein	MEPE	3	0.080	9.70E-05	-0.006	6.90E-01	-0.019	2.30E-01	0.036	2.70E-02
Lymphotoxin-beta receptor	LTBR	3	0.070	7.90E-04	0.010	5.00E-01	-0.046	2.60E-03	0.055	5.00E-04
Neurogenic locus notch homolog protein 3	Notch3	3	0.053	7.20E-03	-0.008	5.50E-01	0.026	8.30E-02	-0.006	7.00E-01
Cadherin-5	CDH5	3	0.060	5.20E-03	-0.013	3.80E-01	0.029	6.70E-02	0.049	2.70E-03
Trem-like transcript 2 protein	TLT2	3	0.116	7.50E-08	-0.014	3.60E-01	-0.019	2.20E-01	0.033	4.10E-02
Transferrin receptor protein 1	STR	3	0.062	3.60E-03	-0.004	7.70E-01	-0.007	6.50E-01	0.037	2.10E-02
Azurocidin	AZU1	3	0.053	1.20E-02						
Myeloperoxidase	MPO	3	0.060	5.00E-03	0.029	5.00E-02	-0.050	1.60E-03	0.052	1.60E-03
Resistin	RETN	3	0.092	1.80E-05	0.025	7.90E-02	-0.056	2.70E-04	0.078	8.30E-07
Insulin-like growth factor-binding protein 1	IGFBP1	3	0.075	2.60E-04	-0.050	6.90E-04	0.062	6.50E-05	0.042	8.00E-03
Epithelial cell adhesion molecule	EpCAM	3	-0.075	4.90E-04	-0.002	8.90E-01	0.021	1.70E-01	-0.012	4.50E-01
Tyrosine-protein kinase receptor UFO	AXL	3	0.064	3.00E-03	0.016	2.90E-01	0.006	7.20E-01	0.044	6.50E-03
Interleukin-1 receptor type 1	IL1RT1	3	0.071	7.90E-04	-0.012	4.20E-01	-0.004	7.90E-01	0.080	6.70E-07
Myoglobin	MB	3	0.064	9.10E-04	0.003	8.50E-01	0.012	4.10E-01	0.059	1.70E-04
Myeloblastin	PRTN3	3	0.079	2.30E-04						
Urokinase plasminogen activator surface receptor	UPAR	3	0.067	5.40E-04	0.020	1.50E-01	-0.045	1.90E-03	0.067	8.30E-06
Osteopontin	OPN	3	0.067	1.40E-03	0.013	3.80E-01	-0.020	1.80E-01	0.022	1.70E-01
Peptidoglycan recognition protein 1	PGLYRP1	3	0.064	2.60E-03	0.027	6.20E-02	-0.032	3.80E-02	0.044	6.20E-03
Carboxypeptidase A1	CPA1	3	-0.061	4.20E-03	0.028	6.30E-02	-0.040	1.10E-02	-0.035	3.10E-02
Galectin-4	Gal4	3	-0.056	8.00E-03	-0.035	1.60E-02	-0.009	5.70E-01	-0.003	8.70E-01
Epidermal growth factor receptor	EGFR	3	-0.059	5.10E-03	0.005	7.40E-01	0.044	3.70E-03	-0.045	4.80E-03
Complement component C1q receptor	CD93	3	0.100	2.60E-06	-0.010	5.10E-01	0.020	2.00E-01	0.072	8.20E-06
Interleukin-18-binding protein	IL18BP	3	0.059	3.90E-03	0.002	8.60E-01	-0.050	8.90E-04	0.041	8.60E-03
Collagen alpha-1(I) chain	COL1A1	3	0.062	3.70E-03	-0.020	1.90E-01	0.014	3.60E-01	0.010	5.40E-01
Tumor necrosis factor receptor 1	TNFR1	3	0.058	4.20E-03	0.011	4.20E-01	-0.060	4.60E-05	0.033	3.10E-02

Insulin-like Growth Factor-Binding Protein 2	IGFBP2	3	0.078	1.40E-04		-0.019	1.80E-01	0.031	3.60E-02	0.039	1.30E-02

			Fast food and alcohol			**Western/traditional**		**Healthy**		**Light meal**	
Protein	Abbreviation	CVD Panel	*β*-estimate	*P*-value		*β*-estimate	*P*-value	*β*-estimate	*P*-value	*β*-estimate	*P*-value
Brother of CDO	ProteinBOC	2	-0.073	7.20E-04		-0.050	8.30E-04	0.019	2.20E-01	0.065	6.20E-05
Stem cell factor	SCF	2	-0.065	2.60E-03		-0.009	5.50E-01	-0.001	9.50E-01	0.043	7.80E-03
V-set and immunoglobulin domain-containing protein 2	VSIG2	2	-0.068	1.40E-03		-0.057	8.20E-05	-0.021	1.60E-01	0.053	8.90E-04
Decorin	DCN	2	-0.075	2.80E-04		-0.015	2.70E-01	-0.029	4.60E-02	0.001	9.30E-01
Programmed cell death 1 ligand 2	PDL2	2	-0.086	8.00E-05		-0.020	1.70E-01	-0.019	2.20E-01	0.056	5.20E-04
Scavenger receptor cysteine-rich type 1 protein M130	CD163	3	-0.068	1.80E-03		0.002	9.00E-01	-0.013	4.20E-01	0.047	3.20E-03
Galectin-3	Gal3	3	-0.085	5.50E-05		-0.001	9.40E-01	-0.010	5.00E-01	0.050	1.70E-03
Contactin-1	CNTN1	3	-0.062	2.50E-03		-0.040	6.90E-03	0.055	4.60E-04	0.027	1.00E-01
Insulin-like growth factor-binding protein 1	IGFBP1	3	-0.074	4.30E-04		-0.050	6.90E-04	0.062	6.50E-05	0.042	8.00E-03
Kallikrein-6	KLK6	3	-0.076	5.40E-04							

	Postive association Epihealth
	Negative association Epihealth
	Not quantified in SMCC.
	Replicated in SMCC, *P*<0.05
	Were not replicated in SMCC at all, *P*>0.05

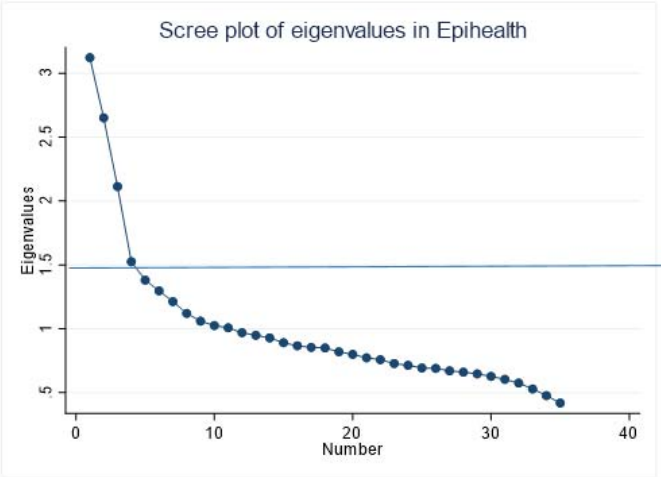
Covariates in Epihealth were age physical activity, educational level, smoking status. Covariates in SMCC were age, physical activity, educational level, smoking status, chip nos and phase (Model 1).

Table S5. Information on the functions and the biological processes of the 21 validated plasma proteins. Found in the table is also the direction (+/-) of the association between the PCA generated dietary patterns and protein biomarker in SMCC.

Protein	Dietary pattern in SMCC Direction of association			Functions	Biological process	Ref.
	Western/ traditional	Healthy	Light meal			
SPON-2		-		Is also known as mindin and is critical for inflammatory cell recruitment in vivo by acting as a ligand for intergrins. Is part of the innate immune response in response to microbial pathogens	Inflammation and immune response	(1, 2)
FST		-		FST is a multifunctional regulatory protein with the primary function to neutralize actions of activins, influencing the inflammation and subsequent tissue damage	Inflammation	(3)
MMP-7		-		MMP-7 is an enzyme that regulate cell-matrix composition. Part of the cascade reactions following atherosclerotic tissue destruction and upregulated during inflammation.	Inflammation	(4, 5)
PON-3		+		Predominantly expressed in the liver, released to the circulation where it binds to HDL particles. Is found in atherosclerotic lesions and animal studies have shown that PON3 possesses protective properties against both atherogenesis and adiposity.	Inflammation	(6)
Gal4	-			One of several galactoside-binding proteins and may play a role for intestinal inflammation and cancer development.	Inflammation Cell adhesion	(7)
TRAIL-R2			-	TRAIL-R2 is one of several known tumour necrosis factor receptors which are ubiquitously expressed.	Inflammation and immune response	(8)
MPO		-	+	A pro-oxidant enzyme that may promote plaque formation and rupture.	Inflammation	(9, 10)
RETN		-	+	A pro-inflammatory adipokine, is involved in pathways of adiposity, insulin resistance and inflammation.	Metabolism Inflammation	(11-14)

IL1RT1			+	IL1R-T1 is one of two isoforms of the IL-1 receptor which regulates IL-1 activity. IL-1 is a cytokine which has pro-inflammatory effects.	Inflammation	(15)
U-PAR			+	Reflects increased inflammation and is positively correlated with pro-inflammatory biomarkers, such as CRP.	Inflammation Coagulation	(16)
TM			+	A biomarker of endothelial dysfunction that has been negatively associated with a healthier diet.	Platelet activation	(17, 18)
CEACAM8			+	Is part of the innate immune system and has been shown to inhibit the Toll-like receptor 2 immune response together with CEACAM1	Immune response	(19)
LPL			+	Plays a critical role in lipid metabolism and transport by catalyzing the rate-limiting step in the hydrolysis of triglycerides of circulating chylomicrons and VLDL.	Lipid metabolism	(20)
IL2RA			+	IL2RA is one subunit of the IL2-receptor and is involved in immune response.(15)	Immune system	(21)
ALCAM			+	Is a member of the immunoglobulin superfamily.	Immune system	(22)
CPA-1			-	Is a digestive carboxypeptidases, which are pancreatic metalloproteases that hydrolyze dietary polypeptide chains.	Metabolism	(23)
EGFR			-	Is a member of the receptor tyrosine kinase family and have together with its ligands been detected in atherosclerotic plaques. Myeloid EGFR deficiency was reported to be protective, both in early and late stages of atherosclerosis development.	Cell adhesion	(24)
ProteinBOC	-			Is part of a cell-surface receptor complex mediating cell to cell interactions between muscle precursor cells.	Promotes differentiation of myogenic cells	(25)
VSIG2	-			Not much is known about this protein. One SNP (rs112219769) demonstrated association in patients with Systemic lupus erythematosus		(26)
CNTN1	-			Is a neural adhesion protein.	Cell adhesion Metabolism	(27)
IGFBP-1	-			Regulates insulin-like growth factors and may promote cell migration. May have biological actions independent of insulin-like growth factors.	Metabolism	(28)

Figure S1. Scree plots of eigenvalues in Epihealth and SMCC.



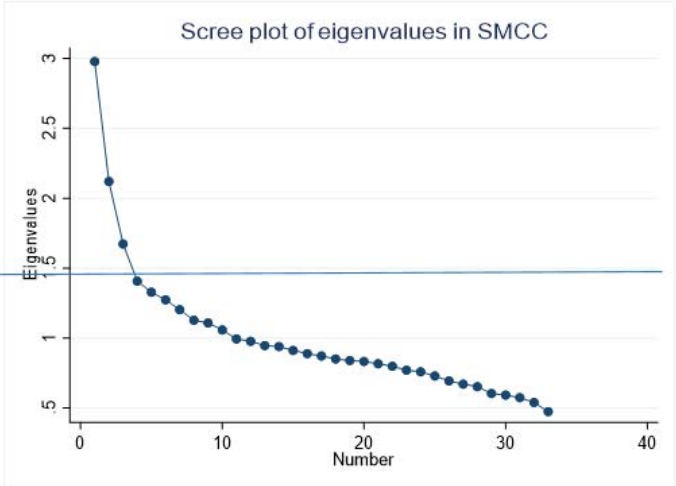
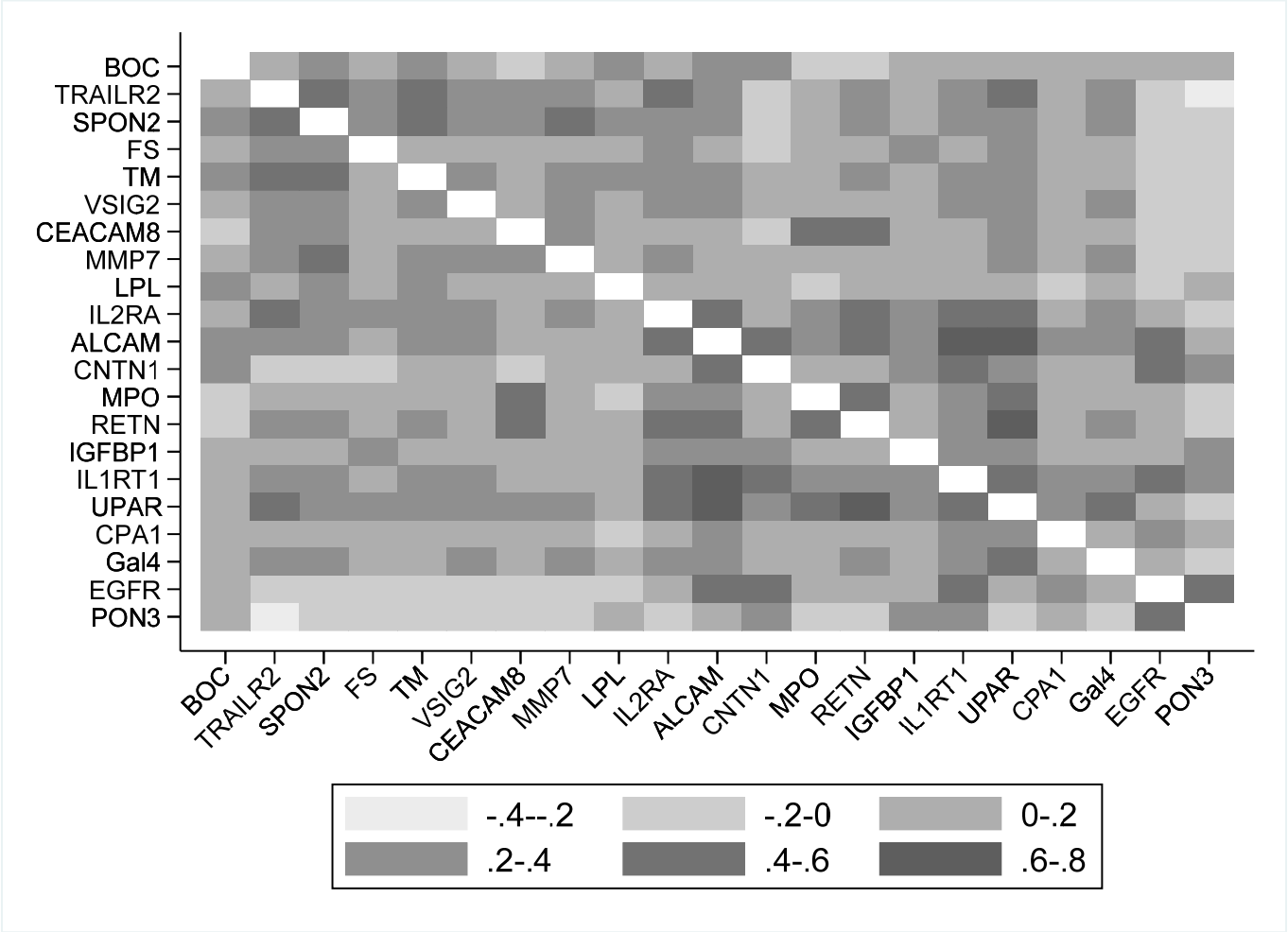


Figure S2. Correlation matrix between the 21 validated proteins in the Swedish Mammography Cohort Clinical. The magnitude of the correlations (r) is depicted by the different shadings as indicated in the figure legend. The abbreviations of proteins are explained in Table S1.



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