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 (n=20,817 men and women) and the SMCC (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 SMCC. 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 SMCC, with effect estimates ranging from 0.057 to 0.083 (P-value range, 5.0 × 10⁻²−1.4 × 10⁻³) 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.

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. Healthy dietary patterns emphasized in CVD prevention, including the recommendations of the American Heart Association, 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. 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, 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.

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 sets 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. 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. 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, 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 (D2 and D3). 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 proteins, respectively. Two of the proteins were associated with any proteins, and the Western/traditional pattern, myeloperoxidase and paraoxonase 3). Of the 44 Western/traditional pattern–protein associations discovered in EpiHealth were replicated in the SMCC (spindin-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
| Component Loadings for the Dietary Patterns Generated Through PCA in the EpiHealth and the SMCC | EpiHealth | Dairy and Sandwich | Western/Traditional | Fast Food/Alcohol | SMCC | 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* | 0.1203* | −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 |
| Meat | −0.0502 | 0.2304* | −0.0310 | 0.0331 | 0.1526* | 0.1876* | −0.0648 |
| 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* | 0.1876* | −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 | 0.3050 | 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 | 0.0533 | −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 | −0.3538 |
| Light beer | 0.0993 | 0.0193 | 0.0753 | 0.0993 | 0.0193 | 0.0753 | 0.0993 |
| 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.

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|          | EpiHealth | Women | Low | Middle | High | SMCC  | Women | Low | Middle | High |
|----------|-----------|-------|-----|--------|------|-------|-------|-----|--------|------|
| Tertiles of the Healthy Pattern | | | | | | | | | | |
| No. of individuals | 484 | 387 | 373 | 1510 | 1520 | 1530 | 11 | 12 | 13 | 14 |
| Age, y | 63 (8) | 60 (9) | 61 (8) | 68 (6.8) | 67 (6.7) | 67 (6.4) | 68 (6.8) | 68 (6.7) | 67 (6.4) | 68 (6.8) |
| HDL cholesterol, mmol/L | 1.3 (0.3) | 1.4 (0.3) | 1.6 (0.4) | 1.7 (0.4) | 1.8 (0.4) | 1.6 (0.4) | 1.7 (0.4) | 1.6 (0.4) | 1.6 (0.4) | 1.7 (0.4) |
| LDL cholesterol, mmol/L | 3.8 (1.0) | 3.9 (1.0) | 4.0 (1.0) | 4.0 (1.0) | 4.0 (1.0) | 4.0 (1.0) | 3.6 (1.0) | 3.6 (1.0) | 3.6 (1.0) | 3.6 (1.0) |
| BMI, kg/m² | 26 (3) | 27 (3) | 26 (4) | 26 (4) | 26 (4) | 26 (4) | 26 (4) | 26 (4) | 26 (4) | 26 (4) |
| Body fat percentage, % | 36 (7) | 37 (8) | 38 (7) | 38 (7) | 39 (7) | 38 (7) | 37 (8) | 37 (8) | 38 (7) | 37 (8) |
| Total vitamin D, nmol/L | 57 (17) | 58 (17) | 60 (19) | 60 (19) | 60 (19) | 60 (19) | 60 (19) | 60 (19) | 60 (19) | 60 (19) |
| Cystatin C, mg/L | 0.98 (0.33) | 0.93 (0.22) | 0.88 (0.19) | 0.88 (0.19) | 0.88 (0.19) | 0.88 (0.19) | 0.88 (0.19) | 0.88 (0.19) | 0.88 (0.19) | 0.88 (0.19) |
| ALAT, lkat/L | 0.24 (0.28) | 0.23 (0.13) | 0.23 (0.13) | 0.23 (0.13) | 0.23 (0.13) | 0.23 (0.13) | 0.23 (0.13) | 0.23 (0.13) | 0.23 (0.13) | 0.23 (0.13) |
| Systolic blood pressure, mm Hg | 139 (17) | 136 (16) | 137 (18) | 136 (18) | 134 (18) | 131 (19) | 134 (19) | 133 (19) | 133 (19) | 133 (19) |
| Diastolic blood pressure, mm Hg | 85 (10) | 85 (9) | 85 (9) | 83 (9) | 83 (9) | 81 (9) | 77 (9) | 78 (9) | 78 (9) | 78 (9) |
| History of diabetes, % | 1.0 | 0.2 | 2.4 | 2.1 | 1.1 | 0.4 | 0.1 | 0.1 | 0.1 | 0.1 |
| History of stroke, %* | 2.5 | 1.3 | 1.8 | 0.4 | 0.5 | 0.2 | 0.1 | 0.1 | 0.1 | 0.1 |
| ≥12 y of schooling, % | 28 | 45 | 58 | 30 | 42 | 30 | 57 | 42 | 30 | 42 |
| Current smokers, % | 9 | 7 | 7 | 4 | 5 | 6 | 8 | 6 | 8 | 6 |
| 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) | 4.4 (1.2) | 4.0 (1.6) | 4.4 (1.2) |
| Fish‡ | 1.0 (0.8) | 1.2 (0.8) | 1.2 (0.8) | 1.2 (0.8) | 1.2 (0.8) | 1.2 (0.8) | 1.2 (0.8) | 1.2 (0.8) | 1.2 (0.8) | 1.2 (0.8) |
| Whole grain‡ | 0.2 (0.2) | 0.3 (0.3) | 0.5 (0.3) | 0.2 (0.2) | 0.3 (0.3) | 0.5 (0.3) | 0.2 (0.2) | 0.3 (0.3) | 0.5 (0.3) | 0.2 (0.2) |
| Energy intake, kcal/d | 1814 (616) | 1955 (548) | 2281 (725) | 1356 (509) | 1579 (519) | 1824 (587) | 1487 (380) | 1733 (380) | 2171 (479) | 2701 (537) |
| Fiber, g/d | 20 (5) | 21 (5) | 23 (6) | 19 (6) | 21 (5) | 22 (5) | 19 (6) | 21 (5) | 22 (5) | 19 (6) |
| PUFA, g/d | 11 (3) | 12 (3) | 13 (3) | 10 (2) | 11 (3) | 12 (3) | 7 (2) | 9 (2) | 11 (4) | 13 (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.
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.

**Figure 1.** \( \beta \) 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, \( \beta \) 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.
Table 3. Fully Adjusted β Estimates and P Values for the Linear Association Between Dietary Patterns and Proteins That Were Replicated in the SMCC

| Protein | EpiHealth | SMCC | Western/Traditional | Healthy | Light Meal |
|---------|-----------|------|---------------------|---------|------------|
|         | β Estimate | P Value | β Estimate | P Value | β Estimate | P Value | β Estimate | P Value |
| Healthy | -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 | 0.060 | 2.00e-03 | ... | ... | -0.039 | 1.6e-02 | ... | ... |
| Gal-4 | -0.056 | 8.00e-03 | -0.039 | 2.0e-02 | ... | ... | ... | ... |
| TRAIL-R2 | 0.060 | 5.00e-03 | ... | ... | -0.061 | 2.2e-03 | 0.046 | 9.0e-03 |
| Myeloperoxidase | 0.092 | 1.80e-05 | ... | ... | -0.044 | 1.6e-02 | 0.058 | 2.7e-04 |
| Resistin | 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 | 0.073 | 7.20e-04 | -0.072 | 3.2e-05 | ... | ... | ... | ... |
| Protein BOC | -0.068 | 1.40e-03 | -0.071 | 1.4e-05 | ... | ... | ... | ... |
| VSIG2 | -0.062 | 2.50e-03 | -0.057 | 1.0e-03 | ... | ... | ... | ... |
| Contactin-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 (D2 and D3). 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 models27 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 stenosis29 and incident type 2 diabetes mellitus.28 There is not much evidence about the potential role of either brother of CDO30 or V-set and immunoglobulin domain–containing protein 2.31 In the FHS (Framingham Heart Study), contactin-1 was inversely

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**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.\(^\text{52}\)

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.\(^\text{33}\) CEACAM8\(^\text{34}\) and IL2RA\(^\text{35}\) have been involved in the immune responses, and LPL plays a critical role in lipid metabolism and its transport.\(^\text{36}\)

Higher circulating serum levels of ALCAM have been observed in patients with type 2 diabetes mellitus,\(^\text{37}\) 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.\(^\text{38}\) Expression of UPAR also reflects increased inflammation and has been presented as a new emerging biomarker for CVD and critical illness.\(^\text{39}\) 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.\(^\text{40}\) 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\(^\text{41}\); and TRAIL-R2 predicted major cardiovascular events in type 2 diabetic patients.\(^\text{42}\)

**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.\(^\text{10}\) 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,\(^\text{43}\) or separate food groups and do not take the full complexity of the food matrix into account.\(^\text{44}\) 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\(^\text{45,46}\) as well as in the mother study of SMCC.\(^\text{15,47}\) 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.\(^\text{48}\) In this study, dietary patterns and ethnicity were associated with high-abundance plasma protein groups of 54 proteins involved in inflammation and lipid metabolism.\(^\text{48}\) 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.\(^\text{18}\) 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 ($r=0.51$),\(^\text{15}\) 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\(^\text{19}\) 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 Michäelsson designed the research. All authors were involved in conducting the research. Warensjö Lemming and Statin 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.

References
1. Forouzanfar MH, Alexander L, Anderson HR, Bachman VF, Biryukov S, Brauer M, et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;386:2287–2323.
2. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, Lee IM, Lichtenstein AH, Lorin CM, Miller BE, Nonas CA, Sacks FM, Smith SC Jr, Svetkey LP, Wadden TA, Yanovski SZ, Kendal KA, Morgan LC, Trigatti ML, Velasco G, Wex J, Anderson JL, Halperin JL, Albert NM, Bozko B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Selike FW, Shen WK, Smith SC Jr, Tomsenell LF. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S76–S99.
3. Nordic Nutrition Recommendations 2012. 2014. Nordic Council of Ministers, Copenhagen, Denmark. Available at: https://www.norden.diva-portal.org/smash/get/diva2:704251/FULLTEXT01.pdf. Accessed December 21, 2018.
4. 2015–2020 dietary guidelines for Americans. 2015. U.S. Department of Health and Human Services and U.S. Department of Agriculture. Available at: https://health.gov/dietaryguidelines/2015/guidelines/. Accessed December 21, 2018.
5. Mica R, Penalo JL, Cudheya F, Imamura F, Rehm CD, Mozaffarian D. Association between dietary factors and mortality from heart disease, stroke, and type 2 diabetes in the United States. JAMA. 2017;317:912–924.
6. Barnett M, Young W, Cooney J, Roy N. Metabolomics and proteomics, and what to do with all these “Omes”: insights from Nutrigenomic Investigations in New Zealand. J Nutrigenet Nutrigenomics. 2014;7:274–282.
7. Jenab M, Slimani N, Bictash M, Ferrari P, Bingham SA. Biomarkers in nutritional epidemiology: applications, needs and new horizons. Hum Genet. 2009;125:507–525.
8. Celis-Morales C, Livingstone KM, Marsaux CF, Macready AL, Fallaize R, O’Donovan CB, Woolhead C, Forster H, Walsh MC, Navas-Carretero J, San-Cristobal M, Tsirigoti L, Lambriniou CP, Mavrogiovanni C, Moschenh G, Kolossa S, Hallmann J, Godlewksa M, Survillo A, Traczyk I, Drevon CA, Bouwman J, van Oommen B, Grimaldi K, Farnell LD, Matthews JN, Manios Y, Daniel H, Martinez JA, Lovegrove JA, Gibney ER, Brennan L, Saris WH, Gibney M, Mathers JC. Food4Me Study. Effect of personalized nutrition on health-related behaviour change: evidence from the Food4Me European randomized controlled trial. Int J Epidemiol. 2017;46:578–588.
9. Libby P. Inflammatory mechanisms: the molecular basis of inflammation and disease. Nutr Rev. 2007;65:S140–S146.
10. Houston M, Munich D, Sinatra ST, Kahn JK, Guerrieri M. Recent science and clinical application of nutrition to coronary heart disease. J Am Coll Nutr. 2018;37:169–187.
11. Cervantes Gracia K, Llanas-Cornejo D, Huih J. CVD and oxidative stress. J Clin Med. 2016;5:82.
12. Ahmad S, Mowry MV, Demler OV, Hu FB, Ridker PM, Chasman DI, Mora S. Assessment of risk factors and biomarkers associated with risk of cardiovascular disease among women consuming a Mediterranean diet. JAMA Intern Med. 2018;1:165708.
13. Lind L, Elmstahl S, Bergman E, Englund M, Lindberg E, Michäelsson K, Nilsson PM, Sundstrom J. EpiHealth: a large population-based cohort study for investigation of gene-lifestyle interactions in the pathogenesis of common diseases. Eur J Epidemiol. 2013;28:169–197.
14. Almqvist C, Adami H-O, Franks PW, Groop L, Ingelsson E, Kere J, Lissner L, Palmberg P, Pershagen G, Ploner A, Sullivan PF, Tybring G, Pedersen NL. LifeGene—a large prospective population-based study of global relevance. Eur J Epidemiol. 2011;26:67–77.
15. Warensjö Lemming E, Byberg L, Melhus H, Wolk A, Michäelsson K. Long-term a posteriori dietary patterns and risk of hip fractures in a cohort of women. Eur J Epidemiol. 2017;32:605–616.
16. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. Am J Clin Nutr. 1997;65:12205–12283; discussion 12295–12313.
17. Charlson ME, Pompei P, Alex KL, Mackenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373–383.
18. Assarsson E, Lundberg M, Holmquist B, Bjørksten J, Thorsen SB, Ekman D, Eriksson A, Renel Dickens E, Ohlsson S, Edelfeldt G, Andersson AC, Lindstedt:
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P. Stenvang J, Gullberg M, Fredriksson S. Homogenous 96-plex PEA immunoassay exhibiting high sensitivity, specificity, and excellent scalability. PloS One. 2014;9:e95192.

19. Newson R. Multiple-test procedures and smile plots. Stata J. 2003;3:109–132.

20. Ganna A, Lee D, Ingelsson E, Pawitan Y. Redundancy rate estimation for assessing the validation of significant findings in high-throughput studies. Brief Bioinform. 2015;16:563–575.

21. Brennan ML, Penn MS, Van Lente F, Nambi V, Shishhebhor MH, Aviles RJ, Goorman M, Pepoy ML, McElrane ES, Topal EJ, Nissen SE, Hazen SL. Prognostic value of myeloperoxidase in patients with chest pain. N Engl J Med. 2003;349:1595–1604.

22. Fontana A, Spadaro S, Copetti M, Spoto B, Salvenini L, Pizzini P, Fritztta L, Mallamaci F, Pellegrini F, Trischitta V, Menzaghi C. Association between resistin levels and all-cause and cardiovascular mortality; a new study and a systematic review and meta-analysis. PloS One. 2015;10:e0120419.

23. Harisl CL, Frohlich JJ, Hill JS. Myeloperoxidase and C-reactive protein have combined utility for long-term prediction of cardiovascular mortality after coronary angiography. J Am Coll Cardiol. 2010;55:1102–1109.

24. Gencer B, Au er R, de Rekeneire N, Bauer DC, Kitcheva SB, Mijovic I, Vittinghoff E, Harris T, Rodondi N. Association between resistin levels and cardiovascular disease events in older adults: the Health, Aging and Body Composition study. Atherosclerosis. 2016;255:181–186.

25. Tuomainen AM, Korni M, Havulinna AS, Tervahartiala T, Salomaa V, Sorsa T, Pussinen PJ. Serum tissue-degrading proteases and incident cardiovascular disease events. Eur J Prev Cardiol. 2014;21:806–812.

26. Skau E, Henriksen E, Wagner P, Hedberg P, Siegbahn A, Leppert J. GDF-15 and TRAIL-R2 are powerful predictors of long-term mortality in patients with acute myocardial infarction. Eur J Prev Cardiol. 2017;24:1576–1583.

27. Chistiakov DA, Melnichenko AA, Orekhov AN, Bobryshev YV. Paraoxonase 2 activity is associated with distinct plasma proteomic groups. J Mol Med (Berl). 2015;93:647–657.

28. Skarl K, Vittorio E, Carvajal R, Ziegler C, Ganna A, de Rekeneire N, Patel L, Berenson G, Johnson C. Comparison of serum resistin levels and cardiovascular disease events in older adults: the Health, Aging and Body Composition study. Atherosclerosis. 2016;255:181–186.

29. Ljungberg J, Janiec M, Bergdahl IA, Holmgren A, Hultdin J, Johansson B, Naslund P, Stenvang J, Gullberg M, Fredriksson S. Homogenous 96-plex PEA immunoassay exhibiting high sensitivity, speci

30. Oufella H. Selective EGFR (epidermal growth factor receptor) deletion in myocardial infarction. Eur J Prev Cardiol. 2014;21:806–812.

31. Kariuki SN, Franek BS, Kumar MA, El-Sohemy A. Dietary patterns and ethnicity are associated with distinct plasma proteomic groups. J Mol Med (Berl). 2015;93:647–657.

32. Ho JE, Lyass A, Courchesne P, Chen G, Liu C, Yin X, Wang SJ, Massaro JM, Larson MG, Levy D. Protein biomarkers of cardiovascular disease and mortality in the community. J Am Heart Assoc. 2018;7:e008108. DOI: 10.1161/JAHA.117.008108.

33. van Bussel BC, Henrick M, Schreiber F, Binding-Liermann R, Berrocal-Almanza LC, Heyl KA, Muller MM, Weimann A, Zweigner J, Slevogt H. Soluble CEACAM8 interacts with CEACAM1 inhibiting TLR2-triggered immune responses. PloS One. 2014;9:e94106.

34. Boyaso B, Sprent J. The role of interleukin-2 during homeostasis and activation of the immune system. Nat Rev Immunol. 2012;12:180–190.

35. Mead JR, Irvine SA, Ranji DP. Lipoprotein lipase: structure, function, regulation, and role in disease. J Mol Med (Berl). 2002;80:753–769.

36. Sulaj A, Grone E, Schleicher E, Haring HU, Schwenger V, Herzig S, Fleming T, Nawroth PP, van Bauer R. ALCAM a novel biomarker in patients with type 2 diabetes mellitus complicated with diabetic nephropathy. J Diabetes Complications. 2017;31:1058–1065.

37. Banerjee M, Saxena M. Interleukin-1 (IL-1) family of cytokines: role in type 2 diabetes. Clin Chim Acta. 2012;413:1163–1170.

38. Cyrille NB, Villablanca PA, Ramakrishna H. Soluble urokinase plasminogen activation receptor—an emerging new biomarker of cardiovascular disease and critical illness. Ann Card Anaesth. 2016;19:214–216.

39. Zeboudj L, Giraud A, Guyonnet L, Zhang Y, Laurans L, Esposito B, Villar J, Chipot A, Papac-Milicic N, Binder C, Tedgui A, Malitza Z, Tharaux PL, Alt-Oufella H. Selective EGFR (epidermal growth factor receptor) deletion in myeloid cells limits atherosclerosis: brief report. Arterioscler Thromb Vasc Biol. 2018;38:114–119.

40. Sternow M, Nowak C, Byberg L, Sundstrom J, Giedraitis V, Lind L, Ingelsson E, Fall T, Arnlov J. Circulating proteins as predictors of incident heart failure in the elderly. Eur J Heart Fail. 2015;18:35–42.

41. Nowak C, Carlsson AC, Oftgren C, Nystrom FH, Alam M, Feldreich T, Sundstrom J, Carrero JJ, Leppert J, Hedberg P, Henriksen E, Cordeiro AC, Giedraitis V, Lind L, Ingelsson E, Fall T, Arnlov J. Multiplex proteomics for prediction of major cardiovascular events in type 2 diabetes. Diabetesologia. 2016;59:1748–1757.

42. Wajiers PMCM, Feskenz EJ, Ocké MC. A critical review of predefined diet quality scores. Br J Nutr. 2007;97:219–231.

43. Tapsell LC, Neale EP, Satija A, Hu FB. Foods, nutrients, and dietary patterns: interconnections and implications for dietary guidelines. Adv Nutr. 2010;4:45–45.

44. Ax E, Warensjo Lemming E, Becker W, Andersson A, Lindroos AK, Cederholm T, Spigren P, Fung TT. Dietary patterns in Swedish adults: results from a national dietary survey. Br J Nutr. 2016;115:95–104.

45. Ericson U, Brunkwall L, Alves Dias J, Drake I, Hellstrand S, Gullberg B, Sonestedt E, Nilsson PM, Wirfalt E, Ortho-Melander M. Food patterns in relation to weight change and incidence of type 2 diabetes, coronary events and stroke in the Malmo Diet and Cancer cohort. Eur J Nutr. 2018. DOI: 10.1007/s00394-018-1727-9. Available at: https://link.springer.com/article/10.1007%2Fs00394-018-1727-9. Accessed May 25, 2019.

46. Newby PK, Weismayer A, Akesson A, Tucker KL, Wolk A. Long-term stability of food patterns identified by use of factor analysis among Swedish women. J Nutr. 2006;136:626–633.

47. Garcia-Bailo B, Brenner DR, Nielsen D, Lee HJ, Domanski D, Kuzyk M, Borchers CH, Badawi A, Domanski D, Kuzyk M, Borchers CH, Badawi A, Domanski D. Critical illness. Eur J Clin Nutr. 2010;74:633.

48. Ho JE, Lyass A, Courchesne P, Chen G, Liu C, Yin X, Wang SJ, Massaro JM, Larson MG, Levy D. Protein biomarkers of cardiovascular disease and mortality in the community. J Am Heart Assoc. 2018;7:e008108. DOI: 10.1161/JAHA.117.008108.

49. van Bussel BC, Henry RM, Ferreira I, van Greevenbroek MM, van der Kallen CJ, Twisk JW, Feskens EJ, Schalkwijk CG, Stehouwer CD. A healthy diet is associated with less endothelial dysfunction and less low-grade inflammation over a 7-year period in adults at risk of cardiovascular disease. J Nutr. 2015;145:532–540.

50. Singer BB, Opp L, Heinrich A, Schreiber F, Binding-Liermann R, Berrocal-Almanza LC, Heyl KA, Muller MM, Weimann A, Zweigner J, Slevogt H. Soluble CEACAM8 interacts with CEACAM1 inhibiting TLR2-triggered immune responses. PloS One. 2014;9:e94106.
Supplemental Material
Table S1. The protein biomarkers included in the CVD2 and CVD3 assay panels are depicted.

| CVD 2                                   | Abbreviation | CVD 3                                   | 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 chemokine 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** |
| Molecule Name                                      | Gene Symbol | Protein Description                          | Protein Description Refs |
|---------------------------------------------------|-------------|----------------------------------------------|--------------------------|
| 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         | Plasminogen activator inhibitor 1            | PAI                      |
| Programmed cell death 1 ligand 2                  | PD-L2       | Proprotein convertase subtilisin/kexin type 9| PCSK9                    |
| Polymeric immunoglobulin receptor                 | PIlgR       | Platelet-derived growth factor subunit A     | PDGF subunit A           |
| Placenta growth factor                            | PIGF        | 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                      |
| Prostasain                                        | 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                  |
| Protein Name                                                                 | Gene Symbol | Description                                                                 | Protein Symbol |
|----------------------------------------------------------------------------|-------------|-------------------------------------------------------------------------------|----------------|
| 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 CVD2 | CVD 3         | SMCC CVD2 | CVD 3         |
|---------------|--------------|-----------|--------------|
| BNP           | NT-ProBNP    | ITGB1BP2  | AZU1         |
| CA5A          | CA5A         | BNP       | PI3          |
| SLAMF7        | IL4RA        | PARP1     | PAPP9        |
| IgGFcceptorIib| IL4RA        | PAPP9     | 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.

| Protein | Healthy β-estimate | Healthy P-value | Dairy and sandwich β-estimate | Dairy and sandwich P-value | Western/ Traditional β-estimate | Western/ Traditional P-value | Fast food and alcohol β-estimate | Fast food and alcohol 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                      |
| PIGF    | -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                      |
| Gene   | Value1 | Value2    | Value3 | Value4 | Value5 | Value6 | Value7 | Value8 | Value9 |
|--------|--------|-----------|--------|--------|--------|--------|--------|--------|--------|
| 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|
| PlgR   | -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|
| DECR12 | -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|
| Gene     | Value1 | Value2 | Value3 | Value4 | Value5 | Value6 | Value7 |
|----------|--------|--------|--------|--------|--------|--------|--------|
| 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 |
| ITG1BP2  | -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 |
| Gene          | Fold Change | log2 Fold Change | p-value | log2 Fold Change | p-value |
|--------------|-------------|------------------|---------|-----------------|---------|
| VEGFD        | 0.030       | -0.008           | 7.10E-01| -0.018          | 3.80E-01|
| PARP1        | -0.029      | 2.10E-01         | 8.20E-01| 0.010           | 6.50E-01|
| HAOX1        | -0.035      | 1.20E-01         | 5.20E-01| -0.046          | 3.10E-02|
| TNFRSF14     | -0.021      | 3.50E-01         | 8.80E-01| 0.072           | 5.10E-04|
| LDLreceptor  | -0.050      | 2.60E-02         | 8.40E-01| 0.022           | 3.00E-01|
| ITGB2        | 0.003       | 9.00E-01         | 8.80E-02| 0.075           | 3.30E-04|
| IL17RA       | 0.024       | 3.00E-01         | 6.40E-02| -0.008          | 7.00E-01|
| TNFR2        | -0.014      | 5.10E-01         | 4.60E-01| 0.030           | 1.50E-01|
| MMP9         | -0.053      | 1.70E-02         | 3.50E-01| 0.007           | 7.50E-01|
| EPHB4        | -0.010      | 6.60E-01         | 8.20E-01| 0.053           | 1.30E-02|
| IL2RA        | -0.014      | 5.20E-01         | 8.00E-01| 0.065           | 1.90E-03|
| OPG          | -0.020      | 3.40E-01         | 1.60E-01| 0.023           | 2.40E-01|
| ALCAM        | 0.021       | 3.40E-01         | 2.40E-02| 0.079           | 1.00E-04|
| TFF3         | -0.013      | 5.60E-01         | 3.90E-01| 0.008           | 7.10E-01|
| SELP         | -0.014      | 5.20E-01         | 5.70E-01| 0.015           | 4.80E-01|
| CSTB         | 0.006       | 7.90E-01         | 6.50E-01| 0.012           | 5.50E-01|
| MCP1         | -0.024      | 2.80E-01         | 5.60E-01| 0.044           | 3.50E-02|
| CD163        | 0.018       | 4.40E-01         | 7.10E-01| 0.010           | 6.50E-01|
| Gal3         | 0.026       | 2.30E-01         | 5.40E-01| 0.015           | 4.70E-01|
| GRN          | 0.007       | 7.70E-01         | 9.70E-01| -0.026          | 2.30E-01|
| MEPE         | -0.014      | 5.30E-01         | 2.20E-01| 0.080           | 9.70E-05|
| BLHydrolase  | -0.007      | 7.50E-01         | 2.90E-01| 0.019           | 3.80E-01|
| PLC          | -0.008      | 7.00E-01         | 4.90E-01| 0.051           | 1.30E-02|
| LTBR         | -0.038      | 8.90E-02         | 5.20E-01| 0.070           | 7.90E-04|
| Notch3       | 0.023       | 2.80E-01         | 2.80E-01| 0.053           | 7.20E-03|
| TIMP4        | 0.014       | 5.20E-01         | 7.30E-01| 0.022           | 2.80E-01|
| CNTN1        | 0.051       | 1.60E-02         | 4.00E-03| 0.005           | 8.20E-01|
| CDH5         | 0.029       | 2.00E-01         | 1.10E-01| 0.060           | 5.20E-03|
| TLT2         | -0.024      | 3.10E-01         | 1.40E-01| 0.116           | 7.50E-08|
| FABP4        | -0.003      | 9.00E-01         | 8.90E-01| -0.032          | 9.00E-02|
| Gene     | TFPI   | PAI    | CCL24  | TR     | TNFRSF10C | SGDF15 | SELE   | AZU1   | DLK1   | SPON1  | MPO    | CXCL16 | IL6RA  | RETN   | IGF1BP1| CHIT1  | TRAP   | CCL22  | PSPD   | PI3    | EpCAM  | APN    | AXL    | IL1RT1 | MMP2   | FAS    | MB     | TNFSF13B | PRTN3 | PCSK9  |
|----------|--------|--------|--------|--------|-----------|---------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
|          | -0.002 | 9.20E-01 | 0.022  | 3.20E-01 | 0.010  | 6.30E-01 | 0.020  | 3.60E-01 |
| TFPI     | -0.043 | 5.80E-02 | 0.019  | 4.00E-01 | -0.026 | 2.20E-01 | 0.032  | 1.50E-01 |
| PAI      | 0.016  | 4.80E-01 | -0.006 | 7.90E-01 | 0.006  | 7.70E-01 | 0.030  | 1.70E-01 |
| CCL24    | -0.003 | 8.90E-01 | 0.033  | 1.40E-01 | 0.062  | 3.60E-03 | -0.062 | 4.80E-03 |
| TR       | -0.035 | 1.20E-01 | 0.052  | 1.90E-02 | 0.049  | 2.00E-02 | -0.021 | 3.40E-01 |
| TNFRSF10C| -0.012 | 5.20E-01 | -0.018 | 3.10E-01 | 0.014  | 4.30E-01 | -0.021 | 2.50E-01 |
| SGDF15   | -0.035 | 1.20E-01 | 0.005  | 8.10E-01 | -0.010 | 6.30E-01 | -0.001 | 9.70E-01 |
| SELE     | -0.050 | 2.70E-02 | 0.018  | 4.30E-01 | 0.053  | 1.20E-02 | -0.022 | 3.10E-01 |
| AZU1     | 0.046  | 4.30E-02 | 0.041  | 6.10E-02 | 0.045  | 3.20E-02 | -0.055 | 1.10E-02 |
| DLK1     | 0.003  | 8.70E-01 | 0.028  | 1.90E-01 | 0.026  | 2.10E-01 | -0.013 | 5.50E-01 |
| SPON1    | -0.047 | 3.80E-02 | 0.037  | 1.00E-01 | 0.060  | 5.00E-03 | -0.045 | 4.20E-02 |
| MPO      | 0.001  | 9.80E-01 | -0.002 | 9.30E-01 | 0.000  | 9.80E-01 | -0.021 | 3.40E-01 |
| CXCL16   | -0.002 | 9.30E-01 | -0.004 | 8.70E-01 | -0.013 | 5.30E-01 | 0.010  | 6.50E-01 |
| IL6RA    | -0.037 | 1.10E-01 | 0.039  | 8.00E-02 | 0.092  | 1.80E-05 | -0.010 | 6.40E-01 |
| RETN     | 0.003  | 8.80E-01 | 0.003  | 8.80E-01 | 0.075  | 2.60E-04 | -0.074 | 4.30E-04 |
| IGF1BP1  | -0.009 | 7.00E-01 | -0.015 | 4.90E-01 | 0.033  | 1.20E-01 | -0.013 | 5.50E-01 |
| CHIT1    | -0.021 | 3.50E-01 | -0.015 | 4.80E-01 | -0.029 | 1.60E-01 | 0.031  | 1.50E-01 |
| TRAP     | -0.016 | 4.70E-01 | 0.032  | 1.40E-01 | -0.023 | 2.70E-01 | 0.023  | 2.90E-01 |
| CCL22    | -0.011 | 6.20E-01 | 0.011  | 6.20E-01 | 0.034  | 1.10E-01 | 0.010  | 6.50E-01 |
| PSPD     | -0.022 | 3.30E-01 | 0.011  | 6.10E-01 | 0.052  | 1.50E-02 | -0.028 | 2.10E-01 |
| PI3      | 0.027  | 2.30E-01 | 0.036  | 1.10E-01 | -0.075 | 4.90E-04 | 0.036  | 1.00E-01 |
| EpCAM    | 0.023  | 3.20E-01 | 0.034  | 1.30E-01 | -0.012 | 5.70E-01 | -0.003 | 9.00E-01 |
| APN      | 0.007  | 7.50E-01 | 0.008  | 7.10E-01 | 0.064  | 3.00E-03 | -0.036 | 1.10E-01 |
| AXL      | 0.000  | 1.00E+00 | 0.020  | 3.60E-01 | 0.071  | 7.90E-04 | -0.044 | 4.50E-02 |
| IL1RT1   | 0.036  | 1.10E-01 | 0.025  | 2.50E-01 | 0.029  | 1.70E-01 | -0.024 | 2.70E-01 |
| MMP2     | 0.010  | 6.40E-01 | 0.007  | 7.50E-01 | 0.004  | 8.40E-01 | -0.017 | 4.20E-01 |
| FAS      | 0.022  | 2.90E-01 | 0.017  | 4.00E-01 | 0.064  | 9.10E-04 | -0.057 | 4.00E-03 |
| MB       | -0.034 | 1.20E-01 | 0.007  | 7.30E-01 | 0.043  | 3.60E-02 | 0.004  | 8.40E-01 |
| TNFSF13B | -0.054 | 1.90E-02 | 0.001  | 9.50E-01 | 0.079  | 2.30E-04 | -0.018 | 4.20E-01 |
| PRTN3    | -0.047 | 3.60E-02 | -0.040 | 7.00E-02 | 0.010  | 6.40E-01 | -0.038 | 8.10E-02 |
| Gene       | P-value | Fold Change | FDR   | Log2FC | P-value | Fold Change | FDR   | Log2FC |
|------------|---------|-------------|-------|--------|---------|-------------|-------|--------|
| 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|
| CH3L1      | -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|
| Gene      | Z Score | p Value  | Z Score | p Value  | Z Score | p Value  | Z Score | p Value  |
|-----------|---------|----------|---------|----------|---------|----------|---------|----------|
| 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 $\beta$-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.

| Protein | Abbreviation | CVD Panel | $\beta$-estimate | $P$-value | CVD Panel | $\beta$-estimate | $P$-value | CVD Panel | $\beta$-estimate | $P$-value | CVD Panel | $\beta$-estimate | $P$-value |
|---------|--------------|-----------|------------------|-----------|-----------|------------------|-----------|-----------|------------------|-----------|-----------|------------------|-----------|
| Spordin-2 | SPON2 | 2 | -0.081 | 2.80E-04 | Healthy | 0.030 | 3.60E-02 | Western/traditional | -0.082 | 9.00E-08 | Healthy | 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 |
| 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 | 0.007 | 6.30E-01 | -0.089 | 4.80E-09 | 0.002 | 8.90E-01 |
| 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 antigen-related 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 | 0.006 | 7.00E-01 | 0.037 | 2.10E-02 |
| Cadherin-5 | CDH5 | 3 | 0.060 | 5.20E-03 | -0.013 | 3.80E-01 | 0.029 | 6.50E-01 | 0.037 | 2.10E-02 |
| 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 | 0.029 | 5.00E-02 | -0.050 | 1.60E-03 | 0.052 | 1.60E-03 |
| Myeloperoxidase | MPO | 3 | 0.060 | 5.00E-03 | 0.025 | 7.90E-02 | -0.056 | 2.70E-04 | 0.078 | 8.30E-07 |
| Insulin-like growth factor-binding protein 1 | IGBP1 | 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 | 0.020 | 1.50E-01 | -0.045 | 1.90E-03 | 0.067 | 8.30E-06 |
| Urokinase plasminogen activator surface receptor | UPAR | 3 | 0.067 | 5.40E-04 | 0.013 | 3.80E-01 | -0.020 | 1.80E-01 | 0.022 | 1.70E-01 |
| Osteopontin | OPN | 3 | 0.067 | 1.40E-03 | 0.027 | 6.20E-02 | -0.032 | 3.80E-02 | 0.044 | 6.20E-03 |
| Peptidoglycan recognition protein 1 | PGLYRP1 | 3 | 0.064 | 2.60E-03 | 0.028 | 6.30E-02 | -0.040 | 1.10E-02 | -0.035 | 3.10E-02 |
| Carboxypeptidase A1 | CPA1 | 3 | -0.061 | 4.20E-03 | -0.035 | 1.60E-02 | -0.009 | 5.70E-01 | -0.003 | 8.70E-01 |
| Galectin-4 | Gal4 | 3 | -0.056 | 8.00E-03 | 0.005 | 7.40E-01 | 0.044 | 3.70E-03 | -0.045 | 4.80E-03 |
| Epidermal growth factor receptor | EGFR | 3 | -0.059 | 5.10E-03 | -0.010 | 5.10E-01 | 0.020 | 2.00E-01 | 0.072 | 8.20E-06 |
| Complement component C1q receptor | CD93 | 3 | 0.100 | 2.60E-06 | 0.002 | 8.60E-01 | -0.050 | 8.90E-04 | 0.041 | 8.60E-03 |
| Interleukin-18-binding protein | IL18BP | 3 | 0.059 | 3.90E-03 | -0.020 | 1.90E-01 | 0.014 | 3.60E-01 | 0.010 | 5.40E-01 |
| Collagen alpha-1(I) chain | COL1A1 | 3 | 0.062 | 3.70E-03 | 0.011 | 4.20E-01 | -0.060 | 4.60E-05 | 0.033 | 3.10E-02 |
### Protein Groups

| Protein                                              | Abbreviation | CVD Panel | β-estimate | P-value | β-estimate | P-value | β-estimate | P-value | β-estimate | P-value | β-estimate | P-value | β-estimate | P-value |
|------------------------------------------------------|--------------|-----------|------------|---------|------------|---------|------------|---------|------------|---------|------------|---------|------------|---------|
| 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                                            |              |           |            |         |            |         |            |         |            |         |            |         |            |         |
| 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|           |         |           |         |           |         |           |         |           |         |

- Positive 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. |
|---------|-------------------------|---------------------------|-----------|--------------------|------|
| SPON-2  | Western/ traditional    | -                         | 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) |
| Gene   | Sign | Description                                                                 | Function                        | Reference |
|--------|------|------------------------------------------------------------------------------|----------------------------------|-----------|
| 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. | 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 | Cell adhesion                    | (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.
Supplemental References:

1. Jia W, Li H, He YW. The extracellular matrix protein mindin serves as an integrin ligand and is critical for inflammatory cell recruitment. Blood 2005;106:3854-9.

2. He Y-W, Li H, Zhang J, Hsu C-L, Lin E, Zhang N, Guo J, Forbush KA, Bevan MJ. The extracellular matrix protein mindin is a pattern-recognition molecule for microbial pathogens. Nature Immunology 2003;5:88.

3. Zhang L, Liu K, Han B, Xu Z, Gao X. The emerging role of follistatin under stresses and its implications in diseases. Gene 2018;639:111-6.

4. Chakraborti S, Mandal M, Das S, Mandal A, Chakraborti T. Regulation of matrix metalloproteinases: An overview. Molecular and Cellular Biochemistry 2003;253:269-85.

5. Tuomainen AM, Kormi I, Havulinna AS, Tervahartiala T, Salomaa V, Sorsa T, Pussinen PJ. Serum tissue-degrading proteinases and incident cardiovascular disease events. European journal of preventive cardiology 2014;21:806-12.

6. Chistiakov DA, Melnichenko AA, Orekhov AN, Bobryshev YV. Paraoxonase and atherosclerosis-related cardiovascular diseases. Biochimie 2017;132:19-27.

7. Cao ZQ, Guo XL. The role of galectin-4 in physiology and diseases. Protein & cell 2016;7:314-24.

8. Skau E, Henriksen E, Wagner P, Hedberg P, Siegbahn A, Leppert J. GDF-15 and TRAIL-R2 are powerful predictors of long-term mortality in patients with acute myocardial infarction. European journal of preventive cardiology 2017;24:1576-83.

9. Heslop CL, Frohlich JJ, Hill JS. Myeloperoxidase and C-reactive protein have combined utility for long-term prediction of cardiovascular mortality after coronary angiography. Journal of the American College of Cardiology 2010;55:1102-9.

10. Brennan ML, Penn MS, Van Lente F, Nambi V, Shishehbor MH, Aviles RJ, Goormastic M, Pepoy ML, McErlean ES, Topol EJ, et al. Prognostic value of myeloperoxidase in patients with chest pain. The New England journal of medicine 2003;349:1595-604.

11. Burnett MS, Lee CW, Kinnaird TD, Stabile E, Durrani S, Dellum MK, Devaney JM, Fishman C, Stamou S, Canos D, et al. The potential role of resistin in atherogenesis. Atherosclerosis 2005;182:241-8.

12. Menzaghi C, Coco A, Salvenini L, Thompson R, De Cosmo S, Doria A, Trischitta V. Heritability of serum resistin and its genetic correlation with insulin resistance-related features in nondiabetic Caucasians. The Journal of clinical endocrinology and metabolism 2006;91:2792-5.

13. Reilly MP, Lehrke M, Wolfe ML, Rohatgi A, Lazar MA, Rader DJ. Resistin is an inflammatory marker of atherosclerosis in humans. Circulation 2005;111:932-9.

14. Fontana A, Spadaro S, Copetti M, Spoto B, Salvenini L, Pizzini P, Frittitta L, Mallamaci F, Pellegrini F, Trischitta V, et al. Association between resistin levels and all-cause and cardiovascular mortality: a new study and a systematic review and meta-analysis. PloS one 2015;10:e0120419.

15. Banerjee M, Saxena M. Interleukin-1 (IL-1) family of cytokines: role in type 2 diabetes. Clinica chimica acta; international journal of clinical chemistry 2012;413:1163-70.
16. Cyrille NB, Villablanca PA, Ramakrishna H. Soluble urokinase plasminogen activation receptor--An emerging new biomarker of cardiovascular disease and critical illness. Ann Card Anaesth 2016;19:214-6.

17. van Bussel BC, Henry RM, Schalkwijk CG, Ferreira I, Feskens EJ, Streppel MT, Smulders YM, Twisk JW, Stehouwer CD. Fish consumption in healthy adults is associated with decreased circulating biomarkers of endothelial dysfunction and inflammation during a 6-year follow-up. The Journal of nutrition 2011;141:1719-25.

18. van Bussel BC, Henry RM, Ferreira I, van Greevenbroek MM, van der Kallen CJ, Twisk JW, Feskens EJ, Schalkwijk CG, Stehouwer CD. A healthy diet is associated with less endothelial dysfunction and less low-grade inflammation over a 7-year period in adults at risk of cardiovascular disease. The Journal of nutrition 2015;145:532-40.

19. Singer BB, Opp L, Heinrich A, Schreiber F, Binding-Liermann R, Berrocal-Almanza LC, Heyl KA, Muller MM, Weimann A, Zweigner J, et al. Soluble CEACAM8 interacts with CEACAM1 inhibiting TLR2-triggered immune responses. PloS one 2014;9:e94106.

20. Mead JR, Irvine SA, Ramji DP. Lipoprotein lipase: structure, function, regulation, and role in disease. Journal of molecular medicine (Berlin, Germany) 2002;80:753-69.

21. Boyman O, Sprent J. The role of interleukin-2 during homeostasis and activation of the immune system. Nature reviews Immunology 2012;12:180-90.

22. Sulaj A, Kopf S, Grone E, Grone HJ, Hoffmann S, Schleicher E, Haring HU, Schwenger V, Herzig S, Fleming T, et al. ALCAM a novel biomarker in patients with type 2 diabetes mellitus complicated with diabetic nephropathy. Journal of diabetes and its complications 2017;31:1058-65.

23. Witt H, Beer S, Rosendahl J, Chen JM, Chandak GR, Masamune A, Bence M, Szmola R, Oracz G, Macek M Jr., et al. Variants in CPA1 are strongly associated with early onset chronic pancreatitis. Nature genetics 2013;45:1216-20.

24. Zeboudj L, Giraud A, Guyonnet L, Zhang Y, Laurans L, Esposito B, Vilar J, Chipont A, Papac-Milicevic N, Binder CJ, et al. Selective EGFR (Epidermal Growth Factor Receptor) Deletion in Myeloid Cells Limits Atherosclerosis-Brief Report. Arteriosclerosis, thrombosis, and vascular biology 2018;38:114-9.

25. Internet: https://www.uniprot.org/uniprot/Q9BWV1.

26. Kariuki SN, Franek BS, Kumar AA, Arrington J, Mikolaitis RA, Utset TO, Jolly M, Crow MK, Skol AD, Niewold TB. Trait-stratified genome-wide association study identifies novel and diverse genetic associations with serologic and cytokine phenotypes in systemic lupus erythematosus. Arthritis research & therapy 2010;12:R151.

27. Ho JE, Lyass A, Courchesne P, Chen G, Liu C, Yin X, Hwang SJ, Massaro JM, Larson MG, Levy D. Protein Biomarkers of Cardiovascular Disease and Mortality in the Community. Journal of the American Heart Association 2018;7.

28. Hwa V, Oh Y, Rosenfeld RG. The Insulin-Like Growth Factor-Binding Protein (IGFBP) Superfamily*. Endocrine Reviews 1999;20:761-87.