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Original research article

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Cardiovascular disease-linked plasma proteins are mainly associated with lung volume

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Summary

Several cardiovascular disease-linked proteins were associated with FEV_1 and FVC, but not with FEV_1/FVC ratio, suggesting that the relationships are mainly with lung volume, not airflow obstruction.

Running title: Plasma proteins and lung function

Word count: Abstract: 246 words. Manuscript: 3780 words; 5 tables and 1 figure.

Abstract

Background: Impaired lung function is common and associated with increased risk of cardiovascular disease in epidemiological studies. Increased levels of several inflammatory and cardiovascular disease-related plasma proteins have been associated with impaired lung function. The aim was to study the association between plasma proteomics and forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) and FEV_1/FVC ratio.

Methods: We used a discovery and replication approach in two community-based cohorts, EpiHealth and the Malmö Offspring Study (total n=2874), to cross-sectionally study 242 cardiovascular disease- and metabolism-linked proteins in relation to FEV_1, FVC (both %predicted) and FEV_1/FVC ratio. A false discovery rate of 5% was used as the significance threshold in the discovery cohort.

Results: Plasma fatty acid-binding protein 4, interleukin-1 receptor antagonist, interleukin-6 and leptin were negatively associated with FEV_1 and paraoxonase 3 was positively associated therewith. Fatty acid-binding protein 4, fibroblast growth factor 21, interleukin-1 receptor antagonist, interleukin-6 and leptin were negatively associated with FVC and agouti-related protein, insulin-like growth factor-binding protein 2, paraoxonase 3 and receptor for advanced glycation end products were positively associated therewith. No proteins were associated with FEV_1/FVC ratio. A sensitivity analysis in EpiHealth revealed only minor changes after excluding individuals with known cardiovascular disease, diabetes, or obesity.

Conclusions: Five proteins were associated with both FEV_1 and FVC. Four proteins associated with only FVC and none with FEV_1/FVC ratio, suggesting associations mainly through lung volume, not airway obstruction. However, additional studies are needed to investigate underlying mechanisms for these findings.

Key words: Plasma proteins, proteomics, lung function

Introduction

Impaired lung function is common and associated with increased risk of cardiovascular disease (CVD) and overall mortality [1-4]. The lung function trajectories leading to impaired lung function vary: some individuals achieve a normal peak value in young adulthood and then have an accelerated decline in lung function, others start from a lower peak value and have a physiological age-associated decline [5]. Therefore, it is difficult to predict which individuals are going to develop impaired lung function. New diagnostic tools are warranted [5].

CVD is a common comorbidity and cause of death among patients with chronic obstructive pulmonary disease (COPD), with low-grade systemic inflammation suggested as an important mediator [6]. Previous studies have identified several inflammatory biomarkers associated with both impaired lung function and CVD, including C-reactive protein, blood neutrophil counts, blood eosinophil counts, fibrinogen, and interleukin (IL)-6 [7-9]. However, there are likely many mechanisms linking impaired lung function and CVD, e.g., oxidative stress, extracellular matrix destruction and defective immunomodulation [10].

Knowledge of pathophysiological mechanisms leading to impaired lung function remains limited [5]. Proteomics detects and quantifies many proteins simultaneously and can indicate pathways involved in disease development [11]. Proteins associated with low spirometry values could increase knowledge of the continuum from normal to impaired lung function [12]. Thus, large proteomics studies could increase knowledge of impaired lung function and its association with CVD.

We have previously studied the association between forced expiratory volume in one second (FEV_1) and proteomics, focusing on inflammatory processes [13]. The primary aim of this paper was to study associations between broader proteomics data, focusing on CVD-related proteins, and lung function in a large population. More specifically, we tested the associations between proteomics and spirometry data in two community-based cohorts in a discovery and replication approach. The proteomics data included cardiovascular and inflammation-associated proteins and proteins involved in metabolic processes, e.g., cellular stress or apoptosis. The analyses encompassed FEV_1, forced vital capacity (FVC) and FEV_1/FVC ratio.

Material and methods

More details on the material and methods are available in online Supplementary file 1a and 1b.

Cohort descriptions

This study was based on two independent community-based Swedish cohorts, EpiHealth and the Malmö Offspring Study (MOS).

Discovery cohort

The EpiHealth study was conducted in 2011–2018. The primary objective was to study how interactions between lifestyle factors and genotypes contributed to development of common disorders in humans (e.g., cancer, cardiovascular and respiratory diseases). For details, see www.epihealth.lu.se. Briefly, individuals living in Malmö and Uppsala, aged 45–70 years, were randomly selected from the Swedish population registry. A total of 25,104 answered an extensive online questionnaire and visited a test centre for blood sampling, spirometry and anthropometric measuring [14]. For this study, only participants from Uppsala were included, because they had proteomics measurements. All participants with measurements on proteomics, lung function and covariates were included in this study and the final cohort comprised 2229 participants.

Replication cohort

The MOS was a population-based cohort study performed in 2013–2021 (n=5300). The aim was to map family traits as risk factors of chronic diseases based on gene-environment interaction. Participants include the children and grandchildren of participants in the Malmö Diet and Cancer Study-Cardiovascular Cohort; for details, see https://www.malmo-kohorter.lu.se/malmo-offspring-study-mos. Briefly, individuals aged ≥18 years and living in Skåne in southern Sweden were recruited using registry information from the Swedish Tax Agency. They were invited by post and visited a research centre for anthropometric measurement, spirometry, and blood sampling. There were no exclusion criteria except understanding information in Swedish [15]. All participants with measurements on proteomics, lung function and confounders were included in this study and the final cohort comprised 645 participants.

Measurements and questionnaires

Trained staff collected blood samples. Participants were fasting for ≥6 hours for EpiHealth and overnight for MOS. The blood samples were immediately centrifuged and frozen at -80 °C until analysis. Participant height (cm) and weight (kg) were measured. Information about smoking status and physical activity was obtained through questionnaires. Smoking status was divided into three categories: never smokers, previous smokers, and current smokers. Pack-years were calculated as numbers of cigarettes per day/20 * years of smoking. Physical activity was also divided into three categories: sedentary (physical activity ≤2 hours/week (no sweating)), moderate (regular physical activity 1–2 * 30 min/week (sweating)) and high (regular physical activity ≥3 * 30 min/week (sweating)). CVD was assessed from questionnaires in EpiHealth and defined as any of the following self-reported conditions: previous myocardial infarction, stroke, heart failure, atrial fibrillation, or angina pectoris. Similarly, diabetes, hypertension and hyperlipidemia were questionnaire-assessed.

Spirometry

In EpiHealth, a simplified resting lung function test was performed using a MiniSpir spirometer (Medical International Research, Waukesha, WI, USA) and in MOS, a lung function test was performed using spirometry (Jaeger Masterscope). Spirometry was conducted in accordance with the instructions of the American Thoracic Society/European

Respiratory Society [16]. At least three maneuvers were performed, with the highest value of FEV_1 and FVC recorded. The Global Lung Function Initiative (GLI) equations were used to calculate predicted FEV_1 and FVC adjusted for age, sex, height, and ethnicity [17], with FEV_1/FVC ratios presented as absolute values.

Proteomics

A total of 276 preselected proteins were analyzed in three OLINK Multiplex panels: CVD II, CVD III, and metabolism. These assays are based on the proximity extension assay technology [18], in which each sample can bind to any of 92 oligonucleotide-labelled antibody probe pairs. The characteristics, validation, and coefficients of variance for the panels are available online: https://www.olink.com/resources-support/document-download-center/.

The proteomics analyses were conducted by SciLifeLab, Uppsala, in a random subgroup (n=2472) within the Uppsala portion of the EpiHealth cohort. Proteins with ≥15% of the values below limit of detection (LOD) were excluded (n=4 for CVD II, n=1 for CVD III and n=29 for metabolism). Valid proteomics data were obtained from 2360, 2466 and 2410 individuals using the CVD II, CVD III and metabolism panels, respectively. After exclusion of individuals with missing data on covariates, the final dataset encompassed 2229 individuals (Figure 1).

OLINK Bioscience, Uppsala, did the analyses in a subgroup of the MOS cohort (n=923; consecutive subjects from 6 March 2013 to 17 June 2015). Proteins with ≥15% of the values below LOD were excluded (n=7 for CVD II, n=4 for CVD III and n=20 for metabolism). Valid proteomics data were obtained from 915, 922 and 919 individuals using the CVD II, CVD III and metabolism panels, respectively. When the three proteomics data files were combined with the questionnaire data, the cohort comprised 750 individuals with complete data on lung function and proteomics. After exclusion of individuals with missing data on covariates, the final dataset encompassed 645 individuals (Figure 1).

Ethical permission

All individuals gave informed consent, also covering biobank storing. EpiHealth was approved by the Ethics Board in Uppsala (Dnr 2010/402) and MOS by the Regional Ethics Committee in Lund (Dnr 2012/594). This study was approved by the Ethics Board in Uppsala (Dnr 2019-03968).

Statistical analyses

Baseline continuous variables are presented as means and standard deviations and categorical variables as *n* (%). The EpiHealth cohort was used for discovery and the MOS cohort for replication.

For the discovery cohort, a total of 2229 subjects and 242 proteins on 28 plates were analyzed. Proteins were used as independent variables and spirometry values (FEV_1, FVC and FEV_1/FVC ratio) as dependent variables.

Proteins with <15% of the values below LOD were imputed with LOD/sqrt(2). Then, the protein values were pre-processed by adjusting for storage time and plates to remove the potential non-random effects created thereby. The standardized residuals (z-scores) of each protein were used in further statistical analyses rather than the observed protein values.

The results were summarized as arithmetic means and β coefficients with 95% confidence intervals (95% CIs). Multiple linear regressions were run repeatedly using one of the 242 proteins as a predictor, with age, sex (binary), body mass index (BMI), smoking status (3 categories), pack-years and self-reported physical activity (3 categories) as confounders. For sensitivity analyses, individuals with known CVD, diabetes, or obesity (BMI ≥30) were

excluded. This multivariable linear regression model was adjusted for hypertension, hyperlipidemia, and waist circumference (normal vs high) instead of BMI.

An interaction analysis was made for the effects of current vs never and previous vs never smoking on the association between each protein and lung function (FEV_1, FVC and FEV_1/FVC ratio) in the discovery cohort.

The p-values were adjusted for multiple testing using the Benjamini-Hochberg method [19] to control for a false discovery rate of 5%. Proteins that were significantly associated with lung function were tested in the replication cohort using an identical approach. In the replication study, a nominal significance threshold of 0.05 was used. All analyses were performed using R version 4.1.2.

Results

Baseline characteristics are shown in Table 1. The participants in EpiHealth were older, exercised to a lesser extent than the individuals in MOS. A similar proportion of BMI ≥30 (obesity) was found in both cohorts while the prevalence of central obesity appeared to be larger in EpiHealth. There was a difference in smoking patterns between the two cohorts with a slightly higher prevalence of current smokers in MOS. The prevalence of diabetes mellitus was low in both cohorts while hypertension and hyperlipidemia were slightly higher in EpiHealth than MOS. On the other hand, MOS had more individuals with known CVD than EpiHealth. Finally, more individuals had a normal spirometry in EpiHealth than in MOS. The prevalence of different pathological spirometry patterns is presented in Table 1.

Associations between proteomics and lung function – Discovery cohort EpiHealth

In the discovery cohort, 19 of 242 proteins were significantly associated with FEV_1 and 24 proteins with FVC. Of the 19 proteins, 14 were negatively associated with FEV_1 (Table 2). Of the 24 proteins, 17 were negatively associated with FVC (Table 3). Two proteins, metalloproteinase inhibitor 4 (TIMP4) and hydroxy acid oxidase 1 (HAOX1), were associated with FEV_1/FVC ratio (regression coefficient and 95% CI -0.76 (-1.13, -0.39) and 0.69 (0.33, 1.05), p=0.02, respectively). All analyses were adjusted for age, sex, BMI, physical activity, smoking status (never vs previous smokers vs current smokers) and pack-years. For smoking status, never smokers were used as the reference group.

Associations between proteomics and lung function – Replication cohort MOS

Of the 19 proteins associated with FEV_1 in the discovery cohort, five could be replicated: plasma fatty acid-binding protein 4 (FABP4), IL-1 receptor antagonist (IL-1RA), IL-6, leptin and paraoxonase 3 (PON3). Increased levels of four of these proteins were associated with lower FEV_1, while increased levels of PON3 were associated with higher levels of FEV_1 (Table 2).

Of the 24 proteins associated with FVC in the discovery cohort, 9 could be replicated: agouti-related protein (AGRP), FABP4, fibroblast growth factor 21 (FGF21), insulin-like growth factor-binding protein 2 (IGFBP2), IL-1RA, IL-6, leptin, PON3 and receptor for advanced glycation end products (RAGE). Increased levels of FABP4, FGF21, IL-1RA, IL-6 and leptin had negative associations with FVC (Table 3). In contrast, increased levels of AGRP, IGFBP2, PON3 and RAGE were associated with higher FVC (Table 3). No proteins were associated with FEV_1/FVC ratio in the replication cohort (Supplementary Table 2).

Sensitivity analyses - EpiHealth

In EpiHealth, the sensitivity analyses showed that 11/19 and 18/25 proteins were significantly associated with FEV_1 and FVC respectively after excluding individuals with known CVD, diabetes, or obesity (BMI ≥30) and additional adjustment for hypertension, hyperlipidemia, and waist circumference (table 4 and table 5). In addition, 5 proteins became significantly associated with FVC only after exclusion (Table 5).

Interaction between smoking status and proteins

Accounted for multiple testing, no significant interactions with smoking status could be seen in the discovery cohort.

Discussion

Principal findings

In this paper, we studied the associations between proteins known for involvement in CVD and metabolism and lung function assessed with spirometry. We used multivariable models in a discovery and replication approach and found that higher levels of four proteins (FABP4, IL-1RA, IL-6, leptin) were associated with lower FEV_1, and higher levels of five proteins (FABP4, FGF21, IL-1RA, IL-6, Leptin) were associated with lower FVC. Higher levels of four proteins (AGRP, IGFBP2, PON3, RAGE) were associated with higher FVC. Increased levels of PON3 were also associated with higher FEV_1. No proteins were associated with FEV_1/FVC ratio consistently in both the discovery and validation cohort and we could not find any interaction with smoking status.

After excluding individuals with known CVD, diabetes, or obesity a sensitivity analysis in EpiHealth, 11/19 proteins were statistically associated with FEV_1, whereas 18/24 proteins were significantly associated with FVC. In addition, 5 proteins was only significantly associated with FVC in the sensitivity analysis.

Comparison with literature, individual proteins, and potential mechanisms

This study had some novel findings. PON3 was positively associated with both FEV_1 and FVC, IGFBP2 was positively associated with FVC, and FGF21 was negatively associated with FVC.

PON3 is an antioxidant enzyme protecting against low-density lipoprotein oxidation and was associated with both FEV_1 and FVC in our analyses, but only with FVC in our sensitivity analysis. To the best of our knowledge, PON3 has not previously been studied in the lung function context. However, increased PON3 levels have previously been reported in both coronary and peripheral artery disease [20]. A closely related protein, PON1, shares properties with PON3 and has been studied more extensively in relation to lung function. Lower levels have been associated with COPD [21], asthma and poorer asthma control [22]. Reduced levels of PON1 could indicate lower antioxidative protection [21]. Since both PON1 and PON3 seem to have protective roles, we speculate that the increased levels of PON3 in this study reflect how the body copes with increased oxidative stress and inflammation early in the disease process.

IGFBP2 was positively associated with FVC in both cohorts and in the sensitivity analysis in EpiHealth. IGFBP2 is a known tumor biomarker, expressed in many different types of cancers [23]. No previous study has reported any associations between increased levels of IGFBP2 and lung function in a community-based setting. However, Guiot *et al.* reported higher levels of IGFBP2 in idiopathic pulmonary fibrosis [24], although no association with lung function was found in this patient group. The signal may differ between a community-based setting and subjects with idiopathic pulmonary fibrosis, which warrants further research.

FGF21 was significantly associated with FVC in both cohorts and in the sensitivity analysis in EpiHealth. FGF21 has not previously been reported in the lung function context. FGF21 seems to be involved in protecting against CVD, with many potential pathways, e.g., endothelial function, inflammation and oxidative stress [25]. However, both lower and higher values of FGF21 have been associated with overall and cardiovascular mortality [26]. FGF21. To summarize, we can merely speculate why increased FGF21 levels was associated to lower lung volume in the present study.

Some additional proteins from the analyses are worth to mention in this section. Unsurprisingly, many of the proteins associated with lower spirometry values in this study

are involved in inflammatory pathways. IL-6 for example is a well-known marker of systemic inflammation and has previously been associated with lower FEV_1 and FVC in otherwise healthy individuals [27]. However, despite IL-6's close association with inflammation, these results are not necessarily evidence of inflammation as damaged lung epithelial cells can increase IL-6 without chronic systemic inflammation [28]. Given this situation, it is hardly surprising that IL-6 levels are elevated, but we cannot be entirely certain how much inflammation and/or damaged endothelial cells contributes. The association between increased levels of IL-6 and lower FEV_1 and FVC respectively was seen in both cohorts and in the sensitivity analysis in EpiHealth.

IL-1RA is a member of the IL-1 cytokine family and a natural inhibitor of the pro-inflammatory activities of IL-1alpha and IL-1beta, modulating a variety of IL-1-related immune and inflammatory responses. IL-1RA completely inhibits the activity of IL-1alpha and IL-1beta by binding to receptor IL-1R1 and preventing its association with the coreceptor IL-1RAP for signaling [29]. Lowered IL-1RA levels have been found in asthma [30] and COPD [31], causing increased IL-1 activity due to the lack of adequate anti-inflammatory regulation. Therefore, we might expect an association between lower IL-1RA levels and lower lung function based on these results from people with established airway disease. However, our results were the opposite, and we speculate that higher levels of IL-1RA could reflect how the body copes with a heightened inflammatory state early in the disease process. Interestingly, the association was not significantly associated with FEV_1 in the sensitivity analysis whereas the association with FVC was unchanged.

Leptin is a hormone secreted mainly by human adipose tissue cells, proportionally to the adipose tissue depot. Formerly thought to only modulate bodyweight through decreased appetite, leptin has other important roles in the body, including both the immune and the endocrine system [32]. We previously reported an association between leptin and FEV_1 [13]. In this study, we replicated this association and extended it to FVC. The association does not seem to be driven by increased BMI, as the findings were consistent after BMI adjustment in our primary analysis, and after exclusion of individuals with obesity in our sensitivity analysis. Our results that leptin isn't just a proxy for obesity are also supported by previous studies. For example have Sin et al shown already two decades ago that higher leptin levels have been associated with lower FEV_1 in non-obese individuals [33], and recently have Peters et al shown that individuals with asthma, insulin resistance rather than obesity was associated with lower lung function values suggesting that higher insulin levels rather than high BMI are an important driver for lung function decline [34]. Further studies need to answer what factors associated with obesity that really are the driver behind the accelerated decline in lung volume and airway obstruction.

FABP4 or adipocyte protein 2 is expressed mainly in adipocytes, but also in other cells such as macrophages. Increased levels are associated with several disease states, e.g., insulin resistance, type 2 diabetes, and hypertension. FABP4 increased with decreasing lung function in COPD-stable patients [35] and with decreasing FEV_1 in our previous analyses [13]. This association could be mediated through MMP-9, as suggested in ischemic stroke animal models [36]. However, MMP-9 was not associated with any of the spirometry values in this study. Moreover, FABP4 was associated with FEV_1 and FVC also after excluding individuals with known CVD, diabetes, or obesity.

In our primary analysis, a higher level of RAGE was associated with higher FEV_1 and FVC in EpiHealth, but the association could only be replicated for FVC. RAGE is highly expressed in the lungs and our results contrasted with those of previous studies that linked increased levels of RAGE to respiratory diseases, e.g., COPD and asthma [37]. We can only speculate as to why increased levels of a proinflammatory protein were associated with lung volume but not airway obstruction in this study. However, it is important to note that the

significant association for FEV_1 and FVC in EpiHealth disappeared in the sensitivity analysis (table 4 and 5).

Previous research has linked GDF-15 to both COPD [38] and COPD with concomitant subclinical coronary artery disease [39]. In a previous study in community-based cohorts, we reported an association between higher levels of GDF-15 and lower FEV_1 [13]. In this study, we did not find any consistent association between GDF-15 and lung function in both cohorts. But we found an association with FEV_1 in EpiHealth, and the signal was also there in the sensitivity analysis (table 4). EpiHealth encompassed a much larger cohort and participants were of a narrower age range and older than participants in MOS. It is possible that GDF-15 levels are associated with lung function later in the disease process and no signal could therefore be found in the younger MOS cohort.

Clinical implications and future directions

The effect sizes of the associations between proteins and lung function indicate that they are unlikely to be of clinical importance in a community-based population. This is also expected because the overall goal with this present study was not to find a biomarker for use in clinical practice, but rather to find early signals of associations that could have pathophysiological implications in the future. Moreover, it is likely that several proteins might relate to the same pathophysiological pathway, for instance by causing poorer antioxidative protection. As several of the proteins are involved in CVD and metabolism, some could be interesting in analyses of common disease mechanisms. Lastly, it should be kept in mind that finding individual proteins and implementing them into clinical practice is not an easy task. For example, less than 100 biomarkers were in clinical use in 2015, while over 150,000 articles on biomarkers had been published [40]. Still, it is necessary to continue the search for proteins that could be of clinical use in this cardiopulmonary context. Especially since there seems to be a point of no return in the disease process, making early discovery of the individuals at risk the only way forward with today's treatment standards [41].

Strengths and limitations

Study strengths include the use of a discovery and replication approach using two different study cohorts and including many proteins. Moreover, we did a sensitivity analysis after excluding individuals with known CVD, obesity, and diabetes. The main limitation is the cross-sectional design. A prospective cohort study with repeated measurements of lung function and proteomics data would provide both more information about fluctuations over time and stronger evidence of potential causal relationships.

When testing the associations between many proteins using several different measurements of lung function, there is an increased risk of spurious associations. However, we adjusted our results for a false discovery rate of 5% in the discovery cohort and nominal p-values in the replication cohort. The rationale was that we wanted to balance the risks of type 1 and type 2 errors and did not want to be overly conservative.

Conclusions

Several CVD-linked proteins were associated with FEV_1 and FVC, but not with FEV_1/FVC ratio, suggesting that the relationships are mainly with lung volume, not airflow obstruction. That increased levels of several proteins are associated with better lung function warrants further studies.

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Conflicts of interest

AR has received lecturing and advisory board fees from AstraZeneca. JA has received lecturing fees from AstraZeneca and Novartis and served on advisory boards for AstraZeneca and Boehringer Ingelheim on subjects unrelated to this study. PMN has received lecturing fees from Novartis, Novo Nordisk, Amgen and Boehringer Ingelheim.

Table 1. Baseline characteristics for the EpiHealth and Malmö offspring study (MOS) cohorts.

	EpiHealth n=2229	**MOS n=645**
Age, years	60.7 ± 8.4	40.2 ± 13.4
Sex (female), n (%)	1122 (50.3)	335 (51.9)
Height, cm	172 ± 9	174 ± 9
Weight, kg	78.6 ± 14.3	78.8 ± 16.8
Body mass index (BMI), kg/m^2	26.5 ± 3.8	26.1 ± 4.6
BMI category, n (%)		
<18.5 (underweight)	8 (0.4)	6 (0.9)
≥18,5 to <25 (normal weight)	772 (34.6)	296 (45.9)
≥25 to < 30 (overweight)	1083 (48.6)	227 (35.2)
≥ 30 (obesity)	366 (16.4)	116 (18)
Central Obesity (cm) n (%) (male >= 102, female >=88)	879 (39.4)	206 (31.9)
Physical activity, n (%)		
Sedentary	907 (40.7)	281 (43.6)
Moderate	934 (41.9)	163 (25.3)
High	388 (17.4)	201 (31.1)
Smoking history, n (%)		
Never	1108 (49.7)	393 (60.9)
Previous	946 (42.4)	173 (26.8)
Current	175 (7.9)	79 (12.3)
Pack-years [#]	14.6 ± 13.1	11.7 ± 10.8
Diabetes, n (%)	77 (3.5)	21 (3.3)
Hypertension, n (%)	602 (27.0)	107 (16.6)
Hyperlipidemia, n (%)	486 (21.8)	81 (12.6)
Cardiovascular disease, n (%)	165 (7.4)	80 (12.7)
FEV_1 mean, liters	3.1 ± 0.8	3.5 ± 0.8
$FEV_{1,}$ % predicted GLI	100 ± 16	94 ± 12
FVC mean, liters	4.0 ± 1.1	4.5 ± 1.0
FVC, % predicted GLI	101 ± 16	98 ± 12
FEV_1/FVC	0.77 ± 0.07	0.78 ± 0.07
FEV_1/FVC, % predicted GLI	99 ± 9	95 ± 8
Normal spirometry, n (%)	2002 (89.8)	506 (78.4)
Obstructive spirometry, n (%)	124 (5.6)	91 (14.1)
Restrictive spirometry, n (%)	26 (1.2)	5 (0.8)
PRISm, n (%)	77 (3.5)	43 (6.7)

Date are means ± standard deviation for continuous variables and n (%) for dichotomous variables. Abbreviations: MOS: Malmö Offspring Study, FEV_1: forced expiratory volume in 1 second, GLI: Global Lung Function Initiative, FVC: forced vital capacity, LLN: Lower Limit of Normal. [#] Calculated only for subjects with a history of smoking. Cardiovascular disease: a history of myocardial infarction, stroke, angina pectoris, heart failure or atrial fibrillation. Normal spirometry: $FEV_1/FVC \geq LLN$ & $FEV_1 \geq LLN$ & $FVC \geq LLN$. Obstructive spirometry: $FEV_1/FVC < LLN$. Restrictive spirometry: $FEV_1/FVC \geq LLN$ & $FVC < LLN$ & $FEV_1 \geq LLN$. Preserved Ratio Impaired Spirometry (PRISm): $FEV_1/FVC \geq LLN$ & $FEV_1 < LLN$

Table 2. Cross-sectional associations between plasma proteins and FEV_1 % predicted in EpiHealth (discovery cohort) and MOS (replication cohort). Multivariable linear regression analysis for each protein. Sorted based on p-value in replication cohort.

Proteins	Abbreviation	UniProtNo	Discovery cohort (EpiHealth) n=2229		Replication cohort (MOS) n=645	
			FEV_1 %pred		FEV_1 %pred	
			B-coeff (95% CI)	Adjusted p-value	B-coeff (95% CI)	p-value
Leptin	LEP	P41159	-4.80 (-5.87, -3.74)	$4.9\ 10^{-16}$	-2.17 (-3.52, -0.81)	0.002
Interleukin-6	IL-6	P05231	-1.86 (-2.54, -1.18)	$5.8\ 10^{-6}$	-1.49 (-2.48, -0.51)	0.003
Paraoxonase 3	PON3	Q15166	1.87 (1.12, 2.61)	$4.5\ 10^{-5}$	1.45 (0.47, 2.44)	0.004
Interleukin-1 receptor antagonist	IL-1RA	P18510	-1.54 (-2.32, -0.77)	0.003	-1.50 (-2.57, -0.43)	0.006
Fatty acid-binding protein 4	FABP4	P15090	-2.61 (-3.51, -1.72)	$1.4\ 10^{-6}$	-1.62 (-2.86, -0.38)	0.01
Agouti-related protein	AGRP	O00253	1.01 (0.35, 1.67)	0.04	1.01 (-0.04, 2.05)	0.06
Growth hormone	GH	P01241	1.15 (0.39, 1.92)	0.04	1.12 (-0.08, 2.32)	0.07
Plasminogen activator inhibitor	KIM1	Q96D42	-1.30 (-2.00, -0.60)	0.007	-0.88 (-1.96, 0.20)	0.11
C-C motif chemokine 16	CCL16	O15467	-1.23 (-1.91, -0.54)	0.01	-0.57 (-1.51, 0.38)	0.24
Metalloproteinase inhibitor 4	TIMP4	Q99727	-1.20 (-1.89, -0.50)	0.01	-0.61 (-1.61, 0.41)	0.24
Retinoic acid receptor responder 2	RARRES2	Q99969	-1.96 (-2.68, -1.24)	$5.8\ 10^{-6}$	-0.59 (-1.60, 0.41)	0.25
Receptor for advanced glycosylation and products	RAGE	Q15109	1.02 (0.36, 1.68)	0.04	0.46 (-0.46, 1.38)	0.33
Trefoil factor 3	TFF3	Q07654	-1.08 (-1.77, -0.39)	0.04	-0.43 (-1.38, 0.53)	0.38
Matrix metalloproteinase 7	MMP7	P09237	-1.15 (-1.85, -0.45)	0.02	0.34 (-0.60, 1.29)	0.48
Plasminogen activator inhibitor	PAI	P05121	-1.00 (-1.66, -0.34)	0.04	-0.26 (-1.24, 0.72)	0.60
Adrenomedullin	ADM	P35318	-1.92 (-2.69, -1.15)	$4.5\ 10^{-5}$	-0.22 (-1.20, 0.75)	0.65
Growth/differentiation factor 15	GDF15	Q99988	-1.36 (-2.15, -0.57)	0.01	0.11 (-0.84, 1.06)	0.82
Tissue-type plasminogen activator	tPA	P00750	-1.56 (-2.28, -0.58)	0.0006	0.09 (-0.95, 1.12)	0.87
Adhesion G protein-coupled receptor G2	ADGRG2	Q8IZP9	1.64 (0.95, 2.32)	$4.5\ 10^{-5}$	-0.006 (-1.02, 1.01)	0.99

Data are presented as regression coefficients for proteins increased by at least one standard deviation. Adjusted for age, sex, cohort, body mass index, smoking, pack-years, and physical activity. Abbreviations: MOS: Malmö Offspring Study, FEV_1: forced expiratory volume in 1 second, CI: confidence interval.

Table 3. Cross-sectional associations between plasma proteins and FVC % predicted in EpiHealth (discovery cohort) and MOS (replication cohort). Multivariable linear regression analysis for each protein.

Proteins	**Abbreviation**	**UniProtNo**	**Discovery cohort (EpiHealth) n=2229**		**Replication cohort (MOS) n=645**	
			FVC %pred		**FVC %pred**	
			B-coeff (95% CI)	**Adjusted p-value**	**B-coeff (95% CI)**	**p-value**
Leptin	LEP	P41159	-5.31 (-6.40, -4.22)	$6.8\ 10^{-19}$	-2.63 (-3.93, -1.32)	$8.8\ 10^{-05}$
Paraoxonase 3	PON3	Q15166	2.17 (1.41, 2.93)	$3.4\ 10^{-06}$	1.69 (0.74, 2.64)	0.0005
Fatty acid-binding protein 4	FABP4	P15090	-2.35 (-3.27, -1.43)	$2.6\ 10^{-05}$	-2.09 (-3.29, -0.89)	0.0006
Interleukin-6	IL-6	P05231	-1.34 (-2.04, -0.64)	0.003	-1.77 (-2.72, -0.81)	0.0003
Insulin-like growth factor-binding protein 2	IGFBP2	P18065	1.66 (0.91, 2.42)	0.001	1.42 (0.44, 2.40)	0.004
Interleukin-1 receptor antagonist protein	IL-1RA	P18510	-1.55 (-2.35, -0.76)	0.003	-1.40 (-2.44, -0.36)	0.008
Receptor for advanced glycosylation and products	RAGE	Q15109	0.97 (0.30, 1.65)	0.05	1.20 (0.31, 2.09)	0.008
Agouti-related protein	AGRP	O00253	1.19 (0.51, 1.87)	0.008	1.13 (0.12, 2.14)	0.03
Fibroblast growth factor 21	FGF21	Q9NSA1	-1.02 (-1.71, -0.31)	0.05	-1.01 (-2.00, -0.03)	0.04
Kidney injury molecule	KIM1	Q96D42	-1.40 (-2.11, -0.68)	0.0028	-1.01 (-2.06, 0.03)	0.06
Retinoic acid receptor responder 2	RARRES2	Q99969	-1.96 (-2.70, -1.22)	$1.2\ 10^{-5}$	-0.84 (-1.81, 0.13)	0.09
Hydroxyacid oxidase 1	HAOX1	Q9UJM8	-1.41 (-2.08, -0.73)	0.001	-0.71 (-1.65, 0.23)	0.14
C-C motif chemokine 16	CCL16	O15467	-1.46 (-2.16, -0.76)	0.001	-0.68 (-1.60, 0.24)	0.15
Insulin-like growth factor-binding protein 1	IGFBP1	P08833	1.53 (0.75, 2.30)	0.0027	0.76 (-0.32, 1.83)	0.17
Plasminogen activator inhibitor	PAI	P05121	-1.28 (-1.95, -0.60)	0.0035	-0.62 (-1.57, 0.33)	0.20
Tissue-type plasminogen activator	tPA	P00750	-1.41 (-2.15, -0.68)	0.003	-0.58 (-1.59, 0.42)	0.25
Growth hormone	GH	P01241	1.24 (0.45, 2.02)	0.025	0.61 (-0.56, 1.78)	0.31
C-C motif chemokine 17	CCL17	Q92583	-1.03 (-1.70, -0.36)	0.03	0.44 (-0.46, 1.33)	0.34
C-C motif chemokine 3	CCL3	P10147	-1.02 (-1.71, -0.33)	0.04	-0.34 (-1.27, 0.59)	0.47
Matrix metalloproteinase 7	MMP7	P09237	-1.34 (-2.06. -0.62)	0.0043	0.33 (-0.58, 1.25)	0.48
Adhesion G protein-coupled receptor G2	ADGRG2	Q8IZP9	1.89 (1.19, 2.59)	$1.0\ 10^{-5}$	0.31 (-0.67, 1.30)	0.53
Thrombospondin-2	THBS2	P35442	-1.02 (-1.68, -0.36)	0.03	-0.27 (-1.19, 0.64)	0.55
Spondin-2	SPON2	Q9BUD6	-1.15 (-1.83, -0.46)	0.013	-0.25 (-1.14, 0.63)	0.57
Adrenomedullin	ADM	P35318	-1.91 (-2.70, -1.12)	$9.5\ 10^{-5}$	-0.25 (-1.19, 0.70)	0.61

Data are regression coefficients for proteins increased by at least one standard deviation. Adjusted for age, sex, cohort, body mass index, smoking, pack-years, and physical activity. Abbreviations: MOS: Malmö Offspring Study, FVC: forced vital capacity, CI: confidence interval

Table 4. Sensitivity analysis in EpiHealth. Cross-sectional associations between plasma proteins and FEV_1 % predicted in EpiHealth before and after exclusion of individuals with known CVD, diabetes, or obesity. Multivariable linear regression analysis for each protein.

Proteins	**Abbreviation**	**UniProtNo**	**EpiHealth n=2229**		**EpiHealth n=1685**	
			FEV_1 %pred		**FEV_1 %pred**	
			B-coeff (95% CI)	**Adjusted p-value**	**B-coeff (95% CI)**	**Adjusted p-value**
Leptin	LEP	P41159	-4.80 (-5.87, -3.74)	$4.9\ 10^{-16}$	-3.44 (-4.46, -2.41)	$1.6\ 10^{-8}$
Interleukin-6	IL-6	P05231	-1.86 (-2.54, -1.18)	$5.8\ 10^{-6}$	-1.78 (-2.54, -1.03)	0.0003
Paraoxonase 3	PON3	Q15166	1.87 (1.12, 2.61)	$4.5\ 10^{-5}$	0.91 (0.69, 1.75)	0.27*
Interleukin-1 receptor antagonist	IL-1RA	P18510	-1.54 (-2.32, -0.77)	0.003	-1.16 (-2.07, 0.46)	0.17*
Fatty acid-binding protein 4	FABP4	P15090	-2.61 (-3.51, -1.72)	$1.4\ 10^{-6}$	-2.3 (-3.27, -1.33)	0.0003
Agouti-related protein	AGRP	O00253	1.01 (0.35, 1.67)	0.04	0.7 (-0,07 1.46)	0.36*
Growth hormone	GH	P01241	1.15 (0.39, 1.92)	0.04	1.21 (0.33, 2.08)	0.11*
Plasminogen activator inhibitor	KIM1	Q96D42	-1.30 (-2.00, -0.60)	0.007	-1.37 (-2.20, -0.55)	0.025
C-C motif chemokine 16	CCL16	O15467	-1.23 (-1.91, -0.54)	0.01	-0.90 (-1.66, -0.14)	0.22*
Metalloproteinase inhibitor 4	TIMP4	Q99727	-1.20 (-1.89, -0.50)	0.01	-1.36 (-2.15, -0.57)	0.023
Retinoic acid receptor responder 2	RARRES2	Q99969	-1.96 (-2.68, -1.24)	$5.8\ 10^{-6}$	-1.68 (-2.46, 0.9)	0.001
Receptor for advanced glycosylation and products	RAGE	Q15109	1.02 (0.36, 1.68)	0.04	0.92 (0.17, 1.67)	0.2*
Trefoil factor 3	TFF3	Q07654	-1.08 (-1.77, -0.39)	0.04	-1.30 (-2.08, -0.53)	0.025
Matrix metalloproteinase 7	MMP7	P09237	-1.15 (-1.85, -0.45)	0.02	-0.81 (-1.65, 0.02)	0.31*
Plasminogen activator inhibitor	PAI	P05121	-1.00 (-1.66, -0.34)	0.04	-0.76 (-1.50, -0.01)	0.31*
Adrenomedullin	ADM	P35318	-1.92 (-2.69, -1.15)	$4.5\ 10^{-5}$	-1.65 (-2.54, -0.76)	0.01
Growth/differentiation factor 15	GDF15	Q99988	-1.36 (-2.15, -0.57)	0.01	-1.58 (-2.54, 0.63)	0.03
Tissue-type plasminogen activator	tPA	P00750	-1.56 (-2.28, -0.58)	0.0006	-1.52 (-2.32, -0.73)	0.009
Adhesion G protein-coupled receptor G2	ADGRG2	Q8IZP9	1.64 (0.95, 2.32)	$4.5\ 10^{-5}$	1.34 (0.56, 2.11)	0.02

Data are presented as regression coefficients for proteins increased by at least one standard deviation. Adjusted for age, sex, cohort, body mass index, smoking, pack-years, and physical activity. For the sensitivity analysis this multivariable linear regression model was adjusted for hypertension, hyperlipidemia, and waist circumference (normal vs high) instead of BMI. *non-significant. Abbreviations: MOS: Malmö Offspring Study, FEV_1: forced expiratory volume in 1 second, CI: confidence interval.

Table 5. Sensitivity analysis in EpiHealth. Cross-sectional associations between plasma proteins and FVC % predicted in EpiHealth before and after exclusion of individuals with known CVD, diabetes, or obesity. Multivariable linear regression analysis for each protein.

Proteins	**Abbreviation**	**UniProtNo**	**EpiHealth n=2229**		**EpiHealth* n=1685**	
			FVC %pred		**FVC %pred**	
			B-coeff (95% CI)	**Adjusted p-value**	**B-coeff (95% CI)**	**Adjusted p-value**
Leptin	LEP	P41159	-5.31 (-6.40, -4.22)	$6.8\ 10^{-19}$	-4.64 (-5.7, -3.58)	$5.1\ 10^{-15}$
Paraoxonase 3	PON3	Q15166	2.17 (1.41, 2.93)	$3.4\ 10^{-06}$	1.52 (0.65, 2.39)	0.013
Fatty acid-binding protein 4	FAB4	P15090	-2.35 (-3.27, -1.43)	$2.6\ 10^{-05}$	-2.93 (-3.93, -1.93)	$1.3\ 10^{-6}$
Interleukin-6	IL-6	P05231	-1.34 (-2.04, -0.64)	0.003	-1.35 (-2.14, -0.56)	0.015
Insulin-like growth factor-binding protein 2	IGFBP2	P18065	1.66 (0.91, 2.42)	0.001	1.37 (0.51, 2.23)	0.02
Interleukin-1 receptor antagonist protein	IL-1RA	P18510	-1.55 (-2.35, -0.76)	0.003	-1.78 (-2.73, -0.83)	0.007
Receptor for advanced glycosylation and products	RAGE	Q15109	0.97 (0.30, 1.65)	0.05	0.95 (0.17, 1.73)	0.1*
Agouti-related protein	AGRP	O00253	1.19 (0.51, 1.87)	0.008	1.07 (0.27, 1.86)	0.07*
Fibroblast growth factor 21	FGF21	Q9NSA1	-1.02 (-1.71, -0.31)	0.05	-1.27 (-2.08, -0.46)	0.03
Kidney injury molecule	KIM1	Q96D42	-1.40 (-2.11, -0.68)	0.0028	-1.59 (-2.44, -0.73)	0.008
Retinoic acid receptor responder 2	RARRES2	Q99969	-1.96 (-2.70, -1.22)	$1.2\ 10^{-5}$	-2.07 (-2.88, 1.26)	$4.4\ 10^{-5}$
Hydroxyacid oxidase 1	HAOX1	Q9UJM8	-1.41 (-2.08, -0.73)	0.001	-1.33 (-2.11, -0.55)	0.015
C-C motif chemokine 16	CCL16	O15467	-1.46 (-2.16, -0.76)	0.001	-1.31 (-2.09, -0.53)	0.02
Insulin-like growth factor-binding protein 1	IGFBP1	P08833	1.53 (0.75, 2.30)	0.0027	1.59 (0.72, 2.47)	0.008
Plasminogen activator inhibitor	PAI	P05121	-1.28 (-1.95, -0.60)	0.0035	-1.16 (-1.93, -0.39)	0.04
Tissue-type plasminogen activator	tPA	P00750	-1.41 (-2.15, -0.68)	0.003	-1.59 (-2.41, -0.76)	0.007
Growth hormone	GH	P01241	1.24 (0.45, 2.02)	0.025	1.53 (0.62, 2.45)	0.02
C-C motif chemokine 17	CCL17	Q92583	-1.03 (-1.70, -0.36)	0.03	-1.09 (-1.86, -0.33)	0.05*
C-C motif chemokine 3	CCL3	P10147	-1.02 (-1.71, -0.33)	0.04	-1.22 (-2.08, -0.35)	0.06*
Matrix metalloproteinase 7	MMP7	P09237	-1.34 (-2.06. -0.62)	0.0043	-1.18 (-2.05, -0.32)	0.06*
Adhesion G protein-coupled receptor G2	ADGRG2	Q8IZP9	1.89 (1.19, 2.59)	$1.0\ 10^{-5}$	1.79 (0.97, 2.59)	0.0006
Thrombospondin-2	THBS2	P35442	-1.02 (-1.68, -0.36)	0.03	-1.0 (-1.8, -0.19)	0.1*
Spondin-2	SPON2	Q9BUD6	-1.15 (-1.83, -0.46)	0.013	-1.49 (-2.27, -0.7)	0.007
Adrenomedullin	ADM	P35318	-1.91 (-2.70, -1.12)	$9.5\ 10^{-5}$	-2.14 (-3.07, -1.21)	0.0004
Angiopoietin Like 1	ANGPTL1	O95841	0.74 (0.07, 1.4)	0.18*	31 (0.54, 2-08)	0.01
Tumor necrosis factor receptor 2	TNFR2	P20333	-0.87 (-1.59, -0.14)	0.13*	-1.25 (-2.04, -0.46)	0.03
Versican core protein	VCAN	P13611	0.93 (0.26, 1.6)	0.06*	1.21 (0.44, 1.97)	0.03
Trefoil factor 3	TFF3	Q07654	-0.92 (-1.63, -0.21)	0.095*	-1.19 (-1.99, -0.39)	0.04
Low-density lipoprotein receptor	LDLreceptor	P01130	-0.88 (-1.58, -0.19)	0.1*	-1.19 (-1.99, -0.38)	0.04

Data are regression coefficients for proteins increased by at least one standard deviation. Adjusted for age, sex, cohort, body mass index, smoking, pack-years, and physical activity. For the sensitivity analysis this multivariable linear regression model was adjusted for hypertension, hyperlipidemia, and waist circumference (normal vs high) instead of BMI. *non-significant. Abbreviations: MOS: Malmö Offspring Study, FVC: forced vital capacity, CI: confidence interval

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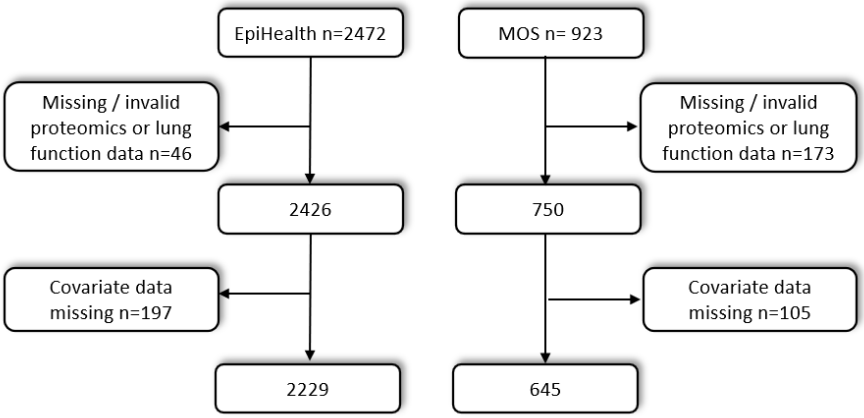

Figure 1. Flowchart of subjects included in the analyses. MOS: Malmö Offspring Study.

Supplementary table 1a. Discovery cohort: Output of the cross-sectional association between proteins and FEV_1 % pred. Significantly associated at FDR 5 %. Sorted by p-value. Marked in grey are proteins replicated in MOS

Variable	β-coff.	(95% CI)	Adjusted p-value
LEP	-4.80	(-5.87; -3.74)	$4.9\ 10^{-16}$
FABP4	-2.61	(-3.51, -1.72	$1.4\ 10^{-06}$
RARRES2	-1.96	(-2.68, -1.24)	$5.8\ 10^{-06}$
IL6	-1.86	(-2.54, -1.18)	$5.8\ 10^{-06}$
PON3	1.87	(1.12, 2.61)	$4.5\ 10^{-05}$
ADM	-1.92	(-2.69, -1.15)	$4.5\ 10^{-05}$
ADGRG2	1.64	(0.95, 2.32)	$9.7\ 10^{-05}$
tPA	-1.56	(-2.28, -0.85)	0.0006
IL1ra	-1.54	(-2.32, -0.77)	0.003
TIM	-1.30	(-2.00, -0.60)	0.007
CCL16	-1.23	(-1.91, -0.54)	0.010
TIMP4	-1.20	(-1.89, -0.50)	0.014
GDF15	-1.36	(-2.15, -0.57)	0.014
MMP7	-1.15	(-1.85, -0.45)	0.024
TFF3	-1.08	(-1.77, -0.39	0.04
RAGE	1.02	(0.36 1.68),	0.04
AGRP	1.01	(0.35, 1.67)	0.04
PAI	-1.00	(-1.66, -0.34)	0.04
GH	1.15	(0.39, 1.92)	0.04
TNFR2	-1.01	(-1.71, -0.31)	0.06
THBS2	-0.93	(-1.57, -0.28)	0.06
IGFBP2	1.04	(0.30, 1,77)	0.06
NTproBNP	-0.98	(-1.69, -0,27)	0.07
CCL3	-0.90	(-1.58, -0,22)	0.09
SPON2	-0.87	(-1.54, -0,21)	0.10
SCGB3A2	0.89	(0.20, 1,59)	0.11
FGF23	-0.88	(-1.56, -0,19)	0.11
CCL17	-0.83	(-1.49, -0,18)	0.11
IGFBP1	0.94	(0.19, 1,70)	0.12
ROR1	0.81	(0.14, 1.47)	0.14
FGF21	-0.81	(-1.49, -0.12)	0.16
REN	-0.81	(-1.49, -0.12)	0.16
TIE2	0.74	(0.10, 1.38)	0.17
FAS	0.76	(0.10, 1.43)	0.17
BAG6	0.75	(0.09, 1.42)	0.18
Gal4	-0.74	(-1.40, -0.09)	0.18
TNFR1	-0.77	(-1.46, -0.08)	0.19
CTSD	-0.78	(-1.48, -0.07)	0.19
CD84	0.71	(0.06, 1.36))	0.19
XCL1	-0.71	(-1.36, -0.06)	0.19
LDL receptor	-0.73	(-1.41, -0.06)	0.19

Variable	β-coff.	(95% CI)	Adjusted p-value
CLMP	-0.78	(-1.50, -0.05)	0.20
UPAR	-0.77	(-1.49, -0.05)	0.20
DECR1	-0.68	(-1.33, -0.04)	0.20
MCP1	-0.71	(-1.38, -0.04)	0.20
PLC	-0.74	(-1.44, -0.04)	0.20
AMBP	-0.69	(-1.36, -0.02)	0.21
IGFBP7	-0.68	(-1.33, -0.02)	0.21
LPL	0.74	(0.01, 1.47)	0.23
TRAILR2	-0.74	(-1.48, 0.00)	0.24
SOD2	0.66	(0.00, 1.32)	0.24
KLK6	-0.65	(-1.31, 0.01)	0.24
TNFRSF11A	-0.69	(-1.39, 0.01)	0.24
ProteinBOC	0.65	(-0.02, 1.31)	0.24
HAOX1	-0.64	(-1.30, 0.02)	0.24
ADGRE2	0.65	(-0.02, 1.32)	0.24
GHRL	0.67	(-0.02, 1.37)	0.25
CXCL16	-0.62	(-1.28, 0.03)	0.25
HSP27	-0.61	(-1.25, 0.04)	0.26
PCSK9	-0.61	(-1.27, 0.04)	0.26
PSPD	-0.61	(-1.26, 0.04)	0.26
CCL22	0.59	(-0.05, 1.22)	0.28
PI3	-0.61	(-1.28, 0.06)	0.28
GDF2	0.66	(-0.07, 1.38)	0.28
PlGF	-0.66	(-1.38, 0.07)	0.28
THPO	-0.59	(-1.24, 0.07)	0.29
vWF	-0.56	(-1.21, 0.08)	0.31
THOP1	0.58	(-0.09, 1.25)	0.31
PRELP	-0.62	(-1.36, 0.11)	0.33
ACP6	0.55	(-0.10, 1.20)	0.33
CTSL1	-0.56	(-1.21, 0.10)	0.33
IDTA	-0.53	(-1.18, 0.13)	0.38
TR	-0.52	(-1.17, 0.13)	0.38
GAL	0.54	(-0.14, 1.22)	0.38
MMP12	-0.58	(-1.31, 0.15)	0.38
CTSZ	-0.54	(-1.21, 0.14)	0.38
CDHR5	-0.53	(-1.21, 0.15)	0.38
CCL24	0.49	(-0.14, 1.13)	0.38
CCL15	-0.50	(-1.14, 0.15)	0.38
NEMO	-0.50	(-1.16, 0.15)	0.38
MPO	-0.50	(-1.14, 0.15)	0.38
OPN	-0.51	(-1.17, 0.15)	0.38
DDC	0.50	(-0.15, 1.14)	0.38
TM	0.50	(-0.16, 1.16)	0.38
CHIT1	0.50	(-0.16, 1.17)	0.38

Variable	β-coff.	(95% CI)	Adjusted p-value
CD163	-0.50	(-1.16, 0.16)	0.38
VCAN	0.49	(-0.16, 1.15)	0.39
TNFRSF10A	-0.51	(-1.18, 0.17)	0.39
CDH5	0.47	(-0.18, 1.12)	0.42
LILRA5	-0.48	(-1.16, 0.19)	0.43
CD1C	0.46	(-0.19, 1.11)	0.44
COL1A1	0.46	(-0.20, 1.11)	0.45
MMP9	-0.46	(-1.13, 0.20)	0.45
IGFBPL1	-0.48	(-1.17, 0.21)	0.45
Notch3	-0.48	(-1.17, 0.22)	0.45
SRC	-0.44	(-1.09, 0.21)	0.46
ANGPTL1	0.43	(-0.22, 1.09)	0.48
FABP2	-0.43	(-1.08, 0.22)	0.49
TNFRSF13B	-0.43	(-1.09, 0.23)	0.50
AXL	0.41	(-0.23, 1.05)	0.50
IL2RA	-0.42	(-1.07, 0.24)	0.51
CD93	0.40	(-0.24; 1.05)	0.52
LTBR	-0.41	(-1.06, 0.25)	0.52
CHI3L1	-0.43	(-1.12, 0.26)	0.52
TYRO3	0.41	(-0.26, 1.07)	0.53
EpCAM	-0.39	(-1.03, 0.25)	0.54
SCF	0.40	(-0.27, 1.08)	0.54
SIGLEC7	0.40	(-0.27, 1.07)	0.54
CTSO	-0.40	(-1.07, 0.27)	0.54
SELE	-0.39	(-1.05, 0.27)	0.54
TINAGL1	0.39	(-0.27, 1.05)	0.54
LOX1	-0.39	(-1.06, 0.28)	0.56
LRP11	0.37	(-0.29, 1.04)	0.57
CLUL1	0.38	(-0.29, 1.05)	0.57
TNFRSF14	-0.37	(-1.04, 0.30)	0.58
Dkk1	-0.36	(-1.02, 0.29)	0.58
STK4	-0.35	(-1.00, 0.30)	0.59
SERPINB6	0.35	(-0.30, 1.00)	0.59
AZU1	0.35	(-0.31, 1.01)	0.60
HO1	0.35	(-0.31, 1.02)	0.60
ANGPT2	-0.35	(-1.04, 0.33)	0.62
MB	-0.36	(-1.08, 0.36)	0.64
PDGFsubunitA	-0.32	(-0.95, 0.32)	0.65
ACE2	-0.35	(-1.05, 0.36)	0.65
BMP6	0.31	(-0.34, 0.95)	0.68
FAM3C	-0.32	(-0.98, 0.35	0.68
SDC4	0.30	(-0.34, 0.95)	0.68
IL17D	0.32	(-0.37, 1.01)	0.68
DCN	-0.32	(-1.01, 0.37)	0.68

Variable	β-coff.	(95% CI)	Adjusted p-value
ANGPTL7	0.31	(-0.37, 0.99)	0.69
TNFSF13B	-0.30	(-0.98, 0.37)	0.69
ADAMTS13	0.29	(-0.36, 0.95)	0.69
uPA	0.29	(-0.36, 0.93)	0.69
SORT1	-0.30	(-0.97, 0.37)	0.69
ST2	0.30	(-0.38, 0.98)	0.69
CLEC5A	-0.30	(-0.97, 0.38)	0.69
ENO2	0.28	(-0.36, 0.92)	0.69
SERPINA12	-0.29	(-0.96, 0.38)	0.70
APN	-0.27	(-0.91, 0.36)	0.70
FCRL1	0.28	(-0.38, 0.93)	0.70
EPHB4	0.27	(-0.37, 0.91)	0.71
TRAP	-0.27	(-0.93, 0.39	0.72
PDL2	-0.27	(-0.93, 0.39)	0.72
PARP1	-0.27	(-0.93, 0.39	0.72
hOSCAR	0.26	(-0.39, 0.92)	0.72
TF	0.27	(-0.40, 0.94)	0.72
CANT1	0.26	(-0.39, 0.91)	0.73
ICAM2	-0.25	(-0.88, 0.39)	0.73
IL6RA	-0.24	(-0.88, 0.39)	0.73
TNFRSF10C	-0.25	(-0.89, 0.40)	0.73
GRN	-0.25	(-0.89, 0.40)	0.73
PAPPA	-0.26	(-0.95, 0.43)	0.73
MEPE	0.25	(-0.42, 0.92)	0.73
IL17RA	0.24	(-0.39, 0.87)	0.73
MARCO	-0.25	(-0.91, 0.42)	0.73
PRTN3	0.24	(-0.41, 0.88)	0.73
VSIG2	-0.25	(-0.93, 0.43)	0.73
IL27	-0.24	(-0.90, 0.42	0.73
CA13	0.23	(-0.41, 0.87)	0.74
TLT2	0.22	(-0.41, 0.86)	0.74
PDGFsTbTnitB	-0.23	(-0.88, 0.42)	0.74
NPDC1	-0.24	(-0.91, 0.44)	0.74
PTX3	0.22	(-0.42, 0.87)	0.74
APLP1	-0.23	(-0.90, 0.45)	0.74
VEGFD	0.23	(-0.45, 0.91)	0.74
KLK10	0.21	(-0.43, 0.85)	0.74
GT	0.22	(-0.44, 0.87)	0.74
CLSTN2	-0.21	(-0.86, 0.43)	0.74
IL18	-0.22	(-0.90, 0.45)	0.74
BLMhydrolase	-0.22	(-0.89, 0.46)	0.74
IL1RT1	-0.20	(-0.85, 0.44)	0.74
CEACAM8	-0.21	(-0.89, 0.46)	0.74
FS	-0.21	(-0.87, 0.45)	0.74

Variable	β-coff.	(95% CI)	Adjusted p-value
ITGB2	-0.21	(-0.86, 0.45)	0.74
SPON1	-0.21	(-0.88, 0.46)	0.74
TFPI	-0.20	(-0.84, 0.45)	0.74
LRIG1	-0.20	(-0.85, 0.45)	0.74
PIgR	0.21	(-0.47, 0.88)	0.74
PSGL1	-0.20	(-0.86, 0.46)	0.74
ALCAM	-0.20	(-0.87, 0.47)	0.74
CDH2	-0.21	(-0.90, 0.48)	0.74
CXCL1	0.19	(-0.46, 0.84)	0.76
Gal3	0.20	(-0.49, 0.88)	0.76
TFF2	-0.20	(-0.89, 0.49)	0.76
REG4	-0.17	(-0.83, 0.50)	0.82
SUMF2	-0.16	(-0.83, 0.50)	0.82
HBEGF	-0.15	(-0.80, 0.49)	0.83
PGLYRP1	-0.15	(-0.80, 0.49)	0.83
Gal9	-0.17	(-0.89, 0.55)	0.83
PAR1	-0.15	(-0.82, 0.51)	0.83
IL18BP	0.15	(-0.52, 0.82)	0.83
SEMA3F	-0.14	(-0.80, 0.53)	0.86
METRNL	0.14	(-0.54, 0.81)	0.87
PRSS8	-0.15	(-0.89, 0.60)	0.87
NPTXR	0.13	(-0.52, 0.78)	0.87
QDPR	-0.13	(-0.79, 0.54)	0.87
PECAM1	0.12	(-0.52, 0.76)	0.87
CASP3	-0.11	(-0.75, 0.52)	0.88
NOMO1	0.12	(-0.56, 0.79)	0.89
GLO1	-0.11	(-0.76, 0.55)	0.90
MCFD2	-0.11	(-0.78, 0.56)	0.90
MMP3	0.13	(-0.68, 0.93)	0.90
TSHB	0.10	(-0.55, 0.75)	0.90
SNAP23	-0.10	(-0.75, 0.55)	0.91
MMP2	0.10	(-0.56, 0.75)	0.91
IL1RT2	0.09	(-0.55, 0.73)	0.92
TGM2	-0.08	(-0.73, 0.57)	0.93
IL16	0.08	(-0.58, 0.75)	0.93
NADK	0.08	(-0.59, 0.76)	0.93
MERTK	-0.08	(-0.76, 0.60)	0.94
EGFR	0.07	(-0.57, 0.72)	0.94
ENPP7	-0.07	(-0.73, 0.58)	0.94
RETN	-0.07	(-0.72, 0.58)	0.94
JAMA	-0.07	(-0.70, 0.57)	0.94
CPB1	-0.07	(-0.71, 0.58)	0.94
TYMP	-0.07	(-0.73, 0.60)	0.94
CCDC80	-0.07	(-0.77, 0.64)	0.94

Variable	β-coff.	(95% CI)	Adjusted p-value
CSTB	-0.07	(-0.79, 0.65)	0.94
CD2AP	-0.06	(-0.71, 0.59)	0.94
ITGB1BP2	-0.06	(-0.70, 0.59)	0.94
DLK1	0.06	(-0.60, 0.71)	0.94
OPG	-0.06	(-0.76, 0.64)	0.94
SOST	-0.06	(-0.74, 0.62)	0.94
CD4	-0.06	(-0.74, 0.63)	0.94
GIF	0.05	(-0.60, 0.71)	0.94
NECTIN2	0.04	(-0.62, 0.70)	0.97
PILRB	0.03	(-0.63, 0.68)	0.98
PRSS27	0.03	(-0.63, 0.68)	0.98
CHRDL2	-0.03	(-0.68, 0.63)	0.98
CNTN1	0.02	(-0.67, 0.72)	0.98
CD79B	0.02	(-0.64, 0.68)	0.98
CPA1	0.02	(-0.63, 0.66)	0.98
SELP	-0.02	(-0.66, 0.62)	0.98
IL1RL2	0.02	(-0.64, 0.68)	0.98
IL4RA	-0.02	(-0.67, 0.64)	0.98
ANG1	-0.01	(-0.66, 0,64)	1.00
SHPS1	0.005	(-0.64, 0.65)	1.00
CTRC	0.004	(-0.65, 066)	1.00
CD40L	0.004	(-0.65, 0.65)	1.00
CD164	0.003	(-0.65, 0.65)	1.00
KYAT1	0.001	(-0.65, 0.65)	1.00

Supplementary table 1b. Discovery cohort: Output of the cross-sectional association between proteins and FVC% pred. Significantly associated at FDR 5 %. Sorted by p-value. Marked in grey are proteins replicated in MOS

Protein	B-coff.	95% CI	Adjusted p-value
LEP	-5.31	(-6.40, -4,22)	$6.8\ 10^{-19}$
PON3	2.17	(1.40, 2.93)	$3.4\ 10^{-06}$
ADGRG2	1.89	(1.19, 2.59)	$1.0\ 10^{-05}$
RARRES2	-1.96	(-2.70, -1.22)	$1.2\ 10^{-05}$
FABP4	-2.35	(-3.27, -1.43)	$2.6\ 10^{-05}$
ADM	-1.91	(-2.70, -1.12)	$9.5\ 10^{-05}$
IGFBP2	1.66	(0.91, 2.42)	0.0005
HAOX1	-1.41	(-2.08, -0.73)	0.001
CCL16	-1.46	(-2,16, -0.76)	0.001
IGFBP1	1.53	(0.75, 2.30)	0.003
IL1ra	-1.55	(-2.35, -0.76)	0.003
TIM	-1.40	(-2,11, -0.68)	0.003
tPA	-1.41	(-2.15, -0.68)	0.003
IL-6	-1.34	(-2.04, -0.64)	0.003
PAI	-1.28	(-1.95, -0.60)	0.004
MMP7	-1.34	(-2.06, -0.62)	0.004
AGRP	1.19	(0.51, 1.87)	0.008
SPON2	-1.15	(-1.83, -0.46)	0.01
GH	1.24	(0.45, 2.02)	0.03
THBS2	-1.02	(-.,68, -0.36)	0.03
CCL17	-1.03	(-1.70, 0.36)	0.03
CCL3	-1.02	(-1.72, -0.33)	0.04
FGF21	-1.02	(-1.72, -0.31)	0.05
RAGE	0.97	(0.30, 1.65)	0.05
CD84	0.93	(0,26, 1.59)	0.06
VCAN	0.93	(0.26, 1.60)	0.06
CTSD	-0.95	(-1.66, -0.23)	0.08
TFF3	-0.92	(-1.63, -0.21)	0.10
LDL receptor	-0.88	(-1.58, -0.19)	0.10
GDF15	-1.04	(-1.85, -0.22)	0.10
GHRL	0.90	(0.19, 1.62)	0.10
THPO	-0.85	(-1.52, -0.17)	0.10
ROR1	0.86	(0.17, 1.54)	0.11
LPL	0.92	(0.17, 1.67)	0.11
TIE2	0.80	(0.14, 1.46)	0.12
TNFR2	-0.87	(-1.59, -0.14))	0.13
REN	-0.82	(-1.52, -0.12)	0.14
CDHR5	-0.80	(-1.50, -0.11)	0.15
PARP1	-0.78	(-1.46, -0,10)	0.15
Gal4	-0.77	(-1.45, -0.10	0.15
TNFRSF13B	-0.75	(-1.43, -0.07)	0.18

Protein	B-coff.	95% CI	Adjusted p-value
ANGPTL1	0,74	(0.07, 1.40)	0.18
XCL1	-0,73	(-1.40, -0.06)	0.18
AMBP	-0.74	(-1.42, -0.06	0.19
FGF23	-0.75	(-1.46, -0.05)	0.19
AXL	0.70	(0.04, 1.35)	0.19
MCP1	-0.72	(-1.40, -0.03)	0.21
ACE2	-0.74	(-1.46, -0.02)	0.22
PSPD	-0.68	(-1.34, -0.01)	0.23
uPA	0.66	(0.00, 1.32)	0.25
APN	-0.65	(-1.30, 0.01)	0.25
CLMP	-0.72	(-1.46, 0.02)	0.25
BAG6	0.66	(-0.02, 1.34)	0.25
CDH5	0.65	(-0.02, 1.31)	0.25
PI3	-0.63	(-1.31, 0.06)	0.31
DECR1	-0.60	(-1.26, 0.06)	0.31
TNFRSF11A	-0.65	(-1.37, 0.06)	0.31
PDGFsubunitA	-0.59	(-1.24, 0.06)	0.31
PCSK9	-0.61	(-1.27, 0.06)	0.31
ACP6	0.59	(-0.08, 1.26)	0.34
FAS	0.59	(-0.09, 1.27)	0.36
TNFR1	-0.61	(-1.31, 0.10)	0.36
GAL	0.59	(-0.10, 1.29)	0.37
PSGL1	-0.56	(-1.24, 0.11)	0.38
TRAILR2	-0.63	(-1.38, 0.12)	0.38
TNFRSF10A	-0.57	(-1.26, 0.12)	0.38
CXCL16	-0.54	(-1.21, 0.12)	0.40
SCGB3A2	0.58	(-0.13, 1.30)	0.40
NEMO	-0.53	(-1.20, 0.14)	0.41
TYRO3	0.54	(-0.14, 1.22)	0.41
SRC	-0.52	(-1.19, 0.14)	0.41
MMP12	-0.59	(-1.33, 0.16)	0.42
ProteinBOC	0.53	(-0.15, 1.20)	0.42
PLC	-0.56	(-1.28, 0.16)	0.42
TINAGL1	0.52	(-0.15, 1.20)	0.42
EPHB4	0.50	(-0.15, 1.16)	0.42
SELE	-0.51	(-1.18, 0.17)	0.43
LILRA5	-0.52	(-1.21, 0.17)	0.43
TIMP4	-0.53	(-1.24, 0.18)	0.43
PDGFsTbTnitB	-0.49	(-1.16, 0.17)	0.43
CD1C	0.49	(-0.17, 1.16)	0.43
IL18BP	0.50	(-0.18. 1.19)	0.43
SOD2	0.50	(-0.18, 1.17)	0.43
THOP1	0.50	(-0.18, 1.18)	0.43
NTproBNP	-0.53	(-1.27, 0.20)	0.43

Protein	B-coff.	95% CI	Adjusted p-value
KLK6	-0.49	(-1.16, 0.18)	0.43
Dkk1	-0.48	(-1.15, 0.18)	0.43
MARCO	-0.49	(-1.17, 0.19)	0.43
GRN	-0.48	(-1.14, 0.19)	0.43
CTSO	-0.49	(-1.18, 0.20)	0.43
CD93	0.47	(-0.19, 1.13)	0.43
HSP27	-0.46	(-1.12, 0.19)	0.43
COL1A1	0.47	(-0.20, 1.14)	0.43
IGFBP7	-0.47	(-1.14, 0.20)	0.43
IDTA	-0.47	(-1.14, 0.20)	0.43
AZU1	0.47	(-0.20, 1.15)	0.43
SHPS1	0.45	(-0.21, 1.11)	0.44
SORT1	-0.47	(-1.16, 0.22)	0.44
PlGF	-0.51	(-1.25, 0.24)	0.44
CD163	-0.45	(-1.13, 0.22)	0.46
STK4	-0.44	(-1.10, 0.23)	0.47
TLT2	0.43	(-0.22, 1.09)	0.47
TR	-0.44	(-1.10, 0.23)	0.47
CCL15	-0.43	(-1.09, 0.23)	0.47
FABP2	-0.43	(-1.10, 0.23)	0.47
EpCAM	-0.43	(-1.08, 0.23)	0.47
GDF2	0.48	(-0.27, 1.22)	0.47
QDPR	-0.43	(-1.11, 0.25)	0.48
HBEGF	-0.41	(-1.07, 0.25)	0.49
ADGRE2	0.40	(-0.28, 1.08)	0.55
TM	0.39	(-0.29, 1.06)	0.57
SERPINB6	0.38	(-0.28, 1.04)	0.57
PRELP	-0.42	(-1.17, 0.33)	0.59
UPAR	-0.39	(-1.13, 0.34)	0.62
PRTN3	0.35	(-0.31, 1.02)	0.62
TYMP	-0.36	(-1.04, 0.32)	0.63
Gal3	0.37	(-0.34, 1.07)	0.63
EGFR	0.34	(-0.32, 1.00)	0.63
CTSZ	-0.36	(-1.05, 0.34)	0.63
SUMF2	-0.34	(-1.03, 0.34)	0.63
LRP11	0.34	(-0.34, 1.02)	0.63
TFPI	-0.33	(-0.99, 0.33)	0.63
CCL24	0.33	(-0.32, 0.98)	0.63
MEPE	0.34	(-0.34, 1.03)	0.63
CDH2	-0.35	(-1.06, 0.36)	0.65
LOX1	-0.34	(-1.02, 0.35)	0.65
MMP9	-0.32	(-1.00, 0.36)	0.67
CTSL1	-0.32	(-0.99, 0.36)	0.68
ENO2	0.31	(-0.35, 0.97)	0.68

Protein	B-coff.	95% CI	Adjusted p-value
ANGPTL7	0.32	(-0.38, 1.02)	0.68
IL17D	0.32	(-0.38, 1.03)	0.68
IL17RA	0.29	(-0.35, 0.94)	0.68
KLK10	0.29	(-0.36, 0.95)	0.68
GT	0.30	(-0.37, 0.97)	0.68
CHIT1	0.30	(-0.38, 0.99)	0.68
TNFRSF14	-0.31	(-0.99, 0.38)	0.68
CLUL1	0.30	(-0.39, 0.99)	0.69
NPTXR	0.29	(-0.38, 0.95)	0.70
IGFBPL1	-0.30	(-1.01, 0.41)	0.70
METRNL	0.29	(-0.40, 0.99)	0.70
FAM3C	-0.29	(-0.97, 0.39)	0.70
PECAM1	0.27	(-0.39, 0.93)	0.71
CTRC	-0.27	(-0.94, 0.40)	0.71
PAR1	-0.28	(-0.96, 0.40)	0.71
PTX3	0.26	(-0.40, 0.93)	0.71
IL27	0.27	(-0.41, 0.95)	0.71
ENPP7	-0.26	(-0.93, 0.41)	0.71
ANG1	-0.26	(-0.93, 0.41)	0.71
IL6RA	-0.25	(-0.91, 0.40)	0.71
IL16	-0.27	(-0.95, 0.42)	0.71
IL18	-0.27	(-0.96, 0.42)	0.71
CCL22	0.25	(-0.40, 0.91)	0.71
CHRDL2	-0.26	(-0.92, 0.41)	0.72
IL2RA	-0.25	(-0.93, 0.42)	0.72
MMP2	0.25	(-0.42, 0.92)	0.72
ITGB2	-0.25	(-0.92, 0.42)	0.72
TF	0.24	(-0.45, 0.93)	0.77
IL1RL2	-0.23	(-0.91, 0.44)	0.77
MMP3	0.27	(-0.55, 1.10)	0.78
ST2	0.23	(-0.46, 0.92)	0.78
MPO	-0.22	(-0.88, 0.45)	0.78
SELP	0.21	(-0.45, 0.87)	0.79
VEGFD	0.22	(-0.47, 0.92)	0.79
KYAT1	-0.21	(-0.88, 0.45)	0.79
NADK	-0.22	(-0.90, 0.47)	0.79
VSIG2	-0.22	(-0.91, 0.48)	0.79
DCN	-0.21	(-0.92, 0.50)	0.81
PGLYRP1	0.19	(-0.47, 0.86)	0.81
ICAM2	0.18	(-0.47, 0.83)	0.82
Notch3	-0.20	(-0.91, 0.51)	0.82
REG4	-0.19	(-0.87, 0.49)	0.82
CD40L	-0.18	(-0.85, 0.48)	0.82
CANT1	0.18	(-0.48, 0.85)	0.82

Protein	B-coff.	95% CI	Adjusted p-value
vWF	-0.18	(-0.84, 0.48)	0.83
SIGLEC7	0.18	(-0.50, 0.87)	0.83
BLMhydrolase	-0.18	(-0.87, 0.51)	0.84
IL1RT1	0.17	(-0.49, 0.83)	0.84
SPON1	-0.17	(-0.86, 0.51)	0.84
DDC	0.17	(-0.50, 0.83)	0.84
ITGB1BP2	-0.16	(-0.83, 0.50)	0.84
CEACAM8	0.17	(-0.52, 0.86)	0.84
GIF	-0.16	(-0.84, 0.51)	0.84
CCDC80	-0.17	(-0.90, 0.55)	0.84
NPDC1	-0.17	(-0.86, 0.53)	0.84
RETN	0.16	(-0.51, 0.83)	0.84
Gal9	-0.17	(-0.92, 0.57)	0.84
FS	-0.16	(-0.84, 0.52)	0.84
SNAP23	-0.15	(-0.82, 0.51)	0.84
ANGPT2	-0.16	(-0.86, 0.54)	0.84
CLEC5A	0.15	(-0.55, 0.85)	0.86
CD2AP	0.14	(-0.53, 0.80)	0.86
SERPINA12	-0.14	(-0.83, 0.55)	0.86
CA13	0.13	(-0.53, 0.79)	0.86
JAMA	-0.13	(-0.78, 0.52)	0.86
hOSCAR	0.13	(-0.54, 0.81)	0.86
OPN	-0.13	(-0.81, 0.54)	0.86
CSTB	0.14	(-0.59, 0.88)	0.86
SEMA3F	-0.12	(-0.80, 0.56)	0.88
LRIG1	0.12	(-0.55, 0.79)	0.88
SOST	-0.12	(-0.81, 0.58)	0.89
CD4	-0.12	(-0.82, 0.58)	0.89
NOMO1	0.11	(-0.58, 0.81)	0.90
GLO1	0.11	(-0.56, 0.77)	0.90
PRSS8	-0.11	(-0.87, 0.65)	0.91
TFF2	0.10	(-0.60, 0.81)	0.91
NECTIN2	0.10	(-0.58, 0.78)	0.91
DLK1	-0.09	(-0.76, 0.58)	0.93
CNTN1	0.09	(-0.62, 0.81)	0.93
TNFRSF10C	0.07	(-0.58, 0.73)	0.96
CD164	0.07	(-0.60, 0.73)	0.97
ALCAM	0.07	(-0.62, 0.75)	0.98
PDL2	-0.06	(-0.74, 0.61)	0.98
IL1RT2	0.06	(-0.60, 0.72)	0.98
HO1	0.06	(-0.62, 0.74)	0.98
BMP6	-0.05	(-0.72, 0.61)	0.98
MCFD2	-0.05	(-0.74, 0.63)	0.98
ADAMTS13	-0.05	(-0.72, 0.62)	0.98

Protein	B-coff.	95% CI	Adjusted p-value
PAPPA	0.05	(-0.66, 0.76)	0.98
CHI3L1	-0.05	(-0.76, 0.66)	0.99
OPG	0.04	(-0.68, 0.76)	1.00
CASP3	-0.03	(-0.68, 0.62)	1.00
PRSS27	-0.03	(-0.70, 0.64)	1.00
MERTK	0.03	(-0.67, 0.72)	1.00
TNFSF13B	0.03	(-0.67, 0.72)	1.00
LTBR	0.02	(-0.65 0.69)	1.00
CPB1	0.02	(-0.65, 0.68)	1.00
PILRB	0.02	(-0.65, 0.69)	1.00
CLSTN2	-0.02	(-0.68, 0.65)	1.00
TRAP	-0.02	(-0.69, 0.66)	1.00
TSHB	-0.02	(-0.68, 0.65)	1.00
CD79B	0.02	(-0.66, 0.69)	1.00
APLP1	0.01	(-0.68, 0.70)	1.00
SCF	-0.01	(-0.70, 0.68)	1.00
CPA1	-0.01	(-0.67, 0.65)	1.00
CXCL1	-0.01	(-0.68, 0.65)	1.00
SDC4	0.01	(-0.65, 0.67)	1.00
GRAP2	0.01	(-0.65, 0.67)	1.00
FCRL1	0.00	(-0.68, 0.67)	1.00
IL4RA	0.00	(-0.67, 0.67)	1.00
MB	0.00	(-0.73, 0.74)	1.00
TGM2	0.00	(-0.67, 0.67)	1.00
PIgR	0.00	(-0.69, 0.69)	1.00