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Modifiable risk factors and plasma proteomics in relation to complications of type 2 diabetes

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A comprehensive assessment of combined modifiable risk factors with common complications of type 2 diabetes (T2D) is lacking, and the potential role of proteomics remains unclear. Here, we examine the associations of cardiovascular health (CVH) score and degree of risk factor control with common diabetic complications using data from the UK Biobank (n = 14,102). Furthermore, we explore the mediation effects of plasma proteomics in a subset with proteomic data (n = 1287). Over median follow-ups of 12.4–13.4 years, higher CVH score and higher degree of risk factor control are associated with lower risks of 30 and 22 of 45 adverse outcomes among individuals with T2D, respectively. Mediation analyses reveal that mortality and multiple vascular diseases share common mediators, such as uromodulin and pro-adrenomedullin. These findings highlight the importance of risk factors modification in reducing disease burden among people with T2D and facilitate the understanding of mediation effects of plasma proteins underlying these associations.

The growing pandemic of type 2 diabetes poses an enormous public health issue worldwidely[1,2]. In addition to well-established increased risks of mortality and cardiovascular diseases (CVD)[3,4], type 2 diabetes contributes increasingly to the burden of multiple system and organ disorders in the short and long term[5,6]. However, cost-effective strategies to prevent multiple diseases and mortality in individuals with type 2 diabetes are not completely understood.

Beyond glucose control, the American Diabetes Association has emphasized the integral role of healthy lifestyles and optimal management of weight, blood pressure, and lipids in diabetes care[7,8]. Furthermore, large benefits are shown especially when multiple modifiable risk factors are addressed simultaneously[9]. However, the majority of prior research focused on single risk factor, only a few recent studies were conducted to investigate health benefits of modifying multiple risk factors among people with type 2 diabetes[10–12]. Additionally, these studies mostly narrowed on mortality and macro- and microvascular complications, and the beneficial effect on other common complications of type 2 diabetes, especially diseases involving diverse systems and organs, are not characterized. Therefore, a large longitudinal study is warranted to investigate the combined effect of modifying lifestyle and cardiometabolic factors on multiple incident diseases and mortality

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among people with type 2 diabetes, which may offer a holistic view of relationships between combined modifiable risk factors and common diabetic complications and facilitate impactful translation of epidemiology findings into public health practice.

In addition, the intermediate underlying the associations of combined modifiable risk factors with future health outcomes remains undiscovered, leaving practical obstacles to capturing the complexity of modifiable risk factors with diseases. Recent advances in proteomics profiling open a new avenue to unearth the role of combined modifiable risk factors in health risks[13]. Most previous proteomic studies used plasma proteins to discriminate disease cases from healthy populations and facilitate incident disease prediction[14,15], while only a few research investigated proteomic profiles correlated with risk factors, primarily singular risk factor[16–18]. Considering that multiple lifestyle and cardiometabolic risk factors generally coexist, identifying the proteomic profile of combined modifiable risk factors may offer insight into individual's physiological and pathological states from a holistic perspective. Furthermore, appraising whether and to what extent plasma proteins could link modifiable risk factors to future health risks may enhance understanding of these associations and provide evidence support for better management of type 2 diabetes in the future.

In this work, we investigate the associations of combined modifiable risk factors with the risk of common complications of type 2 diabetes, then identify proteomic profile associated with combined modifiable risk factors, and further assess the potential mediating effects of plasma proteins on associations between combined modifiable risk factors and future health risks among individuals with type 2 diabetes. The research may provide us a more comprehensive picture of health benefits of modifying lifestyle and cardiometabolic risk factors for common complications of type 2 diabetes and facilitate our understanding of plasma proteomics underlying these associations.

Results

Participants' characteristics

The selection of participants is shown in Fig. 1. Among 14,102 eligible participants with type 2 diabetes, 4930 (percentage = 35.0%) were female, with a mean age of 60.0 years. The baseline characteristics of participants according to cardiovascular health score are shown in Table 1. Overall, participants with higher cardiovascular health score were relatively older, were more likely to be female, non-white, employed, and have higher education qualifications, better economic status, and moderate drinking.

Associations of combined modifiable risk factors with common complications of type 2 diabetes

During the median follow-ups of 12.4–13.4 years, 9954 participants developed at least one disease studied, and the most common outcomes were major adverse cardiovascular events (MACE) ($n = 2826$), cancer ($n = 2541$) and all-cause mortality ($n = 2508$). After multiple adjustments, higher cardiovascular health score was significantly associated with lower risks of 30 (percentage = 66.7%) of 45 primary outcomes, and higher degree of risk factor control was significantly associated with lower risk of 22 (percentage = 48.9%) of 45 primary outcomes (false discovery rate [FDR] corrected $p < 0.05$, Fig. 2). For every 10-point increase in the cardiovascular health score, the top 3 significant associations were chronic obstructive pulmonary disease (hazard ratio [HR] = 0.69; 95% confidence interval [CI] = 0.66–0.73), sleep disorder (HR = 0.70; 95% CI = 0.65–0.74), and peripheral artery disease (HR = 0.70; 95% CI = 0.66–0.75). For every one additional risk factor control, the top 3 significant associations were myocardial infarction (HR = 0.80; 95% CI = 0.75–0.84), peripheral artery disease (HR = 0.80; 95% CI = 0.76–0.84), and intracranial hemorrhage (HR = 0.83; 95% CI = 0.73–0.95). Additionally, higher cardiovascular health score was significantly associated with lower risks of 8 (percentage = 88.9%) of 9 secondary outcomes, and higher degree of risk factor control was

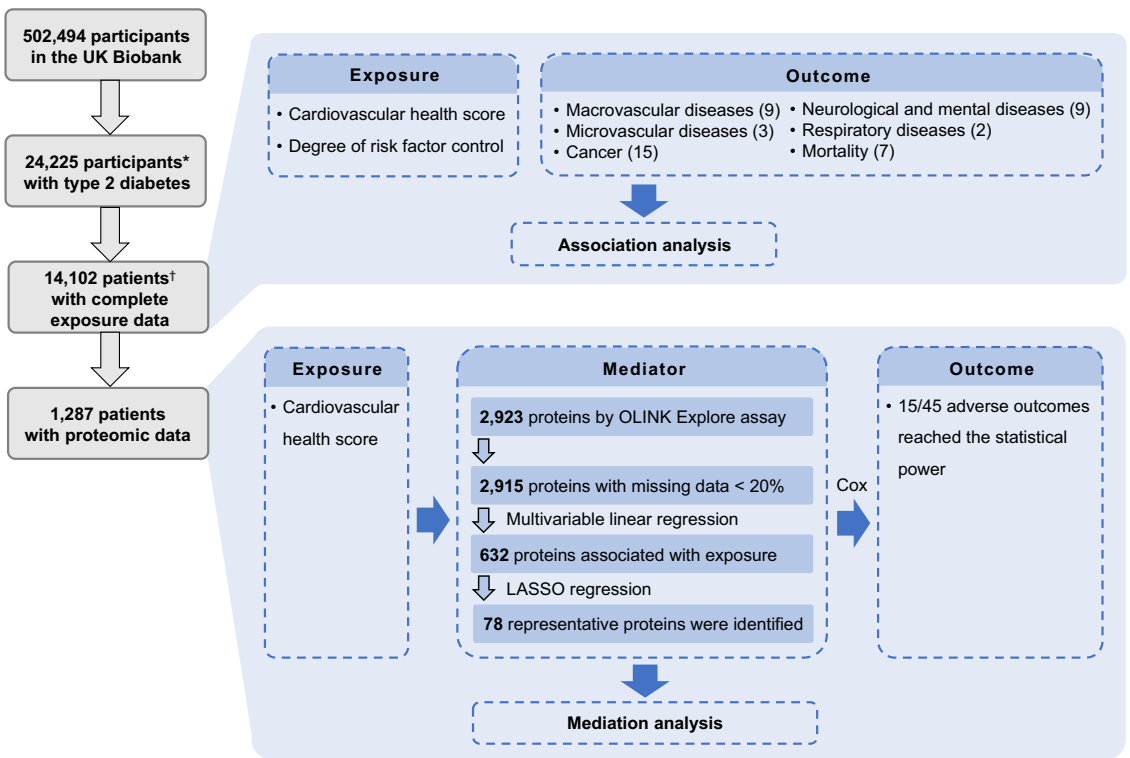

Fig. 1 | Flow chart of study design. *After excluding individuals who refused to participant in follow-up ($n = 127$), and those free from type 2 diabetes at baseline ($n = 478,142$), 24,225 participants with type 2 diabetes were included. †A total sample of 14,102 type 2 diabetes patients with complete exposure data was used in the main analysis after exclusion of participants with missing information on modifiable risk factors ($n = 10,123$). LASSO, the least absolute shrinkage and selection operator.

Table 1 | Baseline characteristics of participants

Characteristics	Cardiovascular health score				*P*-value
	Q1	Q2	Q3	Q4	
No. of participants	3588	3315	3695	3504	
Cardiovascular health score, median (IQR)	43.8 (39.4, 46.9)	53.8 (51.9, 55.6)	61.9 (60.0, 63.8)	71.3 (68.1, 75.0)	<0.001
Age (years), mean (SD)	58.8 ± 7.0	60.1 ± 6.7	60.6 ± 6.6	60.6 ± 6.9	<0.001
Female (%)	1231 (34.3)	1048 (31.6)	1313 (35.5)	1338 (38.2)	<0.001
Ethnicity, White (%)	3331 (92.8)	3028 (91.3)	3309 (89.6)	2977 (85.0)	<0.001
Townsend deprivation index, median (IQR)	−0.7 (−3.0, 2.6)	−1.3 (−3.3, 2.0)	−1.7 (−3.4, 1.3)	−2.0 (−3.5, 0.8)	<0.001
Education (%)					<0.001
High	721 (20.3)	763 (23.3)	942 (25.8)	1164 (33.6)	
Intermediate	1824 (51.5)	1677 (51.1)	1808 (49.5)	1625 (46.9)	
Low	1000 (28.2)	839 (25.6)	905 (24.8)	673 (19.4)	
Income (%)					<0.001
Less than £18,000	1233 (39.6)	1049 (36.9)	1067 (33.4)	855 (28.8)	
£18,000 to £30,999	832 (26.7)	829 (29.1)	953 (29.9)	899 (30.3)	
£31,000 to £51,999	619 (19.9)	578 (20.3)	674 (21.1)	711 (24.0)	
£52,000 to £100,000	366 (11.8)	318 (11.2)	411 (12.9)	402 (13.5)	
Greater than £100,000	62 (2.0)	70 (2.5)	86 (2.7)	101 (3.4)	
Moderate drinking (%)	2174 (61.0)	2154 (65.3)	2432 (66.2)	2364 (67.9)	<0.001
Unemployed (%)	675 (19.0)	408 (12.4)	336 (9.2)	208 (6.0)	<0.001
Diabetes duration, years (IQR)	4.0 (1.6,7.0)	4.0 (1.9, 7.0)	3.8 (1.5, 7.0)	4.0 (1.8, 7.3)	0.290
Diabetes medication					<0.001
None	1008 (28.1)	1011 (30.5)	1175 (31.8)	1183 (33.8)	
Oral medicine only	1958 (54.6)	1837 (55.4)	2032 (55.0)	1810 (51.7)	
Insulin and others	622 (17.3)	467 (14.1)	488 (13.2)	511 (14.6)	
Health score, mean (SD)	42.3 ± 6.1	53.9 ± 2.3	61.8 ± 2.3	72.0 ± 4.7	<0.001
Diet score	39.0 ± 31.0	53.0 ± 31.9	63.6 ± 30.0	79.8 ± 24.3	<0.001
Physical activity score	27.8 ± 38.5	53.2 ± 42.8	78.4 ± 34.5	91.6 ± 21.3	<0.001
Nicotine exposure score	57.4 ± 38.9	73.3 ± 31.5	80.5 ± 26.0	88.8 ± 18.0	<0.001
Sleep health score	76.0 ± 25.9	84.2 ± 22.5	88.8 ± 18.7	93.4 ± 14.1	<0.001
Body mass index score	29.2 ± 24.4	39.2 ± 27.0	48.4 ± 28.1	67.6 ± 26.0	<0.001
Blood lipids score	51.5 ± 28.0	60.7 ± 25.6	65.5 ± 23.1	73.6 ± 18.9	<0.001
Blood glucose score	30.8 ± 11.8	33.3 ± 10.0	34.6 ± 8.9	36.1 ± 7.5	<0.001
Blood pressure score	26.9 ± 21.1	30.9 ± 21.7	34.4 ± 22.6	44.9 ± 26.2	<0.001

Two-sided *t*-test was used for normally distributed continuous variables, Wilcoxon rank-sum test for non-normally distributed continuous variables, and Chi-square test for categorical variables. Percentages may not sum to 100% due to rounding. *P*-values were based on two-sided tests. *SD* standard deviation, *IQR* interquartile range.

significantly associated with lower risk of 5 (percentage = 55.6%) of 9 secondary outcomes ($p_{FDR} < 0.05$, Supplementary Fig. 1). The associations were mostly similar when cardiovascular health score was treated as quartiles (Supplementary Table 1). When using the restricted cubic spline analyses to detect the dose-response relationship, the associations between cardiovascular health score and future health outcomes were generally linear (Supplementary Fig. 2, 3). In stratified analyses by sex (male, female), results were largely consistent, with no significant interactions (Supplementary Table 2, 3). When stratified by age (<60 years, ≥60 years), the health benefit of risk factor control on diabetic retinopathy was more pronounced among individuals aged 60 years or younger (p_{FDR} <0.05, Supplementary Table 4, 5). In sensitivity analyses, the results remained essentially unchanged when using competing risk model, excluding participants whose outcomes occurred within 1 year of follow-up, or including those who had missing information on any cardiovascular health metrics (Supplementary Table 6–11).

Identifying proteins associated with cardiovascular health score

Proteomic analyses were conducted among 1287 participants with type 2 diabetes who were randomly selected by the UK Biobank Pharma Proteomics Project for proteomic detection. The characteristics of participants with proteome data are presented in Supplementary Table 12, and no significant difference was found between populations included in the main cohort and those included in proteomic subset (Supplementary Table 13). After multiple linear regression, 632 of 2915 proteins were significantly associated with cardiovascular health score ($p_{Bonferroni}$ <0.05, Fig. 3, Supplementary Data 1). Out of these proteins, 20 proteins showed positive associations with cardiovascular health score, and the top 2 significant proteins were WFIKKN2 (WAP, Kazal, immunoglobulin, Kunitz and NTR domain-containing protein 2) and NCAN (neurocan core protein); 612 proteins showed negative associations with cardiovascular health score, and the top 2 significant proteins were LEP (leptin) and FABP4 (fatty acid-binding protein, adipocyte). Then, Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) enrichment analyses were conducted for the 632 proteins; these proteins are mainly involved in leukocyte migration, cell adhesion, immune response, and cytokine-cytokine receptor interaction (Supplementary Fig. 4). After the least absolute shrinkage and selection operator (LASSO) regression, 78 representative proteins were identified for

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Conditions	Events/person-years	HR (95% CI) per 10 points increment of CVH score	P_{FDR}*	HR (95% CI) per 1 additional risk factor control	P_{FDR}*
Macrovascular complications					
Peripheral artery disease	760/172135	0.70 (0.66, 0.75)	<.001	0.80 (0.76, 0.84)	<.001
Heart failure	1501/168361	0.74 (0.71, 0.77)	<.001	0.85 (0.82, 0.89)	<.001
Myocardial infarction	785/159792	0.78 (0.74, 0.83)	<.001	0.80 (0.75, 0.84)	<.001
MACE	2826/124531	0.79 (0.76, 0.81)	<.001	0.86 (0.83, 0.88)	<.001
Ischemic stroke	672/172104	0.80 (0.74, 0.85)	<.001	0.84 (0.80, 0.89)	<.001
Ischemic heart disease	2147/135166	0.80 (0.77, 0.83)	<.001	0.86 (0.84, 0.89)	<.001
Stroke	731/167260	0.81 (0.76, 0.86)	<.001	0.85 (0.81, 0.90)	<.001
Atrial fibrillation	1850/162262	0.81 (0.78, 0.85)	<.001	0.90 (0.87, 0.94)	<.001
Intracranial hemorrhage	125/176007	0.84 (0.72, 0.98)	0.05	0.83 (0.73, 0.95)	0.01
Microvascular complications					
Diabetic kidney disease	2326/166970	0.77 (0.74, 0.80)	<.001	0.88 (0.85, 0.90)	<.001
Diabetic neuropathy	787/172006	0.83 (0.78, 0.88)	<.001	0.91 (0.87, 0.96)	0.001
Diabetic retinopathy	1658/167117	0.89 (0.85, 0.93)	<.001	0.90 (0.87, 0.93)	<.001
Cancer					
Esophagus cancer	70/176559	0.73 (0.60, 0.90)	0.006	0.88 (0.73, 1.05)	0.23
Hepatocellular carcinoma	89/176562	0.76 (0.63, 0.91)	0.005	0.84 (0.72, 0.99)	0.06
Lung cancer	220/176278	0.82 (0.73, 0.92)	0.002	0.94 (0.85, 1.04)	0.32
Kidney cancer	276/176123	0.83 (0.69, 1.00)	0.07	0.96 (0.82, 1.12)	0.66
Colorectal cancer	81/173978	0.87 (0.78, 0.97)	0.01	0.92 (0.84, 1.01)	0.12
Bladder cancer	89/175937	0.88 (0.72, 1.08)	0.27	0.95 (0.81, 1.13)	0.65
Endometrial cancer	63/62533	0.97 (0.78, 1.20)	0.82	1.03 (0.86, 1.24)	0.78
All site cancer	2541/146254	0.99 (0.95, 1.02)	0.61	1.01 (0.98, 1.04)	0.51
Gastric cancer	47/176589	1.02 (0.79, 1.32)	0.89	1.13 (0.91, 1.40)	0.33
Leukemia	60/176366	1.02 (0.81, 1.29)	0.86	1.01 (0.83, 1.22)	0.94
Malignant melanoma cancer	418/175731	1.03 (0.85, 1.25)	0.80	1.00 (0.85, 1.17)	1.00
Pancreatic cancer	96/176597	1.06 (0.88, 1.27)	0.62	1.07 (0.92, 1.24)	0.49
Breast cancer	79/59907	1.08 (0.96, 1.22)	0.25	1.06 (0.96, 1.17)	0.30
Prostate cancer	87/109086	1.10 (1.00, 1.20)	0.06	1.08 (1.00, 1.16)	0.06
Non-Hodgkin lymphoma	212/176049	1.13 (0.92, 1.39)	0.29	1.12 (0.95, 1.33)	0.23
Neurological and mental diseases					
Sleep disorder	730/164494	0.70 (0.65, 0.74)	<.001	0.86 (0.81, 0.90)	<.001
Depression	840/155009	0.80 (0.75, 0.85)	<.001	0.88 (0.84, 0.92)	<.001
Vascular dementia	220/176383	0.81 (0.72, 0.91)	0.001	0.87 (0.79, 0.96)	0.01
Epilepsy	179/174182	0.83 (0.73, 0.95)	0.009	0.98 (0.87, 1.09)	0.71
Anxiety	826/166552	0.87 (0.82, 0.92)	<.001	0.95 (0.90, 1.00)	0.06
All-cause dementia	712/174887	0.90 (0.84, 0.96)	0.004	0.94 (0.89, 1.00)	0.06
Migraine	166/171362	0.95 (0.83, 1.09)	0.56	0.88 (0.79, 0.99)	0.06
Parkinson's disease	206/175901	0.97 (0.86, 1.10)	0.71	0.97 (0.87, 1.07)	0.62
Alzheimer's diseases	235/176221	1.03 (0.92, 1.16)	0.68	1.06 (0.96, 1.16)	0.34
Respiratory system disorders					
COPD	1102/165556	0.69 (0.66, 0.73)	<.001	0.86 (0.82, 0.89)	<.001
Asthma	493/149355	0.86 (0.80, 0.93)	<.001	0.93 (0.87, 0.99)	0.04
Mortality					
Digestive mortality	115/167397	0.74 (0.63, 0.87)	<.001	0.85 (0.74, 0.98)	0.05
CVD mortality	702/167397	0.75 (0.70, 0.80)	<.001	0.84 (0.79, 0.89)	<.001
Respiratory mortality	190/167397	0.79 (0.70, 0.90)	<.001	0.85 (0.76, 0.94)	0.007
All-cause mortality	2508/167397	0.81 (0.78, 0.83)	<.001	0.88 (0.86, 0.91)	<.001
Other cause mortality	413/167397	0.81 (0.74, 0.88)	<.001	0.90 (0.84, 0.97)	0.009
Cancer mortality	960/167397	0.86 (0.81, 0.91)	<.001	0.92 (0.88, 0.97)	0.002
Neurodegenerative mortality	128/167397	0.87 (0.74, 1.02)	0.11	0.89 (0.78, 1.01)	0.12

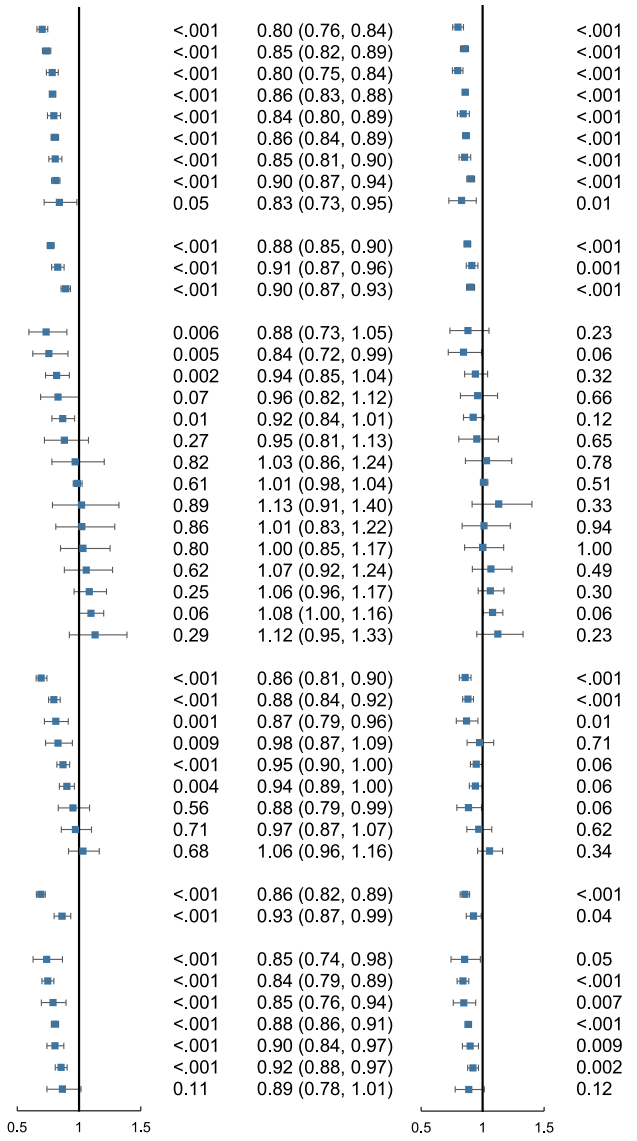

Fig. 2 | Associations between cardiovascular health score and risk factor control with six types of common complications of type 2 diabetes. The squares represent the estimated HRs and error bars represent the 95% confidence intervals. The vertical line represents HR = 1.0. Multiple Cox proportional hazards regression model was adjusted for age (continuous, years), sex (male, female), ethnicity (white, others), Townsend Deprivation Index (continuous), educational attainment (high, intermediate, low), employment status (employed, unemployed), household income (<£18 000, £18 000-£30 999, £31 000-£51 999, £52 000-£100 000, > £100 000), alcohol consumption (yes, no), diabetes duration (continuous, years), and use of diabetes medication (none, oral hypoglycemic drugs only, insulin therapy and others). *FDR method was applied to adjust two-sided *p*-values. HR hazard ratio, CI confidence interval, CVH cardiovascular health, FDR false discovery rate, CVD cardiovascular disease, MACE major adverse cardiovascular events, COPD chronic obstructive pulmonary disease.

mediation analysis (Supplementary Fig. 5). For sensitivity analysis using elastic net regression, a total of 87 representative proteins were identified, of which 78 proteins overlapped with the LASSO-identified proteins (Supplementary Fig. 6).

Mediation analysis

In proteomic subset, cardiovascular health score was negatively associated with 11 of 15 primary outcomes (the process of outcome selection was shown in the Methods) (p_{FDR} <0.05, Supplementary Fig. 7). By evaluating mediation effects of 78 representative proteins on associations of cardiovascular health score with 11 outcomes, 39 significant mediators were detected (Supplementary Table 14). These 39 proteins are mainly involved in cytokine-cytokine receptor interaction, mitogen-activated protein kinase (MAPK) cascade, leukocyte migration, and hypoxic response (Supplementary Fig. 8). UMOD (uromodulin), ACVRL1 (serine/threonine-protein kinase receptor R3), ADM (pro-adrenomedullin), CD59 (CD59 glycoprotein), HAVCR1 (hepatitis A virus cellular receptor 1), and VWC2 (brorin) were the top 6 proteins that exhibited the highest frequency in mediation analyses (Fig. 4). UMOD showed consistent mediation effects on associations of cardiovascular health score and 9 outcomes, with mediation proportions ranging from 10.1% (95% CI = 4.4%–21.3%) to 37.1% (95% CI = 12.4%–71.2%). ADM exhibited the highest mediation proportions in 6 associations, including cardiovascular health score with all-cause and CVD mortality, MACE, ischemic heart disease, heart failure, and peripheral artery disease; the mediation proportions ranged from 20.7% (95% CI = 10.1%–37.7%) to 49.4% (95% CI = 12.4%–87.1%). The association between cardiovascular health score and diabetic kidney disease

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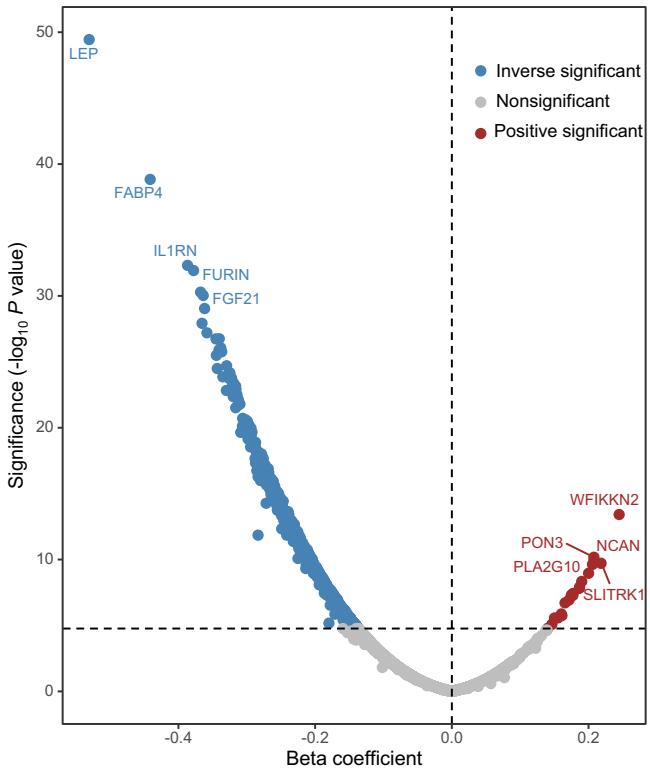

Fig. 3 | Volcano plot of associations between cardiovascular health score and 2915 proteins among participants with type 2 diabetes. The *x*-axis shows the correlation coefficient (β) of cardiovascular health score with protein, and the *y*-axis represents its statistical significance (-$\log_{10}$ *p*-values). The two-sided *p*-values of less than 0.05/2915 were considered significant. Multiple linear regression model was adjusted for age (continuous, years), sex (male, female), ethnicity (white, others), Townsend Deprivation Index (continuous), educational attainment (high, intermediate, low), employment status (employed, unemployed), household income (<£18 000, £18 000-£30 999, £31 000-£51 999, £52 000-£100 000, > £100 000), alcohol consumption (yes, no), diabetes duration (continuous, years), and use of diabetes medication (none, oral hypoglycemic drugs only, insulin therapy and others). LEP leptin, FABP4 fatty acid-binding protein, adipocyte, IL1RN interleukin-1 receptor antagonist protein, FURIN furin, FGF21 fibroblast growth factor 21, PLA2G10 group 10 secretory phospholipase A2, SLITRK1 SLIT and NTRK-like protein 1, PON3 serum paraoxonase/lactonase 3, NCAN neurocan core protein, WFIKKN2 WAP, Kazal, immunoglobulin, Kunitz and NTR domain-containing protein 2. Source data are provided as a Source Data file.

was mediated by the largest number of plasma proteins, with HAVCR1 exhibiting the highest mediation proportions (84.4%; 95% CI = 2.9%–99.9%). We also performed mediation analysis for the nine additionally identified proteins in elastic net regression as a supplement, and six proteins showed mediation effect on associations of cardiovascular health score with mortality and macro- and microvascular diseases (Supplementary Table 15). Additionally, we further performed mediation analysis for four non-significant exposure-outcome associations on request of the peer reviewer, and seven proteins were detected to mediate the association of cardiovascular health score with atrial fibrillation (Supplementary Table 16). In sensitivity analysis that estimated the potential influence of unmeasured confounding, the above mediation analyses were relatively sensitive to the possible existence of unmeasured confounders (Supplementary Table 17).

Discussion

In this prospective cohort study, a combination of healthy lifestyles and favorable metabolic status was associated with lower risks of mortality and diseases involving multiple systems and organs among individuals with type 2 diabetes. The proteome associations with cardiovascular health score identified 632 out of 2915 proteins, with WFIKKN2 and NCAN exhibiting the strongest positive and LEP and FABP4 exhibiting the strongest negative associations with cardiovascular health score. Among LASSO-identified representative proteins, 39 proteins showed mediation effects and UMOD, ACVRL1, ADM, CD59, HAVCR1, and VWC2 were the top 6 proteins that exhibited mediating role in the largest number of associations between combined modifiable risk factors and future health risks.

Numerous studies have demonstrated increased risks of various diseases in people with type 2 diabetes compared to healthy individuals[8]. To improve the quality of life, there needs more measures, beyond glucose control to prevent premature and adverse health conditions among people with type 2 diabetes. Recently, there has been growing interest in understanding the updated definition of cardiovascular health, defined by Life's Essential 8 (LE8), with physical and psychological health. Although epidemiological studies have observed that maintaining ideal cardiovascular health was associated with lower risks of mortality and some chronic diseases in the general population[19,20], few studies were conducted to investigate the health benefits among people with type 2 diabetes. Furthermore, the application of cardiovascular health on outcomes among diabetic patients was predominantly narrowed to mortality and vascular diseases[10,21,22], evidence linking cardiovascular health to a broader range of health outcomes is scarce, which restricted our perception of the health benefits of modifying these risk factors among individuals with type 2 diabetes. This study filled this gap and added evidence about the protective effect of combined healthy lifestyle and favorable metabolic status on common complications of type 2 diabetes, including certain cancers and disorders of diverse systems and organs, beyond mortality and vascular diseases. Our results suggested that each additional risk factor within the target, or even just an improvement in modifiable risk factor may yield significant health benefits for individuals with type 2 diabetes. Nevertheless, we acknowledged that the included complications were not exhaustive, though six types of common complications and four types of additional complications of type 2 diabetes were included based on the UK Biobank data and previous studies[23,24]. Therefore, further research is warranted to confirm the validity of our findings. Additionally, compared with a prior study that reported associations between cardiovascular health score and risk of multiple non-communicable chronic diseases among the general population[20], we found that several associations with specific outcomes may differ by diabetes status, such as atrial fibrillation and sleep disorders. This may be partially explained by disparity of metabolism status and pathophysiologic factors between populations with and without type 2 diabetes. Similarly, the associations with outcomes may also be influenced by types of diabetes, and future research should explore whether distinct patterns of associations emerge among individuals with type 1 diabetes.

Despite the health benefits of modifying risk factors, how they relate to health at a molecular level remains poorly understood. In our study, 632 of 2915 proteins were significantly associated with combined modifiable risk factors among individuals with type 2 diabetes. Among these identified proteins, WFIKKN2 and NCAN were the top two proteins that were positively associated with cardiovascular health score. WFIKKN2 was reported to be implicated in the regulation of muscle growth and development[25], and showed a bi-directional causal relationship with body mass index (BMI)[26]. NCAN was found to play a role in the regulation of lipid concentrations[27], and be negatively associated with onset of type 2 diabetes[28] and positively associated with BMI[29]. In addition, LEP and FABP4 exhibited the strongest negative associations with cardiovascular health score. Both LEP and FABP4 have been revealed pronounced effects on energy metabolism and fat deposition[30,31], and were previously reported to correlate with diet[17],

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physical activity, and body fat[14] in population-based studies. Beyond observational studies, LEP and FABP4 showed the strongest positive causal associations with BMI in two Mendelian randomization studies from the UK and China[18,29]. These results suggest that one of the most direct impacts of modifying these eight risk factors may be improvement in metabolism status and further benefit individual's health.

The mediation analyses contribute to facilitating our understanding of the associations between modifiable risk factors and future

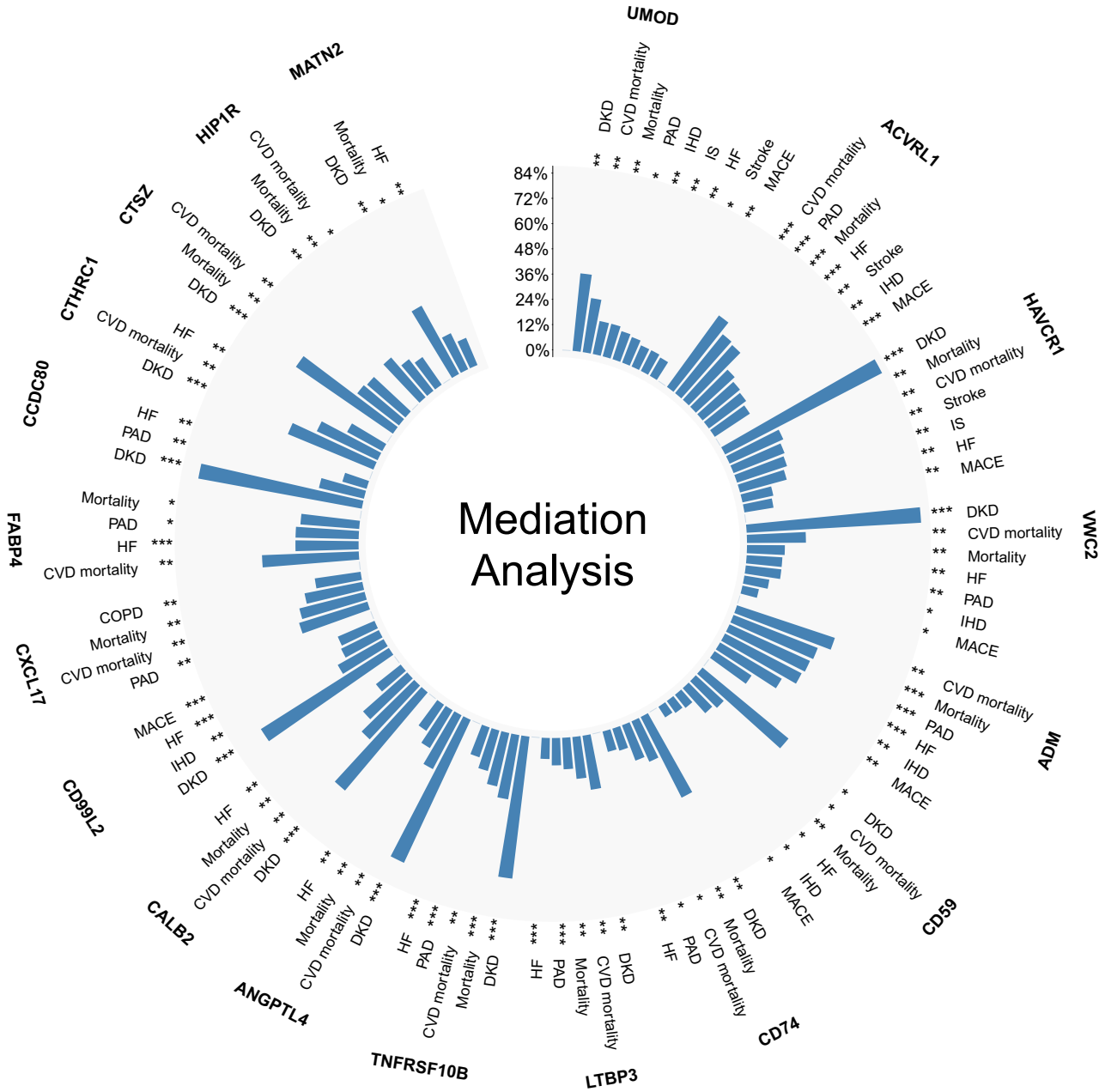

Fig. 4 | The estimated mediation proportions of proteins on the associations of cardiovascular health score with adverse health conditions among participants with type 2 diabetes[†]. The bars represent the estimated mediation proportion of protein on the association of cardiovascular health score with corresponding adverse outcomes. Mediation analyses were adjusted for age (continuous, years), sex (male, female), ethnicity (white, others), Townsend Deprivation Index (continuous), educational attainment (high, intermediate, low), employment status (employed, unemployed), household income (<£18 000, £18 000-£30 999, £31 000-£51 999, £52 000-£100 000, >£100 000), alcohol consumption (yes, no), diabetes duration (continuous, years), and use of diabetes medication (none, oral hypoglycemic drugs only, insulin therapy and others). The false discovery rate (FDR) method was applied to adjust two-sided *p*-values. *0.01 ≤ FDR adjusted *p*-value < 0.05; **0.001 ≤ FDR adjusted *p*-value < 0.01; ***FDR adjusted *p*-value < 0.001; [†] The figure shows estimated mediation proportions of 19 proteins mediating at least three associations between cardiovascular health score and adverse health conditions. DKD diabetic kidney disease, CVD cardiovascular disease, PAD peripheral artery disease, IHD ischemic heart disease, IS ischemic stroke, HF heart failure, MACE major adverse cardiovascular events, COPD chronic obstructive pulmonary disease, Mortality all-cause mortality. UMOD uromodulin, ACVRL1 serine/threonine-protein kinase receptor R3, HAVCR1 hepatitis A virus cellular receptor 1, VWC2 brorin, ADM pro-adrenomedullin, CD59 CD59 glycoprotein, CD74 HLA class II histocompatibility antigen gamma chain, LTBP3 latent-transforming growth factor beta-binding protein 3, TNFRSF10B tumor necrosis factor receptor superfamily member 10B, ANGPTL4 angiopoietin-related protein 4, CALB2 calretinin, CD99L2 CD99 antigen-like protein 2, CXCL17 C-X-C motif chemokine 17, FABP4 fatty acid-binding protein, adipocyte, CCDC80 coiled-coil domain-containing protein 80, CTHRC1 collagen triple helix repeat-containing protein 1, CTSZ cathepsin Z, HIP1R huntingtin-interacting protein 1-related protein, MATN2 matrilin-2. Source data are provided as a Source Data file.

health risks. We found that 39 proteins mediated at least one association between exposure and outcomes. These proteins are mainly involved in cytokine-cytokine receptor interaction, MAPK cascade, leukocyte migration, and hypoxic response. Nevertheless, mechanism research of these proteins is needed to elucidate their function upon our exploratory results and offer more immediate insights into their effects linking modifiable risk factors and adverse health outcomes. Intriguingly, we observed that UMOD, a protein exclusively produced by renal, plays a relevant role in the largest number of associations between modifiable risk factors and outcomes; nine exposure-disease associations collectively mediated by UMOD, including associations of modifiable risk factors with all-cause mortality, CVD mortality, and 7 macro- and microvascular diseases. UMOD was previously indicated to be involved in the regulation of ion transport and blood pressure, immunomodulation, and protection against urinary tract infections[32]. Population-based studies observed a positive association of serum UMOD level with kidney function among healthy individuals or those with chronic kidney diseases[33,34]. Furthermore, a negative correlation between serum UMOD level and risk of metabolic syndrome and cardiovascular diseases was also observed among individuals with diabetes or coronary artery disease[35,36]. Increasing research implicated that serum UMOD may serve as a valuable biomarker of cardiovascular diseases extending beyond kidney function[37]. Our findings support the potential role of UMOD in association between modifiable risk factors and cardiovascular diseases as well as kidney diseases among individuals with type 2 diabetes and suggest that UMOD may be worthy of deeper exploration in the future. Another remarkable protein was ADM, which exhibited the highest mediation proportion in associations of combined modifiable risk factors with all-cause mortality, CVD mortality, and four vascular diseases, and also showed a relatively high mediation proportion in the association with sleep disorders. As a stable precursor of adrenomedullin, ADM has increasingly shown promise for prognostic assessment in patients with heart failure[38] or atherosclerotic vascular diseases, such as myocardial infarction[39,40]. Our results provided further evidence for a mediating role of ADM in association of modifiable risk factors with vascular diseases. Evidence regarding the association of ADM with sleep disorder is limited[41], therefore more research is warranted in the future. In addition, several proteins exhibited notable mediation proportions in association between combined modifiable risk factors and diabetic kidney disease. Among these proteins, HAVCR1, also known as kidney injury molecule 1, showed the highest mediation proportion in the above association. HAVCR1 was proved to be at a low level in healthy individuals but significantly increased in people with acute and chronic kidney diseases[42]. Available evidence demonstrated a close relationship between HAVCR1 and kidney damage and the US Food and Drug Administration has approved HAVCR1 as a valuable predictor for acute kidney injury for preclinical drug development[43]. Although the exact reason for the notable mediation effects remains to be discovered, our findings still have an important implication that HAVCR1 and other proteins with high mediation proportions may play a critical role in association of modifiable risk factors with diabetic kidney disease. Of note, careful interpretation is needed considering the restricted sample size, potential disparity of proteomic subset with the main cohort, and the potential influence of unmeasured confounding. Nevertheless, the mediation analysis of proteomics may still provide preliminary insights and generate hypotheses for future research. Subsequent studies, with more rigorous designs and larger sample sizes, are required to validate our results. In addition, although research exploiting other methods, such as Mendelian randomization, could provide further causal inference, there are notable limitations to apply this method in our studied population. Because GWAS studies are generally conducted in the general populations, which may not adequately capture the unique genetic effects in people with type 2 diabetes. Further, given the distinct genetic profiles, disordered metabolic status, and complex medication histories of individuals with type 2 diabetes, it remains largely unclear whether pleiotropy and effect modification may occur. Thus, well-designed Mendelian randomization studies are warranted to confirm and expand upon our findings in the future.

This study comprehensively investigates the relationship of the combination of lifestyle behaviors and cardiometabolic status with a wide range of future health risks among individuals with type 2 diabetes. Furthermore, the application of high throughput proteomic technology offers an opportunity to delineate the proteomic profile of combined modifiable risk factors and enables us to evaluate the potential role of plasma proteins in associations between modifiable risk factors and future health risks. Nevertheless, several limitations of this study warrant acknowledged. Firstly, due to the observational study design, causal relationships between modifiable risk factors, plasma proteins, and future health risks could not be demonstrated, and residual or unknown confounding could not be completely ruled out. Additionally, given that sensitivity analysis indicated that the estimated mediation proportion was sensitive to potential unmeasured confounding, mechanistic investigations and well-designed Mendelian randomization studies are needed to confirm and expand upon our findings. Secondly, the information on lifestyle behaviors was self-reported, which is prone to measurement errors and misclassification bias. Thirdly, complete information on eight modifiable risk factors was available for 58% of type 2 diabetic patients from the UK Biobank, thus selection bias might exist. Nevertheless, the results remained similar after imputing missing information on modifiable risk factors. Fourthly, there is potential discrepancy between the main cohort and the subset for mediation analyses, though we did not observe significant difference in the major characteristics. Additionally, weak associations might be overlooked due to the limited sample size of the proteomic subset. Hence, future study, with more rigorous designs and larger sample sizes, is warranted to confirm these results. Fifthly, the lack of an external validation cohort of the proteins related to combined modifiable risk factors is a potential concern, even though we conducted 10-fold internal cross-validations. Sixthly, mediation analysis assumes causality between modifiable risk factors and plasma proteome, while both modifiable risk factors and plasma proteome were collected at the same time in the UK Biobank. Seventhly, we recognized that the selected proteins for mediation analyses may not be completely independent, although we used the LASSO regression to reduce the collinearity between the selected proteins. This limitation may result in potential overlap in mediation effect between mediators. Additional mechanism research is still warranted to explore potential correlations among proteins. Eighthly, lifestyle and cardiometabolic risk factors tend to change over time, while the exposure in our study was measured only once, which could not account for longitudinal changes. Further research is needed to investigate the effects of changes in modifying risk factors over time on health risks. Finally, the ethnic homogeneity of the study may restrict the generalizable of our results to other ethnic groups.

In conclusion, adherence to healthy lifestyle behaviors and favorable cardiometabolic status was associated with lower risks of a wide range of diseases and mortality among individuals with type 2 diabetes. Our findings bolster the importance of public health programs aimed at improving modifiable risk factors to mitigate future health risks for people with type 2 diabetes. Additionally, a number of plasma proteins were observed to correlate with combined modifiable risk factors and showed significant mediation effects on the above relationships.

Methods

Ethics statement

The UK Biobank received ethical approval from the North West Multicentre Research Ethical Committee. All participants provided written

informed consent. This research was done under UK Biobank application number 109546.

Study population

The UK Biobank is a large population-based cohort study, which recruited around half a million participants aged 37–73 years in 2006–2010 across England, Scotland, and Wales. Each participant completed touchscreen questionnaires, underwent physical examinations, and provided biological samples[44].

Prevalent cases of type 2 diabetes were identified through a validated algorithm developed by UK Biobank that used self-reported medical history and medication information at baseline and has been shown to be a reliable measurement with 96% accuracy[45]. A total of 24,225 participants with type 2 diabetes were identified. After exclusion of participants with incomplete data on modifiable risk factors (n = 10,123), 14,102 were included in the association analyses. After excluding those without proteome data, 1287 participants with type 2 diabetes were included in the proteomic analyses and mediation analyses (Fig. 1). Condition-specific exclusions were performed; those with previous diagnosis of a disease at baseline were excluded from the corresponding analysis.

Definition of cardiovascular health score and degree of risk factors control

The cardiovascular health score was calculated based on the LE8 metrics according to the American Heart Association in 2022[46]. In brief, the components of LE8 include four life behaviors (diet, physical activity, nicotine exposure, and sleep duration) and four cardiometabolic factors (BMI, blood lipids, blood glucose, and blood pressure). Each component metric score ranges from 0 to 100 points, with a higher score indicating a better lifestyle or cardiometabolic status. Data on diet, physical activity, nicotine exposure, and sleep duration, was self-reported. The dietary quality was evaluated using a recommendation for cardiovascular health which considered consumption of fruits, vegetables, whole grains, refined grains, fish, dairy products, vegetable oils, processed meats, unprocessed meats, and sugar-sweetened beverages[47]. Physical activity was evaluated according to the total duration of moderate or vigorous physical activity per week. Nicotine exposure was evaluated based on self-reported use of cigarettes, smoking cessation, and secondhand smoke exposure. Sleep health was assessed according to average hours of sleep per night. Weight and height were measured during physical examination. BMI was determined as weight in kilograms divided by the square of height in meters. Random blood samples at baseline were drawn for blood biomarkers, including total cholesterol, high-density lipoprotein (HDL) cholesterol, glucose levels, and glycosylated hemoglobin (HbA_{1c}); the blood biomarkers have been externally validated in the UK Biobank[48]. Serum total and HDL cholesterol levels and self-reported use of antihyperlipidemic medication were used to evaluate blood lipid metric. Serum glucose levels (among those with fasting time >8 h) and HbA_{1c} were used to evaluate blood glucose metric. The blood pressure metric was based on systolic and diastolic blood pressures (SBP, DBP) measured during physical examination and self-reported use of antihypertensive medication. Detailed information is shown in Supplementary Table 18. All self-reported information, physical examination data, and blood sample for each participant were obtained at the initial assessment visit. The cardiovascular health score was calculated as the average of eight component metric scores and was treated as both a continuous score as well as quartiles in the analyses.

In addition, we defined degree of risk factor control according to the target ranges of these 8 risk factors based on guidelines for diabetes[7,8,49,50] and combined with the LE8 definition: healthy diet (adherence to at least five items of the recommendations); at least 150 min physical activity each week; non-current smoker; sleep duration ≥7 h and <9 h; BMI <25 kg/m^2; HbA_{1c} < 7%; non-HDL cholesterol <130 mg/dL; and SBP <140 mmHg and DBP <90 mmHg. A detailed definition of risk factor control can be found in Supplemental Table 19. Each risk-factor variable on target receives 1 point, resulting in a total risk factor control score ranging from 0 –8, with a higher degree indicating more risk factors within the target range.

Proteomics data

The UK Biobank Pharma Proteomics Project includes 53,017 participants, among whom 46,788 individuals were randomly selected from baseline. The randomized samples are highly representative of the overall UK Biobank population and were included in our analyses[51]. Details of data processing and quality control have been described on the UK Biobank online resource[52,53]. In brief, the plasma samples were stored in a −80 °C freezer before being shipped on dry ice to Olink Analysis Service in Sweden. Proximity Extension Assay, in combination with Next-Generation Sequencing, was utilized to parallelly measure relative concentrations of 2923 unique proteins using the Olink proteomics platform. Measurements are expressed as normalized protein expression values (log_2-transformed). After excluding eight proteins with missing values of >20%, a total of 2915 proteins were included in the proteomic analyses. All protein levels were standardized in the analyses.

Ascertainment of outcomes

Based on UK Biobank data and previous research on complications of type 2 diabetes, ten types of complications were taken into consideration[23,24]. In the primary analyses, six types of common complications were included, including macro- and microvascular diseases, cancer, neurological and mental diseases, respiratory diseases, and mortality. In the secondary analyses, disorders of digestive, endocrine, genitourinary, and musculoskeletal system were included. International Classification of Disease version 10 was used to define outcomes (Supplementary Table 20). Information on cancer and death was obtained from cancer registry data and death registry data. Other incident outcomes were identified through linkage with hospital admissions data. Death data were available up to 12 November 2021 for all participants. The electronic health records were available up to 1 November 2022, 25 September 2021, and 29 May 2021 for centers in England, Scotland, and Wales, respectively. Patients were censored at time of events onset, death, loss to follow-up, or end of follow-up, whichever occurred first.

Assessment of covariates

Demographic (age, sex, and ethnicity) and socioeconomic factors (household income, educational attainment, employment status, and Townsend deprivation index), alcohol consumption, and diabetes-related factors (diabetes duration and use of diabetes medication) were collected at baseline through a touchscreen questionnaire and nurse-led interviews. Household income before tax included five groups, i.e., <£18 000, £18 000-£30 999, £31 000-£51 999, £52 000-£100 000, and >£100 000. Educational attainment was classified into three groups, i.e., high (college or university degree), intermediate (A levels, AS levels, or equivalent; O levels, GCSEs, or equivalent; CSEs or equivalent; NVQ, HND, HNC, or equivalent; other professional qualifications), and low qualification (none of the above). Employment status was divided into employed (those in paid employment or self-employed, retired, doing unpaid or voluntary work, or being full or part-time students) and unemployed (those unemployed, looking after home and/or family, or unable to work because of sickness or disability). Townsend deprivation index scores represented the levels of socioeconomic deprivation. Moderate drinking was defined as 1–14 g alcohol consumption per day for women or 1–28 g alcohol consumption per day for men[54].

Statistical analysis

Baseline characteristics were examined using Chi-squared test or *t*-test (Wilcoxon rank-sum test for non-normal distributed continuous variables) according to the quartiles of cardiovascular health score.

Multiple Cox proportional hazards regression model was used to calculate the HRs and 95% CIs for the associations of cardiovascular health score (as a continuous score and quartiles) and degree of risk factor control (as a continuous score) with primary and secondary outcomes in the main cohort (n = 14,102). Schoenfeld residuals were used to test the proportional hazards assumption, and no violation was observed. The multiple regression models adjusted for age (continuous, years), sex (male, female), ethnicity (white, non-white), Townsend deprivation index (continuous), education attainment (high, intermediate, and low qualifications), employment status (employed, unemployed), household income before tax (<£ 18 000, £ 18 000-£ 30 999, £ 31 000-£ 51 999, £ 52 000-£ 100 000, >£ 100 000), moderate alcohol consumption (yes, no), diabetes duration (continuous, years), and diabetes medicine use (none, oral hypoglycemic drugs only, insulin therapy and others). The missing values of covariates were <20% and were imputed using multiple imputations with 5 imputations (SAS PROC MI). The results from the Cox regression analyses were pooled using Rubins's rule. In addition, a restricted cubic spline model with three knots (10th, 50th, and 90th percentiles) was performed to explore the dose-response relationship between cardiovascular health score and risk of primary and secondary outcomes.

Stratified analyses were performed to examine the association of cardiovascular health score and degree of risk factor control with risks of outcomes by age (<60 years, ≥60 years) and sex (male, female). Potential modifying effects of stratified factors were examined by testing the corresponding multiplicative interaction terms. Regarding sensitivity analyses, we used competing risk model to correct the competitive risk of death. To reduce the risk of reverse causation, which might arise from the influence of pre-existing or latent conditions on the modifiable risk factors at baseline, we conducted sensitivity analyses after excluding individuals who died or developed endpoints within the first year of follow-up. Additionally, 42% of participants with type 2 diabetes were excluded from our analyses due to missing values of any modifiable risk factors, potentially leading to selection bias. To address this concern, we conducted multiple imputation to impute missing information on risk factors, subsequently repeating the above analyses to test the robustness of our results.

All analyses below that related to plasma proteomics were carried out in the proteomic subset (n = 1287). To build proteomics profiles for cardiovascular health score, multiple linear regression model was used to assess the association between every one of 2915 proteins and cardiovascular health score adjusting for the same confounders as the Cox model. Bonferroni's correction was applied for multiple testing. Further, we conducted the KEGG and GO enrichment analyses to elucidate the pathways and biological processes related to proteins that were derived from the previous step[55,56], using the online software Hiplot (https://hiplot.com.cn/). Hiplot is a comprehensive data computing and visualization cloud platform based on the R language. The clusterProfiler package produced GO and KEGG enrichment analyses in Hiplot. The KEGG database with the species selected as *Homo sapiens* was used to analyze the relevant genes. GO analysis involves biological processes (BP), cell composition (CC), and molecular function (MF). The rankings of relevant pathways, BP, CC, or MF terms were based on the p-value, which represents the statistical significance of the enrichment observed for a particular KEGG pathway or GO term.

In order to further select representative proteins for mediation analyses, the LASSO regression (R package glmnet) was utilized to select candidate proteins from the proteomic profile of cardiovascular health score[57]. A 10-fold cross-validation was performed to screen the optimal tuning parameter lambda.min. Firstly, the original dataset was randomly divided into ten subsets of equal size. Secondly, nine of the subsets are selected as the training set to train the model, while the remaining subset serves as the testing set to evaluate the model's performance. The training and testing process was conducted ten times with a different testing set each time. The final estimate of the model's performance was calculated as the average of these ten performance metrics. Since the small sample size of the proteomic subset might influence the stability of results and the cross-validation estimator can have high variance, we set 1000 seeds (ranging from 1 – 1000) to repeat the LASSO regression 1000 times to prevent overfitting and promote stability. Only the proteins with 100% repeatability (non-zero coefficients during 1000 LASSO regressions) would be selected as representative proteins for further analyses[58,59]. Additionally, we performed a sensitivity analysis using elastic net regression, which applies a weaker penalty to coefficients to select proteins[60].

The mediation analysis was performed to evaluate the mediation effect of representative proteins on associations of combined modifiable risk factors with risk of common complications of type 2 diabetes. Nevertheless, given the limited sample size of proteomic subset, we estimated statistical power using PASS (version 15.0.5) before association analyses to ensure that these analyses had sufficient sensitivity to detect true associations at an adjusted significant level[61]. Specifically, the power calculation was based on the following parameters: sample size (N), effect size (HR), significant level (α), event rate (P) and two-sided test. The sample size was set to 1200, and hazard ratio was set to 0.75 as estimated from the Cox regression in the main cohort. In this case, associations between cardiovascular health score and 15 outcomes for which the event rate was not less than 6.42% (corresponding to 77 cases) reached 80% power at a significant level of 0.05/15. Therefore, these 15 outcomes (i.e., MACE, ischemic heart diseases, atrial fibrillation, heart failure, peripheral artery disease, diabetic kidney diseases, diabetic retinopathy, stroke, ischemic stroke, all site cancer, depression, COPD, all-cause mortality, CVD mortality, and cancer mortality) were taken forward for mediation analysis. The difference method that compares estimates from model with and without hypothesized mediator was used to calculate mediation proportion (the SAS Macro %mediate)[62]. The same covariates as aforementioned in Cox regression were adjusted in the mediation analyses. Besides, as the SAS Macro %mediate does not work with multiple data sets, the imputed dataset (first iteration) was used in the mediation analysis. In addition, to test the robustness of mediation effect, sensitivity analysis was conducted using the medsens function from R package mediation[63].

All analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC) and R software (version 4.3.2; R Foundation for Statistical Computing) unless otherwise specified. All p-values were based on two-sided tests, and FDR-corrected or Bonferroni-corrected p-value < 0.05 was considered statistically significant.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The data supporting the findings from this study are available within the manuscript and its Supplementary Information. The raw UK Biobank data are protected and are not available due to data privacy laws. Researchers can apply to use the UK Biobank resource for health-related research and public interest via the UK Biobank Access Management System (https://ams.ukbiobank.ac.uk/ams/). Source data are provided with this paper.

Code availability

The analytic code used in this study will be made available from the corresponding author upon request.

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G.L., Y.L., A.P. and R.Y.L. designed the research; R.Y.L. and S.T. accessed and verified the data, performed statistical analysis, and drafted the manuscript with contributions from R.L., K.Z., Q.L., Z.Q., H.Y., and L.L.; J.L., R.L., K.Z., O.H.F., A.P., Y.L., and G.L. participated in the interpretation of the results and critical revision of the manuscript. All authors approved the manuscript. G.L. has primary responsibility for the final content, the accuracy of the data analysis and decision to submit to publication.

Competing interests

The authors declare no competing interests.

Additional information

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