Cardiovascular Diabetology

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Proteomic signatures of type 2 diabetes predict the incidence of coronary heart disease

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Abstract

Emerging evidence reveals a complex association between type 2 diabetes (T2D) and coronary heart disease (CHD), which share common risk factors and biological pathways. This study aims to identify the shared proteomic signatures of T2D and CHD, as well as whether the shared proteins predict incident CHD in T2D patients, and to develop predictive models. Utilizing data from 53,014 UK Biobank participants and 2923 plasma proteins, we identified 488 proteins associated with T2D, of which 125 proteins were also associated with CHD. Among the shared proteins, we determine nine proteins showing causal associations with CHD, including PCSK9, NRP1, and CD27. Mediation analyses suggest that the nine proteins mediate the association between T2D and CHD. By integrating these proteins into our predictive model, we achieved a desirable prediction (AUC = 0.819) for future CHD onset in T2D patients. Additionally, druggability evaluation show 32 potential therapeutic agents, including established antihypertensives and nine novel compounds, suggesting avenues for dual-targeted treatment strategies. Collectively, our findings unveil the proteomic signatures associated with both T2D and CHD, providing implications for screening and predicting future CHD onset in T2D patients.

Introduction

Type 2 diabetes (T2D) is a major global health issue characterized by insulin resistance and a relative deficiency of insulin [1, 2]. This condition leads to hyperglycemia and various complications, such as cardiovascular disease. Among these complications, coronary heart disease (CHD) poses a critical risk for patients with T2D, significantly increasing mortality rate. People with T2D have a two–four fold increased risk of developing CHD compared to those without diabetes [3, 4]. This highlights the urgent need for effective prevention and management strategies. Currently, managing T2D mainly depends on lifestyle changes and medications focused on controlling blood sugar levels; however, these interventions often fail to effectively reduce the risk of CHD [5–7]. This reveals a significant gap in understanding the underlying mechanisms of disease and underscores the need for a deeper understanding of how T2D is linked to CHD. Research shows that T2D and CHD share environmental exposure risk factors, such as lifestyle and obesity [8]. At the same time, they also share some genetic factors, such as *PCSK9* and *RAC1* [9]. The interaction of genetic, environmental, and lifestyle factors makes this association complex, requiring a comprehensive approach to explore the underlying mechanisms and create effective predictive tools.

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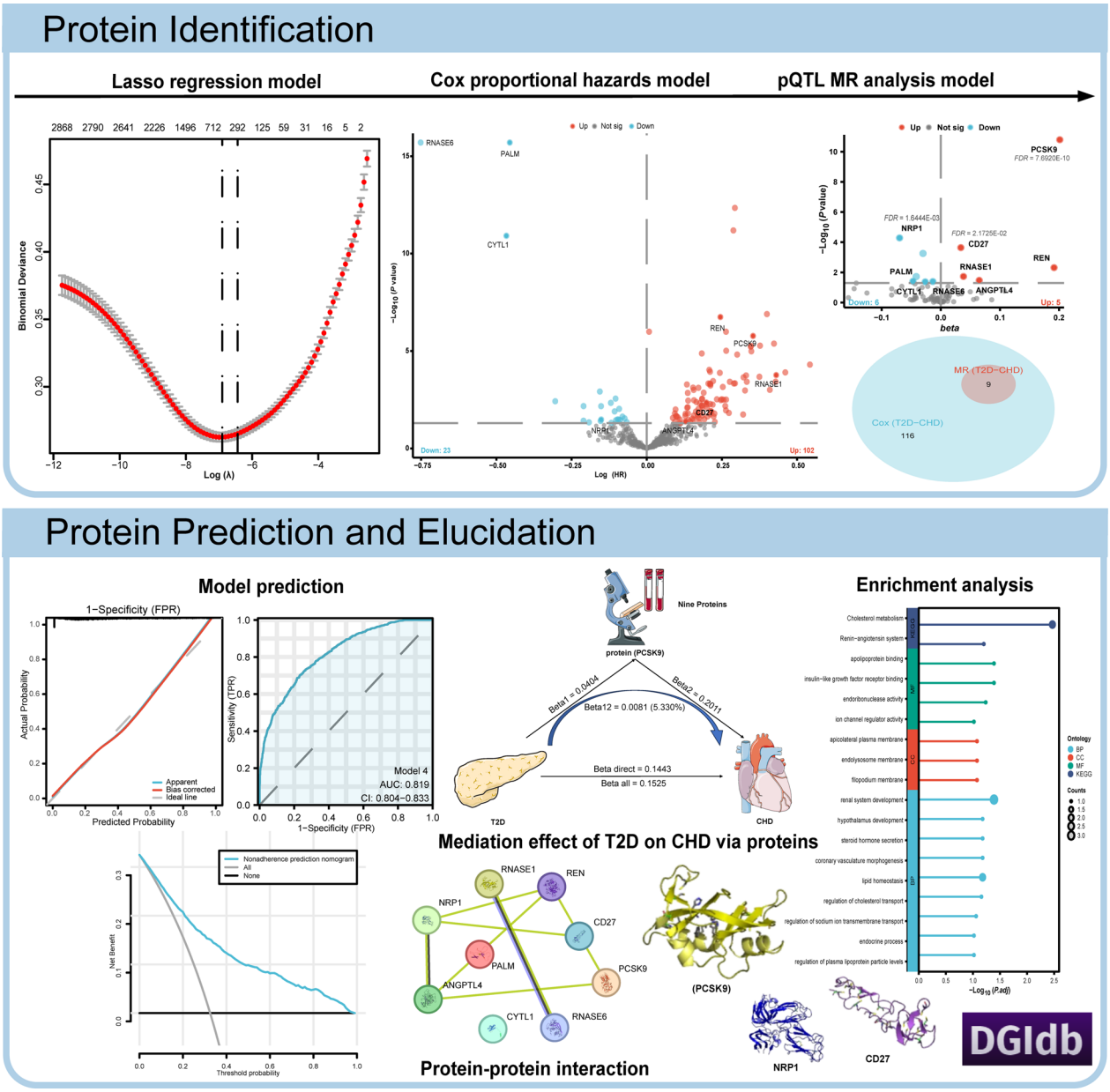
Graphical abstract



Keywords Type 2 diabetes, Coronary heart disease, Proteomic, Mendelian randomization, Predictive model, Therapeutic drugs

Proteins, which are the intricate molecular products resulting from the complex interactions between genes and the surrounding environment, have the potential to serve as more reliable indicators for predicting the onset of various diseases [10]. Plasma proteins, as a more accessible source of protein, have better disease relevance in clinical research and are a great choice for proteomic studies. Despite this promising capability, the specific protein molecules that are shared between T2D and CHD remain largely unknown at this time. Furthermore, it is still unclear whether the protein molecules that influence the development of T2D can also serve as predictive markers for the occurrence of CHD [11]. Therefore, employing advanced proteomics techniques to develop a comprehensive predictive model for CHD specifically in patients suffering from diabetes will be crucial [12].

In addition, the integration of machine learning (ML) algorithms and Mendelian randomization (MR) analysis methods with traditional epidemiological statistical approaches to support proteomics technology not only broadens the spectrum of analytical techniques available but also significantly enhances the reliability and robustness of the final predictive model [13, 14]. This approach will significantly enhance the prognostic management of diabetic patients and contribute to alleviating the burden of comorbidities associated with these conditions.

This study aims to identify the shared proteomic signatures of T2D and CHD, as well as whether the shared proteins predict incident CHD in T2D patients, and to develop predictive models, considering the complexity of T2D and its link to CHD. First, we screened core proteins related to T2D from a total of 2,923 plasma proteins using ML techniques and built an interaction network for these proteins. Subsequently, we employed the Cox proportional hazards model to preliminarily identify proteins linked to CHD occurrence in T2D patients. Third, we performed causal association validation on proteins associated with CHD occurrence in the T2D population using protein quantitative trait loci (pQTL) MR analysis. Fourth, we constructed a predictive model for future CHD incidence in T2D patients. This model utilized proteins validated by the Cox proportional hazards model and pQTL MR analysis, and we assessed its effectiveness. Fifth, mediation analysis was used to explain how the aforementioned proteins influence the progression from T2D to CHD. Finally, we elucidated the potential proteins through protein–protein interaction analysis, enrichment analysis, etc., and predicted drugs that could prevent CHD occurrence in T2D patients.

Methods

Population and study design

The UK Biobank (UKB) (https://www.ukbiobank.ac.uk/) is a long-term study that has recruited over 500,000 participants aged 40 to 69 [15]. The protein data in this study was obtained from the UKB database, which included 53,014 participants and measured 2,923 plasma proteins. The data for the Cox proportional hazards model was also sourced from the UKB, primarily comprising T2D and CHD data, as well as demographic and lifestyle information. For the pQTL MR and mediation analyses, the pQTL data was obtained from the Icelandic database, with 35,559 participants and 4,907 plasma proteins [16]. T2D and CHD data were obtained from the FinnGen consortium, which included 440,735 and 453,733 participants, respectively [17]. This approach ensured population uniformity and minimized bias from a single data source.

Figure 1 illustrates the overall design of the study. We conducted a comprehensive proteomics study to identify

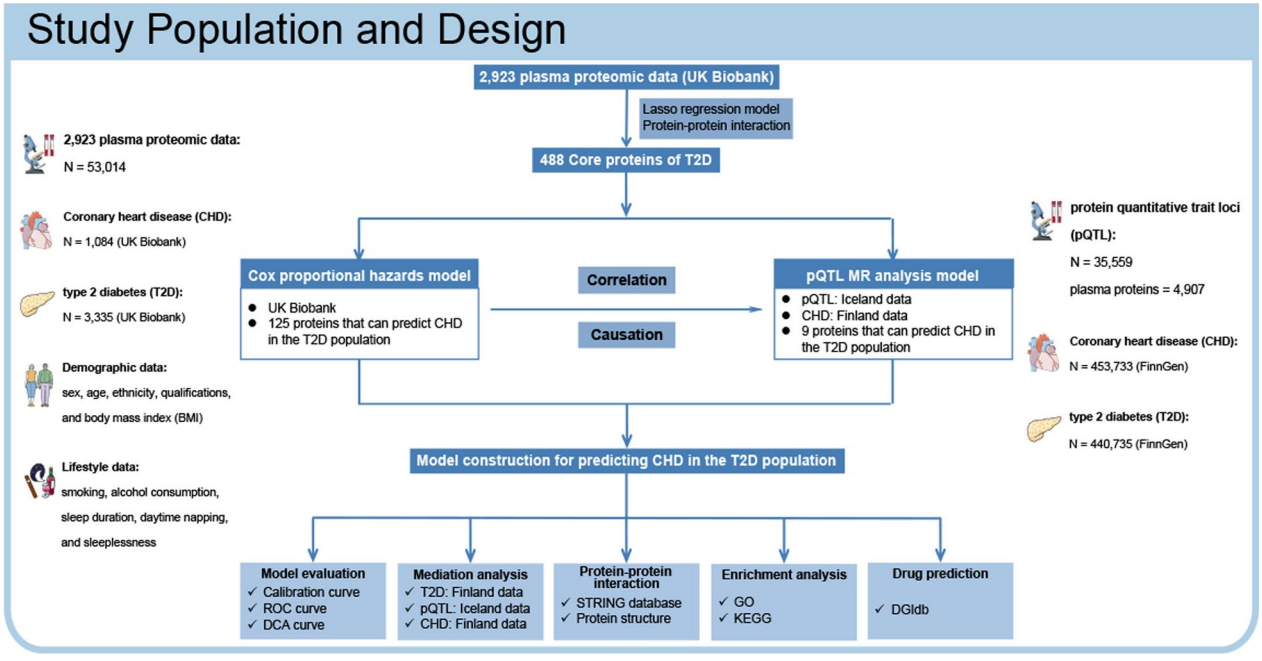


Fig. 1 The flow chart. First, screen core proteins related to T2D from a total of 2923 plasma proteins and build an interaction network for these proteins; second, identify proteins linked to CHD occurrence in T2D patients; third, perform causal association validation on proteins associated with CHD occurrence in the T2D population; fourth, construct a predictive model for future CHD incidence in T2D patients and verify the model's effectiveness; fifth, explain how the aforementioned proteins influence the progression from T2D to CHD; sixth, elucidate the potential proteins through protein–protein interaction analysis, enrichment analysis, etc., and predicted drugs that could prevent CHD occurrence in T2D patients. *T2D* Type 2 diabetes, *CHD* Coronary heart disease

proteins that predict future CHD in patients with T2D. Simultaneously, we developed predictive models using these proteins and further clarified their effects within the models.

Proteomic profiling

The expression of proteins was standardized and quantified by utilizing baseline blood samples on the advanced antibody-based Olink Explore 3072 platform, which is renowned for its precision and reliability in proteomic analysis. Detailed methodologies for sample processing, Olink proteomics detection, plasma analysis, and data processing can be found in previous studies that laid the groundwork for this research [18]. A total of 2,923 proteins were detected using this platform. To maintain data integrity, we excluded any proteins that exhibited missing values exceeding 20% of the participants, ensuring that our findings would be both robust and reliable.

Diagnosis of T2D and CHD

The UKB database defines disease phenotypes using various data sources, including hospital records, primary care information, and death registrations, providing a strong framework for disease classification. In our study, we use the time of blood collection as the baseline, which is crucial for our analysis. The identification of cases of T2D at this baseline is conducted in accordance with the International Classification of Diseases, 10th Revision (ICD-10), including the codes E110 to E119, which pertain to Non-insulin-dependent diabetes mellitus. Furthermore, the identification of new-onset CHD during the follow-up period is similarly grounded in the ICD-10 classification system, encompassing a range of relevant codes including I20 (angina pectoris), I21 (acute myocardial infarction), I22 (subsequent myocardial infarction), I23 (certain current complications following acute myocardial infarction), I24 (other acute ischaemic heart diseases), and I25 (chronic ischaemic heart disease). This approach offers a comprehensive overview of potential cardiovascular conditions.

Additional data

Demographic factors such as sex, age, ethnicity, qualifications, and body mass index (BMI), as well as lifestyle factors like smoking, alcohol consumption, sleep duration, daytime napping, and sleeplessness, were included as covariates in this study. Including this data effectively eliminates potential confounding biases and clearly demonstrates the impact of lifestyle on protein expression, thereby enhancing the reliability and validity of the results.

Statistical analyses

Identification of core proteins for T2D

First, the 2,923 plasma protein data from the UKB database required data quality control. Proteins with over 20% missing participant data were excluded to ensure data quality and reliability of the results. Second, the R programming language's mice package (version 3.14.0) was used to impute missing values in the protein data. Third, the Lasso regression model was used to screen for core proteins for T2D. Finally, the STRING database (https://string-db.org) was utilized to clarify the interact ion associations among the core proteins associated with T2D [19].

Cox proportional hazards model

The dplyr package (version 1.0.9) and purrr package (version 0.3.4) were utilized to integrate various datasets, including protein, T2D, CHD, demographic, and lifestyle data from the UKB database, based on the analysis requirements. After integrating the core proteins related to T2D with demographic and lifestyle data, we used the Cox proportional hazards model to analyze the association between these proteins and the future incidence of CHD in individuals diagnosed with T2D. A *P*-value of less than 0.05 suggested a significant association between the corresponding protein and the future CHD events in the T2D population.

MR analysis

pQTL MR analysis was employed to further investigate the causal association between proteins predicting future CHD in the T2D population and the onset of CHD itself. The Inverse Variance Weighted (IVW) method was employed as the primary method, and MR Egger, Weighted median, Simple mode, Weighted mode were employed as the supplementary methods. P value < 0.05 indicated a genetic causal association between protein and CHD. The instrumental variables (IVs) for pQTL and CHD had to satisfy four screening criteria: (1) IVs were associated with exposure ($P < 5e{-}8$); (2) Linkage disequilibrium (LD) was excluded ($r^2 < 0.001$, kb = 10,000); (3) IVs had sufficient strength of association with exposure ($F > 10$); (4) Confounding factors for IVs were excluded using the OpenGWAS database (https://gwas.mrcieu.ac.uk/) [20].

Heterogeneity tests, leave-one-out sensitivity analysis, and MR-PRESSO were employed to validate the positive results of the MR analysis to further enhance the credibility of the results. To validate positive results, we began by conducting heterogeneity tests to assess whether the IVs were heterogeneous. A *P*-value greater than 0.05 indicated no heterogeneity among the IVs, leading to the use of a fixed-effect model for MR analysis. Conversely, a *P*-value less than 0.05 suggested heterogeneity,

prompting the use of a random-effect model. Next, we conducted leave-one-out sensitivity analysis to examine the impact of individual IVs on the overall results of the MR analysis. Furthermore, because the MR Egger method includes the intercept term in regression analysis, we compared it with the IVW method to test for horizontal pleiotropy among the IVs. $P > 0.05$ indicated no horizontal pleiotropy among the IVs, and the IVW method was used as the result of the MR analysis; conversely, the MR Egger method was used as the result of the MR analysis. Finally, the MR-PRESSO method was applied to identify any outliers among the IVs included in the study. We strictly tested each IV for outliers, and if outliers were found, they needed to be excluded and reanalyzed until no outliers remained among all IVs [21].

Prediction model construction and evaluation

Proteins validated through Cox proportional hazards model and pQTL MR analysis model were utilized to develop a prediction model for future CHD occurrences in the T2D population. The nomogram, as a graphical method for comprehensive analysis of multiple variables to predict the occurrence of a specific event, was used to display the results of the prediction model. Calibration curves, which transform continuous data into discrete categories, were used to evaluate how closely the model's predicted probabilities matched the actual probabilities. Receiver Operating Characteristic (ROC) Curve, Area Under ROC Curve (AUC), and Concordance Index (C-Index) were used to evaluate the accuracy of the model's predictions. Decision curve analysis (DCA) Curve illustrate how net benefits change when patient interventions are based on model predictions as the threshold probability varies, thereby helping to evaluate the model's clinical value.

Mediation analysis

To further clarify how proteins influence the occurrence of CHD in the T2D population, mediation analysis was used to reveal this process. We performed MR analyses separately for T2D and CHD, T2D and proteins, and proteins and CHD. Following these, we conducted a two-step mediation MR analysis to assess how each protein mediates the occurrence of CHD in the T2D population. The screening criteria for IVs included: $P < 5e{-}8$, $r^2 < 0.001$, kb = 10,000, $F > 10$, and confounding factors were excluded [20, 21].

Protein–protein interaction and enrichment analysis

To explore the associations between proteins that predict CHD in individuals with T2D, the STRING database was utilized to clarify how these proteins interact. The Gene Ontology (GO) database classifies gene and protein functions into three categories: Biological Process, Cellular Component, and Molecular Function. These categories help in studying the functional characteristics of genes and proteins. The Kyoto Encyclopedia of Genes and Genomes (KEGG) database is a well-established and publicly accessible resource for pathway research. Enrichment analysis, supported by hypergeometric distribution, effectively clarifies the functions and pathways of various proteins. We employed the clusterProfiler (version 4.4.4) package to conduct this analysis on the proteins mentioned earlier.

Drug prediction

The DGIdb database (https://www.dgidb.org/) is a publi c database designed for drug prediction [22]. To further enhance the clinical value of this study, the DGIdb database was used to predict potential drugs. These drugs may impact the occurrence of CHD in individuals with T2D.

Results

Identification of core proteins for T2D

After a thorough screening, we identified six proteins from the 2,923 plasma proteins obtained from the UKB that had missing participant values exceeding 20%. These proteins are CTSS, PCOLCE, C3, CST1, NPM1, and GLIPR1. Subsequently, 2,917 proteins were included in the analyses, which involved 3,335 T2D patients and 49,679 controls from a total of 53,014 participants. Following data imputation and selection with the Lasso regression model, we identified 488 core proteins associated with T2D (Figure S1A–B, Table S1). Furthermore, a protein–protein interaction analysis demonstrated 212 interactions among the 488 core plasma proteins associated with T2D, using a high confidence threshold of 0.70 (Figure S1C, Table S2).

Identification of proteins linked to CHD in the T2D patients

A dataset of 488 core proteins related to T2D was created from 3,335 T2D patients through thorough data screening and integration. The dataset includes 1,084 T2D patients who developed CHD after diagnosis as the experimental group, and 2,251 T2D patients who did not develop CHD as the control group. The dataset also included relevant demographic and lifestyle data for the participants. The Cox proportional hazards model results showed that 125 proteins were linked to the occurrence of CHD in the T2D population. Among these, 102 proteins, such as PCSK9, had a positive correlation (Hazard Ratio [HR] = 1.2777, 95% CI 1.1558–1.4125), while 23 proteins, such as NRP1, displayed a negative correlation ($HR = 0.9004$, 95% CI 0.8178–0.9914) (Fig. 2A, Table S3).

Causal effects between plasma proteins and CHD

The Genome-wide association study (GWAS) data for CHD was sourced from the FinnGen consortium (https://ww

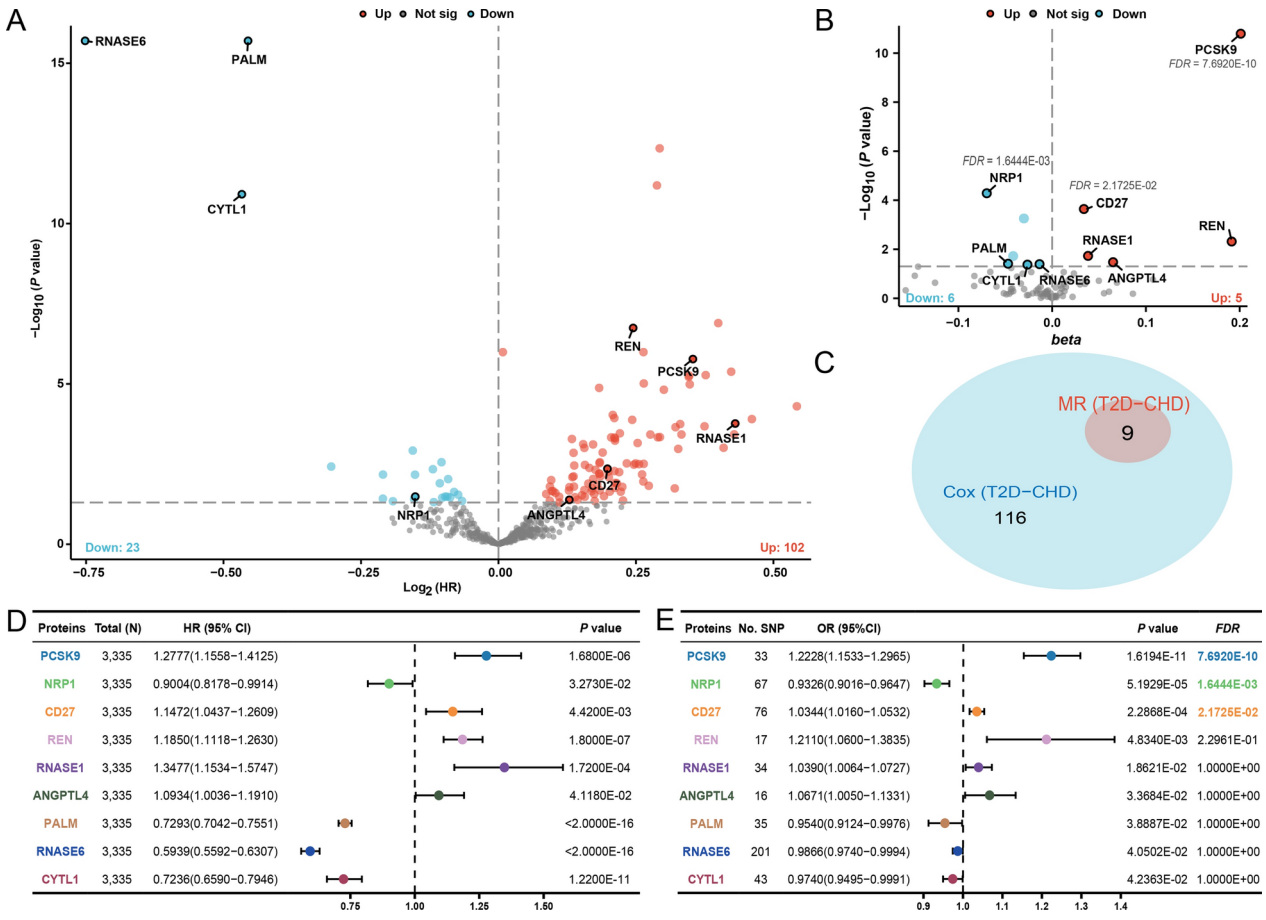


Fig. 2 Identification and validation of proteins linked to CHD in the T2D patients. **A** Volcano plot of Cox proportional hazards model results. **B** Volcano plot of MR analysis results. **C–E** The correspondence between positive results from the Cox proportional hazards model and the MR analysis. *MR* Mendelian randomization

w.finngen.fi/en/access_results) under the accession number finngen_R11_I9_CHD, which included 51,098 CHD patients and 402,635 controls. After obtaining the GWAS data of proteins associated with the occurrence of CHD in the T2D population from the pQTL data in Iceland, pQTL MR analysis was conducted. The results indicated that 11 proteins, including PCSK9, were successfully validated with suggestive evidence of a causal association with CHD.

The sensitivity analysis indicated that the proteins NEFL and NRP2 showed evidence of horizontal pleiotropy, leading to their exclusion from the study. Additionally, some protein results showed heterogeneity, leading to the use of a random effects model to present the final results. Ultimately, nine proteins were validated as having suggestive evidence of a causal association with CHD, suggesting their potential to predict CHD incidence in the T2D population. Among these nine proteins, five, including PCSK9, exhibited a positive causal association (Odd Ratio [OR] = 1.2228, 95% CI 1.1533–1.2965). In contrast, four proteins, including NRP1, demonstrated a negative causal association (*OR* = 0.9326, 95% CI 0.9016–0.9647). Additionally, PCSK9 has been previously reported in the literature, whereas the other eight proteins were newly discovered in this study. The correction results showed that among these nine proteins, PCSK9 (*FDR* = 7.6920E−10), NRP1 (*FDR* = 1.6444E−03), and CD27 (*FDR* = 2.1725E−02) provided statistically significant evidence of a causal association (Fig. 2B, Figure S2, Table S4). The correspondence between positive results from the Cox proportional hazards model and the pQTL MR analysis model is shown in Fig. 2C–E.

Prediction model construction and evaluation

To evaluate the clinical value of the identified proteins in predicting CHD incidence among individuals with T2D, we first created a basic model (Model 1) using demographic and lifestyle data from this population. The ROC curve indicated that model 1 had an AUC of 0.729 (95% CI 0.710–0.748) and a C-index of 0.727 (95% CI 0.708–0.746), reflecting moderate predictive accuracy (Figure S3A–B). Subsequently, nine proteins with predictive potential were used to construct Model 2. For Model 2, the ROC curve revealed an AUC of 0.733 (95% CI 0.715–0.751) and a C-index of 0.733 (95% CI 0.715–0.751), both

reflecting moderate predictive accuracy and an improvement over Model 1 (Figure S4A–B). PCSK9 was validated by both the Cox proportional hazards model and the pQTL MR analysis model, providing stronger statistical evidence after FDR correction. Consequently, we integrated PCSK9 into Model 1, thereby developing Model 3. The ROC curve analysis indicated that Model 3 had an AUC of 0.734 (95% CI 0.715–0.753) and a C-index of 0.733 (95% CI 0.716–0.752) (Figure S5A–B). Its predictive accuracy was comparable to that of Model 2. These findings highlight the potential of the identified proteins, especially PCSK9, for predicting CHD in individuals with T2D. Finally, we developed Model 4 by merging the nine previously identified proteins with Model 1. The ROC curve indicated that Model 4 had an AUC of 0.819 (95% CI 0.804–0.833) and a C-index of 0.818 (95% CI 0.803–0.833). This indicates a notable enhancement in predictive accuracy over the earlier three models (Fig. 3A–B, Table 1).

To better evaluate the effects of the four models we constructed, both individually and in relation to each other, we also used calibration curves and DCA curves in addition to the ROC curve and C-index. The results from the calibration and DCA curves demonstrated that our four models effectively predicted probabilities and offered net benefits. Among the four models, the calibration curve showed that model 4 was closer to the true predictive probability (Figure S3C, S4C, S5C, Fig. 3C).

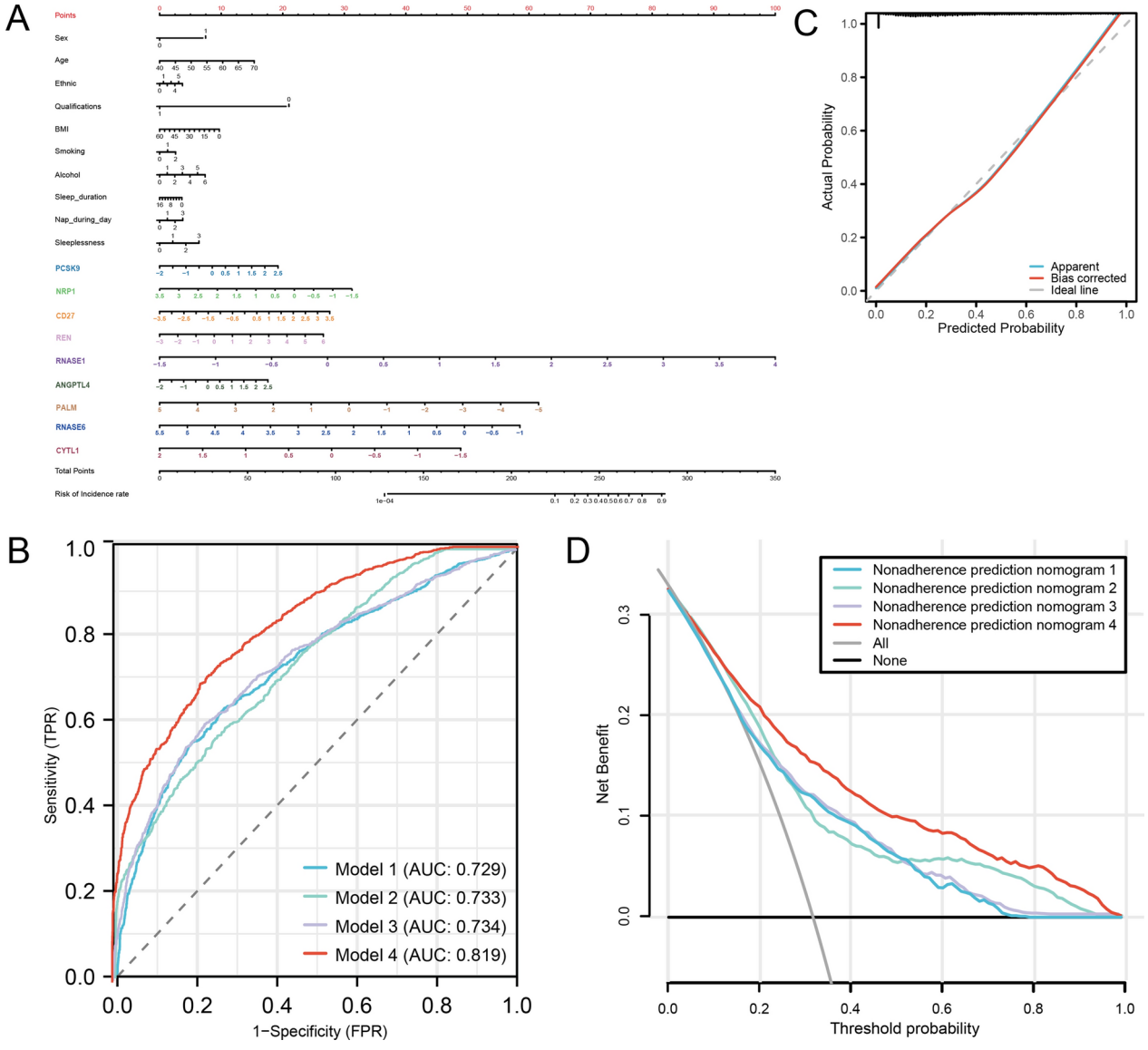


Fig. 3 Prediction model construction and evaluation. **A** Nomogram curves of Model 4. **B** ROC curve of Model 1 to Model 4. **C** Calibration curves of Model 4. **D** DCA curve of Model 1 to Model 4. Model 1: Base model; Model 2: nine proteins; Model 3: Base model + PCSK9; Model 4: Base model + nine proteins; *ROC* Receiver operating characteristic; *DCA* Decision curve analysis

Table 1 Predictive performance of traditional risk factors and identified plasma proteins for predicting future CHD events in T2D patients

Predictive feature	AUC (95% CI)	Concordance index (95% CI)
Base model	0.729 (0.710–0.748)	0.727 (0.708–0.746)
nine proteins	0.733 (0.715–0.751)	0.733 (0.715–0.751)
Base model + PCSK9	0.734 (0.715–0.753)	0.733 (0.716–0.752)
Base model + ninie proteins	0.819 (0.804–0.833)	0.818 (0.803–0.833)

The base model included sex, age, ethnicity, qualifications, body mass index (BMI), smoking status, alcohol frequency, sleep duration, nap during day, sleeplessness

Nine proteins included PCSK9, NRP1, CD27, REN, RNASE1, ANGPTL4, PALM, RNASE6 and CYTL1

T2D Type 2 diabetes, *CHD* Coronary heart disease

Additionally, the DCA curve indicated that model 4 provided significantly better net benefits, suggesting a higher clinical application value (Fig. 3D).

The mediation effect of T2D on CHD via proteins

The GWAS data for T2D were obtained from the FinnGen consortium (https://www.finngen.fi/en/access_results) under accession number finngen_R11_T2D, which included 71,728 T2D patients and 369,007 control individuals. The mediation analysis revealed that the mentioned proteins regulated the influence of T2D on CHD. The results indicated a causal association between T2D and CHD, with a total effect β value of 0.1525. Among the nine proteins, PCSK9 played a significant mediating effect. Its expression level increased in the T2D population, leading to a higher incidence of CHD, with a mediation proportion of 5.330%. Additionally, NRP1 and CD27 also demonstrated statistically significant causal associations after FDR correction, with mediation proportions of 1.546% and 1.010%, respectively (Table 2, Figure S6).

Construction of protein module networks and results of protein enrichment analysis

The protein–protein interaction analysis identified 10 primary and 20 secondary associated proteins related to the nine proteins predictive of CHD in the T2D population, creating a network of 168 interactions (threshold: high confidence (0.70)) (Fig. 4A, Table S5). The enrichment analysis results indicated that these nine predictive proteins were involved in 302 biological processes, 8 cellular components, and 36 molecular functions. Additionally, they were primarily enriched in two pathways. Specifically, these nine proteins were primarily located in the pseudopod, endolysosomal, and apical plasma membranes of cells related to circulation and metabolism. They were involved in biological processes such as coronary vascular morphogenesis, lipid homeostasis, and systemic hormone regulation, with functions including insulin-like growth factor receptor binding, apolipoprotein binding, and ion channel regulatory activity. Moreover, these nine proteins were involved in cholesterol metabolism and the renin-angiotensin system (Fig. 4B, Table S6).

Drug prediction

Using the DGIdb database, we successfully predicted and identified corresponding drugs for five of the nine previously obtained proteins, yielding a total of 32 potential drugs. A total of 23 drugs have been reported in relation to conditions such as CHD, myocarditis, and hypertension. Among these, the REN-related drug *aliskiren* has been approved as an antihypertensive agent (Interaction score = 5.2508), and the PCSK9-related drug *alirocumab* has been approved as a cholesterol-lowering agent (Interaction score = 4.0391). Additionally, we identified nine previously unreported drugs, marking new discoveries. Among these, *cytidine-3′*-monophosphate had the highest predicted score of 105.0153, indicating its potential for treating comorbid T2D and CHD, as well as for preventing CHD while managing T2D (Fig. 4C, Table S7).

Table 2 The mediation effect of T2D on CHD via proteins

T2D-proteins-CHD	Total effect	Direct effect 1	Direct effect 2	Direct effect	Mediation effect	Mediated proportion (%) (95%CI)
	β	*β*	*β*	*β*	*β* (95%CI)	
PCSK9	0.1525	0.0404	0.2011	0.1443	0.0081(0.0021, 0.0142)	5.330(1.368, 9.292)
NRP1	0.1525	− 0.0338	− 0.0698	0.1501	0.0024(0.0010, 0.0037)	1.546(0.684, 2.408)
CD27	0.1525	0.0455	0.0338	0.1509	0.0015(0.0008, 0.0023)	1.010(0.504, 1.515)
REN	0.1525	− 0.0350	0.1915	0.1592	− 0.0067(− 0.0197, 0.0063)	− 4.394(− 12.930, 0.000)
RNASE1	0.1525	0.0577	0.0383	0.1503	0.0022(0.0012, 0.0032)	1.449(0.800, 2.097)
ANGPTL4	0.1525	0.0358	0.0650	0.1501	0.0023(0.0003, 0.0044)	1.526(0.185, 2.866)
PALM	0.1525	− 0.0693	− 0.0471	0.1492	0.0033(0.0018, 0.0047)	2.138(1.194, 3.082)
RNASE6	0.1525	− 0.0367	− 0.0135	0.1520	0.0005(1.9254E−05, 0.0010)	0.324(0.013, 0.635)
CYTL1	0.1525	0.0429	− 0.0264	0.1536	− 0.0011(− 0.0018, − 0.0005)	− 0.741(− 1.164, − 0.319)

T2D Type 2 diabetes, *CHD* Coronary heart disease

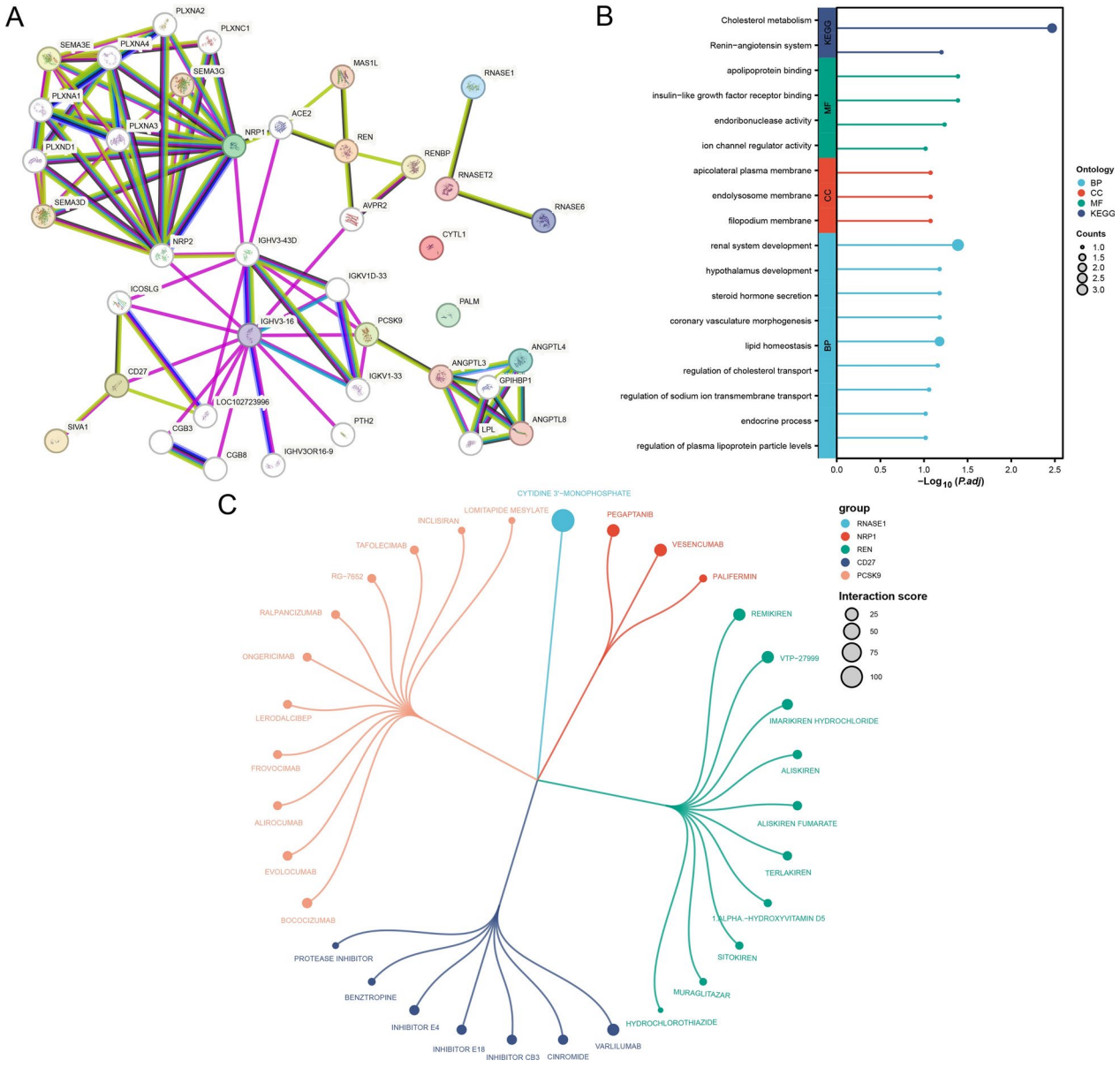


Fig. 4 Mechanism analysis. **A** Protein module networks. **B** Enrichment analysis of proteins. **C** Protein-drug interaction networks

Discussion

In this large-scale proteomic analysis, we first identified 488 core proteins related to T2D and their interactions, of which 125 proteins were associated with the occurrence of CHD in the T2D population. Among the shared proteins, nine proteins were causally associated with CHD. Our study identifies significant associations between the established protein PCSK9 and newly discovered proteins, such as NRP1, in relation to CHD risk. This highlights the potential of these biomarkers to improve clinical risk assessment and inform targeted treatment strategies. Mediation and enrichment analyses clarify how these proteins are involved in the link between T2D and CHD. Our drug screening identified 32 drugs that may prevent CHD in the T2D population, including nine that are newly discovered. In this discussion, we will examine the significance of our findings and the biological effects of the identified proteins. We will also explore how these proteins may contribute to the mechanisms linking T2D and CHD. Additionally, we will assess the potential value of predictive drugs for future personalized treatments in the T2D population.

Utilizing ML methods to identify core proteins linked to T2D marks a major step in comprehending the disease's complex interactions. Our study identified 488 core proteins associated with T2D. It also revealed 212 interactions among these proteins, which enhances the potential for early biomarkers in clinical settings.The

functions of these core proteins, especially their effects in metabolic pathways and vascular health, warrant further investigation. Research has shown that elevated levels of inflammatory markers such as C-reactive protein (CRP) are associated with an increased risk of T2D, underscoring the importance of inflammation in this context [23]. Furthermore, the connections between metabolic syndrome, insulin resistance, and cardiovascular health are well-documented, indicating that targeting these pathways may benefit patients [24–26]. Understanding protein interactions better may clarify the mechanisms behind T2D. This insight could lead to targeted therapies that address the disease's root causes. The identification of these biomarkers has significant clinical implications; it could transform management practices and facilitate personalized interventions tailored to individual risk profiles, ultimately improving patient outcomes and quality of life.

This study applied Cox proportional hazards models and MR analysis, providing strong evidence that specific proteins, including PCSK9, NRP1, and CD27, are linked to the risk of CHD in patients with T2D. The Cox proportional hazards model identified 125 proteins associated with CHD among 488 core proteins linked to T2D. The MR analysis performed a follow-up validation of the 125 identified proteins, ultimately revealing nine proteins that may have causal links to CHD, especially the well-known protein PCSK9, which enhances the reliability of our results [27]. Identifying PCSK9 as a core protein linked to CHD risk supports previous literature on its effect in lipid metabolism and cardiovascular disease, making PCSK9 inhibitors a promising therapeutic strategy that may reduce CHD risk in T2D patients [28–30]. Additionally, discovering NRP1 and other proteins like CD27 and REN provides new insights into the pathophysiology of CHD in T2D patients. NRP1 is involved in several biological processes, such as angiogenesis and neuroprotection, which may influence cardiovascular health [31, 32]. These proteins may be crucial targets for innovative therapies that focus on lowering CHD risk in individuals with diabetes. The integration of genetic data reinforces the value of these biomarkers in clinical practice, enabling personalized medicine approaches that could greatly improve the management of T2D and related cardiovascular risks.

Creating a predictive model with an AUC of 0.819 for CHD in patients with T2D represents a significant step forward in cardiovascular risk assessment. This model uses specific protein biomarkers, showing their ability to improve early detection and intervention strategies for CHD in this high-risk group. The robustness of the model is further supported by calibration curves, C-index, and DCA, all of which affirm its clinical applicability and authenticity. Additionally, the model's predictive accuracy could be greatly enhanced by including more biomarkers and clinical data, leading to a more comprehensive approach to risk stratification. Future research should focus on validating this predictive model in various populations to confirm its general applicability. Furthermore, incorporating more clinical variables, like lifestyle factors and genetic predispositions, may improve the model's accuracy and usefulness. This model has significant implications, as it can guide clinical decisions, allowing healthcare providers to start earlier interventions for T2D patients at high risk for CHD. This proactive strategy may improve patient management and reduce the burden of comorbidities linked to T2D and CHD on healthcare systems. In light of these findings, it is critical to prioritize further research on the complex interactions between biomarkers, clinical variables, and patient outcomes in T2D and CHD.

We investigated how proteins like PCSK9, NRP1, and CD27 interact in T2D and CHD, highlighting their crucial effects in disease processes. The enrichment analysis shows that these proteins are involved in lipid metabolism and vascular regulation, which supports the proposed ways they may affect disease outcomes. Recent studies have clarified the effect of PCSK9 in lipid metabolism, showing how it affects low-density lipoprotein (LDL) levels, a core factor in atherosclerosis and related cardiovascular events [33, 34]. The protein NRP1 is involved in vascular homeostasis and angiogenesis [32, 35]. These pathways are often disrupted in diabetic patients, increasing their risk of cardiovascular complications. Moreover, CD27, a member of the tumor necrosis factor receptor superfamily, has been linked to immune system modulation, which may contribute to the chronic inflammation observed in T2D and its association with cardiovascular diseases [36, 37]. The convergence of these pathways and the identification of novel therapeutic targets carry substantial significance for future research. As research progresses, the identification of novel therapeutic targets will be crucial in developing effective interventions that can improve patient outcomes across various medical disciplines. This multifaceted approach may pave the way for the development of innovative pharmacological treatments that not only lower blood glucose levels but also modulate the activities of PCSK9 and other related proteins, thereby improving lipid profiles and enhancing vascular function. Gaining a deeper understanding of the biological factors that underpin these associations will enable us to devise targeted interventions that address both glucose control and cardiovascular risk factors, ultimately leading to improved patient management and better health outcomes.

By utilizing the DGIdb database, we identified potential drug candidates that could lead to innovative therapeutic interventions for T2D and CHD. We discovered

32 potential drugs, such as established antihypertensive and cholesterol-lowering agents like *alirocumab* and *aliskiren*, along with nine previously unreported drugs like *cytidine-3′*-monophosphate, which underscores the versatility of our findings [30, 38, 39]. Research indicates that PCSK9 inhibitors, like *alirocumab* and *evolocumab*, significantly reduce low-density lipoprotein cholesterol (LDL-C) and cardiovascular risk in people with diabetes [40]. Consequently, these findings support the idea that targeting PCSK9 may offer dual benefits: improving glycemic control and reducing cardiovascular morbidity. This dual action is particularly important because many individuals suffer from both T2D and CHD, which complicates treatment plans and makes optimal management difficult [41, 42]. The intricate association between nucleotide metabolism, particularly focusing on *cytidine-3′*-monophosphate, glucose metabolism, and cardiovascular health necessitates further exploration. As indicated in prior research, nucleotide metabolism is not only pivotal for cellular signaling but also plays a significant role in energy homeostasis, which is crucial in the context of metabolic disorders such as T2D and CHD [43]. Previous studies have found that inhibitors of *cytidine-3′*-monophosphate can bind to the active site of ribonuclease, thereby altering the structure and some characteristics and functions of the enzyme. This will evidently affect energy metabolism, gene expression, and protein modification, and the diseases related to this are likely its potential indications, further confirming the possibility of *cytidine-3′*-monophosphate as a potential drug [44]. Emerging evidence suggests that alterations in nucleotide levels, including *cytidine-3′*-monophosphate, may influence the regulation of key metabolic pathways involved in glucose homeostasis. For instance, studies have demonstrated that nucleotide metabolism can affect insulin signaling pathways, thereby impacting glucose uptake and utilization in peripheral tissues. This dysregulation is often observed in T2D, where insulin resistance is a hallmark feature [45]. These factors are essential in the pathophysiology of both T2D and CHD [46]. Applying these findings in clinical practice could result in more tailored treatment approaches. It is regrettable that there is still relatively little research on *cytidine 3′-monophosphate*, and this drug has not yet been approved by the FDA. Future studies must assess the efficacy and safety of these candidate drugs in clinical settings. This will help ensure that our findings lead to practical applications that improve the health of patients with T2D who are at risk for CHD. In summary, the biochemical pathways governed by *cytidine-3′*-monophosphate and its interaction with glucose metabolism represent a promising area of research.

This study combines a comprehensive approach to proteomics research with advanced ML techniques, detailed MR analysis, and traditional epidemiological statistical methods to create a strong framework for investigation. Additionally, it uses various datasets from multiple sources along with individual data, enhancing the analysis's depth and breadth. Finally, the study employs strict inclusion and exclusion criteria and clearly defined cut-off values, ensuring that the findings are both reliable and relevant. This study has several limitations to consider. Firstly, although the sample size was relatively large, it may not fully represent the entire population of individuals with T2D. This limitation could affect the generalizability of our results. Additionally, differences between datasets may lead to batch effects, which complicate data integration and impact the robustness of our conclusions. Thirdly, the plasma proteins used for analysis may also have certain limitations, such as: the protein content exists within a dynamic range, which is influenced by factors like age and gender, and the impact of extreme dynamic ranges on results cannot be completely ruled out; during protein detection, the high-abundance proteins that dominate plasma may affect the detection of low-abundance proteins; the impact of protein modification events on protein abundance; and the effects of pre-analytical variability such as sample collection, processing time, storage conditions, and whether the samples have been contaminated on protein detection. Finally, without independent clinical validation assessments, we cannot clearly establish the clinical utility of the predictive model created in this study. In the future, if conditions allow, it may be possible to create a dataset by collecting clinical data to further validate the predictive model.

In conclusion, this research identifies multiple proteins associated with T2D and constructs an effective model to predict CHD occurrence in T2D patients. These findings offer valuable insights for early identification and intervention strategies in clinical practice, which may lead to better health outcomes for patients. Additionally, this study further investigates the effects and mechanisms of the identified proteins in relation to T2D and CHD, and proposes potential drug candidates for managing these comorbidities. Future research should concentrate on validating these proteins in clinical settings and exploring their effects in personalized treatment approaches. Ultimately, this may enhance the management of T2D and its related cardiovascular issues by enabling disease prevention before onset, facilitating early intervention for serious illnesses, and supporting the co-management of multiple diseases.

Abbreviations

T2D	Type 2 diabetes
CHD	Coronary heart disease
UKB	UK Biobank
BMI	Body mass index

ML	Machine learning
MR	Mendelian randomization
HR	Hazard Ratio
OR	Odds Ratio
ROC	Receiver Operating Characteristic
AUC	Area Under ROC Curve
C-Index	Concordance Index
DCA	Decision curve analysis
CI	Confidence interval
GWAS	Genome-wide association study
IVW	Inverse variance weighted
IVs	Instrumental variables
LD	Linkage disequilibrium
pQTL	Protein quantitative trait loci
GO	Gene Ontology
KEGG	Kyoto Encyclopedia of Genes and Genomes

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02670-3.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

Supplementary Material 5.

Supplementary Material 6.

Supplementary Material 7.

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Author contributions
YL: Formal analysis, Methodology, Software, Visualization, Writing—original draft. DL: Investigation, Methodology, Writing—review & editing. JL: Validation. LZ: Validation. WY: Validation. XY: Writing—review & editing. CX: Data curation, Funding acquisition. ZC: Conceptualization, Investigation, Methodology, Project administration, Writing—review & editing. YW: Conceptualization, Funding acquisition, Investigation, Project administration, Writing—review & editing.

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Availability of data and materials
The datasets analyzed in this study are from: 1. UK Biobank (https://www.ukbiobank.ac.uk/); 2. Icelandic database (https://www.decode.com/summarydata/) (accession nos. PMID: 34857953); 3. FinnGen consortium (https://www.finngen.fi/en/access_results) (accession nos. finngen_R11_T2D; finngen_R11_I9_CHD).

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. UK Biobank has ethics approval from the North West Multi–Centre Research Ethics Committee (11/NW/0382). Appropriate informed consent was obtained from participants, and ethical approval was covered by the UK Biobank. This research has been conducted using the UK Biobank Resource under project number 79095.

Competing interests
The authors declare no competing interests.

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