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RESEARCH

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Decoding the impact of glucose-dependent insulinotropic polypeptide receptor (GIPR) agonist on cardiometabolic health: inflammatory mediators at the focus

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Abstract

Background The Glucagon-like peptide-1 receptor (GLP-1R) and the glucose-dependent insulinotropic polypeptide receptor (GIPR) are well-established drug targets for the treatment of diabetes and obesity. Studies have linked GLP-1R agonist to cardiometabolic diseases (CMDs), while the therapeutic potential of the GIPR agonist remains a topic of debate.

Methods Using genetic variants as instrumental variables, we performed a two-sample Mendelian randomization (MR) analysis to investigate causal relationships between genetically proxied GIPR agonist and 23 CMD outcomes, and a two-step mediation analysis to identify mediating inflammatory biomarkers. The inverse variance weighted (IVW) method served as the primary analytical approach, supplemented by sensitivity analyses to validate robustness.

Results The genetic mimicry of GIPR enhancement showed significant protective associations with 14 CMDs. Mediation analysis revealed that Fms-related tyrosine kinase 3 ligand (Flt3L) partially mediated the effects of GIPR agonist on angina (OR 0.997 [0.995–0.999], $P=0.0048$) and myocardial infarction(MI) (OR 0.998 [0.996–0.999], $P=0.0077$), accounting for 15.49% and 16.71% of the total risk reduction, respectively.

Conclusion Our study revealed that GIPR agonist lowers the risk of 14 CMDs. Flt3L is pinpointed as a key mediating factor in reducing angina and MI risk, suggesting a new therapeutic avenue.

Keywords Antidiabetic drugs, Fms-related tyrosine kinase 3 ligand, Mendelian randomization

Introduction

Cardiometabolic diseases (CMDs) are associated with dyslipidemia and characterized by chronic inflammation due to excessive nutrient intake [1]. Dysregulation of circulating inflammatory factors have been observed in CMDs, including type 2 diabetes (T2D) [2], obesity [3], cardiovascular diseases (CVDs) [4, 5], non-alcoholic fatty liver disease (NAFLD) [6], and chronic kidney disease (CKD) [7].

Given the intersection of T2D and CMDs, evaluating the efficacy and safety of anti-diabetic therapies on cardiometabolic health is crucial for optimizing patient care.

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Glucagon-like peptide-1 (GLP-1), an incretin hormone, plays a crucial role in regulating postprandial glycemia through various mechanisms, including the enhancement of glucose-dependent insulin secretion, the delay of gastric emptying, and the suppression of appetite [8]. These multifaceted effects contribute to the metabolic advantages associated with the GLP-1 axis, which has facilitated the development of GLP-1-based pharmacological interventions. The class of GLP-1 receptor (GLP-1R) agonist is now well-established as a therapeutic option for both T2D and obesity [9], and it may also provide additional benefits for T2D patients with cardiorenal dysfunction [8, 10]. Nevertheless, despite the benefits offered by GLP-1R agonist therapeutics, a significant number of patients do not meet their glycemic and weight loss objectives [11]. This challenge, coupled with the widespread prevalence of obesity and T2D, highlights the urgent need to identify complementary agents that can enhance the efficacy of GLP-1R agonist [12].

One promising strategy in metabolic research involves the development of single peptide agonist that simultaneously targets both the GLP-1R and the glucose-dependent insulinotropic polypeptide receptor (GIPR). This dual-target approach seeks to enhance metabolic benefits while minimizing adverse effects. GIP, similar to GLP-1, functions as an incretin hormone. In healthy individuals, GIP plays a significant role in postprandial insulin secretion, contributing approximately 44% of the total, whereas GLP-1 accounts for about 22%. Consequently, GIP is responsible for roughly two-thirds of the incretin effect, establishing it as a major contributor to this physiological phenomenon [13]. GIP regulates pancreatic β-cell function through a β-arrestin 2-dependent signaling pathway distinct from GLP-1 [14]. Unlike GLP-1, which exerts only indirect effects on white adipose tissue (WAT), GIP demonstrates dual tissue-specific actions: indirect modulation of WAT combined with direct regulation of lipid/amino acid metabolism and inflammatory responses in brown adipose tissue (BAT) [15]. These complementary mechanisms enable GIP to enhance systemic fat metabolism and insulin sensitivity [16]. Critically, pharmacological studies reveal that GIPR/GLP-1R co-agonist exerts synergistic effects in enhancing metabolic benefits—including superior glycemic control and weight loss—compared to GLP-1R mono-agonist [16, 17]. Nevertheless, while GLP-1 has been shown to reduce the incidence of major adverse cardiovascular events in human subjects, the understanding of the cardiometabolic effects of GIP remains limited. A randomized controlled trial (RCT) is widely regarded as the gold standard for evaluating the efficacy of therapeutic agents [18]. However, large-scale RCTs remain infrequent, and several challenges persist. One notable issue is the cumbersome nature of dynamically monitoring therapeutic effects in individuals, particularly when invasive procedures, such as kidney biopsies, are considered the gold standard. Additionally, the high costs and extended durations associated with drug testing further complicate the evaluation process. There are also ongoing concerns regarding the potential adverse effects of the drugs of interest on participants, particularly among individuals who are neither diabetic nor obese [19, 20]. Mendelian Randomization (MR) employs genetic variants as instrumental variables (IVs) to infer causal relationships between exposures and outcomes, thereby assessing whether observed associations are indicative of true causality. This methodology aids in mitigating confounding biases by leveraging the random allocation of genetic variants at conception and effectively eliminates the possibility of reverse causation —— given that genetic determinants precede the onset of disease [21]. MR has been utilized to evaluate the efficacy of pharmaceuticals and to investigate potential safety concerns associated with approved medications [22, 23], validating its significance for clinical trial design.

In this study, we investigated recent findings regarding the previously overlooked significance of the GIPR signaling axis in the regulation of CMDs. Furthermore, we propose a novel rationale for the potential benefits of GIPR agonist in enhancing cardiometabolic health by inflammatory pathway modulation.

Methods

Study design

This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) guidelines [24]. We employed a two-sample MR design to assess causal effects (refer to Additional file1: Fig. S1). The MR analysis is based on three core assumptions: (1) Relevance—genetic variation must exhibit a strong association with the exposure; (2) Independence—genetic variation must be independent of confounding factors; and (3) Exclusion restriction—genetic variation should influence the outcome exclusively through the exposure. Figure 1 depicts the comprehensive methodology employed in our study. Initially, we selected genetic IVs for GIPR agonist and conducted a drug-target MR analysis to investigate the causal relationships between these IVs and 23 CMDs. A two-step MR analysis was performed to identify potential pathways through which GIPR agonist may exert influence on these interrelated health outcomes.

Genetic instruments for GIPR agonist

We identified IVs based on the following criteria: (1) They were significantly associated with T2D ($P <$

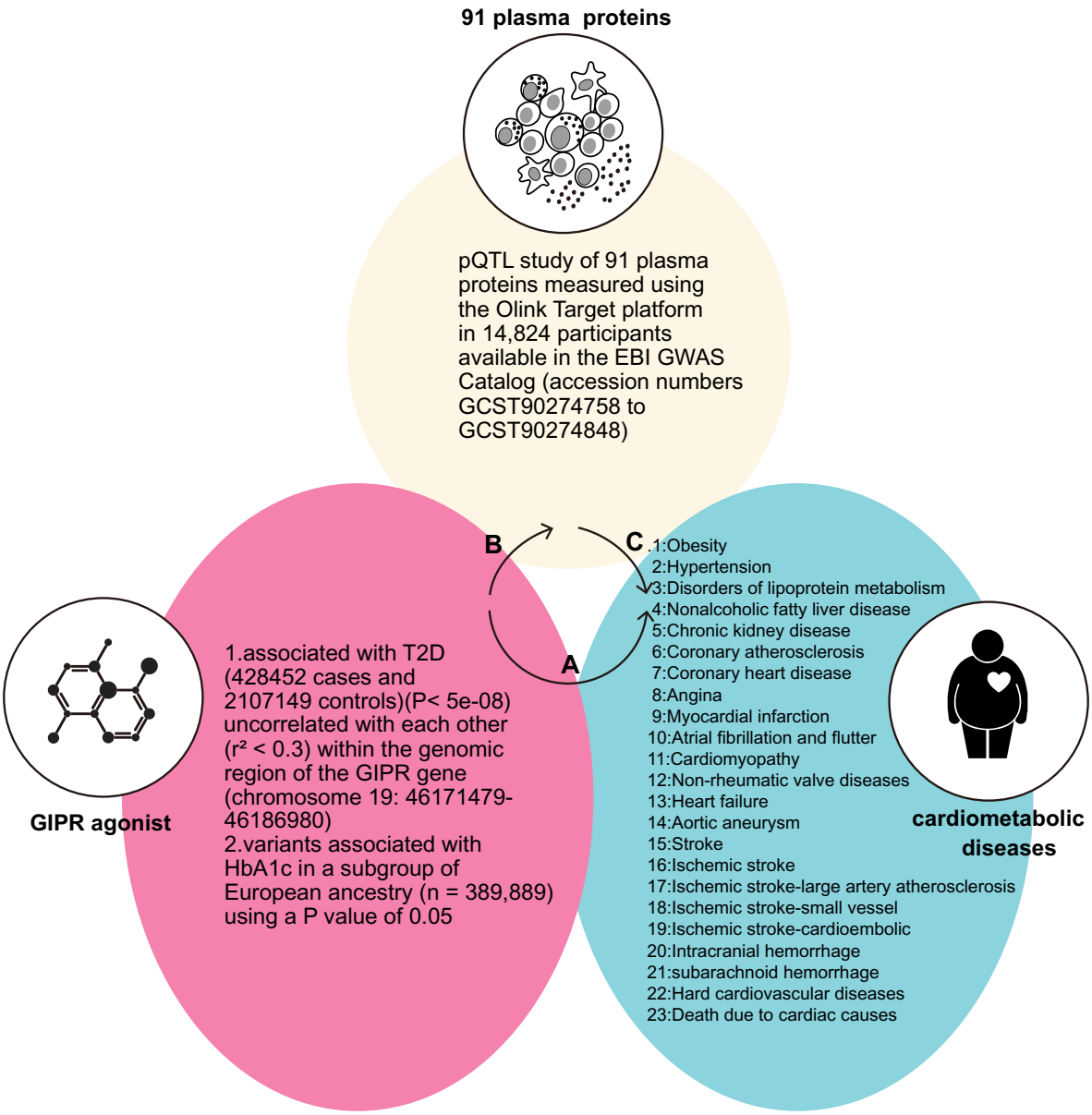

Fig. 1 Overview of the MR study design. The study is to explore whether there is a causal association of inflammatory factors (mediators) in mediating the effect of GIPR agonist (exposures) on CMDs (outcomes). **A** Estimate the associations between GIPR agonist and CMDs. **B** Estimate the associations between GIPR agonist and inflammation factors. **C** Estimate the associations between inflammation factors and CMDs. GIPR: glucose-dependent insulinotropic polypeptide receptor; CMD: Cardiometabolic disease; T2D: type 2 diabetes; pQTL: protein quantitative trait locus; GWAS: Genome-Wide Association Study

5×10^{-8}) in a dataset comprising 428,452 cases and 2,107,149 controls from the DIAGRAM Consortium (http://diagram-consortium.org/) [25]. Additionally, these variants were uncorrelated with each other ($r^2 < 0.3$) within the genomic region of the GIPR gene (Chr19:46,171,479–46,186,980) (2) We evaluated the correlation between each selected variant and HbA1c levels, which serve as a reliable indicator of glucose-lowering effects, retaining only those variants associated with HbA1c in a subgroup of individuals of European ancestry (n = 389,889) [26], using a P-value threshold of 0.05. (3) Single nucleotide polymorphisms (SNPs) with effects on HbA1c in the opposite direction to T2D were excluded, as these associations likely reflect pleiotropic mechanisms that could introduce bias in subsequent MR analyses. (4) SNPs that were palindromic with intermediate allele frequencies were also removed from consideration.

Genetic instruments for inflammatory biomarkers

Genetic variants associated with circulating inflammatory factors were identified through a comprehensive genome-wide meta-analysis, which incorporated a genome-wide protein quantitative trait locus (pQTL) study involving 91 plasma proteins measured using the Olink Target platform across 14,824 participants [27]. Data on these 91 plasma inflammatory proteins, including pQTL findings, are available in the EBI GWAS Catalog (accession numbers GCST90274758-GCST90274848). Our analysis focused exclusively on those genetic variants independently associated (linkage disequilibrium $r^2 < 0.001$ within10,000 kb) and exhibited genome-wide significance ($P < 5 \times 10^{-6}$) at the gene level for each inflammatory biomarker.

Outcome sources

From the latest release of the FinnGen project database (https://r11.finngen.fi/) [28] and other extensive genome-wide association studies (GWAS), we identified 23 CMDs as outcomes. These include: Obesity, Hypertension, Disorders of lipoprotein metabolism and other lipidemias (LIPOPROT), NAFLD, CKD, Coronary atherosclerosis (CORATHER), Major coronary heart disease (CHD), Angina, Myocardial infarction (MI), Atrial fibrillation and flutter (AF), Cardiomyopathy, Nonrheumatic valve diseases (NONRHEVALV), Heart failure (HF), Aortic aneurysm (AA), Stroke, Ischemic stroke (IS), Ischemic stroke due to large artery atherosclerosis (LAS), Ischemic stroke due to small vessel disease (SVS), Ischemic stroke due to cardioembolism (CES), Intracranial hemorrhage (ICH), Subarachnoid hemorrhage (SAH), Hard cardiovascular diseases (CVD_HARD), and Death due to cardiac causes (CARDIAC). The outcomes were chosen due to their high prevalence, ability to comprehensively represent cardiometabolic diseases, and significant public health impact. Furthermore, we prioritized data with a large sample size whenever feasible during the selection process. To mitigate the potential bias associated with population stratification, we limited the study population in the summary data to individuals of predominantly European ancestry. Comprehensive details regarding the GWAS included in the current MR study are presented in Additional file 1: Table S1.

Statistical analysis

To clarify the causal effects of GIPR agonist on 23 outcomes, we performed a MR analysis to estimate the associations between IVs and outcomes applying the random-effects inverse-variance weighted (IVW) method [29]. In conditions exhibiting a significant association with GIPR agonist (hereinafter referred to as "sig"), we further explored whether genetically proxied GIPR agonist plays an indirect role on them through mediator variables, employing the "Two-Step Cis-MR" method. First, we estimated the effects of GIPR agonist on 91 inflammatory markers (β1). Subsequently, we identified the inflammatory markers that exhibited a significant association with GIPR agonist and assessed their impact on "sig" (β2). The mediation proportion for each marker was calculated as $(\beta_1 \times \beta_2)$/total effect. Compared to the multivariable MR approach, the "Two-Step Cis-MR" method reduces bias arising from high linkage disequilibrium among genetic variants in cis-MR analysis. Indirect effects, denoting the influence of genetically proxied GIPR agonist on the risk of CMDs through each potential mediator, as well as the mediated proportions, were evaluated utilizing the "product of coefficients" method. The standard errors for the indirect effects were computed employing the Delta method. To account for multiple hypothesis testing, we employed the Benjamini–Hochberg sequential P-value method to calculate false discovery rate (FDR) adjusted P-values, referred to as q-values [30]. A q-value of 0.05 or lower was considered statistically significant.

Sensitivity analysis

We evaluated heterogeneity utilizing Cochran's Q test [31], where a *P*-value of less than 0.05 signifies significant heterogeneity. To assess the potential for horizontal pleiotropy among the SNPs used as IVs, we conducted MR Egger regression analysis [32]. In MR Egger regression, the intercept term serves to identify directional horizontal pleiotropy, with a *P*-value of less than 0.05 indicating evidence of such pleiotropy. Furthermore, we implemented MR-PRESSO analysis to detect and adjust for horizontal pleiotropic outliers. A *P*-value of less than 0.05 in the Global test of MRPRESSO suggests the existence of such outliers [33]. All MR analyses were performed in R software (Version 4.3.2), using the 'TwoSampleMR' [34], 'MRPRESSO' [33] packages.

Results

Impact of GIPR agonist on CMDs

We identified 17 SNPs as genetic instruments for the GIPR, as detailed in Additional file 1: Table S2. The genetic mimicry of GIPR enhancement, which corresponds to a 1 mmol/mol reduction in HbA1c, was significantly associated with a reduced risk for 14 health outcomes. Specifically, these outcomes include obesity (odds ratio [OR] =0.474 [0.323,0.695], *P*= 0.0001, FDR-corrected *P*= 0.0008), hypertension (OR =0.728 [0.592,0.896], *P*= 0.0027, FDR-corrected *P*= 0.0073), LIPOPROT (OR =0.542 [0.411,0.714], *P*= 0.0000, FDR-corrected *P*= 0.0002), NAFLD (OR =0.135 [0.051,0.358], *P*= 0.0000, FDR-corrected *P*= 0.0004), CORATHER

(OR =0.650 [0.490,0.863], *P*= 0.0028, FDR-corrected *P*= 0.0073), CHD (OR =0.655 [0.478,0.897], *P*= 0.0083, FDR-corrected *P*= 0.0173), angina (OR =0.980 [0.968,0.993], *P*= 0.0021, FDR-corrected *P*= 0.0073), MI (OR =0.986 [0.975,0.997], *P*= 0.0167, FDR-corrected *P*= 0.0295), stroke (OR =0.642 [0.468,0.881], *P*= 0.0061, FDR-corrected *P*= 0.0140), IS (OR =0.502 [0.369,0.684], *P*= 0.0000, FDR-corrected *P*= 0.0002), LAS (OR =0.260 [0.124,0.546], *P*= 0.0004, FDR-corrected *P*= 0.0017), SVS(OR =0.385 [0.208,0.712], *P*= 0.0023, FDR-corrected *P*= 0.0073), CVD_HARD (OR =0.730 [0.570,0.935], *P*= 0.0128, FDR-corrected *P*= 0.0245), and CARDIAC (OR =0.656 [0.459,0.938], *P*= 0.0209, FDR-corrected *P*= 0.0343). The detailed information are presented in Table 1 and Additional file 1: Table S3.

Table 1 Impact of GIPR agonist on 23 cardiometabolic diseases

Outcome	Number of SNPs	OR (95% CI)	*P* value	FDR adjusted *P* value
Obesity	12	0.474 (0.323–0.695)	0.0001	0.0008
Hypertension	14	0.728 (0.592–0.896)	0.0027	0.0073
LIPOPROT	15	0.542 (0.411–0.714)	0.0000	0.0002
NAFLD	15	0.135 (0.051–0.358)	0.0000	0.0004
CKD	16	1.509 (0.911–2.498)	0.1100	0.1265
CORATHER	14	0.650 (0.490–0.863)	0.0028	0.0073
CHD	11	0.655 (0.478–0.897)	0.0083	0.0173
Angina	17	0.980 (0.968–0.993)	0.0021	0.0073
MI	15	0.986 (0.975–0.997)	0.0167	0.0295
AF	13	2.164 (0.962–4.866)	0.0620	0.0891
NONRHEVALV	17	1.176 (0.831–1.664)	0.3610	0.3774
Cardiomyopathy	17	1.728 (0.931–3.207)	0.0829	0.1059
HF	16	0.827 (0.608–1.125)	0.2272	0.2488
AA	13	2.164 (0.962–4.866)	0.0620	0.0891
Stroke	16	0.642 (0.468–0.881)	0.0061	0.0140
IS	17	0.502 (0.369–0.684)	0.0000	0.0002
LAS	17	0.260 (0.124–0.546)	0.0004	0.0017
SVS	16	0.385 (0.208–0.712)	0.0023	0.0073
CES	15	0.544 (0.276–1.073)	0.0788	0.1059
ICH	14	0.845 (0.358–1.993)	0.7005	0.7005
SAH	17	1.954 (0.860–4.438)	0.1096	0.1265
CVD_HARD	17	0.730 (0.570–0.935)	0.0128	0.0245
CARDIAC	17	0.656 (0.459–0.938)	0.0209	0.0343

LIPOPROT: Disorders of lipoprotein metabolism and other lipidaemias; NAFLD: Nonalcoholic fatty liver disease; CKD: Chronic kidney disease; CORATHER: Coronary atherosclerosis; CHD: Major coronary heart disease; MI: Myocardial infarction; AF: Atrial fibrillation and flutter; Cardiomyopathy; NONRHEVALV: Non- rheumatic valve diseases; HF: Heart failure; AA: Aortic aneurysm; Stroke; IS: Ischemic stroke; LAS: Ischemic stroke due to large artery atherosclerosis; SVS: Ischemic stroke due to small vessel disease; CES: Ischemic stroke due to cardioembolism; ICH: Intracranial hemorrhage; SAH: Subarachnoid hemorrhage; CVD_HARD: Hard cardiovascular diseases; CARDIAC: Death due to cardiac causes. SNP: single nucleotide polymorphism; OR: Odds ratio; CI: confidence interval; FDR: false discovery rate

Impact of GIPR agonist on inflammatory factors

We conducted an analysis to evaluate the effects of GIPR agonist on 91 circulating inflammatory factors and identified significant associations with 21 of these biomarkers (Figs. 2, 3 and Additional file 1: Table S4–S6). Our findings indicate that GIPR agonist significantly reduced the levels of Fms-related tyrosine kinase 3 ligand (Flt3L), with β= − 1.029 (95% CI: − 1.456, − 0.603), *P*= 0.0000, FDR-corrected *P*= 0.0000.

Impact of inflammatory factors on 14 CMDs

We observed that Flt3L levels were associated with an increased risk of angina (OR =1.003 [1.001,1.005], *P*= 0.0004, FDR-corrected *P*= 0.0467) (Additional file 1: Table S25) and MI (OR =1.002[1.001,1.004], *P*= 0.0013, FDR-corrected *P*= 0.0266) (Additional file 1: Table S28). The remaining 12 CMD outcomes were not associated with any inflammatory factor, with no evidence of heterogeneity or horizontal pleiotropy in all analyses (Additional file 1: Tables S8–48).

Mediation effects of inflammatory factors

Our observations indicate that GIPR agonist exerted an indirect effect on the total effect of angina through Flt3L, with an OR of 0.997 (95% CI: 0.995,0.999) and a *P*-value of 0.0048. The mediation proportion for this effect is calculated to be 15.486% (4.720%, 26.252%). Similarly, GIPR agonist also influenced MI mediated by Flt3L, with an OR of 0.998 (95% CI: 0.996,0.999), a *P*-value of 0.0077, and a mediation proportion of 16.709% (4.413%, 29.005%) (refer to Fig. 4 and Additional file 1: Tables S49 and S50).

Discussion

To the best of our knowledge, this study represents the first comprehensive investigation utilizing MR to explore the association between genetic predictors of GIPR agonist and CMDs. Our findings provide robust evidence indicating that GIPR agonist is associated with a reduced risk of several CMD outcomes. Specifically, these diseases include obesity, hypertension, LIPOPROT, NAFLD, CORATHER, CHD, angina, MI, stroke, IS, LAS, SVS, CVD_HARD, and CARDIAC. Furthermore, the secondary analysis, which focused on inflammatory factors, demonstrated significant indirect effects of GIPR agonist on CMD outcomes. Our findings indicate that GIPR agonist influences CMD outcomes partially through their effects on specific inflammatory proteins, with Flt3L potentially acting as a mediating factor—accounting for approximately 15.49% and 16.67% of the effects of GIPR agonist on the risks of angina and MI, respectively.

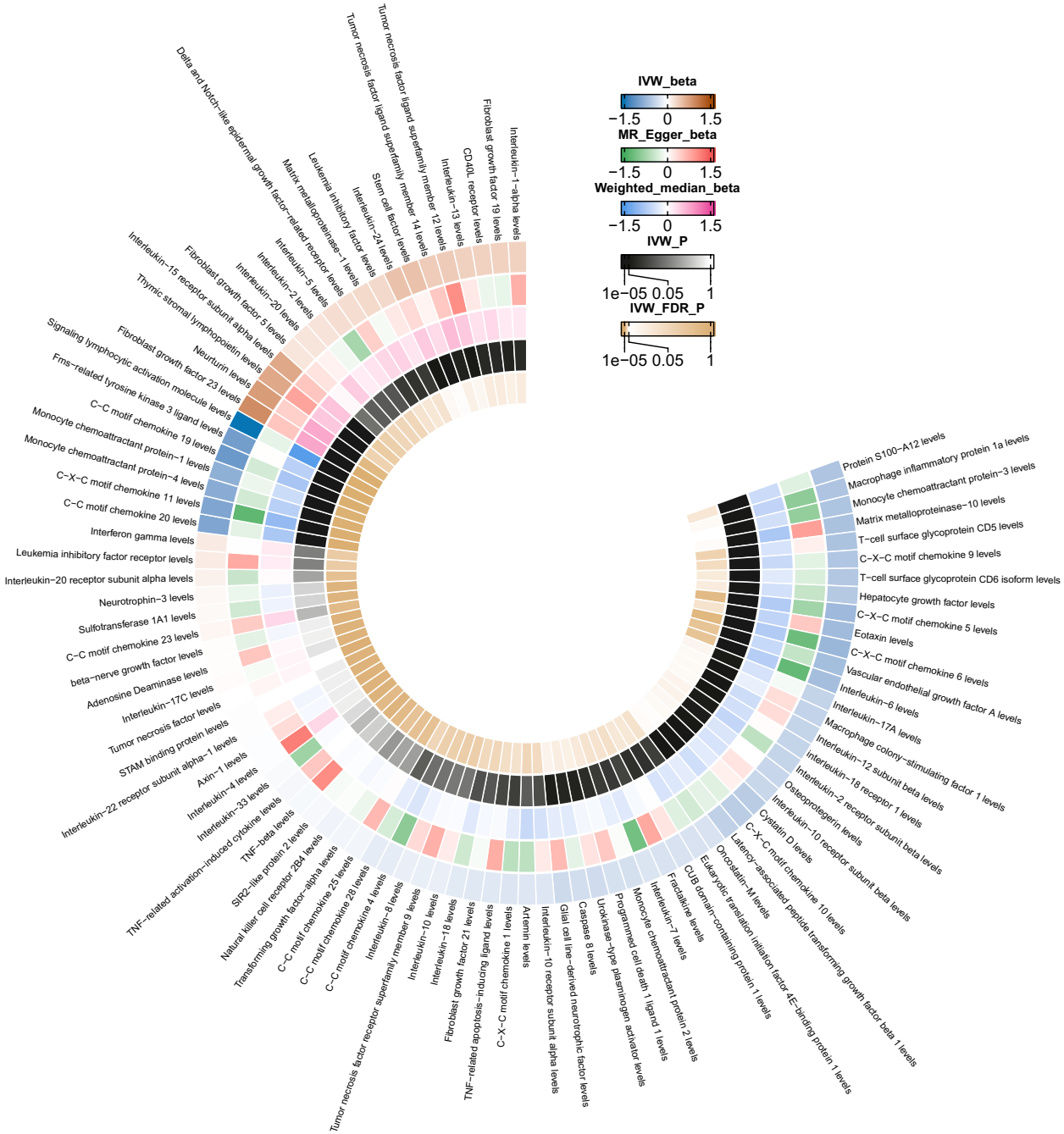

Fig. 2 The effects of GIPR agonist on the 91 inflammation biomarkers. The heatmap depicts the relationship between GIPR agonist and 91 inflammatory biomarkers: the outer ring represents immune cell phenotypes, while the inner ring uses different colors to indicate the β-values and *P*-values of relevant analysis results. GIPR:glucose-dependent insulinotropic polypeptide receptor

The association of GIPR agonist on CMDs

Historically, GIP was considered lacking therapeutic potential. However, recent breakthroughs have revealed that dual GIPR and GLP-1R co-agonist like tirzepatide demonstrates superior efficacy in both glycemic control and weight management compared to a selective GLP-1R agonist. This paradigm shift has reignited scientific interest in GIP, sparking a resurgence of exploration into its therapeutic applications. The GIPR serves as the pivotal pharmacological target through which tirzepatide exerts its therapeutic effects, with multifaceted mechanisms of action [35]. An exploratory analysis revealed that

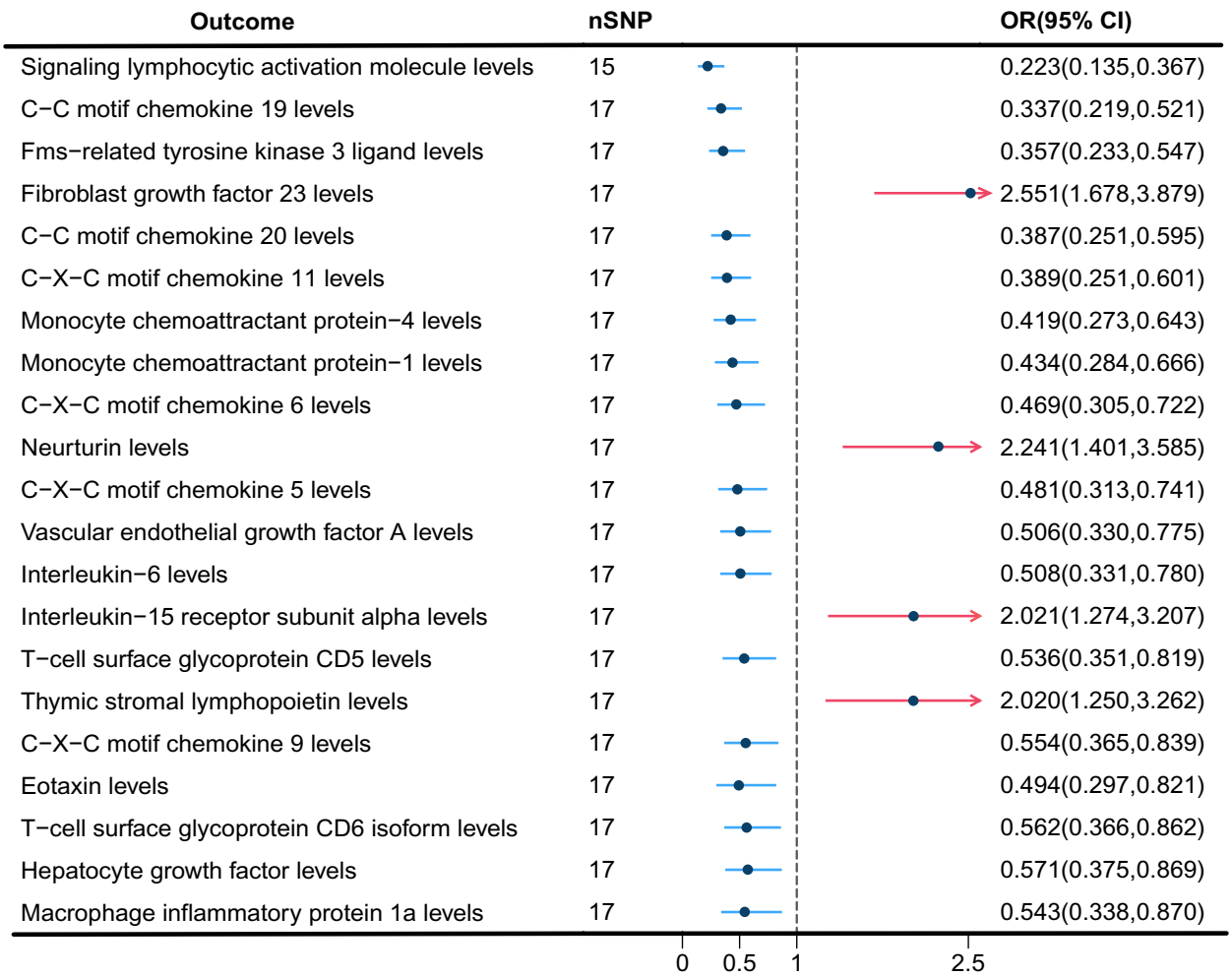

Fig. 3 The effects of GIPR agonist on the 21 selected inflammation biomarkers. The effects of GIPR agonist on the 21 selected inflammation biomarkers from 91 inflammation biomarkers, which were significantly associated with GIPR agonist. GIPR: glucose-dependent insulinotropic polypeptide receptor; SNP: single nucleotide polymorphism; OR: Odds ratio; CI: confidence interval; FDR: false discovery rate

Tirzepatide reduces several cardiovascular—risk—related biomarkers, including YKL-40, ICAM-1, leptin, and growth differentiation factor 15 [36]. It has been found that human epicardial adipose tissue(EAT) expresses the gene encoding the GIPR and the GIPR in EAT is negatively correlated with genes involved in the oxidation and transport of free fatty acids (FFAs), as well as genes that promote FFA biosynthesis and adipogenesis. Since the myocardium mainly relies on FFAs as a fuel source and is directly adjacent to EAT, these findings may have significant implications for the regulation of myocardial activity and performance [37]. Tirzepatide has also been shown to alleviate LPS—induced left ventricular remodeling and dysfunction by inhibiting the TLR4/NF-kB/NLRP3 pathway [38]. Most recently, it was found that Tirzepatide can mitigate doxorubicin-induced cardiotoxicity by regulating HRD1-mediated Nrf2 expression and activity, reducing oxidative stress and cardiomyocyte apoptosis. This suggests Tirzepatide may be a promising therapeutic approach for reducing chemotherapy-related cardiotoxicity [39]. In hepatic metabolism, Ying et al. reported that the GLP-1R agonist, when administered alone, attenuates hepatic steatosis. Furthermore, the addition of a GIPR agonist further reduces lipid accumulation in the liver. Additionally, GIPR agonist may prevent the spillover of postprandial lipids into the liver [40]. And Hu et al. found that tirzepatide has demonstrated the capacity to ameliorate hepatic steatosis in diabetic murine models while concomitantly modulating gut microbiota composition and bile acid metabolism, thereby providing novel therapeutic strategies and mechanistic targets for metabolic dysfunction-associated steatotic liver disease (MASLD) [41]. In the renal metabolic aspect, tirzepatide can slow the decline of the estimated glomerular filtration rate (eGFR) and lower the urine albumin-to-creatinine ratio (UACR) in a clinically meaningful way as compared to

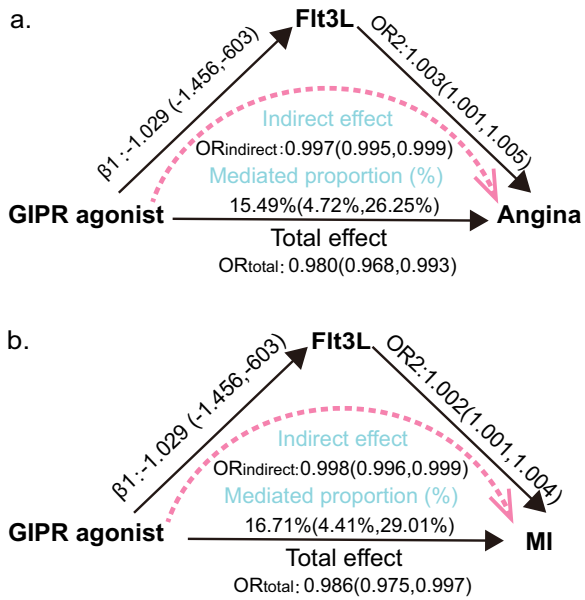

Fig. 4 The Flt3L mediated the causal effect of GIPR agonist on angina/MI. **a** The β1 value between the GIPR agonist and Flt3L and the OR2 value between inflammation factor and angina are MR estimates using the inverse–variance weighted method. **b** The β1 value between the GIPR agonist and Flt3L and the OR2 value between inflammation factor and MI are MR estimates using the inverse–variance weighted method. OR: Odds ratio; Flt3L: Fms-related tyrosine kinase 3 ligand; GIPR: glucose-dependent insulinotropic polypeptide receptor; MI: Myocardial infarction; MR: mendelian randomization

glargine insulin. It also can normalizes diabetic nephropathy via PI3 K/AKT mediated suppression of oxidative stress [42]. Compared to these studies, our findings have provided evidence of a causal relationship between GIPR agonist and CMDs from a genetic standpoint And we have examined the potential pathways of GIPR through the lens of inflammatory metabolism.

Research status of Flt3L

The latest research has linked Flt3L to a wide range of diseases. In the exploration of the causal association between circulating inflammatory proteins and neurodegenerative diseases, a positive causal relationship was identified between Flt3L (OR = 1.0005, $p = 0.0210$) and Alzheimer's disease risk [43]. In another study, Long et al. found that Flt3L can increase the risk of developing Autism Spectrum Disorder (ASD) [44]. Similarly, in a MR study exploring the relationship between circulating inflammatory proteins and multi-site chronic pain (MCP) as well as site-specific chronic pain (SSCP), Flt3L was identified as a risk factor for headache [45]. Yan et al. demonstrated that serum Flt3L levels were significantly elevated in patients with non-Hodgkin's lymphoma (NHL) following chemotherapy, with this biomarker showing correlation to the severity of post-chemotherapy infections, thereby establishing its utility as a novel predictive indicator for infectious complications after treatment. [46]. Our study revealed that Flt3L elevates the risk of angina pectoris and MI. Notably, the GIPR agonist can mitigate these risks by suppressing Flt3L, marking a significant advancement beyond previous research findings. Furthermore, recent studies on early T-cell precursor acute lymphoblastic leukemia (ETP-ALL) and hematopoietic progenitor cell differentiation suggest that Flt3L-mediated metabolic reprogramming and asymmetric cell division may influence progenitor cell behavior [47]. Meanwhile, in hematopoietic progenitor cells, Flt3L signaling regulates anabolic activation and proliferation, associated with dendritic cell differentiation, and affects lineage bias through metabolic processes [48]. These findings collectively highlight the potential of targeting Flt3L signaling to modulate progenitor cell behavior for therapeutic purposes.

Other underlying molecular mechanisms related to GIPR and Flt3L

It has been found that GIP enhances glucose transporter 3 (GLUT3) expression by upregulating hypoxia-inducible factor 1α (HIF-1α) levels through an Akt-dependent pathway. This mechanism promotes glucose uptake in neurons and protects them from oxidative stress [49]. Meanwhile, GIP alleviates oxidative stress in BV-2 microglia by inhibiting reactive oxygen species (ROS) production and nitric oxide (NO) release, while simultaneously enhancing the expression of antioxidant enzymes such as glutathione peroxidase 1 (GPx1) and superoxide dismutase 1 (SOD1). Additionally, GIP inhibits apoptosis in primary murine microglia and upregulates brain-derived neurotrophic factor (BDNF) expression in these cells [50]. Notably, previous studies have shown that FLT3 silencing reduces ROS production, decreases the levels of apoptosis-related protein Bax, and inhibits caspase-3 activity, thereby suppressing cell apoptosis and protecting against ischemia/reperfusion injury [51]. Intriguingly, both GIP-mediated mechanisms (such as the Akt/HIF-1α signaling pathway and antioxidant enzyme regulation) and FLT3 are involved in antioxidation and apoptosis inhibition. However, the specific interaction between them—such as whether Flt3L acts as an upstream regulator or downstream target of these pathways—remains unclear. Further research is needed to clarify this relationship, particularly in the context of oxidative stress during ischemic injury and neurovascular repair processes.

Implications and future directions

Our findings emphasize that GIPR agonist not only directly reduce the risk of CMDs but also influence inflammatory pathways. This indicates that GIPR agonist may provide broader therapeutic advantages beyond simple glycemic control. For instance, targeting inflammatory mediators such as Flt3L could potentially enhance the effectiveness of GIPR agonist therapy. Additionally, longitudinal studies and clinical trials are essential to validate these findings and clarify the specific mechanisms that govern the interaction between GIPR agonist on inflammatory factors and CMDs.

Strengths and limitations of the study

This study represents the first investigation into the relationship between GIPR agonist, inflammatory factors, and CMDs utilizing MR analysis. Furthermore, in our model, we employed genetic variants as IVs through a two-sample MR approach to mitigate biases arising from confounding factors and reverse causation. This methodology was supplemented by sensitivity analyses, and we maximized the sample size to enhance the robustness of our findings. Finally, to reduce the potential for population stratification bias, we restricted our analysis to individuals of predominantly European ancestry within the summary data. Despite the contributions of our study, it is important to acknowledge its limitations. The genetic variations associated with GIPR agonist may provide a more accurate representation of life-long exposure, the effect sizes derived from this approach may not adequately reflect short-term effects. Consequently, MR analysis is more appropriate for investigating potential causal relationships rather than for quantifying effect sizes. For mediation analysis, the product of coefficients method assumes a linear relationship between GIPR agonist and CMDs, but in reality, the relationship may be more complex. Future studies can consider more flexible methods to handle possible nonlinear relationships to improve understanding and accuracy. Nevertheless, the anticipated direction of effect can inform subsequent investigations into therapeutic outcomes in clinical trials.

Conclusion

In conclusion, our study provides evidence for the advantageous effects of GIPR agonist in mitigating the risk of various CMDs through the modulation of inflammatory pathways. The identification of Flt3L as a key mediator offers novel insights into the mechanisms by which GIPR agonist exerts their effects. These findings enhance our understanding of the therapeutic potential of GIPR agonist and indicate promising directions for future research in the management of cardiometabolic diseases.

Abbreviations

GLP-1	Glucagon-like peptide-1
GIPR	Glucose-dependent insulinotropic polypeptide
CMD	Cardiometabolic disease
MR	Mendelian randomization
SNP	Single nucleotide polymorphism
IVW	Inverse variance weighted
pQTL	Protein quantitative trait locus
LIPOPROT	Disorders of lipoprotein metabolism and other lipidaemias
NAFLD	Nonalcoholic fatty liver disease
CKD	Chronic kidney disease
CORATHER	Coronary atherosclerosis
CHD	Major coronary heart disease
MI	Myocardial infarction
AF	Atrial fibrillation and flutter
NONRHEVALV	Non-rheumatic valve diseases
HF	Heart failure
AA	Aortic aneurysm
IS	Ischemic stroke
LAS	Ischemic stroke due to large artery atherosclerosis
SVS	Ischemic stroke due to small vessel disease
CES	Ischemic stroke due to cardioembolism
ICH	Intracranial hemorrhage
SAH	Subarachnoid hemorrhage
CVD_HARD	Hard cardiovascular diseases
CARDIAC	Death due to cardiac causes
Flt3L	Fms-related tyrosine kinase 3 ligand

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-025-01744-2.

Additional file 1.

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Author contributions

Fang Cheng: Conceptualization, Methodology, Software, Investigation, Formal Analysis, Writing—Original Draft Xinyu Niu: Data Curation,Software and Visualization, Writing-Review & editing. Yaoling Wang: Validation;Software and Visualization, Writing-Review & editing. Fan Yang: Investigation, Methodology. Kang Yang: Investigation, Methodology. Wei Li: Conceptualization,Funding Acquisition and Supervision All authors read and approved the final manuscript.

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