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# The Impact of SGLT1 Inhibition on Frailty and Sarcopenia: A Mediation Mendelian Randomization Study

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**Keywords:** frailty | Mendelian randomization | sarcopenia | SGLT1 inhibition

## ABSTRACT

**Background:** Although pharmacological effects of SGLT2 inhibitors on the development of frailty and sarcopenia were known, the role of SGLT1 remained less clear. The present study investigated the possible effect of SGLT1 inhibition on these conditions and explored potential mediators.

**Methods:** A two-sample Mendelian randomization (MR) analysis was performed to assess the effect of SGLT1 inhibition on frailty index (FI) and low grip strength in individuals aged 60 years and older using both the FNIH and EWGSOP criteria. Subsequently, a two-step MR analysis was conducted to investigate the mediating role of insulin resistance phenotype and identify potential mediators of the effect of SGLT1 inhibition on the FI and low grip strength from 1558 plasma proteins and 1352 metabolites.

**Results:** Genetically predicted SGLT1 inhibition was associated with decreased FI ($\beta$: −0.290 [95% CI: −0.399, −0.181]) and reduced risk of low grip strength in individuals aged 60 years and older under both FNIH ($\beta$: −0.796 [95% CI: −1.216, −0.376]) and EWGSOP criteria ($\beta$: −0.287 [95% CI: −0.532, −0.041]). The two-step MR analysis demonstrated the role of insulin resistance phenotype in mediating SGTL1 inhibition on alleviating frailty (mediation proportion = 19.56% [95% CI: 8.42%, 30.70%]). After screening, 24 proteins and 16 metabolites were identified as mediators of the impact of SGLT1 inhibition on FI. Additionally, 13 proteins and 16 metabolites were found to mediate the effect of SGLT1 inhibition on low grip strength according to FNIH criteria

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while 22 proteins and 6 metabolites were shown to mediate the impact of SGLT1 inhibition on low grip strength under EWGSOP criteria.

**Conclusions:** SGLT1 inhibition potentially mitigated frailty and sarcopenia through several biological mediators, shedding new light for therapeutic intervention.

## 1 | Introduction

The ageing population worldwide is placing an increasing strain on healthcare systems [1], leading to heightened awareness of age-related issues, such as frailty and sarcopenia. Recent systematic reviews have reported that approximately 11% of elderly adults residing in the community experienced frailty [2] while the prevalence of sarcopenia was ranging from 9.9% to 18.6% according to different diagnostic criteria [3]. Therefore, investigating the potential pathological mechanisms of frailty and sarcopenia is of utmost importance for identifying novel and effective therapeutic targets for the elderly.

Studies have demonstrated that senior people with frailty had a higher risk of sarcopenia [4], and sarcopenia was associated with a greater risk of frailty in community-dwelling elderly adults [5]. The crosstalk between frailty and sarcopenia probably attributed to the shared underlying pathophysiological mechanisms [6–8] in which insulin resistance in the skeletal muscle may be a key player. Indeed, some of the antihyperglycaemic medications have been reported to exhibit protective effects on skeletal muscle by alleviating the insulin resistance in diabetes [9]. A recent study reported that sotagliflozin, one of the newest antihyperglycaemic drugs inhibiting both sodium-glucose co-transporter 1 (SGLT1) and sodium-glucose co-transporter 2 (SGLT2), mitigated the impairment of viability, proliferation and migration abilities of skeletal muscle cells induced by high glucose and hypoxia [10]. However, whether the protective role of sotagliflozin on skeletal muscle resulted from the inhibition of SGLT1 or SGLT2 has not been fully elucidated. Previous studies have demonstrated the beneficial role of SGLT2 inhibition on skeletal muscle either in patients or animal models with frailty and sarcopenia [11–14]. However, the impact of SGLT1, a related member of the SGLTs family, on frailty and sarcopenia still remained poorly understood.

Hence, the aim of this study was to explore the role of SGLT1 inhibition on frailty and sarcopenia and identify the potential mediators by using Mendelian randomization (MR) analysis.

## 2 | Method

### 2.1 | Study Design

First, two-sample MR analyses were conducted in the present study to assess the causal association between SGLT1 inhibition and frailty index (FI), as well as low grip strength in individuals aged 60 years and older. Second, genome-wide association study (GWAS) statistics for 1558 proteins, 1352 metabolites and insulin resistance phenotype were utilized to identify the potential targets that were associated with FI and low grip strength. After screening, the casual associations between SGLT1 inhibition and the potential targets were evaluated. Finally, the delta method [15] was employed to estimate the mediating effect among the targets showing causal associations with both SGLT1 inhibition and outcomes (Figure 1).

### 2.2 | Instrumental Variables for SGLT1 Inhibition

Candidate instrumental variables were screened and filtered through a multi-step process in primary analysis. First, genetic variants linked to mRNA expression levels of SLC5A1, known as the gene of SGLT1, were identified by using data from the Genotype-Tissue Expression (GTEx) [16]. Second, selected variants were further refined to identify the SNPs associated with the glycated haemoglobin (HbA1c), a supposed indicator of SGLT1 inhibitor for its glucose-lowering effect [17, 18], at a statistical significance threshold of $1\times10^{-4}$. GWAS data for HbA1c based on an unrelated group of European individuals

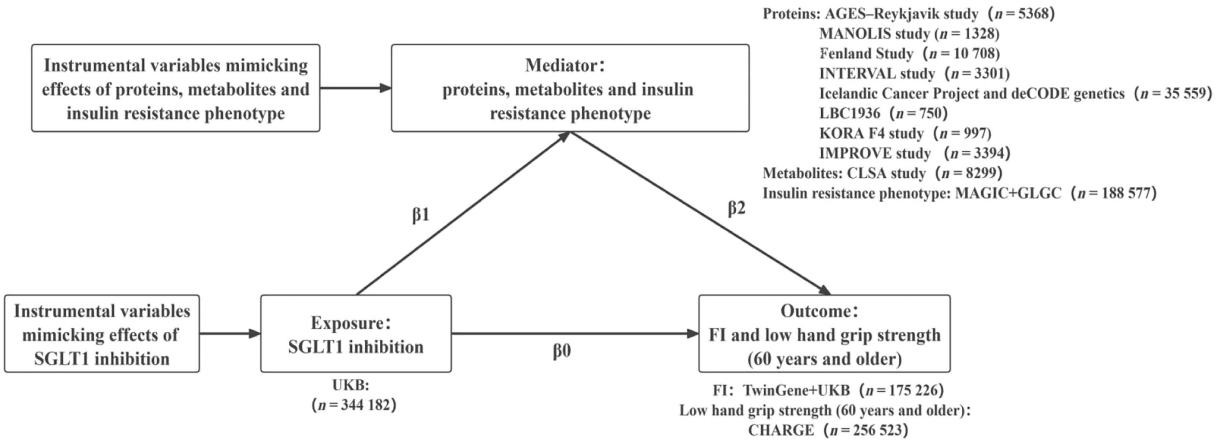


**FIGURE 1** | A flowchart illustrating the methodological framework and sources of GWAS databases utilized in the study. FI, frailty index; GWAS, genome-wide association study; SGLT1, sodium-glucose co-transporter 1.

without diabetes in the UK Biobank were used [19] (Table S1). Subsequently, SNPs in linkage disequilibrium (LD) of $r^2 > 0.8$ within 250 kb were removed, according to the 1000 Genomes European reference panel [19]. Finally, the statistical power of these variants were estimated by $F$ statistics, where $F > 10$ indicated a low probability for weak instrument bias [20]. Consequently, 16 SNPs were selected to mimic the effect of SGLT1 inhibition (Table S2). Similarly, the instrumental variables for insulin resistance phenotype, plasma proteins and metabolites were also identified (Method S1, Table S3).

### 2.3 | Study Outcomes

In the present study, FI was utilized as an indicator of frailty severity [21]. The GWAS summary data of FI were derived from participants of the UK Biobank ($n = 164\,610$, aged 60–70 years and 51.3% females) and TwinGene ($n = 10\,616$, aged 41–87 years and 52.5% females), where the FI was calculated based on self-reported items (49 items in UK Biobank, 44 items in TwinGene) on symptoms, disabilities and diagnosed diseases and presented as a proportion of the sum of all deficits (Table S4) [22]. Additionally, the diagnosis of low grip strength, a key characteristic of sarcopenia, was referred to the criteria established by the Foundation for the National Institutes of Health (FNIH) [23] and the European Working Group on Sarcopenia in Older People (EWGSOP) [24], respectively. The GWAS statistics of low grip strength in individuals aged 60 years and older under both FNIH (grip strength: < 26 kg male; < 16 kg female) and EWGSOP (grip strength: < 30 kg male; < 20 kg female) criteria was from the CHARGE study, including 256 523 individuals of European descent [25] (Table S1).

### 2.4 | Statistical Analysis

Two-sample MR analyses were performed to investigate the effect of SGLT1 inhibition on frailty and low grip strength (β0). In the analysis, the inverse variant weighted (IVW) method [26] was used as the primary analytical approach, offering the most efficient and powerful estimates. Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) [27] was employed to identify and correct potential horizontal pleiotropy and heterogeneity by removing outlier SNPs. Moreover, MR-PRESSO also provided the casual estimation of the MR analysis. The Cochran's $Q$ statistic in IVW and MR-Egger were used to assess the presence of heterogeneity in results [28]. In addition, two-step MR analyses were used to identify the potential mediators (Method S2). Furthermore, sensitivity analyses were performed to validate the stability of the results (Method S3, Table S5).

## 3 | Results

### 3.1 | SGLT1 Inhibition Attenuated Frailty and Low Grip Strength

In the primary analysis, genetic variants associated with both HbA1c levels and mRNA expression of the SLC5A1 gene were identified as instrumental variables for MR analysis. The results of the IVW method indicated that SGLT1 inhibition was associated with decreased FI ($\beta$: −0.290 [95% CI: −0.399, −0.181]) and reduced risk of low grip strength in individuals aged 60 years and older under both FNIH criteria ($\beta$: −0.796 [95% CI: −1.216, −0.376]) and EWGSOP criteria ($\beta$: −0.287 [95% CI: −0.532, −0.041]). Furthermore, a similar trend was observed in the association between SGLT1 inhibition and low grip strength across both genders. Under FNIH criteria, SGLT1 inhibition was associated with a decreased risk of low grip strength in both male ($\beta$: −0.870 [95% CI: −1.494, −0.246]) and female ($\beta$: −0.875 [95% CI: −1.385, −0.365]) individuals aged 60 years and older. For EWGSOP criteria, statistical significance was observed in the relationship between SGLT1 inhibition and low grip strength in males ($\beta$: −1.395 [95% CI: −1.836, −0.953]), whereas no significant relationship was found in females ($\beta$: 0.167 [95% CI: −0.131, 0.465]). In addition, the directions of the MR-Egger and MR-PRESSO method estimates were consistent with those of IVW method (Figure 2A). Sensitivity analysis indicated that there was no evidence of heterogeneity in the results based on Cochran's $Q$ statistic in the IVW and MR-Egger methods. Moreover, the intercept in MR-Egger and global test in MR-PRESSO suggested that horizontal pleiotropy did not impact the results (Table S6). In the validation analysis, genetic variants previously reported to represent the loss-of-function of SLC5A1 gene were employed to mimic the effect of SGLT1 inhibition, and consistent results were observed (Figure 2B, Table S7).

### 3.2 | SGLT1 Inhibition Ameliorated Frailty Through Alleviating Insulin Resistance

First, we assessed the impact of the insulin resistance phenotype on FI. Results in the IVW method revealed a robust causal association between insulin resistance and FI ($\beta$: 0.274 [95% CI: 0.163, 0.386]). After removing outlier SNPs, there was no evidence of heterogeneity and pleiotropy (Table S8). However, insulin resistance phenotype turned out to be unrelated with low grip strength under both FNIH ($\beta$: −0.139 [95% CI: −0.538, 0.259]) and EWGSOP ($\beta$: −0.218 [95% CI: −0.479, 0.044]) criteria. Next, we further estimated the effect of SGLT1 inhibition on insulin resistance phenotype and found out a significant casual association ($\beta$: −0.207 [95% CI: −0.289, −0.125]). Subsequently, the two-step MR analysis was conducted to assess the role of insulin resistance in mediating the causal effect of SGLT1 on FI. As shown in Table S9, insulin resistance accounted for 19.56% (95% CI: 8.42%, 30.70%) of the total effect of SGLT1 inhibition on FI.

### 3.3 | Mediation MR of SGLT1 Inhibition, Plasma Proteins and FI as Well as Low Grip Strength

After MR analysis, 167 proteins were found to be associated with FI, with 79 proteins showing positive associations and 88 proteins showing negative associations (Figure 3A, Table S10). Then we further estimated the effect of SGLT1 inhibition on these screened proteins and identified 24 proteins as mediators of the protecting effect of SGLT1 inhibition on frailty. For instance, neuroendocrine convertase 1 (PCSK1), mesencephalic astrocyte-derived neurotrophic factor (MANF) and serum paraoxonase/

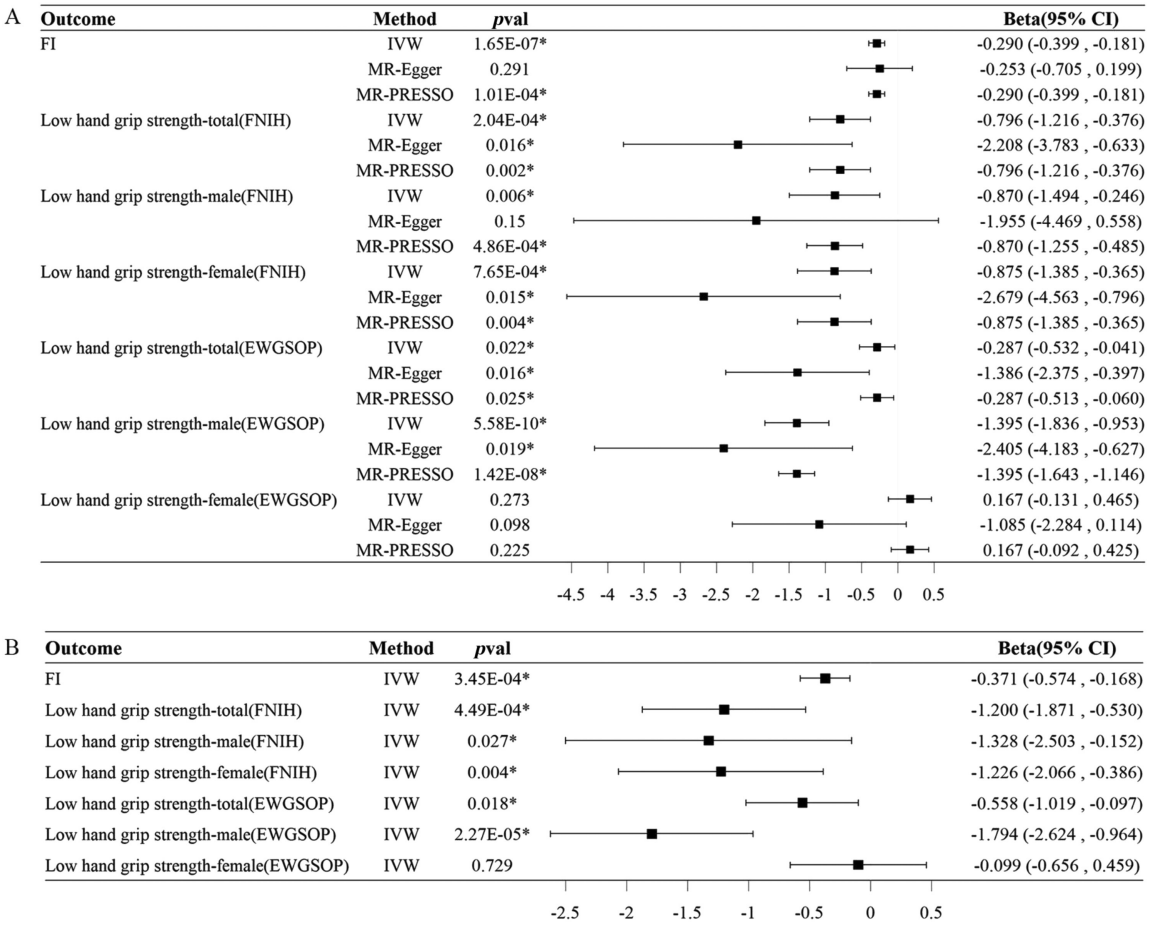


**FIGURE 2** | Causal effect of SGLT1 inhibition on FI, as well as low grip strength in both male and female individuals aged 60 years and older under both FNIH and EWGSOP criteria. (A) In the primary analysis, genetic variants demonstrating significant associations with both HbA1c levels and mRNA expression of the SLC5A1 gene were identified as instrumental variables for MR analysis to investigate the causal relationship between SGLT1 inhibition and outcomes. (B) In the validation analysis, functionally damaging missense variants within the SLC5A1 gene, previously documented in literature, were employed to mimic the effect of SGLT1 inhibition in the MR analysis. CI, confidence interval; EWGSOP, European Working Group on Sarcopenia in Older People; FI, frailty index; FNIH, Foundation for the National Institutes of Health; IVW, inverse variance weighted; MR, Mendelian randomization; *p*val, *p* value; SGLT1, sodium-glucose co-transporter 1.

lactonase 3 (PON3) were identified as mediators, accounting for 13.49% (95% CI: 5.08%, 21.91%), 18.94% (95% CI: 0.93%, 36.95%) and 44.90% (95% CI: 10.90%, 78.90%) of the total effect of SGLT1 inhibition on FI, respectively (Figure 4, Table S9).

Through MR analysis, 143 proteins were found to be linked to low grip strength under the FNIH criteria, with 72 showing positive associations and 71 showing negative associations (Figure 3B, Table S11). Similarly, 163 proteins were demonstrated to be associated with low grip strength under the EWGSOP criteria, with 75 displaying positive associations and 88 displaying negative associations (Figure 3C, Table S12). Then we assessed the causal effect of SGLT1 inhibition on these screened proteins in order to identify potential mediators. Consequently, 13 proteins were identified as mediators of the effect of SGLT1 inhibition on low grip strength under the FNIH criteria while 22 proteins were identified as mediators of the effect of SGLT1 inhibition on low grip strength under the EWGSOP criteria. Specifically, ribonucleoside-diphosphate reductase subunit M2 B (RRM2B) was found to mediate the effect of SGLT1 inhibition on low grip strength under both FNIH and EWGSOP criteria, explaining 26.98% (95% CI: 6.69%, 47.26%) and 44.06% (95% CI: 6.28%, 81.83%) of the overall effect, respectively (Figure 5, Table S9). Different GWAS databases of protein mediators were used in the validation analysis to strengthen the credibility of the mediating effects. The results validated the mediating effects of nine protein mediators on the relation between SGLT1 inhibition and outcomes (Table S13).

Further investigation of protein mediators involving in the inhibiting effect of SGLT1 on low grip strength across genders was performed. Eleven proteins were identified as mediators of the effect of SGLT1 inhibition on low grip strength in males while 16 proteins were proved to be mediators in females (Tables S9, S14–S15).

### 3.4 | Mediation MR of SGLT1 Inhibition, Plasma Metabolites and FI as Well as Low Grip Strength

We subsequently examined the correlation between 1352 metabolites and outcomes, revealing that 113 metabolites were linked to FI, with 63 showing positive associations and 50 showing negative associations (Figure 3D, Table S16). Among

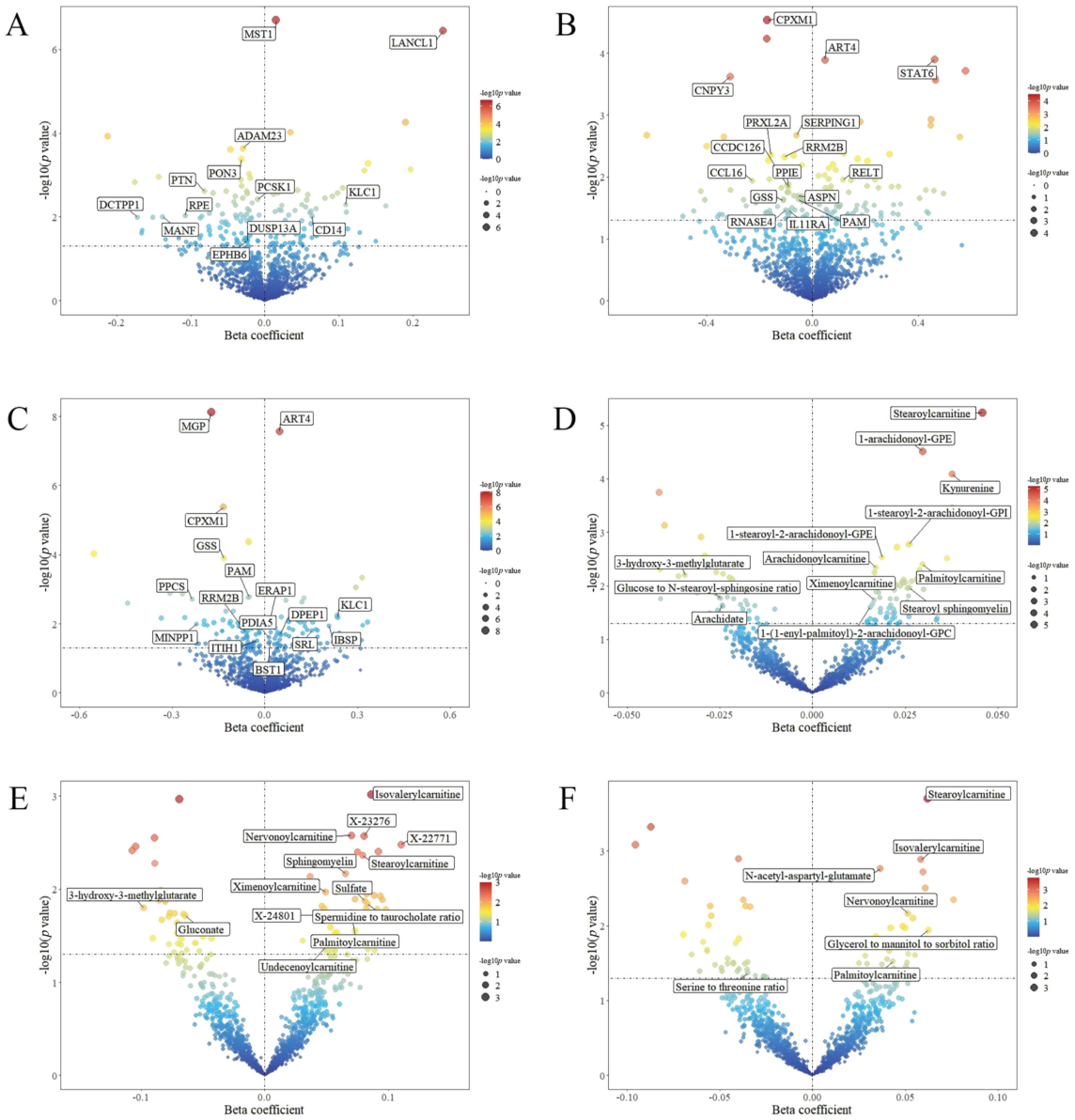


**FIGURE 3** | Causal effect of plasma proteins and metabolites on FI, as well as low grip strength aged 60 years and older under both FNIH and EWGSOP criteria. (A) Volcano gram illustrating the association between plasma proteins and FI. (B) Volcano gram illustrating the association between plasma proteins and low grip strength (60 years and older) under EWGSOP criteria. (C) Volcano gram illustrating the association between plasma proteins and low grip strength (60 years and older) under FNIH criteria. (D) Volcano gram illustrating the association between plasma metabolites and FI. (E) Volcano gram illustrating the association between plasma metabolites and low grip strength (60 years and older) under EWGSOP criteria. (F) Volcano gram illustrating the association between plasma metabolites and low grip strength (60 years and older) under FNIH criteria. EWGSOP, European Working Group on Sarcopenia in Older People; FI, frailty index; FNIH, Foundation for the National Institutes of Health.

these metabolites, 16 were identified as mediators of the effect of SGLT1 inhibition on FI. For instance, SGLT1 inhibition was related with decreased levels of kynurenine, palmitoylcarnitine and arachidate, all of which were strongly correlated with FI, explaining 12.11% (95% CI: 3.27%, 20.95%), 9.69% (95% CI: 1.28%, 18.11%) and 9.59% (95% CI: 0.23%, 18.94%) of the total effect, respectively (Figure 4, Table S9).

Similarly, metabolite–phenotype association was accessed to identify potential mediators of the impact of SGLT1 inhibition and low grip strength in individuals aged 60 years and older under both FNIH and EWGSOP criteria. After screening, it was found that 80 metabolites were significantly correlated with low grip strength according to the FNIH criteria, with 46 exhibiting positive associations and 34 exhibiting negative associations (Figure 3E, Table S17). Additionally, 70 metabolites were screened to be associated with low grip strength under EWGSOP criteria, with 34 showing positive associations and 36 showing negative associations (Figure 3F, Table S18). Then the causal effect of SGLT1 inhibition on the metabolites that significantly associated with outcomes was assessed to identify the potential mediators. As a result, we identified 16 metabolites mediating the effect of SGLT1 inhibition on low grip strength under FNIH criteria and 6 metabolites mediating

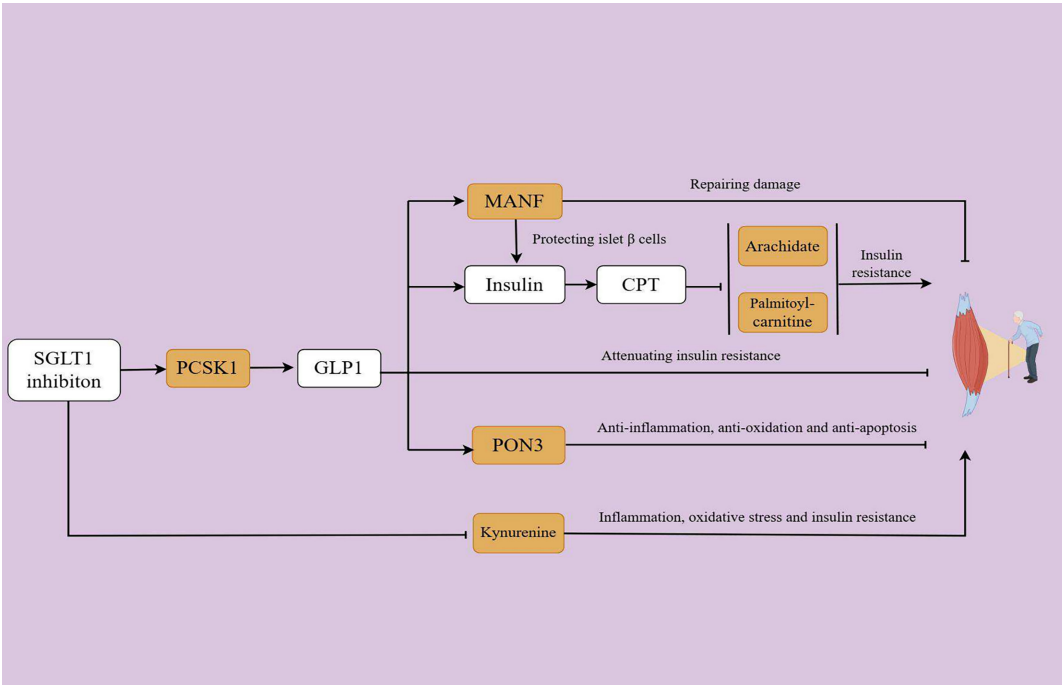


**FIGURE 4** | Roadmap suggesting potential mechanisms of SGLT1 inhibition on attenuating frailty through mediators. SGLT1 inhibition led to increased expression of PCSK1 which in turn up-regulated the GLP1 levels. The interaction between GLP1 and its receptor in skeletal muscle could attenuate the insulin resistance. Moreover, GLP1 acted as a stimulus for insulin secretion which could activate the CPT expression, consequently inhibiting the insulin resistance in skeletal muscle induced by long chain saturated fatty acid, such as palmitoylcarnitine and arachidate. In addition, the activation of GLP1 increased the MANF level, facilitating the repair of skeletal muscle damage and promoting the survival of pancreatic β cells, which were responsible for insulin secretion. Meanwhile, GLP1 also increased the expression levels of PON3, which could protect the skeletal muscle by anti-inflammation, anti-oxidation and anti-apoptosis. In addition, SGLT1 inhibition suppressed the level of kynurenine, a molecule participating in the biological process of inflammation, oxidative stress and insulin resistance, thereby safeguarding skeletal muscle health. CPT, carnitine palmitoyltransferase; GLP1, glucagon-like peptide-1; MANF, mesencephalic astrocyte-derived neurotrophic factor; PCSK1, neuroendocrine convertase 1; PON3, serum paraoxonase/lactonase 3; SGLT1, sodium-glucose co-transporter 1.

the effect of SGLT1 inhibition on low grip strength under EWGSOP criteria. Among these metabolites, palmitoylcarnitine, which was the mediator of FI, also played a key role in mediating the impact of SGLT1 inhibition on low grip strength, contributing to 8.35% (95% CI: 0.21%, 16.48%) of the total effect. Additionally, metabolites involved in lipid metabolism, such as sphingomyelin, were also identified as contributors mediating the effect of SGLT1 inhibition on low grip strength (Figure 5, Table S9).

Specifically, gender differences in the mediating effects of metabolites were detected. In males, 10 metabolites were found to mediate the association between SGLT1 inhibition and low grip strength while in females, 12 metabolites were identified as mediators (Tables S9, S19–S20).

## 4 | Discussion

In the present study, we found the protective role of SGLT1 inhibition on frailty and sarcopenia through MR analysis. Furthermore, we proved the intermediary role of insulin resistance on the association between SGLT1 inhibition and frailty, suggesting that the attenuation of frailty by SGLT1 inhibition was possibly mediated by the alleviation of insulin resistance. After screening, a series of proteins and metabolites were identified to mediate the effect of SGLT1 inhibition on frailty and sarcopenia, indicating plausible mechanistic pathways.

The effect of SGLT1 inhibition on the presence of frailty and sarcopenia was seldom discussed previously. It was well known that SGLT1, together with SGLT2, played an essential role in human physiological function by facilitating the cellular uptake of glucose alongside sodium ions [29]. SGLT2 inhibitor has been widely used in type 2 diabetes patients because of its ability to reduce glucose re-absorption from urine [30]. However, recent studies indicated a better glucose-lowering effect of dual inhibitor of both SGLT1 and SGLT2 [31]. Apart from the glucose-lowering effect, the dual inhibitor was recently reported to attenuate the injuries of skeletal muscle caused by ischaemia in diabetic mice and decrease the impairment of C2C12 cells induced by high glucose and hypoxia [10]. This finding sheds light on the potential effect of SGLT1 and SGLT2 inhibition on protecting skeletal muscle cells, offering a novel approach to address ageing and degeneration in skeletal muscle, such as frailty and sarcopenia. Although existing researches have highlighted the protective role of SGLT2 inhibition on the development of frailty and sarcopenia, the influence of SGLT1 inhibition on these conditions has been relatively unexplored. In the present study, we explored the casual relationship between SGLT1 inhibition and FI as well as low grip strength using MR analysis and

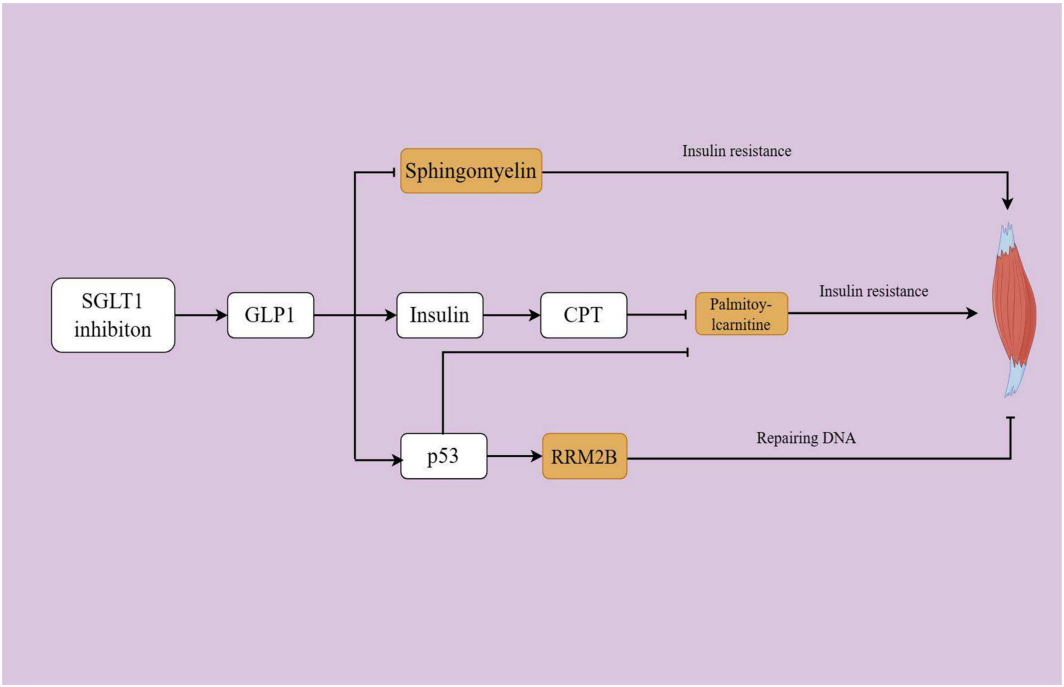


**FIGURE 5** | Roadmap suggesting potential mechanisms of SGLT1 inhibition on attenuating sarcopenia through mediators. GLP1 activation, promoted by SGLT1 inhibition, decreased the level of sphingomyelin that was widely recognized as a trigger of insulin resistance in skeletal muscle. In addition, the activation of GLP1 promoted the insulin secretion and CPT upregulation, thereby mitigating palmitoylcarnitine-induced insulin resistance in skeletal muscle. Additionally, GLP1 was demonstrated to be related to higher level of p53 which in turn increased the RRM2B expression, facilitating the DNA repair of skeletal muscle. In particular, p53 also showed the ability of attenuating palmitoylcarnitine-induced insulin resistance in skeletal muscle. CPT, carnitine palmitoyltransferase; DNA, deoxyribonucleic acid; GLP1, glucagon-like peptide-1; SGLT1, sodium-glucose co-transporter 1.

found out strong associations, indicating that SGLT1 inhibition could ameliorate frailty and sarcopenia.

In this study, we demonstrated the crucial role of insulin resistance in mediating the protective effect of SGLT1 inhibition on frailty. Insulin resistance, characterized by impaired insulin-mediated regulation of glucose metabolism in tissues, was usually caused by disturbances in downstream signalling pathways of insulin [32]. Skeletal muscle was recognized as a targeted tissue for insulin simulation as well as a primary regulator of glycaemic control. It was well established that insulin played a crucial role in promoting glucose uptake and protein synthesis in skeletal muscle, thus contributing to the maintenance of physiological function of skeletal muscle [33]. Insulin sensitivity of the skeletal muscle declines with age, which was probably caused by mitochondrial dysfunction, β-oxidation of fatty acids disorder, reactive oxygen species (ROS) production and inflammatory factors secretion, finally leading to skeletal muscle dysfunction and frailty [34–37]. SGLT1 inhibition could increase insulin secretion to alleviate insulin resistance by several intracellular mechanisms. Upon exposure to high levels of glucose, SGLT1 in pancreatic α cells facilitated sodium influx, affecting the function of sodium proton exchangers and resulting in the decrease of cellular PH levels. Consequently, PH-sensitive metabolic enzymes were activated, prompting the release of glucagon and disrupting the secretion of insulin, which was suppressed by SGLT1 inhibition [38, 39]. Additionally, inhibition of SGLT1 in the intestine was proved to promote the glucagon-like peptide-1 (GLP1) secretion, which in turn, stimulated the β cells to release insulin [40, 41]. Recently, Wu et al. have detected the expression of receptors of GLP1 in the skeletal muscle of mice. Their research indicated that over-expression of GLP1 in the skeletal muscle improved the endurance capacity through regulating glycogen synthesis, enhancing glucose uptake, increasing mitochondrial biogenesis and elevating oxidative metabolism [42]. This finding laid the foundation that high levels of GLP1 resulting from SGLT1 inhibition improved insulin sensitivity and physiological function of skeletal muscle.

In this paper, we further confirmed that in the casual association between SGLT1 inhibition and FI, PON3 explained 44.90% of total casual effect, followed by MANF (18.94%), PCSK1 (13.49%), kynurenine (12.11%), palmitoylcarnitine (9.69%) and arachidate (9.59%). Specifically, PON3, as one of members of the PON family of hydrolytic enzymes, was a calcium-dependent glycoprotein synthesized in the liver, playing a role of hydrolysing lactones and eicosanoids [43]. PON3 has been reported to exhibit the anti-inflammatory [44], antioxidant [45] and anti-apoptotic [46] abilities. Moreover, the expression of PON3 has been detected in skeletal muscle [47], and the upregulation of PON3 was demonstrated to promote the proliferation of bovine skeletal muscle satellite cells [48]. These findings probably explained the protective role of PON3 in skeletal muscle. Additionally, liraglutide, a GLP1 receptor agonist, has been reported to elevate the expression of PON3 [49], indicating that inhibiting SGLT1 possibly led to an increase of PON3 expression in the skeletal muscle through the elevation of GLP1 levels. Hence,

PON3 may establish the connection between SGLT1 inhibition and skeletal muscle ageing.

Basically, MANF was a member of the new family of neurotrophic factors (NTFs) and broadly expressed in mature tissues [50]. A recent research has reported a notable increase in MANF levels after skeletal muscle injury, which facilitated the repair processes of skeletal muscle. However, in aged animals, the increase in MANF after injury was suppressed. This finding underscored the essential role of MANF in skeletal muscle injury repair [51]. Moreover, MANF has been shown to protect β cells from endoplasmic reticulum stress [52], potentially enhancing insulin sensitivity in skeletal muscle. Furthermore, the activation of the GLP1 receptor, a downstream signalling pathway of SGLT1 inhibition, was reported to trigger increased expression of MANF [52], which may partly explain the beneficial effect of SGLT1 inhibition on frailty.

Prohormone convertase 1/3 (PC1/3), encoded by the PCSK1, was a serine endoprotease [53], playing an important role in processing GLP1 [54]. Researches have indicated that the inhibition of SGLT2, a closely related member of the SGLT family, had the potential to enhance PCSK1 expression and subsequently elevated GLP1 levels [55]. Therefore, the inhibition of another member of SGLTs, SGLT1, may exhibit a similar effect. Additionally, PCSK1 was also proved to be expressed in the skeletal muscle (https://www.genecards.org/cgi-bin/carddisp.pl?gene=PCSK1). On the basis of the evidences, it was suggested that SGLT1 inhibition probably elevated the GLP1 level through the upregulation of PCSK1 in the skeletal muscle, potentially contributing to alleviation in frailty.

Kynurenine, one of the metabolic mediators identified in our investigation, was generated by tryptophan metabolism [56]. Studies showed that kynurenine levels increased with age and led to muscle loss [57, 58]. Furthermore, Valdiglesias et al. reported a strong relationship between plasma kynurenine level and frailty in elderly people [59], which was consistent with the present study. Kynurenine increased the level of oxidative stress, inflammation and insulin resistance [57, 58, 60–62], elucidating its possible role in the impairment of skeletal muscle function. In addition, a recent study utilized muscle biopsies to examine metabolic characteristics in skeletal muscles of heart failure patients treated with or without SGLT2 inhibitors. The results indicated a significant reduction of kynurenine levels in skeletal muscles and alleviation of skeletal muscle atrophy, after SGLT2 inhibitor treatment [63]. It was well documented that SGLT2 inhibitors also exhibited partial inhibition effect on SGLT1 due to their pharmacological similarity [64]. Therefore, we hypothesized that SGLT1 inhibition suppressed kynurenine level and eliminated its deleterious effect on skeletal muscle.

As was shown, lipid metabolism played an important role in mediating the effect of SGLT1 inhibition on frailty. Emerging evidence suggested that fatty acids were significantly related with frailty in elderly [65]. Our data also demonstrated that palmitoylcarnitine and arachidate, recognized as metabolic products of long-chain saturated fatty acids, was positively associated with frailty. In essence, long-chain saturated fatty acids have been shown to induce insulin resistance in skeletal muscle [66–68]. Fatty acids and their metabolites were transported into the mitochondria for β-oxidation, which was facilitated by carnitine palmitoyltransferase (CPT) [69, 70]. Moreover, CPT was crucial in safeguarding muscle tissue against insulin resistance by promoting the metabolism of long-chain saturated fatty acids [71, 72]. Additionally, insulin signals upregulated the level of CPT, promoting the β-oxidation of fatty acid in skeletal muscle [73]. It was possible that inhibiting SGLT1 may have reduced the levels of palmitoylcarnitine and arachidate in skeletal muscle by stimulating insulin secretion and activating CPT, ultimately mitigating frailty.

Our study identified several proteins and metabolites, such as RRM2B, palmitoylcarnitine and sphingomyelin, that were found to be associated with low grip strength. Of particular interest was the observation that palmitoylcarnitine was related with both FI and low grip strength, indicating the crucial role of long-chain saturated fatty acid in aged-related muscle dysfunction. Actually, the accumulation of lipid in skeletal muscle was reported to promote the muscle atrophy by inducing insulin resistance [74]. Our data further supported the previous findings, suggesting that palmitoylcarnitine served as a mediator in the impact of SGLT1 inhibition on both frailty and sarcopenia.

Additionally, sphingomyelin, a key structural component of biological membranes, was found to be positively correlated with sarcopenia in the current investigation. It has been well established that sphingomyelin and its metabolic derivatives acted as secondary messengers in multiple tissues, playing a role in the development of insulin resistance [74]. In particular, the sphingomyelin signalling pathway in muscle has been identified as a determinant of insulin resistance in humans [75]. Inhibition of the acid sphingomyelinase was reported to improve the insulin sensitivity in elderly individuals [76]. In our study, we demonstrated that sphingomyelin played an intermediary role in the relationship between SGLT1 inhibition and low grip strength. GLP1 receptor activation could reduce the accumulation of sphingomyelin and its metabolic products [77]. Therefore, SGLT1 inhibition may suppress the sphingomyelin level by elevating the level of GLP1, subsequently improved the grip strength.

RRM2B was recognized as one of the mediators participating in the effect of SGLT1 inhibition on sarcopenia. It was a critical ribonucleotide reductase subunit, playing an essential role in DNA synthesis and repair in p53-dependent manner [78, 79]. Researches have demonstrated that patients with mutations in RRM2B experienced impaired mitochondrial DNA synthesis in skeletal muscle, resulting in serious dysfunction of skeletal muscle [80, 81]. Furthermore, the knockout of RRM2B in myofibres resulted in weakness of muscles and triggered the differentiation of skeletal muscle stem cells (MuSCs) [82]. p53, widely acknowledged as a classical biomarker of ageing, exhibited the capacity to impede cell proliferation in response to DNA damage and initiated DNA repair by activating RRM2B, thereby promoting cell survival [83–85]. It was suggested that the p53/RRM2B pathway played a critical role in the survival of skeletal muscle during ageing. Moreover, p53 was reported to attenuate the insulin resistance induced by palmitate through NF-κB and p38/ERK MAPK pathways [86]. These findings provided a reliable evidence that p53 exhibited a beneficial effect on skeletal muscle

by either promoting DNA repair through activation of RRM2B or ameliorating insulin resistance, which in turn mitigated the sarcopenia.

The crosstalk between frailty and sarcopenia has been extensively studied and confirmed in our research. For example, asparagine was identified as an amino acid-related metabolite negatively correlated with both frailty and sarcopenia in our study. Previous studies revealed a negative correlation between asparagine levels and frailty in the elderly [87] and a decrease of asparagine levels in skeletal muscle of elderly individuals with sarcopenia [88]. Moreover, supplementation of asparagine in the diet enhanced the capacity of the muscle to utilize free fatty acids and spare glycogen, prolonging the exhaustion time during exercise [89], indicating a crucial role of asparagine in both frailty and sarcopenia. In our study, the effects of SGLT1 inhibition on both frailty and sarcopenia shared some co-mediators. Specifically, palmitoylcarnitine, stearoylcarnitine, ximenoylcarnitine and 3-hydroxy-3-methylglutarate, all identified as lipid metabolites, mediated the impact of SGLT1 inhibition on both conditions. It may be attributed to the fact that SGLT1 inhibitor suppressed the lipid-induced insulin resistance. In addition, our study also found that some metabolic byproducts of plasma membrane played a crucial role in mediating the SGLT1 inhibition's effect on both frailty and sarcopenia. For frailty, phosphatidylcholine (GPC), phosphatidylethanolamine (GPE) and phosphatidylinositol (GPI) were demonstrated to be mediators. Consistently, previous studies have shown that these byproducts of phospholipids exhibited an inverse correlation with muscle volume and peak power, contributing to the decline in skeletal muscle mass and function among elderly individuals [90]. However, sphingomyelin, also known as a component of plasma membrane, was identified as a key mediator for low grip strength which participated in insulin resistance. Some proteins with the ability of repairing injury and maintaining survival of skeletal muscle also played a role. Specifically, MANF was demonstrated as a mediator of FI, while RRM2B mediated the effect of SGLT1 inhibition on low grip strength. Molecules involved in biological process of inflammation, oxidative stress and apoptosis, like PON3 and kynurenine, were demonstrated as mediators of FI rather than low grip strength. It may be because low grip strength, which was recognized as an important indicator of early stage of ageing [91], has not yet developed many detectable changes, such as inflammation, oxidative stress and apoptosis [92].

We further analysed the potential proteins and metabolites that were associated with low grip strength in both genders. Specifically, SERPING1 showed a close association with low grip strength in individuals of both genders. It was known for the capacity of regulation of vascular permeability and suppression of inflammation [93], probably exhibiting some beneficial effects on skeletal muscle. Studies have indicated that SERPING1 mitigated the reperfusion injury of skeletal muscle in rats [94], which may explain its role of alleviating sarcopenia. SERPING1 was also identified as mediators of the effects of SGLT1 inhibition on low grip strength across genders, indicating that SGLT1 inhibition attenuated the low grip strength in different genders through the common targets.

Our research acknowledged several limitations. First, the potential effects of protein levels within specific cells and tissues have not been adequately investigated because the abundances of these circulating proteins may differ from those within cells and tissues. Second, despite employing multiple MR approaches to address pleiotropy confounding, residual bias persisted. Third, although sensitivity and validation analyses were conducted to ensure the reliability of our findings, further experiments in vivo and vitro were needed to be explored.

## 5 | Conclusion

In conclusion, SGLT1 inhibition exhibited a protective role in attenuating frailty and sarcopenia. Furthermore, potential mediators of these effects were involved in various biological processes.


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### Conflicts of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

The GWAS Summary statistics used in this study were publicly accessed from the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/), GWAS Catalog (https://www.ebi.ac.uk/gwas/), deCODE genetics (https://www.decode.com/summarydata/) and LBC 1936 (https://datashare.ed.ac.uk/handle/10283/3408).

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## Supporting Information

Additional supporting information can be found online in the Supporting Information section.