Sodium-glucose cotransporter 1 inhibition may delay aging: a Mendelian randomization study

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Abstract

Introduction: Previous studies have shown that sodium-glucose cotransporter 2 (SGLT2) inhibition has a significant impact on both cardiovascular disease and aging. However, available evidence on the relationship between sodium-glucose cotransporter 1 (SGLT1) inhibition and aging is currently very limited. We aimed to investigate the causal effect of SGLT1 inhibition on aging by Mendelian randomization (MR) analysis.

Material and methods: The summary-level data for SGLT1 inhibition and aging of European ancestry were extracted from publicly available genome-wide association studies (GWAS). The main analysis used in this study was the random inverse variance weighted (IVW) method. We also employed weighted median and the MR-Egger method as supplementary evidence for IVW results. Sensitivity analyses were performed to assess the stability of the results.

Results: Finally, the exposure data for SGLT1 inhibition were derived from the UK Biobank, including 344,182 European individuals. The GWAS data for telomere length included 472,174 participants, and for frailty index, 175,226 individuals were included. Sixteen single nucleotide polymorphisms (SNPs) that met the SNP screening criteria were retrieved. The results indicated that SGLT1 inhibition increases telomere length (odds ratio $[OR]_{IVW}$ = 1.10, 95% CI: 1.03–1.18; p = 0.007) and reduces the frailty index (OR_{IVW} = 0.84, 95% CI: 0.73–0.95; p = 0.008). No evidence of significant pleiotropy or heterogeneity was observed, which was further substantiated by the sensitivity analysis results.

Conclusions: The present study determined that SGLT-1 inhibition exhibited a significant negative correlation with aging, suggesting a theoretical basis for the strategy of delaying the aging process.

Key words: SGLT1, aging, cardiovascular drugs, Mendelian randomization.

Introduction

Aging is a degenerative physiological process that occurs after cell maturation. The precise mechanism of this process remains to be fully elucidated, although current hypotheses suggest that telomere shortening, DNA damage, and mitochondrial dysfunction may mediate its development [1]. Estimates suggest that the number of individuals aged 60 and

over in China has reached 240 million, with projections indicating that this figure will exceed 400 million by 2035, constituting approximately one-third of the total population [2]. European countries have also been witnessing an increase in population ageing, whereby the elderly demographic constitutes approximately 24% of the total population [3]. Aging has been demonstrated to be a significant contributing factor to the development of numerous pathological conditions, including, but not limited to, Alzheimer's disease [4], pan-vascular disease [5], and neoplasms [6]. The phenomenon of population ageing represents a significant challenge to global public health, exerting a substantial strain on healthcare systems and significantly impacting the economic and social development of societies.

Sodium-glucose cotransporter 2 inhibitors (SGLT2is), including empagliflozin and dapagliflozin, act chiefly on the renal proximal tubule to inhibit the reabsorption of glucose. This results in a reduction of blood glucose levels, and their use is recommended by clinical guidelines for the treatment of diabetes [7]. SGLT2 is not only associated with hypoglycemia but is also involved in the regulation of metabolism and the improvement of cardiac and renal function. Consequently, it is widely used in the standard treatment of heart failure [8]. Research has shown that SGLT2is can remove senescent cells [9] and improve cognitive dysfunction, acting as a delayer of aging [10]. It is evident from the results of recent studies that sotagliflozin, a dual inhibitor of SGLT2 and SGLT1, has a positive impact on mitochondrial function [11]. SGLT1, a key member of the sodium-glucose cotransporter family, has yet to be fully elucidated in terms of its role in the aging process. Further exploration is required to ascertain whether sotagliflozin exhibits a superior anti-ageing effect in comparison to SGLT2is. Furthermore, it is not possible to establish a definitive causal relationship, owing to the inherent limitations of observational study design. Large-scale randomized controlled trials (RCTs) necessitate significant human and material resources, as well as protracted follow-up periods.

Mendelian randomization (MR) is a research method employed to ascertain the correlation between instrumental variables (IVs) and exposures and outcomes. Using genetic variables as IVs enables the analysis of the correlation between IVs and exposures with a view to elucidating the causal relationship between exposures and outcomes [12]. The foundation of MR studies lies in Mendel's second law, namely the principle of random assignment of alleles. It is noteworthy that these studies are impervious to influences arising from other factors that may arise in subsequent life [13]. In contrast to observational studies, MR analyses have the capacity to minimize the effects of potential confounders and reverse causality, and therefore they are widely used in causal association analyses. Consequently, this study employed MR to examine the causal association between SGLT1 inhibition and aging.

Material and methods

Study design

In this study we performed by a two-sample MR analysis with three fundamental assumptions (Figure 1): (1) genetic variants are strongly associated with SGLT1 inhibition; (2) selected IVs are independent of confounding factors; (3) IVs affect aging only through SGLT1 inhibition. The study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology Using MR (STROBE-MR) guidelines [14].

Exposure and outcome data

Exposure data for SGLT1 inhibition selection were from UK Biobank and included 344,182 European individuals. The present study used outcome data on telomere length and frailty index and associated GWAS obtained from the following database: https://gwas.mrcieu.ac.uk/ (Table I).

IV selection

The genetic tools used for SGLT1 inhibition went through a number of stages, a process

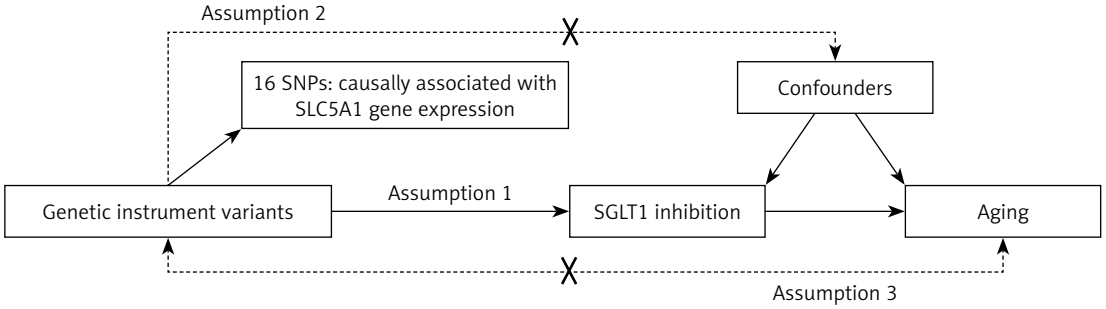

Figure 1. Design for the MR study. MR assumptions: (1) Assumption 1 states that genetic variants correlate with SGLT1 inhibition and affect aging through SGLT1 inhibition. (2) Assumptions 2 and 3 state that SNPs are not associated with any confounders and do not influence aging through other ways

Table I. Detailed information on the included GWAS data

Exposure	GWAS ID	Sample size	Year	Ancestry
Telomere length	ieu-b-4879	472,174	2021	European
Frailty index	ebi-a-GCST90020053	175,226	2021	

that was also described in a previous study [15]. (1) To find loci associated with SLC5A1 mRNA levels, a search was performed in the Genotype-Tissue Expression (GTEx) database [16]. (2) The association between certain genetic polymorphisms in SGLT1 inhibitors and glycated hemoglobin (HbA_{1c}) has been demonstrated [17]. (3) Selected SNPs were deleted, with a linkage disequilibrium (LD) coefficient $r^2 > 0.8$ within 250 kilobases and an F-statistic of not less than 10 [18]. Finally, 16 SNPs were selected (Supplementary Table SI).

MR analysis

This study aimed to ascertain the causal relationship between SGLT1 and aging. We used three methods to establish this relationship: inverse variance weighting (IVW), MR-Egger, and weighted median. The IVW method was the main approach because of its high statistical efficiency and its widespread use in relevant research areas [19]. The remaining two robust methods were used as adjunctive methods. The "Two-Sample MR" package was used to visualize the results of the MR analysis by forest plots, scatter plots and sensitivity analysis plots.

Sensitivity analysis

To assess the stability of our results, we performed sensitivity analyses. This included the MR-Egger and IVW tests to assess heterogeneity, and a *p*-value of less than 0.05 was considered significant. In addition, we conducted the MR-Egger intercept test to assess the pleiotropy of our results, and $p < 0.05$ indicated the presence of pleiotropy. For sensitivity analysis, the leave-one-out method was used to ensure that the effects of individual SNPs on the overall results were rigorously investigated.

Statistical analysis

Analyses were performed using the R software (version 4.2.1) with the packages "Two Sample MR", "Forest plot", "Radial MR" and "MR PRESSO". The effect sizes are presented with 95% confidence intervals (CIs). Two-sample statistical tests were used, and $p < 0.05$ was considered statistically significant.

Results

MR analysis

Using the IVW method, the evidence clearly supported a causal association between SGLT1 inhibition and telomere length (OR_{IVW} = 1.10, 95% CI: 1.03–1.18; $p = 0.007$) and frailty index (OR_{IVW} = 0.84, 95% CI: 0.73–0.95; $p = 0.008$) (Figure 2). The intercept term in the scatterplot represents the composite pleiotropic effect among the genetic variances, which mirrors the average direct effect of the genetic variance on the aging indices (Figure 3). Furthermore, the global test ($p > 0.05$) revealed the absence of influential outliers in the data. Nevertheless, the MR-Egger regression analysis suggested that such directional pleiotropy was unlikely to bias the results ($p > 0.05$). In contrast, the MR-Egger regression showed no statistically significant causal link between SGLT1 inhibition and telomere length (OR =1.24, 95% CI: 0.95–1.64; $p = 0.143$). Notwithstanding the equivocal findings pertaining to the causal relationship between SGLT1 inhibition and telomere length, the primary IVW method indicated a causal effect of SGLT1 inhibition on the risk of telomere shortness. Moreover, the Wald ratio of each SNP to the outcome suggested a significant causal association between SGLT1 inhibition and aging indices (Figure 4).

Heterogeneity and sensitivity

Cochran's Q-test indicated an absence of significant heterogeneity among the IV estimates de-

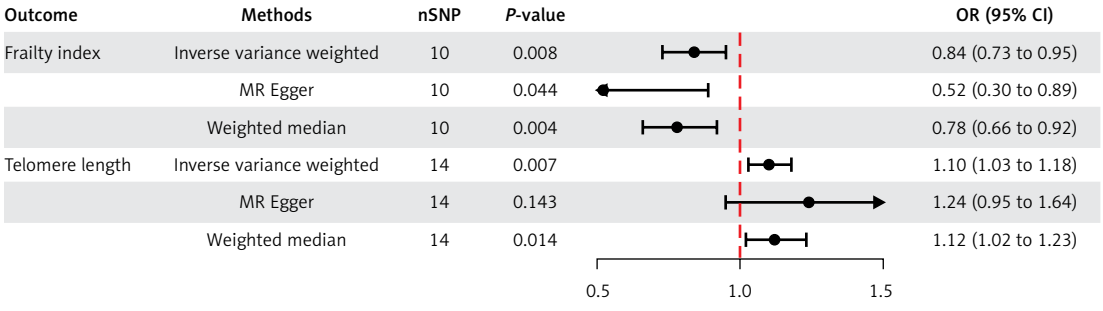

Figure 2. Summary plot of MR results between SGLT1 inhibition and aging indices

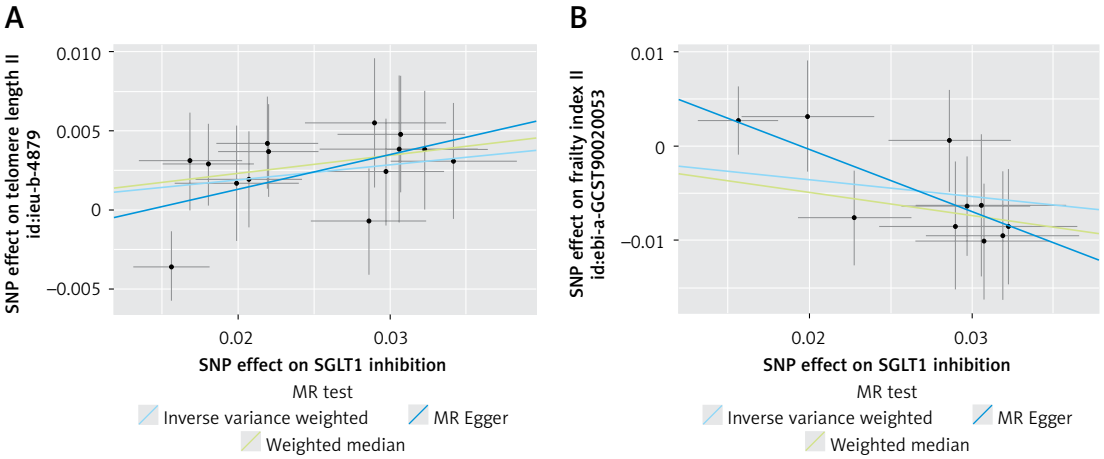

Figure 3. Scatter plots of genetic associations with SGLT1 inhibition and aging indices. **A** – telomere length; **B** – frailty index

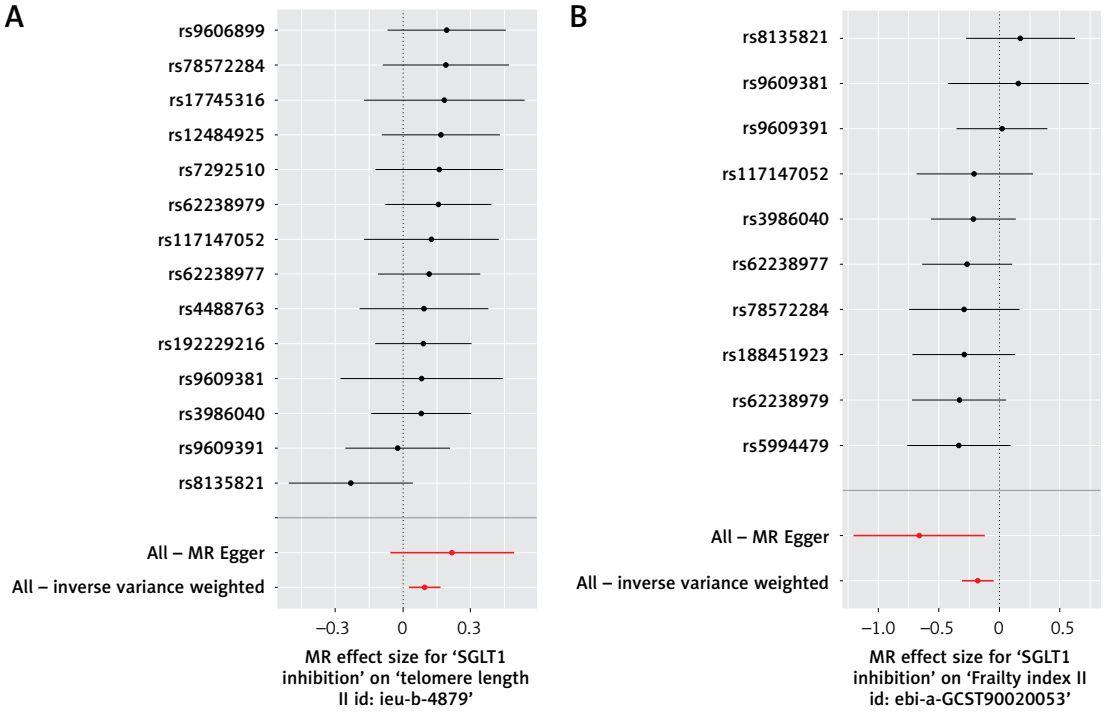

Figure 4. Forest plots of genetic associations between SGLT1 inhibition and aging indices. **A** – telomere length; **B** – frailty index

rived from individual variants for telomere length (IVW method, Q statistics = 8.45, p = 0.813), and for frailty index (IVW method, Q statistics = 6.56, p = 0.682). These findings collectively suggested a high degree of reliability of the MR estimates. The results of the "leave-one-out" strategy demonstrated that none of the individual SNPs had a significant effect on the IVW estimates (Figure 5). This suggests that the overall causal relationship was not influenced by a particular SNP. The implementation of "Radial MR" was undertaken with the objective of identifying outliers. No outliers were identified for frailty index, while "Radial MR" identified 2 outliers for telomere length. After removing the outliers, the causal effect between exposure and outcome was stable (p < 0.05). The Q-Statistic for heterogeneity was not significant (p = 0.813) (Figure 6).

Discussion

This study represents the earliest systematic examination of the causal relationship between SGLT1 inhibition and aging traits in the European population with MR analysis. The MR analysis revealed a positive causal association between SGLT1 inhibition and telomere length, and a negative causal relationship with the frailty index. In further sensitivity analyses, the association between SGLT1 inhibition and the aging indices was reinforced.

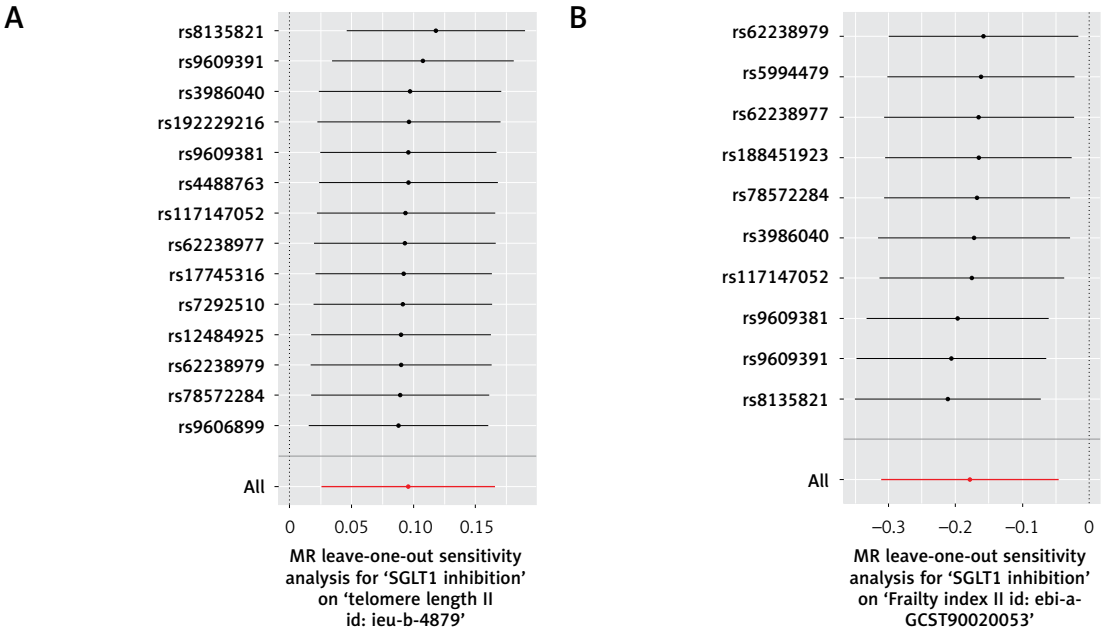

Figure 5. Leave-one-out analysis plots of genetic associations between SGLT1 inhibition and aging indices. **A** – telomere length; **B** – frailty index

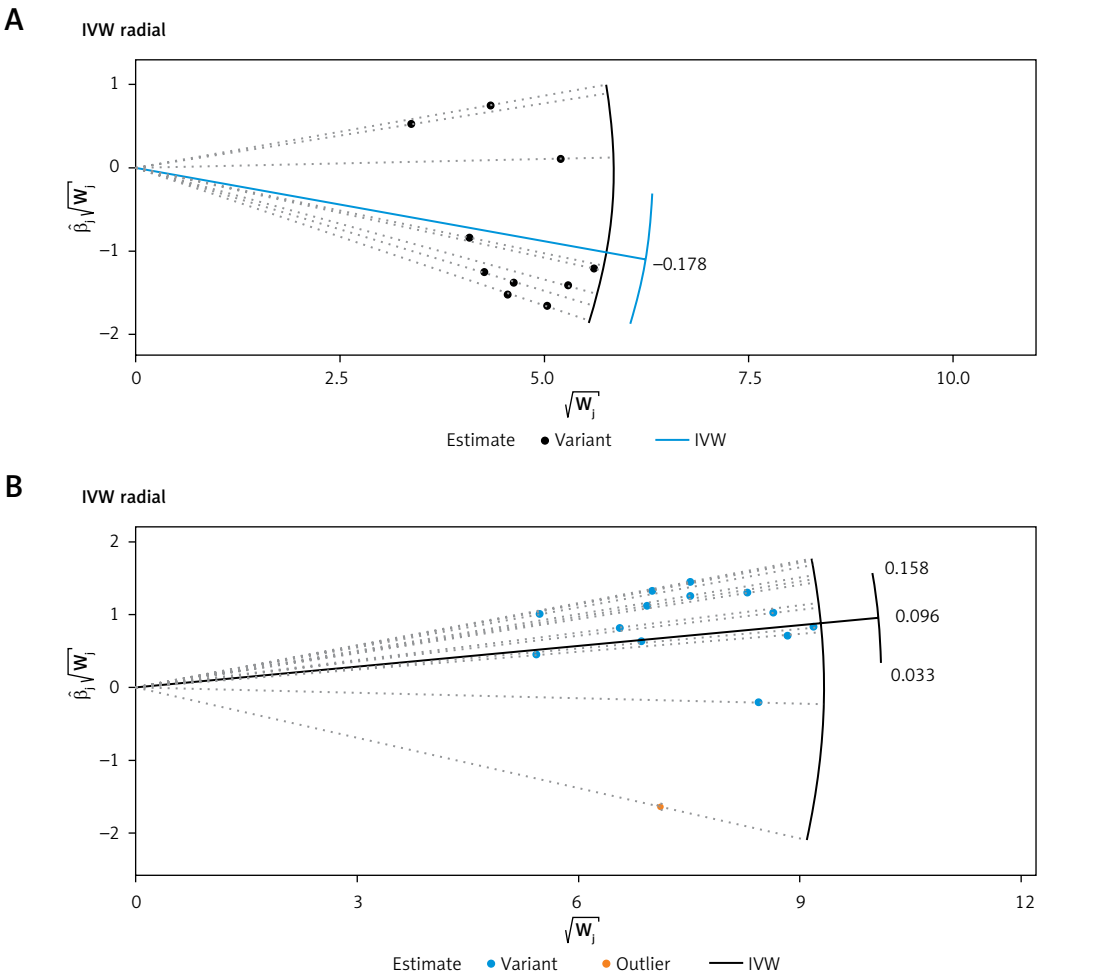

Figure 6. Radial MR analysis plots of genetic associations between SGLT1 inhibition and aging indices. **A** – telomere length; **B** – frailty index

Glucose and aging are closely interrelated, and biological ageing has been shown to mediate the effect of climate change and air pollution on glucose metabolism impairment [20]. Gaspar *et al.* found that aging rats exhibited increased levels of glucose-6-phosphatase and insulin resistance, leading to elevated liver glucose secretion [21]. The triglyceride-glucose (TyG) index has been regarded as a promising marker for the assessment of insulin resistance (IR), as it can be calculated expeditiously from triglyceride and fasting glucose levels [22]. Pan *et al.* demonstrated that each 1-unit rise of TyG correlated with a 0.40-year increment in phenotypic age, yielding a 15% higher risk of advanced aging [23]. Frailty represents a progressive age-related syndrome marked by a reduced physical capacity for homeostasis and an accelerated susceptibility to exogenous stress [24]. A 10-year follow-up cohort study of Chinese individuals showed that elevated TyG index levels were associated with an increased risk of frailty (OR = 2.17, 95% CI: 1.01–3.88) [25]. Telomeres are defined as the TTAGGG sequence at the ends of chromosomes to maintain the integrity of the chromosome during cell division [26]. Telomere length has been identified as a significant biomarker of biological age, and individuals with short telomere length tend to develop accelerated aging and aging-associated disease [27]. In a cross-sectional study, a TyG index value of 8.77 or higher was found to be significantly associated with reduced telomere length (β = –93.33, 95% CI: –134.33 to –52.32) [28]. Aging contributes to a variety of chronic diseases, and evidence suggests that leukocyte telomere length and telomerase activity can distinguish patients with coronary artery disease (CAD) from healthy individuals, thereby relating CAD to oxidative stress [29]. It is hypothesized that inflammation plays a mediating role in the process of ageing. However, an MR study indicated that anti-inflammatory or pro-inflammatory markers exert no significant causal influence on telomere length [30]. Previous studies proved that muscle training and lifestyle modification could be used to tackle aging-related health problems [31, 32]. The present study demonstrated that SGLT1 inhibition reduces the frailty index and increases telomere length. This phenomenon is hypothesized to be attributable to the SGLT1 inhibition property of glucose homeostasis regulation. Therefore, strategies for the maintenance of glucose homeostasis would inhibit aging and aging-related disorders. SGLT1 inhibition enhances glucose regulation through reduction of glucose uptake in the intestine and increased release of glucagon-like peptide-1 (GLP-1), involved in glucose-dependent insulin secretion from the pancreas [33].

It is widely acknowledged that SGLT1 and SGLT2 contribute to physiological processes in humans and play an essential role in facilitating the cellular absorption of glucose in addition to sodium in the body [34]. A recent study indicated that sotagliflozin, a dual inhibitor of both SGLT1 and SGLT2, exhibited a superior glucose-lowering effect [11]. Furthermore, it was reported that inhibition of SGLT1 in the intestine promoted GLP-1 secretion. GLP-1, in turn, stimulates β-cells to release insulin [35]. The stimulation of the GLP-1 receptor promotes DNA repair by stimulating the synthesis of apurinic/apyrimidinic endonuclease 1 (APE1), thereby providing anti-aging benefits [36]. Increased GLP-1 levels have also been demonstrated to alleviate oxidative stress-induced senescence, modulate the antioxidant defense system, and attenuate cellular senescence and DNA damage [37]. Semaglutide, a GLP-1 analogue, has been demonstrated to be highly efficacious in the glycemic control of patients with diabetes and in the weight management of individuals with obesity. The mechanism by which this drug exerts its effects is through its binding to GLP-1 receptors (GLP-1R) present in diverse tissues [38]. A series of biopsies of subcutaneous adipose tissue were conducted on a group of eight participants diagnosed with type 2 diabetes. The results of these biopsies revealed an increase in stem cell proliferation after 6 months of treatment with semaglutide [39]. This finding provides novel insights into the potential impact of SGLT1 inhibition on the process of anti-ageing. As proven in previous investigations, SGLT2 inhibition attenuates aging in both molecular and MR studies [40, 41]. On the other hand, an SGLT2 inhibitor (dapagliflozin) induced a substantial increase in SGLT1 expression, which was associated with elevated glucagon release [42]. We first established that inhibition of SGLT1 reduces ageing, and combined with the previous study, we hypothesized that dual inhibition of both SGLT1 and SGLT2 may have potentially superior benefits for delaying ageing. Sotagliflozin, a recently discovered dual inhibitor of SGLT1 and SGLT2, may provide a protective role in anti-aging and a wide range of health benefits in addition to its glucose-lowering effect.

Strengths: (1) Using MR analysis, we determined, for the first time, that SGLT1 is causally associated with telomere length and frailty index and slows aging. (2) Our study provided a novel potential target for the treatment of aging.

Limitations: (1) Given the specific selection of participants of European descent, the generalizability of the results in this study to other populations remains to be investigated. (2) Only 16 IVs were identified for SGLT1, which is a rather small number. To substantiate the results of the current

study, it is proposed that an updated GWAS database be employed for validation. (3) Despite the use of diverse databases for estimation of exposure and outcomes, the potential for residual overlap remains a possibility that cannot be disregarded. (4) It is impracticable to eliminate all manifestations of pleiotropy in MR studies. The SNP phenotypes of aging and SGLT1 data are affected by exogenous factors, including the environment, inheritable traits, and the population selected. Despite the efforts made to mitigate this issue, it remains a concern. The potential exists for unidentified sources of bias to be present in the pathways and confounding between the exposure and outcome variables, with the consequence that the findings may be biased. (5) It is recommended that subsequent large-scale randomized controlled trials be conducted to ascertain the impact of SGLT1 inhibitors on the aging process and to provide further corroboration of our MR findings.

Clinical impact: Aging is associated with a variety of chronic diseases, including cardiovascular disease, diabetes, and cognitive decline and other health disorders, contributing to an increased social and economic burden. Currently, there is an absence of specific targets for the management of aging. The findings of this MR study have the potential to establish a novel therapeutic target for the treatment of aging in clinical practice.

In conclusion, the present study revealed a significant negative correlation between SGLT-1 inhibition and aging, suggesting a theoretical basis for the strategy of delaying aging. Future clinical research is required to determine the effect of SGLT1 inhibition on aging and to further confirm our MR findings.

Data availability statement

The exposure and outcome GWASs are available in the corresponding previous research.

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Gang Fan and Zi-Han Qu contributed equally to this work.

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Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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