Age and Ageing 2022; **51:** 1–5
https://doi.org/10.1093/ageing/afac079

SHORT REPORT

Lifetime serum concentration of 25-hydroxyvitamin D 25(OH) is associated with hand grip strengths: insight from a Mendelian randomisation

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Abstract

Clinical trials have suggested that increased 25-hydroxyvitamin D (25(OH)D) has positive effect on hand grip strength. This Mendelian randomisation (MR) was implemented using summary-level data from the largest genome-wide association studies on vitamin D ($n = 73{,}699$) and hand grip strength. Inverse variance weighted method (IVW) was used to estimate the causal estimates. Weighted median (WM)-based method, MR-Egger and leave-one-out were applied as sensitivity analysis. Results showed that genetically higher-serum 25(OH)D levels had a positive effect on both right hand grip (IVW = Beta: 0.038, $P = 0.030$) and left hand grip (IVW = Beta: 0.034, $P = 0.036$). There was a low likelihood (statistically insignificant) of heterogeneity and pleiotropy, and the observed associations were not driven by single single-nucleotide polymorphisms. Furthermore, MR pleiotropy residual sum and outlier did not highlight any outliers. In conclusion, our results highlighted the causal and beneficial effect of serum 25(OH) D on right- and left-hand grip strengths.

Keywords: vitamin D, grip strength, Mendelian randomisation, older people

Key Points

- Higher vitamin D concentration in life time is associated with higher grip strength.
- Vitamin D serum level in the UK Biobank sample associated with greater muscle strength.
- Mandellian randomisation for vitamin D serum and grip strength in general population.

Introduction

The link between vitamin D deficiency with several health outcomes is evident [1]. Physical functions such as grip strength have been an important primary outcome for clinical trials in older and younger adults [2–4]. However, it is difficult to determine effect of vitamin D on grip strength (and other functional outcomes) in a clinical trials given that it is hard to control for confounders [3], and that most of population have already a wide use of vitamin D supplement. In Mendelian randomisation (MR), first causality is inferred from associations between genetic variants that mimic the influence of a modifiable environmental exposure and the outcome of interest (Figure 1); second, the genetic sequence

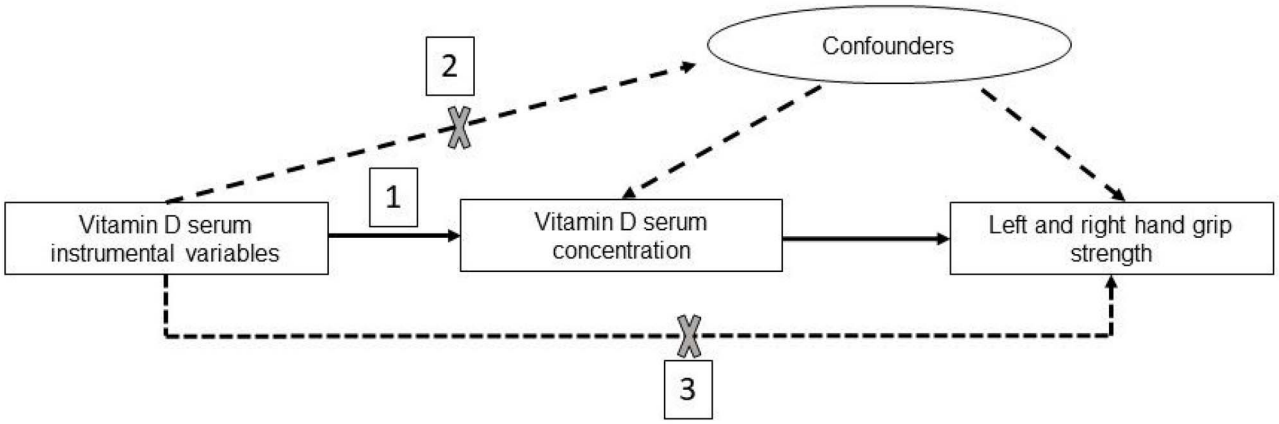

Figure 1. Schematic representation of MR analysis. Illustrates three assumptions of MR analysis as follows: (i) instrumental variables must be associated with exposure, (ii) instrumental variables must not be associated with confounders and (iii) instrumental variables must influence outcome only through exposure.

Table 1. Summary results of the six genetic loci of serum vitamin D

SNP	Nearest gene	GX	GX SE	EA	OA	EAF	*P*-value
rs3755967	GC	−0.089	0.0023	T	C	0.28	4.74E−343
rs10741657	CYP2R1	0.031	0.0022	A	G	0.4	2.05E−46
rs12785878	NADSYN1/DHCR7	0.036	0.0022	T	G	0.75	3.80E−62
rs10745742	AMDHD1	0.019	0.002	T	C	0.4	2.10E−20
rs8018720	SEC23A	-0.019	0.0027	C	G	0.82	1.11E−11
rs17216707	CYP24A1	0.026	0.0027	T	C	0.79	8.14E−23

All of the serum vitamin D markers were associated at genome-wide significance ($P < 5 \times 10^{-8}$). EA, effect allele: EAF, effect allele frequency; GX, the per-allele effect on standard deviation units of the telomere length; GX SE, standard error of GX; OA, other allele.

is fixed from conception and therefore free from reverse causation [5]. Hence, in this study we utilised MR to explore causality in a large Mendelian randomisation (MR) using an improved genetic instrument for circulating 25-OHD with hand grip strength in the UK Biobank population.

Grip strength is highly heritable (h2 = 30–65%) [6]. Although grip candidate gene approaches have implicated multiple loci, two genome-wide association studies (GWAS) in up to 27,000 individuals have been reported to date [7], yielding one intergenic genome-wide significant association [7]. Stronger hand grip strength is shown to associate with lower multimorbidity [8], lower cardiovascular disease, cancer outcomes and all-cause mortality [9], lower risk for falls [10] and better mental health [11].

Methods

In a two-sample MR, study design was used [12]. The summary statistics are provided from various studies for the bidirectional association of the genetic instruments with the exposure and outcome. In our study, we obtained the summary statistics from the largest GWAS on vitamin D (exposure; [13]) and handgrip (outcome; [14]). For description of vitamin D six single-nucleotide polymorphisms, see method as previously published [15, 16]. We retrieved the association of the six genetic instruments with handgrip using data from the largest available published GWAS on handgrip [16, 17]. All individuals were of European descent. See Appendix 1 (supplementary data are available in *Age and Ageing* online) for detailed MR analysis description. The MR studies assume that the SNPs (instrumental variables) are associated with the outcome only via the exposure [18], so we performed sensitivity analysis excluding SNPs with potentially pleiotropic effects. To assess the instrumental variable analysis 'exclusion-restriction' assumption we used Ensembl release (http://useast.ensembl.org/index.html). Ensembl contains a base of SNP phenotypes. No original data were collected for this manuscript. Ethical approval for each of the studies included in the investigation can be found in the original publications (including informed consent from each subject).

Results

The list of all instruments associations for 25(OH)D is shown in Table 1. The results of MR, as beta-coefficient for interested outcomes per increase in 25(OH)D, demonstrate a positive and statistically significant effect on both right-hand grip (MR-Egger = β:0.039, SE: 0.032, $P = 0.078$ and inverse variance weighted, IVW = β: 0.038, SE: 0.018, $P = 0.030$; respectively, Figures 2), as well as left-hand grip ((MR-Egger = β:0.047, SE: 0.032, $P = 0.098$ and IVW = β: 0.034, SE: 0.081, $P = 0.036$, respectively, Figures 2).

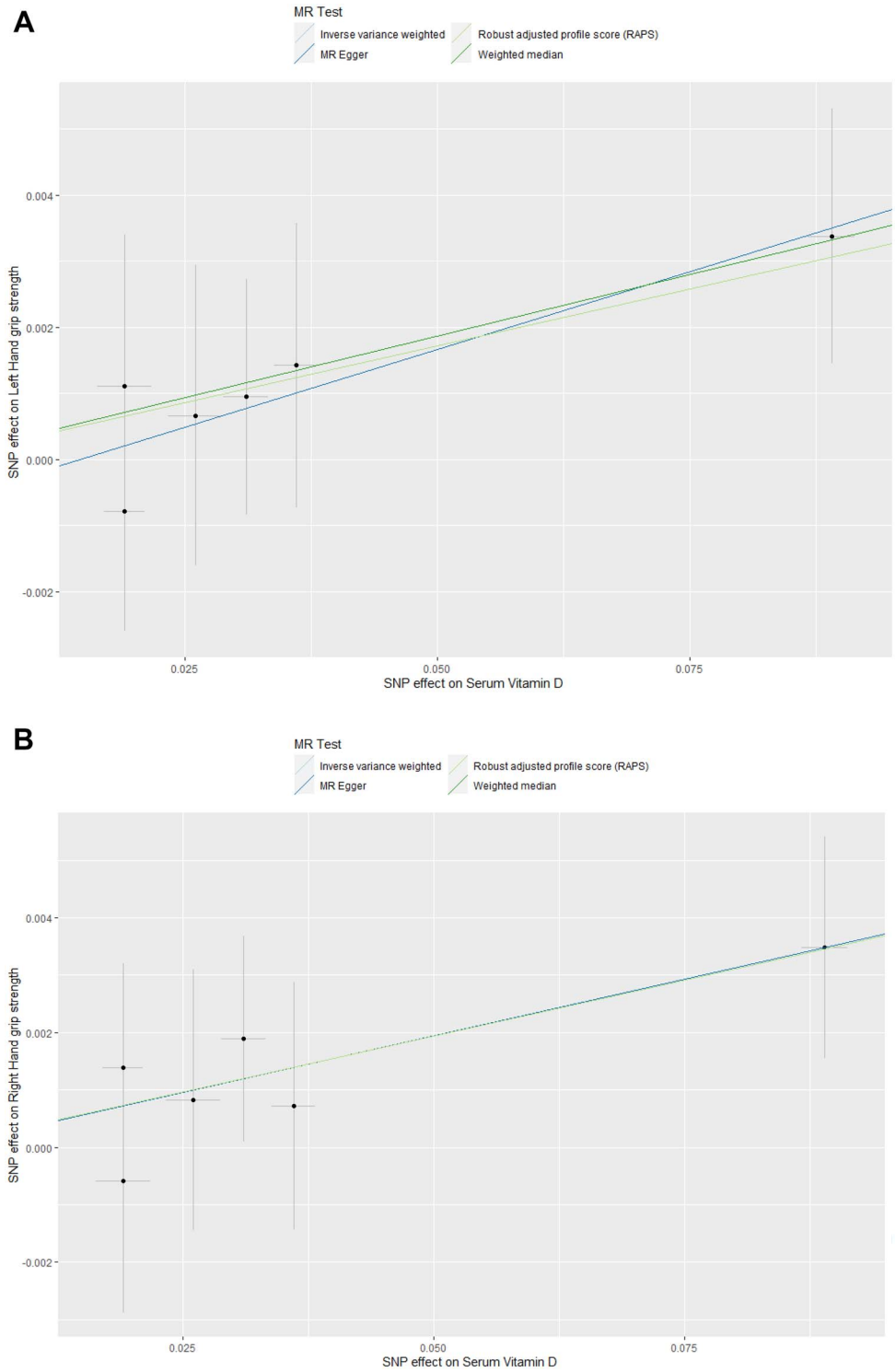

Figure 2. The scatter plots (A and B) of genetic associations with plasma 25-hydroxyvitamin D (25(OH)D) level against genetic associations with right- and left-hand grip. The slopes of each line represent causal associations for each method.

The horizontal pleiotropy test, with very negligible Egger regression intercept, also showed a low likelihood of pleiotropy for all of our estimations (all $P > 0.667$). Further the result of the MR-RAPS was identical with the IVW prediction, which again indicated statistically low chance of pleiotropy. Heterogeneity tests highlighted no trace of heterogeneity (right-hand grip: IVW = 0.716, *P*-value = 0.982; MR-Egger intercept = 0.714, *P*-value = 0.942, Left-hand grip: right-hand grip: IVW = 0.725, *P*-value = 0.981; MR-Egger intercept = 0.511, *P*-value = 0.972). Furthermore, MR pleiotropy residual sum and outlier analysis did not indicate any outliers for all estimates. Results of leave-

one-out method demonstrated that the links are not driven by any single SNPs.

Discussion

This MR analyses indicated a causal and beneficial effect of serum 25(OH) D on right- and left-hand grip strengths, which is less and interfered with confounding factors and offers a causality for beneficial role of vitamin D for hand grip strength. The positive association between the vitamin D SNPs and hand grip strength in our data consortium provides a compelling case that higher 25(OH)D positively affects hand grip strength over long periods. Regarding the biological pathways, the effect of low vitamin D and muscle strength could be expected to be stronger than the effect of hand grip strength on vitamin D, as discussed by [28]. Large number of observational and clinical trials are designed to test the effect of vitamin D and serum levels relationship with human health and muscle strength [19–21]. The mechanism of vitamin D role in skeletal muscle strength in humans remains a controversial issue due to inconsistent clinical results as discussed by [19, 22, 23]. Overall, observational studies are inconsistent due to evident large impact of confounding factors on vitamin D. Whereas clinical trials cannot capture long-term effect and study populations are relatively small, not heterogenous by age, and there is a wide range of supplementation use in these population. Thusly, MR analyses are able to unravel these limitations by providing long-term (life-time) role of vitamin D serum SNP with heritable characteristics such as handgrip.

Recent studies have confirmed expression of the Vitamin D receptor [24]. Notably, multiple studies have explored the implications of loss of the Vitamin D receptor, primarily in whole-body knockout animal models, with reductions in muscle fibre size and strength being observed [25]. Interestingly, the overexpression of vitamin D *in vivo* was associated with muscle hypertrophy, and increases in the muscle protein synthesis [26]. Vitamin D may influence muscle function by intracellular effects on calcium handling homeostasis, which is an important factor in interplay between the cytosol and mitochondria that is involved in muscle energy metabolism [24]. In addition, it maybe that vitamin D influence reactive oxygen species regeneration and possibly involved with reduction of oxidative stress in skeletal muscle [27].

Given the lack of 25(OH)D measures in large scale hand grip studies, this study was designed utilising a two-sample MR approach [29], that allowed genetic variants to be used as unconfounded measures of 25(OH)D. The present study used six SNPs affecting vitamin D synthesis or metabolism as instruments for MR analyses, it is possible that selected SNPs were to some extent influenced by geographical region, and a potential issue with regional variation/ancestry. Also, the observed causal relationship can be due to effect of these SNPs on other biological functions rather than 25(OH)D in human, which are unknown. It is important that MR analysis utilising GWAS can benefit when the spline regression are possible, at the time of this study, the 25 (OH)D SNP levels could not be linked to serum concentrations.

The major strength of our study was the large sample population study with relevant SNPs available for both hand grip strength and low vitamin D serum concentration from the UK Biobank. The SNPs included in these analyses are not functional but were chosen as they showed the strongest association with 25(OH)D in the published GWAs meta-analyses [15, 30]. The present study included maximally measured hand grip strength for both hands to reduce the confounding factors of measurement methods.

Although our study improved on previous MR studies on this topic, there are several limitations. We used six SNPs in this study, which could be limiting our ability to detect violations of the MR assumption (such as residual pleiotropy). However, these SNPs were previously found to be implicated in different stages of the vitamin D synthesis and metabolic pathway [30], and current evidence including this study showing no strong evidence for a pleiotropic association with potential confounders.

In conclusion, in this study MR approach analysis revealed causal association of higher-serum 25(OH)D concentration with greater right- and left-hand grip strength.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Declaration of Conflicts of Interest: Dr Penson owns four shares in AstraZeneca PLC and has received honoraria and/or travel reimbursement for events sponsored by AKCEA, Amgen, AMRYT, Link Medical, Mylan, Napp, Sanofi.

Declaration of Sources of Funding: None declared.

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Received 29 July 2021; editorial decision 17 February 2022