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CAUSAL RELATIONSHIP OF GRIP STRENGTH WITH THE RISK OF CHRONIC DISEASE AND MORTALITY (NARRATIVE REVIEW)

V.V. Sverchkov, E.V. Bykov
Ural State University of Physical Culture, Chelyabinsk, Russia

Abstract. Grip strength and common chronic diseases often coexist, but establishing a causal relationship in observational studies is difficult. Mendelian randomization studies are a rational method for determining cause and effect. To analyze Mendelian randomization studies examining the association between grip strength and various chronic diseases and mortality. A search was conducted in the information databases PubMed/MEDLINE, Scopus, Google Scholar for the period from June 20, 2017 to September 1, 2024. The analysis included 42 studies with Mendelian randomization, establishing causal relationships between grip strength and chronic diseases (cardiovascular disease, cancer, depression, cognitive functions, chronic obstructive pulmonary disease, osteoarthritis, osteoporosis, type 2 diabetes, resistance insulin), and cardiovascular and all-cause mortality. Results from Mendelian randomization studies demonstrate a causal relationship between low grip strength and adverse health outcomes. Grip strength is an important risk factor for many chronic diseases and is also a predictor of all-cause mortality and cardiovascular disease. Maintaining muscle strength is an important factor in preventing many common diseases, as well as reducing the risk of mortality in the population.
Keywords: Mendelian randomization, grip strength, cardiovascular diseases, type 2 diabetes, depression, chronic obstructive pulmonary disease.

Introduction. Grip strength is a reliable indicator of total muscle strength among adults. Its decrease is associated with increased all-cause mortality along middle-aged and elderly people [1]. Grip strength measurement is an inexpensive and simple test, which makes it one of the most frequently used muscle strength markers. Grip strength, a predictive marker of healthy aging, was connected with a risk of chronic diseases in observational studies [2]. In particular, higher grip strength was associated with lower risk of cardiovascular diseases (CVDs) [3], type 2 diabetes mellitus (T2DM) [4], metabolic syndrome (MS) [5], chronic obstructive pulmonary disease (COPD) [6], lupus [7], oncological diseases [1], cognitive disorders [8]. However, such studies may be subject to distortions related to a causal relationship.

Observational epidemiological studies have repeatedly identified several beneficiary associations that were rejected when tested in standard randomized controlled trials (RCTs). A more feasible method, very similar to RCTs and with the potential to establish a causal relationship between modifiable exposures and disease outcomes, is known as Mendelian randomization (MR). This method uses genetic variants associated with modifiable traits/ exposures as tools to detect causal and directional associations with outcomes [9].

Objective: to analyze MR studies examining the association between grip strength and various chronic diseases, as well as mortality.

Methods and organization. Search for, processing and systematization of scientific data, theoretical analysis, logical generalization, translation.

The study's tasks:

1. Analyze MR studies examining the causal relationship between grip strength and mortality.
2. Analyze MR studies examining the causal relationship between grip strength and various chronic diseases.
3. Identify potential mechanisms of a positive effect of grip strength on chronic diseases and mortality.

Results and discussion. We have conducted a literature search on the set topic in PubMed, Scopus and Google Scholar for the period from June 20, 2017 to September 1, 2024. 42 MR articles dedicated to the causal relationship between grip strength and various chronic diseases, as well as mortality, were included in the analysis.

The causal relationship between grip strength and mortality. With the use of MR, when studying 111 348 tests subjects with the available genetic and phenotypic data, it was found that genetically predicted higher grip strength reduced CVD and all-cause mortality [10]. In another study involving 337 138 people of white British origin, genetically predicted low grip strength was associated with a higher risk of all-cause mortality [11]. MR conducted on European population-based data using inverse-variance weighting found significant causal associations between low grip strength in people aged 60 years and older and an increased risk of all-cause mortality [12]. Thus, several MR studies have found that sarcopenia, which includes low grip strength, is associated with higher both CVD and all-cause mortality, emphasizing the role of grip strength as an important predictive tool.

The causal relationship between grip strength and various chronic diseases. The CVD incidence and mortality increase around the world due to population aging [13]. A series of observational studies have investigated the association between grip strength and CVDs, however the data from these studies are contradictory. Thus, a meta-analysis of prospective cohort studies revealed that grip strength is an independent CVD predictor in the communities [14], but this association was eliminated after correcting the initial risk factors of CVDs in another prospective cohort study [15]. Therefore, the application of MR analysis to identify the association between grip strength and CVDs remains an important issue in the epidemiology of non-communicable diseases.

Genetically predicted low grip strength showed a causal effect on an increased risk of coronary heart disease (CHD) in an independent cohort of 337 138 people of white British origin (odds ratio (OR): 1.13; 95% CI: 1.04-1.22) [11]. Another bidirectional MR study using inverse-variance weighting found that high grip strength of both left and right hands was associated with a lower risk of CHD and myocardial infarction (MI), but not stroke [16]. However, there was no statistically significant causal effect of CVDs (CHD, stroke, MI) on grip strength. Meanwhile, another MR analysis demonstrated that increasing left hand grip strength by 1 kilogram reduced the likelihood of CHD by 36% (OR: 0.64; 95% confidence interval: 0.49-0.82), and increasing right hand grip strength by 1 kilogram reduced it by 41% (OR: 0,59; 95% CI: 0.48-0.75) [17]. Again, no causal effect of CHD on grip strength was found. Yet another MR analysis found that increasing genetically predicted grip strength by 1 kilogram reduced the likelihood of CHD by 6% (OR: 0,94; 95% CI: 0.91-0.99) and the likelihood of MI by 7% (OR: 0.93; 95% CI: 0.89-0.98) [18]. In the MR analysis of Ye C. et al [19] it was revealed that each decrease of genetically predicted grip strength by 1 standard deviation was associated with an increased risk of arterial hypertension (OR: 1.32; 95% CI: 1.09-1.60), CHD (OR: 1.42; 95% CI: 1.15-1.75) and MI (OR: 1.45; 95% CI: 1,15-1.82), but not small vessel stroke (OT: 1.25; 95% CI: 0.86-1.81). Earlier MR analysis discovered that higher grip strength protects from CHD (OR: 0.69; 95% CI: 0.60-0.79) and atrial fibrillation (OR: 0.75; 95% CI: 0.62-0.90) [20]. In addition, the MR analysis by Mendo C. et al [2] found that grip strength was inversely related to carotid intima-media thickness, i.e. a marker of vascular atherosclerosis. MR analysis of the UK Biobank cohort found that an increase in grip strength was associated with an increase in high-density lipoproteins and a decrease in low-density lipoproteins.

Therefore, the current data from MR studies shed light on the causal relationship between grip strength and major CVDs, suggesting a positive impact of improved muscle strength for both primary and secondary prevention of CVDs.

Depression is a severe mental illness that greatly affects physical and mental well-being, as well as quality of life in total [23]. More and more data from epidemiological studies reflect association between grip strength and depression. For example, a longitudinal study involving 115 601 elderly test subjects from 24 countries showed that grip strength was inversely associated with depression [24]. A genome-wide association study (GWAS) of the frailty index found an association with depression and neuroticism [25]. However, a direct causal relationship between grip strength and depression has hardly been studied at the population level. It is still uncertain whether there is a bidirectional causal relationship or whether it is due to the coexistence of mixed or shared risk factors such as aging.

An MR analysis with inverse-variance weighting, weighted median and MR-Egger methods demonstrated the statistically significant causal relationship between right and left hand grip strength and major depressive disorder [26]. In this case, major depressive disorder had a significant causal effect on appendicular muscle mass. In other MR analysis with weighted median, MR-Egger and MR-PRESSO (Mendelian Randomization Pleiotropy RESidual Sum and Outlier) methods, it was found that higher frailty index (OR: 1.86; 95% CI: 1.37-2.53), higher frailty phenotype score (OR: 3.00; 95% CI: 2.06-4.38) and lower grip strength (OR: 1.20; 95% CI: 1.05-1.37) were associated with a higher risk of depression. In terms of reverse direction, genetic predisposition to depression revealed a consistent association with higher strength index and higher frailty phenotype score, but not grip strength. Depression has also been found to be causally associated with telomere length shortening, increased frailty index and accelerated epigenetic aging [28].

Z. Li et al [29] discovered that low grip strength is associated with quicker loss of grey matter, especially in the hippocampus area, while S. Su et al [30] associated higher grip strength with an increase in the surface area of the medial orbitofrontal cortex and precentral gyrus. C. Lu et al [31] revealed that higher grip strength was associated with better cognitive indicators. In addition, Y. She et al [32] in their bidirectional MR analysis established the inversed causal relationship between grip strength and Parkinson’s disease. Moreover, T. Wang et al [33] found that higher right and left hand grip strength were associated with a lower risk of levodopa-induced dyskinesia C. Ye et al. [34] found the causal relationship between lower grip strength and a higher risk of Alzheimer’s disease.

Thus, MR analyses confirm the causal relationship between grip strength and depression, neurological diseases, brain aging and cognitive functions, which sets important prospects for the development of intervention strategies to maintain/support muscle strength and alleviate the aforementioned diseases.

COPD is a major global health problem, being the third leading cause of death globally [35]. A recent systematic review and meta-analysis found that people with lower grip strength have higher COPD incidence and mortality [36]. Although prior studies tried to identify a complicated association between grip strength and COPD incidence, this field remains understudied.

A bidirectional MR analysis conducted with the GWAS data from patients of European origin, examining the effect of grip strength on COPD using inverse-variance weighting found that genetically predicted lower grip strength was unidirectionally associated with higher COPD incidence, with gait speed being bidirectionally associated with COPD [37]. Moreover, another MR analysis discovered that genetic predisposition to higher grip strength was directly related to forced vital capacity of the lungs and forced expiratory volume in one second [39]. Another MR analysis found that Fried frailty index was associated not only with COPD but also with bronchial asthma [39].

Thus, the few data from MR studies provide preliminary evidence for using grip strength as an indicator for predicting COPD.

Osteoarthritis (OA) is a disease characterized by pain, stiffness, deformity and dysfunction of a joint and is one of the leading cause of disability [40]. In a longitudinal cohort study, lower muscle strength and muscle mass of the lower limbs were associated with higher knee OA incidence, and patients with sarcopenia were more likely to have symptomatic OA than patients without it [41]. Nonetheless, this and similar studies are based on observational cross-sectional analysis, and it is still unclear whether there is the causal relationship between traits associated with sarcopenia and OA.

Chen S. et al. [42] in their MR analysis with MR-Egger found that higher right hand grip strength was associated with a reduced risk of knee OA (OR: 0.26; 95% CI: 0.09-0.67), total OA (OR: 0.37; 95% CI: 0.17-0.82). Similar estimation of the causal relationship for knee and total OA were received with inverse-variance weighting for both right and left hand grip strength. However, no statistically significant association between right and left hand grip strength and hip OA was discovered [42]. Another MR analysis found an association between lower grip strength with a higher risk of knee OA (OR: 1.46; 95% CI: 1.20-1.77) [43]. Moreover, OA was not associated with any sarcopenia signs (grip strength, appendicular muscle mass, gait speed). The MR analysis by Yang J. et al [44], only appendicular muscle mass had the causal relationship with knee and hip OA, but not grip strength.

Therefore, MR analyses have heterogeneity regarding the causal relationship between grip strength and OA. Perhaps the body composition (amount of muscle and fat tissues) may be a factor that contributes significantly in the study of association between sarcopenia (muscle strength and muscle mass) and OA. It is likely that the subgroups of sarcopenia and sarcopenic obesity need to be analyzed to better understand how grip strength and OA are associated.

With global population aging, incidence of osteoporosis (OP) and sarcopenia increases rapidly, which is associated with a high risk of fracture, reduced quality of life and early mortality. It is known that people with frailty often suffer from osteosarcopenia [45]. Moreover, there is a clinical study showing that sarcopenia increases a risk of 5-year mortality in patients with osteoporotic hip fractures [45]. Thus, elucidating the causal relationship between grip strength and OP is a clinically relevant problem.

We have found three MR analyzes examining association between grip strength and OP. An MR analysis by Ma X. et al [47] found that left and right hand grip strength were directly associated with mineral density of lumbar vertebrae. In an MR analysis by Y. Zhu et al. [48], decreased grip strength was associated with a risk of OP in people aged 45-60 years. On the other hand, an MR analysis by C. Liu et al [49] revealed that only appendicular muscle mass was directly causally related to mineral density of lumbar spine, but not to grip strength. The heterogeneity in the data of these MR studies may be due to different bone composition (cortical and trabecular bone, as well as significant regional variations in bone microstructure) from different areas of the skeleton, which is determined by genetic factors [50].

Thus, further studies are needed for a thorough research of the causal effect of muscle strength on bone mineral density in different segments of the skeleton.

Type 2 diabetes mellitus (T2DM) is one of the common metabolic disorders and is associated with comorbidities such as obesity, hyperlipidemia, hypertension, metabolic syndrome and CVDs [51]. A recent systematic review and meta-analysis found that higher both absolute and relative grip strength was associated with a reduced risk of T2DM [52]. Accordingly, establishing a causal relationship between grip strength and T2DM is necessary to develop new methods for the prevention, diagnosis and treatment of T2DM and other metabolic diseases.

A bidirectional MR analysis with inverse-variance weighting, MR-Egger and weighted median methods found that genetically predicted low grip strength was associated with T2DM (OR: 1.11; 95% CI: 1.01-1.22) [53]. In another MR study, grip strength was associated with T2DM when applying MR-PRESSO and MR-Egger methods, but it was not associated with it in case of inverse-variance weighting [54]. In another MR analysis by C. Ye [34], lower grip strength was associated with a higher risk of T2DM, non-alcoholic liver disease and insulin resistance. On the other hand, an analysis by L. Ren et al [55] revealed that decreased appendicular muscle mass increased a risk of diabetic nephropathy, and diabetic nephropathy was associated with decreased grip strength. In turn, the effect of T2DM on decreased grip strength has been demonstrated in most MR analyses.

Thus, grip strength and T2DM may have a reciprocal effect on each other. Data from MR studies provide strong evidence that grip strength is a possible T2DM predictor in middle-aged and elderly patients.

In addition, low grip strength was also causally associated with adverse pregnancy and perinatal outcomes [56]. An analysis by Z. He et al [57] showed that increased grip strength was associated with reduced breast cancer risk and longer survival time of breast cancer patients, but a reduced grip strength in an MR analysis by J Cao et al [58] was associated with an increased risk of hepatocellular carcinoma. Also, grip strength was inversely associated with inflammatory bowel disease [59].

The results of MR studies reflect the causal relationship between low grip strength and adverse health consequences. They have shown that men and women with lower grip strength face higher all-cause and CVD mortality, and are subject to a higher risk of chronic diseases.

The results of MR analyses have important public health implications. Lower grip strength is strongly associated with an increased risk of various diseases and mortality, indicating the importance of maintaining proper muscle strength for overall health. The mechanisms underlying this association are multifaceted. Grip strength serves as a surrogate marker for the early development of sarcopenia, reduced physical fitness and functional capabilities [60]. Meanwhile, lower grip strength potentially indicates reduced physical activity levels, increased systemic inflammation and impaired cardiovascular and metabolic function [61]. In addition, low grip strength may reflect a general decline in muscle mass and strength, which is often associated with age-related diseases and increased risk of adverse health outcomes [62, 63].

Conclusion. Thus, this review of MR studies emphasizes the importance of low grip strength as an independent risk factor for many chronic diseases, as well as a significant predictor of all-cause mortality. These results note the importance of maintaining muscle strength in the general population, as well as regular screening of this indicator for clinical practice and public health interventions.

Conflict of interest. The authors declare no conflict of interest.

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INFORMATION ABOUT THE AUTHORS:
Vadim V. Sverchkov – Junior Researcher, Research Institute of Olympic Sports, Lecturer, Department of Sports Medicine and Physical Rehabilitation, Ural State University of Physical Culture, Chelyabinsk, e-mail: Vadim.Sverchkov@yandex.ru, ORCID: 0000-0003-3650-0624.
Evgenij V. Bykov – Doctor of Medical Sciences, Professor, Vice-Rector for Research, Head of the Department of Sports Medicine and Physical Rehabilitation, Ural State University of Physical Culture, Chelyabinsk, e-mail: bev58@yandex.ru, ORCID: 0000-0002-7506-8793.

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