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Association of handgrip strength with aortic stenosis among adults aged 60 years and older: evidence from the 157097 UK Biobank participants

Cheng-Xiang SONG[1,2,*], Qing LI[1,3,*], Cong-Ying XIA[2,*], Lu LONG[4], Xiao-Xi ZENG[5,6], Jun-Li LI[1,✉], Mao CHEN[1,2,✉]

1. Laboratory of Cardiac Structure and Function, Institute of Cardiovascular Diseases, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China; 2. Department of Cardiology, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China; 3. National Clinical Research Center for Geriatrics, the Center of Gerontology and Geriatrics, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China; 4. Department of Epidemiology and Health Statistics, West China School of Public Health and West China Fourth Hospital, Sichuan University, Chengdu, Sichuan Province, China; 5. West China Biomedical Big Data Center, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China; 6. Division of Nephrology, Kidney Research Institute, West China hospital, Sichuan University, Chengdu, Sichuan Province, China

[*]The authors contributed equally to the work.

✉ Correspondence to: lijunlilily@163.com (LI JL); chenmao@scu.edu.cn (CHEN M)

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ABSTRACT

Objective To examine the association of handgrip strength with aortic stenosis incidence among adults aged 60 years and older.

Methods We conducted a cohort study using the UK Biobank data to assess the relationship between handgrip strength and incident aortic stenosis in individuals aged 60 years and older. Handgrip strength was measured using a Jamar J00105 hydraulic hand dynamometer. Adjusted Cox proportional hazards regression models were conducted to assess the association between handgrip strength and incident aortic stenosis.

Results We included 157,097 UK Biobank participants (78,151 women and 78,946 men) in our study, with mean age of 64 ± 2.9 years. During a median follow-up of 8.1 (7.4–8.8) years, 1543 (1.0%) participants developed incident aortic stenosis. Compared with those with the lowest handgrip strength (tertile 1), the adjusted hazard ratios (95% confidence interval) of incident aortic stenosis in the middle (tertile 2) and the highest (tertile 3) were 0.86 (0.77–0.97) and 0.76 (0.67–0.87), respectively.

Conclusions Higher handgrip strength was associated with lower risk of developing aortic stenosis in older adults. Future studies warrant preventive strategies for older adults with lower handgrip strength.

The prevalence of aortic stenosis rises strikingly with advancing age, with a prevalence of nearly 0.1% in the general population and about 2.8 % in the population ≥ 75 years old.[1] Nowadays, owing to lack of effective medications to attenuate or halt disease progression, surgical or transcatheter aortic valve replacement is the most common and widely used treatments for symptomatic aortic stenosis.[2] However, the complications during the operation are relatively high, especially for elderly.[3] Hence, it is particularly important to find predictors that can predict the incidence of aortic stenosis in the elderly population. Several factors have been reported to be associated with aortic stenosis incidence, such as smoking, alcohol, obesity, dyslipidemia, renal function and other health-related factors, but a better understanding of aortic stenosis predictors is necessary to find potential treatment targets.

Handgrip strength, commonly used as a typical measure of muscular strength and a proxy for physical fitness, is declining with increasing ageing.[4] Previous studies have demonstrated handgrip strength was a potential risk factor for age-related diseases such as metabolic syn-

drome, cardiovascular disease, and mortality.[5,6] Although aortic stenosis shares similar risk factors of cardiovascular disease, evidence regarding the association of handgrip strength with aortic stenosis is scarce. Apart from this, skeletal muscle strength and endurance exercise training could improve insulin resistance[7,8] and contracting skeletal muscle can secrete various myokines, such as irisin and fibroblast growth factor 21.[9,10] Together these data indicate that the measurement of handgrip strength may have clinical utility in risk screening for aortic stenosis.

To address the aforementioned gaps in knowledge, the aim of this study was to investigate the relationship between handgrip strength and the incidence of aortic stenosis among adults aged 60 years and older in the UK Biobank.

METHODS

Study Population

The UK Biobank is a prospective cohort, including over 500000 participants aged 37 to 73 years recruited from 22 assessment centers between 2006 and 2010, spanning England, Scotland, and Wales.[11] In brief, participants completed a touch-screen questionnaire, had physical measurements taken, and provided biological samples at baseline. More data about the UK Biobank study can be found online (https://biobank.ndph.ox.ac.uk). The UK Biobank was approved by the North West Multicentre Research Ethics Committee (REC reference: 16/NW/0274), and all individuals provided written informed consent at the time of recruitment to the UK Biobank study.

Handgrip Strength

The handgrip strength was measured using the Jamar J00105 hydraulic hand dynamometer (Patterson Medical, Sutton-in-Ashfield, UK).[12] The mean value of the right and left hand was calculated and expressed in absolute units (kilogram) according to previous studies.[13,14] The handgrip strength is reported in absolute terms since a previous study reported that the association of handgrip strength with health outcomes did not differ according to whether it was expressed in absolute or relative terms.[15] In this present study, individuals were divided into three groups based on the tertile of handgrip strength in each gender (< 19 kg, 19–24 kg, ≥ 24 kg for women; < 34 kg, 34–41 kg, ≥ 41 kg for men).

Study Outcome

The study outcome of interest was first aortic stenosis event after cohort entry. Aortic stenosis event was identified from linked hospital inpatient data using International Classification of Diseases (10th version, ICD-10) codes of I350 and I352. Detailed information can be found online (https://biobank.ndph.ox.ac.uk/showcase/refer.cgi?id=141140). Aortic stenosis events were identified from baseline to March 31, 2017.

Covariates

Age at baseline was calculate d from date of birth and date of baseline assessment. Type of ethnicity, education level, smoking status, alcohol frequency intake, and walking pace were based on self-reported records collected through touch-screen questionnaires. Area-based socioeconomic status was defined using the Townsend deprivation index. Hypertension and diabetes mellitus status were self-reported at the nurse-validated baseline assessment. The volume of physical activity was derived from the sum of self-reported time spent walking, moderate, and vigorous activity over the previous week, measured as metabolic equivalents (METs min/week) using the International Physical Activity Questionnaire short form, and then categorized into three groups: low (MET< 600 min/week), moderate (600 to 3000 MET), and high (MET > 3000 min/week).[16] A cumulative dietary risk factor score was applied, ranging from 0 (most healthy) to 9 (least healthy). This score was derived from 9-food items based on current UK guidelines using baseline data and has been described elsewhere.[17] Biochemistry markers were measured immediately at the central laboratory using serum samples collected at baseline. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[18] Further details of these measurements are available on the UK Biobank website (http://www.ukbiobank.ac.uk).

Statistical Analysis

Continuous variables were expressed as mean ± SD or median (interquartile range) and compared using Student's *t* test or Mann-Whitney. Categorical variables were expressed as frequencies and percentage and compared by Fisher's exact test or Chi-square test. Associ-

ation between handgrip strength and aortic stenosis was investigated using Cox proportional hazard model by tertile of handgrip strength. Individuals in the lowest tertile were used as the reference group. The results are reported as hazard ratios (HR) and their 95% CIs. Covariable adjustments were selected based on variables with significant associations ($P < 0.05$) in the univariate Cox analysis model (Supplementary table 1) or previous study reported factor related to influence incident aortic stenosis.[19] Model 1 was adjusted for age and sex; model 2 was further adjusted for ethnicity, smoking status, alcohol frequency intake, college or university degree, and Townsend deprivation index; model 3 was further adjusted for hypertension, diabetes mellitus, body mass index (BMI), walking pace, physical activity, cumulative dietary risk factors score, C-reactive protein, low density lipoprotein cholesterol (LDL-C), and eGFR. We also performed subgroup analyses to determine handgrip strength associated with incident aortic stenosis in specific patient groups. To assess whether adding handgrip strength to original risk factors model is associated with improvement in prediction of future aortic stenosis, we calculated measures of discrimination for censored time-to-event data: Harrell's C-statistic, the continuous net reclassification improvement, and integrated discrimination improvement. Receiver operating characteristic (ROC) curve analysis was used to evaluate the value of handgrip strength to predict the occurrence of aortic stenosis. To further test the robustness of our estimates, we conducted three different sensitivity analyses. First, we carried out sensitivity analyses excluding individuals with any incident aortic stenosis occurring in the first 2 years of the follow-up. Second, we excluded patients with extreme values of handgrip strength (± 2.5 SD from the sex-specific mean). Third, as walking pace might be considered a potential mediator of the relationship between handgrip strength and aortic stenosis, we performed sensitivity analyses excluding individuals with slow walking pace. All statistical analyses were performed using R language (version 4.0, R Foundation, Vienna, Austria), and a two-sided *P*-value below 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

A total of 157,097 participants were included in the study (Supplementary Figure 1). The average age was 64 ± 2.9 years, and most participants (152,972 (97.4%)) were white. There were 78,151 women (49.7%) and 78,946 men (50.3%). Baseline characteristics stratified by sex-specific tertiles of handgrip strength are shown in Table 1. Individuals with a higher handgrip strength were younger, more likely to be white and drink alcohol daily or almost daily, and had had a higher proportion of college or university degree compared to those with a lower handgrip strength. Participants in the highest tertile of handgrip strength had a lower prevalence of hypertension, diabetes mellitus, and cumulative dietary risk factors score compared to those in the lowest tertile.

Association of Handgrip Strength and Incident Aortic Stenosis

Over the median follow-up period of 8.1 (7.4–8.8) years, 1543 (1.0%) participants developed aortic stenosis. The incidence of aortic stenosis was highest in the low tertile of handgrip strength among three groups (1.3% *vs.* 0.9% *vs.* 0.8%, $P < 0.001$) (Table 1). Results from the unadjusted model showed that higher handgrip strength were associated with a lower risk of aortic stenosis (Table 2). In the fully adjusted model, individuals in the middle or the high tertile of handgrip strength had lower risk of aortic stenosis when compared to those in the low tertile of handgrip strength (HRmiddle tertile = 0.86, 95% CI: 0.77–0.97, $P = 0.012$ and HRhigh tertile = 0.76, 95% CI: 0.67–0.87, $P < 0.001$) (Figure 1). Addition of sex-specific tertiles of handgrip strength to the original model resulted in a significant predictive improvement in Harrell's C - statistic, net reclassification improvement, and integrated discrimination improvement (Supplementary Table 2). The optimal cut-off value of handgrip strength for predicting the risk of aortic stenosis was 26 kg (sensitivity 63.4%, specificity 62.2%), with an area under the curve of 0.64 (95% CI: 0.62-0.68, $P < 0.001$) (Supplementary Figure 2). When the analyses were stratified by specific patient groups, the associations were similar in those subgroups (Figure 2). No significant interaction was observed in all subgroups.

Sensitivity Analyses

To minimize reverse causation, we excluded participants with any aortic stenosis diagnosis in the first 2 years of follow-up, the associations between handgrip strength and aortic stenosis were still observed (Figure 1). Applying other exclusion conditions (exclusion of parti-

Table 1 Characteristics of the participants by sex-specific tertiles of handgrip strength.

Variable	Low (*n* = 53914)	Middle (*n* = 55555)	High (*n* = 47628)	*P*-value
Age, yrs	65 ± 2.9	64 ± 2.8	64 ± 2.7	< 0.001
Men	27642 (51.3%)	27598 (49.7%)	23706 (49.8%)	< 0.001
Townsend deprivation index				< 0.001
Low	16056 (29.8%)	18915 (34.0%)	17399 (36.5%)	
Middle	17502 (32.5%)	18679 (33.6%)	16180 (34.0%)	
High	20356 (37.8%)	17961 (32.3%)	14049 (29.5%)	
College or university degree	13593 (25.2%)	15678 (28.2%)	15309 (32.1%)	< 0.001
Ethnicity				< 0.001
White	51644 (95.8%)	54385 (97.9%)	46943 (98.6%)	
Black	201 (0.4%)	123 (0.2%)	98 (0.2%)	
Asian	1343 (2.5%)	521 (0.9%)	167 (0.4%)	
Others	726 (1.3%)	526 (0.9%)	420 (0.9%)	
Smoking status				< 0.001
Never	27009 (50.1%)	27723 (49.9%)	23346 (49.0%)	
Previous	22526 (41.8%)	23498 (42.3%)	20533 (43.1%)	
Current	4379 (8.1%)	4334 (7.8%)	3749 (7.9%)	
Alcohol frequency intake				< 0.001
Never	5510 (10.2%)	4091 (7.4%)	2892 (6.1%)	
Special occasions only	6940 (12.9%)	5950 (10.7%)	4740 (10.0%)	
1–3 times a month	5337 (9.9%)	5318 (9.6%)	4460 (9.4%)	
Once or twice a week	12658 (23.5%)	13331 (24.0%)	11138 (23.4%)	
3–4 times a week	11330 (21.0%)	13016 (23.4%)	11549 (24.2%)	
Daily or almost daily	12139 (22.5%)	13849 (24.9%)	12849 (27.0%)	
Hypertension	20734 (38.5%)	19245 (34.6%)	16112 (33.8%)	< 0.001
Diabetes mellitus	5022 (9.3%)	3332 (6.0%)	2412 (5.1%)	< 0.001
BMI, kg/m^2	27.6 ± 4.6	27.3 ± 4.3	27.5 ± 4.3	< 0.001
Walking pace				< 0.001
Slow pace	7711 (14.3%)	3970 (7.1%)	2406 (5.1%)	
Steady average pace	31055 (57.6%)	31366 (56.5%)	25421 (53.4%)	
Brisk pace	15148 (28.1%)	20219 (36.4%)	19801 (41.6%)	
Physical activity				< 0.001
Low	10369 (19.2%)	8816 (15.9%)	7126 (15.0%)	
Moderate	23274 (43.2%)	23346 (42.0%)	19492 (40.9%)	
High	20271 (37.6%)	23393 (42.1%)	21010 (44.1%)	
Cumulative dietary risk factors score	4.5 ± 1.4	4.4 ± 1.4	4.4 ± 1.4	< 0.001
CRP, mg/L	3.1 ± 5.0	2.6 ± 4.4	2.5 ± 4.1	< 0.001
LDL-C, mmol/L	3.5 ± 0.9	3.6 ± 0.9	3.6 ± 0.9	< 0.001
eGFR, mL/min per 1.73 m^2	85.2 ± 12.8	85.1 ± 11.9	84.2 ± 11.8	< 0.001
AS	679 (1.3%)	505 (0.9%)	359 (0.8%)	< 0.001

Data are presented as mean ± SD or median (interquartile range) for quantitative variables and as *n* (%) for categorical variables. *P*-value in this table was compared among the three groups. AS: aortic stenosis; BMI: body mass index; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; TG: triglyceride; TC: total cholesterol.

Table 2 Unadjusted and adjusted Cox regression model analysis for the association between sex-specific tertiles of handgrip strength and aortic stenosis.

Model	Total	
	HR (95%CI)	*P*-value
Unadjusted model		
Low	Reference	
Middle	0.72 (0.64–0.80)	< 0.001
High	0.58 (0.51–0.66)	< 0.001
Model 1		
Low	Reference	
Middle	0.76 (0.68–0.85)	< 0.001
High	0.66 (0.58–0.75)	< 0.001
Model 2		
Low	Reference	
Middle	0.78 (0.69–0.87)	< 0.001
High	0.68 (0.60–0.78)	< 0.001
Model 3		
Low	Reference	
Middle	0.86 (0.77–0.97)	0.012
High	0.76 (0.67–0.87)	< 0.001

Model 1: adjusted for age and sex. Model 2: adjusted for model 1 + ethnicity, smoking status, alcohol frequency intake, college or university degree, and Townsend deprivation index. Model 3: adjusted for model 2 + hypertension, diabetes mellitus, body mass index, walking pace, physical activity, cumulative dietary risk factors score, C-reactive protein, low density lipoprotein cholesterol, and estimated glomerular filtration rate.

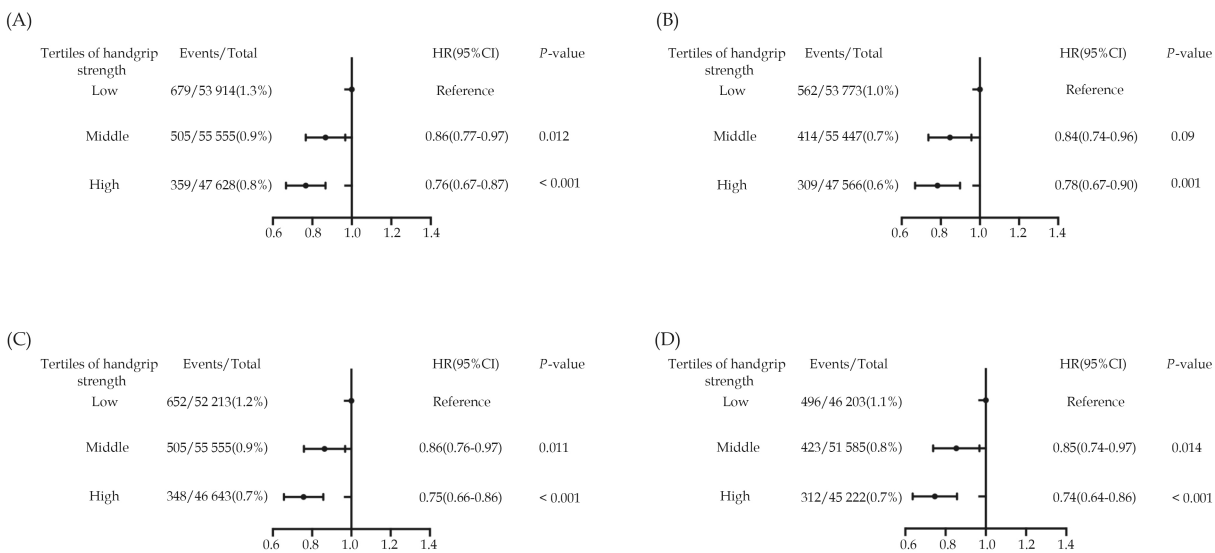

Figure 1 Association between sex-specific tertiles of handgrip strength and aortic stenosis. (A): In all participants; (B): after exclusion participants with any aortic stenosis diagnosis in the first 2 years of follow-up; (C): after exclusion participants with extreme handgrip strength, and; (D): after exclusion participants with slow walking pace. Individuals in the low tertiles were used as the reference group. Model was adjusted for age, sex, ethnicity, smoking status, alcohol frequency intake, college or university degree, Townsend deprivation index, hypertension, diabetes mellitus, body mass index, walking pace, physical activity, cumulative dietary risk factors score, C-reactive protein, low density lipoprotein cholesterol, and estimated glomerular filtration rate.

cipants with extreme handgrip strength values resulted in comparable estimates) (Figure 1). The observed associations were consistent after excluding individuals with slow walking space (Figure 1).

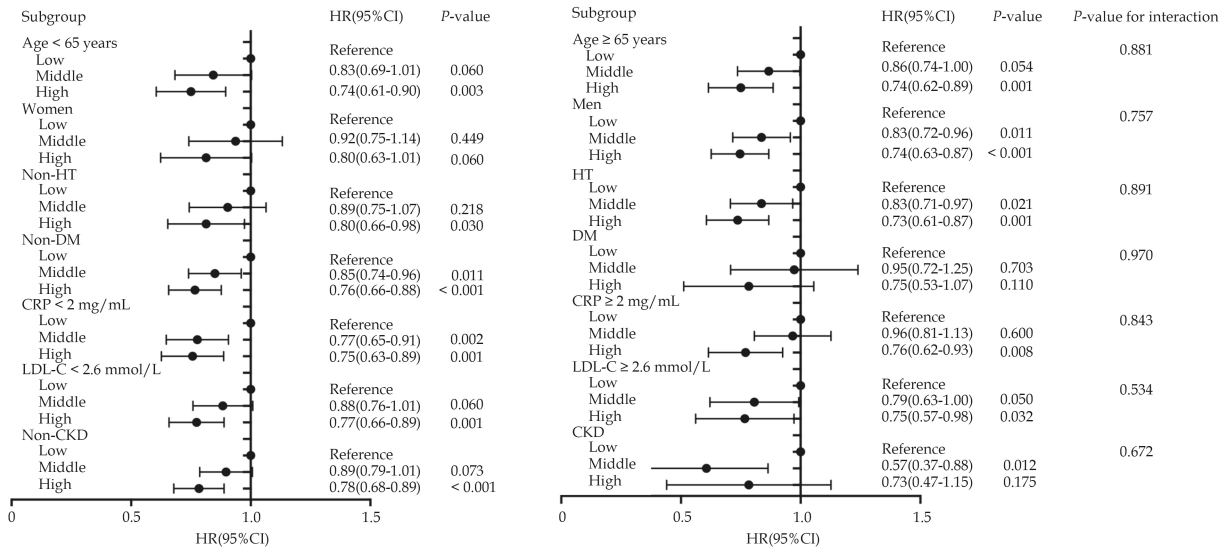

Figure 2 Subgroup analysis of the prognostic value of handgrip strength for incident aortic stenosis in individuals aged 60 years and older. CKD: chronic kidney disease; CRP: C-reactive protein; DM: diabetes mellitus; HT: hypertension; LDL-C: low density lipoprotein cholesterol.

DISCUSSION

The major finding of the present study was that higher handgrip strength was associated with a lower incidence of aortic stenosis in adults aged 60 years or older. Besides, handgrip strength may improve predictive discrimination ability in identifying people at high risk of aortic stenosis when added to the traditional risk factors. This finding warrants preventive strategies for older adults with lower handgrip strength.

The handgrip strength has been demonstrated as a good predictor for numerous age-related diseases, such as non-alcoholic fatty liver disease, dementia, and hypertension.[13,14,20] Apart from those diseases, Zhang, *et al*.[21] reported higher handgrip strength was associated with a lower incidence of carotid atherosclerosis in 3093 participants aged 45–85 years without cardiovascular disease at baseline during a median follow-up of 4 years. The Survey of Health, Ageing and Retirement in Europe also observed a significant inverse association between handgrip strength and cardiovascular mortality in adults aged 50 years or older.[22] The association between handgrip strength and cardiovascular disease in adults has been well-studied, but whether that association extends to incident aortic stenosis has been unclear as they both share similar underlying biological mechanisms, namely, dyslipidemia, inflammation, and obesity. One study enrolled 176 individuals aged 65 years old and found elderly with aortic stenosis had lower handgrip strength in comparison to healthy older volunteers.[23] However, the study did not further explore if handgrip strength was a predictor for aortic stenosis. Moreover, data about the association between handgrip strength and incident aortic stenosis from prospective studies is lacking. Moreover, handgrip strength is easily measured, cheap, and highly reproducible in clinical practice and is associated with better health outcomes, irrespective of which handgrip strength marker is used.[15] Our findings fill gaps in the current literature and imply that handgrip strength may be a valid and practical indicator to monitor for aortic stenosis.

The underlying mechanisms for the association of handgrip strength with aortic stenosis are yet to be explored, it could be partly explained by the following aspects. First, skeletal muscle is essential for glucose clearance and is responsible for over 80% of glucose uptake in the postprandial state.[24] Second, the skeletal muscle has recently been identified as an endocrine organ, that produces and releases myokines, such as irisin, insulin-like growth factor 1 and fibroblast growth factor 21.[9] Hence, the loss in muscle quantity could trigger insulin resistance,[10] result in excessive lipid accumulation,[25] and increase the level of inflammation factors,[26] which could contribute to the development and/or progression of aortic stenosis. Third, individuals with a decline in muscle strength or loss of physical functional capability was observed to predict lower intention to participate in physical activity,[27] which could then predispose to aor-

tic stenosis. Future studies are warranted to explore the biological mechanisms underlying the association.

Our findings highlight that the improvement of muscle strength in people aged 60 years and older may be worthwhile for aortic stenosis prevention. In addition, owing to the costs of medical care are substantially high in elderly with aortic stenosis,[28] the preservation of handgrip strength has the potential to reduce medical expenditures. However, it is unclear whether interventions like physical activity and daily nutrition supplementation aimed at enhancing muscle strength can bring benefit in preventing aortic stenosis incidence. Therefore, future studies are needed to determine which form of interventions can most effectively improve muscle strength in aging adults to reduce the risk of aortic stenosis.

Limitations

There are some limitations in our study. First, the UK Biobank is a population-based cohort study and cannot fully represent the general population. However, Batty *et al.*[29] found a series of risk factor associations originated from the UK Biobank are approximately in accord with other representative cohorts. Second, although several common potential confounders associated with aortic stenosis had been adjusted at baseline, there might be other confounding factors that would affect the outcomes. Third, some studies suggested that adopting this way of defining outcomes by ICD-10 codes might underestimate the cases of diseases, but it has the advantage of being more in accord with the actual health care environment.[30] Fourth, we did not evaluate the association between handgrip strength and the severity of aortic stenosis. Lastly, we cannot infer causality from these results owing to the nature of observational study. Consequently, the potential causal association between handgrip strength and incident aortic stenosis should be studied in future studies.

Conclusion

In conclusion, using prospective data from UK Biobank, we found that higher handgrip strength was associated with a lower incidence of aortic stenosis in individuals aged 60 years and older. This finding suggests that the improvement of handgrip strength may have a potentially beneficial effect on aortic stenosis in older adults. Future studies should be aimed at clarifying the cause-and-effect relationship between handgrip strength and aortic stenosis incidence.

DECLARATIONS

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Competing Interest

None.

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