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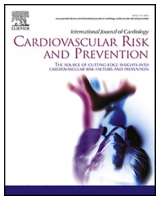

Association between grip strength, walking pace and incident peripheral artery disease: A prospective study of 430,886 UK biobank participants

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ABSTRACT

Background and aims: Patients with peripheral artery disease (PAD) presented overall muscle weakness and reduced physical performance. Previous study focused on the impact of muscle weakness on outcomes of established PAD, however the relationship between compromised muscle function and incident PAD remained unclear.

Methods: A prospective study involving 430,886 participants aged 40–69 y from UK biobank was conducted. The main outcome was incident PAD. Grip strength and walking pace were used as indicators for muscle function. Grip strength was measured using a Jamar J00105 hydraulic hand dynamometer, while walking pace was self-reported by the participants. Cox proportional hazard models were employed to investigate the relationship between grip strength, walking pace, and incident PAD.

Results: A total of 430,886 individuals were included in the final analysis. The mean age of the participants were 56.44 years, and 55.3 % were female. Over a median follow-up period of 13.81 years, 5,661 participants developed PAD. Higher grip strength, whether absolute or relative, exhibited a dose-dependent inverse association with incident PAD. Each 1 kg increment in absolute grip strength and each 0.01 kg/kg increase in relative grip strength were associated with reduced PAD risk by 2 % (HR: 0.98; 95 % CI [0.97–0.98]) and 83 % (HR: 0.17; 95 % CI [0.13–0.23]), respectively. Slow walking pace significantly correlated with increased PAD risk, while brisk walking pace was associated with decreased PAD risk.

Conclusion: Absolute grip strength, relative grip strength and walking pace were inversely associated with the risk of incident PAD.

1. Introduction

Peripheral artery disease (PAD) is a common vascular disorder characterized by the narrowing or blockage of peripheral arteries, leading to reduced blood flow and tissue ischemia [1,2]. It was estimated that PAD affected more than 230 million individuals worldwide in 2015 [3], and was responsible for 1.54 million disability-adjusted life years (DALYs) in 2019 as well as increased cardiovascular risks [4,5]. However, a higher burden of PAD could be anticipated due to the underdiagnosis of asymptomatic patients [6].

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Therefore, identifying candidate markers for the early prevention and risk assessment for PAD is of great importance.

Patients with PAD presented overall body disability, muscle weakness, and reduced physical performance [7,8]. Skeletal muscle area and strength were reduced in individuals with PAD [9–11]. Patients with a high burden of macrovascular issues, including PAD, exhibited poorer grip strength and gait speed [12]. PAD patients with decreased walking pace and grip strength had significantly increased total mortality and cardiovascular mortality [13–16]. Therefore, musculoskeletal factors might serve as candidate markers for the risk assessment of PAD.

Grip strength and walking pace, two readily accessible indicators of physical capability, are commonly employed to reflect muscle function. It has been reported that lower grip strength was associated with elevated comorbidity and cardiac risk in patients with vascular diseases, including PAD [16,17]. Grip strength and gait speed were proved to be effective in the early detection of PAD among patients with type 2 diabetes (T2DM) in cross-sectional studies [18,19]. Among elderly Chinese adults aged over 65 years, grip strength and walking speed demonstrated a negative correlation with PAD [20]. It could be inferred that PAD diminished physical capability, which in turn correlates with unfavorable outcomes in PAD patients. However, evidence from longitudinal studies regarding the association between grip strength, walking speed, and incident PAD is still lacking.

In this study, we aimed to investigate the associations of grip strength and walking pace with the risk of incident PAD by utilizing data from the United Kingdom (UK) Biobank cohort.

2. Materials and methods

2.1. Study population

The UK Biobank is a prospective cohort comprising over 500,000 participants aged 40–69 from 22 assessment centers across England, Scotland, and Wales during 2006–2010 [21]. Comprehensive demographic, clinical, and biochemical data were gathered through self-administered touch-screen questionnaires, physical assessments, computer-assisted interviews, and biological sample analyses (including blood, urine, and saliva). Follow-up information was obtained via linkages to national datasets, including primary care records, cancer screening data, and disease-specific registries. Ethical approval for the UK Biobank was granted by the North West Multi-Centre Research Ethics Committee (Ref: 11/NW/0382), with electronic consent obtained from participants prior to their initial assessment. This study was conducted under access application number 109546. Further details about the UK Biobank can be accessed online at www.ukbiobank.co.uk. A flowchart detailing the recruitment process was available in Fig. S1. Briefly, 502,356 individuals at baseline were included. We excluded participants who developed PAD during the first 2 years follow-up to minimize the potential reverse causality and those with baseline PAD (n = 2,091), cancer at baseline (n = 14,514), incomplete data for the exposures (n = 12,304 for grip strength and n = 3,465 for walking pace), missing data for follow-up (n = 36,814) and missing data for covariates (n = 2,282) were excluded. PAD and cancer were identified by linkage to hospital inpatient admissions and death registries. International Classification of Disease Tenth Version (ICD-10) and the Office of Population Censuses and Surveys Classification of Interventions and Procedures, version 4 (OPCS-4) were used to define PAD (ICD-10 codes: I700, I7000, I7001, I702, I7020, I7021, I708, I7080, I709, I7090, I738, and I739; OPCS-4 codes: X093, X094, X095, L216, L513, L516, L518, L521, L522, L541, L544, L548, L591, L592, L593, L594, L595, L596, L597, L598, L601, L602, L631, L635, L639, and L667) [22]. All cancers were determined by the following ICD-10 codes: C0-C97, D37-D48 [23].

2.2. Assessment of grip strength and walking pace

Grip strength was measured using a Jamar J00105 hydraulic hand dynamometer [24]. Both hands were assessed and the mean value expressed in absolute units (kg) were used for further analysis. It has been reported that grip strength was related to total body weight [25]. Therefore, relative grip strength was derived by absolute grip strength/body weight (kg/kg). Furthermore, grip strength was also categorized into quintiles to facilitate comparability based on age and sex (Table S1).

Walking pace was self-reported at baseline in the touchscreen questionnaire. As detailed in UK biobank, slow walking pace was defined as less than 3 miles per hour, average pace was defined as between 3 and 4 miles per hour, and brisk pace was defined as more than 4 miles per hour.

2.3. Covariates

Sociodemographic factors included age, sex, ethnicity, qualification, body mass index (BMI), and deprivation. Participants provided self-reported information on sex, ethnicity, and educational qualifications at baseline through a touchscreen questionnaire. Ethnicity was categorized as white, Black, South Asian, Chinese, or mixed. Educational attainment was stratified based on attendance at college or university. Age was computed from participants' date of birth. BMI was calculated as weight in kilograms divided by the square of height in meters. Body height measured to the nearest 1 cm and weight to the nearest 0.1 kg were measured by trained nurses.

Deprivation was assessed using the Townsend score [26].

Lifestyle factors included smoking status, dietary habits, drinking status and physical activity levels were self-reported at baseline. Smoking statue was categorized as never, former or current smoker. Dietary habits were evaluated using a composite score derived from nine food items in line with current UK dietary guidelines, with lower scores indicating healthier dietary patterns [27]. Drinking status was assessed by a touchscreen questionnaire and categorized as never, previous and current drinker. Physical activity levels were assessed using the International Physical Activity Questionnaire short-form, quantified as metabolic equivalents of task (MET min/week). Adequate physical activity was defined as moderate activity for $\geq$150 min/week and/or vigorous activity for $\geq$75 min/week [28].

Inflammatory diseases (arthritis, inflammatory bowel disease, and asthma) were self-reported at baseline in a nurse-led interview at baseline. Central obesity was defined as a waist circumference of 88 cm or more in women and 102 cm or more in men. Hyperglycemia or diabetes was diagnosed based on fasting glucose levels exceeding 5.6 mmol/L or a self-reported history of diabetes. High blood pressure was diagnosed if baseline blood pressure measurements surpassed 130/85 mmHg or if there was a self-reported history of hypertension. Dyslipidemia included elevated triglyceride levels above 1.7 mmol/L and low levels of high-density lipoprotein (HDL) cholesterol below 1.3 mmol/L in women and below 1.0 mmol/L in men. Waist circumference was measured by study stuff. Glucose was measured by hexokinase analysis on a Beckman Coulter AU5800. Triglycerides was measured by GPO-POD analysis on a Beckman Coulter AU5800. HDL cholesterol was

measured by enzyme immune-inhibition analysis on a Beckman Coulter AU5800. Blood pressure was automatedly read by the Omron device. Two measures of blood pressure were taken a few moments apart. Additional information on the measurements is available on the UK Biobank website (http://www.ukbiobank. ac.uk).

2.4. Outcome

Incident PAD was identified by linkage to primary care, hospital admission, self-reported data, and death registry records. As detailed in Table S2, PAD was defined based on primary and secondary diagnosis and surgical codes from hospital episodes, as well as self-reported PAD diagnoses and surgeries [22,29].

2.5. Statistical analysis

Baseline characteristics for participants with or without incident PAD were presented as mean with standard deviation (SD) for quantitative data and numbers (percentages) for categorical data. Difference between the two groups were compared by student t-tests for continuous variables and $\chi 2$ tests for categorical variables.

Cox proportional hazard models were employed to explore the association of grip strength and walking pace with incident PAD. Model 1 was adjusted for age and gender. Model 2 was further adjusted for sociodemographic factors (age, gender, ethnicity, educational attainment, body mass index, and Townsend deprivation index), as well as lifestyle factors (smoking, dietary score, and physical activity). Model 3 incorporated additional adjustments for inflammatory diseases and metabolic syndromes (central obesity, hyperglycemia/diabetes, hypertension, low HDL, and high triglycerides). Nonlinear relationships between grip strength and PAD were evaluated using restricted cubic splines (RCS) fitted within Cox proportional hazard models with three knots. Proportional hazards assumptions for all models were assessed using Schoenfeld residuals.

To assess the multicollinearity among covariates, we calculated the variance inflation factor (VIF) for each independent variable and found that all VIF remained below 2.5 (Table S3). Additionally, we explored the multiplicative interactions between grip strength and walking pace (Table S4). Subgroup analyses stratified by age and sex were performed. To testify the robustness of observed associations, sensitivity analyses were conducted by excluding participants with extreme values of grip strength (±2.5 standard deviation, SD) and included only PAD patients received surgery. All subgroup and sensitivity analyses were adjusted according to model 3.

A significance level of $p < 0.05$ (two-tailed) was adopted as statistically significant. Statistical analyses were conducted using SAS and R version 4.3.2.

3. Results

3.1. Baseline characteristics of participants

A total of 430,886 participants were included in the final analysis and the baseline characteristics were summarized in Table 1. The mean age of the participants was 56.44 years, with females accounting for 55.3 % of the cohort. Over a median follow-up period of 13.81 years, 5,661 participants developed PAD. Individuals who progressed to PAD were characterized by older age (mean age 62.04 years vs. 56.36 years), higher BMI (mean BMI 28.71 vs. 27.30), and a higher likelihood of experiencing socioeconomic deprivation (mean deprivation score −0.40 vs. −1.39). Notably, individuals with a college education exhibited a lower susceptibility to PAD compared to those with lower educational attainment ($p < 0.001$). Smoking, alcohol consumption, poor dietary habits, and physical inactivity were significantly more prevalent among patients with incident PAD (all $p < 0.001$). Participants with PAD were more likely to have concurrent metabolic disorders such as central

Table 1
Baseline characteristics of the participants.

Characteristics	Overall	No PAD	Incident PAD	*P* values
No.	430886	425225	5661	
Age, years, mean (SD)	56.44 (8.07)	56.36 (8.07)	62.04 (6.42)	<0.001
Sex, n (%)				
female	238434 (55.3)	236517 (55.6)	1917 (33.9)	<0.001
male	192452 (44.7)	188708 (44.4)	3744 (66.1)	
BMI, mean (SD)	27.32 (4.70)	27.30 (4.68)	28.71 (5.29)	<0.001
Deprivation index, mean (SD)	−1.38 (3.04)	−1.39 (3.03)	−0.40 (3.46)	<0.001
Deprivation index, n (%)				
Least deprived	86176 (20.0)	85401 (20.1)	775 (13.7)	<0.001
Second least deprived	86177 (20.0)	85239 (20.0)	938 (16.6)	
Medium deprivation	86177 (20.0)	85136 (20.0)	1041 (18.4)	
Second most deprived	86177 (20.0)	84986 (20.0)	1191 (21.0)	
Most deprived	86179 (20.0)	84463 (19.9)	1716 (30.3)	
Qualification, n (%)				
College	143392 (33.3)	142450 (33.5)	942 (16.6)	<0.001
Other	287494 (66.7)	282775 (66.5)	4719 (83.4)	
Ethnicity, n (%)				
White	406237 (94.3)	400815 (94.3)	5422 (95.8)	<0.001
Mixed	2606 (0.6)	2586 (0.6)	20 (0.4)	
South Asian	8414 (2.0)	8317 (2.0)	97 (1.7)	
Black	6961 (1.6)	6895 (1.6)	66 (1.2)	
Chinese	6668 (1.5)	6612 (1.6)	56 (1.0)	
Smoking, n (%)				
Never	242836 (56.4)	241315 (56.7)	1521 (26.9)	<0.001
Previous	145694 (33.8)	143177 (33.7)	2517 (44.5)	
Current	42356 (9.8)	40733 (9.6)	1623 (28.7)	
Drinking, n (%)				
Never	18308 (4.2)	18052 (4.2)	256 (4.5)	<0.001
Previous	13917 (3.2)	13571 (3.2)	346 (6.1)	
Current	398661 (92.5)	393602 (92.6)	5059 (89.4)	
Diet score, n (%)				
Highest	9874 (2.3)	9791 (2.3)	83 (1.5)	<0.001
High/Middle	140989 (32.7)	139498 (32.8)	1491 (26.3)	
Middle	208263 (48.3)	205534 (48.3)	2729 (48.2)	
Middle/Low	67940 (15.8)	66699 (15.7)	1241 (21.9)	
Lowest	3820 (0.9)	3703 (0.9)	117 (2.1)	
Diet score, mean (SD)	4.10 (1.43)	4.10 (1.43)	4.43 (1.50)	<0.001
Physical activity, MET-min/week, mean (SD)	2070.53 (2582.94)	2072.99 (2582.05)	1885.42 (2642.25)	<0.001
Physical activity, n (%)				
not enough	110398 (25.6)	108490 (25.5)	1908 (33.7)	<0.001
enough	320488 (74.4)	316735 (74.5)	3753 (66.3)	
Central obesity, n (%)	127959 (29.7)	125468 (29.5)	2491 (44.0)	<0.001
Hyperglycaemia/ diabetes, n (%)	72000 (16.7)	69634 (16.4)	2366 (41.8)	<0.001
Hypertension, n (%)	301397 (69.9)	296213 (69.7)	5184 (91.6)	<0.001

(*continued on next page*)

Table 1 (*continued*)

Characteristics	Overall	No PAD	Incident PAD	*P* values
Low HDL, n (%)	132982 (30.9)	130648 (30.7)	2334 (41.2)	<0.001
Hyperglyceridemia, n (%)	158864 (36.9)	156097 (36.7)	2767 (48.9)	<0.001
Inflammatory diseases, n (%)	58741 (13.6)	57787 (13.6)	954 (16.9)	<0.001
Absolute grip strength, kg	30.85 (11.02)	30.85 (11.02)	30.87 (10.90)	0.888
Absolute grip strength category, n (%)				
Lowest	86176 (20.0)	84993 (20.0)	1183 (20.9)	<0.001
Middle/Low	86177 (20.0)	85301 (20.1)	876 (15.5)	
Middle	86177 (20.0)	85142 (20.0)	1035 (18.3)	
High/Middle	86177 (20.0)	84669 (19.9)	1508 (26.6)	
Highest	86179 (20.0)	85120 (20.0)	1059 (18.7)	
Relative grip strength, kg/kg	0.40 (0.13)	0.40 (0.13)	0.38 (0.13)	<0.001
Relative grip strength category, n (%)				
Lowest	86176 (20.0)	84735 (19.9)	1441 (25.5)	<0.001
Middle/Low	86177 (20.0)	85026 (20.0)	1151 (20.3)	
Middle	86177 (20.0)	85060 (20.0)	1117 (19.7)	
High/Middle	86177 (20.0)	85131 (20.0)	1046 (18.5)	
Highest	86179 (20.0)	85273 (20.1)	906 (16.0)	
Walking pace category, n (%)				
Slow pace	28788 (6.7)	27390 (6.4)	1398 (24.7)	<0.001
Average pace	227004 (52.7)	223844 (52.6)	3160 (55.8)	
Brisk pace	175094 (40.6)	173991 (40.9)	1103 (19.5)	

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; PAD, peripheral artery disease; SD, standard deviation.

obesity, type 2 diabetes, hypertension, low HDL, high triglyceride levels, and inflammatory conditions at baseline. Additionally, individuals with PAD demonstrated reduced relative grip strength and a slower walking pace.

3.2. Linear associations of grip strength, walking pace and incident PAD

As depicted in Fig. 1 and Table S5, when categorized into quintiles, absolute grip strength exhibited an inverse association with the risk of incident PAD in a dose-dependent manner. The Hazard Ratios (HR) across quintiles of absolute grip strength were 1.47 (95 % confidence interval [CI]: 1.33–1.61), 1.15 (95 % CI: 1.05–1.27), 1.00 (reference), 0.85 (95 % CI: 0.78–0.92), and 0.68 (95 % CI: 0.62–0.75), respectively. Similar results were observed when grip strength was expressed in relative terms and divided into quintiles. When grip strength was analyzed as a continuous variable, each 1 kg increment in absolute grip strength and each 0.01 kg/kg increase in relative grip strength were associated with a 2 % (HR: 0.98; 95 % CI [0.97–0.98], $p < 0.001$) and 83 % (HR: 0.17; 95 % CI [0.13–0.23], $p < 0.001$) decreased risk of PAD. Slow walking pace significantly correlated with an increased risk of PAD (HR: 2.27; 95 % CI: 2.12–2.43, $p < 0.001$), while brisk walking pace was associated with a decreased risk of PAD (HR: 0.65; 95 % CI: 0.60–0.70, $p < 0.001$) (Table S5). The cumulative incident curve also indicated that the risk of incident PAD decreased with increasing absolute or relative grip strength, as well as with improved walking pace (Fig. 2A–C).

3.3. Non-linear associations of grip strength and incident PAD

Fig. 3 A&B illustrated the non-linear relationship between grip strength and PAD. L-shaped associations were observed between both absolute grip strength and relative grip strength with PAD. A higher absolute grip strength exhibited a significantly decreased risk of PAD in a linear pattern (overall $p < 0.0001$, non-linear $p = 0.0761$). Conversely, the relationship between relative grip strength and PAD displayed a non-linear pattern (non-linear $p < 0.0001$). The risk of incident PAD reduced substantially within the lower range of relative grip strength, which reached the lowest risk around 0.5 kg/kg and increased flatly thereafter.

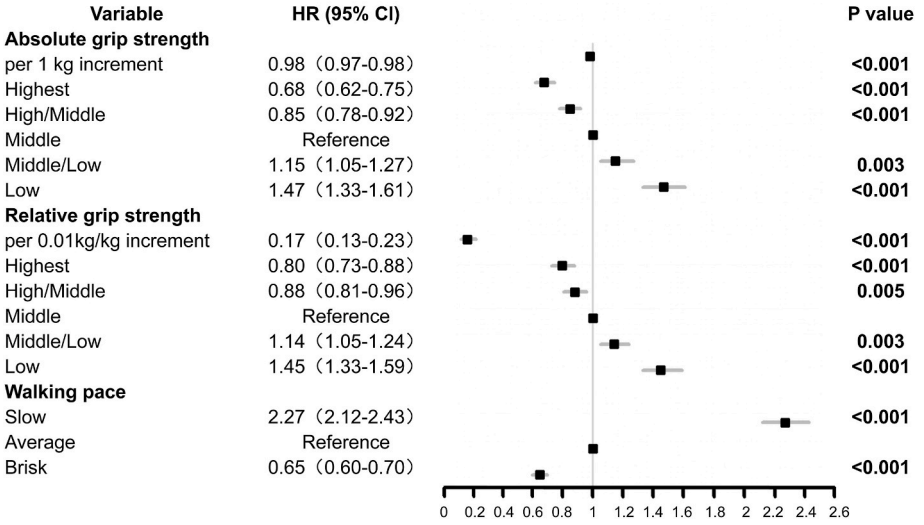

Fig. 1. Associations of grip strength, walking pace and incident PAD. Associations between grip strength, walking pace and the risk of incident PAD were investigated by Cox proportional hazard models. Grip strength, both in absolute and relative terms, was treated as continuous variables and categorized into quintiles. Individuals in the middle quintile were used as the reference group. Analyses were adjusted for age, sex, ethnicity, qualifications, body mass index, Townsend deprivation index, smoking, physical activity, inflammatory diseases, and metabolic syndromes (central obesity, high glycaemia/diabetes, high blood pressure/hypertension, low HDL, and high triglyceride). A *p* value below 0.05 was considered statistically significant. PAD, peripheral artery disease.

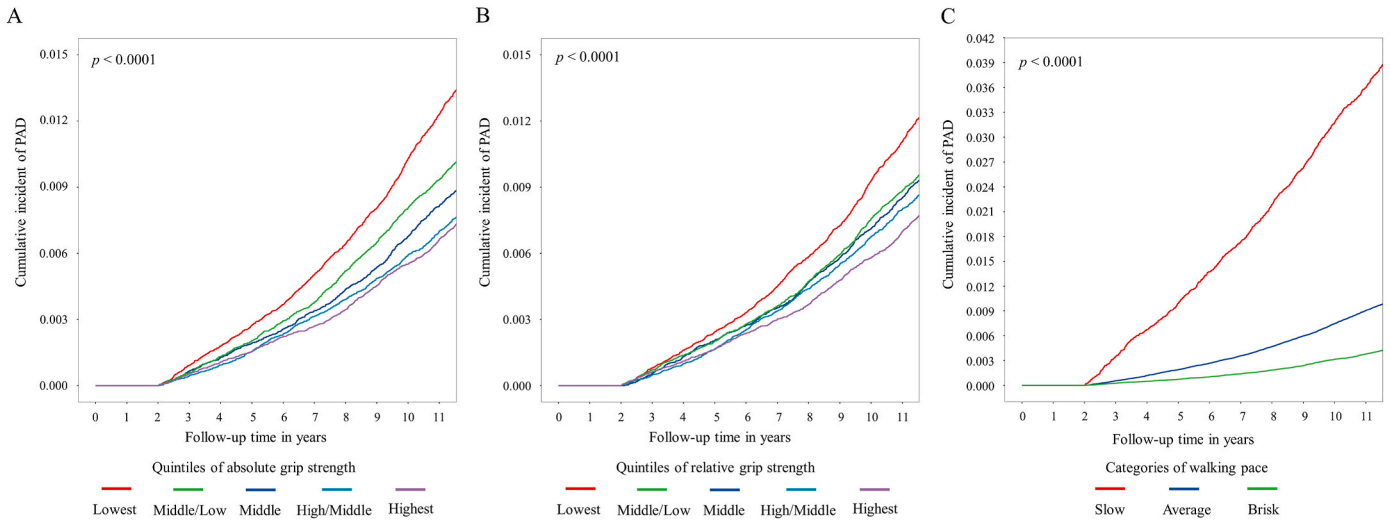

Fig. 2. Cumulative incident of PAD stratified by grip strength and walking pace. (A) Cumulative incident of PAD stratified by quintiles of absolute grip strength; (B) Cumulative incident of PAD stratified by quintiles of relative grip strength; (C) Cumulative incident of PAD stratified by walking pace. Analyses were adjusted for age, sex, ethnicity, qualifications, body mass index, Townsend deprivation index, smoking, physical activity, inflammatory diseases, and metabolic syndromes (central obesity, high glycaemia/diabetes, high blood pressure/hypertension, low HDL, and high triglyceride). PAD, peripheral artery disease.

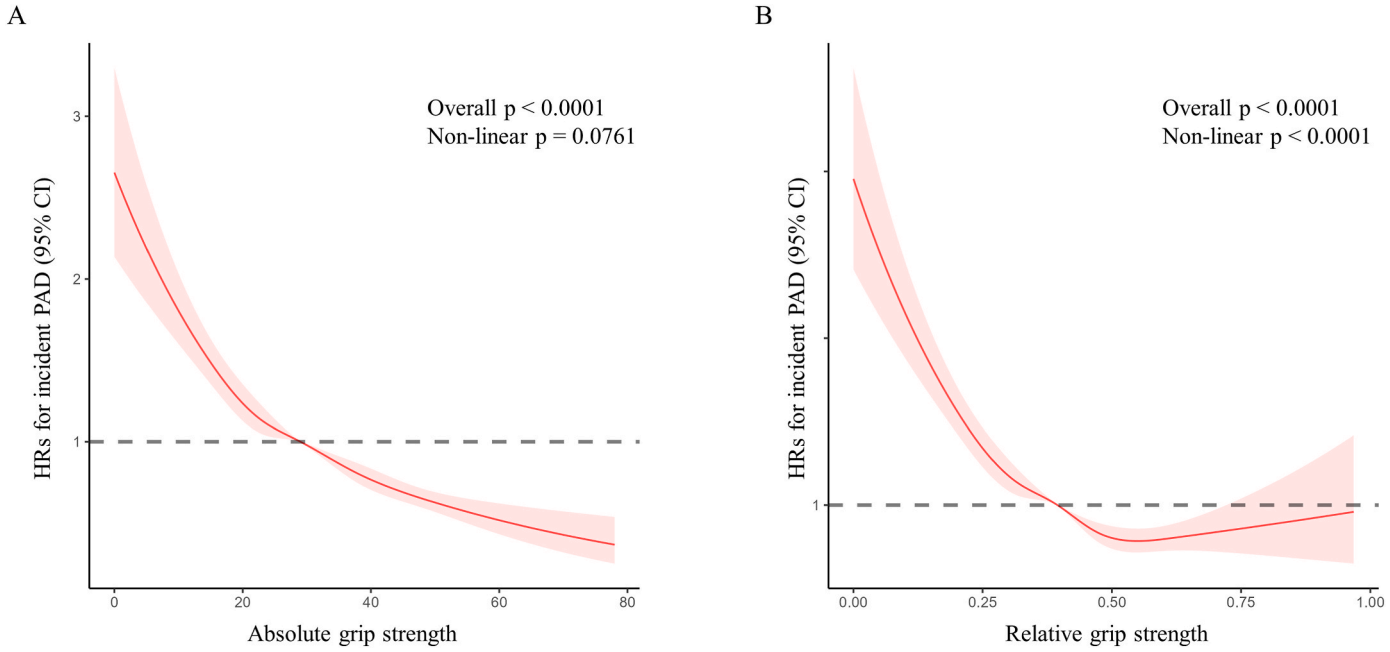

Fig. 3. Restricted cubic spline for the association of grip strength and incident PAD. (A) Restricted cubic spline for the association of absolute grip strength and incident PAD; (B) Restricted cubic spline for the association of relative grip strength and incident PAD. Analyses were adjusted for age, sex, ethnicity, qualifications, body mass index, Townsend deprivation index, smoking, physical activity, inflammatory diseases, and metabolic syndromes (central obesity, high glycaemia/diabetes, high blood pressure/hypertension, low HDL, and high triglyceride). HDL, high density lipoprotein; PAD, peripheral artery disease.

3.4. Gender-specific and age-specific analyses

We next performed subgroup analysis by sex and age. Grip strength was inversely associated with the risk of incident PAD in both male and female group (Table S6). The HRs for per 1 kg increment in absolute grip strength were 0.98 (95 % CI: 0.97–0.98) in male and 0.97 (95 % CI: 0.96–0.97) in female. When categorized into quintiles, the lowest quintile of absolute grip strength and relative grip strength were both related with increased PAD risk (Fig. 4A & Table S6). However, the highest and high-to-middle quintiles of both absolute and relative grip strength were only associated with decreased PAD risk in male. Additionally, walking pace exhibited a negative association with incident PAD in both genders, with females showing a higher susceptibility (Fig. 4B & Table S6).

Across all age groups, the risk of incident PAD diminished with enhanced grip strength and walking pace (Table S7). When categorized into quintiles, the lowest quintile of absolute and relative grip strength was related with increased PAD risk (Fig. 4C & Table S7). Regarding walking pace, slow walking pace was associated with increased PAD risk, whereas a brisk pace correlated with reduced PAD incidence especially in participants aged over 65 years (Fig. 4D).

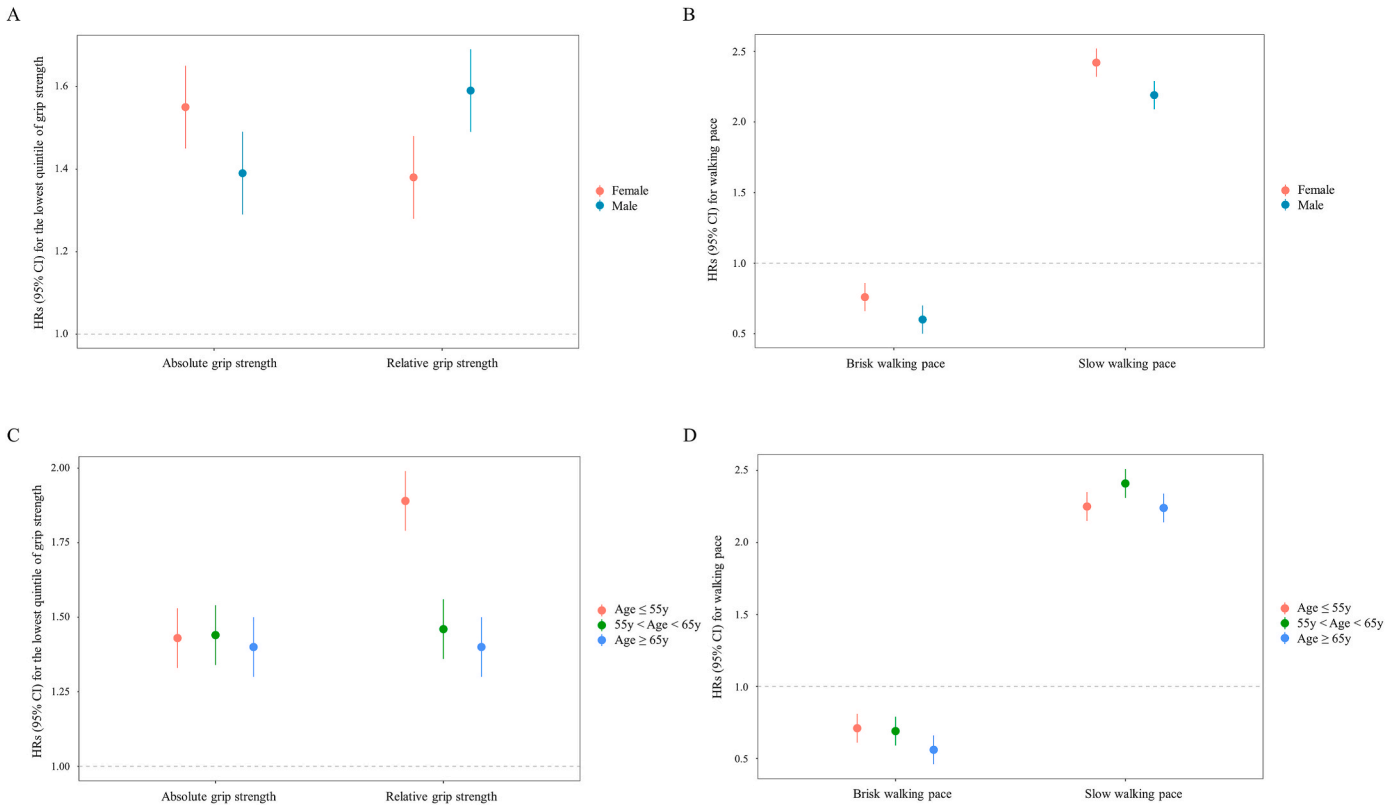

Fig. 4. Association of grip strength, walking pace and incident PAD stratified by sex and age. (A) Association of grip strength and incident PAD stratified by sex; (B) Association of walking pace and incident PAD stratified by sex; (C) Association of grip strength and incident PAD stratified by age; (D) Association of walking pace and incident PAD stratified by age. Analyses were adjusted for age, sex, ethnicity, qualifications, body mass index, Townsend deprivation index, smoking, physical activity, inflammatory diseases, and metabolic syndromes (central obesity, high glycaemia/diabetes, high blood pressure/hypertension, low HDL, and high triglyceride). PAD, peripheral artery disease.

3.5. Sensitivity analyses

As illustrated in Table S8, each 1 kg increase in absolute grip strength was related with a 2 % reduction in the risk of incident PAD requiring surgery (HR: 0.98; 95 % CI: 0.98–0.99). Higher quintiles of grip strength were associated with a decreased risk of PAD requiring surgery when compared to the middle quintile. Consistently, both continuous and categorical terms of grip strength were associated with a reduced risk of incident PAD that necessitated surgery. The relationship between absolute grip strength and the risk of surgical PAD exhibited linearity, whereas non-linear association was evident for relative grip strength and incident surgical PAD (Fig. S2). Furthermore, we conducted an analysis excluding participants with extreme grip strength values. Both absolute and relative grip strength as well as walking pace remained significantly associated with incident PAD (Table S9). Notably, the linear association between absolute grip strength and the risk of incident PAD persisted, while the relationship between relative grip strength and PAD risk remained non-linear (Fig. S3).

4. Discussion

This study revealed an inverse association between grip strength, walking pace, and the risk of incident PAD, which persisted across all age groups and genders. Furthermore, low grip strength and slow walking pace were negatively associated with PAD necessitating surgery. These findings suggested that grip strength and walking pace could serve as candidate indicators in risk and prognosis assessment for PAD.

Previous study highlighted that the association of grip strength with health outcomes remained consistent whether grip strength is assessed in absolute or relative terms [25], which was in line with our results. Additionally, our analysis revealed that while the mean absolute grip strength did not differ significantly between the non-incident and the incident PAD group, relative grip strength emerged as a distinguishing factor. This suggests that relative grip strength may possess greater sensitivity in predicting the risk of PAD. Although PAD typically manifests as weaker leg muscles, as indicated by reduced plantar flexion and knee extension strength [11,30], grip strength has been shown to be highly correlated with overall limb muscle strength across all age groups [31]. Given the simplicity of measuring grip strength compared to other muscle strength assessments, it could serve as a widely accessible indicator for identifying individuals at risk of PAD.

It's well-documented that PAD is linked to impaired blood flow and musculoskeletal performance in the lower limbs [32]. Intermittent claudication, a common symptom of PAD, typically occurs in the disease's later stages and therefore is inappropriate for early detection. Our research unveiled a noteworthy connection between slow walking pace and an elevated risk of incident PAD compared to an average walking pace, highlighting the potential of walking pace in early screening of PAD. This finding is consistent with the Pro.V.A. study, which associated

gait speed with the onset of cardiovascular diseases, including PAD [33]. However, it's worth noting that the Pro.V.A. study had a smaller sample size and didn't specifically analyze PAD as an independent outcome. Moreover, for claudicating patients with PAD, increasing walking speed by 0.03 m/s or more during supervised exercise therapy has been linked to improvements in walking impairment [34], which underscores the utility of walking pace in assessing the effectiveness of interventions for PAD.

Numerous studies investigating the associations between grip strength, walking pace, and cardiovascular outcomes by utilizing UK biobank have been published. Carlos A. reported that grip strength was negatively related with incident cardiovascular events [35,36]. Emmi Tikkanen found that higher grip strength was associated with lower risk of incident coronary heart disease, atrial fibrillation, heart failure and hemorrhagic stroke [37]. Both relative and absolute higher grip strength were associated with lower risk of incident cardiovascular diseases (CVD), however the relationship of grip strength and PAD was not further investigated [25]. Grip strength and walking pace were inversely associated with incidence of composite CVD [38]. Individual grip strength, gait speed and their combination were negatively related with CVD (myocardial infarction and stroke) incidence and mortality [39]. Physical frailty (defined by weight loss, exhaustion, low physical activity, slow gait speed and low grip strength) was associated with CVD (coronary heart disease, heart failure and stroke) incidence [40]. The aforementioned UK biobank studies either exclude PAD in the CVD outcomes or did not treat PAD as an independent outcome. Our study addressed the gaps in previous literature by demonstrating the independent associations of grip strength and walking pace with the incidence of PAD. However, further research is necessary to confirm the effectiveness of these measures in screening for PAD risk.

The understanding of the mechanisms underlying grip strength, walking pace, and PAD pathophysiology is still evolving, but there are some key insights to consider. Decreased muscle area and performance resulted in series of metabolic disorders [41], including established risk factors for PAD. A cross-sectional analysis of 1,919 participants from the Framingham Offspring Study found that slower walking pace was associated with elevation of makers of inflammatory and oxidative stress [42]. What's more, skeletal muscle is known as an endocrine organ which produces various molecules called myokines [43]. Several myokines have been proved to be associated with chronic inflammatory status and energy metabolism [44,45]. Chronic inflammation and oxidative stress are known contributors to the development of PAD [46, 47]. It has been recognized that Chronic low-grade inflammation, and mitochondrial dysfunction are shared features in muscle weakness and PAD [47–50]. Understanding the interplay between these factors could provide valuable insights into the mechanisms linking muscle function and PAD development.

Several limitations warrant mentioning. We used grip strength to estimate muscle strength. Although it has been proved that grip strength is highly correlated with leg strength [31], plantar flexion and knee extension strength which directly reflect lower leg muscle strength should be further evaluated in risk assessment of PAD. Self-reported walking pace could be influenced by many factors such as age. Although previous studies have proved that self-reported walking pace was an accurate indicator of objectively measured walking speed, reporting bias could still be introduced [51]. What's more, incident PAD was identified by electronic records. Since most patients with PAD were asymptomatic and might remained undiagnosed, the incident cases could be underestimated. Additionally, our study participants mainly consisted of European population, which restricted the generalization of our findings to other population. Also, we could not infer the causality between grip strength, walking pace and incident PAD due to the observational nature of this study. Although multiple risk factors were adjusted during analysis, residual confounding was still possible.

5. Conclusion

Grip strength and walking pace were inversely associated with the risk of incident PAD. Since grip strength and walking pace are easily accessible measurements, they could be widely utilized in the risk and prognosis assessment of PAD. Improving grip strength and walking performance might be effective in reducing the risk of PAD.

Data sharing statement

The datasets used and analyzed during the current study are available on application to the UK Biobank (www.ukbiobank.ac.uk/). This research has been conducted using the UK Biobank Resource under Application Number 109546.

Fundings

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Table S1
Cut-off point for absolute and relative grip strength quintiles.

Grip strength	Sex	Age group	Lowest	Middle/Low	Middle	High/Middle	Highest
Absolute grip strength, kg	Female	<56 years	<20.5	20.5–24.0	24.0–27.0	27.0–30.5	>30.5
		56–65 years	<18.0	18.0–21.0	21.0–24.0	24.0–27.0	>27.0
		>65 years	<16.5	16.5–20.0	21.0–24.0	22.0–25.5	>25.5
	Male	<56 years	<35.0	35.0–40.0	40.0–44.0	44–49.5	>49.5
		56–65 years	<32.5	32.5–37.0	37.0–41.0	41–46.0	>46.0
		>65 years	<30.0	30.0–35.0	35.0–38.5	38.5–43.0	>43.0
Relative grip strength, kg/kg	Female	<56 years	<0.280	0.280–0.341	0.341–0.395	0.395–0.459	>0.459
		56–65 years	<0.245	0.245–0.299	0.299–0.347	0.347–0.405	>0.405
		>65 years	<0.228	0.228–0.280	0.280–0.324	0.324–0.378	>0.378
	Male	<56 years	>0.400	0.400–0.467	0.467–0.524	0.524–0.591	>0.591
		56–65 years	>0.373	0.373–0.437	0.437–0.491	0.491–0.554	>0.554
		>65 years	>0.355	0.355–0.415	0.415–0.467	0.467–0.528	>0.528

Table S2
UK biobank codes for peripheral artery disease diagnosis and classifications.

Field name	Data Code	Data code definition
Non-cancer illness code, self-reported (20002)	1067	Peripheral vascular disease
	1087	Leg claudication/intermittent claudication
	1088	Arterial embolism
Diagnoses: main ICD10; secondary ICD10; Underlying (primary)/Contributory (secondary) cause of death ICD10	I70.0	Atherosclerosis of aorta
	I70.00	Atherosclerosis of aorta (without gangrene)
	I70.01	Atherosclerosis of aorta (with gangrene)
	I70.2	Atherosclerosis of arteries of the extremities
	I70.20	Atherosclerosis of arteries of extremities (without gangrene)
	I70.21	Atherosclerosis of arteries of extremities (with gangrene)
	I70.8	Atherosclerosis of other arteries
	I70.80	Atherosclerosis of other arteries (without gangrene)
	I70.9	Generalized and unspecified atherosclerosis
	I70.90	Generalized and unspecified atherosclerosis (without gangrene)
	I73.8	Other specified peripheral vascular diseases
	I73.9	Peripheral vascular disease, unspecified
Diagnoses: main ICD9; secondary ICD9	4400	Atherosclerosis of aorta
	4402	Atherosclerosis of arteries of the extremities
	4438	Other specified peripheral vascular disease
	4439	Peripheral vascular disease, unspecified
Operation code, self-reported (20004)	1102	Fem-pop bypass/leg artery bypass
	1108	Leg artery angioplasty±stent
	1440	Amputation of leg
Operative procedures main OPCS; Operative procedures secondary OPCS	X09.3	Amputation of leg above knee
	X09.4	Amputation of leg through knee
	X09.5	Amputation of leg below knee
	L21.6	Bypass of bifurcation of aorta by anastomosis of aorta to iliac artery NEC
	L51.3	Bypass of artery of leg by anastomosis of aorta to common femoral artery NEC
	L51.6	Bypass of artery of leg by anastomosis of iliac artery to femoral artery NEC
	L51.8	Other specified other bypass of iliac artery
	L52.1	Endarterectomy of iliac artery and patch repair of iliac artery
	L52.2	Endarterectomy of iliac artery NEC
	L54.1	Percutaneous transluminal angioplasty of iliac artery
	L54.4	Percutaneous transluminal insertion of stent into iliac artery
	L54.8	Other specified transluminal operations on iliac artery
	L59.1	Bypass of femoral artery by anastomosis of femoral artery to femoral artery NEC
	L59.2	Bypass of femoral artery by anastomosis of femoral artery to popliteal artery using prosthesis NEC
	L59.3	Bypass of femoral artery by anastomosis of femoral artery to popliteal artery using vein graft NEC
	L59.4	Bypass of femoral artery by anastomosis of femoral artery to tibial artery using prosthesis NEC
	L59.5	Bypass of femoral artery by anastomosis of femoral artery to tibial artery using vein graft NEC
	L59.6	Bypass of femoral artery by anastomosis of femoral artery to peroneal artery using prosthesis NEC
	L59.7	Bypass of femoral artery by anastomosis of femoral artery to peroneal artery using vein graft NEC
	L59.8	Other specified other bypass of femoral artery
	L60.1	Endarterectomy of femoral artery and patch repair of femoral artery
	L60.2	Endarterectomy of femoral artery NEC
	L63.1	Percutaneous transluminal angioplasty of femoral artery
	L63.5	Percutaneous transluminal insertion of stent into femoral artery
	L63.9	Unspecified transluminal operations on femoral artery
	L66.7	Percutaneous transluminal placement of peripheral stent in artery

Abbreviations: ICD, International Classification of Disease; NEC, not elsewhere classified; OPCS, the Office of Population Censuses and Surveys Classification of Interventions and Procedures.

Table S3
Multicollinearity analysis of incident PAD.

	Absolute grip strength		Relative grip strength		Walking pace	
	VIF	Tolerance (1/VIF)	VIF	Tolerance (1/VIF)	VIF	Tolerance (1/VIF)
Sex	2.267005	0.441110628	1.595399	0.626802449	1.106916	0.903410918
Age	1.156272	0.864848409	1.140511	0.876799961	1.122125	0.891166314
Deprivation	1.108645	0.902001993	1.104073	0.905737211	1.119345	0.89337961
Ethnic	1.065098	0.938880741	1.059806	0.943568917	1.061489	0.942072881
Qualification	1.047501	0.954653027	1.045444	0.956531388	1.053521	0.949197975
Inflammatory disease	1.019729	0.980652703	1.01789	0.982424427	1.033504	0.967582128
Central obesity	1.930881	0.517898307	1.966418	0.508538876	1.935677	0.516615117
Diabetes Mellitus	1.119242	0.893461825	1.117325	0.894994742	1.12656	0.887658003
Hypertension	1.060472	0.942976335	1.059481	0.943858361	1.060978	0.942526612
Low HDL	1.075562	0.929746495	1.074612	0.930568428	1.080894	0.925160099
Hyperglyceridemia	1.085718	0.921049481	1.085498	0.921236152	1.087621	0.919437929
Physical activity	1.049738	0.952618653	1.047348	0.954792485	1.065253	0.938744129
Smoking	1.163418	0.859536297	1.125711	0.888327466	1.134885	0.881146548
Diet quintile	1.127274	0.887095773	1.163415	0.859538514	1.179592	0.847750748
BMI	2.016083	0.496011325	2.209292	0.452633694	2.073573	0.482259366

Abbreviations: BMI, body mass index; HDL, high density lipoprotein; VIF, Variance inflation factors.

Table S4
Interaction between grip strength and walking pace with incident PAD.

		Walking pace	
		Slow	**Brisk**
Absolute grip strength	per 1 kg increment	<0.001	<0.001
	Highest	0.010	0.116
	High/Middle	0.145	0.567
	Middle	Reference	
	Middle/Low	0.777	<0.001
	Lowest	0.354	<0.001
Relative grip strength	per 0.01 kg/kg increment	0.024	<0.001
	Highest	0.451	0.086
	High/Middle	0.033	0.449
	Middle	Reference	
	Middle/Low	0.152	0.007
	Lowest	0.554	0.003

Adjusted for all covariates.

Table S5
The association of grip strength and walking pace with incident PAD.

		Model 1				Model 2				Model 3			
		HR	95 % CI		*P*	HR	95 % CI		*P*	HR	95 % CI		*P*
Absolute grip strength	per 1 kg increment	0.96	0.96	0.97	<0.001	0.97	0.97	0.97	<0.001	0.98	0.97	0.98	<0.001
	Highest	0.60	0.55	0.66	<0.001	0.65	0.59	0.71	<0.001	0.68	0.62	0.75	
	High/Middle	0.77	0.71	0.84	<0.001	0.82	0.76	0.90	<0.001	0.85	0.78	0.92	<0.001
	Middle	Reference				Reference				Reference			
	Middle/Low	1.26	1.15	1.39	<0.001	1.18	1.07	1.30	0.001	1.15	1.05	1.27	0.003
	Lowest	1.73	1.57	1.91	<0.001	1.57	1.43	1.73	<0.001	1.47	1.33	1.61	<0.001
Relative grip strength	per 0.01 kg/kg increment	0.042	0.032	0.054	<0.001	0.11	0.051	0.15	<0.001	0.17	0.13	0.23	<0.001
	Highest	0.65	0.60	0.71	<0.001	0.75	0.69	0.83	<0.001	0.80	0.73	0.88	<0.001
	High/Middle	0.79	0.73	0.86	<0.001	0.85	0.78	0.93	<0.001	0.88	0.81	0.96	0.005
	Middle	Reference				Reference				Reference			
	Middle/Low	1.27	1.17	1.38	<0.001	1.17	1.08	1.28	<0.001	1.14	1.05	1.24	0.003
	Lowest	1.90	1.75	2.07	<0.001	1.55	1.42	1.69	<0.001	1.45	1.33	1.59	<0.001
Walking Pace	Slow	3.37	3.17	3.59	<0.001	2.52	2.36	2.70	<0.001	2.27	2.12	2.43	<0.001
	Average	Reference				Reference				Reference			
	Brisk	0.52	0.48	0.55	<0.001	0.62	0.58	0.67	<0.001	0.65	0.60	0.70	<0.001

Model 1: Adjusted for age and sex.
Model 2: Adjusted for sociodemographic factors (age, sex, ethnicity, qualifications, body mass index, and Townsend deprivation index) and lifestyle factors (smoking and physical activity).
Model 3: Adjusted for Model 2 factors and additional disease risk factors (Inflammatory diseases and metabolic syndromes).
Abbreviation: HR, Hazard ratios; CI, Confidential intervals.

Table S6
The association of grip strength and walking pace with incident PAD stratified by gender.

		Male (N = 192452, PAD = 3744)				Female (N = 238434, PAD = 1917)			
		HR	95 % CI		P	HR	95 % CI		P
Absolute grip strength	per 1 kg increment	0.98	0.97	0.98	<0.001	0.97	0.96	0.97	<0.001
	Highest	0.67	0.61	0.74	<0.001	0.47	0.07	3.35	0.452
	High/Middle	0.83	0.76	0.91	<0.001	1.20	0.91	1.59	0.201
	Middle	Reference				Reference			
	Middle/Low	1.17	1.02	1.34	0.021	1.19	1.03	1.38	0.017
	Lowest	1.39	1.18	1.64	<0.001	1.55	1.35	1.77	<0.001
Relative grip strength	per 0.01 kg/kg increment	0.20	0.14	0.28	<0.001	0.13	0.07	0.22	<0.001
	Highest	0.79	0.71	0.87	<0.001	1.12	0.82	1.54	0.473
	High/Middle	0.87	0.79	0.96	0.005	0.98	0.80	1.21	0.881
	Middle	Reference				Reference			
	Middle/Low	1.11	1.00	1.23	0.056	1.18	1.02	1.37	0.031
	Lowest	1.59	1.42	1.79	<0.001	1.38	1.19	1.60	<0.001
Walking Pace	Slow	2.19	2.01	2.37	<0.001	2.42	2.15	2.71	<0.001
	Average	Reference				Reference			
	Brisk	0.60	0.55	0.65	<0.001	0.76	0.68	0.86	<0.001

Adjusted for all covariates.
Abbreviation: HR, Hazard ratios; CI, Confidential intervals; PAD, peripheral artery disease.

Table S7
The association of grip strength and walking pace with incident PAD stratified by age.

		Age ≤55 (N = 186313, PAD = 872)				Age = 56-64 (N = 163935, PAD = 2327)				Age ≥65 (N = 80638, PAD = 2462)			
		HR	95 % CI		P	HR	95 % CI		P	HR	95 % CI		P
Absolute grip strength	per 1 kg increment	0.97	0.96	0.97	<0.001	0.97	0.97	0.98	<0.001	0.98	0.97	0.98	<0.001
	Highest	0.68	0.59	0.78	<0.001	0.67	0.58	0.77	<0.001	0.75	0.65	0.87	<0.001
	High/Middle	0.85	0.75	0.96	0.007	0.84	0.74	0.96	0.011	0.88	0.78	1.01	0.061
	Middle	Reference				Reference				Reference			
	Middle/Low	1.20	1.04	1.38	0.014	1.06	0.91	1.24	0.42	1.15	1.01	1.30	0.031
	Lowest	1.43	1.24	1.66	<0.001	1.44	1.24	1.68	<0.001	1.40	1.23	1.60	<0.001
Relative grip strength	per 0.01 kg/kg increment	0.09	0.05	0.18	<0.001	0.17	0.11	0.27	<0.001	0.15	0.10	0.24	<0.001
	Highest	0.73	0.59	0.91	0.005	0.82	0.71	0.95	0.007	0.75	0.65	0.87	<0.001
	High/Middle	0.76	0.61	0.95	0.017	0.92	0.8	1.05	0.198	0.88	0.78	1.01	0.061
	Middle	Reference				Reference				Reference			
	Middle/Low	1.22	0.98	1.53	0.078	1.13	0.99	1.29	0.076	1.15	1.01	1.30	0.031
	Lowest	1.89	1.50	2.37	<0.001	1.46	1.27	1.68	<0.001	1.40	1.23	1.60	<0.001
Walking Pace	Slow	2.25	1.88	2.70	<0.001	2.41	2.17	2.68	<0.001	2.24	2.03	2.48	<0.001
	Average	Reference				Reference				Reference			
	Brisk	0.71	0.60	0.84	<0.001	0.69	0.62	0.76	<0.001	0.56	0.50	0.63	<0.001

Adjusted for all covariates.
Abbreviation: HR, Hazard ratios; CI, Confidential intervals; PAD, peripheral artery disease.

Table S8
The association of grip strength and walking pace with PAD necessitating surgery.

		PAD necessitating surgical or endovascular interventions (N = 430,886, PAD = 1,885)			
		HR	95 % CI		P
Absolute grip strength	per 1 kg increment	0.98	0.98	0.99	<0.001
	Highest	0.70	0.60	0.81	<0.001
	High/Middle	0.85	0.74	0.97	0.019
	Middle	Reference			
	Middle/Low	1.03	0.87	1.22	0.719
	Lowest	1.16	0.97	1.37	0.101
Relative grip strength	per 0.01 kg/kg increment	0.36	0.22	0.59	<0.001
	Highest	0.79	0.67	0.92	0.003
	High/Middle	0.97	0.84	1.11	0.643
	Middle	Reference			
	Middle/Low	1.21	1.05	1.39	0.010
	Lowest	1.26	1.07	1.47	0.004
Walking Pace	Slow	2.71	2.42	3.02	<0.001
	Average	Reference			
	Brisk	0.56	0.49	0.64	<0.001

Adjusted for all covariates.
Abbreviation: HR, Hazard ratios; CI, Confidential intervals; PAD, peripheral artery disease.

Table S9
The association of grip strength and walking pace with PAD after excluding extreme values.

		Excluding people with extreme valves of grip strength (±2.5 SD from the median) (N = 420,313, PAD = 5,441)			
		HR	95 % CI		*P*
Absolute grip strength	per 1 kg increment	0.98	0.97	0.98	<0.001
	Highest	0.68	0.62	0.74	<0.001
	High/Middle	0.85	0.78	0.92	<0.001
	Middle	Reference			
	Middle/Low	1.14	1.04	1.26	0.007
	Lowest	1.43	1.29	1.59	<0.001
Relative grip strength	per 0.01 kg/kg increment	0.18	0.13	0.25	<0.001
	Highest	0.81	0.74	0.89	<0.001
	High/Middle	0.89	0.81	0.97	0.006
	Middle	Reference			
	Middle/Low	1.14	1.05	1.24	0.002
	Lowest	1.39	1.27	1.53	<0.001
Walking Pace	Slow	2.25	2.10	2.42	<0.001
	Average	Reference			
	Brisk	0.65	0.61	0.70	<0.001

Adjusted for all covariates.
Abbreviation: HR, Hazard ratios; CI, Confidential intervals; PAD, peripheral artery disease; SD, standard deviation.

CRediT authorship contribution statement

Duqiu Liu: Writing – review & editing, Formal analysis, Data curation. **Chenxing Yang:** Software, Methodology. **Gang Liu:** Methodology. **Tianyu Guo:** Software. **Sen Liu:** Software. **Yi Guo:** Methodology. **Jinjie Xiong:** Methodology. **Ru Chen:** Writing – original draft, Investigation, Formal analysis. **Shan Deng:** Writing – review & editing, Supervision, Conceptualization. **Kai Huang:** Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

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