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ASSOCIATION OF GRIP STRENGHT WITH CARDIOVASCULAR RISK MARKERS

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ABSTRACT

Background: Mechanisms underlying the association between grip strength (GS) and cardiovascular mortality are poorly understood. We aimed to assess the association of GS with a panel of cardiovascular risk markers.

Design: Cross-sectional analysis of 3468 adults aged 50 to 75 years (1891 women) from a population-based sample in Lausanne, Switzerland.

Methods: GS was measured using a hydraulic hand dynamometer. Cardiovascular risk markers included anthropometry, blood pressure (BP), lipids, glucose, adiposity, inflammatory and other metabolic markers.

Results: In both genders, GS was negatively associated with fat mass (Pearson correlation coefficient: women: -0.170, men: -0.198), systolic blood pressure (women: -0.096, men: -0.074), fasting glucose (women: -0.048, men: -0.071), log-transformed leptin (women: -0.074, men: -0.065), log-transformed hs-CRP (women: -0.101, men: -0.079) and log-transformed homocysteine (women: -0.109, men: -0.060). In men, GS was also positively associated with diastolic BP (0.068), total (0.106) and LDL-cholesterol (0.082), and negatively associated with interleukin-6 (-0.071); in women, GS was negatively associated with triglycerides (-0.064) and uric acid (-0.059). After multivariate adjustment, GS was negatively associated with waist circumference (change per 5 kg increase in GS: -0.82 cm in women and -0.77 cm in men), fat mass (-0.56% in women; -0.27% in men) and hs-CRP (-6.8% in women; -3.2% in men) in both genders, and with body mass index (0.22 kg/m^2) and leptin (-2.7%) in men.

Conclusion: GS shows only moderate associations with cardiovascular risk markers. The effect of muscle strength as measured by GS on CVD does not seem to be mediated by cardiovascular risk markers.

Keywords: grip strength; anthropometry; blood pressure; lipids; glucose; inflammation; Switzerland; population-based study.

INTRODUCTION

Muscle strength is an important predictor of health [1], partly explained by the beneficial effect of muscle resistance activities on physical fitness [2]. Compared to other muscular tests such as trunk and knee extension or flexion, grip strength is the most appropriate marker of muscle strength [3] and has also been related to fitness [4]. Therefore, it remains the simplest and most largely recommended technique to assess muscle strength in clinical practice [5]. Grip strength has been shown to be inversely associated with overall and cardiovascular mortality in all age groups [6, 7], but the mechanisms involved have been less well established. Several cross-sectional studies assessed the associations between grip strength and cardiovascular (CV) risk factors, metabolic syndrome or inflammatory markers, but have been limited by the fact that they assessed a small set of variables [8, 9], relied on a small sample size [10] or were based only on elderly participants [9, 10]. Further, several studies have suggested that fitness can exert its effects independently of physical activity levels [11], and that not all types of physical activity are beneficial for health [12]. For instance, leisure-time physical activity (LTPA) has been shown to be beneficial while occupational physical activity (OPA) has been shown to be deleterious regarding all-cause mortality [13]. Still, no previous study took into account this finding.

Thus, the aim of this study was to assess the associations between grip strength and nineteen CV risk markers using a large population-based sample aged 50-75 years from the city of Lausanne, Switzerland (CoLaus study), taking into account the effects of LTPA and OPA.

MATERIALS AND METHODS

Recruitment

A detailed description of the recruitment of the CoLaus study has been published previously [14]. Briefly, the CoLaus study assesses the prevalence and determinants of CV disease in the city of Lausanne, Switzerland. A non-stratified, representative sample of the Lausanne population aged 35-75 years was drawn from the population register of the city. A letter was sent to these individuals, and subjects who volunteered to participate were then contacted by phone to set up an appointment. The baseline Colaus study was conducted between 2003 and 2006 and included 6733 participants.

Grip strength

Participants of the CoLaus study aged over 50 were invited to participate in a sub-study on frailty, which included grip strength. Grip strength was assessed using the Baseline® Hydraulic Hand Dynamometer and positioning of the participants was done according to the American Society of Hand Therapists's guidelines [5]: subject seated, shoulders adducted and neutrally rotated, elbow flexed at 90°, forearm in neutral and wrist between 0 and 30° of dorsiflexion. Three measurements were performed consecutively at the right hand and the highest value (expressed in kg) was included in the analyses. Participants were also asked about their handedness.

Exclusion criteria

Participants were excluded if they presented any condition precluding adequate measurement of grip strength, i.e. pain, injury, recent surgery, osteoarthritis and rheumatoid arthritis, among others.

Other data

A self administered questionnaire collected demographic data. Information on education level, job and on several lifestyle factors, including tobacco and LTPA (weekly number of ≥20min bouts of exercise) were also collected. OPA was categorized as non-physical (when sitting or standing) and physical (carrying light or heavy load). History of CVD and CV risk factor was elicited with a standardized interview-based questionnaire filled in by a trained recruiter. Participants indicated if they have been diagnosed with hypertension, dyslipidemia, diabetes, and if they were treated for these conditions.

Body weight and height were measured to the nearest 0.1 kg and 5 mm (Seca® scale, Seca® height gauge, Hamburg, Germany), with participants in light indoor clothes standing without shoes. Body mass index (BMI) was computed as weigth/height^2. Waist circumference (WC) was measured at mid-way between the lowest rib and the iliac crest as recommended [15]. Body composition was assessed by bioimpedance (Bodystat® 1500 analyzer, Isle of Man, UK) and expressed as percentage of fat. Blood pressure (BP) was measured using an Omron® HEM-907 automated oscillometric sphygmomanometer after at least 10 minutes' rest in a seated position and the average of the last two measurements was used. Hypertension was defined as a systolic BP ≥140 mmHg and/or a diastolic BP ≥90 mmHg and/or presence of an anti-hypertensive treatment.

A fasting venous blood sample was drawn and most measurements performed by the clinical laboratory of the Lausanne university hospital. Lipid markers included total and HDL-cholesterol, triglycerides and apolipoprotein B; LDL-cholesterol was calculated using the Friedewald formula if triglycerides were <4.6 mmol/L. Dyslipidemia was defined either by the presence of a lipid lowering drug or using the LDL-cholesterol thresholds according to

the PROCAM cardiovascular score adapted for Switzerland [16]. Glucometabolic markers included glucose and insulin; diabetes was defined by a fasting glucose ≥7.0 and/or presence of antidiabetic drug treatment. Inflammatory markers included high sensitivity C-reactive protein (hs-CRP), interleukin 6 (IL-6) and tumour necrosis factor alpha (TNF-α). Other markers included leptin, adiponectin, homocysteine and uric acid.

CV absolute risk was calculated using the European Society of Cardiology SCORE recalibrated and validated for the Swiss population [17]. This risk equation uses age, gender, smoking, systolic BP and total cholesterol to compute the 10-year absolute risk of fatal CV disease. No CV absolute risk was calculated for participants with history of CV disease.

Statistical analysis

Statistical analyses were stratified by gender and conducted using Stata version 14.0 for windows (Stata Corp, College Station, Texas, USA). Descriptive results were expressed as number of participants (percentage) or as average ± standard deviation. Between-group comparisons were performed using chi-square or Student t-test for categorical and continuous variables, respectively. Natural log transformation was applied to variables with a skewed distribution: triglycerides, insulin, leptin, adiponectin, hs-CRP, IL-6, TNF-α and homocysteine. Bivariate associations were assessed by Pearson correlation. Multivariate associations were assessed using linear regression and the results were expressed as multivariate-adjusted standardized coefficients, which can be interpreted as multivariate-adjusted correlation coefficients.

The effect of a 5 kg increase in grip strength on the different CV risk markers was assessed by linear regression, and the results were expressed as coefficient and (95% confidence interval). For log-transformed dependent variables, results were expressed as

percentage change of the untransformed dependent variable and (95% confidence interval), as recommended [18]. Multivariate analyses were conducted using linear or quadratic regression models and the adequacy of the linear model relative to the quadratic one was tested by likelihood ratio test. Multicollinearity of the dependent variables was assessed by computing the variance inflation factor; values ranged from 1.02 to 1.21, suggesting lack of collinearity.

All multivariate models were adjusted for age (continuous), smoking status (current/other), LTPA (3 categories), OPA (physical/non-physical) and BMI (except for anthropometry). Further adjustments were performed on: weight (continuous) for WC; hypertensive drug treatment (yes/no) for BP; lipid lowering drug treatment (yes/no) for lipid markers and antidiabetic drug treatment (yes/no) for glucometabolic markers. Sensitivity analyses were performed by further stratifying on tertiles of age. Statistical significance was assessed for a two-sided test with $p<0.05$.

Ethical statement

The CoLaus study was approved by the Ethics Committee of the University of Lausanne and all participants gave their signed informed consent before entering the study.

RESULTS

Characteristics of excluded participants

Of the initial 3704 participants invited to the sub-study on frailty, 3550 (95.8%) accepted. A further 82 (2.3%) participants were excluded because of issues related to grip strength measurement. Included and excluded participants' characteristics are presented in **Supplementary Table 1**. Included participants were more likely right-handed than the excluded ones, while no significant differences were found for all other variables analyzed.

The final sample consisted of 3468 participants; their characteristics overall and according to gender are summarized in **Supplementary Table 2**. Men had higher grip strength, were more likely to be current or former smoker, to have a university level of education, to be full-time worker, to perform a physical job, and to have a higher 10-year CV absolute risk than women.

Association of grip strength with cardiovascular risk markers

The bivariate and multivariate-adjusted associations using linear regression between grip strength and CV risk markers are described in **Table 1**; the corresponding changes in CV risk markers due to a 5 kg-increase in grip strength are described in **Table 2**. Bivariate analysis showed that grip strength was negatively associated with fat mass, systolic BP, fasting glucose, leptin, hs-CRP and homocysteine in both genders. In men, grip strength was positively associated with diastolic BP, total and LDL-cholesterol, and negatively associated with IL-6; in women, grip strength was negatively associated with triglycerides and uric acid. Finally, grip strength was negatively associated with 10-year CV absolute risk as assessed by the SCORE equation in both genders (Pearson correlation coefficient: women: -0.245, $p<0.001$, men: -0.264, $p<0.001$). Most of the previous associations were no longer significant after multivariate adjustment. In both genders, grip strength was negatively associated with WC, fat mass and hs-CRP; in men, grip strength was positively associated with BMI and negatively associated with leptin (**Table 1 and 2**).

Comparison between linear and quadratic models for homocysteine, total and LDL-cholesterol are expressed in **Supplementary Table 3**. For log-transformed homocysteine, total and LDL-cholesterol, the quadratic regression model showed a better fit than the linear one. An inverse U-shaped association between grip strength and total and LDL-cholesterol

was found in women. A U-shaped association between grip strength and homocysteine was found in men.

The linear associations between grip strength and CV risk markers stratified by tertiles of age are represented in **Supplementary Tables 4** (women) **and 5** (men), and the quadratic associations for homocysteine, total and LDL-cholesterol in **Supplementary Table 6**. Most associations remained identical through tertiles of age.

DISCUSSION

This study assessed the associations between grip strength and a large panel of CV risk markers in a population-based setting. Our results suggest that grip strength is only moderately associated with CV risk markers and CV absolute risk. Thus, the reported associations between grip strength and CV disease might not be mediated via those CV risk markers.

Grip strength, anthropometric and adiposity-related markers

Grip strength was negatively associated with WC and fat mass in both genders, and positively with BMI in men. The negative association with WC is consistent with a large cross-sectional population-based study [8] but not with another including older participants [10]. Fitness and regular exercise have been shown to improve body composition by reducing fat mass [19, 20], but the effect of grip strength on CV mortality has also been suggested to be independent of body composition [21]. According to a large 8.3-year follow-up study [22], muscle strength (measured using bench and leg press tests) showed a strong inverse prediction of excessive WC and fat mass after adjusting for fitness. The results suggest that grip strength is negatively related to body fat and positively to BMI, possibly due to the

larger muscle mass of overweight and obese subjects. Still, the changes in WC, fat mass and BMI induced by 5 kg change in grip strength were modest (1.2 cm, 1.2% and 0.30 kg/m^2, respectively) at the individual level.

A negative association between grip strength and leptin was found in men but not in women, and no association was observed for adiponectin. These findings are partly in agreement with a cross-sectional study [10] where no association was found between grip strength and adiposity-related hormones. Exercise has been shown to decrease leptin levels [23] but not adiponectin levels [23]. Overall, our results suggest that grip strength is moderately associated with leptin levels in men, but further studies should be conducted to confirm this association.

Grip strength, blood pressure, lipids and glucometabolic markers

On multivariate analysis, no significant association was found between grip strength and BP levels. These findings are in agreement with a recent cross-sectional study [10] but not with another [8]. Fitness and regular exercise have been shown to decrease BP levels [24], while muscle strength (measured using bench and leg press tests) showed no effect on 19-year incidence of hypertension after adjustment for fitness [25]. Overall, our results suggest that grip strength is not associated with BP levels, or that the association is too small to be detected using our sample size.

In both genders, an inverse U-shaped association between grip strength and total and LDL-cholesterol was found, this association being more prominent in women. Conversely, no association was found between grip strength and HDL-cholesterol, triglycerides and apolipoprotein B. These findings are partly in agreement with a cross-sectional study [10] which found no association between grip strength and triglycerides, total

and HDL-cholesterol. The inverse U-shaped association between grip strength and total and LDL cholesterol might be explained by two differing phenomena: first, increased fitness is associated with an improved lipids profile [19], which would explain the negative association between high grip strength values and lipid levels on the right hand side of the curve. Second, low lipid levels have been associated with mortality in an elderly cohort [26]; as low grip strength is also associated with increased mortality, this would explain the positive association between grip strength and lipid levels on the left hand side of the curve. Thus, our results suggest that grip strength has a complex association with the lipid profile, high values of grip strength being associated with a "beneficial" low lipid profile, while low values of grip strength are associated with a "deleterious" low lipid profile. Nevertheless, these findings should be further confirmed in other studies.

No association was found between grip strength and fasting glucose and insulin, a finding in agreement with two cross-sectional studies [8, 10]. Fitness and regular exercise have been shown to improve glucose profile [19, 27] while muscle strength showed no beneficial effects on glucose levels after adjustment for fitness [28]. The results suggest that grip strength is not associated with glucose metabolism or that the association is too small to be detected using the current sample size.

Grip strength and inflammation

Grip strength was negatively associated with hs-CRP levels, a finding in agreement with the literature [9, 10]. Fitness and regular exercise decrease CRP levels [29], probably by a decrease in adiposity levels and adiposity-related inflammation. Indeed, a previous study [30] showed an association between poor muscle quantity and quality (i.e. fat deposition in skeletal muscle) and adiposity-related inflammation. Conversely, the association between

grip strength and IL-6 or TNF-α is still a matter of debate : some studies reported a negative association [9, 31] while others reported no association [10]. Thus, our findings confirm that grip strength is negatively associated with hs-CRP levels, but not with IL-6 or TNF-α. Still, the change in CRP levels were moderate (8.5% decrease per 5 kg increase in grip strength) compared for example to the reduction induced by statin treatment [32]. Thus, whether decrease in CRP levels due to grip strength is clinically significant remains to be assessed.

Grip strength, homocysteine and uric acid

A U-shaped association between grip strength and homocysteine was found in men. Low grip strength was associated with high homocysteine levels, a finding also reported in a recent review [33], while the high homocysteine levels found among subjects with high grip strength deserve further clarification. Finally, no clear association was found between grip strength and uric acid levels, a finding in agreement with the literature [34].

Grip strength and cardiovascular absolute risk

Grip strength was negatively associated with CV absolute risk in both genders, a finding in agreement with the beneficial effects of fitness [11] and muscle strength [7] on CV mortality.

Study strengths and limitations

This is one of the largest studies assessing the associations between grip strength and a wide panel of cardiovascular risk markers. Importantly, the specific effects of grip strength were separated from those of LTPA and OPA.

This study also has several limitations worth acknowledging. Firstly, grip strength was assessed on the right hand whereas approximately 8% of our participants were left-handed.

However, it has been shown that grip strength does not differ between dominant and non-dominant hands in left-handed people [5]. Secondly, the cross-sectional design of our study precludes the assessment of any causal effect of grip strength on CV risk markers; the ongoing follow-up of the CoLaus participants will enable assessing the prospective effects of grip strength on CV risk markers. Thirdly, only participants aged between 50 and 75 were included, so our findings cannot be extrapolated to younger or older ages. Finally, most of the associations between grip strength and CV risk markers were weak, suggesting that grip strength might exert its effect on CV disease via other pathways, such as changes in endothelial function or autonomic nervous system.

Conclusion

In a population-based sample aged between 50 and 75 years, grip strength was only moderately associated with some CV risk markers. Thus, the reported associations between grip strength and CV disease might not be mediated via CV risk markers.

DECLARATION OF CONFLICTING INTERESTS

The authors declare that there is no conflict of interest.

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AUTHORS' CONTRIBUTIONS

CG made part of the statistical analyses and wrote most of the article; PMV made part of the statistical analysis and wrote part of the article; PV revised the article.

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TABLES

Table 1: bi- and multivariate associations between grip strength and cardiovascular risk markers.

	Pearson correlation coefficient		Multivariate-adjusted standardized coefficient	
	Women	**Men**	**Women**	**Men**
Anthropometry				
Body mass index (kg/m^2)	-0.034	0.022	-0.000	0.092 **
Waist circumference (cm)	-0.005	0.039	-0.069 [1] **	-0.114 [1] **
Fat mass (%)	-0.170**	-0.198**	-0.078 *	-0.084 *
Blood pressure (mmHg)				
Systolic	-0.096**	-0.074*	0.038 [2]	0.003 [2]
Diastolic	0.007	0.068*	0.015 [2]	0.045 [2]
Lipid markers (mmol/L)				
Total cholesterol	-0.028	0.106**	0.004 [3]	0.082 [3] *
HDL-cholesterol	0.015	0.002	-0.001 [3]	0.029 [3]
LDL-cholesterol	-0.025	0.082*	0.001 [3]	0.055 [3] *
Triglycerides §	-0.064*	0.048	-0.003 [3]	0.026 [3]
Apolipoprotein B (mg/dL)	-0.007	0.010	0.003 [3]	-0.006 [3]
Glucometabolic markers				
Fasting glucose (mmol/L)	-0.048*	-0.071*	-0.006 [4]	-0.036 [4]
Insulin (µU/mL) §	-0.031	-0.049	0.007 [4]	-0.032 [4]
Adipokines (µU/mL)				
Leptin §	-0.074*	-0.065*	-0.026 [5]	-0.059 [5] *
Adiponectin §	-0.036	-0.014	-0.024 [5]	0.012 [5]
Inflammatory markers				
hs-CRP (mg/L) §	-0.101**	-0.079*	-0.071 [5] *	-0.052 [5] *
IL-6 (pg/mL) §	-0.009	-0.071*	-0.009 [5]	-0.054 [5]
TNF-α (pg/mL) §	-0.005	-0.043	0.016 [5]	-0.024 [5]
Homocysteine (µmol/L) §	-0.109**	-0.060*	-0.022 [5]	0.032 [5]
Uric acid (µmol/L)	-0.059*	0.012	0.017 [5]	0.018 [5]

§, log-transformed. hs-CRP, high sensitivity C-reactive protein; IL-6, interleukin 6; TNF-α, tumour necrosis factor alpha. Bivariate associations assessed using Pearson correlation or multivariable linear regression; results are expressed as Pearson correlation coefficient or as multivariate-adjusted standardized coefficient. Multivariable linear model was adjusted for age, current smoking, leisure-time physical activity and occupational physical activity, with a further adjustment on [1] weight; [2] body mass index and antihypertensive drug treatment; [3] body mass index and lipid lowering drug treatment; [4] body mass index and antidiabetic drug treatment; [5] body mass index. *, $p<0.05$; **, $p<0.001$.

Table 2: Unadjusted and multivariate-adjusted changes in cardiovascular risk marker levels per 5 kg increase in grip strength, stratified by gender.

	Women				Men			
	Unadjusted	**P-value**	**Multivariate-adjusted**	**P-value**	**Unadjusted**	**P-value**	**Multivariate-adjusted**	**P-value**
Anthropometry								
Body mass index (kg/m^2)	-0.16 (-0.37 ; 0.05)	0.143	0.00 (-0.22 ; 0.22)	0.985	0.05 (-0.07 ; 0.17)	0.384	0.22 (0.10 ; 0.35)	<0.001
Waist circumference (cm)	-0.06 (-0.60 ; 0.49)	0.839	-0.82 (-1.13 ; -0.52) [1]	<0.001	0.26 (-0.07 ; 0.59)	0.121	-0.77 (-0.93 ; -0.61) [1]	<0.001
Fat mass (%)	-1.23 (-1.55 ; -0.90)	<0.001	-0.56 (-0.89 ; -0.22)	0.001	-0.63 (-0.78 ; -0.47)	<0.001	-0.27 (-0.43 ; -0.11)	0.001
Blood pressure (mmHg)								
Systolic	-1.67 (-2.46 ; -0.89)	<0.001	0.66 (-0.12 ; 1.43) [2]	0.098	-0.77 (-1.28 ; -0.26)	0.003	0.04 (-0.48 ; 0.56) [2]	0.892
Diastolic	0.07 (-0.38 ; 0.52)	0.762	0.15 (-0.31 ; 0.61) [2]	0.522	0.44 (0.12 ; 0.76)	0.007	0.29 (-0.05 ; 0.63) [2]	0.090
Lipid markers (mmol/L)								
Total cholesterol	-0.03 (-0.07 ; 0.02)	0.230	0.00 (-0.04 ; 0.05) [3]	0.863	0.06 (0.03 ; 0.09)	<0.001	0.05 (0.02 ; 0.08) [3]	0.002
HDL-cholesterol	0.01 (-0.01 ; 0.03)	0.505	0.00 (-0.02 ; 0.02) [3]	0.969	0.00 (-0.01 ; 0.01)	0.939	0.01 (0.00 ; 0.02) [3]	0.257
LDL-cholesterol	-0.02 (-0.06 ; 0.02)	0.273	0.00 (-0.04 ; 0.04) [3]	0.961	0.04 (0.02 ; 0.07)	0.001	0.03 (0.00 ; 0.06) [3]	0.036
Triglycerides §	-2.7 (-4.5 ; -0.8)	0.006	-0.1 (-2.0 ; 1.7) [3]	0.884	1.6 (-0.1 ; 3.2)	0.058	0.8 (-0.8 ; 2.5) [3]	0.312
Apolipoprotein B (mg/dL)	-0.91 (-7.02 ; 5.20)	0.770	0.35 (-6.21 ; 6.90) [3]	0.918	0.83 (-3.34 ; 5.01)	0.695	-0.52 (-5.01 ; 3.97) [3]	0.820
Glucometabolic markers								
Fasting glucose (mmol/L)	-0.05 (-0.10 ; 0.00)	0.036	-0.01 (-0.05 ; 0.04) [4]	0.777	-0.06 (-0.10 ; -0.02)	0.005	-0.03 (-0.07 ; 0.01) [4]	0.116
Insulin (µU/mL) §	-1.6 (-4.0 ; 0.9)	0.215	0.4 (-2.0 ; 2.7) [4]	0.764	-1.7 (-3.4 ; 0.1)	0.069	-1.1 (-2.7 ; 0.6) [4]	0.201
Adipokines (µU/mL)								
Leptin §	-4.9 (-8.0 ; -1.7)	0.003	-1.8 (-4.4 ; 0.9) [5]	0.198	-2.9 (-5.2 ; -0.5)	0.016	-2.7 (-4.6 ; -0.6) [5]	0.010
Adiponectin §	-2.1 (-4.8 ; 0.6)	0.129	-1.4 (-4.2 ; 1.5) [5]	0.337	-0.5 (-2.4 ; 1.4)	0.598	0.4 (-1.6 ; 2.5) [5]	0.671
Inflammatory markers								
hs-CRP (mg/L) §	-9.6 (-13.5 ; -5.5)	<0.001	-6.8 (-10.7 ; -2.8) [5]	0.001	-4.7 (-7.6 ; -1.8)	0.002	-3.2 (-6.1 ; -0.2) [5]	0.039
IL-6 (pg/mL) §	-1.1 (-6.6 ; 4.8)	0.713	-1.1 (-7.0 ; 5.2) [5]	0.730	-5.4 (-9.1 ; -1.5)	0.007	-4.1 (-8.2 ; 0.1) [5]	0.055
TNF-α (pg/mL) §	-0.4 (-4.0 ; 3.3)	0.828	1.2 (-2.6 ; 5.3) [5]	0.534	-2.1 (-4.5 ; 0.4)	0.094	-1.2 (-3.8 ; 1.5) [5]	0.392
Homocysteine (µmol/L) §	-2.9 (-4.0 ; -1.7)	<0.001	-0.6 (-1.8 ; 0.7) [5]	0.359	-1.1 (-2.0 ; -0.2)	0.019	0.6 (-0.4 ; 1.6) [5]	0.212
Uric acid (µmol/L)	-3.93 (-6.92 ; -0.94)	0.010	1.12 (-1.79 ; 4.04) [5]	0.449	0.53 (-1.75 ; 2.80)	0.650	0.84 (-1.52 ; 3.21) [5]	0.485

hs-CRP, high sensitivity C-reactive protein; IL-6, interleukin 6; TNF-α, tumour necrosis factor alpha. Statistical analyses performed using linear regression. Results are expressed as effect of a 5 kg increase in grip strength and (95% confidence interval). §, on log-transformed data; results are expressed as % change of the risk marker related to a 5 kg increase in grip strength. Multivariate adjustment for age, current smoking, leisure-time physical activity and occupational physical activity, with a further adjustment on [1] weight; [2] body mass index and antihypertensive drug treatment; [3] body mass index and lipid lowering drug treatment; [4] body mass index and antidiabetic drug treatment; [5] body mass index.

SUPPLEMENTARY INFORMATION

Supplementary table 1: socio-demographic and clinical characteristics of excluded and included participants.

	Included	**Excluded**	**P-value**
N	3468	82	
Right-handedness (%)	91.6	79.0	<0.001
Grip strength (kg)	33.5 ± 10.8	28.2 ± 12.9	<0.001
Age (years)	60.8 ± 6.8	61.3 ± 7.5	0.46
Smoking			0.86
Former (%)	36.6	34.6	
Never (%)	40.2	43.2	
Current (%)	23.2	22.2	
University level (%)	16.3	12.4	0.34
Working			0.88
Full time (%)	46.9	48.2	
Part time (%)	46.8	46.9	
None (%)	6.3	4.9	
Physical job (%)	15.7	21.3	0.18
10-year CV absolute risk (%)	3.3 ± 3.9	3.6 ± 4.5	0.51
Body mass index (kg/m^2)	26.4 ± 4.7	26.4 ± 4.8	0.93
Fat mass (%)	32.1 ± 8.7	33.2 ± 7.0	0.24
Hypertension (%)	50.1	53.7	0.53
Dyslipidemia (%)	41.1	45.1	0.47
Diabetes (%)	9.8	13.4	0.27

CV, cardiovascular. Results are expressed as mean ± standard deviation or as percentage. Statistical analyses by chi-square for categorical variables or Student's t-test for quantitative variables.

Supplementary table 2: Characteristics of participants, overall and by gender

	All	Women	Men	P-value
N	3468	1891	1577	
Right-handedness (%)	91.6	92.1	91.1	0.49
Grip strength (kg)	33.5 ± 10.8	26.0 ± 5.4	42.6 ± 8.4	<0.001
Age (years)	60.8 ± 6.8	60.8 ± 6.8	60.7 ± 6.8	0.80
Smoking				<0.001
Former (%)	36.6	29.2	45.5	
Never (%)	40.2	49.4	29.1	
Current (%)	23.2	21.4	25.4	
University level (%)	16.3	11.8	21.7	<0.001
Working				<0.001
Full time (%)	46.9	39.4	55.8	
Part time (%)	46.8	54.4	37.7	
None (%)	6.3	6.2	6.5	
Physical job (%)	15.7	13.0	18.9	<0.001
10-year CV absolute risk (%)	3.3 ± 3.9	2.3 ± 3.1	4.6 ± 4.5	<0.001
Anthropometry				
Body mass index (kg/m^2)	26.4 ± 4.7	25.8 ± 5.0	27.1 ± 4.1	<0.001
Waist circumference (cm)	91.5 ± 13.6	85.9 ± 12.8	98.2 ± 11.3	<0.001
Fat mass (%)	32.1 ± 8.7	37.0 ± 7.7	26.1 ± 5.4	<0.001
Lean mass (%)	67.9 ± 8.7	63.0 ± 7.7	73.9 ± 5.4	<0.001
Blood pressure				
Systolic BP (mmHg)	133.7 ± 18.5	130.8 ± 18.7	137.1 ± 17.6	<0.001
Diastolic BP (mmHg)	80.7 ± 10.9	79.1 ± 10.6	82.8 ± 11.0	<0.001
Hypertension (%)	50.1	43.3	58.3	<0.001
Lipid markers				
Total cholesterol (mmol/L)	5.8 ± 1.0	5.9 ± 1.0	5.6 ± 1.0	<0.001
HDL-cholesterol (mmol/L)	1.7 ± 0.5	1.8 ± 0.5	1.5 ± 0.4	<0.001
LDL-cholesterol (mmol/L)	3.5 ± 0.9	3.5 ± 0.9	3.4 ± 0.9	<0.001
Triglycerides §	1.4 ± 1.0	1.3 ± 0.7	1.7 ± 1.3	<0.001
Apolipoprotein B (mg/dL)	182.1 ± 140.0	182.4 ± 141.7	181.7 ± 137.9	0.90
Dyslipidemia (%)	88.9	89.3	88.3	0.36
Glucometabolic markers				
Fasting glucose (mmol/L)	5.7 ± 1.3	5.5 ± 1.1	6.0 ± 1.4	<0.001
Insulin (µU/mL) §	9.2 ± 6.4	8.3 ± 5.4	10.2 ± 7.3	<0.001
Diabetes (%)	9.8	5.7	14.6	<0.001
Adipokines				
Leptin (µU/mL) §	14.2 ± 11.1	18.0 ± 12.0	9.5 ± 7.7	<0.001
Adiponectin (µU/mL) §	10767 ± 8610	13213 ± 9754	7860 ± 5801	<0.001
Inflammatory markers				
hs-CRP (mg/L) §	2.7 ± 3.6	2.8 ± 3.8	2.6 ± 3.4	0.20
IL-6 (pg/mL) §	9.0 ± 105.4	9.1 ± 128.1	8.8 ± 69.2	<0.001
TNF-α (pg/mL) §	5.3 ± 18.0	5.6 ± 23.2	4.9 ± 8.2	0.25
Homocysteine (µmol/L) §	11.0 ± 4.7	10.0 ± 3.3	12.2 ± 5.7	<0.001
Uric acid (µmol/L)	324.3 ± 85.0	286.3 ± 71.0	369.8 ± 77.6	<0.001

CV, cardiovascular. §, on log-transformed data. Results are expressed as mean ± standard deviation or as percentage. Statistical analyses by chi-square or Student's t-test.

Supplementary table 3: comparison between the linear and the quadratic model for the associations between grip strength and selected cardiovascular risk markers.

	Grip strength	Grip strength^2	Likelihood ratio §§	P-value
Men				
Total cholesterol, linear model	0.082 [1]	-	3.88	0.049
Total cholesterol, quadratic model	0.367 [1] *	-0.288 [1]		
LDL cholesterol, linear model	0.055 [1]	-	3.54	0.060
LDL cholesterol, quadratic model	0.345 [1] *	-0.293 [1]		
Homocysteine §, linear model	0.032	-	7.11	0.008
Homocysteine §, quadratic model	-0.488 *	0.526 *		
Women				
Total cholesterol, linear model	0.004 [1]	-	9.23	0.002
Total cholesterol, quadratic model	0.432 [1] *	-0.434 [1] *		
LDL cholesterol, linear model	0.001 [1]	-	8.22	0.004
LDL cholesterol, quadratic model	0.427 [1] *	-0.432 [1] *		
Homocysteine §, linear model	-0.022	-	1.23	0.268
Homocysteine §, quadratic model	-0.271	0.252		

§ log-transformed, §§ likelihood ratio test comparing the quadratic to the linear model. Results are expressed as standardized coefficients. Adjustments for age, current smoking, leisure-time physical activity, occupational physical activity and body mass index with a further adjustment on [1] lipid lowering drug treatment; *, $p<0.05$; **, $p<0.001$.

Supplementary table 4: multivariate-adjusted changes in cardiovascular risk marker levels per 5 kg increase in grip strength, women, stratified by tertile of age

	All	P-value	First tertile	P-value	Second tertile	P-value	Third tertile	P-value
Anthropometry								
Body mass index (kg/m^2)	0.00 (-0.22 ; 0.22)	0.985	-0.28 (-0.67 ; 0.10)	0.151	-0.01 (-0.39 ; 0.37)	0.946	0.33 (-0.04 ; 0.71)	0.079
Waist circumference (cm)	-0.82 (-1.13 ; -0.52) [1]	<0.001	-1.00 (-1.49 ; -0.51) [1]	<0.001	-0.68 (-1.17 ; -0.18) [1]	0.008	-1.18 (-1.77 ; -0.59) [1]	<0.001
Fat mass (%)	-0.56 (-0.89 ; -0.22)	0.001	-1.21 (-1.78 ; -0.64)	<0.001	-0.27 (-0.86 ; 0.32)	0.362	-0.43 (-0.99 ; 0.13)	0.132
Blood pressure (mmHg)								
Systolic	0.66 (-0.12 ; 1.43) [2]	0.098	-0.60 (-1.71 ; 0.50) [2]	0.284	1.73 (0.33 ; 3.12) [2]	0.015	0.02 (-1.51 ; 1.56) [2]	0.979
Diastolic	0.15 (-0.31 ; 0.61) [2]	0.522	-0.51 (-1.25 ; 0.22) [2]	0.170	0.91 (0.12 ; 1.71) [2]	0.025	0.52 (-0.32 ; 1.37) [2]	0.222
Lipid markers								
Total cholesterol (mmol/L)	0.00 (-0.04 ; 0.05) [3]	0.863	-0.08 (-0.15 ; -0.01) [3]	0.035	0.07 (-0.01 ; 0.15) [3]	0.067	-0.01 (-0.08 ; 0.07) [3]	0.893
HDL-cholesterol (mmol/L)	0.00 (-0.02 ; 0.02) [3]	0.969	-0.02 (-0.05 ; 0.01) [3]	0.277	0.00 (-0.03 ; 0.04) [3]	0.752	0.01 (-0.02 ; 0.05) [3]	0.475
LDL-cholesterol (mmol/L)	0.00 (-0.04 ; 0.04) [3]	0.961	-0.06 (-0.13 ; 0.01) [3]	0.071	0.05 (-0.02 ; 0.12) [3]	0.147	-0.01 (-0.08 ; 0.07) [3]	0.877
Triglycerides (mmol/L) §	-0.1 (-2.0 ; 1.7) [3]	0.884	-0.6 (-3.6 ; 2.6) [3]	0.719	1.7 (-1.5 ; 5.0) [3]	0.306	-2.4 (-5.6 ; 0.9) [3]	0.154
Apolipoprotein B (mg/dL)	0.35 (-6.21 ; 6.90) [3]	0.918	-4.67 (-15.60 ; 6.27) [3]	0.402	4.23 (-7.94 ; 16.40) [3]	0.495	0.49 (-10.10 ; 11.08) [3]	0.927
Glucometabolic markers								
Fasting glucose (mmol/L)	-0.01 (-0.05 ; 0.04) [4]	0.777	-0.01 (-0.07 ; 0.06) [4]	0.860	0.02 (-0.06 ; 0.11) [4]	0.615	-0.04 (-0.11 ; 0.03) [4]	0.288
Insulin (µU/mL) §	0.4 (-2.0 ; 2.7) [4]	0.764	0.7 (-3.1 ; 4.6) [4]	0.725	0.5 (-3.6 ; 4.7) [4]	0.828	-0.9 (-4.9 ; 3.3) [4]	0.664
Adipokines (µU/mL)								
Leptin §	-1.8 (-4.4 ; 0.9) [5]	0.198	-3.9 (-7.9 ; 0.4) [5]	0.072	-2.4 (-7.0 ; 2.4) [5]	0.314	1.2 (-3.7 ; 6.4) [5]	0.639
Adiponectin §	-1.4 (-4.2 ; 1.5) [5]	0.337	0.1 (-4.4 ; 4.9) [5]	0.963	-3.6 (-8.4 ; 1.5) [5]	0.161	-0.5 (-5.3 ; 4.5) [5]	0.838
Inflammatory markers								
hs-CRP (mg/L) §	-6.8 (-10.7 ; -2.8) [5]	0.001	-7.7 (-13.9 ; -1.0) [5]	0.024	-3.8 (-10.3 ; 3.3) [5]	0.289	-8.5 (-15.3 ; -1.2) [5]	0.024
IL-6 (pg/mL) §	-1.1 (-7.0 ; 5.2) [5]	0.730	3.4 (-7.3 ; 15.3) [5]	0.552	-5.8 (-15.3 ; 4.7) [5]	0.265	-0.6 (-10.7 ; 10.6) [5]	0.909
TNF-α (pg/mL) §	1.2 (-2.6 ; 5.3) [5]	0.534	3.8 (-3.1 ; 11.1) [5]	0.288	1.9 (-4.5 ; 8.7) [5]	0.574	-4.1 (-10.4 ; 2.6) [5]	0.223
Homocysteine (µmol/L) §	-0.6 (-1.8 ; 0.7) [5]	0.359	0.4 (-1.6; 2.5) [5]	0.682	0.3 (-1.7; 2.3) [5]	0.790	-4.4 (-6.6; -2.1) [5]	<0.001
Uric acid (µmol/L)	1.12 (-1.79 ; 4.04) [5]	0.449	-1.28 (-5.87 ; 3.32) [5]	0.586	4.68 (-0.19 ; 9.56) [5]	0.060	-2.6 (-8.13; 2.99) [5]	0.365

hs-CRP, high sensitivity C-reactive protein; IL-6, interleukin 6; TNF-α, tumour necrosis factor alpha. Statistical analyses performed using linear regression. Results are expressed as effect of a 5 kg increase in grip strength and (95% confidence interval). §, on log-transformed data; results are expressed as % change of the risk marker related to a 5 kg increase in grip strength. Multivariate adjustment for age (not for tertiles of age) current smoking, leisure-time physical activity and occupational physical activity, with a further adjustment on [1] weight; [2] body mass index and antihypertensive drug treatment; [3] body mass index and lipid lowering drug treatment; [4] body mass index and antidiabetic drug treatment; [5] body mass index.

Supplementary table 5: multivariate-adjusted changes in cardiovascular risk marker levels per 5 kg increase in grip strength, men, stratified by tertile of age

	All	P-value	First tertile	P-value	Second tertile	P-value	Third tertile	P-value
Anthropometry								
Body mass index (kg/m^2)	0.22 (0.10 ; 0.35)	<0.001	0.22 (0.01 ; 0.43)	0.038	0.30 (0.10 ; 0.51)	0.004	0.12 (-0.12 ; 0.35)	0.328
Waist circumference (cm)	-0.77 (-0.93 ; -0.61) [1]	<0.001	-0.71 (-0.96 ; -0.46) [1]	<0.001	-0.78 (-1.06 ; -0.50) [1]	<0.001	-0.94 (-1.24 ;-0.63) [1]	<0.001
Fat mass (%)	-0.27 (-0.43 ; -0.11)	0.001	-0.17 (-0.45 ; 0.10)	0.215	-0.26 (-0.53 ; 0.02)	0.065	-0.54 (-0.81 ; -0.27)	<0.001
Blood pressure (mmHg)								
Systolic	0.04 (-0.48 ; 0.56) [2]	0.892	0.34 (-0.43 ; 1.11) [2]	0.386	0.21 (-0.67 ; 1.09) [2]	0.642	-1.01 (-2.05 ; 0.03) [2]	0.056
Diastolic	0.29 (-0.05 ; 0.63) [2]	0.090	0.21 (-0.35 ; 0.77) [2]	0.458	0.74 (0.19 ; 1.30) [2]	0.008	0.03 (-0.61 ; 0.66) [2]	0.935
Lipid markers								
Total cholesterol (mmol/L)	0.05 (0.02 ; 0.08) [3]	0.002	0.06 (0.00 ; 0.11) [3]	0.033	0.00 (-0.05 ; 0.05) [3]	0.946	0.11 (0.05 ; 0.17) [3]	<0.001
HDL-cholesterol (mmol/L)	0.01 (0.00 ; 0.02) [3]	0.257	0.00 (-0.01 ; 0.02) [3]	0.630	0.01 (-0.01 ; 0.02) [3]	0.531	0.01 (-0.01 ; 0.03) [3]	0.527
LDL-cholesterol (mmol/L)	0.03 (0.00 ; 0.06) [3]	0.036	0.04 (-0.01 ; 0.08) [3]	0.091	-0.03 (-0.08 ; 0.02) [3]	0.237	0.09 (0.04 ; 0.14) [3]	<0.001
Triglycerides (mmol/L) §	0.8 (-0.8 ; 2.5) [3]	0.312	0.5 (-2.3 ; 3.5) [3]	0.712	1.4 (-1.3 ; 4.2) [3]	0.311	0.6 (-2.1 ; 3.4) [3]	0.656
Apolipoprotein B (mg/dL)	-0.52 (-5.01 ; 3.97) [3]	0.820	-4.33 (-12.63 ; 3.96) [3]	0.305	-2.09 (-8.60 ; 4.37) [3]	0.525	4.67 (-3.72 ; 13.06) [3]	0.275
Glucometabolic markers								
Fasting glucose (mmol/L)	-0.03 (-0.07 ; 0.01) [4]	0.116	0.00 (-0.06 ; 0.05) [4]	0.944	-0.07 (-0.14 ; -0.01) [4]	0.029	-0.02 (-0.10 ; 0.06) [4]	0.621
Insulin (µU/mL) §	-1.1 (-2.7 ; 0.6) [4]	0.201	-3.2 (-6.0 ; -0.3) [4]	0.029	-0.1 (-2.9 ; 2.7) [4]	0.934	-0.3 (-3.2 ; 2.6) [4]	0.814
Adipokines (µU/mL)								
Leptin §	-2.7 (-4.6 ; -0.6) [5]	0.010	-3.9 (-7.3 ; -0.4) [5]	0.031	-0.3 (-3.5 ; 3.0) [5]	0.859	-4.9 (-8.4 ; -1.4) [5]	0.007
Adiponectin §	0.4 (-1.6 ; 2.5) [5]	0.671	-0.2 (-3.5 ; 3.2) [5]	0.904	-1.3 (-4.6 ; 2.1) [5]	0.437	2.1 (-1.5 ; 5.9) [5]	0.252
Inflammatory markers								
hs-CRP (mg/L) §	-3.2 (-6.1 ; -0.2) [5]	0.039	-1.1 (-5.9 ; 3.9) [5]	0.657	-2.1 (-7.0 ; 3.10) [5]	0.416	-8.1 (-13.3 ; -2.6) [5]	0.004
IL-6 (pg/mL) §	-4.1 (-8.2 ; 0.1) [5]	0.055	-2.3 (-9.2 ; 5.1) [5]	0.534	-1.9 (-9.0 ; 5.7) [5]	0.611	-9.0 (-15.5 ; -1.9) [5]	0.013
TNF-α (pg/mL) §	-1.2 (-3.8 ; 1.5) [5]	0.392	-2.2 (-6.2 ; 2.1) [5]	0.308	-0.5 (-4.9 ; 4.0) [5]	0.811	-0.4 (-5.5 ; 4.9) [5]	0.869
Homocysteine (µmol/L) §	0.6 (-0.4 ; 1.6) [5]	0.212	2.1 (0.5 ; 3.7) [5]	0.009	0.3 (-1.4 ; 2.0) [5]	0.741	-1.9 (-3.7 ; 0.0) [5]	0.050
Uric acid (µmol/L)	0.84 (-1.52 ; 3.21) [5]	0.485	1.80 (-1.92 ; 5.52) [5]	0.342	0.34 (-3.84 ; 4.52) [5]	0.873	-0.40 (-4.78 ; 3.98) [5]	0.858

hs-CRP, high sensitivity C-reactive protein; IL-6, interleukin 6; TNF-α, tumour necrosis factor alpha. Statistical analyses performed using linear regression. Results are expressed as effect of a 5 kg increase in grip strength and (95% confidence interval). §, on log-transformed data; results are expressed as % change of the risk marker related to a 5 kg increase in grip strength. Multivariate adjustment for age (not for tertiles of age), current smoking, leisure-time physical activity and occupational physical activity, with a further adjustment on [1] weight; [2] body mass index and antihypertensive drug treatment; [3] body mass index and lipid lowering drug treatment; [4] body mass index and antidiabetic drug treatment; [5] body mass index.

Supplementary table 6: multivariate associations between grip strength and selected cardiovascular risk markers using quadratic model, stratified by tertile of age

	All		First tertile		Second tertile		Third tertile	
	Grip strength	Grip strength^2	Grip strength	Grip strength^2	Grip strength	Grip strength^2	Grip strength	Grip strength^2
Men								
Total cholesterol	0.367 [1] *	-0.288 [1]	0.090 [1]	0.010 [1]	0.483 [1]	-0.497 [1]	0.456 [1]	-0.315 [1]
LDL cholesterol	0.345 [1] *	-0.293 [1]	0.046 [1]	0.034 [1]	0.551 [1]	-0.622 [1] *	0.304 [1]	-0.160 [1]
Homocysteine §	-0.488 *	0.526 *	-0.228	0.350	-0.305	0.341	-0.745 *	0.712 *
Women								
Total cholesterol	0.432 [1] *	-0.434 [1] *	0.694 [1] *	-0.773 [1] *	0.023 [1]	0.059 [1]	0.302 [1]	-0.314 [1]
LDL cholesterol	0.427 [1] *	-0.432 [1] *	0.662 [1] *	-0.729 [1] *	0.065 [1]	-0.004 [1]	0.294 [1]	-0.304 [1]
Homocysteine §	-0.271	0.252	0.050	-0.016	-0.033	0.056	-0.619 *	0.501

§ log-transformed. Statistical analyses performed using quadratic regression model. Results are expressed as standardized coefficients. Adjustments for age, current smoking, leisure-time physical activity, occupational physical activity and body mass index with a further adjustment on [1] lipid lowering drug treatment; *, $p<0.05$; **, $p<0.001$.