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NO ASSOCIATION BETWEEN GRIP STRENGTH AND CARDIOVASCULAR RISK; THE COLAUS POPULATION-BASED STUDY

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ABSTRACT

Background: Decreased grip strength (GS) is predictive of cardiovascular (CV) disease but whether it improves CV risk prediction has not been evaluated. We assessed the predictive value of low GS on incident CV events and overall mortality taking into account CV risk equations in a population-based study from Switzerland.

Methods: 2707 adults (54.8% women, age range 50-75 years) were followed for a median time of 5.4 years. GS was assessed using a hydraulic hand dynamometer. CV absolute risk at baseline was assessed using recalibrated SCORE, Framingham and PROCAM risk equations. Incident CV events were adjudicated by an independent committee.

Results: 160 deaths and 188 incident CV events occurred during follow-up. On bivariate analysis, low GS was associated with increased incident CV events: Hazard Ratio (HR) and (95% confidence interval) 1.76 (1.13-2.76), $p<0.01$ but not with overall mortality: HR=1.51 (0.94-2.45), p=0.09. The association between low GS and incident CV events disappeared after adjusting for baseline CV risk: HR=1.23 (0.79-1.94), p=0.36; 1.34 (0.86-2.10), p=0.20 and 1.47 (0.94-2.31), p=0.09 after adjusting for SCORE, Framingham and PROCAM scores, respectively.

Conclusion: Low GS is not predictive of incident CV events when taking into account CV absolute risk.

Abstract word count: 192

Keywords: grip strength; CV events incidence; cardiovascular risk assessment; Switzerland; population-based study; adult.

INTRODUCTION

Grip strength (GS) has been shown to be inversely associated with risk of incident cardiovascular (CV) events (1, 2) and overall mortality (1, 3). The effect of low GS on CV events might be partly mediated by changes in CV risk factors (4); thus, the analysis of the effect of low GS on CV events and overall mortality should take into account basal CV risk. Basal CV risk can be estimated using equations such as SCORE (5), Framingham (6) and PROCAM (7). Although the associations of GS with incident CV events (1, 2) and overall mortality (1, 3, 8) have been assessed in several longitudinal studies, they were only partially adjusted on CV risk factors. Finally, whether low GS improves the predictive value of the existing CV risk equations remains to be assessed.

Thus, the aim of this study was to assess the predictive value of low GS on CV events incidence and overall mortality, taking into account absolute CV risk at baseline as assessed by SCORE, Framingham or PROCAM equations, in a well-characterised population-based sample from the city of Lausanne, Switzerland (CoLaus study).

MATERIALS AND METHODS

Recruitment

The detailed description of the recruitment of the CoLaus study has been published previously (9). Briefly, the CoLaus study is a population-based cohort exploring the biological, genetic and environment determinants of CV diseases. A non-stratified, representative sample of the population of Lausanne (Switzerland) was recruited between 2003 and 2006 based on the following inclusion criteria: a) age 35-75 years and b) willingness to participate. Participants

aged over 50 years (3704 of the 6733 initially recruited, 55%) were invited to participate in a sub-study on frailty, which included GS assessment.

Grip strength

GS 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 (10): subject seated, shoulders adducted and neutrally rotated, elbow flexed at 90°, forearm in neutral position and wrist between 0 and 30° of dorsiflexion. Three measurements were performed consecutively with the right hand. Coefficient of variation between measurements was 5.3%. The highest value (expressed in kg) was included in the analyses. Participants were also asked about their handedness. Grip strength was categorized as low or normal according to Fried criterion (11) that takes into account gender and body mass index.

Clinical data

Socio-demographic data such as education level, job position and social help, together with tobacco, leisure-time and occupational physical activity data were collected by questionnaire. Leisure-time physical activity was categorized as <2 or ≥2 periods of ≥20 minutes per week. Occupational activity was categorized as non-physical (when sitting or standing) and physical (carrying light or heavy load). Personal and family history of CV disease was elicited with a standardized interview questionnaire filled in by a trained recruiter. Participants also indicated if they were treated for hypertension, dyslipidemia or diabetes.

Body weight and height were measured to the nearest 0.1 kg and 5 mm, respectively, using a Seca® scale and height gauge (Hamburg, Germany), with participants in light indoor

clothes standing without shoes. Waist and hip circumferences were measured as recommended (12) at mid-way between the lowest rib and the iliac crest, and at the greater trochanters, respectively. Blood pressure (BP) was measured using an Omron® HEM-907 automated oscillometric sphygmomanometer (13) 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.

Biological data

A fasting venous blood sample was drawn and measurements performed by the clinical laboratory of the Lausanne university hospital. CV risk factors included glucose, total and HDL-cholesterol, triglycerides; LDL-cholesterol was calculated using the Friedewald formula if triglycerides were <4.6 mmol/L. Diabetes was defined by a fasting glucose ≥7.0 and/or presence of antidiabetic drug treatment. Dyslipidemia was defined either by the presence of a hypolipidemic drug or using the LDL-cholesterol thresholds according to the PROCAM CV score (7) adapted for Switzerland (14).

Cardiovascular risk assessment

CV risk was calculated using internationally used risk equations. As there is no consensus regarding which risk equation to use in Switzerland (15), we opted for the three most used equations: the European Society of Cardiology SCORE (5), Framingham-2001 (6) and PROCAM-2007 (7). Framingham-2001 and SCORE have been recalibrated (16, 17) and validated on the Swiss population (17, 18). The SCORE, Framingham 2001 and PROCAM 2007 risk equations use

age, gender, parental history, smoking, blood pressure, lipids and diabetes data to compute the 10-year absolute risk of CV death, coronary heart disease (CHD) and CV events, respectively. Participants were categorized as low, medium, high or very high CV risk according to cutoffs shown in **Supplementary Table 1**. Participants with previous history of CV disease were considered at very high CV risk.

Outcomes

Outcomes of interest were CV events and overall deaths. CV events included cerebrovascular events (CBV) and CHD. CBV events were defined as transient ischemic attack, ischemic or hemorrhagic stroke, *amaurosis fugax* and transient global amnesia. CHD events were defined as myocardial infarction, stable or unstable angina, coronary revascularization or bypass grafting. Outcomes were first verified and medically documented by a trained investigator, and further validated using pre-defined criteria by an independent adjudication committee composed of internists, cardiologists and a neurologist.

Exclusion criteria

Participants were excluded if they presented a questionable GS or if no follow-up data were available. Questionable GS values were considered if the participant reported any condition precluding adequate measurement (i.e. pain, injury, recent surgery, osteoarthritis and rheumatoid arthritis, among others), irrespectively of the observed value.

Statistical analysis

Statistical analyses were conducted using Stata version 14.0 for windows (Stata Corp, College Station, Texas, USA). Descriptive analyses were expressed as number of participants

(percentage) for categorical variables or as average ± standard deviation for continuous variables. Between-group comparisons were performed using chi-square and Student t-test for categorical and continuous variables, respectively.

The effect of low GS on incident CV events and overall mortality was assessed using Cox proportional hazards models and results were expressed as hazard ratio (HR) and 95% confidence interval (95%CI). Bivariate and multivariate analyses were performed, and the following multivariate models were used: 1) adjusted on age and gender; ; 2) age, gender, education level, job position and social help; 3) age, gender, education level, job position, social help, waist-to-hip ratio and height; 4) adjusted on absolute CV risk according to SCORE; 5) adjusted on absolute CV risk according to Framingham 2001, and 6) adjusted on absolute CV risk according to PROCAM 2007. Adjustments on CV risk factors' treatment were also performed. To take into account the decline in muscular performance occurring with age, sensitivity analyses were performed by further stratifying on tertiles of age. Statistical significance was assessed for a two-sided test with $p<0.05$.

Power analysis was conducted using the **power cox** function of Stata. The following parameters were calculated: 1) power to consider the observed HR as statistically significant at $p=0.05$; 2) the minimum sample size to consider the observed HR as statistically significant at a power of 0.80 and $p=0.05$, and 3) the minimum detectable HR taking into account a sample size of 2707, 160 deaths and 188 incident CV events, a power of 0.80 and $p=0.05$. Power analyses were not performed if the observed HR was less than 1.

Ethical statement

The institutional Ethics Committee of the University of Lausanne (19) approved the baseline CoLaus study (protocol reference 16/03, decisions of 13th January and 10th February 2003) and the approval was renewed for its follow-up (protocol reference 33/09, decision of 23rd February 2009). All participants gave their signed informed consent before entering the study.

RESULTS

Characteristics of included and excluded participants

The selection procedure is indicated in **Figure 1.** Of the initial 3704 participants aged 50 and over, 2707 (73.1%) were retained for analysis. The characteristics of the included and excluded participants are summarized in **Supplementary Table 2**. Included participants were more likely right-handed and to perform leisure-time physical activity, more educated, had a higher job position and were less prone to smoke, to receive social help, to present with hypertension or dyslipidemia than excluded ones. No association was found in absolute CV risk using SCORE and Framingham risk equations, whereas excluded participants had slightly higher CV risk according to the PROCAM risk equation.

Participants' characteristics overall and according to GS category are summarized in **Table 1**. Participants with a low GS were older, less likely to have a high education level, working or performing leisure-time physical activity. Participants with a low GS were also more likely to receive social help and had a higher baseline absolute CV risk. GS values according to gender are represented in **Supplementary Figure 1**. Mean±standard deviation GS were 26.1±5.3 kg for women and 42.7±8.4 kg for men.

Association of grip strength with outcomes

During a median follow-up time of 5.4 years, there were 160 deaths and 188 incident CV events. Survival curves for all causes and CV events according to GS category are shown in **Supplementary Figure 2**. Five-year overall survival was 96.9% (95% confidence interval: 96.1-97.5) and 93.5% (88.9-96.3) for normal and low GS (P value: 0.09), respectively. Five-year CV events-free survival was 95.5% (94.6-96.3) and 89.0% (83.4-92.7) for normal and low GS (P value: 0.01), respectively.

The unadjusted and multivariate-adjusted associations between low GS and overall mortality or incident CV events are described in **Table 2**. Unadjusted analyses showed that low GS was associated with a higher incidence of CV events, while no association was found with overall mortality. The association between low GS and incident CV events was no longer significant after multivariate adjustment (**Table 2**). Results did not change after adjustment on CV risk factors' treatment (**Supplementary Table 3**) or after stratification by tertiles of age (**Supplementary Tables 4** and **5**).

DISCUSSION

This study assessed the impact of low GS on overall mortality and incident CV events in a prospective, population-based sample with a median 5.4-year follow-up time. Our results suggest that the association between low GS and incident CV events is no longer significant after adjusting for baseline absolute CV risk. Thus, GS measurement does not seem to be useful in assessing CV risk beyond traditional CV risk estimation equations.

Grip strength and incident cardiovascular events

Low GS was significantly associated with an increase in incident CV events on bivariate analysis, but this association disappeared after multivariate adjustment. These findings are in agreement with the study by Fujita et al. from Japan (20). However our results differ from those of the PURE study (1). It has to be mentioned that in the latter study, GS was reported as 5-kg decrease and not dichotomized in low and normal, and furthermore CV risk factors were self-reported. Discrepancies could therefore possibility result from those methodological aspects. Other longer follow-up studies (2, 3, 21, 22) also showed an inverse association between different markers of GS (i.e. standard deviation, deciles or tertiles) and incident CV events, after adjustment on a small number of CV risk factors. Thus, several studies have shown an inverse association between GS and incident CV events, but the results are difficult to apply in a clinical setting as different metrics for GS have been used and no threshold below which the CV risk can be considered as increased was suggested. Similarly, although several studies (1, 22) adjusted the results for gender, this adjustment might not have cancelled out the considerable difference in GS levels between genders. In this study, we assessed whether a common definition of low GS was associated with incident CV events. Our results suggest that the effect of low GS on incident CV events is mediated by CV risk factors, as the association disappears after adjusting for absolute CV risk. Still, it would be of interest to replicate our study in other population-based samples, in order to confirm or infirm if a low GS is associated with incident CV events independently of the other CV risk factors.

Grip strength and overall mortality

Low GS was associated with overall mortality neither on bivariate, nor on multivariate analysis. These findings are partially in agreement with two studies (20, 22) showing similar results for women though not for men but it has been contradicted by other studies (1, 3, 8, 21) showing that different markers of GS were negatively associated with overall mortality. A possible explanation might be the relatively short follow-up time in our sample, or the fact that we adjusted for absolute CV risk while the other studies only adjusted on self-reported (1) or on a limited number of CV risk factors (3, 8, 21). Overall, our results suggest that low GS has no impact on overall mortality when absolute CV risk is taken into account.

Study limitations

This study has several limitations worth acknowledging. Firstly, GS was assessed on the right hand whereas approximately 7% of our participants were left-handed. Although the use of the non-dominant hand might lead to lower GS values, most studies reported no difference (23-25), while some reported slightly higher values for the dominant compared to the non-dominant hand (26, 27). Thus, GS measurement at the right hand irrespective of handedness will have a limited impact on the observed values. Secondly, the exclusion of questionable GS was based on self-reported information given by the participant (i.e. condition that may preclude adequate measurement), and did not rely on objective criteria. However, including all GS measurements led to similar conclusions for overall mortality and partially for incident CV events, for which small significant positive associations ($p<0.05$) were found after adjustment for Framingham or PROCAM risk equations (see **Supplementary Table 6**). Still, the p-values would not resist Bonferroni correction, and the PROCAM risk equation hasn't been validated for

the Swiss population. Thirdly, some events such as *amaurosis fugax* (AF) and transient global amnesia (TGA) might be wrongly reported as CV. Still, in this study, AF (N=1) and TGA (N=4) represented only 2.7% of CV events, so that the impact of a possible ascertainment bias is low. Further, excluding AF and TGA events led to similar conclusions (see **Supplementary Table 7**). Fourthly, our sample size and follow-up time period are relatively small for our low-risk population. However, on the whole sample, power calculations showed that the overall power to consider the bivariate and multivariate-adjusted HR as significant was higher than 70% in most cases (**Table 3**). The ongoing follow-up of the CoLaus study will enable assessing the 10-year outcomes of the participants. Fifthly, one-fifth of the participants did not participate to follow-up, but this participation rate is comparable to the literature (5), and loss to follow-up has only limited impact on relative risks for exposure-risk associations (28). Sixthly, our data have been collected between 2003 and 2012, whereas some previous findings' data were collected before 2000 (2, 22, 29). At this time, the incidence of fatal CV events was higher (30), which might have allowed to demonstrate the association between GS and incident CV events. Finally, only participants aged between 50 and 75 were included, so our findings cannot be extrapolated to other ages.

Conclusion

In a prospective, population-based sample aged 50 to 75 years, low GS was associated neither with overall mortality nor with incident CV events when adjusting for absolute CV risk.

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AUTHORS' CONTRIBUTIONS

CG made most 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 for important intellectual content.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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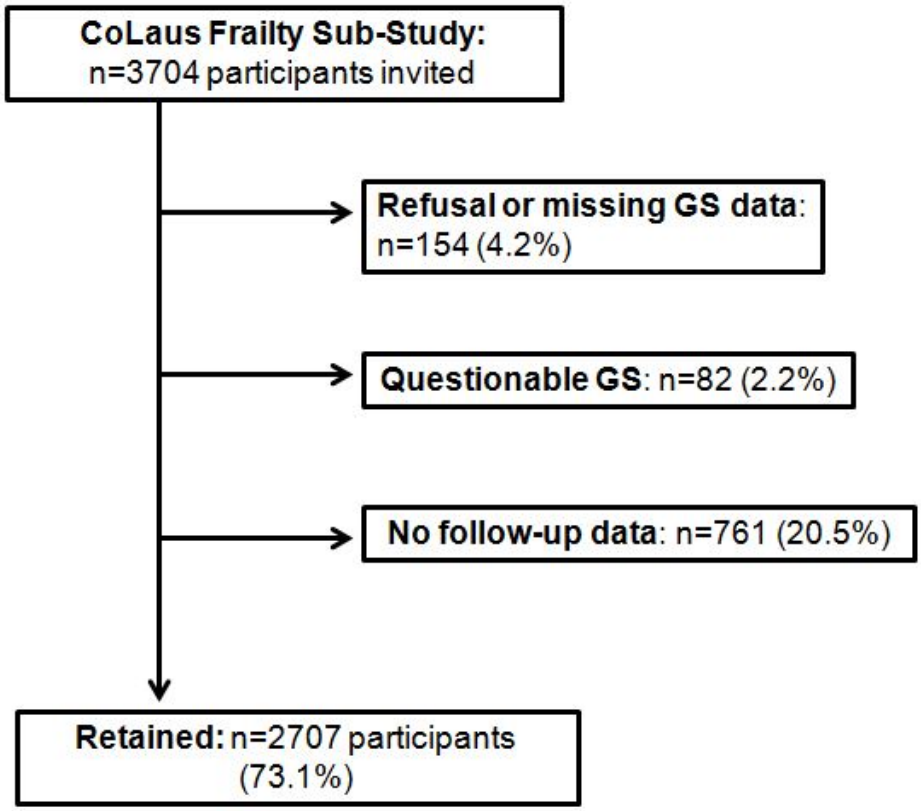
Figure 1: Selection procedure. CoLaus Study, Lausanne, Switzerland, 2003-2012.



GS: grip strength. Percentages were calculated using the baseline sample size as denominator.

Table 1: Characteristics of participants, overall and by grip strength categories. CoLaus Study, Lausanne, Switzerland, 2003-2012.

	All	Normal	Low	P value
N	2707	2521	186	
Right-handedness (%)	92.0	91.9	93.2	0.52
Grip strength (kg)	33.6 ± 10.7	34.5 ± 10.5	21.7 ± 6.5	<0.01
Age (years)	60.7 ± 6.8	60.4 ± 6.7	64.5 ± 7.0	<0.01
Female (%)	54.8	55.0	51.6	0.37
Smoking (%)				0.42
Current	22.9	23.2	19.4	
Never	39.1	38.8	42.5	
Former	38.0	38.0	38.2	
Physical job (%)	15.2	15.2	14.1	0.67
Weekly leisure-time physical activity				<0.01
<2 periods of 20+ minutes	42.2	41.4	53.2	
≥2 periods of 20+ minutes	57.8	58.6	46.8	
Living alone (%)	35.1	34.9	38.2	0.37
Education level (%)				<0.01
Low	58.5	57.7	69.4	
Middle	24.5	24.9	19.4	
High	17.0	17.4	11.3	
Job position (%)				<0.01
Low	12.7	12.4	16.7	
Middle	33.8	35.1	15.1	
High	10.7	11.2	4.8	
Not working	42.9	41.3	63.4	
Receiving social help (%)	30.0	28.1	55.4	<0.01
Risk categories (SCORE) (%)				<0.01
Low	41.3	42.6	24.3	
Medium	14.3	14.4	12.4	
High	16.7	17.1	11.9	
Very high	27.7	25.9	51.4	
Risk categories (Framingham) (%)				<0.01
Low	75.8	76.8	61.8	
Medium	10.1	10.0	11.3	
High	3.7	3.6	5.9	
Very high	10.4	9.6	21.0	
Risk categories (PROCAM) (%)				<0.01
Low	55.7	56.7	43.3	
Medium	20.4	20.1	23.3	
High	10.5	10.7	7.8	
Very high	13.5	12.6	25.6	

Results are expressed as mean ± standard deviation or as percentage. Statistical analyses by chi-square or Student's t-tests comparing normal and low grip strength categories.

Table 2: Association between low grip strength, overall mortality and incident cardiovascular events, unadjusted and multivariate-adjusted. CoLaus Study, Lausanne, Switzerland, 2003-2012.

	Overall mortality			Incident cardiovascular events		
	HR	**[95% CI]**	**P value**	**HR**	**[95% CI]**	**P value**
Unadjusted	1.51	0.94-2.45	0.09	1.76	1.13-2.76	0.01
Model 1	1.15	0.71-1.88	0.57	1.22	0.78-1.93	0.39
Model 2	1.08	0.66-1.77	0.75	1.07	0.68-1.70	0.76
Model 3	0.98	0.59-1.63	0.95	0.96	0.60-1.55	0.87
Model 4	1.13	0.69-1.85	0.62	1.23	0.79-1.94	0.36
Model 5	1.40	0.86-2.27	0.17	1.34	0.86-2.10	0.20
Model 6	1.40	0.86-2.27	0.18	1.47	0.94-2.31	0.09

Results are expressed as Hazard Ratio (HR) and 95% confidence interval (CI) for low grip strength using normal grip strength as the reference. Statistical analyses performed by Cox proportional hazard model, unadjusted and adjusted for: 1) age and gender; 2) age, gender, education level, job position and social help; 3) age, gender, education level, job position, social help, waist-to-hip ratio and height; 4) absolute CV risk according to SCORE risk equation; 5) absolute CV risk according to Framingham 2001 risk equation, and 6) absolute CV risk according to PROCAM 2007 risk equation.

Table 3: power analyses for the results indicated in table 2. CoLaus Study, Lausanne, Switzerland, 2003-2012.

	Overall mortality			Incident cardiovascular events		
	Power	**MSS**	**MDHR**	**Power**	**MSS**	**MDHR**
Unadjusted	0.899	5,722	1.82	0.966	2,225	1.67
Model 1	0.719	80,981	2.15	0.756	36,694	2.08
Model 2	0.657	308,097	2.27	0.659	397,587	2.27
Model 4	0.689	113,599	2.21	0.756	33,857	2.08
Model 5	0.866	9,593	1.88	0.836	13,820	1.94
Model 6	0.866	9,593	1.88	0.896	6,630	1.83

Results are expressed as power to consider the observed HR>1 as statistically significant at p=0.05; the minimum sample size (MSS) to consider the observed HR>1 as statistically significant at a power of 0.80 and p=0.05, and the minimum detectable HR (MDHR) taking into account a sample size of 2707, 160 deaths and 188 incident CV events, a power of 0.80 and p=0.05. Calculations using the **power cox** function of Stata. Power analyses were not performed for model 3 as the observed HR were less than 1.

Supplementary information

Supplementary table 1: 10-year absolute CV risk categorization for SCORE, Framingham and PROCAM cardiovascular risk equations. CoLaus Study, Lausanne, Switzerland, 2003-2012.

Risk categories	**SCORE**	**Framingham**	**PROCAM**
Low (%)	[0, 1.5[	[0, 5[	[0, 5[
Medium (%)	[1.5, 2.5[	[5, 10[	[5, 10[
High (%)	[2.5, 5.0[	[10, 20[	[10, 20[
Very high (%)	[5.0 +	[20 +	[20 +

Supplementary table 2: Socio-demographic and clinical characteristics of included and excluded participants. CoLaus Study, Lausanne, Switzerland, 2003-2012.

	Included	Excluded	P value
N	2707	843	
Right-handedness (%)	92.0	89.3	0.02
Grip strength (kg)	33.6 ± 10.7	32.7 ± 11.2	0.03
Age (years)	60.7 ± 6.8	61.0 ± 6.9	0.30
Female (%)	54.8	54.6	0.91
Smoking status (%)			<0.01
Current	22.9	24.0	
Never	39.1	44.1	
Former	38.0	31.9	
Physical job (%)	15.2	17.9	0.06
Weekly leisure-time physical activity			<0.01
<2 periods of 20+ minutes	42.2	48.8	
≥2 periods of 20+ minutes	57.8	51.3	
Living alone (%)	35.1	35.9	0.69
Education level (%)			<0.01
Low	58.5	68.1	
Middle	24.5	18.3	
High	17.0	13.6	
Job position (%)			<0.01
Low	12.7	19.9	
Middle	33.8	27.9	
High	10.7	6.8	
Not working	42.9	45.4	
Receive social help (%)	30.0	36.3	<0.01
Hypertension (%)	47.9	57.4	<0.01
Dyslipidemia (%)	38.7	45.2	<0.01
Diabetes (%)	9.6	10.6	0.42
Risk categories (SCORE)			0.19
Low	41.3	37.3	
Medium	14.3	14.4	
High	16.7	17.9	
Very high	27.7	30.4	
Risk categories (Framingham)			0.27
Low	75.8	73.4	
Medium	10.1	12.5	
High	3.7	3.6	
Very high	10.4	10.6	
Risk categories (PROCAM)			0.01
Low	55.7	49.6	
Medium	20.4	21.8	
High	10.5	13.4	
Very high	13.5	15.2	

Results are expressed as mean ± standard deviation or as percentage. Statistical analyses by chi-square or Student t-test.

Supplementary Table 3: Association between low grip strength, overall mortality and incident cardiovascular events, unadjusted and adjusted for cardiovascular absolute risk and cardiovascular risk factors' treatment. CoLaus Study, Lausanne, Switzerland, 2003-2012.

	Overall mortality			Incident cardiovascular events		
	HR	**[95% CI]**	**P value**	**HR**	**[95% CI]**	**P value**
Unadjusted	1.51	0.94-2.45	0.09	1.76	1.13-2.76	0.01
Model A	0.99	0.60-1.64	0.97	1.12	0.71-1.77	0.62
Model B	1.13	0.68-1.87	0.65	1.21	0.76-1.91	0.42
Model C	1.12	0.67-1.87	0.66	1.37	0.86-2.17	0.18

Results are expressed as Hazard Ratio (HR) and 95% confidence interval (CI) for low grip strength using normal grip strength as the reference. Statistical analyses performed by Cox proportional hazard model, unadjusted and adjusted for treatment for hypertension, dyslipidemia and diabetes, with a further adjustment on: A) absolute CV risk according to SCORE risk equation; B) absolute CV risk according to Framingham 2001 risk equation, and C) absolute CV risk according to PROCAM 2007 risk equation.

Supplementary Table 4: Association between low grip strength and overall mortality, unadjusted and multivariate-adjusted, stratified by tertiles of age. CoLaus Study, Lausanne, Switzerland, 2003-2012.

	1st tertile			2nd tertile			3rd tertile		
	HR	**[95% CI]**	**P value**	**HR**	**[95% CI]**	**P value**	**HR**	**[95% CI]**	**P value**
Unadjusted	1.14	0.15-8.43	0.897	0.80	0.19-3.34	0.762	1.32	0.77-2.28	0.316
Model 1	1.18	0.16-8.77	0.870	0.85	0.20-3.57	0.826	1.20	0.70-2.07	0.508
Model 2	0.81	0.10-6.32	0.842	0.42	0.09-1.88	0.256	1.24	0.72-2.16	0.442
Model 3	0.63	0.08-5.01	0.661	0.43	0.09-2.06	0.289	1.05	0.59-1.89	0.866
Model 4	1.16	0.16-8.59	0.883	0.57	0.13-2.48	0.455	1.23	0.71-2.13	0.458
Model 5	1.07	0.14-7.98	0.946	0.61	0.14-2.66	0.508	1.34	0.77-2.30	0.293
Model 6	1.48	0.20-11.1	0.703	0.57	0.13-2.49	0.458	1.42	0.82-2.46	0.207

Results are expressed as Hazard Ratio (HR) and 95% confidence interval (CI) for low grip strength using normal grip strength as the reference. Statistical analyses performed by Cox proportional hazard model, unadjusted and adjusted for: 1) age and gender; 2) age, gender, education level, job position and social help; 3) age, gender, education level, job position, social help, waist-to-hip ratio and height; 4) absolute CV risk according to SCORE risk equation; 5) absolute CV risk according to Framingham 2001 risk equation, and 6) absolute CV risk according to PROCAM 2007 risk equation.

Supplementary Table 5: Association between low grip strength and cardiovascular event incidence, unadjusted and multivariate-adjusted, stratified by tertiles of age. CoLaus Study, Lausanne, Switzerland, 2003-2012.

	1st tertile			2nd tertile			3rd tertile		
	HR	**[95% CI]**	**P value**	**HR**	**[95% CI]**	**P value**	**HR**	**[95% CI]**	**P value**
Unadjusted	1.00	0.14-7.41	0.993	1.35	0.49-3.75	0.562	1.41	0.84-2.38	0.195
Model 1	1.09	0.15-8.03	0.934	1.49	0.54-4.15	0.444	1.21	0.71-2.04	0.483
Model 2	0.65	0.09-5.02	0.683	0.95	0.34-2.70	0.927	1.14	0.67-1.94	0.628
Model 3	0.51	0.06-4.02	0.523	0.95	0.33-2.77	0.924	0.99	0.57-1.73	0.971
Model 4	1.05	0.14-7.74	0.964	1.06	0.38-2.98	0.906	1.30	0.77-2.19	0.332
Model 5	0.94	0.13-7.02	0.950	1.15	0.41-3.23	0.795	1.21	0.72-2.04	0.473
Model 6	1.09	0.15-8.10	0.930	1.23	0.44-3.45	0.695	1.40	0.83-2.37	0.208

Results are expressed as Hazard Ratio (HR) and 95% confidence interval (CI) for low grip strength using normal grip strength as the reference. Statistical analyses performed by Cox proportional hazard model, unadjusted and adjusted for: 1) age and gender; 2) age, gender, education level, job position and social help; 3) age, gender, education level, job position, social help, waist-to-hip ratio and height; 4) absolute CV risk according to SCORE risk equation; 5) absolute CV risk according to Framingham 2001 risk equation, and 6) absolute CV risk according to PROCAM 2007 risk equation.

Supplementary table 6: Association between low grip strength, overall mortality and incident cardiovascular events, unadjusted and multivariate-adjusted, including questionable grip strength measurements. CoLaus Study, Lausanne, Switzerland, 2003-2012.

	Overall mortality			Incident cardiovascular events		
	HR	**[95% CI]**	**P value**	**HR**	**[95% CI]**	**P value**
Unadjusted	1.46	0.92-2.32	0.11	1.95	1.30-2.93	<0.01
Model 1	1.13	0.70-1.80	0.62	1.37	0.90-2.07	0.14
Model 2	1.00	0.62-1.62	1.00	1.20	0.79-1.83	0.39
Model 3	0.91	0.55-1.49	0.70	1.11	0.72-1.71	0.65
Model 4	1.08	0.67-1.73	0.76	1.35	0.90-2.04	0.15
Model 5	1.37	0.86-2.18	0.18	1.53	1.01-2.30	0.04
Model 6	1.32	0.82-2.11	0.25	1.65	1.09-2.48	0.02

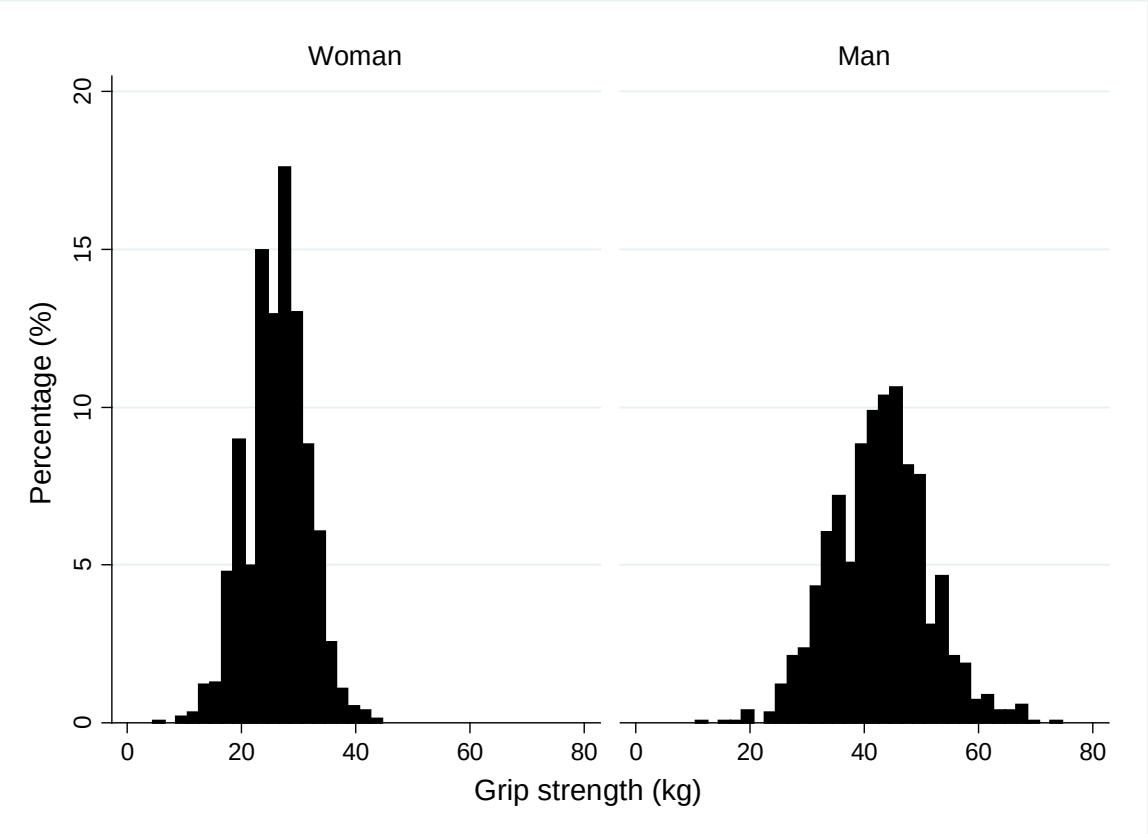
Results are expressed as Hazard Ratio (HR) and 95% confidence interval (CI) for low grip strength using normal grip strength as the reference. Statistical analyses performed by Cox proportional hazard model, unadjusted and adjusted for: 1) age and gender; 2) age, gender, education level, job position and social help; 3) age, gender, education level, job position, social help, waist-to-hip ratio and height; 4) absolute CV risk according to SCORE risk equation; 5) absolute CV risk according to Framingham 2001 risk equation, and 6) absolute CV risk according to PROCAM 2007 risk equation.

Supplementary Table 7: Association between low grip strength and cardiovascular event incidence, unadjusted and multivariate-adjusted, after exclusion of a*maurosis fugax* and transient global amnesia events. CoLaus Study, Lausanne, Switzerland, 2003-2012.

	Incident cardiovascular events		
	HR	**[95% CI]**	**P value**
Unadjusted	1.72	1.09-2.72	0.02
Model 1	1.19	0.75-1.89	0.46
Model 2	1.03	0.65-1.65	0.90
Model 3	0.93	0.57-1.51	0.77
Model 4	1.21	0.76-1.91	0.43
Model 5	1.30	0.82-2.06	0.26
Model 6	1.43	0.90-2.26	0.13

Results are expressed as Hazard Ratio (HR) and 95% confidence interval (CI) for low grip strength using normal grip strength as the reference. Statistical analyses performed by Cox proportional hazard model, unadjusted and adjusted for: 1) age and gender; 2) age, gender, education level, job position and social help; 3) age, gender, education level, job position, social help, waist-to-hip ratio and height; 4) absolute CV risk according to SCORE risk equation; 5) absolute CV risk according to Framingham 2001 risk equation, and 6) absolute CV risk according to PROCAM 2007 risk equation.

Supplementary figure 1: Distribution of grip strength according to gender. CoLaus Study, Lausanne, Switzerland, 2003-2012.



Supplementary figure 2: Survival and incidence graphs for overall mortality and cardiovascular events. CoLaus Study, Lausanne, Switzerland, 2003-2012.