Grip strength and walking pace and CVD risk prediction in 406,834 UK Biobank participants

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ABSTRACT

Objective

To investigate whether the addition of grip strength and/or self-reported walking pace to established CVD risk scores improves their predictive abilities.

Patients and Methods

A total of 406,834 participants from UK Biobank, with baseline measurements between March 13, 2006, and October 1, 2010, without CVD at baseline were included in this study. Associations of grip strength and walking pace with CVD outcomes were investigated using Cox models adjusting for classical risk factors (as included in established risk scores), and predictive utility was determined by changes in C-index and categorical net reclassification index (NRI).

Results

Over a median of 8.87 years of follow-up (Q1-Q3 8.25-9.47) there were 7,274 composite fatal/nonfatal events (based on the ACC/AHA outcome) and 1,955 fatal events (based on SCORE). Both grip strength and walking pace were inversely associated with CVD outcomes, after adjusting for classical risk factors. Addition of grip strength (change in C-index AHA/ACC +0.0017 SCORE +0.0047), usual walking pace (AHA/ACC +0.0031 SCORE +0.0130) and both (AHA/ACC +0.0041 SCORE +0.0148) improved the C-index and also improved the NRI (grip +0.55%, walking pace +0.53% and combined 1.12%).

Conclusion

The current study has shown that the addition of grip strength or usual walking pace to existing risk scores results in improved CVD risk prediction, with an additive effect when both are added. As both these measures are cheap and easy to administer, these tools could provide an important addition to CVD risk screening, although further external validation is required.

List of Abbreviations

SD = Standard deviation

CI = Confidence interval

CVD = Cardiovascular disease

UK = United Kingdom

TC = Total cholesterol

Q = Quartile

HR = Hazard ratio

NRI = Net reclassification index

HDL = High density lipoprotein

HbA1c = Glycated haemoglobin

AHA = American heart association

ACC = American college of cardiology

SCORE = Systematic Coronary Risk Evaluation

BMI = Body mass index

DBP = Diastolic blood pressure

SBP = Systolic blood pressure

ICD = International classification of disease

Background

There is strong evidence that better physical capabilities, such as walking pace and grip strength, are associated with improved health outcomes. For example, in 2010, a systematic review demonstrated that poorer grip strength, walking speed, chair rise time and standing balance time were associated with an increase in all-cause mortality risk [1]. This has been supported in more recent studies where both grip strength and walking pace have been shown to be associated with several health outcomes beyond all-cause mortality [2–6].

Indeed, it has been shown, in a study of 800 people, that higher grip strength is associated with a lower risk of CVD mortality [7], with similar findings reported in larger studies. For example, in a study of 1.1 million men (aged 16-19 years) high muscular strength was associated with 35% lower CVD mortality, [8] with similar findings in the PURE [9] and Tromsø [10] studies, and analyses of the UK Biobank data where a lower risk of incident CVD, including heart failure, outcomes was also observed [2,11,12]. Similarly, self-reported walking pace has been shown to be strongly associated with CVD mortality. For example, our recent work showing that brisk-pace walkers have a lower risk of CVD mortality and incidence, compared to slow-pace walkers [3]. This is further supported by pooled analysis of the Scottish and English Health Surveys which found that walking at brisk, relative to slow pace, is associated with a lower risk of CVD mortality [13].

Extending these findings, the addition of handgrip strength to an office-based risk score (age, sex, diabetes diagnosed, BMI, systolic BP and smoking but without lipids) improved prediction of cardiovascular mortality; with a change in the C-index of 0.012 [2]. Similarly, self-reported walking pace has been shown to be a strong predictor of mortality in both men (C-index 0·72 [95% CI 0·71–0·73]) and women (0·69 [0·68–0·70); stronger than smoking habits and other

lifestyle measurements [11] . The effect of adding walking pace to an office-based risk score, to our knowledge, remains unexplored. Furthermore, whether grip strength and/or walking pace improve established and widely used CVD risk scores, which also include blood lipids, such as the AHA/ACC [14] and SCORE [15,16] remains to be established.

The aim of this study, therefore, was to investigate whether the addition of grip strength and/or self-reported walking pace to established CVD risk scores improves their predictive abilities.

Methods

Data Source

UK Biobank recruited 502,636 participants (aged 37 to 73 years) from 22 assessment centres across the UK between April 2007 and December 2010. A range of baseline biological measurements were recorded and touch-screen questionnaires were self-completed, as described elsewhere [17,18]. UK Biobank received ethical approval from the North West Multi-Centre Research Ethics Committee (REC reference: 11/NW/03820). All participants gave written, informed consent before enrolment in the study, which was conducted in accord with the principles of the Declaration of Helsinki. Date and cause of hospital admission were ascertained via record linkage to Health Episode Statistics records for participants in England and Wales, and date and cause of death were obtained from death certificates held by the National Health Service (NHS) Information Centre for participants from England and Wales and the NHS Central Register Scotland for participants from Scotland.

Covariates

The covariates included in the study models conformed to those used in the published AHA/ACC and SCORE CVD risk scores [16,19]. These included continuous measures (used as

continuous covariates) of; age, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol and high density lipoprotein (HDL) cholesterol, and categorical variables describing; ethnicity (white, black, South Asian or 'other'), sex, smoking status (never, former or current, or ever/never) and diabetes (present/absent). All models excluded participants with CVD (angina, ischaemic stroke, myocardial infarction or transient ischaemic attack) reported at baseline.

Systolic and diastolic blood pressure were taken as the first baseline measurement, preferentially using an automated measurement (a manual measurement was available in 33,111 (6.5%) people where an automated measurement was not available). Smoking status was categorised into never or former/current smoking. Ethnicity was coded as white, black, South Asian, or mixed/other, with white as the referent group. Blood collection sampling procedures for the study have been previously described and validated [17]. Biochemistry measures were performed at a dedicated central laboratory on around 480,000 samples between 2014 and 2017. These included serum total cholesterol (TC) and high-density lipoprotein (HDL) cholesterol (Beckman Coulter AU5400) and plasma glycated haemoglobin (HbA1c, Bio-Rad VARIANT II Turbo). Data were adjusted by UK Biobank centrally before release to adjust for pre-analytical variables. Further details of these measurements can be found in the UK Biobank online showcase and protocol (http://www.ukbiobank.ac.uk).

As described previously [2], the mean grip strength was measured using a Jamar J00105 hydraulic hand dynamometer and the mean was derived from the right and left hand values expressed in absolute units (kg). In the main analyses, these were categorised into sex-specific quintiles, with the third quintile used as the referent group. As described previously [3], self-

reported walking pace was rated by each participant as 'slow', 'steady/average' or 'brisk', with 'steady/average' used as the referent group.

Outcomes

The main outcome of interest was that used in the AHA/ACC risk score, namely composite fatal or non-fatal incident myocardial infarction, ischaemic heart disease, and haemorrhagic or ischaemic stroke (ICD-10 codes I20-25, I60-64 for fatal events and I21,I22, I60, I61, I63 and I64 for nonfatal events)[14]. We also used the outcome description used in SCORE for fatal CVD events which includes ICD-10 codes I10-15, I20-25, I61-73 and I44-51[15]. A list of the clinical entities associated with these codes is included in the supplemental material.

Statistical Analyses

Continuous variables were expressed as mean (standard deviation, SD). Categorical and binary variables were expressed as numbers and percentages. Participants were excluded if they reported prevalent or historic CVD at baseline (n=30,687), reported taking cholesterol lowering medications (n=58,883) or were missing grip strength (n=3,405) or walking pace (n=2,727) measurements.

A risk matrix was developed based on Cox regression models by age and sex strata (40-50, 50-60, 60+ years for both women and men). Self-reported walking pace and sex-specific quintiles of handgrip were mutually adjusted in the models, and were additionally adjusted for ethnicity, diabetes, systolic blood pressure, total cholesterol, HDL-cholesterol, and smoking. Cox models were used to derive hazard ratios, which were used to populate the risk matrix.

The effects of the addition of sex-specific average grip strength quintiles, self-reported walking pace, or both to the AHA/ACC Cox proportional-hazard model risk score was assessed by the change in Harrell's C-Index for survival data. To further quantify the additional prediction value of handgrip and walking pace, we used a categorical net reclassification index (NRI), with 1,000 bootstraps to estimate 95% confidence intervals to investigate the changes in predicted risk classification across the 7.5% 10-year risk cut-off used to determine who should receive statins in the ACC/AHA model [19].

Interactions between mean grip strength or walking pace and each of the existing AHA/ACC risk score covariates were assessed for statistical significance. These analyses were then repeated using the CVD outcome and covariates used in the SCORE risk score. The proportional hazard assumption was tested by visual inspection of Schöenfeld residuals.

Results

Baseline results

Of the original 502,536 participants, 30,687 (6.1%) with pre-existing CVD were excluded, as were 58,883 (11.7%) on statins, 3,405 (0.7%) with missing grip data, 2,727 (0.5%) with missing self-reported walking pace data, leaving a study population of 406,834. Table 1 reports grip strength range for each sex-specific quintile. Over a median of 8.87 years of follow-up (Q1-Q3 8.25-9.47) there were 7,274 composite fatal/nonfatal events (based on the ACC/AHA outcome) and 1,955 fatal events (based on SCORE).

Participants in higher quintiles of grip strength were more likely to be younger and non-smokers, have lower SBP and higher DBP, and were less likely to be taking antihypertensive medications or have diabetes (Supplemental Table S1). Participants in the second lowest

quintile of mean grip strength had the highest total and HDL cholesterol levels, with those in the highest and lowest quintiles showing similar levels. Participants who reported brisk walking pace were more likely to be young, white, male, and non-smokers, have lower SBP and DBP, and were less likely to report taking antihypertensive medications (Supplemental Table S2). The Spearman rank correlation between continuous mean grip and walking pace was +0.138 (P<.001).

Associations of grip strength and usual walking pace with CVD outcomes

Higher quintiles of grip strength and faster usual walking pace were associated with lower event rates of both CVD outcomes (Table 1). Figure 1 displays the age and sex-specific risk matrix for HR of CVD incidence by grip strength and walking pace. The CVD hazard ratio for women aged 40-50 years who reported a slow walking pace and who have a low grip strength was 2.9, compared to 1.8 and 3.2 for those aged 50-60 and >=60 years, respectively. A similar trend was observed for men; however, the HR was lower compared to women – 2.1, 2.0, 2.6 for men aged 40-50, 50-60 and 60+, respectively. Being a slow walker, regardless of grip strength, was associated with a higher risk of CVD in both men and women.

Prediction of CVD events

For the composite fatal/nonfatal (ACC/AHA) CVD outcome (Figure 2), classical risk factors yielded a C-index of 0.7463 (95% CI 0.7406-0.7521). This was improved upon with the addition of either grip strength (change in C-index +0.0017, 95% CI 0.0009-0.0026), or self-reported walking pace (+0.0031, 95% CI 0.0019-0.0043), with the largest improvement seen when both were added (+0.0041, 95% CI 0.0027-0.0055). Excluding total and HDL cholesterol from the ACC/AHA model yielded a C-index of 0.7378 (95% CI 0.7324-0.7432). This was

also improved by the addition of grip strength (+0.0017, 95% CI 0.0008-0.0026), usual walking pace (+0.0043, 95% CI 0.0029-0.0056), or both (+0.0052, 95% CI 0.0037-0.0067) (Figure 2).

For the fatal CVD outcome, based on the SCORE CVD risk model (Figure 3), classical risk factors yielded a C-index of 0.7707 (95% CI 0.7600-0.7813) which was improved by the addition of grip strength (+0.0047, 95% CI 0.002-0.0074), self-reported walking pace (+0.0130, 95% CI 0.0088-0.0171), or both (+0.0148, 95% CI 0.0102-0.0194). When the SCORE model run without total and HDL cholesterol, the remaining risk factors yielded a C-index of 0.7700 (95% CI 0.7601-0.7800) which was improved by the addition of grip strength (+0.0052, 95% CI 0.0025-0.0078), self-reported walking pace (+0.0156, 95% CI 0.0114-0.0199) or both (+0.0177, 95% CI 0.0131-0.0224).

For the CVD outcome, we investigated improvement in risk classification across the 7.5% 10 year risk threshold for statin therapy, used in the AHA/ACC guidelines [19] (Table 2). We found that the addition of grip strength resulted in a 0.55% (95% CI 0.12-0.96%) improvement in overall reclassification. Similarly, the addition of self-reported walking pace resulted in a 0.53% (95% CI 0.01-1.06%) improvement in overall reclassification. Adding both grip and walking pace resulted in a 1.12% (95% CI 0.58-1.69%) improvement in overall reclassification.

Discussion

The main finding of the current study is that, in this large and comprehensive single-protocol cohort, the addition of grip strength and/or usual walking place resulted in an improvement in the prediction of CVD when added to established CVD risk scores (AHA/ACC and SCORE) and therefore the ability to classify people as high or low risk. Usual walking pace improved

prediction to a greater extent than grip strength, but the combination of the two provided the greatest improvement. These findings clearly suggest that grip strength and usual walking place, both of which are cheap, fast and easy to measure, may have utility in clinical practice in improving the identification of people at high risk of fatal and non-fatal CVD outcomes who would benefit most from primary prevention.

As mentioned previously, several studies have demonstrated that higher grip strength is associated with lower risk of a broad range of health outcomes, including CVD [1,2,7–10,12,20–22] and the current study confirms this association with CVD. Comparatively few studies have investigated the association between walking pace and health outcomes, and many of these were in older people where they have consistently shown that there is an inverse association between objectively measured walking pace and all-cause mortality [1,23]. Interestingly, recent work has also shown, using data from UK Biobank, that self-reported walking pace is associated with a broad range of health outcomes, including CVD [3,24]. In fact, usual walking pace was, alongside self-reported health, the strongest predictor of death from a range of causes in an early analysis of UK Biobank by Ganna and Ingelsson [11]. Low walking pace and grip strength are also key in the diagnosis of sarcopenia, the age related loss of muscle mass and strength, which has been shown to be associated with higher risk of CVD [25,26].

Whilst, to our knowledge, there are no studies which have investigated the addition of walking pace to a CVD risk score, our previous work has shown that the addition of grip strength resulted in an improvement in risk prediction on top of an office based risk score – which included age, sex, diagnosed diabetes, body mass index, systolic blood pressure and smoking but did not include lipids [2]. The current study has confirmed our previous findings with grip strength, and also shown that the addition of usual walking pace improves risk prediction in

office-based risk scores (AHA/ACC and SCORE models minus lipids). Improvements in prediction were strongest with the addition of usual walking pace and this is consistent with previous work showing usual walking pace is more strongly associated with health outcomes than grip strength [11,24]. Interestingly, the current data also show that the improvement in risk prediction of these office-based scores is additive, with larger improvements in C index when both grip strength and usual walking pace were included in the model. Such information has clinical utility and highlights that these markers of physical capability may improve risk prediction when blood lipid data are not available, as is the case in many rural communities and in developing countries.

When lipids were included in the risk score models, similar results were seen. The addition of grip strength or usual walking pace improved risk prediction, as demonstrated by the C-index, with usual walking pace providing the greatest improvements in the full ACC/AHA and SCORE models. When both grip strength and usual walking pace were added to the ACC/AHA and SCORE models, the change in C-index was greater than when either were added to the models alone suggesting they provide complementary information about risk. The findings were corroborated by the change in classification of participants. The addition of grip strength and walking pace individually resulted in 0.55% and 0.53% increases in NRI and when combined there was a 1.12% increase in overall net reclassification. These increases in C-index and NRI are similar to those seen when adding, for example, troponin I [27] or CRP/fibrinogen [28] and was indeed of greater magnitude than the addition of, for example, HbA1c [29] or lipid related markers [30] to similar risk scores. These data indicate that the addition of grip strength and self-reported usual walking pace can modestly improve CVD risk prediction and as they are both cheap and easy to administer they may warrant further consideration for implementation in CVD risk prediction in clinical practice.

Strengths and Limitations

The current study benefits from a large cohort size with an age that is relevant for CVD risk prediction with biochemical assays performed consistent with the internationally recognized standard for testing and calibration laboratories (ISO17025). Furthermore, the number of events accrued in the current study are considerable in the context of the existing literature. However, the study is not without limitations. UK Biobank aimed to be representative of the general population in terms of age, sex, ethnicity and socioeconomic status but is unrepresentative in terms of lifestyle, with participants less likely to be obese and a lower disease frequency – indicative of a "healthy volunteer" selection bias [31]. Therefore, caution should be heeded in generalizing summary statistics, such as prevalence and incidence, to the general population. However, effect sizes should nonetheless be generalizable. We have not carried out an external validation of our model and this should be done before adoption into clinical practice.

Conclusions

The addition of both grip strength and usual walking pace to existing risk scores results in modest improvements in CVD risk prediction, with an additive effect when both are included. As both these measures are cheap, fast and easy to administer these data further indicate that these tools could have a useful role in CVD risk screening. More work in this area would, therefore, seem prudent.

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Figure Legends

Figure 1. CVD Risk matrix for the combine effect of grip strength and walking pace by sex and age.

Risk matrices were developed based on Cox regression models for the overall data, by sex and by age and sex groups (40-50, 50-60, 60+ years for both female and male). Self-reported walking pace and sex-specific quartiles of handgrip were mutually adjusted in the models, and were additional adjusted for age, sex, ethnicity, diabetes, systolic blood pressure, total cholesterol, HDL-cholesterol, and smoking. ***P<0.001, **P<0.01, *P<0.05

Figure 2. Change in C-Index for the AHA/ACC composite CVD outcome with the addition of grip strength, usual walking pace and both together.

Data presented as C index and 95% CI and as differences in C index versus classical risk factors. Classical risk factors including information on age, sex, ethnicity, systolic blood pressure, diastolic blood pressure, antihypertensive medications, smoking and diabetes. Handgrip strength was added into the model as quintiles of the continuous average measure (categorical), and usual walking pace was a categorical variable.

Figure 3. Change in C-Index for the SCORE fatal CVD outcome with the addition of grip strength, usual walking pace and both together

Data presented as C index and 95% CI and as differences in C index versus classical risk factors. Classical risk factors including information on age, sex, ethnicity, systolic blood pressure, diastolic blood pressure, antihypertensive medications, smoking and diabetes. Handgrip strength was added into the model as quintiles of the continuous average measure (categorical), and usual walking pace was a categorical variable.

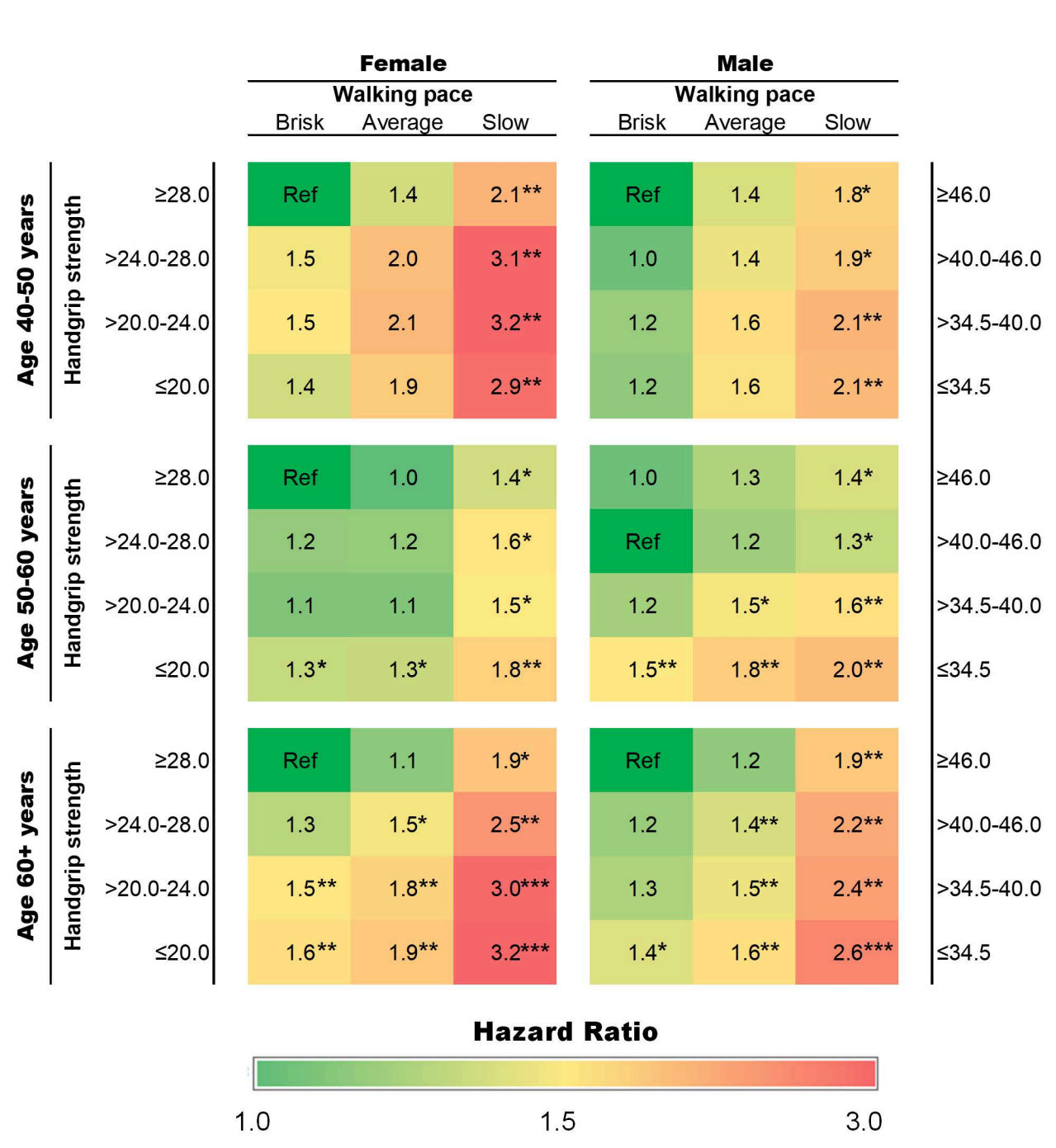
Tables

Table 1. Event rates of both CVD outcomes (composite outcome based on ACC/AHA and fatal outcome based on SCORE) among 406,834 UK Biobank participants.

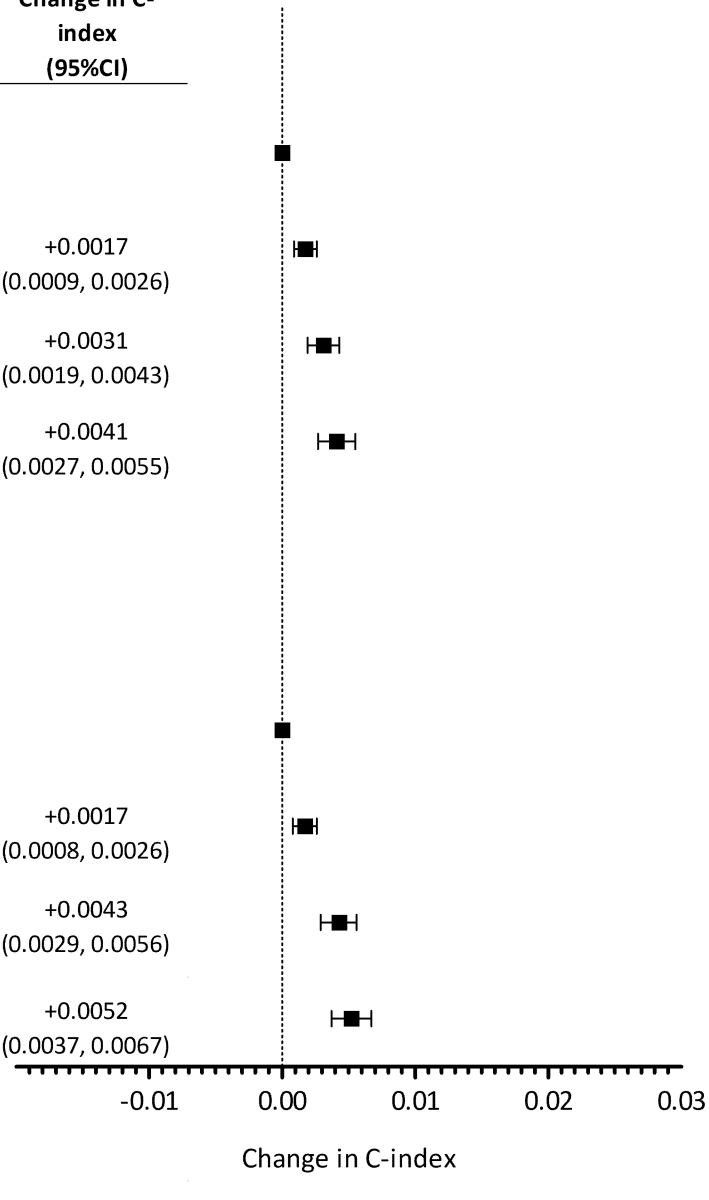
		Composite CVD (ACC/AHA)		Fatal CVD (SCORE)	
		Event rate per 100,000 person years	**95% CI**	**Event rate per 100,000 person years**	**95% CI**
Grip strength sex-specific quintile *Grip strength range in italics (F: Female, M: Male)*	1 *F: 0-18kg M: 0-32kg*	295.50	282.43-309.16	94.69	87.46-102.53
	2 *F: 18.5-22kg M: 32.5-37kg*	224.07	213.70-234.96	59.24	54.04-64.96
	3 *F: 22.5-25kg M: 37.5-41.5kg*	205.04	194.72-215.90	53.83	48.69-59.52
	4 *F: 25.5-28.5kg M: 42-47kg*	178.57	169.02-188.66	41.74	37.27-46.75
	5 *F: 29-57kg M: 47.5-85kg*	129.40	121.53-137.78	28.00	24.48-32.04
Usual walking pace	Slow	428.04	401.14-456.74	169.48	152.98-187.77
	Average	220.35	213.69-227.22	58.97	55.59-62.56
	Brisk	152.00	145.89-158.36	32.38	29.64-35.39

Table 2. Net Reclassification Index for composite fatal/non-fatal CVD outcomes for grip strength, usual walking place and both combined.

Comparator	Addition	Overall NRI (95% CI)	Case NRI (95%CI)	Non-case NRI (95% CI)
Classical risk factors	+Grip	+0.55% (+0.12, +0.96%)	+0.66% (+0.24, +1.08%)	-0.12% (-0.14, -0.09%)
	+Walking pace	+0.53% (+0.01, +1.06%)	+0.69% (+0.16, +1.22%)	-0.16% (-0.19, -0.13%)
	+Both	+1.12% (+0.58, +1.69%)	+1.36% (+0.82, +1.93%)	-0.24% (-0.27, -0.21%)


Female
Walking pace
Brisk
Average
Slow
Male
Walking pace
Brisk
Average
Slow
Age 40-50 years
Handgrip strength
≥28.0
Ref
1.4
2.1**
Ref
1.4
1.8*
≥46.0
>24.0-28.0
1.5
2.0
3.1**
1.0
1.4
1.9*
>40.0-46.0
>20.0-24.0
1.5
2.1
3.2**
1.2
1.6
2.1**
>34.5-40.0
≤20.0
1.4
1.9
2.9**
1.2
1.6
2.1**
≤34.5
Age 50-60 years
Handgrip strength
≥28.0
Ref
1.0
1.4*
1.0
1.3
1.4*
≥46.0
>24.0-28.0
1.2
1.2
1.6*
Ref
1.2
1.3*
>40.0-46.0
>20.0-24.0
1.1
1.1
1.5*
1.2
1.5*
1.6**
>34.5-40.0
≤20.0
1.3*
1.3*
1.8**
1.5**
1.8**
2.0**
≤34.5
Age 60+ years
Handgrip strength
≥28.0
Ref
1.1
1.9*
Ref
1.2
1.9**
≥46.0
>24.0-28.0
1.3
1.5*
2.5**
1.2
1.4**
2.2**
>40.0-46.0
>20.0-24.0
1.5**
1.8**
3.0***
1.3
1.5**
2.4**
>34.5-40.0
≤20.0
1.6**
1.9**
3.2***
1.4*
1.6**
2.6***
≤34.5
Hazard Ratio
1.0
1.5
3.0

	N participants	n cases	C-index (95%CI)	Change in C-index (95%CI)
CVD (AHA/ACC)	406,834	7,274		
Classical risk factors			0.7463 (0.7406, 0.7521)	
Classical risk factors plus grip				+0.0017 (0.0009, 0.0026)
Classical risk factor plus walking pace				+0.0031 (0.0019, 0.0043)
Classical risk factors plus grip & walking pace				+0.0041 (0.0027, 0.0055)
CVD (AHA/ACC)	406,834	7,274		
Classical risk factors (no lipids)			0.7378 (0.7324, 0.7432)	
Classical risk factors (no lipids) plus grip				+0.0017 (0.0008, 0.0026)
Classical risk factors (no lipids) plus walking pace				+0.0043 (0.0029, 0.0056)
Classical risk factors (no lipids) plus grip & walking pace				+0.0052 (0.0037, 0.0067)



	N participants	n cases	C-index (95%CI)	Change in C-index (95%CI)
CVD (SCORE)	406,834	1,955		
Classical risk factors			0.7707 (0.7600, 0.7813)	
Classical risk factors plus grip				+0.0047 (0.002, 0.0074)
Classical risk factor plus walking pace				+0.0130 (0.0088, 0.0171)
Classical risk factors plus grip & walking pace				+0.0148 (0.0102, 0.0194)
CVD (SCORE)	406,834	1,955		
Classical risk factors (no lipids)			0.7700 (0.7601, 0.7800)	
Classical risk factors (no lipids) plus grip				+0.0052 (0.0025, 0.0078)
Classical risk factors (no lipids) plus walking pace				+0.0156 (0.0114, 0.0199)
Classical risk factors (no lipids) plus grip & walking pace				+0.0177 (0.0131, 0.0224)