The associations between diabetes and both cardiovascular disease and all-cause mortality are modified by grip strength: evidence from UK Biobank a prospective population-based cohort study

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Abstract

Objective

Grip strength and diabetes are predictors of mortality and cardiovascular disease (CVD), but it is not known whether these risk factors interact in predisposing to adverse health outcomes. The aim of the current study was to determine the interactions between diabetes and grip strength and their association with health outcomes.

Research Design and Methods

We undertook a prospective, general population cohort study using UK Biobank. Cox proportional hazard models were used to explore the associations between both grip strength and diabetes and the outcomes of all-cause mortality and CVD incidence/mortality, and to test for interactions between diabetes and grip strength.

Results

Of 347,130 UK Biobank participants with full data available (mean age 55.9 years, BMI 27.2 $kg.m^{-2}$, 54.2% were women), 13,373 (4.0%) people who reported having diabetes were included in the analysis. Over a median follow-up of 4.9 years [range: 3.3-7.8], 6,209 died; (594 from CVD) and 4,301 participants developed CVD. People with diabetes were at higher risk of all-cause and CVD mortality and CVD incidence. There were significant interactions ($p<0.05$) whereby the risk of CVD mortality was higher in participants with diabetes with low (HR: 4.05 [2.72; 5.80]) compared to high grip strength (HR: 1.46 [0.87; 2.46]). Similar results were observed for all-cause mortality and CVD incidence.

Conclusions

Risk of adverse health outcomes among people with diabetes is lower in those with high grip strength. Low grip strength may be useful to identify a higher risk sub-group of diabetes patients. Intervention studies are required to determine if resistance exercise can reduce risk.

Introduction

Low muscle function, measured by grip strength, is associated with an increased risk of all-cause mortality, cardiovascular mortality and cardiovascular disease (CVD) (1). Even during healthy ageing, muscle function and mass decrease from around 40-45 years of age, with the mechanisms underlying this observation currently unknown (2). This loss of muscle mass and function appears to be accelerated in people with type 2 diabetes. Indeed, it has been shown in cross-sectional analysis of data from the Health, Ageing and Body Composition Study (485 adults 70-79 years of age with type 2 diabetes and 2,133 without) that people with type 2 diabetes have lower leg (men only) and grip strength (3) and, after 6 years of follow-up, lose leg, but not grip, strength at a greater rate compared to healthy counterparts of comparable age (4,5).

As skeletal muscle function is associated with health outcomes this lower muscle function could potentially contribute to the greater risk of developing co-morbidities and mortality in people with type 2 diabetes. In that regard, as well as the accelerated loss of muscle mass/function, it has been shown that people with type 2 diabetes are at a greater risk of all-cause and CVD mortality (6,7), with this risk higher again the longer a person has type 2 diabetes (8,9). Prior research has reported that, within a group of people (mean age 63.6 years) with impaired fasting glucose/impaired glucose tolerance or type 2 diabetes (n=12,516), a higher grip strength was associated with lower all-cause and cardiovascular mortality (10) reflecting the findings observed in general population studies. This analysis was, however, only adjusted for BMI, waist circumference, and hip circumference and not wider lifestyle factors and had no comparison of this relationship to people without diabetes. Whether this relationship holds after more robust adjustment and how these risks compare to people without type 2 diabetes remains to be established.

The aim of the current study was to explore the associations of diabetes and grip strength with risk of all-cause mortality/CVD incidence in UK Biobank, a large population cohort study of participants aged 40-69 years.

Methods

Study design

Between April 2007 and December 2010, UK Biobank recruited 502,628 participants (5.5% response rate), the majority of whom were aged 40-70 years, from the general population (11). Participants attended one of 22 assessment centres across England, Wales and Scotland (12,13) where they completed a touch-screen

questionnaire, had physical measurements taken and provided biological samples, as described in detail elsewhere (12,13). In this population-based study, all-cause and CVD mortality, and incident CVD events were the main outcomes; and diabetes was the exposure of interest. Handgrip strength was treated as a potential effect modifier. Socio-demographic factors (age, ethnicity, Townsend deprivation index, professional qualifications, income, employment and month of recruitment), health-related variables (duration of years with diabetes, systolic blood pressure, medication history for diabetes (insulin), cholesterol and blood pressure as well as prevalent diabetes and hypertension at baseline) and lifestyle factors including smoking status, body mass index categories, time spent on TV-viewing, discretionary PC-screen time, total physical activity, sleep duration categories and dietary intake (processed meat, red meat, oily fish, fruit and vegetables and alcohol intake) were treated as potential confounders. Presence of diabetes was determined from self-report of a physician diagnosis. This will capture both people with type 1 and type 2 diabetes and in our analysis we have excluded those who developed diabetes under the age of 30 (n=1,663) and so will capture, primarily, people with type 2 diabetes. We also excluded participants who did not answer this question (n=1,747) and who had prior gestational diabetes (n=1,072), the latter due to its often temporary nature. To reduce the effect of reverse causality all-analysis were performed as landmark with follow-up commencing two years after recruitment and including participants who were event-free at this time. In addition, participants with comorbidities at baseline were excluded from all-analysis (depression, COPD, chronic asthma, chronic liver diseases, alcohol problems, substance abuse, eating disorders, schizophrenia, cognitive impartment, Parkinson, dementia, chronic pain syndrome, heart diseases, inflammatory diseases, arthrosis, arthritis and cancer (n= 103,755). We included 13,373 people with diabetes in the study.

Study procedures

Date of death was obtained from death certificates held within the National Health Service (NHS) Information Centre (England and Wales) and the NHS Central Register Scotland (Scotland). Date and cause of hospital admissions were identified via record linkage to Health Episode Statistics (HES) (England and Wales) and to the Scottish Morbidity Records (SMR1) (Scotland). Detailed information regarding the linkage procedure can be found at http://www.ic.nhs.uk/services/medical-research-information-service. At the time of analysis, mortality data were available up to 31st January 2016. Mortality analysis was therefore censored at these dates or date of death if this occurred earlier. Hospital admission data were available until 31st March 2015, resulting in disease specific outcome analysis being censored at these dates, or the date of first disease incident or death if these

occurred earlier. Incident CVD was defined as a hospital admission or death with ICD10 code I60, I61, I63, I64, I21, I21.4 and I21.9.

Grip strength, as a proxy for muscular strength, was measured using a Jamar J00105 hydraulic hand dynamometer. Isometric grip force was assessed from a single 3-second maximal grip effort of the right and left arms with the participant seated upright with their elbow by their side and flexed at 90º so that their forearm was facing forwards and resting on an armrest. The mean of the right and left values, expressed in absolute units (kg), as reported elsewhere was used in the current study (14). For the purpose of this study and to take into account biological differences in grip strength within sex and age groups we derived age and sex-specific categories of grip strength (Table S1).

Physical activity was based on self-report, using the IPAQ short form (15), and total physical activity was computed as the sum of walking, moderate and vigorous activity, measured as metabolic equivalents (MET-hours/week). Participants were excluded from the analyses if they recorded implausible values; defined as the sum of their total physical activity, sleeping time and total screen-time exceeding 24 hours (n=705 participants were excluded). Discretionary time spent on TV-viewing and PC-screen were collected using self-reported questionnaires. Subjective sleep duration was obtained by asking: "About how many hours sleep do you get in every 24 hours?" and then based on this question we derived a categorical sleep duration variable (short sleeper <7 $h.day^{-1}$, normal sleeper 7-9 $h.day^{-1}$ or long sleepers >9 $h.day^{-1}$).

Dietary information was collected in a subset of participants (n=157,223 with dietary and diabetes data available) via the Oxford WebQ; a web-based 24h recall questionnaire which was developed specifically as a low-cost instrument for assessing diet in large-scale prospective studies. Compared with 24 h dietary recall, the mean Spearman's correlation of the 21 nutrients obtained from the WebQ was 0·6, with the majority between 0·5 and 0·9. The mean differences in intake were less than ±10 % for all nutrients except for carotene and vitamins B12 and D (16). The Oxford WebQ derives energy intake (total and from specific macronutrients) from the information recorded in McCance and Widdowson's The Composition of Food, 5th edition (17). For participants who completed more than one online dietary questionnaire, mean values were calculated from all of the information provided, with variation between repeated measurement ranging from 26-34%, as described elsewhere (16). The intake of other food items such as red meat, processed meat, oily fish and fruit and vegetable were collected using a touchscreen questionnaire on the reported frequency of intake of these food items. These data were available for all participants.

Area-based socioeconomic status was derived from postcode of residence, using the Townsend score (18). Other socio-demographic information such as employment (paid employment, retired, unable to work, unemployed, student and other), professional qualifications (college or university, A or O levels, GCSE, CSEs or equivalent levels) and income (<£18,000, £18,000-29,999, £30,000-51,999, £52,000-100,000 and >£100,000) were self-reported at baseline. Age was calculated from dates of birth and baseline assessment. Smoking status was categorised into never, former and current smoker. Medical history (physician diagnosis of depression, COPD, chronic asthma, chronic liver diseases, alcohol problems, substance abuse, eating disorders, schizophrenia, cognitive impartment, Parkinson, dementia, chronic pain syndrome, heart diseases, inflammatory diseases, arthrosis, arthritis and cancer) was collected from the self-completed, baseline assessment questionnaire. Number of years with diabetes was derived from self-reported age at the assessment visit and age when diabetes was diagnosed. History of recent medication for diabetes (insulin), cholesterol and hypertension at baseline were collected by self-reported touch-screen questionnaire. Height and body weight were measured by trained nurses during the initial assessment centre visit. Body mass index (BMI) was calculated as (weight/height^2) and the WHO criteria were used to classify BMI into: underweight <18.5, normal weight 18.5-24.9, overweight 25.0-29.9 and obese ≥30.0 kg.m^{-2}. Waist circumference was measured using a standardised protocol by trained nurses and central obesity was derived using 88cm and 102cm as cut-off points for women and men respectively. Body composition (body fat as percentage and fat free mass in kg) was measured by trained nurses using bio-impedance (Range 1% - 75% in 0.1% increments) using the Tanita BC418MA body composition analyser. Further details of these measurements can be found in the UK Biobank online protocol (http://www.ukbiobank.ac.uk).

Statistical analysis

Associations between diabetes and prospective health outcomes (all-cause mortality, CVD incidence and CVD mortality) were investigated using Cox-proportional hazard models. The results were reported as hazard ratios together with 95% CI. To reduce the effect of reverse causality all-analysis were performed as a landmark analysis with follow-up commencing two years after recruitment and including participants who were event-free at this time. In addition, participants with comorbidities at baseline were excluded from all-analysis (n= 103,755).

First, to investigate whether diabetes diagnose was associated with a higher hazard for mortality and CVD incidence we performed cox-regression analysis fitting diabetes into our model as a binary variable (No=0; Yes=1), all analysis are presented as the 3 models adjusted as specified below.

Second, to investigate whether levels of grip strength modified the associations between diabetes and health outcomes multiplicative interaction between diabetes and age-sex-specific categories of grip strength (coded as ordinal variable i.e. High=0, Middle=1, Low=2) were investigated by fitting the relevant parameters into the model. Linearity was explored with fractional polynomials models for each exposure, with no evidence of deviation from linearity. For all analyses, we ran three incremental models that included an increasing number of covariates: "model 0" included age, sex, ethnicity, deprivation index, professional qualifications, gross income, employment and month of recruitment as covariates; "model 1", was also adjusted for duration of diabetes, systolic blood pressure, baseline prevalence of hypertension and history of recent medication for diabetes (insulin), hypertension and cholesterol; "model 2" was adjusted for model 1 plus lifestyle factors including BMI categories, smoking, TV-viewing, PC-screen time, categories of sleep duration and dietary intake (alcohol, fruit and vegetable, red meat, processed meat and oily fish intake). Physical activity was included as covariate only when the association between diabetes and health outcomes was investigated but not for the interaction between grip strength and diabetes, as grip strength is a proxy of total levels of physical activity across the lifespan. The proportional hazard assumption were checked by tests based on Schoenfeld residuals. All analyses were performed using STATA 14 MD statistical software (StataCorp LP).

Results

Of the 502,628 participants recruited to UK Biobank, 498,348 provided data on diabetes status with 13,373 (diagnosed after 30 years of age and having no baseline co-morbidities) reporting having diabetes being included in this study. The mean follow-up period was 4.9 years [ranging from 3.3-7.8] for all-cause and CVD mortality, and 4.0 years [ranging from 2.4 to 7.0] for CVD incidence. Over the follow-up period, 4,301 participants developed CVD and there were 6,209 deaths: 594 from CVD.

The main characteristics of the participants by diabetes status and categories of grip strength are summarised in Table 1. The hazard ratios for all-cause mortality, and CVD incidence and mortality were significantly higher in individuals with diabetes compared to those without diabetes (Table 2). Although the associations were slightly attenuated after adjustment for further confounding factors, the associations remained significant. Additionally, the association between diabetes and health outcomes was modify by grip strength, with significant interactions between diabetes and grip strength for all-cause mortality (model 3 p=0.020), CVD mortality (model 3 p=0.016) and CVD incidence (model 3 p=0.041) (Figure 1 and Table 3). Compared to non-diabetic individuals with high

grip strength, diabetic individuals with low grip strength had a higher risk of all-cause mortality (HR: 2.79 [2.41; 3.23], p<0.0001), CVD mortality (HR: 4.05 [2.72; 5.80], p<0.0001) and CVD incidence (HR: 2.19 [1.81; 2.64], p<0.0001) in model 3. In contrast, diabetic participants with high grip strength were at higher risk of all-cause mortality (HR: 1.36 [1.15; 1.61], p<0.0001) but did not have significantly increased risk of CVD mortality (HR: 1.46 [0.87; 2.46]) or CVD incidence (HR: 1.11 [0.90; 1.37]) (Figure 1). The trend hazard ratios per category decrease in grip strength for participants with and without diabetes, across all 3 models, are also summarised in Table 3. Although the association were slightly attenuated these remained significant for all three levels of adjustments.

Discussion

The main finding of the current study is that the higher risk of CVD associated with diabetes was restricted to the sub-group of people with diabetes with low grip strength; in contrast people with diabetes and high grip strength were not at significantly increased risk of CVD.

As skeletal muscle is of primary importance from not only a functional point of view (19) but also as the primary protein store and site of glucose disposal (20–22) it has a clearly important metabolic role (23). Indeed, as demonstrated in our previous work, low grip strength is associated with a higher diabetes prevalence (24). The findings of the current study that diabetes is associated with a lower grip strength is in agreement with previously published literature which has demonstrated that a lower, and a more rapid loss of, muscle strength in people with type 2 diabetes (3,5). The precise mechanisms underlying this lower muscle mass in people with diabetes has yet to be determined, and prior to the current study there had been no investigation of how muscle function interacts with the deleterious effects of diabetes on health outcomes.

It is well established that people with type 2 diabetes are at a greater risk of all-cause mortality and that CVD rates are higher (6,7), and that this risk increases the longer a person has type 2 diabetes (8,9). Our data has demonstrated that a low grip strength is associated with further elevations in the already high risk of all-cause mortality, CVD incidence and mortality in people with diabetes. These findings are in agreement with the findings of Lopez-Jaramillo et al (10) and confirming that such associations exist in a larger population and remain even after adjustment for a wide variety of socio-demographic and lifestyle factors, comorbidities and the duration of diagnosed diabetes. We were able to extend this previous work by also comparing these associations with a

population without diabetes. Indeed, relative to those without diabetes and with a high grip strength, those with low grip strength had higher hazards for all-cause and CVD mortality, and CVD incidence in both people with and without diabetes. In those with both diabetes and high grip strength a higher hazard for all-cause mortality, relative to those without diabetes and with a high grip strength, was observed with no difference in the hazard for CVD mortality and incidence. These data have clear implications for public health policies and indicate that, in people with diabetes, targeting interventions at those with low grip strength may have a greater impact. These associations remain to be investigated in appropriately designed randomised controlled trials to determine whether and to what extent they are causal.

There is some precedence to indicate that these associations may be causal and for such interventions to be beneficial. For example, a general lifestyle intervention in people with impaired glucose tolerance has been shown to reduce incidence of cardiovascular and all-cause mortality and diabetes (25). These findings are not ubiquitous, however, with the look AHEAD trial finding no effect of an intensive lifestyle intervention on cardiovascular events in overweight/obese adults with type 2 diabetes (26). Neither of these interventions were, however, designed to increase strength specifically. The main way to increase muscle strength is via resistance exercise training, which has been shown, in trials, to improve many CVD risk factors (27). If causality was demonstrated, the implementation of the measurement of grip strength in a clinical setting would be relatively straightforward as its measurement requires little training, is simple and cheap to administer, and has high reproducibility (28). Grip strength could even be used to screen patients with diabetes (or even more widely) to target interventions where the largest benefits could be gained. It is worth noting that whilst grip strength is highly correlated with leg strength, and this provides a valid index of whole-body muscle strength across the age range (29) it is not as sensitive, relative to lower leg strength, to the effects of short-term resistance exercise training (30). Therefore, whilst monitoring grip strength may be useful in identify at risk populations, it may not be useful in monitoring the efficacy of resistance exercise interventions employed.

Strengths and limitations

Although UK Biobank is not representative of the general population, with evidence of a 'healthy volunteer' selection bias, the valid assessment of exposure-disease relationships may be widely generalizable and does not require participants to be representative of the population at large (31). Therefore, caution should be heeded in generalizing summary statistics, such as the prevalence of diabetes or obesity, to the general population. This does

not detract from the ability to generalize estimates of the magnitude of associations. Our study benefited from a very large number of participants, recruited from the general population, across the whole of the UK. We had sufficient power to undertake analysis by age and grip strength categories. It is possible however that rather than grip strength having a causally protective effect vs. mortality or subsequent disease incidence, it may be a marker of generally better health at baseline and whilst we have attempted to reduce the potential for reverse causality and confounding in our analysis, by performing a 2 years landmark analysis and excluding individuals with medical diagnosis of chronic comorbidities at baseline, the potential for both to influence the results does remain. A further limitation to the current study is that there is bias in our data as it only includes people with diabetes who had survived long enough to be recruited in to the study. Diabetes was ascertained by self-report of a physician diagnosis. Therefore, incomplete ascertainment is possible but unlikely to introduce a systematic error. Indeed, Bays et al. (33) reported that the prevalence of diabetes was similar when based solely on self-report in the SHIELD (Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes) screening survey compared with clinical and laboratory corroboration of self-reports in the National Health and Nutrition Examination Survey. Schneider et al. (34) also showed that self-reported diabetes was >92% reliable and 83% sensitive. We were unable to differentiate between type 1 and type 2 diabetes but with the exclusion of participants <30 years the overwhelming majority of cases will be type 2. Data on physical activity and sedentary behaviour was self-reported which has limitations in accuracy (35) and does not capture specific forms of exercise, such as resistance training, which is likely to have an effect on the associations we have observed in the current study. In all studies involving nutritional epidemiology there are always uncertainties in estimating long-term dietary intake and all methods of dietary assessment can incur both random and systematic errors; the former of which can be diminished, but not eliminated, by studying large numbers (36,37). In this study dietary intake was self-reported outside the clinic, which may encourage more truthful reporting. In addition, online administration of the questionnaires is expected to minimize any reporting bias due to social desirability. The information was collected using a 24-h recall questionnaire which has been shown to produce more accurate results than a food frequency questionnaire (the usual approach adopted in large-scale studies) (38).

The current study shown that the risk all-cause and CVD mortality, and CVD incidence is lower in those with a higher grip strength, in people both with and without diabetes. Our findings therefore suggest that grip strength may have clinical utility in identifying people with diabetes at risk of poorer health outcomes. Furthermore targeting interventions, such as resistance exercise, to those with low grip strength, where the greatest benefits

may be gained could, increase clinical effectiveness. These conclusions remain to be tested in future well designed randomised controlled trials.

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Contribution statement

CCM, SG, JPP, NS, JMRG contributed to the conception and design of the study, advised on all statistical aspects and interpreted the data. CCM, SG, FP and HL performed the statistical analyses. CCM and SG drafted the manuscript. All authors reviewed the manuscript and approved the final version to be published. CCM, SG, JPP, NS and JMRG had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure legend

Figure 1. Association of all-cause mortality and CVD incidence and mortality by diabetes and grip strength strata. Data presented as hazard ratio and their 95% CI. Individuals with diabetes and high grip strength were used as reference group. The model was adjusted for age, sex, ethnicity, deprivation index, professional qualifications, gross income, employment and month of recruitment, duration of diabetes, systolic blood pressure, baseline prevalence of hypertension and history of recent medication for diabetes (insulin), hypertension and cholesterol, BMI categories, smoking, TV-viewing, PC-screen time, categories of sleep duration, physical activity and dietary intake (alcohol, fruit and vegetable, red meat, processed meat and oily fish intake). All-cause mortality was additionally adjusted for CVD diagnosed at baseline.

Table 1. Cohort characteristics by categories of handgrip strength and diabetes diagnosed

		Without diabetes			With diabetes		
Socio-demographics	**Overall**	**Low strength**	**Middle strength**	**Higher strength**	**Low strength**	**Middle strength**	**Higher strength**
Total n	347,130	60,979	136,679	136,099	3,749	5,367	4,257
Women, n (%)	188,171 (54.2)	33,043 (54.2)	75,350 (55.1)	74,562 (54.8)	1,410 (37.6)	2,030 (37.8)	1,776 (41.7)
Age (years), mean (SD)	55.9 (8.1)	55.9 (8.0)	56.0 (8.1)	55.4 (8.2)	59.1 (7.2)	59.4 (7.2)	58.8 (7.2)
Deprivation index quintiles, n (%)							
Lower	120,852 (34.8)	18,352 (30.1)	47,745 (35.0)	51,088 (37.5)	810 (21.6)	1,501 (28.0)	1,356 (31.9)
Middle	118,416 (34.1)	19,981 (32.8)	46,921 (34.3)	47,215 (34.7)	1,112 (29.7)	1,743 (32.5)	1,444 (33.9)
Higher	107,862 (31.1)	22,646 (37.1)	42,013 (30.7)	37,796 (27.8)	1,827 (48.7)	2,123 (39.5)	1,457 (34.2)
Professional qualifications, n (%)							
College or University degree	118,754 (40.4)	18,999 (38.5)	46,573 (40.3)	49,682 (41.9)	908 (34.1)	1,397 (34.0)	1,195 (35.6)
A levels/AS levels or equivalent	39,908 (13.6)	6,714 (13.6)	15,572 (13.5)	16,313 (13.7)	339 (12.7)	567 (13.8)	403 (12.0)
O levels/GCSEs or equivalent	75,581 (25.7)	13,054 (26.4)	30,301 (26.2)	29,464 (24.8)	718 (27.0)	1,144 (27.9)	900 (26.8)
CSEs or equivalent	20,044 (6.8)	3,926 (7.9)	7,919 (6.9)	7,531 (6.3)	210 (7.8)	251 (6.1)	207 (6.1)
NVQ or HND or HNC or equivalent	22,247 (7.6)	3,778 (7.6)	8,543 (7.4)	8,821 (7.4)	268 (10.1)	438 (10.7)	399 (11.9)
Other professional qualifications	17,424 (5.9)	2,980 (6.0)	6,691 (5.7)	6,969 (5.9)	221 (8.3)	307 (7.5)	256 (7.6)
Income categories, n (%)							
Less than £18,000	57,816 (19.2)	12,637 (24.4)	22,813 (19.2)	18,798 (15.7)	1,268 (40.6)	1,377 (30.3)	923 (25.3)
£18,000 to £51,999	157,608 (52.2)	26,720 (51.7)	62,401 (52.5)	62,778 (52.4)	1,434 (45.9)	2,342 (51.6)	1,933 (53.0)
Greater than £52,000	86,251 (28.6)	12,378 (23.9)	33,623 (28.3)	38,209 (31.9)	425 (13.5)	824 (18.1)	792 (21.7)
Employment status, n (%)							
In paid employment or self-employed	216,635 (62.9)	36,259 (60.1)	85,494 (63.1)	88,582 (65.5)	1,579 (42.8)	2,502 (47.1)	2,219 (52.5)
Retired	104,497 (30.4)	18,457 (30.6)	41,648 (30.7)	38,746 (28.7)	1,556 (42.4)	2,385 (44.8)	1,705 (40.4)
Looking after home and/or family	9,845 (2.9)	1,728 (2.9)	3,797 (2.8)	4,026 (3.0)	99 (2.6)	106 (2.0)	89 (2.1)
Unable to work because of sickness or disability	5,269 (1.5)	2,067 (3.4)	1,537 (1.1)	1,094 (0.8)	296 (8.0)	177 (3.3)	98 (2.3)
Unemployed	5,498 (1.6)	1,339 (2.2)	2,140 (1.6)	1,683 (1.3)	132 (3.6)	116 (2.2)	88 (2.1)
Doing unpaid or voluntary work	1,568 (0.5)	278 (0.5)	591 (0.4)	642 (0.5)	15 (0.4)	22 (0.4)	20 (0.5)
Full or part-time student	929 (0.2)	183 (0.3)	336 (0.3)	382 (0.2)	10 (0.2)	11 (0.2)	7 (0.1)
Ethnicity, n (%)							
White	328,088 (94.5)	55,634 (91.2)	130,014 (95.2)	130,896 (96.2)	2,955 (78.8)	4,719 (87.9)	3,870 (90.9)
South Asian	6,601 (1.9)	2,602 (4.3)	2,245 (1.6)	870 (0.6)	478 (12.8)	309 (5.8)	98 (2.3)
Black	5,930 (1.7)	1,084 (1.8)	1,938 (1.4)	2,355 (1.7)	160 (4.3)	194 (3.6)	199 (4.7)
Chinese	1,221 (0.4)	373 (0.6)	512 (0.4)	275 (0.2)	24 (0.6)	25 (0.5)	12 (0.3)
Mixed background / others	5,290 (1.5)	1,287 (2.1)	1,970 (1.4)	1,703 (1.3)	132 (3.5)	120 (2.2)	78 (1.8)
Smoking status, n (%)							

Never	198,235 (57.1)	36,187 (59.3)	79,118 (57.9)	76,381 (56.1)	1,942 (51.8)	2,659 (49.5)	1,948 (45.8)
Previous	115,472 (33.3)	18,597 (30.5)	44,707 (32.7)	46,654 (34.3)	1,429 (38.1)	2,205 (41.1)	1,880 (44.2)
Current	33,423 (9.6)	6,195 (10.2)	12,854 (9.4)	13,064 (9.6)	378 (10.1)	503 (9.4)	429 (10.0)
Obesity-related markers							
BMI, mean (SD)	27.2 (4.6)	27.1 (4.7)	26.8 (4.4)	27.1 (4.4)	31.1 (6.0)	31.0 (5.7)	31.2 (5.6)
BMI Categories, n (%)							
Underweight (<18.5)	1,659 (0.5)	448 (0.7)	754 (0.5)	439 (0.3)	11 (0.3)	4 (0.1)	3 (0.1)
Normal weight (18.5-24.9)	118,469 (34.1)	21,219 (34.8)	49,991 (36.6)	45,661 (33.6)	485 (12.9)	653 (12.2)	460 (10.8)
Overweight (25.0 to 29.9)	148,864 (42.9)	25,418 (41.7)	58,380 (42.7)	60,315 (44.3)	1,319 (35.2)	1,912 (35.6)	1,520 (35.7)
Obese (≥30.0)	78,138 (22.5)	13,894 (22.8)	27,554 (20.2)	29,684 (21.8)	1,934 (51.6)	2,798 (52.1)	2,274 (53.4)
Waist Circumference (cm), mean (SD)	89.6 (13.1)	89.6 (13.1)	88.6 (12.8)	89.3 (12.8)	102.5 (14.5)	101.8 (14.2)	101.6 (14.1)
Central Obesity, n (%)	108,502 (31.3)	19,575 (32.1)	39,323 (28.8)	41,112 (30.2)	2,401 (64.1)	3,355 (62.5)	2,736 (64.3)
% Body fat, mean (SD)	31.0 (8.5)	31.5 (8.6)	30.9 (8.4)	30.6 (8.4)	33.8 (8.6)	33.4 (8.5)	33.4 (8.6)
Fitness, Physical activity and Sleep, mean (SD)							
Grip strength (kg)	31.2 (11.0)	21.3 (7.6)	29.2 (8.3)	37.7 (10.5)	22.0 (7.4)	30.9 (8.0)	38.9 (10.1)
Total physical activity (MET.h.week^{-1})	6.6 (9.1)	5.9 (8.8)	6.5 (9.0)	7.0 (9.3)	4.9 (8.4)	5.6 (8.0)	6.2 (8.9)
TV-viewing (h.day^{-1})	2.7 (1.6)	2.8 (1.7)	2.7 (1.5)	2.6 (1.5)	3.5 (2.0)	3.3 (1.8)	3.2 (1.7)
PC-screen time (h.day^{-1})	1.2 (1.3)	1.2 (1.4)	1.2 (1.3)	1.2 81.3)	1.3 (1.6)	1.3 (1.6)	1.3 (1.4)
Sleep Time categories n (%)							
Normal 7-9 h	259,008 (74.9)	43,542 (71.8)	102,490 (75.2)	103,643 (76.3)	2,480 (66.7)	3,786 (70.9)	3,067 (72.3)
Short sleepers <7 h	82,776 (23.9)	16,059 (26.5)	32,219 (23.7)	30,901 (22.8)	1,108 (29.8)	1,410 (26.4)	1,079 (25.5)
Long sleepers >9 h	4,190 (1.2)	1,035 (1.7)	1,542 (1.1)	1,239 (0.9)	132 (3.5)	148 (2.7)	94 (2.2)
Dietary intakes, mean (SD)							
Total energy (Kcal.day^{-1})	2,118 (645)	2,097 (666)	2,109 (636)	2,136 (641)	2,080 (731)	2,093 (684)	2,128 (686)
Protein intake (% of TE)	15.5 (3.6)	15.5 (3.7)	15.5 (3.6)	15.6 (3.6)	16.2 (4.2)	16.2 (4.0)	16.4 (3.7)
Carbohydrate intake (% of TE)	47.2 (8.1)	47.7 (8.4)	47.2 (8.1)	46.9 (8.0)	47.0 (8.8)	46.4 (8.3)	45.9 (8.3)
Total fat intake (% of TE)	32.0 (6.7)	31.9 (6.8)	32.0 (6.7)	32.1 (6.6)	32.7 (7.2)	32.4 (7.0)	32.8 (7.0)
Saturated intake (% of TE)	12.3 (3.3)	12.2 (3.4)	12.2 (3.3)	12.3 (3.3)	12.4 (3.6)	12.4 (3.5)	12.4 (3.4)
Sugar intake (% of TE)	22.5 (7.0)	22.7 (7.3)	22.5 (6.9)	22.5 (6.8)	20.4 (7.4)	20.2 (6.8)	20.0 (6.7)
Alcohol intake (% of TE)	5.3 (6.5)	4.9 (6.5)	5.3 (6.5)	5.4 (6.4)	4.1 (6.7)	4.9 (7.1)	4.9 (6.9)
Red meat intake (portion.week^{-1})	1.9 (1.4)	1.9 (1.4)	1.9 (1.4)	1.9 (1.4)	2.1 (1.7)	2.1 (1.6)	2.1 (1.5)
Processed meat intake (portion.week^{-1})	1.9 (1.1)	1.9 (1.1)	1.9 (1.1)	1.9 (1.0)	2.0 (1.1)	2.0 (1.1)	2.0 (1.0)
Vegetable and Fruit intake (grams.day^{-1})	330.4 (192.0)	322.9 (201.9)	327.3 (189.0)	334.5 (188.5)	346.8 (201.0)	352.3 (204.5)	361.8 (214.8)
Oily fish (portion.week^{-1})	1.1 (1.0)	1.1 (1.0)	1.1 (1.0)	1.1 (1.0)	1.1 (1.2)	1.2 (1.1)	1.2 (1.1)
Health status							
Number of years with diabetes, mean(SD)	0.2 (1.6)	0	0	0	6.7 (6.4)	6.0 (5.8)	5.5 (5.7)
Systolic blood pressure (mmHg), mean (SD)	139.7 (19.6)	138,1 (19.6)	139.2 (19.7)	140.5 (19.5)	142.8 (18.6)	144.3 (18.1)	145.3 (17.9)

Diastolic blood pressure (mmHg), mean (SD)	82.5 (10.7)	81.7 (10.8)	82.2 (10.7)	83.0 (10.6)	81.6 (10.0)	82.5 (9.9)	83.4 (10.0)
High blood pressure history, n (%)	79,937 (23.0)	14,243 (23.4)	29,264 (21.4)	28,573 (21.0)	2,224 (59.3)	3,178 (59.2)	2,455 (57.7)
Medication for cholesterol or blood pressure, n (%)							
None of the above	310,655 (89.5)	54,200 (88.9)	123,477 (90.3)	123,690 (90.9)	2,614 (69.7)	3,761 (70.1)	2,913 (68.4)
Cholesterol lowering medication	18,119 (5.2)	3,184 (5.2)	5,977 (4.4)	5,461 (4.0)	963 (25.7)	1,393 (26.0)	1,141 (26.8)
Insulin	117 (0.04)	0	0	0	51 (1.2)	39 (0.7)	27 (0.7)
Blood pressure medication	18,356 (5.3)	3,595 (5.9)	7,225 (5.3)	6,948 (5.1)	172 (4.6)	213 (3.9)	203 (4.8)

Data presented as mean and SD for continuous variables or n and % for categorical variables. F&V: fruit and vegetable, CVD: cardiovascular diseases, n: numbers, SD: standard deviation, TE: total energy. *Data was available for n=210,064 participants.

Table 2. Cox proportional hazard ratio for all-cause mortality and CVD incidence and mortality in people with diabetes

	Total n	Deaths / events	HR (95% CI)	P-value
All-cause mortality				
Model 0	347,130	6,209	1.72 (1.58; 1.88)	<0.0001
Model 1	347,130	6,209	1.65 (1.51; 1.81)	<0.0001
Model 2	347,130	6,209	1.55 (1.42; 1.70)	<0.0001
CVD mortality				
Model 0	347,130	594	2.19 (1.71; 2.80)	<0.0001
Model 1	347,130	594	2.07 (1.61; 2.67)	<0.0001
Model 2	347,130	594	1.95 (1.50; 2.52)	<0.0001
CVD incidence				
Model 0	347,130	4,301	1.44 (1.29; 1.61)	<0.0001
Model 1	347,130	4,301	1.36 (1.21; 1.52)	<0.0001
Model 2	347,130	4,301	1.22 (1.09; 1.37)	0.001
Circulatory mortality				
Model 0	347,130	1,811	2.49 (2.17; 2.85)	<0.0001
Model 1	347,130	1,811	2.22 (1.93; 2.55)	<0.0001
Model 2	347,130	1,811	2.00 (1.74; 2.31)	<0.0001
Circulatory incidence				
Model 0	347,130	19,130	1.50 (1.42; 1.58)	<0.0001
Model 1	347,130	19,130	1.34 (1.27; 1.42)	<0.0001
Model 2	347,130	19,130	1.22 (1.16; 1.29)	<0.0001

Data presented as hazard ratio and 95% CI. People without diabetes were used as reference category. Participants who were diagnosed with diabetes before the age of 30 years were removed from the analysis. All-analysis were performed as a landmark analysis with follow-up commenced two years after recruitment and including participants who were event-free at this time. In addition, participants with comorbidities at baseline were excluded from all-analysis (depression, COPD, chronic asthma, chronic liver diseases, alcohol problems, substance abuse, eating disorders, schizophrenia, cognitive impartment, Parkinson, dementia, chronic pain syndrome, heart diseases, inflammatory diseases, arthrosis, arthritis and cancer (n= 103,755).

Model 0 was adjusted for age, sex, ethnicity, deprivation index, professional qualifications, gross income, employment and month of recruitment.

Model 1 was also adjusted for duration of diabetes, systolic blood pressure, and baseline prevalence of hypertension and history of recent medication for diabetes (insulin), hypertension and cholesterol.

Model 2 was also adjusted for BMI categories, smoking, TV-viewing, PC-screen time, categories of sleep duration and dietary intake (alcohol, fruit and vegetable, red meat, processed meat and oily fish intake).

Table 3. Cox proportional hazard ratio for all-cause mortality and CVD incidence and mortality in people with diabetes by grip strength categories.

				Categories of age and sex specific grip strength					
All-cause mortality		**Total n**	**Deaths/ events**	Higher	Middle	Lower	**HR-trend (95% CI)**	**P-trend**	**P-interaction**
Model 0	Without diabetes	333,757	5,640	1.00 (Ref.)	1.22 (1.15; 1.29)	1.69 (1.57; 1.81)	1.29 (1.25; 1.34)	<0.0001	
	With diabetes	13,373	569	1.00 (Ref.)	1.29 (1.05; 1.59)	2.04 (1.65; 2.53)	1.44 (1.29; 1.60)	<0.0001	
Model 1	Without diabetes	333,757	5,640	1.00 (Ref.)	1.23 (1.16; 1.30)	1.70 (1.59; 1.83)	1.30 (1.25; 1.34)	<0.0001	
	With diabetes	13,373	569	1.00 (Ref.)	1.32 (1.07; 1.62)	2.10 (1.70; 2.61)	1.46 (1.31; 1.63)	<0.0001	
Model 2	Without diabetes	333,757	5,640	1.00 (Ref.)	1.23 (1.16; 1.30)	1.70 (1.58; 1.82)	1.30 (1.25; 1.34)	<0.0001	
	With diabetes	13,373	569	1.00 (Ref.)	1.34 (1.09; 1.66)	2.05 (1.65; 2.54)	1.44 (1.29; 1.60)	<0.0001	
CVD mortality									
Model 0	Without diabetes	333,757	519	1.00 (Ref.)	1.27 (1.04; 1.55)	1.71 (1.36; 2.16)	1.30 (1.16; 1.47)	<0.0001	
	With diabetes	13,373	75	1.00 (Ref.)	1.52 (0.82; 2.81)	2.62 (1.42; 4.81)	1.63 (1.20; 2.21)	0.002	
Model 1	Without diabetes	333,757	519	1.00 (Ref.)	1.30 (1.07; 1.58)	1.78 (1.41; 2.25)	1.33 (1.18; 1.49)	<0.0001	
	With diabetes	13,373	75	1.00 (Ref.)	1.61 (0.87; 2.99)	2.83 (1.53; 5.21)	1.69 (1.25; 2.29)	0.001	
Model 2	Without diabetes	333,757	519	1.00 (Ref.)	1.30 (1.07; 1.59)	1.78 (1.40; 2.25)	1.33 (1.18; 1.49)	<0.0001	
	With diabetes	13,373	75	1.00 (Ref.)	1.69 (0.91; 3.13)	2.88 (1.55; 5.35)	1.70 (1.25; 2.30)	0.001	
CVD incidence									
Model 0	Without diabetes	333,757	3,966	1.00 (Ref.)	1.20 (1.12; 1.29)	1.45 (1.33; 1.58)	1.20 (1.15; 1.26)	<0.0001	
	With diabetes	13,373	335	1.00 (Ref.)	1.08 (0.82; 1.42)	1.87 (1.43; 2.46)	1.39 (1.20; 1.60)	<0.0001	
Model 1	Without diabetes	333,757	3,966	1.00	1.23 (1.15; 1.32)	1.51 (1.39; 1.65)	1.23 (1.18;	<0.0001	

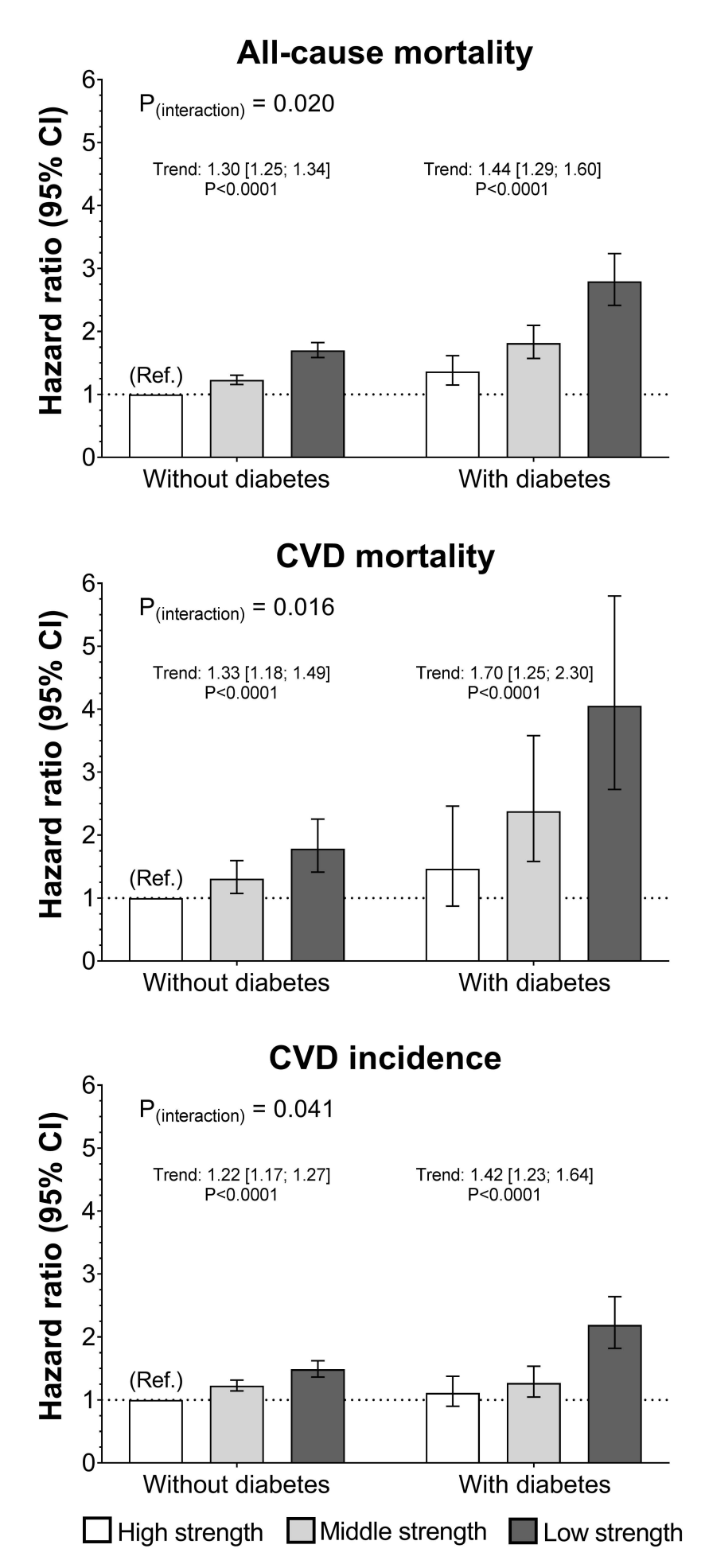
				(Ref.)			1.28)		
	With diabetes	13,373	335	1.00 (Ref.)	1.12 (0.85; 1.47)	1.98 (1.50; 2.59)	1.42 (1.24; 1.64)	<0.0001	
Model 2	Without diabetes	333,757	3,966	1.00 (Ref.)	1.23 (1.14; 1.32)	1.49 (1.36; 1.62)	1.22 (1.17; 1.27)	<0.0001	
	With diabetes	13,373	335	1.00 (Ref.)	1.14 (0.87; 1.50)	1.98 (1.50; 2.60)	1.42 (1.23; 1.64)	<0.0001	

Data is presented as hazard ratio and 95% CI. People on the highest category for grip strength were used as reference category. Participants who were diagnosed with diabetes before the age of 30 years were removed from the analysis. All-analysis were performed as a landmark analysis with follow-up commenced two years after recruitment and including participants who were event-free at this time. In addition, participants with comorbidities at baseline were excluded from all-analysis (depression, COPD, chronic asthma, chronic liver diseases, alcohol problems, substance abuse, eating disorders, schizophrenia, cognitive impartment, Parkinson, dementia, chronic pain syndrome, heart diseases, inflammatory diseases, arthrosis, arthritis and cancer (n= 103,755).

Model 0 was adjusted for age, sex, ethnicity, deprivation index, professional qualifications, gross income, employment and month of recruitment.

Model 1 was also adjusted for duration of diabetes, systolic blood pressure, and baseline prevalence of hypertension and history of recent medication for diabetes (insulin), hypertension and cholesterol.

Model 2 was also adjusted for BMI categories, smoking, TV-viewing, PC-screen time, categories of sleep duration, physical activity and dietary intake (alcohol, fruit and vegetable, red meat, processed meat and oily fish intake).


All-cause mortality
P(interaction) = 0.020
Trend: 1.30 [1.25; 1.34]
P<0.0001
Trend: 1.44 [1.29; 1.60]
P<0.0001
Hazard ratio (95% CI)
(Ref.)
Without diabetes
With diabetes
CVD mortality
P(interaction) = 0.016
Trend: 1.33 [1.18; 1.49]
P<0.0001
Trend: 1.70 [1.25; 2.30]
P<0.0001
CVD incidence
P(interaction) = 0.041
Trend: 1.22 [1.17; 1.27]
P<0.0001
Trend: 1.42 [1.23; 1.64]
P<0.0001
High strength
Middle strength
Low strength

SUPPLEMENTARY MATERIAL

Table S1. Cut-off points for age and sex specific grip strength categories.

Sex	Age group	T1 (Lower)	T2	T3 (Higher)
Women	<56 years	<23	23 – 28	>28
	56 to 65 years	<20	20 – 25	>25
	>65 years	<18	18 – 23	>23
Men	<56 years	<38	38 – 46	>46
	56 to 65 years	<35	35 – 42	>42
	>65 years	<33	33 – 39	>39

Data presented as kg.