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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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

Grip strength and diabetes are predictors of mortality and cardiovascular disease (CVD), but whether these risk factors interact to predispose to adverse health outcomes is unknown. This study determined 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 by using UK Biobank. Cox proportional hazards models were used to explore the associations between both grip strength and diabetes and the outcomes of all-cause mortality and CVD incidence/mortality as well as to test for interactions between diabetes and grip strength.

RESULTS

347,130 UK Biobank participants with full data available (mean age 55.9 years, BMI 27.2 kg/m^2, 54.2% women) were included in the analysis, of which 13,373 (4.0%) had diabetes. Over a median follow-up of 4.9 years (range 3.3–7.8 years), 6,209 died (594 as a result of CVD), and 4,301 developed CVD. Participants with diabetes were at higher risk of all-cause and CVD mortality and CVD incidence. Significant interactions ($P < 0.05$) existed whereby the risk of CVD mortality was higher in participants with diabetes with low (hazard ratio [HR] 4.05 [95% CI 2.72, 5.80]) versus high (HR 1.46 [0.87, 2.46]) grip strength. 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 subgroup of patients with diabetes. Intervention studies are required to determine whether resistance exercise can reduce risk.

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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 aging, muscle function and mass decrease from ~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. A cross-sectional analysis of data from the Health, Aging, and Body Composition Study (485 adults 70–79 years of age with type 2 diabetes and 2,133 without) showed that people with type 2 diabetes have lower leg (men only) and grip strength (3) and that after 6 years' follow-up, they lose leg but not grip strength at a greater rate than healthy counterparts of comparable age (4,5).

Because skeletal muscle function is associated with health outcomes, this lower muscle function could contribute to the greater risk of developing comorbidities and mortality in people with type 2 diabetes. Thus, in addition to the accelerated loss of muscle mass/function, people with type 2 diabetes have been shown to be 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 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 is 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 for wider lifestyle factors and had no comparison of this relationship with that of people without diabetes. Whether this relationship holds after more-robust adjustment and how these risks compare with 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 and CVD incidence in UK Biobank, a large population cohort study of participants age 40–69 years.

RESEARCH DESIGN AND METHODS

Study Design

Between April 2007 and December 2010, UK Biobank recruited 502,628 participants (5.5% response rate, the majority of whom were age 40–70 years) from the general population (11). Participants attended 1 of 22 assessment centers across England, Wales, and Scotland (12,13) where they completed a touch screen questionnaire, had physical measurements taken, and provided biological samples as previously described (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. Sociodemographic factors (age, ethnicity, Townsend deprivation index, professional qualifications, income, employment, and month of recruitment), health-related variables (duration of diabetes in years, systolic blood pressure, and medication history for diabetes [insulin], cholesterol, and blood pressure as well as prevalent diabetes and hypertension at baseline), and lifestyle factors (smoking status, BMI categories, time spent on television [TV] viewing, discretionary personal computer [PC] screen time, total physical activity, sleep duration categories, and dietary intake [alcohol, fruits and vegetables, red meat, processed meat, oily fish]) were treated as potential confounders. Presence of diabetes was determined from self-report of a physician diagnosis and captured people with type 1 and type 2 diabetes. In our analysis, we excluded those who developed diabetes at age <30 years (n = 1,663) to 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 mellitus (n = 1,072), the latter because it is often temporary in nature. To reduce the effect of reverse causality, all analyses were performed as landmark, with follow-up commencing 2 years after recruitment and including participants who were event free at this time. In addition, participants with comorbidities at baseline were excluded from all analyses (depression, chronic obstructive pulmonary disease [COPD], chronic asthma, chronic liver disease, alcohol problems, substance abuse, eating disorders, schizophrenia, cognitive impartment, Parkinson disease, dementia, chronic pain syndrome, heart disease, inflammatory disease, arthrosis, arthritis, CVD, and cancer [n = 103,755]). We included 13,373 people with diabetes in the study.

Study Procedure

Date of death was obtained from death certificates held within the National Health Service Information Centre (England and Wales) and the National Health Service Central Register Scotland (Scotland). Date and cause of hospital admissions were identified through record linkage to Health Episode Statistics (England and Wales) and the Scottish Morbidity Records (Scotland). Detailed information about the linkage procedure can be found at http://content.digital.nhs.uk/services. At the time of analysis, mortality data were available up to 31 January 2016. Mortality analysis was therefore censored at these dates or date of death, whichever occurred earlier. Hospital admission data were available until 31 March 2015, resulting in the disease-specific outcome analysis being censored at these dates or the date of first disease incidence or death, whichever occurred earlier. Incident CVD was defined as a hospital admission or death with ICD-10 code I60, I61, I63, I64, I21, I21.4, or I21.9.

Grip strength, as a proxy for muscular strength, was measured by using a Jamar J00105 hydraulic hand dynamometer. Isometric grip force was assessed from a single 3-s maximal grip effort of the right- and left-side arms with participants seated upright with their elbow by their side and flexed at 90° so that their forearm was facing forward and resting on an armrest. The mean of the right- and left-side values, expressed in absolute units (kilograms), 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 (Supplementary Table 1).

Physical activity was based on self-report by using the International Physical Activity Questionnaire short form (15), and total physical activity was calculated as the sum of walking, moderate, and vigorous activity measured as metabolic equivalents (MET-h/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 >24 h (which excluded 705 participants). Discretionary time spent on TV viewing and PC screen time were collected by using self-reported questionnaires. Subjective sleep

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

Sociodemographic characteristic	Overall	Without diabetes			With diabetes		
		Low strength	Middle strength	High strength	Low strength	Middle strength	High strength
Total participants	347,130	60,979	136,679	136,099	3,749	5,367	4,257
Women	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)	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							
Low	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)
High	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 qualification							
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/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 level/GCSE 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)
CSE 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 qualification	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							
<£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)
£18,000–51,999	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)
>£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							
Paid 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)
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)
Race/ethnicity							
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/other	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							
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)
Former	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	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 category							
Underweight (<18.5 kg/m^2)	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 kg/m^2)	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 kg/m^2)	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 kg/m^2)	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)	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	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 (%)	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							
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)	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)	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)	1.2 (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 category							
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)

Continued on p. 4

Table 1—Continued

Sociodemographic characteristic	Overall	Without diabetes			With diabetes		
		Low strength	Middle strength	High strength	Low strength	Middle strength	High strength
Dietary intake							
TE (kcal/day)	2,118 (645)	2,097 (666)	2,109 (636)	2,136 (641)	2,080 (731)	2,093 (684)	2,128 (686)
Protein (% 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)
Carbohydrates (% 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 (% 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 fat (% 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 (% 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 (% 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 (portions/week)	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 (portions/week)	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)
Fruits and vegetables (g/day)	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 (portions/week)	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							
Duration of diabetes (years)	0.2 (1.6)	0	0	0	6.7 (6.4)	6.0 (5.8)	5.5 (5.7)
Systolic blood pressure (mmHg)	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)	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	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 BP							
None	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	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	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 are *n* (%) for categorical variables or mean (SD) for continuous variables. Data were available for 210,064 participants. A/AS, advanced; CSE, Certificate of Secondary Education; GCSE, General Certificate of Secondary Education; HNC, Higher National Certificate; HND, Higher National Diploma; NVQ, National Vocational Qualification; O, ordinary; TE, total energy.

duration was obtained by asking the following: About how many hours of sleep do you get in every 24 h? On the basis of this question, we derived a categorical sleep duration variable (short sleeper <7 h/day, normal sleeper 7–9 h/day, long sleepers >9 h/day).

Dietary information was collected in a subset of participants (*n* = 157,223 with dietary and diabetes data available) through the Oxford WebQ, a Web-based 24-h recall questionnaire developed specifically as a low-cost instrument for assessing diet in large-scale prospective studies. Compared with 24-h dietary recall, the mean Spearman correlation of the 21 nutrients obtained from the WebQ was 0.6, with the majority between 0.5 and 0.9 (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* (17). For participants who completed more than one online dietary questionnaire, mean values were calculated from all the information provided, with variation between repeated measurements ranging from 26 to 34% as described elsewhere (16). The intake of other food items, such as red meat, processed meat, oily fish, and fruits and vegetable, were collected by using a touch screen questionnaire on the reported frequency of consumption. These data were available for all participants.

Area-based socioeconomic status was derived from postal code of residence by using the Townsend Deprivation Score (18). Other sociodemographic information such as employment (paid employment, retired, unable to work, unemployed, student, and other), professional qualifications (college or university, A [advanced] or O [ordinary] levels, General Certificate of Secondary Education, Certificate of Secondary Education, 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 categorized into never, former, and current. Medical history (physician diagnosis of depression, COPD, chronic asthma, chronic liver disease, alcohol problems, substance abuse, eating disorders, schizophrenia, cognitive impairment, Parkinson disease, dementia, chronic pain syndrome, heart disease, inflammatory disease, 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 visit. BMI was calculated as weight divided by height squared, and the World Health Organization criteria were used to classify BMI as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30.0 kg/m^2). Waist circumference was measured with a standardized protocol by trained nurses, and central obesity was derived by using 88 cm and 102 cm as cutoff points for women and men, respectively. Body composition (body fat as percentage and fat free mass in kilograms) was measured by trained nurses who used bioimpedance (range 1–75% in 0.1% increments on a Tanita BC-418MA body composition analyzer). Additional details about these measurements can be found in the UK

Table 2—Cox proportional hazards models for all-cause mortality and CVD incidence and mortality in participants with diabetes

	Total participants, *n*	Deaths/events, *n*	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

People without diabetes were used as the reference category. Participants who were diagnosed with diabetes before age 30 years were removed from the analysis. All analyses were performed as a landmark analysis, with follow-up commencing 2 years after recruitment and including participants who were event free at that time. In addition, participants with comorbidities at baseline (depression, COPD, chronic asthma, chronic liver disease, alcohol problems, substance abuse, eating disorders, schizophrenia, cognitive impairment, Parkinson disease, dementia, chronic pain syndrome, heart disease, inflammatory disease, arthrosis, arthritis, and cancer [*n* = 103,755]) were excluded from all analyses. Model 0 included age, sex, ethnicity, deprivation index, professional qualifications, gross income, employment, and month of recruitment. Model 1 was 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 adjusted for model 1 plus BMI categories, smoking, TV viewing, PC screen time, categories of sleep duration, and dietary intake (alcohol, fruits and vegetables, red meat, processed meat, and oily fish).

Biobank online protocol (www.ukbiobank.ac.uk).

Statistical Analysis

Associations between diabetes and prospective health outcomes (all-cause mortality, CVD incidence, and CVD mortality) were investigated by using Cox proportional hazards models. The results were reported as hazard ratios (HRs) together with 95% CIs. To reduce the effect of reverse causality, all analyses were performed as a landmark analysis, with follow-up commencing 2 years after recruitment and including participants who were event free at that time. In addition, participants with comorbidities at baseline were excluded from all analyses (*n* = 103,755).

To investigate whether diabetes diagnosis was associated with a higher hazard for mortality and CVD incidence, we performed Cox proportional hazards regression modeling by fitting diabetes into the model as a binary variable (no = 0, yes = 1). All analyses are presented as the three models adjusted as specified below.

To investigate whether levels of grip strength modified the associations between diabetes and health outcomes, multiplicative interaction between diabetes and age- and sex-specific categories of grip strength (coded as an ordinal variable [i.e., high = 0, middle = 1, low = 2]) was assessed by fitting the relevant parameters into the model. Linearity was explored with fractional polynomial 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. Model 1 adjusted for model 0 plus duration of diabetes, systolic blood pressure, baseline prevalence of hypertension, and history of recent medication for diabetes (insulin), hypertension, and cholesterol. Model 2 adjusted for model 1 plus lifestyle factors, including BMI categories, smoking, TV viewing, PC screen time, categories of sleep duration, and dietary intake (alcohol, fruits and vegetables, red meat, processed meat, and oily fish). Physical activity was included as a covariate only when the association between diabetes and health outcomes was investigated but not for the interaction between grip strength and diabetes because grip strength is a proxy of total levels of physical activity across the life span. The proportional hazards assumption were checked by tests that are based on Schoenfeld residuals. All analyses were performed by using Stata 14 statistical software (StataCorp).

RESULTS

Of the 502,628 participants recruited to UK Biobank, 347,130 were included in this study, of which 13,373 reported having diabetes (diagnosed after 30 years of age and having no baseline comorbidities). The mean follow-up period was 4.9 years (range 3.3–7.8 years) for all-cause and CVD mortality and 4.0 years (range 2.4–7.0) for CVD incidence. Over the follow-up period, 4,301 participants developed CVD, and 6,209 deaths occurred (594 as a result of CVD).

The main characteristics of the participants by diabetes status and categories of grip strength are summarized in Table 1. The HRs for all-cause mortality and CVD incidence and mortality were significantly higher in participants with diabetes than in individuals without diabetes (Table 2). Although the associations were slightly attenuated after adjustment for further confounding factors, the associations remained significant. In addition, the association between diabetes and health outcomes was modified 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 $P = 0.041$) (Fig. 1 and Table 3). Compared with individuals without diabetes with high grip strength, participants with diabetes and low grip strength had a higher risk of all-cause mortality (HR 2.79 [95% CI 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, participants with diabetes and 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 a significantly increased risk of CVD

mortality (HR 1.46 [0.87, 2.46]) or CVD incidence (HR 1.11 [0.90, 1.37]) (Fig. 1). The trend of HRs per category decrease in grip strength for participants with diabetes and individuals without diabetes across all three models also are summarized in Table 3. Although the association was slightly attenuated, it remained significant for all three levels of adjustment.

CONCLUSIONS

The main finding of the current study is that the higher risk of CVD associated with diabetes is restricted to a subgroup of people with diabetes and low grip strength. In contrast, people with diabetes and high grip strength are not at significantly increased risk of CVD.

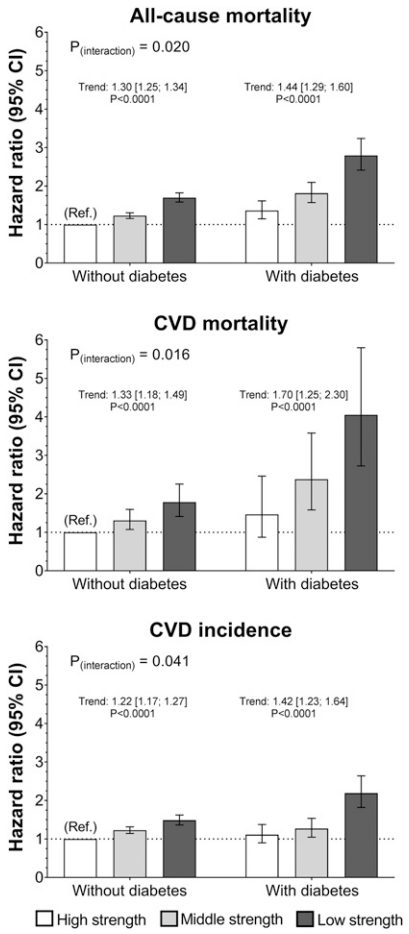

Figure 1—Association of all-cause mortality, CVD mortality, and CVD incidence by diabetes and grip strength strata. Individuals with diabetes and high grip strength were used as the reference group (Ref.). The model was adjusted for age; sex; ethnicity; deprivation index; professional qualifications; gross income; employment; month of recruitment; duration of diabetes; systolic blood pressure; baseline prevalence of hypertension; 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, fruits and vegetables, red meat, processed meat, and oily fish).

Because skeletal muscle is of primary importance not only from a functional point of view (19) but also as the primary protein store and site of glucose disposal (20–22), it plays an important metabolic role (23). 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 agree with the literature that demonstrates a lower and a more rapid loss of muscle strength in people with type 2 diabetes (3,5). The precise mechanisms that underlie this lower muscle mass in people with diabetes has yet to be determined, and before the current study, no investigation to our knowledge has been undertaken to explore how muscle function interacts with the deleterious effects of diabetes on health outcomes.

That people with type 2 diabetes are at a greater risk of all-cause mortality and have higher rates of CVD is well established (6,7), and this risk increases the longer a person has type 2 diabetes (8,9). The current data demonstrate that a low grip strength is associated with further elevations in the already high risk of all-cause mortality, CVD incidence, and CVD mortality in people with diabetes. These findings agree with those of Lopez-Jaramillo et al. (10) and confirm that such associations exist in a larger population and remain even after adjustment for a wide variety of sociodemographic 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. Relative to people without diabetes and a high grip strength, people with and without diabetes and low grip strength have higher hazards for all-cause and CVD mortality and CVD incidence. In those with diabetes and high grip strength, a higher hazard for all-cause mortality, relative to those without diabetes and high grip strength, was observed, with no difference in the hazard for CVD mortality and incidence. These data have 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 randomized controlled trials to determine whether and to what extent they are causal.

Some precedence indicates that these associations may be causal and that such interventions may be beneficial. For example, a general lifestyle intervention in people with impaired glucose tolerance has been shown to reduce the incidence of cardiovascular and all-cause mortality and diabetes (25). These findings are not ubiquitous, however, with the Look AHEAD (Action for Health in Diabetes) 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 designed to increase strength specifically. The main way to increase muscle strength is through resistance exercise training, which has been shown in trials to improve many CVD risk factors (27). If causality were to be demonstrated, the implementation of the measurement of grip strength in a clinical setting would be relatively straightforward because grip strength measurement requires little training, is simple and inexpensive 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. Although grip strength is highly correlated with leg strength and 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, although monitoring grip strength may be useful to identifying at-risk populations, it may not be useful in monitoring the efficacy of resistance exercise interventions.

This study has several 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 (31,32). Therefore, caution should be heeded in generalizing summary statistics, such as the prevalence of diabetes and obesity, to the general population. This does not detract from the ability to generalize

Table 3—Cox proportional hazards models for all-cause mortality and CVD incidence and mortality in participants with diabetes by grip strength category

			Age- and sex-specific grip strength category, HR (95% CI)				*P* value	
	Total, *n*	Deaths/events	Higher	Middle	Lower	Trend	Trend	Interaction
All-cause mortality								
Model 0								
Without diabetes	333,757	5,640	100 (Ref)	1.22 (1.15, 1.29)	1.69 (1.57, 1.81)	1.29 (1.25, 1.34)	< 0.0001	0.009
With diabetes	13,373	569	100 (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	100 (Ref)	1.23 (1.16, 1.30)	1.70 (1.59, 1.83)	1.30 (1.25, 1.34)	< 0.0001	0.010
With diabetes	13,373	569	100 (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	100 (Ref)	1.23 (1.16, 1.30)	1.70 (1.58, 1.82)	1.30 (1.25, 1.34)	< 0.0001	0.020
With diabetes	13,373	569	100 (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	100 (Ref)	1.27 (1.04, 1.55)	1.71 (1.36, 2.16)	1.30 (1.16, 1.47)	< 0.0001	0.019
With diabetes	13,373	75	100 (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	100 (Ref)	1.30 (1.07, 1.58)	1.78 (1.41, 2.25)	1.33 (1.18, 1.49)	< 0.0001	0.017
With diabetes	13,373	75	100 (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	100 (Ref)	1.30 (1.07, 1.59)	1.78 (1.40, 2.25)	1.33 (1.18, 1.49)	< 0.0001	0.016
With diabetes	13,373	75	100 (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	100 (Ref)	1.20 (1.12, 1.29)	1.45 (1.33, 1.58)	1.20 (1.15, 1.26)	< 0.0001	0.042
With diabetes	13,373	335	100 (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	100 (Ref)	1.23 (1.15, 1.32)	1.51 (1.39, 1.65)	1.23 (1.18, 1.28)	< 0.0001	0.037
With diabetes	13,373	335	100 (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	100 (Ref)	1.23 (1.14, 1.32)	1.49 (1.36, 1.62)	1.22 (1.17, 1.27)	< 0.0001	0.041
With diabetes	13,373	335	100 (Ref)	1.14 (0.87, 1.50)	1.98 (1.50, 2.60)	1.42 (1.23, 1.64)	< 0.0001	

People in the highest category for grip strength were used as the reference (Ref) category. Participants who were diagnosed with diabetes before the age of 30 years were removed from the analysis. All analyses were performed as a landmark analysis, with follow-up commencing 2 years after recruitment and including participants who were event free at that time. In addition, participants with comorbidities at baseline (depression, COPD, chronic asthma, chronic liver disease, alcohol problems, substance abuse, eating disorders, schizophrenia, cognitive impairment, Parkinson disease, dementia, chronic pain syndrome, heart disease, inflammatory disease, arthrosis, arthritis, CVD, and cancer [*n* = 103,755]) were excluded from all analyses. Model 0 included age, sex, ethnicity, deprivation index, professional qualifications, gross income, employment, and month of recruitment. Model 1 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 adjusted for model 1 plus BMI category, smoking, TV viewing, PC screen time, category of sleep duration, physical activity, and dietary intake (alcohol, fruits and vegetables, red meat, processed meat, and oily fish).

estimates of the magnitude of associations. The current study benefited from a large number of participants recruited from the general population across the U.K. We had sufficient power to undertake analysis by age and grip strength categories. However, rather than grip strength having a causally protective effect versus mortality or subsequent disease incidence, it may be a marker of generally better health at baseline, and although we attempted to reduce the potential for reverse causality and confounding in our analysis by performing 2-year landmark analysis and excluding individuals with a medical diagnosis of chronic comorbidities at baseline, the potential for both to influence the results remains. Another limitation of the current study is data bias because the study only included people with diabetes who had survived long enough to be recruited into the study, i.e., many people with diabetes who would have been eligible for inclusion in this study will have already died. Diabetes was ascertained by self-report of a physician diagnosis; therefore, incomplete ascertainment is possible but unlikely to introduce a systematic error. In the SHIELD (Study to Help Improve Early Evaluation and Management of Risk Factors Leading to Diabetes) screening survey, Bays et al. (33) reported that the prevalence of diabetes is similar when based solely on self-report compared with clinical and laboratory corroboration of self-reports, as in the National Health and Nutrition Examination Survey. Schneider et al. (34) also showed that self-reported diabetes is >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 of age, the overwhelming majority of cases will be type 2. Data on physical activity and sedentary behavior was self-reported, which has limitations in accuracy (35) and does not capture specific forms of exercise, such as resistance training, likely to have an effect on the associations we have observed in the current study. In all studies involving nutritional epidemiology, uncertainties always exist 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 the current 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 reporting bias as a result of social desirability. The information was collected by 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 shows that the risk of all-cause mortality and CVD incidence and mortality is lower in people with a higher grip strength, both with and without diabetes. The findings suggest that grip strength has clinical utility in identifying people with diabetes at risk for poor health outcomes. Furthermore, targeting interventions such as resistance exercise to people with low grip strength in whom the greatest benefits may be gained could increase clinical effectiveness. These conclusions remain to be tested in future well-designed randomized controlled trials.

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