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In people with type 2 diabetes, sarcopenia is associated with the incidence of cardiovascular disease: A prospective cohort study from the UK Biobank

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Abstract

Aim: To investigate the association of sarcopenia with cardiovascular disease (CVD) incidence in people with type 2 diabetes.

Materials and Methods: A prospective cohort study with 11 974 White European UK Biobank participants with type 2 diabetes, aged 40-70 years, included. Sarcopenia was defined based on the European Working Group on Sarcopenia in Older People as either non-sarcopenic or sarcopenic. Outcomes included CVD, stroke, heart failure (HF) and myocardial infarction (MI). The association between sarcopenia and the incidence of outcomes was investigated using Cox proportional hazard models adjusted for sociodemographic and lifestyle factors. The rate advancement period was used to estimate the time period by which CVD is advanced because of sarcopenia.

Results: Over a median follow-up of 10.7 years, 1957 participants developed CVDs: 373 had a stroke, 307 had an MI and 742 developed HF. Compared with non-sarcopenia, those with sarcopenia had higher risks of CVD (HR 1.89 [95% CI 1.61; 2.21]), HF (HR 2.59 [95% CI 2.12; 3.18]), stroke (HR 1.90 [95% CI 1.38; 2.63]), and MI (HR 1.56 [95% CI 1.04; 2.33]) after adjustment for all covariates. Those with sarcopenia had CVD incidence rates equivalent to those without sarcopenia who were 14.5 years older. Similar results were found for stroke, HF and MI.

Conclusions: In people with type 2 diabetes, sarcopenia increased the risk of developing CVD, which might occur earlier than in those without sarcopenia. Therefore, sarcopenia screening and prevention in patients with type 2 diabetes may be useful to prevent the complications of CVD.

KEYWORDS
gait speed, hand strength, heart diseases, muscle mass, skeleton muscle, type 2 diabetes

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1 | INTRODUCTION

Cardiovascular disease (CVD) is a major cause of death in people with type 2 diabetes.[1] A systematic review summarized data across the world from 2007 to 2017 on 4 549 481 people with type 2 diabetes and reported that the prevalence of CVD in people with type 2 diabetes (from 53 studies) was 32.2%, while the prevalence of stroke, myocardial infarction (MI) and heart failure (HF) 7.6% (from 39 studies), 10.0% (from 13 studies) and 14.9% (from 14 studies), respectively.[2] Moreover, the systematic review reported that CVD was the cause of death in 9.9% of people with type 2 diabetes, which represented one-half of all deaths.[2] Although the association between type 2 diabetes and CVD has been known for many years, the relationship is not fully understood.[3]

Muscle strength is an emerging risk factor for CVD, and it is known that muscle strength is lower in people with type 2 diabetes[4] because of an accelerated loss of muscle with age.[5] The decline in muscle strength and size with age is called sarcopenia, a term initially coined by Irwin H. Rosenberg.[6] The prevalence of sarcopenia in people with type 2 diabetes has been reported as between 7% and 29.3%,[7] and this could potentially be associated with the excess CVD risk in people with type 2 diabetes.

This suggestion is based on previous research that has shown that low muscle strength is associated with an increased risk of a broad range of health outcomes.[8] Furthermore, it has been shown that the excess CVD risk in people with type 2 diabetes was greater in those with low, versus high, muscle strength.[9] Recent evidence has also shown that sarcopenia is associated with a higher risk of CVD in middle-aged and older adults.[10,11] The complex association between sarcopenia and the risk of CVD in people with type 2 diabetes has been partially addressed in an observational study.[12] In this study of people with type 2 diabetes (with and without anaemia), it was shown that the 10-year CVD risk was 46.2% higher in people with sarcopenia without anaemia and doubled in those with type 2 diabetes and anaemia.[12] Although such observational work is important it has several limitations. For example, in the work of Zeng et al.,[12] the diagnosis of sarcopenia was based on measures of muscle mass, with no consideration of grip strength or gait speed, and CVD risk was calculated from the Framingham score, with no direct assessment of CVD events, and so further study is required.

To extend previous findings, this present study aimed to investigate the association between sarcopenia and the incidence of CVD including stroke, HF and MI in people with type 2 diabetes. The associations of the sarcopenia components (grip strength, muscle mass and gait speed[13]) with the incidence of CVD were also investigated.

2 | MATERIALS AND METHODS

2.1 | Study population

Participants were invited to participate in the UK Biobank prospective cohort study. More than 500 000 participants aged 37-73 years were enrolled (5.5% response rate) and attended one of 22 assessment centres across England, Wales and Scotland during 2006-2010. All participants completed touch screen questionnaires and physical measurements, as well as providing biological samples at baseline. The UK Biobank study was approved by the North West Multi-Centre Research Ethics Committee (Ref. 11/NW/0382 on 17 June 2011). All participants provided written informed consent to participate. The study protocol is available online (http://www.ukbiobank.ac.uk/). This present research was conducted using the UK Biobank resource under application number 71392.

As the criteria to define sarcopenia varies by ethnicity, and as there are not sufficient people from other ethnic minorities in the UK Biobank, the present analysis was restricted to participants who were White European individuals with self-reported diagnosed diabetes at baseline, aged 40-70 years, with no missing covariate data ($N = 11\,974$). The participants were excluded if they had self-reported diagnoses of heart disease (angina, heart attack and stroke) or HF at baseline when these were the respective outcomes (Figure S1).

2.2 | Ascertainment of sarcopenia

Because we restricted inclusion to only White European participants, sarcopenia was defined using the updated definition of the European Working Group on Sarcopenia in Older People (EWGSOP2).[13] People were categorized into a binary variable of non-sarcopenia or sarcopenia. Non-sarcopenia included those with presarcopenia, while sarcopenia included those with sarcopenia and severe sarcopenia, as described elsewhere.[11] The variables used to define sarcopenia were grip strength, muscle mass and gait speed, which were measured by trained staff using standard methods.[14] Briefly, grip strength was measured using a Jamar J00105 hydraulic hand dynamometer. Muscle mass was measured via bioelectrical impedance based on the Janssen equation.[15] Gait speed was approximated using self-reported walking pace, which was categorized as slow, average or brisk.

2.3 | Ascertainment of CVD, stroke, HF and MI

Incident CVD (fatal and non-fatal) was derived from hospital admission databases and death registers across England, Scotland and Wales. Dates and causes of hospital admissions were identified via record linkage to Health Episode Statistics (HES) (England and Wales) and the Scottish Morbidity Records (SMR01) (Scotland). The date of death was taken from the death certificates held within the National Health Service Information Centre (England and Wales) and the National Health Service Central Register Scotland (Scotland). The start of the follow-up was the date of the first assessment visit. Hospital admission data and mortality data were available until 1 June 2020. Based on the International Classification of Diseases (ICD-10), CVD was defined as codes I20-I25, I50, I60-I64 and I70-I74. Stroke was defined as ICD-10 codes I60, I61, I63 and I64; heart failure as I50.0, I50.1 and I50.9; and MI as I21-I23.

2.4 | Covariates

Age at baseline was calculated from the date of birth and the date of baseline assessment. Education and sex were self-reported at baseline. The Townsend deprivation index, an area-based measure of socioeconomic status, was derived from the postcode of residence.[16] Anthropometric assessments were measured by trained nurses using standard procedures as well as calibrated equipment. Body mass index (BMI) was calculated as (weight in kg)/(height in m)^2. Processed meat intake was reported as the frequency of consumption at baseline. Smoking status was self-reported at baseline and categorized as never, previous and current. Alcohol intake was self-reported in the following six categories: daily or almost daily, 3-4 times a week, once or twice a week, 1-3 times a month, on special occasions only and never. Total sedentary time was defined as self-reported discretionary screen time, which was derived by summating TV viewing and leisure PC screen time in hours per day.[17] Total physical activity was calculated from the frequency and duration of walking, moderate and vigorous activity based on the International Physical Activity Questionnaire short form,[18] with categories of less than 300, 300-599 and 600 or more metabolic equivalent of task minutes per week. Type 2 diabetes duration was calculated as age at baseline minus age at diagnosis. Additional details about these measurements can be found in the UK Biobank online protocol.[14]

2.5 | Statistical analyses

The characteristics of the cohort are summarized as mean and standard deviation (SD) for continuous variables, and frequency and percentage (%) for categorical variables. The associations were investigated using Cox proportional hazard models and are reported as hazard ratios (HRs) together with 95% confidence intervals (95% CIs).

The associations between sarcopenia and the incidence of CVD, stroke, HF and MI were adjusted for confounders with two models that included an increasing number of covariates: Model 1 (the minimally adjusted model) included age, sex, deprivation index and education. Model 2 (the fully adjusted model) was also adjusted for processed meat consumption, smoking status, alcohol intake, total sedentary time, total physical activity and type 2 diabetes duration. Sensitivity analysis (Model 3) was conducted by further adjusting for BMI. Non-sarcopenia was the reference group for all analyses.

Propensity score matched analysis was also conducted for the association between sarcopenia in type 2 diabetes and incident CVD. First, the propensity score of having sarcopenia[19] was derived using all covariates (including BMI) in a logistic regression. We then undertook 1:4 nearest neighbour propensity score matching without replacement. Following the matching process, the standardized mean differences and empirical cumulative distribution function statistics for all covariates were less than 0.1 and values of variance ratios were close to 1 (Table S1), indicating a sufficiently balanced matched sample. The distribution plots also showed that matching worked well for the dataset (Figure S2).

Afterwards, the Cox proportional hazard model was used to examine the association between sarcopenia in type 2 diabetes and incident CVD, with the matching group as a strata variable.

The associations of grip strength, muscle mass and walking pace with incident CVD, stroke, HF and MI were examined using the same models mentioned above. Exposures were categorized as binary variables. Grip strength was defined as normal (men ≥ 27 kg; females ≥ 16 kg) and weak (men < 27 kg; females < 16 kg). Muscle mass was classified as normal (men ≥ 7.0 kg/m^2; females ≥ 5.5 kg/m^2) or low (men < 7.0 kg/m^2; females < 5.5 kg/m^2). Walking pace was defined as normal (average or brisk walking pace) and slow.

The rate advancement period (RAP) was used to identify the additional chronological age, where the associated risk of CVD was equivalent to that of sarcopenia.[20] It was calculated as the ratio of log HR of sarcopenia over that of age in years.[20] The RAPs in this current study were based on the HRs from the association between sarcopenia and the incidences of CVD in the fully adjusted model (Model 2).

Statistical analyses were performed using the statistical software STATA 17 (StataCorp LP) and R version 4.1.2 with the package *matchit*. *P* values less than .05 were regarded as statistically significant.

3 | RESULTS

A total of 11 974 participants with type 2 diabetes had available data, with 10 004-11 938 participants included in the different analyses based on the outcomes (Figure **S1**). The median follow-up was 10.7 (interquartile range 9.5; 11.5) years. Over the follow-up period, there were 1957 incident CVD events: 373 of stroke, 742 of HF and 307 of MI.

The baseline characteristics of participants are presented in Table 1. In summary, the mean age of participants was 59.8 (SD 7.0) years, and 68.9% were men. Participants with sarcopenia had higher levels of deprivation and a lower level of education. People with sarcopenia were more probable to be current smokers, but more probable to never drink alcohol. They had higher total sedentary time and lower physical activity.

Figure 1 shows the association between sarcopenia and the incidence of CVD, stroke, HF and MI. In the minimally adjusted model, sarcopenia was associated with a 2-fold (HR 2.04 [95% CI 1.76; 2.37]) higher risk of incident CVD. The risk of CVD in the fully adjusted model (Model 2) was 89% (HR 1.89 [95% CI 1.61; 2.21]) higher among individuals with sarcopenia. After adjusting for BMI (sensitivity analysis), the magnitude of the association was slightly attenuated, but remained statistically significant (HR 1.77 [95% CI 1.51; 2.07]). The propensity score-matching results showed that sarcopenia in patients with type 2 diabetes had a 2-fold (HR 2.01 [95% CI 1.33; 3.16]) higher risk of CVD compared with those without sarcopenia.

For stroke, the magnitude and direction of the association between sarcopenia and incident stroke were similar across all

TABLE 1 Cohort characteristics by sarcopenia.

Characteristics	Non-sarcopenia 11 053 (92.3%)	Sarcopenia 921 (7.7%)	Overall 11 974
Men	7616 (68.9)	504 (54.7)	8120 (67.8)
Age (y), mean (SD)	59.7 (7.0)	61.5 (6.2)	59.8 (7.0)
Townsend deprivation index			
Lower deprivation	3551 (32.1)	156 (16.9)	3707 (31.0)
Middle deprivation	3702 (33.5)	250 (27.1)	3952 (33.0)
Higher deprivation	3800 (34.4)	515 (55.9)	4315 (36.0)
Education qualifications			
College or university degree	3101 (28.3)	131 (14.4)	3232 (27.2)
A levels/AS levels or equivalent	1171 (10.7)	67 (7.4)	1238 (10.4)
O levels/GCSEs or equivalent	2295 (21.0)	163 (17.9)	2458 (20.7)
CSEs or equivalent	486 (4.4)	39 (4.3)	525 (4.4)
NVQ or HND or HNC or equivalent	1034 (9.4)	70 (7.7)	1104 (9.3)
None of the above	2865 (26.2)	441 (48.4)	3306 (27.9)
Smoking status			
Never	4764 (43.1)	350 (38.0)	5114 (42.7)
Previous	5251 (47.5)	435 (47.2)	5686 (47.5)
Current	1038 (9.4)	136 (14.8)	1174 (9.8)
Alcohol intake			
Daily or almost daily	2070 (18.7)	93 (10.1)	2163 (18.1)
3-4 times a week	2135 (19.3)	74 (8.0)	2209 (18.5)
Once or twice a week	2850 (25.8)	184 (20.0)	3034 (25.3)
1-3 times a month	1391 (12.6)	107 (11.6)	1498 (12.5)
Special occasions only	1595 (14.4)	238 (25.8)	1833 (15.3)
Never	1012 (9.2)	225 (24.4)	1237 (10.3)
Processed meat (portion/week)	2.1 (1.0)	2.1 (1.1)	2.1 (1.0)
Body mass index (kg/m^2)	30.6 (5.1)	33.9 (6.6)	30.8 (5.3)
Total sedentary time (hour/day)	5.7 (2.4)	6.2 (3.0)	5.7 (2.4)
Total physical activity			
< 300 MET min per week	1100 (10.0)	351 (38.1)	1451 (12.1)
300-599 MET min per week	1263 (11.4)	138 (15)	1401 (11.7)
≥ 600 MET min per week	8690 (78.6)	432 (46.9)	9122 (76.2)
Walking pace			
Average/brisk pace	11 053 (100.0)	17 (1.9)	11 070 (92.5)
Slow pace	0 (0.0)	904 (98.2)	904 (7.6)
Grip strength			
Normal	11 053 (100.0)	11 (1.2)	11 064 (92.4)
Weak	0 (0.0)	910 (98.8)	910 (7.6)
Muscle mass			
Normal	11053 (100.0)	882 (95.8)	11 935 (99.7)
Low	0 (0.0)	39.0 (4.2)	39.0 (0.3)
Type 2 diabetes duration (y)	8.4 (10.1)	10.3 (11.3)	8.5 (10.2)

Note: Data are presented as mean and SD for continuous variables and as frequency and percentage (%) for categorical variables.

Abbreviations: A level/AS level, advanced/advanced subsidiary level; CSE, certificate of secondary education; GCSE, general certificate of secondary education; HNC, higher national certificate; HND, higher national diploma; MET, metabolic equivalent of task; NVQ, national vocational qualification; O level, ordinary level; SD, standard deviation.

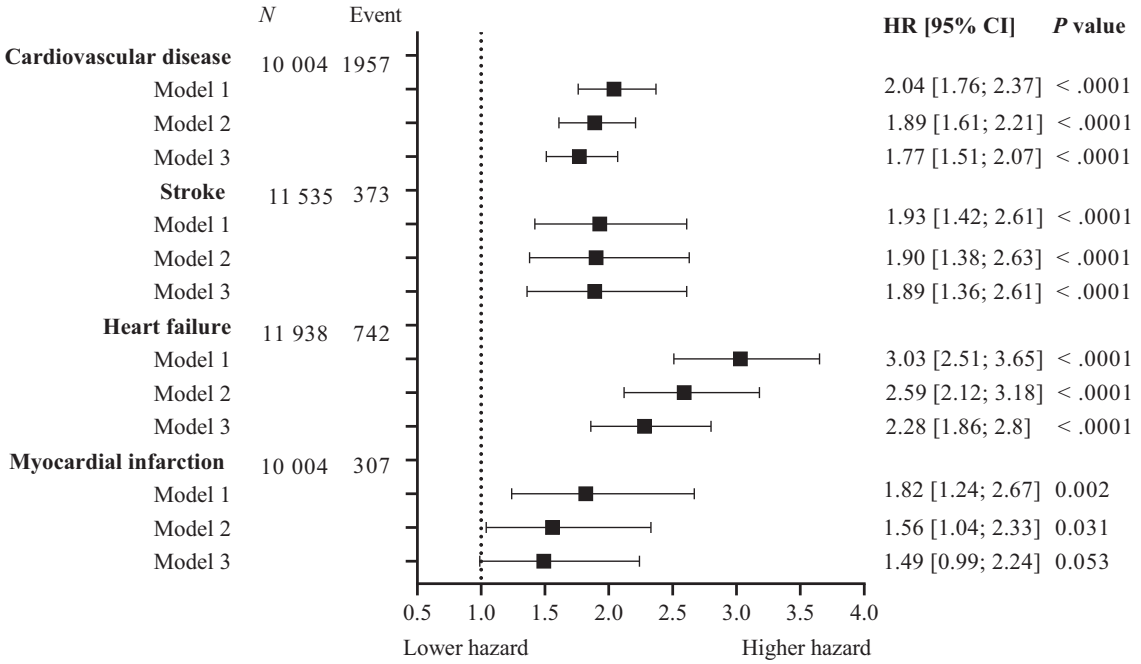

FIGURE 1 Association between sarcopenia and incidence of cardiovascular disease, stroke, myocardial infarction and heart failure in people with type 2 diabetes. Data are presented as hazard ratios (HRs) and their 95% CIs. Non-sarcopenia was the reference group (HR = 1.00). Model 1 (the minimally adjusted model) included age, sex, deprivation index and education. Model 2 (the fully adjusted model) was further adjusted for Model 1, but also included processed meat, smoking status, alcohol intake, total sedentary time, total physical activity and type 2 diabetes duration. Model 3 (sensitivity analysis) was adjusted as in Model 2, but also included body mass index. CI, confidence interval.

models. In Model 2 (the fully adjusted model), sarcopenia was associated with a 90% (HR 1.90 [95% CI 1.38; 2.63]) higher risk of incident stroke. A similar result was found in the sensitivity analysis (HR 1.89 [95% CI 1.36; 2.61]).

For HF, in the minimally adjusted model, sarcopenia was associated with a 3-fold (HR 3.03 [95% CI 2.51; 3.65]) higher risk of incident HF. The magnitude of the association was attenuated when further adjusted for lifestyle factors (HR 2.59 [95% CI 2.12; 3.18]) and in the sensitivity analysis (HR 2.28 [95% CI 1.86; 2.24]).

For MI in the minimally adjusted and fully adjusted model, there was an association of sarcopenia with an 82% (HR 1.82 [95% CI 1.24; 2.67]) and 56% (HR 1.56 [95% CI 1.04; 2.33]) higher risk of incident MI, respectively. However, the association was attenuated when BMI was added as a covariate (sensitivity analysis) (HR 1.49 [95% CI 0.99; 2.24]).

The associations of weak grip strength (Figure S3) and slow walking pace (Figure S4) with incident CVD were examined, the magnitude and direction of the associations were similar as when sarcopenia was the exposure. In the fully adjusted model, participants who had weaker grip strength had a higher risk of CVD (HR 1.85 [95% CI 1.58; 2.17]), stroke (HR 1.82 [95% CI 1.32; 2.53]), HF (HR 2.54 [95% CI 2.07; 3.12]) and MI (HR 1.59 [95% CI 1.06; 2.37]) compared with those with normal grip strength (Figure S3). Likewise, individuals who reported a slow walking pace had a higher risk of CVD (HR 1.92 [95% CI 1.64; 2.24]), stroke (HR 1.84 [95% CI 1.33; 2.55]), HF (HR 2.63 [95% CI 2.15; 3.22]) and MI (HR 1.59 [95% CI 1.06; 2.38]) compared with those with normal pace (Figure S4). The magnitudes of the associations were slightly attenuated but remained statistically significant in the sensitivity analyses after adjustment for BMI.

TABLE 2 The RAP among sarcopenia compared with non-sarcopenia.

Outcomes	RAP (95% CI)
Cardiovascular disease	14.5 (13.1; 15.6)
Stroke	13.7 (10.8; 15.1)
Heart failure	13.7 (13.3; 14.0)
Myocardial infarction	12.8 (2.4; 16.3)

Note: An estimate based on HRs of age and sarcopenia with all outcomes of Model 2 (Figure 1). The unit of RAP estimation was years.
Abbreviations: CI, confidence interval; HR, hazard ratio; RAP, rate advancement period.

The associations between muscle mass and incident CVD varied (Figure S5). There was no association between low muscle mass and incident CVD in the minimal and fully adjusted models, but there was a higher risk of CVD when the analysis was further adjusted for BMI (HR 2.12 [95% CI 1.09; 4.11]). The associations between low muscle mass and incident stroke were similar across the three models, with a 3.4-fold higher risk in the fully adjusted model (Model 2) (HR 3.39 [95% CI 1.25; 9.19]). No association of low muscle mass with incident HF was found (HR 1.07 [95% CI 0.34; 3.34]). The association between low muscle mass and incident MI are not shown because of the small number of participants.

Table 2 shows the RAP in people with sarcopenia, relative to those without. The RAP of 14.5 years for CVD incidence indicated that people with sarcopenia probably had the same CVD incidence as those without sarcopenia who were 14.5 years older. For stroke, HI and MI incidences, people with sarcopenia presumably had the same stroke, HF and MI incidences as those without sarcopenia who were 13.7, 13.7 and 12.8 years older, respectively.

4 | DISCUSSION

The main findings of this current study are that, in people with type 2 diabetes, sarcopenia was associated with a higher risk of incident CVD, stroke, HF, and MI independently of sociodemographic and lifestyle factors. The associations with all outcomes, except MI, were also independent of BMI. When examining which of the components used in the definition of sarcopenia were driving these associations, we found that weak grip strength and slow walking pace were associated with higher incidences of CVD, stroke, HF and MI. People with low muscle mass had a higher risk of stroke and a higher risk of CVD, but only after adjustment for BMI. People with type 2 diabetes who had sarcopenia were probable to have a similar incidence of CVD, stroke and HF 12-15 years earlier than people without sarcopenia.

Evidence of the associations between sarcopenia and its components and the incidence of CVD in people with type 2 diabetes is scarce. The current findings are consistent with a previous study that found that grip strength could modify associations between diabetes and CVD.[9] The study conducted among 347 130 participants in the UK had 4.9 years of follow-up and found that people with type 2 diabetes with lower grip strength had a 98% higher risk of incident CVD compared with people with type 2 diabetes with higher grip strength, after adjusting for major confounders.[9]

Extending these findings, our study found that patients with type 2 diabetes and sarcopenia had a higher risk of stroke, HF and MI than those with type 2 diabetes but without sarcopenia. Therefore, the prevention of sarcopenia in people with type 2 diabetes may be important to protect against the adverse health outcomes associated with type 2 diabetes, particularly in older adults with type 2 diabetes.[21] Our study also found that there was an association between low muscle mass and stroke incidence. While there are no directly comparable studies, a cross-sectional study conducted in 8202 patients with type 2 diabetes in Korea reported that low skeletal muscle mass was at increased risk of carotid atherosclerosis in both women and men.[22]

We also found an association between low muscle mass and CVD incidence after adjusting for BMI. A previous study of patients with type 2 diabetes found that, while lean BMI was not associated with CVD events, those in the top quartile of the predicted fat mass index had a 58% higher risk of CVD events compared with the bottom quartile.[23] The Look Ahead trial investigating CVD risk factors in overweight and obesity with type 2 diabetes concluded that in women who were in the low fat mass index (FMI) group, HbA1c was higher in people with low appendicular muscle mass index (ASMI) when compared with people with high ASMI. Among men, higher HbA1c was only found in those with high FMI compared with those with low FMI at baseline.[24] Because the average BMI of our participants was 30.8 kg/m^2, this might partially explain our findings.

As both sarcopenia and CVD are associated with ageing, we calculated the RAP to estimate the extent to which sarcopenia is associated with the earlier presentation of CVD. To illustrate our findings, 40-year-old participants with sarcopenia were probable to have the same CVD incidence as participants without sarcopenia who were 54.5 years old.

A recent systematic review and meta-analysis of 16 cohort studies summarized the association between muscle-strengthening activities and incident non-communicable diseases (NCDs). They found that muscle-strengthening activities, such as weight/resistance exercise training, were associated with lower risks of all-cause mortality, type 2 diabetes and other major NCDs in adults.[25] Similarly, a systematic review and meta-analysis of randomized controlled trials concluded that medium-term (7-23 weeks) resistance exercise training reduced fasting insulin and insulin resistance.[26] Therefore, we would suggest that increasing muscle strength, via resistance exercise, might be particularly useful in people with type 2 diabetes. As the current data cannot confirm causality then this needs to be tested in an appropriately designed clinical trial.

It is important to note the strengths of the current study. Our findings provided novel knowledge of the association between sarcopenia in people with type 2 diabetes and the incidences of CVD, stroke, HF and MI. We believe that this is the first prospective cohort study to investigate the associations between sarcopenia in people with type 2 diabetes and the incidences of stroke, HF and MI.[27–29] The present study included a large number of participants with a wide age range, which enabled us to include both middle- and older aged adults in the analyses.

Nevertheless, some limitations need to be considered when interpreting our results. The study included only White European participants and used the EWGSOP2 to define sarcopenia. Therefore, caution should be applied when generalizing the results to other ethnic groups or other definitions of sarcopenia. Our sample size for muscle mass was particularly low, therefore, a further study should be conducted on a large population to provide this evidence. The UK Biobank is not representative of the general population in the UK in terms of sociodemographic, physical, lifestyle and health-related characteristics. Despite healthy volunteer selection bias, exposure–disease risk estimates derived from the UK Biobank have been found to be generalizable to the broader population and lifestyle-related factors.[30,31] We attempted to adjust for potential confounders, but some residual confounding may remain, as with any observational study.

In conclusion, sarcopenia in people with type 2 diabetes was associated with a higher risk of developing CVD, stroke, HF and MI. Incident CVD events possibly occurred 14.5 years earlier among those with sarcopenia than those without. Therefore, we suggest that sarcopenia screening in patients with type 2 diabetes may be useful to reduce the complications of CVD. However, further study is required to confirm our findings in an appropriately designed trial.

AUTHOR CONTRIBUTIONS

JB, FKH, CC-M and SRG contributed to the study conception and design. JB, FKH, CC-M and SRG performed the statistical analyses. JB, FKH, CC-M and SRG drafted the manuscript. JB, JPP, FKH, CC-M and SRG interpreted the data, critically reviewed the manuscript and approved the final draft. FKH, CC-M and SRG are the guarantors of this work and, as such, 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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CONFLICTS OF INTERESTS STATEMENT

The authors report no conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15338.

DATA AVAILABILITY STATEMENT

Data can be requested from the UK Biobank (https://www.ukbiobank.ac.uk/).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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