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Dynapenic obesity and the risk of incident type 2 diabetes: The English Longitudinal Study of Ageing

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Abstract

Introduction Obesity is a well-established risk factor for developing type 2 diabetes mellitus (T2DM). Evidence suggests that sarcopenia, the age-related decline in muscle mass and strength, may exacerbate diabetes risk in obese individuals. The aim of this study was to determine the combined effect of obesity and low muscle strength, dynapenia, on the risk of incident T2DM in older adults.

Methods Participants were 5953 (1670 obese) men and women from the English Longitudinal Study of Ageing without known T2DM at baseline and for whom handgrip strength, biochemical and other clinical data were collected. A diagnosis of T2DM was recorded from self-reported physician diagnosis over 6 years.

Results For each unit increase in grip strength there was a reduction in diabetes risk (age and sex, BMI adjusted HR; 0.98; 95% CI 0.96-0.99). The risk of T2DM was elevated in all obese participants, but greatest in those with low handgrip strength (HR=4.93, 95% CI, 2.85, 8.53) compared to non-obese individuals with high handgrip strength. 11 % of the sample met the threshold for weakness (handgrip strength; men <26 kg; women <16kg) that was associated with elevated T2DM risk in obese (HR=3.57, 95% CI, 2.04, 6.24) but not in non-obese (HR=0.86, 95% CI, 0.44, 1.68) compared with normal/non-obese participants.

Conclusion Dynapenic obesity, determined by high body mass index and low handgrip strength, is associated with increased risk of incident T2DM in older people.

Introduction

Sarcopenia describes a syndrome characterised by a progressive, age-related loss of skeletal muscle mass causally related to low muscle strength and impaired physical performance with recent evidence based, clinically relevant diagnostic criteria proposedski [1]. Sarcopenia confers an increased risk of physical disability [2], and death [3]. Reflecting the observations that with ageing the decline in muscle strength exceeds that of muscle mass, a distinct term dynapenia has been proposed to describe the age-related loss of muscle strength[4].

Given that skeletal muscle constitutes the primary site for whole-body insulin-mediated glucose disposal[5], the association between low muscle mass and dysglycemia, independently of obesity, is perhaps unsurprising [6, 7]; there is also a clear association of sarcopenia with frank insulin resistance [8]. Furthermore, several cross-sectional studies have shown an association between handgrip strength, and features of the metabolic syndrome [6, 8]. These data implicate sarcopenia and dynapenia in the pathophysiology of insulin resistance, the metabolic syndrome and type 2 diabetes (T2DM) with advancing age.

Sarcopenic obesity, a co-occurrence of sarcopenia and obesity, is an emerging clinical entity in which these two conditions act in negative synergism in the pathophysiology of both metabolic and functional impairments. The prevalence of sarcopenic obesity depends on the definitions used, and differs considerably when sarcopenia is defined using handgrip strength [9, 10] or muscle mass [11-13]; Batsis *et al.* found that the prevalence of sarcopenic obesity in older adults varied enormously depending on the characteristics of the population and the definition applied [14].

In sarcopenic obesity the metabolic syndrome is more prevalent than in either obesity or sarcopenia alone [15]. There is also cross-sectional evidence to suggest that sarcopenia may exacerbate obesity-associated insulin resistance, a risk factor for T2DM [13] and that

sarcopenic obesity is associated with poorer functional ability than either sarcopenia or obesity alone [16, 17]. However, to our knowledge no prospective evidence is available to determine whether sarcopenia and/or dynapenia has a synergistic effect with obesity on T2DM risk, that is, whether sarcopenic/dynapenic obesity is related to a greater risk of T2DM than non-sarcopenic/dynapenic obesity.

Accordingly, the aim of this study was to utilise longitudinal population data to determine the association between low muscle strength, dynapenia, and risk of incident T2DM in lean and obese non-diabetic older individuals.

Research Design and Methods

Study sample and procedures

The English Longitudinal Study of Ageing (ELSA) is an ongoing cohort study of a nationally representative sample of the English population born on or before 29 February 1952 living in private households. The ELSA data and documentation are publicly available and can be downloaded from the UK Data Service [18]. The sample was drawn using multi-stage stratified probability sampling with postcode sectors selected at the first stage and household addresses selected at the second stage. Participants gave full, informed written consent to participate in the study and ethical approval was obtained from the London multi-centre Research Ethics Committee. Data from participants who had a body mass index (BMI) <18.5 kg/m² were not included in the analysis as underweight is a risk factor for mortality and these participants may have contaminated the ‘normal weight’ category. There were too few underweight participants (n= 48) to be treated as a separate group.

The flow of participants is shown in Figure 1. For the purposes of the present analyses, data collected in 2004/05 (wave 2) were used as the baseline, as this was the first occasion on which clinical information was gathered (n=10,274). From this cohort, 441 were excluded at baseline with a known diagnosis of diabetes. Follow-up was then at two-yearly intervals: 2006/7, 2008/9 and 2010/11. The final analytic sample consisted of 5953 individuals (1670 obese and 4283 non-obese), reflecting 57.9% of the original baseline sample.

Grip strength and anthropometric data collection

Handgrip strength (kg) of the dominant hand was assessed using a hand-held dynamometer, using the average of three measurements[19]. Nurses collected anthropometric data (weight, height, waist circumference). Participants' body weight was measured using Tanita electronic scales without shoes and in light clothing, and height was measured using a Stadiometer with the Frankfurt plane in the horizontal position; body mass index (BMI) was calculated using the standard formula [weight (kg)/height (m) squared]. Waist circumference (cm) was recorded twice mid-way between the iliac crest and lower rib using measuring tape: an average of the first two measurements was used provided these differed by no more than 3cm; otherwise a third reading was taken and the two closest results averaged.

Measurement of clinical characteristics

Demographic and health-related questions included age, sex, cigarette smoking (current, previous, or non-smoker), the frequency of participation in vigorous, moderate, and light physical activities (more than once per week, once per week, one to three times per month, hardly ever), frequency of alcohol intake (daily, 5-6/week, 3-4/week, 1-2/week, 1-2/month, once every couple of months, 1-2/year or never). Depressive symptoms were assessed using the 8-item Centre of Epidemiological Studies Depression (CES-D) scale. Prevalent cardiovascular disease (including angina, heart disease, heart failure, heart murmur,

arrhythmia, stroke) was assessed via self-reported physician diagnosis. Systolic and diastolic blood pressure was measured with an Omron HEM-907 blood pressure monitor three times in the sitting position after 5 min rest between each reading: the initial reading was discarded and the second and third measurements averaged.

Blood samples were obtained from a sub-sample of participants who consented and were eligible and able to give blood; this excluded men and women with clotting and bleeding disorders, or taking anti-coagulant medication. Blood samples were taken and analyzed for C-reactive protein (CRP), fibrinogen, total and high-density lipoprotein (HDL) cholesterol, triglycerides, and glycated haemoglobin (HbA1c). Blood analysis was carried out at the Royal Victoria Infirmary (Newcastle-upon-Tyne, UK). Detailed information on the technicalities of the blood analysis, the internal quality control, and the external quality assessment for the laboratory have been described elsewhere [20].

Incident type 2 diabetes

Diabetes was recorded from self-reported physician diagnosis, which has been previously validated in ELSA through objective HbA1c measures[21]. Participants with known diabetes at baseline were excluded. Incident cases of diabetes were recorded at follow-up in 2006/7, 2008/9, and 2010/11; mean follow-up period 5.9 years. Participants that died, moved away from the UK, or institutionalised over follow up were censored at the date of study exit and retained in the analysis.

Statistical analyses

Characteristics of the study population at baseline were described as means (continuous variables) with standard deviations or the median with interquartile range (skewed variables), and percentages (categorical variables). ANOVA and chi-squared tests were used to test

differences between grip strength groups. C-reactive protein was log-transformed prior to performing these tests. We used Cox proportional hazards models to compute hazard ratios (HR) with 95% confidence intervals (CI) for the association of handgrip strength with incident diabetes. The proportional hazards assumption was examined by comparing the cumulative hazard plots grouped on the various exposure variables, and no appreciable violations were noted. The models were initially run using grip strength as a continuous variable and also fitting a grip strength $\times$ BMI interaction term. A significant ($p < 0.001$) interaction term between hand grip and BMI prompted us to perform these analyses stratified by BMI category (Obesity was defined as $\text{BMI} \geq 30 \text{ kg/m}^2$ and 'non-obese' defined as $\text{BMI} < 30 \text{ kg/m}^2$). We also conducted supplementary analysis according to presence of central obesity defined as waist circumference $>102\text{cm}$ in men and $>88\text{cm}$ in women. Due to the strong associations between sex and grip strength we further categorized the data into sex-specific tertiles of handgrip strength, although no mediating effects of sex were observed after entering an interaction term in relation to diabetes outcome ($p=0.21$). Age was the time scale, and for participants with no record of an event, the data were censored at wave 5 (maximum 6 years follow-up). In multivariate models we adjusted for several covariates in a step-wise fashion: Model 1 contained age and sex; Model 2 contained additional behavioural and health covariates, including smoking, alcohol, physical activity, depressive symptoms and prevalent CVD. All analyses were conducted using SPSS version 21 (IBM SPSS, Armonk, NY, USA).

Results

5953 individuals (1670 obese and 4283 non-obese; 98% white British), who were free of T2DM at baseline, completed follow-up. Of these 124 obese and 92 non-obese individuals were diagnosed with T2DM over the follow-up period.

There were few differences in those excluded compared to those included. For example, the samples were comparable in sex distribution (% men; 42.6% vs. 45%) and age (65 vs. 63y).

The samples differed in physical activity behaviour and mental health, with those excluded reporting higher inactivity (33% vs. 19%), and depressive symptoms (21% vs. 13%).

In men, the range of handgrip strength was 4–35.3, 35.4–44.2, >44.2 kg for bottom, intermediate and top tertiles. The corresponding ranges in women were 4–19.6, 19.7–24.9, >24.9 kg, respectively. Table 1 shows that obese individuals in the lowest sex-specific tertile of handgrip strength were significantly older than those with either intermediate or upper tertile of handgrip strength ($p<0.001$), and were less likely to engage in any moderate or vigorous physical activity (34.4% inactive; $p<0.001$). Despite similar smoking patterns across the three groups, the lowest handgrip strength group had a significantly higher prevalence of cardiovascular disease ($p<0.001$).

Obese participants were well matched in terms of BMI (~ 33 – 34 kg/m^2) and waist circumference, across tertiles of handgrip strength (table 2). At baseline, the low handgrip strength group had significantly higher percentages of glycated haemoglobin compared to those with intermediate or high handgrip strength. Furthermore, the low handgrip strength group had higher circulating concentrations of CRP and fibrinogen compared to those with intermediate strength or low strength ($p<0.001$ and 0.009 respectively).

We assessed the linearity of the association between handgrip strength and incident diabetes in all participants by entering a squared term into the models although no deviation was noted. We observed that for each unit increase in grip strength there is a reduction in diabetes risk (age and sex, BMI adjusted HR; 0.98; 95% CI 0.96–0.99).

The results from the analysis of T2DM risk in *non-obese* and *obese* individuals according to handgrip strength are shown in Table 3. T2DM risk did not significantly differ between the

three tertiles of handgrip strength for non-obese participants after multivariate adjustment. The risk of T2DM was elevated in all obese participants, particularly so in those with low handgrip strength (HR=4.93, 95% CI, 2.85, 8.53) compared to non-obese individuals with high handgrip strength after multivariate adjustment.

Sensitivity analyses

We categorised participants using sex-specific handgrip cut offs (men <26 kg; women <16kg) for those at risk for weakness [1]. 11% of the sample met these thresholds for weakness although the pattern of results largely replicated the original results showing the same finding that sarcopenic obese were at the highest risk of incident diabetes (Table 4). In addition, we used these handgrip cut offs in combination with waist circumference as a measure of central obesity (defined as waist circumference >102cm in men and >88cm in women). When using central obesity rather than body mass index the influence of sarcopenia was less pronounced (Table 5; n= 6134).

Discussion

We found that obese older adults with the lowest tertile of muscle (handgrip) strength had a greater risk of developing T2DM over six years of follow-up compared with individuals of similar age and BMI with greater handgrip strength. Although adjustment for age, sex, physical activity, smoking, alcohol, depressive symptoms and prevalent cardiovascular disease partly attenuated this risk, the association persisted. In contrast, low handgrip strength did not confer a higher risk of incident T2DM in non-obese individuals. This suggests that individuals with dynapenic obesity represent a sub-group of obesity with an amplified risk of T2DM beyond that for individuals with non-dynapenic obesity.

We obtained evidence of a dose-response association, as there was a clear incremental

increase in both incident risk of T2DM and in plasma HbA1c concentration progressively from the upper to lower handgrip strength tertile. There was also a linear reduction in incident diabetes risk for each unit increase in grip strength. Analysis of HbA1c with incident diabetes risk was not performed due to missing biochemistry data.

However, we did not observe significant differences in waist circumference, blood pressure, lipid profile or fasting blood glucose, although low handgrip strength seemed to be accompanied by chronic low-grade inflammation, with significantly higher serum concentrations of highly sensitive CRP (hsCRP) and fibrinogen and a higher prevalence of cardiovascular disease. This association has been noted in several other epidemiological studies [22, 23] and highlights a common pathophysiological defect.

The clinical relevance of measurements of *both* muscle mass and muscle strength is reflected in the revised definition of sarcopenia from the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project to incorporate both anatomical and functional components [1]. These newer guidelines are more clinically meaningful as they denote the functional consequences and thus relate more closely to clinical outcomes. Goodpaster *et al.* examining longitudinal changes in muscle mass and strength in older adults in the Health, Ageing and Body Composition Study demonstrated (annualised) rates of leg strength decline (~3%/year) approximately three times greater than the rates of leg lean mass (~1%/year) [24]. These findings clearly implicate factors other than muscle mass in determining muscle strength and these updated guidelines reflect, and take account of, this important anatomical and functional discrepancy. Thus, low grip strength is likely similarly explained by factors other than low muscle mass. Indeed, many individuals with weakness may not have low muscle mass. This had led to suggestions of a distinct term, dynapenia [25]. For practical reasons, longitudinal measurements collected in this cohort did not extend to quantification of skeletal

muscle mass and we therefore must rely on measurements of muscle strength alone for the current study.

We chose to analyse hand grip as a continuous variable using sex-specific tertiles. In subsequent analysis we used the suggested cut points for weakness according to the FNIH criteria as previously defined (ref). However, only 11.4% of the sample met the threshold for weakness based on their handgrip (this reflects a higher prevalence of sarcopenia as a disabling condition than that observed in the FNIH project of 0.4-4% of elderly women and men) (ref) thus limiting our statistical power. Indeed, one of the limitations of using a cut point, such as the FNIH, is loss of power and information. Thus our approach of using tertiles enabled us to create equal groups across our specific sample, which helped to retain information and better examine linear trends. Interestingly, whichever thresholds for weakness were applied the association between weakness and incident T2DM remained the same for the obese participants.

In many T2DM patients with advancing age, severe obesity and comorbidities including cardiovascular disease and osteoarthritis aerobic exercise is not feasible. In contrast, resistance training provides an effective exercise alternative by increasing muscle mass and strength (and thus counteracting age- and disease-related skeletal muscle loss and muscle weakness), in visceral fat deposition and improvements in insulin sensitivity and glycemic control [26, 27]. Thus our findings are biologically plausible. Skeletal muscle represents a major organ for glucose homeostasis, responsible for up to 75% of post-prandial (i.e. insulin-stimulated) glucose uptake [5]. Low muscle mass might therefore be expected to impair glucose homeostasis. There is epidemiological evidence in obese, older individuals to link sarcopenia with the metabolic syndrome and with T2DM [28], although it is not possible to infer temporality between these conditions from cross-sectional data. Longitudinal studies have shown an accelerated decline in muscle mass over several years in patients already

262 diagnosed with T2DM, compared with age- and BMI-matched healthy controls [29].

263 Although those with low handgrip strength were less likely to be physically active, statistical
264 adjustment for physical activity did not alter the predominant relationship, suggesting that the
265 increased risk of T2DM in weaker individuals does not merely reflect more sedentary
266 behaviour. Evidence from human and transgenic animal models that interventions influencing
267 skeletal muscle growth and/or metabolism are protective against metabolic diseases may
268 provide some further mechanistic insight: preservation of oxidative capacities in aged
269 muscles prevents muscle loss, reduces intramyocellular lipid accumulation and protects
270 against metabolic diseases [30]; up-regulation of PGC1- α , a master regulator of
271 mitochondrial metabolism, protects against age-related muscle loss and improves insulin
272 resistance [31]; and importantly, in patients with T2DM resistance exercise, a potent anabolic
273 stimulus for skeletal muscle, significantly improves glycaemic control [32].

274 We acknowledge some limitations of this study. The nature of large-scale, population-based
275 longitudinal studies makes sample attrition and incomplete data collection inevitable.
276 Biochemical measurements were only available for 4186 from a total of 5953 participants,
277 and this may be a source of selection bias, with participants able to provide samples likely to
278 be in better health. Although we saw that for each unit increase in grip strength there is a
279 reduction in diabetes risk (HR 0.98; 95% CI 0.96-0.99), the missing biochemical data made
280 analysis of the relationship of grip strength with HbA_{1c} impractical.

281 A further limitation is the use of questionnaires to ascertain diagnosis of T2DM, although
282 self-reported physician-diagnosed diabetes has been well validated with HbA_{1c} in the ELSA
283 sample. Since self-reported physician diagnosis of diabetes cannot account for undetected
284 cases, our results might be biased towards the obese sample who may be more likely to be
285 diagnosed because of more frequent contact with health services to treat other risk factors.

Furthermore this potentially could lead to reverse causation with undiagnosed T2DM at baseline being associated with low grip strength. Formal assessment using physical activity monitors and biannual glucose tolerance tests might have afforded further mechanistic insight, particularly with respect to the domains of physical activity and degrees of insulin resistance. Our sample was also predominantly white-European, and results may therefore not directly apply to older adults of other ethnic groups, such as those of black ethnicities.

In conclusion, the risk of developing T2DM was significantly increased in older obese adults with low muscle strength, a finding that cannot be fully explained by levels of physical activity or other risk factors. Our findings suggest that dynapenic obesity in older adults represents a form of obesity which is related to particularly high risk of T2DM. Further research is needed to examine whether strategies to increase muscle strength would reduce diabetes risk in obese older adults.

Author Contributions

All authors were responsible for the conception, design and drafting of the manuscript and approved the final version for publication.

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318

319 **Conflicts of interest**

320 None of the authors have any competing interests to declare.

321

References

1. Studenski SA, Peters KW, Alley DE, Cawthon PM, McLean RR, Harris TB, *et al.* The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. *J Gerontol A Biol Sci Med Sci*. United States 2014: 547-558.
2. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc*. United States 2002: 889-896.
3. Vetrano DL, Landi F, Volpato S, Corsonello A, Meloni E, Bernabei R, *et al.* Association of sarcopenia with short- and long-term mortality in older adults admitted to acute care wards: results from the CRIME study. *J Gerontol A Biol Sci Med Sci* 2014; **69**:1154-1161.
4. Clark BC, Manini TM. Sarcopenia $\neq$ dynapenia. *J Gerontol A Biol Sci Med Sci* 2008; **63**:829-834.
5. DeFronzo RA, Tripathy D. Skeletal Muscle Insulin Resistance Is the Primary Defect in Type 2 Diabetes. *Diabetes Care* 2009; **32**:S157-S163.
6. Sayer AA, Syddall HE, Dennison EM, Martin HJ, Phillips DI, Cooper C, *et al.* Grip strength and the metabolic syndrome: findings from the Hertfordshire Cohort Study. *QJM : monthly journal of the Association of Physicians* 2007; **100**:707-713.
7. Srikanthan P, Hevener AL, Karlamangla AS. Sarcopenia exacerbates obesity-associated insulin resistance and dysglycemia: findings from the National Health and Nutrition Examination Survey III. *PloS one* 2010: e10805.
8. Srikanthan P, Karlamangla AS. Relative muscle mass is inversely associated with insulin resistance and prediabetes. Findings from the third National Health and Nutrition Examination Survey. *J Clin Endocrinol Metab* 2011; **96**:2898-2903.

348 9. Schrager MA, Metter EJ, Simonsick E, Ble A, Bandinelli S, Lauretani F, *et al.*
349 Sarcopenic obesity and inflammation in the InCHIANTI study. *J Appl Physiol (1985)* 2007;
350 **102**:919-925.

351 10. Visser M, van Venrooij LM, Vulperhorst L, de Vos R, Wisselink W, van Leeuwen
352 PA, *et al.* Sarcopenic obesity is associated with adverse clinical outcome after cardiac
353 surgery. *Nutr Metab Cardiovasc Dis* 2013; **23**:511-518.

354 11. Baumgartner RN. Body composition in healthy aging. *Ann N Y Acad Sci* 2000;
355 **904**:437-448.

356 12. Chung JY, Kang HT, Lee DC, Lee HR, Lee YJ. Body composition and its association
357 with cardiometabolic risk factors in the elderly: a focus on sarcopenic obesity. *Arch Gerontol*
358 *Geriatr* 2013; **56**:270-278.

359 13. Srikanthan P, Hevener AL, Karlamangla AS. Sarcopenia exacerbates obesity-
360 associated insulin resistance and dysglycemia: findings from the National Health and
361 Nutrition Examination Survey III. *PloS one* 2010; **5**:e10805.

362 14. Batsis JA, Barre LK, Mackenzie TA, Pratt SI, Lopez-Jimenez F, Bartels SJ. Variation
363 in the prevalence of sarcopenia and sarcopenic obesity in older adults associated with
364 different research definitions: dual-energy X-ray absorptiometry data from the National
365 Health and Nutrition Examination Survey 1999-2004. *J Am Geriatr Soc* 2013; **61**:974-980.

366 15. Lim S, Kim JH, Yoon JW, Kang SM, Choi SH, Park YJ, *et al.* Sarcopenic obesity:
367 prevalence and association with metabolic syndrome in the Korean Longitudinal Study on
368 Health and Aging (KLoSHA). *Diabetes care* 2010; **33**:1652-1654.

369 16. Baumgartner RN, Wayne SJ, Waters DL, Janssen I, Gallagher D, Morley JE.
370 Sarcopenic obesity predicts instrumental activities of daily living disability in the elderly.
371 *Obesity research* 2004; **12**:1995-2004.

- 372 17. Rolland Y, Lauwers-Cances V, Cristini C, Abellan van Kan G, Janssen I, Morley JE,
373 *et al.* Difficulties with physical function associated with obesity, sarcopenia, and sarcopenic-
374 obesity in community-dwelling elderly women: the EPIDOS (EPIDemiologie de
375 l'OSteoporose) Study. *The American journal of clinical nutrition* 2009; **89**:1895-1900.
- 376 18. UK_Data_Archive. ELSA user guide and documentation. 2008.
- 377 19. Hamer M, Stamatakis E. Screen-based sedentary behavior, physical activity, and
378 muscle strength in the English longitudinal study of ageing. *PLoS One* 2013; **8**:e66222.
- 379 20. Graig R, Deverill C, Pickering K. Quality control of blood, saliva and urine analytes.
380 In: Spronston K, J Mindell, eds. *Health Survey for England 2004, Methodology and*
381 *Documentation*. London: The Information Centre 2006: 34-41.
- 382 21. Smith L, Hamer M. Television viewing time and risk of incident diabetes mellitus: the
383 English Longitudinal Study of Ageing. *Diabet Med* 2014; **31**:1572-1576.
- 384 22. Visser M, Pahor M, Taaffe DR, Goodpaster BH, Simonsick EM, Newman AB, *et al.*
385 Relationship of interleukin-6 and tumor necrosis factor-alpha with muscle mass and muscle
386 strength in elderly men and women: the Health ABC Study. *J Gerontol A Biol Sci Med Sci*
387 2002; **57**:M326-332.
- 388 23. Taaffe DR, Harris TB, Ferrucci L, Rowe J, Seeman TE. Cross-sectional and
389 prospective relationships of interleukin-6 and C-reactive protein with physical performance in
390 elderly persons: MacArthur studies of successful aging. *J Gerontol A Biol Sci Med Sci* 2000;
391 **55**:M709-715.
- 392 24. Goodpaster BH, Park SW, Harris TB, Kritchevsky SB, Nevitt M, Schwartz AV, *et al.*
393 The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and
394 body composition study. *J Gerontol A Biol Sci Med Sci* 2006; **61**:1059-1064.
- 395 25. Clark BC, Manini TM. Functional consequences of sarcopenia and dynapenia in the
396 elderly. *Curr Opin Clin Nutr Metab Care* 2010; **13**:271-276.

26. Dunstan DW, Puddey IB, Beilin LJ, Burke V, Morton AR, Stanton KG. Effects of a short-term circuit weight training program on glycaemic control in NIDDM. *Diabetes Res Clin Pract* 1998; **40**:53-61.
27. Eves ND, Plotnikoff RC. Resistance training and type 2 diabetes: Considerations for implementation at the population level. *Diabetes Care* 2006; **29**:1933-1941.
28. Park SW, Goodpaster BH, Strotmeyer ES, de Rekeneire N, Harris TB, Schwartz AV, *et al.* Decreased muscle strength and quality in older adults with type 2 diabetes: the health, aging, and body composition study. *Diabetes* 2006; **55**:1813-1818.
29. Park SW, Goodpaster BH, Lee JS, Kuller LH, Boudreau R, de Rekeneire N, *et al.* Excessive loss of skeletal muscle mass in older adults with type 2 diabetes. *Diabetes care* 2009; **32**:1993-1997.
30. Harrison BC, Leinwand LA. Fighting fat with muscle: bulking up to slim down. *Cell metabolism* 2008; **7**:97-98.
31. Wenz T, Rossi SG, Rotundo RL, Spiegelman BM, Moraes CT. Increased muscle PGC-1alpha expression protects from sarcopenia and metabolic disease during aging. *Proceedings of the National Academy of Sciences of the United States of America* 2009; **106**:20405-20410.
32. Willey KA, Singh MA. Battling insulin resistance in elderly obese people with type 2 diabetes: bring on the heavy weights. *Diabetes care* 2003; **26**:1580-1588.

Figure 1 Flow chart describing the selection of participants for the present study.

Table 1 Demographic characteristics of the sample in relation to grip strength (n=5953)

Variables	Sex-specific handgrip strength tertile ^b				Sex-specific handgrip strength tertile ^b			
	Non-obese (n=4283)				Obese (n=1670)			
	High (n=1391)	Intermediate (n=1502)	Low (n=1390)	p value	High (n=603)	Intermediate (n=571)	Low (n=496)	
Age (y) ^a	58.3±6.1	63.0±8.3	69.6±9.8	<0.05	58.2±6.3	62.8±8.0	67.6±8.9	<0.05
Men (%)	38.0	49.8	50.9	<0.05	39.5	45.5	39.7	0.14
<i>Smoking</i>								
Current	17.8	16.3	16.1	0.44	14.2	15.0	11.3	<0.05
<i>Alcohol intake (%)</i>				<0.05				<0.05
Daily	28.8	27.2	24.3		19.7	19.4	12.9	
At least 1/wk (but not daily)	42.4	41.3	35.2		41.5	34.2	35.5	
Rarely	23.4	24.2	27.5		29.7	35.2	35.1	
Never	5.4	7.3	13.0		9.1	11.2	16.5	
<i>Physical activity (%)</i>								
Inactive	8.8	13.3	27.0	<0.05	16.6	23.8	38.1	<0.05

Moderate (at least 1/week)	48.5	51.4	52.2		55.6	51.5	43.8	
Vigorous (at least 1/week)	42.8	35.3	20.8		27.9	24.7	18.1	
<i>Depressive symptoms (%)</i>	9.3	10.9	16.3	<0.05	12.4	13.3	17.9	<0.05
<i>Prevalent CVD (%)</i>	11.3	12.9	15.8	<0.05	10.8	14.5	15.9	<0.05

^aData presented as mean± SD

^b In men, the range of handgrip strength was 4 – 35.3, 35.4 – 44.2, >44.2 kg for bottom, intermediate and top tertile. The corresponding ranges in women were 4 – 19.6, 19.7 – 24.9, >24.9 kg , respectively.

Table 2 Sarcopenic obesity and biomarkers in the 4,186 individuals in whom biochemical data were available.

Variable	Sex-specific handgrip strength tertile ^a				Sex-specific handgrip strength tertile ^a			
	Non-obese				Obese			
	High (n=1082)	Intermediate (n=1085)	Low (n=908)	p value	High (424)	Intermediate (n=380)	Low (n=307)	p value
Body mass index (kg/m ²)	25.8±2.5	25.7±2.6	25.2±2.7	<0.001	33.9±3.8	33.4±3.6	33.6±3.3	0.38
Waist circumference (cm)	89.0±11.6	90.4±12.2	89.6±13.6	0.005	105.3±16.0	105.6±16.0	105.5±13.1	0.78
Systolic blood pressure (mmHg)	131.2±16.9	133.5±18.9	134.6±19.1	<0.001	138.1±17.1	138.6±18.2	139.5±17.7	0.61
Glycated haemoglobin (%)	5.4±0.5	5.5±0.5	5.5±0.6	<0.001	5.6±0.6	5.6±0.5	5.8±0.8	0.034
Glycated haemoglobin (mmol/mol)	35±5	36±5	37±6		38±8	38±6	40±9	
Total cholesterol (mmol/l)	6.17±1.21	6.02±1.31	5.79±1.19	<0.001	6.16±1.21	5.90±1.31	5.81±1.19	<0.001
HDL cholesterol (mmol/l)	1.62±0.33	1.58±0.33	1.55±0.32	<0.001	1.44±0.33	1.42±0.33	1.42±0.32	0.26
Triglycerides (mmol/l)	1.64±1.33	1.64±1.12	1.63±1.23	0.80	2.08±1.33	2.03±1.12	2.02±1.23	0.58
C-reactive protein (mg/l) ^b	1.3 (1.9)	1.6 (2.4)	1.9 (2.8)	<0.001	3.3 (3.7)	3.0 (4.2)	3.8 (5.4)	<0.001
Fibrinogen (g/l)	2.94±0.67	3.09±0.70	3.23±0.67	<0.001	3.24±0.67	3.28±0.70	3.39±0.67	<0.001

Data presented as mean± SD unless otherwise stated;

^aIn men, the range of handgrip strength was 4 – 35.3, 35.4 – 44.2, >44.2 kg for bottom, intermediate and top tertile. The corresponding ranges in women were 4 – 19.6, 19.7 – 24.9, >24.9 kg , respectively.

^bmedian (interquartile range).

Table 3 Associations between handgrip strength and risk of incident type 2 diabetes among obese and non-obese participants free of physician diagnosed diabetes at baseline (n=5,953).

Sex-specific handgrip strength tertile	Cases/n	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Non-obese participants			
High	21/1391	1.00 (reference)	1.00 (reference)
Intermediate	36/1502	1.54 (0.90, 2.63)	1.49 (0.86, 2.53)
Low	35/1390	1.72 (0.98, 3.02)	1.51 (0.86, 2.66)
Obese participants			
High	33/603	3.47 (2.03, 5.96)	3.25 (1.89, 5.60)
Intermediate	49/571	5.68 (3.42, 9.45)	4.85 (2.90, 8.11)
Low	42/496	5.97 (3.49, 10.23)	4.93 (2.85, 8.53)

Model 1: adjusted for age and sex. **Model 2:** adjusted for age, sex, physical activity, smoking, alcohol, depressive symptoms, prevalent cardiovascular disease (angina, heart disease, heart failure, heart murmur, arrhythmia, stroke)

Table 4 Associations between handgrip strength using a binary cut off point with weakness defined as handgrip < 26kg in men and < 16 kg in women and risk of incident type 2 diabetes among obese and non-obese participants free of physician diagnosed diabetes at baseline (n=5953).

Sex-specific handgrip strength using binary cut *	Cases/n	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Non-obese participants			
Normal	82/3789	1.00 (reference)	1.00 (reference)
Weak	10/494	0.97 (0.49, 1.90)	0.86 (0.44, 1.68)
Obese participants			
Normal	108/1484	3.43 (2.57, 4.57)	3.13 (2.33, 4.18)
Weak	16/186	4.27 (2.47, 7.37)	3.57 (2.04, 6.24)

**Weakness defined as handgrip < 26kg in men and < 16 kg in women.*

Model 1: adjusted for age and sex.

Model 2: adjusted for age, sex, physical activity, smoking, alcohol, depressive symptoms, and prevalent cardiovascular disease (angina, heart disease, heart failure, heart murmur, arrhythmia, stroke)

Table 5 Associations between handgrip strength and risk of incident type 2 diabetes among centrally obese and non-obese participants free of physician diagnosed diabetes at baseline (n=6134).

Sex-specific handgrip strength using binary cut *	Cases/n	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Non-obese participants			
Normal	37/2656	1.00 (reference)	1.00 (reference)
Weak	7/388	1.51 (0.66, 3.43)	1.32 (0.58, 3.00)
Obese participants†			
Normal	158/2742	4.39 (3.07, 6.28)	4.09 (2.85, 5.87)
Weak	19/348	4.82 (2.72, 8.55)	3.99 (2.23, 7.13)

*Weakness defined as handgrip < 26kg in men and < 16 kg in women.

†Central obesity defined as waist circumference >102cm in men and >88cm in women

Model 1: adjusted for age and sex.

Model 2: adjusted for age, sex, physical activity, smoking, alcohol, depressive symptoms, and prevalent cardiovascular disease (angina, heart disease, heart failure, heart murmur, arrhythmia, stroke)