

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

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26 **Abstract**

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

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

36 *Results* For each unit increase in grip strength there was a reduction in diabetes risk (age and
37 sex, BMI adjusted HR; 0.98; 95% CI 0.96-0.99). The risk of T2DM was elevated in all obese
38 participants, but greatest in those with low handgrip strength (HR=4.93, 95% CI, 2.85, 8.53)
39 compared to non-obese individuals with high handgrip strength. 11 % of the sample met the
40 threshold for weakness (handgrip strength; men <26 kg; women <16kg) that was associated
41 with elevated T2DM risk in obese (HR=3.57, 95% CI, 2.04, 6.24) but not in non-obese (HR=
42 0.86, 95% CI, 0.44, 1.68) compared with normal/non-obese participants.

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

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48 **Introduction**

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

55 Given that skeletal muscle constitutes the primary site for whole-body insulin-mediated
56 glucose disposal[5], the association between low muscle mass and dysglycemia,
57 independently of obesity, is perhaps unsurprising [6, 7]; there is also a clear association of
58 sarcopenia with frank insulin resistance [8]. Furthermore, several cross-sectional studies have
59 shown an association between handgrip strength, and features of the metabolic syndrome [6,
60 8]. These data implicate sarcopenia and dynapenia in the pathophysiology of insulin
61 resistance, the metabolic syndrome and type 2 diabetes (T2DM) with advancing age.

62 Sarcopenic obesity, a co-occurrence of sarcopenia and obesity, is an emerging clinical entity
63 in which these two conditions act in negative synergism in the pathophysiology of both
64 metabolic and functional impairments. The prevalence of sarcopenic obesity depends on the
65 definitions used, and differs considerably when sarcopenia is defined using handgrip strength
66 [9, 10] or muscle mass [11-13]; Batsis *et al.* found that the prevalence of sarcopenic obesity
67 in older adults varied enormously depending on the characteristics of the population and the
68 definition applied [14].

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

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

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

80

81 **Research Design and Methods**

82 *Study sample and procedures*

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

94 The flow of participants is shown in Figure 1. For the purposes of the present analyses, data
95 collected in 2004/05 (wave 2) were used as the baseline, as this was the first occasion on
96 which clinical information was gathered (n=10,274). From this cohort, 441 were excluded at
97 baseline with a known diagnosis of diabetes. Follow-up was then at two-yearly intervals:
98 2006/7, 2008/9 and 2010/11. The final analytic sample consisted of 5953 individuals (1670
99 obese and 4283 non-obese), reflecting 57.9% of the original baseline sample.

100 *Grip strength and anthropometric data collection*

101 Handgrip strength (kg) of the dominant hand was assessed using a hand-held dynamometer,
102 using the average of three measurements[19]. Nurses collected anthropometric data (weight,
103 height, waist circumference). Participants' body weight was measured using Tanita electronic
104 scales without shoes and in light clothing, and height was measured using a Stadiometer with
105 the Frankfurt plane in the horizontal position; body mass index (BMI) was calculated using
106 the standard formula [weight (kg)/height (m) squared]. Waist circumference (cm) was
107 recorded twice mid-way between the iliac crest and lower rib using measuring tape: an
108 average of the first two measurements was used provided these differed by no more than
109 3cm; otherwise a third reading was taken and the two closest results averaged.

110 *Measurement of clinical characteristics*

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

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

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

130 *Incident type 2 diabetes*

131 Diabetes was recorded from self-reported physician diagnosis, which has been previously
132 validated in ELSA through objective HbA1c measures[21]. Participants with known diabetes
133 at baseline were excluded. Incident cases of diabetes were recorded at follow-up in 2006/7,
134 2008/9, and 2010/11; mean follow-up period 5.9 years. Participants that died, moved away
135 from the UK, or institutionalised over follow up were censored at the date of study exit and
136 retained in the analysis.

137 *Statistical analyses*

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

141 differences between grip strength groups. C-reactive protein was log-transformed prior to
142 performing these tests. We used Cox proportional hazards models to compute hazard ratios
143 (HR) with 95% confidence intervals (CI) for the association of handgrip strength with
144 incident diabetes. The proportional hazards assumption was examined by comparing the
145 cumulative hazard plots grouped on the various exposure variables, and no appreciable
146 violations were noted. The models were initially run using grip strength as a continuous
147 variable and also fitting a grip strength \times BMI interaction term. A significant ($p < 0.001$)
148 interaction term between hand grip and BMI prompted us to perform these analyses stratified
149 by BMI category (Obesity was defined as $\text{BMI} \geq 30 \text{ kg/m}^2$ and 'non-obese' defined as $\text{BMI} <$
150 30 kg/m^2). We also conducted supplementary analysis according to presence of central
151 obesity defined as waist circumference $>102\text{cm}$ in men and $>88\text{cm}$ in women. Due to the
152 strong associations between sex and grip strength we further categorized the data into sex-
153 specific tertiles of handgrip strength, although no mediating effects of sex were observed
154 after entering an interaction term in relation to diabetes outcome ($p=0.21$). Age was the time
155 scale, and for participants with no record of an event, the data were censored at wave 5
156 (maximum 6 years follow-up). In multivariate models we adjusted for several covariates in a
157 step-wise fashion: Model 1 contained age and sex; Model 2 contained additional behavioural
158 and health covariates, including smoking, alcohol, physical activity, depressive symptoms
159 and prevalent CVD. All analyses were conducted using SPSS version 21 (IBM SPSS,
160 Armonk, NY, USA).

161 **Results**

162
163 5953 individuals (1670 obese and 4283 non-obese; 98% white British), who were free of
164 T2DM at baseline, completed follow-up. Of these 124 obese and 92 non-obese individuals
165 were diagnosed with T2DM over the follow-up period.

166 There were few differences in those excluded compared to those included. For example, the
167 samples were comparable in sex distribution (% men; 42.6% vs. 45%) and age (65 vs. 63y).
168 The samples differed in physical activity behaviour and mental health, with those excluded
169 reporting higher inactivity (33% vs. 19%), and depressive symptoms (21% vs. 13%).

170 In men, the range of handgrip strength was 4–35.3, 35.4–44.2, >44.2 kg for bottom,
171 intermediate and top tertiles. The corresponding ranges in women were 4–19.6, 19.7–24.9,
172 >24.9 kg, respectively. Table 1 shows that obese individuals in the lowest sex-specific tertile
173 of handgrip strength were significantly older than those with either intermediate or upper
174 tertile of handgrip strength ($p<0.001$), and were less likely to engage in any moderate or
175 vigorous physical activity (34.4% inactive; $p<0.001$). Despite similar smoking patterns across
176 the three groups, the lowest handgrip strength group had a significantly higher prevalence of
177 cardiovascular disease ($p<0.001$).

178 Obese participants were well matched in terms of BMI (~ 33 – 34 kg/m²) and waist
179 circumference, across tertiles of handgrip strength (table 2). At baseline, the low handgrip
180 strength group had significantly higher percentages of glycated haemoglobin compared to
181 those with intermediate or high handgrip strength. Furthermore, the low handgrip strength
182 group had higher circulating concentrations of CRP and fibrinogen compared to those with
183 intermediate strength or low strength ($p<0.001$ and 0.009 respectively).

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

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

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

194 Sensitivity analyses

195 We categorised participants using sex-specific handgrip cut offs (men <26 kg; women
196 <16kg) for those at risk for weakness [1]. 11% of the sample met these thresholds for
197 weakness although the pattern of results largely replicated the original results showing the
198 same finding that sarcopenic obese were at the highest risk of incident diabetes (Table 4). In
199 addition, we used these handgrip cut offs in combination with waist circumference as a
200 measure of central obesity (defined as waist circumference >102cm in men and >88cm in
201 women). When using central obesity rather than body mass index the influence of sarcopenia
202 was less pronounced (Table 5; n= 6134).

203 **Discussion**

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

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

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

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

223 The clinical relevance of measurements of *both* muscle mass and muscle strength is reflected
224 in the revised definition of sarcopenia from the Foundation for the National Institutes of
225 Health (FNIH) Sarcopenia Project to incorporate both anatomical and functional components
226 [1]. These newer guidelines are more clinically meaningful as they denote the functional
227 consequences and thus relate more closely to clinical outcomes. Goodpaster *et al.* examining
228 longitudinal changes in muscle mass and strength in older adults in the Health, Ageing and
229 Body Composition Study demonstrated (annualised) rates of leg strength decline (~3%/year)
230 approximately three times greater than the rates of leg lean mass (~1%/year) [24]. These
231 findings clearly implicate factors other than muscle mass in determining muscle strength and
232 these updated guidelines reflect, and take account of, this important anatomical and
233 functional discrepancy. Thus, low grip strength is likely similarly explained by factors other
234 than low muscle mass. Indeed, many individuals with weakness may not have low muscle
235 mass. This had led to suggestions of a distinct term, dynapenia [25]. For practical reasons,
236 longitudinal measurements collected in this cohort did not extend to quantification of skeletal

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

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

250 In many T2DM patients with advancing age, severe obesity and comorbidities including
251 cardiovascular disease and osteoarthritis aerobic exercise is not feasible. In contrast,
252 resistance training provides an effective exercise alternative by increasing muscle mass and
253 strength (and thus counteracting age- and disease-related skeletal muscle loss and muscle
254 weakness), in visceral fat deposition and improvements in insulin sensitivity and glycemic
255 control [26, 27]. Thus our findings are biologically plausible. Skeletal muscle represents a
256 major organ for glucose homeostasis, responsible for up to 75% of post-prandial (i.e. insulin-
257 stimulated) glucose uptake [5]. Low muscle mass might therefore be expected to impair
258 glucose homeostasis. There is epidemiological evidence in obese, older individuals to link
259 sarcopenia with the metabolic syndrome and with T2DM [28], although it is not possible to
260 infer temporality between these conditions from cross-sectional data. Longitudinal studies
261 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.

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

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

298

299 **Author Contributions**

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

302

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318

319 **Conflicts of interest**

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

321

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

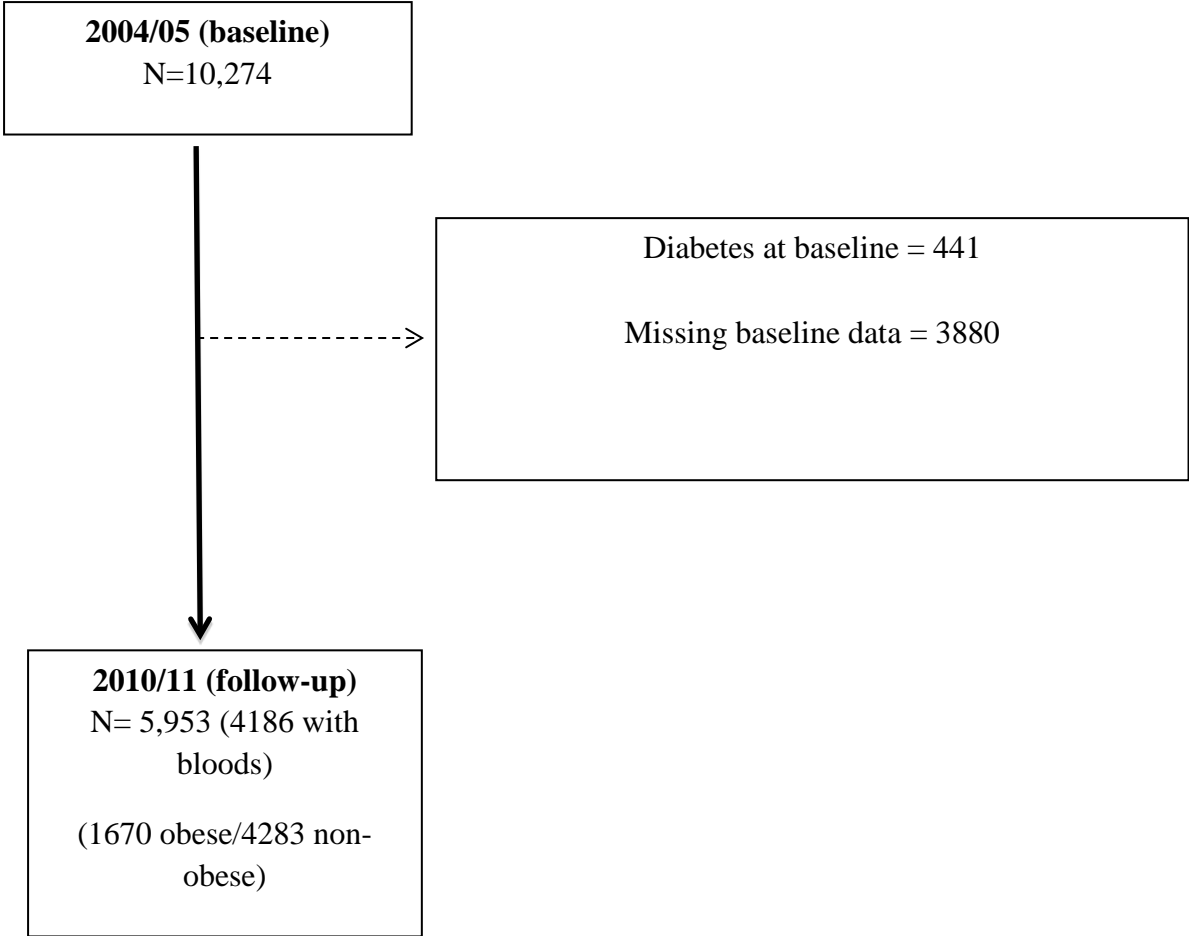


Table 1 Demographic characteristics of the sample in relation to grip strength (n=5953)

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)