Sarcopenic obesity and its association with respiratory disease incidence and mortality

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Abstract

Background - Sarcopenic obesity is defined as a combination of sarcopenia and obesity. Previous studies have shown a positive association between sarcopenia and respiratory disease, while other studies have identified that obese individuals have a lower risk for respiratory diseases. This study aimed to investigate the association of obesity, sarcopenia and sarcopenic obesity with respiratory disease incidence and mortality.

Methods - Data from 170,083 participants from the prospective UK Biobank study were included. Sarcopenic obesity was defined as the combination of sarcopenia with one of the following obesity criteria: BMI ≥30 kg/m^2, waist circumference (WC) ≥ 88 cm in women or ≥ 102 cm in men, or the two highest quintiles of body fat. Respiratory disease incidence and mortality were the outcomes.

Results - The mean follow-up period was 7.0 years. 5,459 (3.2%) participants developed respiratory diseases and 780 (0.5%) died from respiratory diseases. Compared to individuals without obesity or sarcopenia, those who were obese (Hazard Ratio (HR): 1.13 [95 CI: 1.03; 1.23]), sarcopenic (HR: 1.23 [95% CI: 1.10; 1.36]) or sarcopenic obese (based on BMI) (HR: 1.51 [95% CI: 1.30; 1.77]), had a higher risk of respiratory disease incidence. However, the risk of respiratory disease mortality was higher in sarcopenic individuals and lower in obese individuals. No associations were identified between sarcopenic obesity and respiratory mortality (HR: 1.12 [95% CI: 0.76; 1.63]). Similar patterns were found when obesity was defined using WC or body fat.

Conclusion – Obesity, sarcopenia and sarcopenic obesity were associated with a higher risk of respiratory disease incidence. However, while obesity was associated with lower, and sarcopenia with higher respiratory mortality risk, no associations between sarcopenic obesity and respiratory mortality were identified.

Keywords: Sarcopenia; Obesity; Respiratory disease; Respiratory mortality

Word count: 2,805

Introduction

Obesity is a chronic, progressive and recurring disease, and it remains one of the biggest public health challenges worldwide [1, 2]. Sarcopenia, on the other hand, is defined as an age-associated decline in muscle strength, mass and physical performance [3-5]. Both conditions can occur independently of each other; however, they share a common inflammatory pathway and are independently associated with more rapid functional decline and a higher risk of disease and mortality [6-8]. Although older people with sarcopenia are at higher risk of an unintentional weight loss [9], the prevalence of obesity among adults of all ages, including older adults, has increased since 1980. It is not surprising, therefore, that the prevalence of individuals with both sarcopenia and obesity has increased as well [10, 11].

Sarcopenic obesity is the term used to define the presence of both conditions (obesity and sarcopenia). Reduced lean mass with an excess percentage of body fat was one of the first definitions of sarcopenic obesity [12, 13]. Nevertheless, alternative operational definitions have been proposed based on different obesity markers: body mass index (BMI), waist circumference (WC) or visceral fat mass [12].

Previous studies have shown a positive association between sarcopenia and respiratory disease incidence and mortality [14, 15] and interestingly, other studies have shown that being overweight or obese is associated with a reduced risk of respiratory disease [16-18]. Although sarcopenic obesity has been associated with a higher risk of all-cause, cardiovascular disease and cancer mortality [19-22], to our knowledge, no studies have been carried out investigating the associations between different sarcopenic obesity definitions and respiratory diseases. This is particularly important due to the differential associations of sarcopenia and obesity with respiratory disease. Therefore, this study aimed to investigate the association of obesity, sarcopenia and sarcopenic obesity with respiratory disease incidence and mortality using different obesity markers.

Methods

Between April 2007 and December 2010, UK Biobank recruited over 500,000 participants (5.5% response rate), aged 37-73 years from the general population [23]. Participants attended one of 22 assessment centres across England, Wales and Scotland [24, 25] where they completed a touch-screen questionnaire, had physical measurements taken, and provided biological samples, as described in detail elsewhere [24, 25].

The outcomes in the current study were respiratory disease incidence and mortality, and the exposure were adiposity markers, sarcopenia and sarcopenic obesity. Due to ethnic differences in the reference values for sarcopenia, inclusion in the study was restricted to participants of a white European background.

Procedures

Respiratory disease was defined as ICD10 codes J09-J98 and I26-I27 recorded on hospital admission or death records. Date and cause of death were obtained from death certificates held by the National Health Service (NHS) Information Centre (England and Wales) and the NHS Central Register Scotland (Scotland). 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 detailed information regarding the linkage procedure can be found at http://www.ic.nhs.uk/services/medical-research-information-service. End of follow-up for each participant was recorded as the date of death, date of first hospital admission for respiratory disease, or the date of the end of follow-up for the assessment centre attended (31st January 2018 for participants in England or Wales, and 30th May 2017 for participants in Scotland), whichever came first. The period at risk per participant began on the date of their assessment.

Adiposity markers

Height was measured to the nearest centimetre (cm) using a Seca 202 height measure, and a Tanita BC-418 body composition analyser was used to measure weight to the nearest 0.1 kg. Both were used to estimate BMI and the WHO criteria were applied to categorise participants into underweight <18.5, normal weight 18.5-24.9, overweight 25.0-29.9 and obese ≥30.0 $kg.m^{-2}$ [26]. WC was used to derive central or abdominal obesity, defined as ≥ 88 cm for women or ≥ 102 cm for men [26]. Body composition was measured using bioimpedance (BIA) by trained nurses. Obesity by body fat was defined as body fat ≥ 26.9% in men, and ≥ 38.6% in women. These cut-off points values represent the two highest sex-specific quintiles in the UK Biobank population [27]. Using these adiposity markers, we created 3 obesity variables: people with abdominal obesity but without sarcopenia, people with obesity based on BMI but without sarcopenia, and people with obesity by body fat but without sarcopenia (Supplementary Figure 1).

Sarcopenia

The 2010 European Working Group on Sarcopenia in Older People (EWGSOP) guidelines defined sarcopenia as the combination of low muscle mass plus and either low grip strength or slow gait speed [28]. Individuals with any of these classifications but without obesity were classified as sarcopenic (Supplementary Figure 1).

Grip strength was measured using a Jamar J00105 hydraulic hand dynamometer. The means values of the right and left hand were expressed in absolute units (kg) and used in subsequent analyses. The cut-off points used to define low grip strength were <30 kg in men and <20 kg in women [28].

Muscle mass index was derived from skeletal muscle mass (kg) divided by height (m) squared. To estimate the skeletal muscle mass, the Janssen equation was utilised [29] using the resistance value generated during the measurement of body composition measured using BIA. The cut-off points used to define low muscle mass were <8.87 $kg.m^{-2}$ in men and <6.42 $kg.m^{-2}$ for women [28]. Finally, the self-reported walking pace was utilised as a proxy of gait speed. Participants categorised their

usual walking pace as slow, average or brisk and, to derive a proxy for the EWGSOP-2010 definition of usual walking pace, this was then dichotomised into slow or normal (average or brisk pace).

Sarcopenic obesity

There are different criteria and cut-off points used to define sarcopenic obesity [30]. In this study, we define sarcopenic obesity based on three different obesity markers (Supplementary Figure 1). a) sarcopenic obesity based on BMI (sarcopenia plus BMI ≥ 30.0 $kg.m^{-2}$ [26]); b) sarcopenic obesity based on WC (sarcopenia plus WC ≥ 88 cm for women and ≥ 102 cm for men [26]); c) sarcopenic obesity based on body fat (sarcopenia plus body fat ≥ 26.9% in men and ≥ 38.6% in women [27]).

Covariates

Age was calculated from dates of birth and baseline assessment. Area-based socioeconomic status (deprivation) was derived from the postcode of residence, using the Townsend score [31] which generates a deprivation score based on four census variables; unemployment, non-car ownership, non-house ownership and household overcrowding. In this study, the Townsend score is presented by quintiles of deprivation (from the least deprived to the most deprived). Self-reported smoking status was categorised as never, former or current smoker. The mean of forced expiratory volume in one second (FEV1) was estimated in litres using a spirometer (Vitalograph Pneumotrac 6800). The participants were asked to record two to three blows (lasting for at least 6 seconds) within about 6 minutes. The mean FEV1 of these records was used. Physical activity was based on self-reported data, collected using the International Physical Activity Questionnaire (IPAQ) short form [32] and total physical activity was computed as the sum of walking, moderate and vigorous activity, measured as metabolic equivalents (MET-hours/week). Total time spent in sedentary behaviours was derived from the sum of self-reported time spent driving, using a computer and watching television. Medical history (physician diagnosis of depression, stroke, angina, heart attack, hypertension, cancer, diabetes, hypertension, chronic obstructive pulmonary disease [COPD] or

other illness) was self-reported. Further details of these measurements can be found in the UK Biobank online protocol (http://www.ukbiobank.ac.uk).

Statistical analyses

Descriptive characteristics of each variable are presented as mean with standard deviation (SD) for quantitative variables or as a proportion for categorical variables.

Associations between obesity variables, sarcopenia, sarcopenic obesity classifications and respiratory disease incidence and mortality were investigated using Cox-proportional hazard models (individuals without sarcopenia nor obesity were used as the reference group). The results are reported as hazard ratios (HR) and their 95% confidence intervals (95% CI). The proportional hazard assumption was checked by tests based on Schoenfeld residuals. All analyses were performed using a 2-year landmark analysis to exclude participants having respiratory disease events in the first two years of follow-up. Participants with medical diagnoses of respiratory disease at baseline were also excluded. In addition, to predict the number of respiratory deaths per number of cases of respiratory diseases for each obesity variable, sarcopenia and sarcopenic obesity definitions, the case-fatality rate was estimated.

All analyses were adjusted for confounding factors, including socio-demographic covariates (age, sex, gross income and education attainment), prevalent diseases (hypertension, diabetes, depression, major illness, as well as CVD, and cancer) and lifestyle factors (smoking, sleep duration, physical activity, total discretionary sedentary time and dietary intake including alcohol, fruit and vegetable, oily fish, red meat and processed meat intake) at baseline.

STATA 14 statistical software (StataCorp LP) was used to perform the analyses. P-values below 0.05 were regarded as statistically significant.

Ethical Approval

UK Biobank was approved by the North West Multi-Centre Research Ethics Committee, and all participants provided written informed consent to participate in the UK Biobank study. The study protocol is available online (http://www.ukbiobank.ac.uk/).

Results

Of the 502,628 participants recruited to UK Biobank, 170,083 (33.8%) had full data available on exposure, outcomes and covariates (Supplementary Figure 1). The mean follow-up period was 7.0 years (interquartile range: 6.4–7.6) after the landmark period for respiratory disease mortality, and 6.1 years (interquartile range: 5.4–6.7) after the landmark period for respiratory disease incidence. Over the follow-up period, 5,459 (3.2%) participants developed respiratory disease, and 780 (0.5%) participants died from respiratory diseases. The highest respiratory disease-specific case fatality rate was in those with sarcopenia (22.9%), followed by those with sarcopenic obesity based on body fat (20.6%), sarcopenic obesity by WC (19.0%), sarcopenic obesity by BMI (18.2%), people without sarcopenia nor obesity (12.4%) and finally, those with any form of obesity (abdominal obesity [10.4%] obesity based on body fat [10.2%], and obesity by BMI [9.6%]).

The main characteristics of participants are presented in Table 1 and Supplementary Tables 1 and 2. Overall, and in comparison to people without obesity or sarcopenia, fewer women were obese while those with sarcopenia or sarcopenic obesity were older and were the most deprived (Table 1). In comparison to people with obesity, those with sarcopenic obesity had a lower body weight, BMI, WC and body fat. Those with sarcopenia and sarcopenic obesity had the lowest height, lowest levels of grip strength and physical activity whereas those with obesity or sarcopenic obesity had the highest levels of sedentary behaviour, TV viewing and the highest intake of processed and red meat. These two groups also had the highest prevalence of diabetes, CVD diseases and high blood pressure. Finally, FEV1 was lower in those with sarcopenia and even lower in those with sarcopenic obesity (Table 1). Similar characteristics were found in those with sarcopenic obesity defined by WC and body fat (Supplementary Tables 1 and 2, respectively).

As shown in Figure 1a, obesity (defined by BMI), sarcopenia and sarcopenic obesity were associated with a higher risk of respiratory disease incidence. Compared to the reference group (individuals without obesity or sarcopenia), those who were obese and those who had sarcopenia had a 13% and 23% higher risk of respiratory disease incidence (HR 1.13 [95% CI: 1.03 to 1.23] and HR: 1.23 [95% CI: 1.10 to 1.36], respectively). Furthermore, respiratory disease incidence risk was higher in individuals with sarcopenic obesity compared to individuals without sarcopenia nor obesity (HR: 1.51 [95% CI: 1.30 to 1.77]). Similar findings were found when sarcopenic obesity was defined by WC o body fat (Supplementary Table 3).

The associations of respiratory disease mortality with obesity, sarcopenia and sarcopenic obesity are presented in Figure 1b. In comparison to individuals without sarcopenia nor obesity, those with obesity by BMI had a lower risk of respiratory disease mortality (HR: 0.62 [95% CI: 0.48 to 0.79]) whilst those with sarcopenia had a higher risk (HR: 1.45 [95% CI: 1.12 to 1.88]), with no association found of sarcopenic obesity with respiratory mortality (HR: 1.12 [95% CI: 0.76 to 1.63]). When sarcopenic obesity by WC or body fat was the exposure, similar results were found (Supplementary Table 3).

Discussion

Sarcopenic obesity leads to a worse prognosis and increases the risk of all-cause mortality in people with both conditions [19-22]. To our knowledge, the current study is the first to investigate the associations of sarcopenia, obesity and sarcopenic obesity with respiratory diseases. After adjusting for major confounding factors, the primary finding of the current study was that, as with sarcopenia and obesity alone, sarcopenic obesity was associated with a greater risk of respiratory disease incidence. Furthermore, although sarcopenia and obesity showed a higher and lower risk for respiratory mortality, respectively, no associations between sarcopenic obesity and respiratory disease mortality were found.

198 Individuals with any form of obesity are more likely to increase symptoms of dyspnoea, asthma,
199 sleep apnoea and reductions in FEV1. Those with obesity and respiratory disease have an increased
200 risk for cardiovascular and metabolic diseases and, as a consequence, they have a higher reduction
201 in the vital capacity, i.e., lower FEV1 (Table 1 and Supplementary Tables 1 and 2). Contrary to
202 expectations, longitudinal studies have shown a decreased risk of mortality in obese patients with
203 severe COPD in comparison to normal-weight people [18, 33]. These findings may be related to the
204 phenomenon called “obesity paradox” [34]. Obesity may produce different effects depending on the
205 degree of respiratory disease, having a protective effect in those with a severe condition but a worse
206 prognosis in those with mild to moderate respiratory disease [16, 34]. However, the mechanism
207 behind this association remains still unknown, and there are still gaps to elucidate and understand
208 the paradox effect of obesity over respiratory disease. In our study, people with any form of obesity
209 showed the lowest risk of respiratory disease mortality and case-fatality rate, having even a lower
210 rate than people without sarcopenia nor obesity. In terms of sarcopenic obesity, obesity may have
211 reduced the effect of sarcopenia over respiratory mortality, and this could be the explanation behind
212 the decreasing in the magnitude of the association between sarcopenic obesity and respiratory
213 mortality. In other words, the lack of a significant association could be due to the additive effect of
214 obesity (possible protective factor) and sarcopenia (risk factor) in individuals with respiratory
215 disease.

216 Although many studies have been conducted between respiratory diseases, obesity and sarcopenia
217 [14, 15], and between sarcopenic obesity and all-cause and CVD mortality [19-21], this is one of the
218 first studies that examine the association between sarcopenic obesity and respiratory diseases
219 incidence and mortality. In this context, futures studies are needed to support our findings and to
220 determine the mechanism behind the association of sarcopenic obesity and respiratory mortality
221 beyond the association of sarcopenia and obesity itself.

Finally, it is essential to emphasise that although there have been several attempts to define sarcopenic obesity and its cut-off points, the definition and diagnostic criteria remain insufficient and inadequate. Therefore, clarifying the cut-off points and definition beyond those for obesity and sarcopenia is critical to identify the real association between sarcopenic obesity and respiratory diseases. As a result, the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of the Obesity (EASO) did a call for more studies and more actions in this field [30].

Strengths and limitations

UK Biobank is not representative of the UK population in terms of lifestyle and disease prevalence [35]. Therefore, our estimates of absolute incidence and mortality should not be widespread. However, the use of UK Biobank provided the opportunity to test our research question in a large general population cohort as well as the opportunity to work with information collected using validated and standardised methods. In terms of sarcopenia, we did not use the new guideline proposed for the EWGSOP2 since its new cut-off points decrease the numbers of event and, therefore, the statistical power [36]. Dual-energy X-ray absorptiometry (DXA) is the most commonly used method for deriving muscle mass because it can provide a reproducible estimation of the appendicular skeletal muscle mass in a few minutes [37]. In UK Biobank, muscle mass was measured using BIA, but this method has been shown to correlate well with DXA ($r=0.868$, $p<0.0001$) and should provide a reasonable estimate within this large-scale study. Finally, the walking pace was self-reported. While this is potentially a source of bias, it is more easily replicated in clinical practice. Furthermore, the walking pace has been identified as one of the strongest predictors of health outcomes, beyond many traditional risk factors (BMI, blood pressure, and smoking).

In conclusion, all sarcopenic obesity definitions were positively associated with respiratory incidence. However, no significant associations between respiratory mortality and any definition of sarcopenic obesity were identified. Taking into account the lack of consensus related to cut-off

points and operational definition of sarcopenic obesity; futures studies are necessary to identify the possible mechanism behind this outcome as well as how to improve detection of sarcopenic obesity in the clinical practice. As a result, sarcopenic obesity remains a challenge and opportunity at the same time.

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Conflict of interest

None to declare.

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359 **Table 1. Cohort characteristics by sarcopenic obesity defined by Body Mass Index**

	Normal	Obesity	Sarcopenia	Sarcopenic obesity by BMI
Socio-demographics				
Total n	44,138	70,607	20,300	3,509
Sex (Female), n (%)	31,077 (70.4)	32,331 (45.8)	15,358 (75.7)	2,319 (66.1)
Age (years), mean (SD)	52.3 (7.9)	55.6 (7.9)	59.7 (7.0)	61.9 (5.8)
Age categories				
<45 years	9,094 (20.6)	7,738 (11.0)	788 (3.9)	50 (1.4)
45-50 years	9,813 (22.2)	10,212 (14.5)	1,380 (6.8)	93 (2.7)
51-55 years	8,122 (18.4)	12,439 (17.6)	2,279 (11.2)	255 (7.3)
56-60 years	6,963 (15.8)	13,546 (19.2)	3,759 (18.5)	550 (15.7)
61-65 years	6,689 (15.2)	16,300 (23.1)	5,996 (29.5)	1,183 (33.7)
64-70 years	3,382 (7.6)	10,135 (14.3)	5,917 (29.2)	1,349 (38.4)
>70 years	75 (0.2)	237 (0.3)	181 (0.9)	29 (0.8)
Deprivation				
1 (Least Deprived)	9,898 (22.5)	13,438 (19.1)	4,165 (20.5)	556 (15.9)
2	9,453 (21.4)	14,032 (19.9)	4,153 (20.5)	653 (18.6)
3	9,001 (20.4)	14,457 (20.5)	4,185 (20.6)	696 (19.8)
4	8,745 (19.8)	14,656 (20.8)	3,945 (19.5)	713 (20.3)
5 (Most Deprived)	6,995 (15.9)	13,930 (19.7)	3,830 (18.9)	891 (25.4)
Smoking status, n (%)				
Never	26,520 (60.2)	35,883 (51.0)	11,685 (57.8)	1,624 (46.5)
Previous	12,808 (29.1)	27,814 (39.6)	6,201 (30.6)	1,535 (44.0)
Current	4,722 (10.7)	6,643 (9.4)	2,344 (11.6)	330 (9.5)
Obesity-related markers				
Height (meters), mean (SD)	1.68 (0.08)	1.70 (0.09)	1.64 (0.08)	1.65 (0.10)

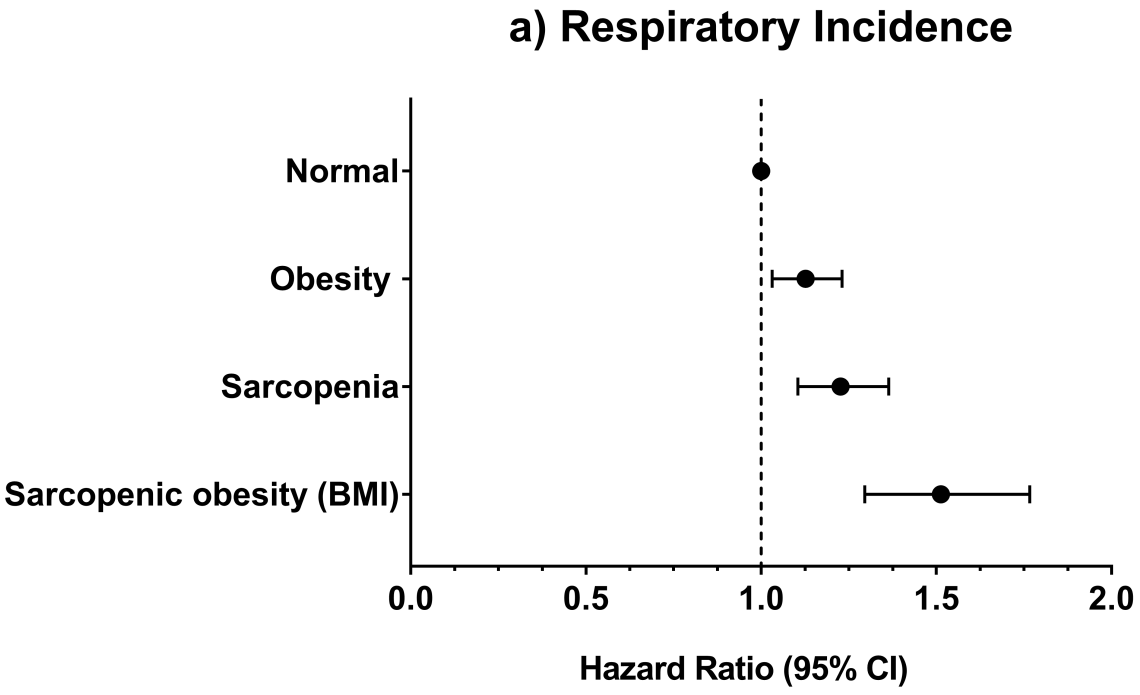
Body weight (kg), mean (SD)	65.3 (8.0)	97.0 (13.5)	61.0 (7.7)	87.1 (11.2)
BMI, mean (SD)	23.2 (1.4)	33.6 (3.4)	22.5 (1.6)	32.0 (1.9)
BMI Categories, n (%)				
Underweight (<18.5 $kg.m^{-2}$)	0	0	0	0
Normal weight (18.5-24.9 $kg.m^{-2}$)	44,138 (100.0)	0	20,300 (100.0)	0
Overweight (25.0 to 29.9 $kg.m^{-2}$)	0	0	0	0
Obese (≥30.0 $kg.m^{-2}$)	0	70,607 (100.0)	0	3,509 (100.0)
Waist Circumference (cm)	77.0 (7.3)	104.6 (10.5)	77.4 (7.7)	102.0 (9.9)
Central Obesity, n (%)	0	60,558 (85.8)	0	3,182 (90.7)
% Body fat, mean (SD)	24.5 (6.8)	36.6 (7.6)	29.4 (6.2)	42.9 (6.0)
% Body fat free (SD)	75.5 (6.8)	63.4 (7.6)	70.6 (6.2)	57.1(6.0)
Fitness and Physical activity				
Total PA ($MET.h^{-1}.week^{-1}$), mean (SD)	3,380.5 (3431.1)	2,919.9 (3,367.2)	2,776.4 (2,949.2)	2,259.3 (2,653.7)
Physically active individuals n, (%)	11.0 (2.8)	8.8 (2.5)	9.2 (2.5)	7.4 (2.1)
Grip Strength (kg), mean (SD)	31.8 (8.7)	35.1 (10.3)	19.3 (6.6)	22.1 (9.0)
TV viewing ($h.day^{-1}$), mean (SD)	2.1 (1.3)	3.0 (1.5)	2.8 (1.6)	3.8 (1.8)
Total Sedentary behaviour ($h.day^{-1}$), mean (SD)	4.2 (1.9)	5.6 (2.4)	4.5 (2.0)	5.6 (2.4)
Health status, n (%)				
FEV1	2.9 (0.7)	2.8 (0.8)	2.4 (0.6)	2.2 (0.6)
Diabetes history	606 (1.4)	6,032 (8.6)	424 (2.1)	342 (9.8)
CVDs history	5,427 (12.3)	29,515 (41.9)	4,293 (21.2)	1,770 (50.7)
High blood pressure history	4,700 (10.7)	25,003 (35.5)	3,353 (16.6)	1,331 (38.1)

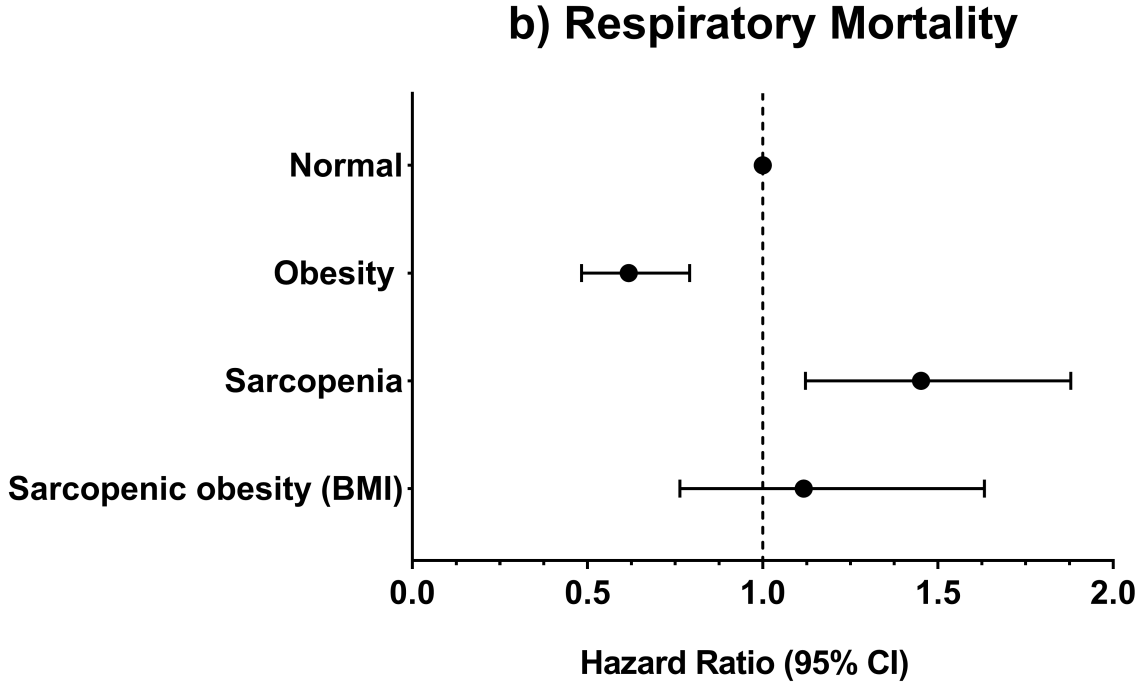
360 BMI: body mass index; n: number; PA: physical activity; MET: metabolic-equivalent; TE: total energy; SD: standard

361 deviation; CVD: cardiovascular disease.

Figure 1. Association between sarcopenic obesity, sarcopenia, obesity and respiratory disease incidence and mortality

Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95%CI). Figure 1a shows the respiratory incidence and Figure b the respiratory mortality, both based on BMI. Normal people (without sarcopenia or obesity) were used as the reference group for the analysis. All analyses were conducted using a 2-years landmark analysis and by excluding participant with major diseases at baseline. Model was fully adjusted by age, sex, gross income, education attainment, hypertension, diabetes, depression, major illness, as well as CVD, cancer, smoking, sleep duration, physical activity, total discretionary sedentary time and dietary intake including alcohol, fruit and vegetable, oily fish, red meat and processed meat intake.


a) Respiratory Incidence
Normal
Obesity
Sarcopenia
Sarcopenic obesity (BMI)
0.0
0.5
1.0
1.5
2.0
Hazard Ratio (95% CI)


b) Respiratory Mortality
Normal
Obesity
Sarcopenia
Sarcopenic obesity (BMI)
0.0
0.5
1.0
1.5
2.0
Hazard Ratio (95% CI)