# Association between sarcopenia and risk of major adverse cardiac and cerebrovascular events-UK Biobank database.

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CLINICAL INVESTIGATION

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# Association between sarcopenia and risk of major adverse cardiac and cerebrovascular events-UK Biobank database

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## Abstract

**Background:** Few studies on the risk of incident major adverse cardiac and cerebrovascular events (MACCEs) in sarcopenia have been reported. The objective was to assess the association between presarcopenia and sarcopenia and a higher risk of MACCEs.

**Methods:** This study on the UK Biobank prospective cohort, used data collected between 2006 and 2021. Community-dwelling Caucasian participants aged 37 to 73 years were included if values for Handgrip Strength (HGS) and Skeletal Muscle Index (SMI) were available and if no history of MACCEs was reported. Exposure was assessed using the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) criteria. Muscle strength was measured using HGS, and muscle mass using the SMI. Presarcopenia was defined through the two definitions available in the literature, as low HGS with normal SMI and as normal HGS with low SMI, whereas sarcopenia was defined as low HGS with low SMI. The main outcome was to determine whether presarcopenia and/or sarcopenia were predictors of MACCEs (composite events).

**Results:** A total of 406,411 included participants (women: 55.7%) were included. At baseline, there were 18,257 (4.7%) presarcopenics—subgroup n°1 (low HGS only), 7940 (2.1%) presarcopenics—subgroup n°2 (low SMI only), and 1124 (0.3%) sarcopenics. Over a median follow-up of 12.1 years (IQR: [11.4; 12.8]), 28,300 participants (7.0%) were diagnosed with at least one event. Compared to NonSarc, presarcopenic (subgroups n°1 and n°2) and sarcopenic status were significantly associated with a higher risk of MACCEs (respectively fully adjusted HRs: HR = 1.25 [95% CI: 1.19; 1.31], HR = 1.33 [95% CI: 1.23; 1.45] and HR = 1.62 [95% CI: 1.34; 1.95]).

**Conclusions:** In a community-dwelling population, the risk of MACCEs was higher in both presarcopenic and sarcopenic participants.

KEYWORDS
major cardiac and cerebrovascular event, presarcopenia, sarcopenia, UK Biobank

# INTRODUCTION

## Context

Sarcopenia has recently been redefined by the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) guidelines.[1] It constitutes a heavy burden for public health systems.[2] Its late recognition as a disease in 2016 by the World Health Organization (WHO) (International Classification of Diseases, ICD-10-CM: M62.84),[3] and a lack of international consensus, partly explain the current state of knowledge.

The EWGSOP2 guidelines[1] are currently the most widely used worldwide, and define 3 sarcopenic thresholds,[1] namely: (i) probable sarcopenia (low muscle strength regardless of SMI value), (ii) sarcopenia (low muscle strength and muscle mass), and (iii) severe sarcopenia (low muscle strength, muscle mass, and physical performance). A *presarcopenia* stage is also used, with various definitions in the literature, including "low muscle mass without impact on muscle strength or physical performance",[2,4] and "low muscle strength with normal muscle mass".[5]

Sarcopenia is directly associated with negative outcomes, some of which are still debated[6] (e.g., cardiac and cerebrovascular prognosis). Sarcopenia and cardiac and cerebrovascular disorders share common triggers, such as malnutrition, physical inactivity, insulin resistance, inflammation, and oxidative stress.[7–9] There is also increasing evidence suggesting an association between biomarkers of oxidative stress and several human conditions, such as obesity, sarcopenia, and cardiovascular diseases.[10] The few studies investigating the association between sarcopenia (EWGSOP2 definition[1]) and cardiac and/or cerebrovascular disorders report contradictory results.[11–13] In one study conducted on 129 dialysis patients, the authors failed to find an association between sarcopenia and cardiovascular events or all-cause mortality.[11] In another study on 396,707 participants from the UK Biobank database,[12] the authors reported a higher risk of cardiovascular outcomes in participants with severe sarcopenia (HR = 2.92, 95% CI = [1.50; 5.67]), but not in participants with sarcopenia.[12] In a third study on 316,980 participants from the UK Biobank database, the combination of sarcopenia/frailty was found to be associated with cardiac and neurovascular diseases (HR = 1.68, 95% CI = [1.22; 2.30]).[13] In all three studies, the methodologies used are debatable, and none of them investigated the risk of major adverse cardiac and cerebrovascular events (MACCEs) in presarcopenic participants, hence the need for further studies.

**Key points**

- Presarcopenic status (whatever the definition used, that is, low muscle strength only or low muscle mass only) and sarcopenic status are independent risk factors for incident MACCEs in a middle-aged and older Caucasian population.

**Why does this paper matter?**

Due to the recognition of sarcopenia as a disease only since 2016, and due to the lack of consensus, the data currently available on this disease are poor and hardly comparable. This study uses the most widely used guidelines in the world, and a high-quality, large cohort, to study its clinical outcomes. Data from this study are intended to refine the cardiovascular and cerebrovascular prognosis of presarcopenic and sarcopenic patients, for preventive and personalized medicine.

Finally, sarcopenic participants can be divided into subgroups based on comorbidities they exhibit, such as obesity. Sarcopenic obesity (SO) is commonly defined as the co-existence of obesity and sarcopenia.[1] It is already known that obesity exacerbates sarcopenia.[1] However, it is not known whether the risk of MACCEs in obese sarcopenics differs from that in non-obese sarcopenics, even if some studies, not based on EWGSOP2 criteria, have suggested that the risk is different in the two populations.[14]

## Objectives

To date, few and hardly comparable studies are available on the risk of MACCEs in participants with presarcopenia or sarcopenia. The main purpose of this study was to investigate whether presarcopenia and sarcopenia are independently associated with a higher risk of incident MACCEs (fatal or non-fatal) in a middle-aged and older, community-dwelling population of women and men from the UK Biobank prospective cohort.

# METHODS

## Participants and ethical approval

We conducted a retrospective analysis on participants from the UK Biobank database, using outcome data obtained from National Health Service (NHS) records. Approximately 500,000 British, community-dwelling volunteers provided their electronic consent.[15,16]

## Data collection

Data were collected at baseline (initial assessment visit, between 2006 and 2010), and later (2012 and later, still ongoing). Participants completed a series of touchscreen computer-based questionnaires, followed by a face-to-face interview.[16] All assessments were performed by trained data collectors, who followed standardized protocols using a *Seca stadiometer* for height measurements, the *Tanita BC 418 MA Body Fat Analyzer* for weight and BIA measurements, and the *Jamar hydraulic hand dynamometer* (*model J00105)* for handgrip strength (HGS) measurements.

## Inclusion and exclusion criteria

Due to the ethnicity-specific *Janssen* equation, we used to calculate Skeletal Muscle Mass (SMM) (see below), our study included only Caucasian participants. Participants were excluded if (i) they withdrew their consent between data acquisition and the end of the study, (ii) HGS values were unavailable or null, (ii) body composition values (measured using Bioelectrical Impedance Analysis, BIA) were unavailable or null, and (iv) they had a self-reported or hospital-admission history of acute myocardial infarction (AMI), angina pectoris (stable or unstable), stroke (ischemic or hemorrhagic), or transient ischemic attack (TIA).

## Principal exposure variable

The main exposure variable was the participants' sarcopenic status. Sarcopenic status was defined in terms of HGS and Skeletal Muscle Index (SMI) values, which were obtained by feature extraction.

The HGS value was defined as the highest of the right- and left-hand scores,[17] and considered pathological if less than 16 kg in women and 27 kg in men.[1]

The SMI value was obtained in two steps. Using BIA data, we first calculated the whole body SMM using the *Janssen* equation.[18] We then calculated the SMI using the following formula[1,5,19,20]: $SMI = SMM/height^2$, where SMM is expressed in kg, and height in meters.

Values were considered pathological if less than 5.5 $kg/m^2$ in women and 7.0 $kg/m^2$ in men.[1]

We defined three main groups according to EWG-SOP2 sarcopenia cut-offs,[1] as follows (Figure 1): (i) Sarcopenic participants (low HGS, low SMI); (ii) Presarcopenic participants: subgroup n°1 (low HGS, normal SMI), subgroup n°2 (normal HGS, low SMI), according to the definitions currently available; and (iii) Non-sarcopenics participants (normal HGS, normal SMI; referred to as the NonSarc participants).

To investigate the impact of obesity, sarcopenic and presarcopenic (subgroup n°1 and n°2) participants were merged to form a single group (PreSarc participants) due to the low number of sarcopenic participants living with obesity. Then, two main groups (NonSarc and PreSarc) were split into subgroups based on obesity status, as follows: "obese" (Body Mass Index (BMI) $\geq$ 30 $kg/m^2$[21]) and "non-obese" (BMI < 30 $kg/m^2$[21]) (Figure 1). As such, the following subgroups were available: PreSarcObese, PreSarcNonObese, NonSarcObese, and NonSarcNonObese.

## Covariates

All covariates were collected at baseline. Directly available covariates were sex, age at recruitment, waist circumference (WC), Townsend Deprivation Index (TDI, measure of material deprivation within a population), smoking and alcohol status, physical activity level, medication use (cholesterol-lowering medication, blood pressure medication, insulin, hormone-replacement therapy (HRT) and oral contraception), laboratory results (albumin, C-reactive protein (CRP)), and loss to follow-up.

Covariates obtained by feature extraction were BMI and medical history. Medical histories were compiled from ICD-9, ICD-10, and self-reported data regarding type-2 diabetes, high blood pressure (HBP), dyslipidemia, chronic kidney disease (CKD), heart failure (HF), and family history of stroke or ischemic heart disease.

## Outcomes

Major adverse cardiac and cerebrovascular events (MACCEs), which are composite events, were defined as fatal or non-fatal cardiovascular events (AMI, angina pectoris, and cardiac arrest), or fatal or non-fatal cerebrovascular events (ischemic and hemorrhagic stroke, and TIA). The incidence of MACCEs was compiled from

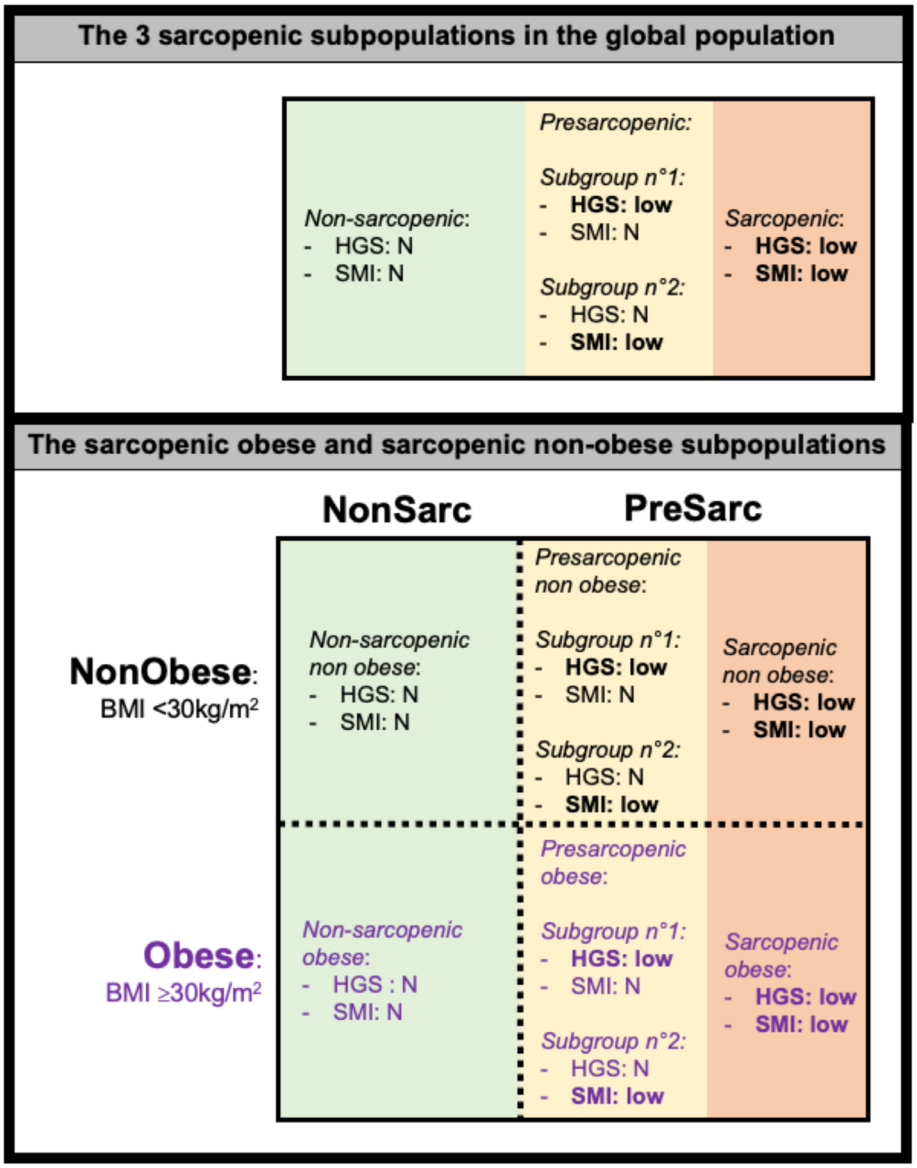



**FIGURE 1** Subpopulation definitions. Non-Sarc: non-sarcopenic participants. Pre-Sarc: presarcopenic (subgroups n°1 and n°2) and sarcopenic participants. HGS: handgrip strength. SMI: skeletal muscle index. N: normal.

ICD-10 and self-reported data. No ICD-9 data were available for post-inclusion MACCEs.

## Study design

We first compared the incidence of MACCEs in non-sarcopenics (reference) versus presarcopenics n°1, presarcopenics n°2, and sarcopenics). We then compared (i) the incidence of cardiovascular events and cerebrovascular events, considered independently, between those groups, still using the non-sarcopenics as the reference group, and (ii) the incidence of MACCEs, in NonSarcNonObese (reference) versus NonSarcObese, PreSarcNonObese and PreSarcObese.

Finally, we performed the following sensitivity analyses: (i) a sensitivity analysis of the main outcome in women only, to add adjusting criteria (HRT and/or contraceptive pill use), (ii) a sensitivity analysis of the composite outcome "incident MACCEs or death from all-cause" in the global population, and (iii) a sensitivity analysis in the population younger than 58.0 years and in the population that was 58.0 years or older.

When the proportion of missing values in the global population was equal to or greater than 1%, we created a "not available" category. When the proportion of missing values in the global population was less than 1%, data were imputed based on expert opinion. Participants were followed up until the first MACCE occurred. Otherwise, they were censored at the date of death (non-MACCE-related death), the lost-to-follow-up date, or the data extraction date (2021-03-25).

We adjusted the final model by adding an increasing number of covariates. Level 1 was the minimally

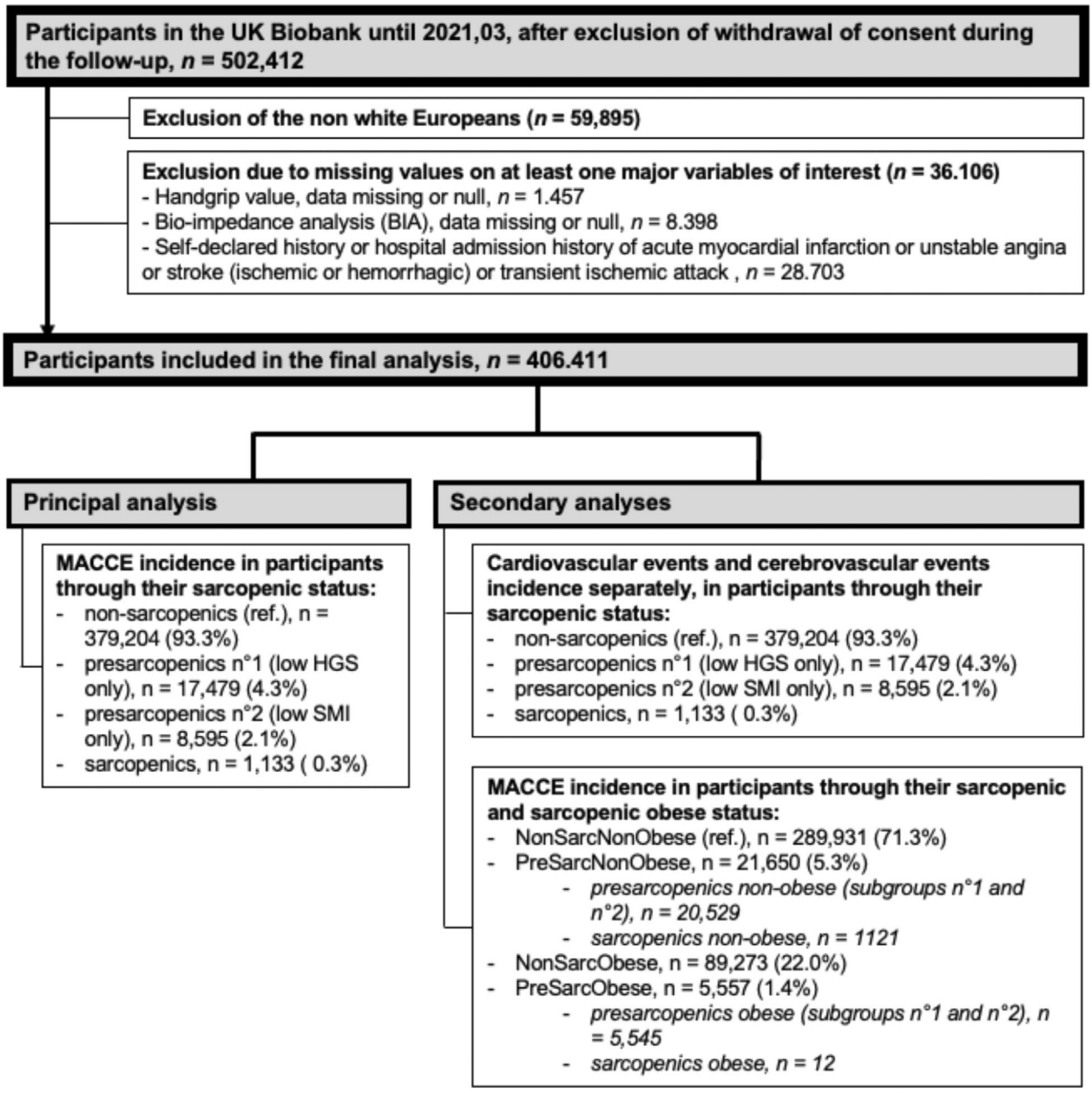



**FIGURE 2** Flow-chart. NonSarcNonObese: non-sarcopenic non obese participants. NonSarcObese: non-sarcopenic obese participants. PreSarcNonObese: presarcopenic (subgroup n°1 and n°2) and sarcopenic non obese participants. PreSarcObese: presarcopenic (subgroup n°1 and n°2) and sarcopenic obese participants. Ref.: reference subgroup for statistical analyses.

adjusted model, on sex, age at recruitment, TDI, and BMI. Level 2 was the maximally adjusted model, on the same covariates as level 1, but further adjusted for WC, smoking and alcohol status, family history of stroke and/or ischemic heart disease, personal history of type-2 diabetes and/or HBP and/or dyslipidemia and/or CKD and/or HF, medication intake (cholesterol-lowering medication, blood pressure medication, insulin), physical activity group, albumin, and CRP. History of HRT and/or contraceptive pill use was added to level 2 only in the sensitivity analysis performed in women.

No stepwise procedures were performed as all the adjusting covariates are scientifically recognized.

## Statistical analysis

For univariate analyses, continuous variables were expressed as mean (and standard deviation, SD), or as median (and interquartile range, IQR). Categorical variables were expressed as count (and percentage). Bivariate analyses were performed using Student's *t*-tests or Mann–Whitney–Wilcoxon tests to compare means, and Chi-2

**TABLE 1** Baseline characteristics in the global population.

| | Global population ($n = 406,411$) | Non-sarcopenics ($n = 379,204$, 93.3%) | Presarcopenics subgroup n°1 – low HGS only ($n = 17,479$, 4.3%) | Presarcopenics subgroup n°2 – low SMI only ($n = 8595$, 2.1%) | Sarcopenics ($n = 1133$, 0.3%) |
|---|---|---|---|---|---|
| Women, *n* (%) | 226,483 (55.7) | 206,057 (54.3%) | 11,061 (63.3%) | 8297 (96.5%) | 1068 (94.3%) |
| Age at recruitment, years | | | | | |
| Median [IQR] | 58.0 [50.0; 63.0] | 57.0 [50.0;63.0] | 61.0 [56.0;65.0] | 62.0 [58.0;66.0] | 64.0 [60.0;67.0] |
| [37, 50], *n* (%) | 105,838 (26.0) | 103,147 (27.2%) | 2117 (12.1%) | 526 (6.12%) | 48 (4.24%) |
| [50, 60], *n* (%) | 146,602 (36.1) | 138,072 (36.4%) | 5590 (32.0%) | 2665 (31.0%) | 275 (24.3%) |
| [60, 73], *n* (%) | 153,971 (37.9) | 137,985 (36.4%) | 9772 (55.9%) | 5404 (62.9%) | 810 (71.5%) |
| BMI, median [IQR], kg/m$^2$ | 26.6 [24.1; 29.7] | 26.7 [24.2;29.8] | 27.4 [24.6;31.1] | 22.4 [20.7;24.4] | 22.7 [20.7;24.8] |
| BMI category, *n* (%), kg/m$^2$ | | | | | |
| Normal weight | 136,326 (33.5) | 124,266 (32.8%) | 4813 (27.5%) | 6459 (75.1%) | 788 (69.5%) |
| Malnutrition, thinness | 2081 (0.5) | 1383 (0.36%) | 107 (0.61%) | 503 (5.85%) | 88 (7.77%) |
| Overweight | 173,221 (42.6) | 164,326 (43.3%) | 7129 (40.8%) | 1521 (17.7%) | 245 (21.6%) |
| Class I & II obesity | 87,554 (21.5) | 82,551 (21.8%) | 4881 (27.9%) | 110 (1.28%) | 12 (1.06%) |
| Class III obesity | 7229 (1.8) | 6678 (1.76%) | 549 (3.14%) | 2 (0.02%) | 0 (0.00%) |
| WC in women, median [IQR], cm | 83.0 [75.0; 92.0] | 83.0 [75.0;92.0] | 86.0 [78.0;96.0] | 76.0 [71.0;82.0] | 77.0 [71.0;84.0] |
| WC in men, median [IQR], cm | 96.0 [89.0; 103.0] | 96.0 [89.0;103] | 97.0 [90.0;106] | 85.0 [79.0;92.0] | 85.0 [78.0;92.0] |
| WC category, *n* (%), cm | | | | | |
| Normal (<80 in women, <94 in men) | 164,071 (40.0) | 152,344 (40.2%) | 5506 (31.5%) | 5540 (64.5%) | 681 (60.1%) |
| High (≥80 in women, ≥94 in men) | 242,340 (59.6) | 226,860 (59.8%) | 11,973 (68.5%) | 3055 (35.5%) | 452 (39.9%) |
| Townsend deprivation index, *n* (%) | | | | | |
| Least disadvantaged | 135,315 (33.3) | 127,385 (33.6%) | 4587 (26.2%) | 3004 (35.0%) | 339 (29.9%) |
| Intermediate | 135,789 (33.4) | 126,922 (33.5%) | 5506 (31.5%) | 2978 (34.6%) | 383 (33.8%) |
| Most disadvantaged | 135,307 (33.3) | 124,897 (32.9%) | 7386 (42.3%) | 2613 (30.4%) | 411 (36.3%) |
| Smoking status, *n* (%) | | | | | |
| Never | 226,483 (55.7) | 211,118 (55.7%) | 9574 (54.8%) | 5117 (59.5%) | 674 (59.5%) |
| Former | 139,199 (34.3) | 130,141 (34.3%) | 6120 (35.0%) | 2604 (30.3%) | 334 (29.5%) |
| Current | 40,729 (10.0) | 37,945 (10.0%) | 1785 (10.2%) | 874 (10.2%) | 125 (11.0%) |
| Alcohol status, *n* (%) | | | | | |
| Never or rarely | 114,064 (28.1) | 103,718 (27.4%) | 6985 (40.0%) | 2842 (33.1%) | 519 (45.8%) |
| Once or twice a week | 107,956 (26.6) | 101,264 (26.7%) | 4436 (25.4%) | 2013 (23.4%) | 243 (21.4%) |

**TABLE 1** (Continued)

| | Global population ($n = 406,411$) | Non-sarcopenics ($n = 379,204$, 93.3%) | Presarcopenics subgroup n°1 – low HGS only ($n = 17,479$, 4.3%) | Presarcopenics subgroup n°2 – low SMI only ($n = 8595$, 2.1%) | Sarcopenics ($n = 1133$, 0.3%) |
|---|---|---|---|---|---|
| Three or four times a week | 98,500 (24.2) | 93,278 (24.6%) | 3149 (18.0%) | 1900 (22.1%) | 173 (15.3%) |
| Daily or almost daily | 85,891 (21.1) | 80,944 (21.3%) | 2909 (16.6%) | 1840 (21.4%) | 198 (17.5%) |
| IPAQ activity group[a], *n* (%) | | | | | |
| Low | 59,895 (18.2) | 55,181 (14.6%) | 3262 (18.7%) | 1223 (14.2%) | 229 (20.2%) |
| Moderate | 134,291 (41.0) | 125,627 (33.1%) | 5319 (30.4%) | 2996 (34.9%) | 349 (30.8%) |
| High | 133,665 (40.8) | 127,057 (33.5%) | 4213 (24.1%) | 2168 (25.2%) | 227 (20.0%) |
| C-reactive protein[b], median [IQR], mg/L | | | | | |
| [0; 5] | 337,897 (83.1) | 316,824 (83.5%) | 12,997 (74.4%) | 7242 (84.3%) | 834 (73.6%) |
| [5; 20] | 38,543 (9.5) | 35,006 (9.23%) | 2735 (15.6%) | 644 (7.49%) | 39 (3.44%) |
| [20; 80] | 4111 (1.0) | 3528 (0.93%) | 441 (2.52%) | 103 (1.20%) | 158 (13.9%) |
| Albumin[c], median [IQR], g/L | | | | | |
| [18; 40] | 7149 (1.8) | 6343 (1.67%) | 652 (3.73%) | 114 (1.33%) | 40 (3.53%) |
| [40; 60] | 342,047 (84.2) | 319,681 (84.3%) | 14,279 (81.7%) | 7185 (83.6%) | 902 (79.6%) |
| History of cholesterol lowering medication, *n* (%) | 53,247 (10.0) | 48,598 (12.8%) | 3558 (20.4%) | 928 (10.8%) | 163 (14.4%) |
| History of blood pressure medication, *n* (%) | 40,971 (10.1) | 37,453 (9.88%) | 2449 (14.0%) | 922 (10.7%) | 147 (13.0%) |
| History of insulin medication, *n* (%) | 592 (0.2) | 534 (0.14%) | 52 (0.30%) | 6 (0.07%) | 0 (0.00%) |
| History of hormone-replacement therapy[d], *n* (%) | 88,006 (38.9) | 77,048 (37.4%) | 6089 (55.0%) | 4265 (51.4%) | 604 (56.6%) |
| History of oral contraception pill or minipill[d], *n* (%) | 5403 (1.3) | 5255 (2.55%) | 97 (0.88%) | 48 (0.58%) | 3 (0.28%) |
| History of diabetes, at baseline, *n* (%) | 7418 (1.8) | 6606 (1.74%) | 757 (4.33%) | 43 (0.50%) | 12 (1.06%) |
| History of arterial hypertension, at baseline, *n* (%) | 24,353 (6) | 21,756 (5.74%) | 2064 (11.8%) | 430 (5.00%) | 103 (9.09%) |
| History of dyslipidemia, at baseline, *n* (%) | 5748 (1.4) | 5114 (1.35%) | 491 (2.81%) | 117 (1.36%) | 26 (2.29%) |
| History of chronic renal failure, at baseline, *n* (%) | 722 (0.2) | 663 (0.17%) | 88 (0.50%) | 17 (0.20%) | 4 (0.35%) |
| History of heart failure, at baseline, *n* (%) | 612 (0.2) | 531 (0.14%) | 61 (0.35%) | 16 (0.19%) | 4 (0.35%) |

(Continues)

**TABLE 1** (Continued)

| | Global population ($n = 406,411$) | Non-sarcopenics ($n = 379,204$, 93.3%) | Presarcopenics subgroup n°1 – low HGS only ($n = 17,479$, 4.3%) | Presarcopenics subgroup n°2 – low SMI only ($n = 8595$, 2.1%) | Sarcopenics ($n = 1133$, 0.3%) |
|---|---|---|---|---|---|
| Family history of stroke and/or ischemic heart disease, *n* (%) | 2096 (0.5) | 1881 (0.50%) | 151 (0.86%) | 52 (0.61%) | 12 (1.06%) |
| Grip strength (best value), kg, median [IQR] | 30.0 [24.0; 40.0] | 32.0 [26.0;42.0] | 14.0 [12.0;22.0] | 22.0 [20.0;26.0] | 12.0 [10.0;14.0] |
| SMI (BIA), kg/m$^2$, median [IQR] | 7.5 [6.47; 8.98] | 7.61 [6.53;9.02] | 7.08 [6.30;8.61] | 5.34 [5.19;5.43] | 5.30 [5.14;5.43] |
| Lost to follow-up, *n* (%) | 844 (0.2) | 796 (0.21%) | 31 (0.18%) | 15 (0.17%) | 2 (0.18%) |
| Death during the follow up period, *n* (%) | 24,995 (6.5%) | 21,312 (5.62%) | 1854 (10.6%) | 718 (8.35%) | 156 (13.8%) |

[a]Significant number of missing values (78,560 in the global population; 71,339 in the non-sarcopenics, 4685 in the presarcopenics subgroup n°1, 2208 in the presarcopenics n°2, 328 in the sarcopenics).
[b]Significant number of missing values (25,860 in the global population; 23,846 in the non-sarcopenics, 1306 in the presarcopenics subgroup n°1, 606 in the presarcopenics n°2, 102 in the sarcopenics).
[c]Significant number of missing values (57,215 in the global population; 53,180 in the non-sarcopenics, 2548 in the presarcopenics subgroup n°1, 1296 in the presarcopenics n°2, 191 in the sarcopenics).
[d]In women only. WC: Waist circumference.

tests or Fisher's exact tests to test for independence among qualitative variables. Survival analyses were performed using Cox models. Non-adjusted hazard ratios ($HR_{na}$) and adjusted hazard ratios ($HR_a$), along with their 95% confidence intervals (95% CI), were reported. $HR_{a1}$ denotes $HR_a$ derived from minimally adjusted models (level 1), whereas $HR_{a2}$ denotes $HR_a$ derived from maximally adjusted models (level 2). Quantitative variables were always discretized. The proportional hazards assumption was checked using the Schoenfeld residuals and graphics methods. Statistical analyses were performed using R (version 4.1.2) and RStudio (version 2022.07.2 + 576), and the knitr, dplyr, lubridate, compareGroups, and survival packages. *p*-values of less than 0.05 were considered statistically significant. All tests were two-sided. When appropriate, 95% CI was computed.

# RESULTS

## Study flow chart

After applying the exclusion criteria, our study included 406,411 participants, of which 379,204 (93.3%) were non-sarcopenic, 17,479 (4.3%) were presarcopenic (subgroup n°1), 8595 (2.1%) were presarcopenic (subgroup n°2), and 1.133 (0.3%) were sarcopenic (Figure 2). Median follow-up was 12.1 years (IQR: [11.4; 12.8]).

## Baseline characteristics

Of the included participants, 226,483 (55.7%) were women, with a median age of 58.0 [50.0; 63.0] years. Among the 1789 participants aged 70 or over, 16 (0.9%) were sarcopenics. Baseline characteristics are shown in detail in Table 1.

## Primary outcome: incident MACCEs, in non-sarcopenics (reference) versus presarcopenics (n°1 and 2) and sarcopenics

Around 93.0% of the MACCEs were collected based on the ICD-10 classification (Table 2). The main analysis was performed on the global population. There were 28,300 first-time MACCEs (Table 2). The cumulative risk of incident MACCEs is shown in Figure 3.

Where the risk of MACCEs was concerned, the presarcopenic subgroup n°1 was associated with $HR_{na} = 1.61$ (1.54; 1.69), $HR_{a1} = 1.37$ (1.3; 1.43), and $HR_{a2} = 1.25$ (1.19; 1.31), the presarcopenic subgroup n°2 was associated with $HR_{na} = 1.06$ (0.98; 1.15), $HR_{a1} = 1.38$ (1.27; 1.50), and $HR_{a2} = 1.33$ (1.23; 1.45),

**TABLE 2** Approximate fatal and non-fatal MACCE counts, with possible duplication of MACCEs based on ICD-10 classifications and self-reported events.

| | Global[a] | Non-fatal events from self-reports | Non-fatal events from ICD-10 | Fatal events from ICD-10 |
|---|---|---|---|---|
| MACCE and all-cause deaths | | | | |
| *n* (%) | 47,610 | 1827 | 26,904 | 24,040 |
| Delay (years), median (IQR) | 7.0 [4.0; 9.7] | - | - | - |
| MACCE and MACCE-related death | | | | |
| *n* (%) | 28,300 | 1827 | 26,904 | 1703 |
| Delay (years), median (IQR) | 6.6 [3.5; 9.4] | - | - | - |
| Cardiovascular events | | | | |
| *n* (%) | 19,414 | 1220 | 18,519 | 860 |
| Delay (years), median (IQR) | 6.3 [3.3; 9.3] | - | - | - |
| Acute myocardial infarction | | | | |
| *n* (%) | 11,883 | 519 | 11,210 | 854 |
| Delay (years), median (IQR) | 6.9 [3.8; 9.5] | - | - | - |
| Angina pectoris | | | | |
| *n* (%) | 12,196 | 778 | 11,888 | 0 |
| Delay (years), median (IQR) | 6.1 [3.1; 9.0] | - | - | - |
| Cerebrovascular events | | | | |
| *n* (%) | 8169 | 631 | 7520 | 842 |
| Delay (years), median (IQR) | 7.3 [4.2; 9.8] | - | - | - |
| Ischemic stroke | | | | |
| *n* (%) | 6426 | 407 | 6066 | 335 |
| Delay (years), median (IQR) | 7.0 [4.3; 9.9] | - | - | - |
| Hemorrhagic stroke | | | | |
| *n* (%) | 1870 | 8 | 1730 | 507 |
| Delay (years), median (IQR) | 7.3 [4.3; 7.0] | - | - | - |
| Transient ischemic attack | | | | |
| *n* (%) | 2887 | 248 | 2677 | 1 |
| Delay (years), median (IQR) | 6.9 [3.7; 9.6] | - | - | - |

[a]Without duplication, that is, count including only the first recorded ICD-10 and self-reported event.

and the sarcopenic group was associated with $HR_{na} = 1.53$ (1.27; 1.84), $HR_{a1} = 1.83$ (1.52; 2.20), and $HR_{a2} = 1.62$ (1.34; 1.95).

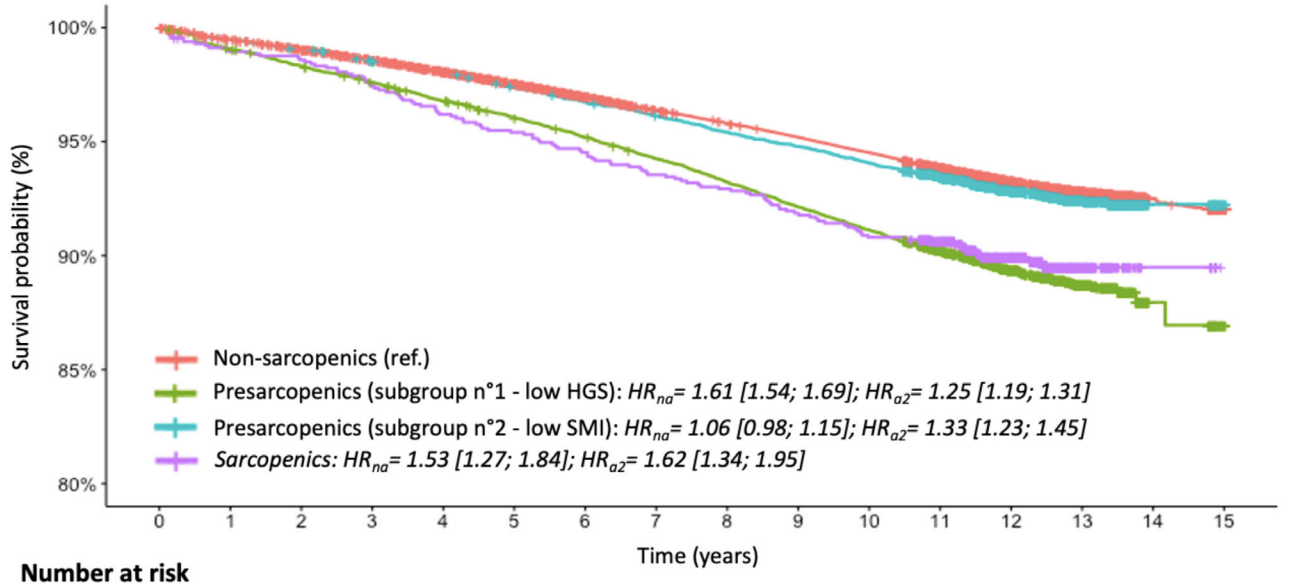
## Secondary outcomes

### Incident cardiovascular or cerebrovascular events, considered independently, in non-sarcopenics (reference) versus presarcopenics (n°1 and 2) and sarcopenics

This secondary analysis was performed on the global population and concerned 19,414 first-time cardiovascular events, and 8169 first-time cerebrovascular events.

Where the risk of cardiovascular events was concerned (See Supplementary Figure S1.A.), the presarcopenic subgroup n°1 was associated with $HR_{na} = 1.59$ (1.50; 1.69), $HR_{a1} = 1.38$ (1.30; 1.46), and $HR_{a2} = 1.24$ (1.17; 1.32), the presarcopenic subgroup n°2 was associated with $HR_{na} = 0.88$ (0.79; 0.98), $HR_{a1} = 1.31$ (1.17; 1.46), and $HR_{a2} = 1.26$ (1.13; 1.40), and the sarcopenic group was associated with $HR_{na} = 1.35$ (1.07; 1.71), $HR_{a1} = 1.85$ (1.46; 2.34), and $HR_{a2} = 1.60$ (1.26; 2.03).

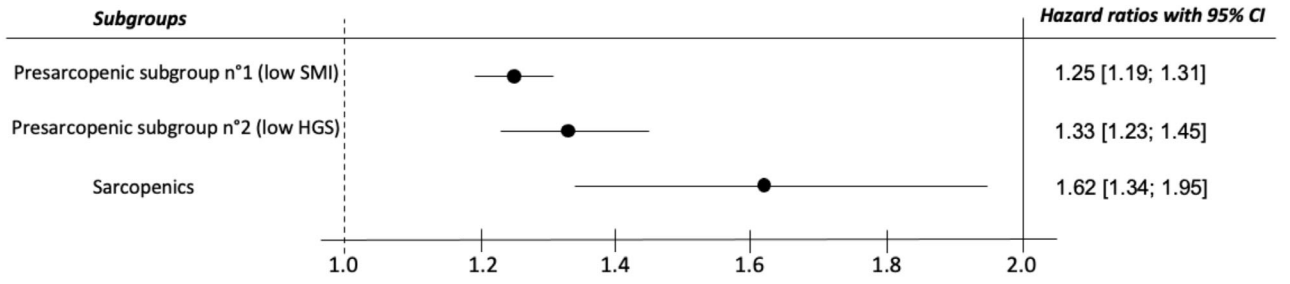
Where the risk of cerebrovascular events was concerned (See Supplementary Figure S1.B.), the presarcopenic subgroup n°1 was associated with $HR_{na} = 1.69$ (1.55; 1.84), $HR_{a1} = 1.37$ (1.26; 1.50), and $HR_{a2} = 1.26$ (1.16; 1.38), the presarcopenic subgroup n°2 was associated with $HR_{na} = 1.36$ (1.19; 1.55), $HR_{a1} = 1.41$ (1.23; 1.62),




**Number at risk**

| Time (y) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Non-sarcopenics | 379,204 | 377,235 | 375,584 | 373,700 | 371,637 | 369,400 | 367,079 | 364,786 | 362,567 | 360,216 | 357,653 | 320,129 | 207,376 | 64,782 | 2,473 | 154 |
| Presarcopenics n°1 (low HGS) | 17,479 | 17,312 | 17,178 | 17,049 | 16,901 | 16,767 | 16,613 | 16,445 | 16,266 | 16,075 | 15,900 | 13,674 | 8,028 | 1,712 | 88 | 7 |
| Presarcopenics n°2 (low SMI) | 8,595 | 8,548 | 8,514 | 8,460 | 8,420 | 8,357 | 8,302 | 8,248 | 8,186 | 8,133 | 8,069 | 7,245 | 4,626 | 1,588 | 71 | 5 |
| Sarcopenics | 1,133 | 1,119 | 1,115 | 1,102 | 1,088 | 1,079 | 1,069 | 1,058 | 1,051 | 1,039 | 1,027 | 914 | 557 | 153 | 8 | 0 |

(A)




(B)

**FIGURE 3** Non-adjusted MACCE-free survival rates (406,411 participants; 28,300 events). (A) Kaplan Meier curve. Ref.: Reference subgroup for statistical analyses. $HR_{na}$: Non-adjusted hazard ratio. $HR_{a2}$: Hazard ratio derived from maximally-adjusted models (adjustment on socio-demographical covariates (sex, age at recruitment, Townsend Deprivation Index), BMI, WC, smoking and alcohol status, family history of stroke and/or ischemic heart disease, personal history of type-2 diabetes and/or high blood pressure and/or dyslipidemia and/or chronic renal failure and/or heart failure, medication intake (cholesterol-lowering medication, blood pressure medication, insulin), physical activity group, albumin, and CRP). (B) Forest plot. *Hazard ratios with 95% CI*: *hazard ratio resulting in maximally adjusted models*.

and $HR_{a2} = 1.37$ (1.19; 1.57), and the sarcopenic group was associated with $HR_{na} = 1.53$ (1.09; 2.15), $HR_{a1} = 1.44$ (1.02; 2.03), and $HR_{a2} = 1.29$ (0.91; 1.82).

## Incident MACCEs in NonSarcNonObese versus others

Participants were divided into 4 subgroups, based on obesity status: NonSarcNonObese (298,414 individuals, 73.4%, reference group), PreSarcNonObese (13,167 individuals, 3.2%), NonSarcObese (89,385 individuals, 22.0%), and PreSarcObese (5445 individuals, 1.4%). Survival analyses were performed on 28,300 events, including 8626 events in obese participants. Where the risk of MACCEs was concerned (See Supplementary Figure S1. C.), the NonSarcObese group was associated with $HR_{na} = 1.46$ (1.42; 1.50), $HR_{a1} = 1.91$ (0.96; 3.82), and $HR_{a2} = 1.71$ (0.85; 3.42), the PreSarcNonObese group was associated with $HR_{na} = 1.41$ (1.35; 1.48), $HR_{a1} = 1.38$ (1.31; 1.45), and $HR_{a2} = 1.29$ (1.22; 1.35), and the PreSarcObese group was associated with $HR_{na} = 2.27$ (2.11; 2.44), $HR_{a1} = 2.66$ (1.33; 5.34), and $HR_{a2} = 2.16$ (1.08; 4.34).

## Sensitivity analyses

Regarding the 226,483 women only (11,429 first-time MACCEs), with non-sarcopenics as the reference group, where the risk of MACCEs was concerned, the presarcopenic subgroup n°1 was associated with $HR_{na} = 1.91$ (1.79; 2.04), $HR_{a1} = 1.43$ (1.34; 1.53), and $HR_{a2} = 1.27$ (1.19; 1.36), the presarcopenic subgroup n°2 was associated with $HR_{na} = 1.48$ (1.36; 1.6), $HR_{a1} = 1.36$ (1.24; 1.48), and $HR_{a2} = 1.3$ (1.19; 1.42), and the sarcopenic group was associated with $HR_{na} = 2.11$ (1.74; 2.57), $HR_{a1} = 1.78$ (1.47; 2.17), and $HR_{a2} = 1.53$ (1.26; 1.86).

In the sensitivity analysis of the composite event "incident MACCEs or death from all-cause" (47,610 first-time events), with non-sarcopenics as the reference group, where the risk of MACCEs was concerned, the presarcopenic subgroup n°1 was associated with $HR_{na} = 1.73$ (1.67; 1.79), $HR_{a1} = 1.42$ (1.37; 1.48), and $HR_{a2} = 1.29$ (1.24; 1.33), the presarcopenic subgroup n°2 was associated with $HR_{na} = 1.22$ (1.15; 1.29), $HR_{a1} = 1.38$ (1.3; 1.46), and $HR_{a2} = 1.33$ (1.25; 1.41), the sarcopenic group was associated with $HR_{na} = 2.03$ (1.79; 2.3), $HR_{a1} = 2.1$ (1.84; 2.38), and $HR_{a2} = 1.83$ (1.61; 2.08).

We finally separated our population into two subgroups using a median age value of 58.0 years, considering the non-sarcopenic group as the reference group. Among participants that were strictly younger than 58.0 years ($N = 199{,}995$, 8143 first-time events), where the risk of MACCEs was concerned, the presarcopenic subgroup n°1 was associated with $HR_{na} = 1.60$ (1.44; 1.79), $HR_{a1} = 1.43$ (1.28; 1.59), and $HR_{a2} = 1.23$ (1.10; 1.37), the presarcopenic subgroup n°2 was associated with $HR_{na} = 0.93$ (0.74; 1.16), $HR_{a1} = 1.53$ (1.21; 1.94), and $HR_{a2} = 1.47$ (1.16; 1.85), the sarcopenic group was associated with $HR_{na} = 1.30$ (0.70; 2.41), $HR_{a1} = 1.88$ (1.01; 3.50), and $HR_{a2} = 1.59$ (0.85; 2.96).

Among participants that were 58.0 years or older ($N = 206{,}416$; 20,157 first-time events), where the risk of MACCEs was concerned, the presarcopenic subgroup n°1 was associated with $HR_{na} = 1.33$ (1.26; 1.40), $HR_{a1} = 1.33$ (1.26; 1.40), and $HR_{a2} = 1.24$ (1.18; 1.31), the presarcopenic subgroup n°2 was associated with $HR_{na} = 0.85$ (0.78; 0.92), $HR_{a1} = 0.85$ (0.78; 0.92), and $HR_{a2} = 1.25$ (1.14; 1.36), the sarcopenic group was associated with $HR_{na} = 1.17$ (0.97; 1.42), $HR_{a1} = 1.17$ (0.97; 1.42), and $HR_{a2} = 1.54$ (1.27; 1.87).

# DISCUSSION

## Main results

In this large-scale study, we found that presarcopenic (whatever the definition used) and sarcopenic participants were at higher risk of MACCEs than non-sarcopenic participants. Furthermore, presarcopenic participants (whatever the definition used) were at higher risk of cardiovascular events and cerebrovascular events (considered independently), and that's also true for sarcopenic participants for cardiovascular events, but not for cerebrovascular events. Our study also found that the risk of MACCEs was subgroup-specific, with a higher risk in PreSarcNonObese and PreSarcObese participants, compared to the NonSarcNonObese.

## Comparison with findings reported in the literature

To the best of our knowledge, few studies have investigated the risk of MACCEs in presarcopenic and sarcopenic participants compared to non-sarcopenic participants in very large cohorts, and none of them used EWGSOP2 criteria. This study is also the first to investigate the risk of MACCEs in participants with a normal HGS but a low SMI value (presarcopenic n°2), whose are considered as non-sarcopenics in EWGSOP2 recommendations.[1]

The number of MACCEs we found appears to be consistent with the previously reported results.[12] The prevalence of sarcopenia was lower in our cohort,[1] maybe because it was a "healthier" community-dwelling cohort.

Nevertheless, it is plausible to hypothesize that an association exists between sarcopenia and MACCEs, since the latter share common pathogenic pathways.[7–9] Although the studies reported in the literature used different guidelines and outcomes,[12,13] two report findings that are somewhat similar to ours.[12,13] In one hand, the authors investigated the risk of MACCEs in sarcopenic and severe sarcopenic participants, but not in presarcopenic participants.[12] On the other hand, the authors investigate only the association between sarcopenia/frailty and MACCEs.[13] Globally, both studies showed a higher risk of MACCEs in participants with severe sarcopenia and in frail-sarcopenic participants, but we found no large-scale studies, based on EWGSOP2 criteria, confirming a higher risk of MACCEs in PreSarc participants.

Regarding the risk of MACCEs in participants with SO, a higher risk was suggested in PreSarcNonObese and PreSarcObese, compared to NonSarcNonObese, but the authors did not use the EWGSOP2 definition of SO.[14]

In the studies that used muscle mass only as the exposure variable,[22–24] a higher risk of MACCEs was found in participants with low SMI.

## Study design choices

Using the highest of the right- and left-hand HGS scores seems advisable.[17] To calculate an approximation

of SMM from BIA data, the EWGSOP2 guidelines recommend prioritizing the *Sergi* equation.[1] However, since "reactance" data – required in the *Sergi* equation – were not available in our dataset, we used the *Janssen* equation,[18] which has also been validated by EWGSOP.[2] As there is no consensus on the exact list of MACCEs,[12,25] we used the events that are most frequently considered as MACCEs, and used HF, CKD, and the conditions associated with metabolic syndrome as adjusting covariates.

## Strengths and limitations of the study

### Strengths

Our study was conducted on a very large prospective cohort, with good-quality data collection. There was probably no reporting bias as most of the MACCEs were collected using hospitalization data. We tried to improve on the methodologies used in recent studies[12,13] by (i) using the highest (not the average) HGS value, (ii) excluding participants with a history of MACCEs in all main analyses, (iii) including angina pectoris and TIA in the list of MACCEs, and (iv) using 3 modes of data collection, namely ICD-9, ICD-10 and self-reports, such that our data were more exhaustive. The increased risk we found in the two age groups (participants strictly younger than 58.0 years, and those 58.0 years and older) in the sensitivity analysis, confirms that the occurrence of the MACCE outcome in presarcopenic and sarcopenic participants is not solely age-related.

### Limitations

Although the UK Biobank database provided a large cohort of participants, it is limited by evidence of a "healthy responder" bias. As such, due to the low proportion of sarcopenic participants, presarcopenia (subgroup n°1 and n°2) and sarcopenia were considered as a single subgroup in our analysis of participants living or not with obesity. Only Caucasian participants were included, which limits the generalizability of our results. The fact that most of the events were recorded through hospitalization data underlines the lack of precision inherent to declarative data. In the sensitivity analysis, we found the same conclusions as for the primary outcome of the principal analysis, but the non-significant risk difference in the sarcopenic participants <58.0 years was probably linked to a lack of power in this minority subgroup ($N = 197$ sarcopenic participants aged <58.0 years). Finally, the very high proportion of women in the presarcopenic subgroup n°2 and sarcopenic groups, compared with the balanced proportion in the others, underlines the importance of choosing personalized thresholds for the calculation of SMI, and partly explains the dispersion of confidence intervals between these four main subgroups of participants.

## Perspectives

As several studies on the same subject reported divergent results and did not compare the same subgroups, future studies should (i) probably be conducted on older prospective cohorts to include more sarcopenic participants, and (ii) use the EWGSOP2 diagnostic criteria to enable their comparison.

In the same way that metabolic syndrome parameters are screened for when assessing cardiovascular risk, it would probably be useful to screen for sarcopenia as well.

The higher risk of MACCEs in participants with a low SMI only, as in those with a low HGS only, compared to non-sarcopenics, suggests that it may be useful to assess muscle mass in all patients at risk of sarcopenia, even when muscle strength is normal, which is not mentioned in the EWGSOP2 recommendations.

## CONCLUSION

This study supports the hypothesis that presarcopenic (whatever the definition used) and sarcopenic status are independent risk factors for incident MACCEs in a middle-aged and older Caucasian population. To confirm these findings, further studies are needed. These should be based on EWGSOP2 criteria and conducted on database populations with more sarcopenic participants, with particular focus on obese sarcopenic participants and participants with low SMI but normal HGS.

### AUTHOR CONTRIBUTIONS

Charlotte Jauffret, Emmanuel Chazard, and Julien Paccou-study conception and design, data acquisition, analysis and interpretation, manuscript drafting, revision and final approval. Renaud Périchon-data acquisition, analysis and interpretation, revision, and final approval. Antoine Lamer-analysis and interpretation, revision, and final approval. Bernard Cortet-study conception and design, revision, and final approval.

### CONFLICT OF INTEREST STATEMENT

CJ, RP, AL, BC, EC, and JP have no competing interests in connection with this study.

### ETHICS STATEMENT

UK Biobank was given a favorable opinion by the Northwest Multi-Centre Research Ethics Committee (Ref: 11/NW/0382). This study was conducted under UK

Biobank application number 66515. The authors certify that they comply with the ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia and Muscle.

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However, the authors received no funding for this study, which was conducted on data obtained from the UK Biobank database (Application ID: 66515). So UK Biobank fundings had no input on the study design, data analysis or interpretation, report writing, approval of the manuscript, or the decision to submit the paper for publication.

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## SUPPORTING INFORMATION

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

**Supplementary figure S1.** Secondary analysis forest plots. (A). Incident cardiovascular events, considered independently, in non-sarcopenics versus presarcopenics (n°1 and 2) and sarcopenics. (B). Incident cerebrovascular events, considered independently, in non-sarcopenics (reference) versus presarcopenics (n°1 and 2) and sarcopenics. (C). Incident major adverse cardiac and cerebrovascular events in NonSarcNonObese (reference) versus NonSarcObese, PreSarcNonObese, and PreSarcObese.

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