



Narrative Review

Identification of factors associated with sarcopenic obesity development: Literature review and expert panel voting



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SUMMARY

Sarcopenic obesity (SO) is defined as the combination of excess fat mass (obesity) and low skeletal muscle mass and function (sarcopenia). The identification and classification of factors related to SO would favor better prevention and diagnosis. The present article aimed to (i) define a list of factors related with SO based on literature analysis, (ii) identify clinical conditions linked with SO development from literature search and (iii) evaluate their relevance and the potential research gaps by consulting an expert panel.

From 4746 articles screened, 240 articles were selected for extraction of the factors associated with SO. Factors were classified according to their frequency in the literature. Clinical conditions were also recorded. Then, they were evaluated by a panel of expert for evaluation of their relevance in SO development. Experts also suggested additional factors.

Thirty-nine unique factors were extracted from the papers and additional eleven factors suggested by a panel of experts in the SO field. The frequency in the literature showed insulin resistance, dyslipidemia, lack of exercise training, inflammation and hypertension as the most frequent factors associated with SO whereas experts ranked low spontaneous physical activity, protein and energy intakes, low exercise training and aging as the most important.

Although literature and expert panel presented some differences, this first list of associated factors could help to identify patients at risk of SO. Further work is needed to confirm the contribution of factors associated with SO among the population overtime or in randomized controlled trials to demonstrate causality.

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Abbreviations: ALM, Appendicular Lean Mass; ASM, Appendicular Skeletal Muscle; BMI, Body Mass Index; CKD, Chronic Kidney Disease; COPD, Chronic Obstructive Pulmonary Disease; DOI, Digital Object Identifier; FFM, Fat-Free Mass; FM, Fat Mass; HeTOP, Health Terminology/Ontology Portal; HGS, Handgrip Strength; HIV, human immunodeficiency virus; mRNA, messenger Ribonucleic Acid; mTOR, mammalian target of rapamycin; NAFLD, Non-alcoholic Fatty Liver Disease; OSO, Osteosarcopenic Obesity; PA, Physical Activity; RA, Rheumatoid Arthritis; SM, Skeletal Muscle; SMM, Skeletal Muscle Mass; SO, Sarcopenic Obesity; T2D, Type 2 Diabetes; WC, waist circumference.

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1. Introduction

Obesity and sarcopenia are two main threats in aging populations. It is also the case in younger population affected by chronic disease, leading to altered quality of life and overall mortality [1,2]. The combination of excess fat mass (obesity), and low skeletal muscle mass and function (sarcopenia) has been defined in 2022 as Sarcopenic Obesity (SO) by expert members of the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) [3]. An algorithm to diagnose patients with SO was proposed based on Body Mass Index (BMI) or waist circumference, clinical symptoms and body characteristics including percent of body fat, handgrip strength, and appendicular lean mass divided by weight [3]. Two stages are defined within this algorithm: level one is a stage without complications and level two with complications attributable to SO such as metabolic diseases and cardiovascular diseases.

However, little is known about the related factors of the sarcopenic obese patients and the potential risk factors leading to the development of SO. Defining a list of potential related factors will help physicians in the screening of people at risk of SO development. An increasing number of scientific articles on SO has been published but the relevance of the factors related to SO has not yet been investigated. The list of factors obtained could then be useful in the creation of a SO phenotype facilitating detection and diagnosis of patients at risk. Pathophysiological disorders and clinical situations of subjects have also to be considered in order to evaluate their importance in the pathogenesis of SO and potentially highlight different pathways leading to SO in different disease conditions. Thus, the present article aimed to (i) define a list of factors related with SO based on literature analysis, (ii) identify clinical conditions linked with SO development from literature search and (iii) evaluate their relevance and the potential research gaps by consulting an expert panel.

2. Methods

To gather the factors found associated to SO, a literature search was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews [4] as these reviews synthesized the literature available on a topic and identify sources of evidence and gaps. To go further, the frequency of factors found in the literature was recorded, compiled, and then evaluated by a panel of experts in the field to rank their relevance. Then, the frequency and the ranking from the expert panel were compared. General methodology is presented in Fig. 1.

2.1. Information sources & search

Search was conducted on March 31st 2021 using PubMed and Embase literature databases. Criteria for selection were as follows: scientific articles published between January 1st 2000 and March 31st 2021 (as the definition of sarcopenia is recent, we focused on a timeframe close to 10 years before and 10 after), focusing on sarcopenia AND obesity, in humans older than 18. As we tried to gather an exhaustive list of factors related to SO, we considered no specific cut-offs for handgrip strength or functional tests for sarcopenia assessment. Inclusion criteria were: BMI higher than 25 kg.m^{-2} (to be able to consider papers from Asian obese population where BMI could be lower than 30 kg.m^{-2}), original articles written in English dealing with the potential causes of SO. We excluded articles not focusing on the consequences, study protocol, animal studies, reviews and studies on mortality. All intervention or observational studies fulfilling the inclusion criteria were included in the search strategy.

To perform the literature analysis, a search terminology has been used. It included all terms related to obesity such as adiposity or fat mass and always combined with a term related to sarcopenia. As osteosarcopenia was also defined in the literature and its physiopathology is closed to SO, we included a combination of sarcopenia and osteoporosis in our definition [5]. All synonyms or equivalent terms were identified using the MESH terms and the Health Terminology/Ontology Portal (HeTOP). The complete terminologies for Pubmed and Embase search are available in supplementary materials (annex 1). Study selection was performed by 5 scientists, reading the title, and if necessary by reading the abstract and the full text. If any doubt existed for exclusion or inclusion, the final decision was taken after consultation of two or more scientists involved in the process.

2.2. Data extraction and collection

For each article, publication date, authors and Digital Object Identifier (DOI) were collected. Associated diseases, clinical conditions and treatments (for intervention studies) were also extracted. Articles were then classified according to the diseases or clinical conditions before screening the full text in order to extract all factors measured and significantly associated with SO, and variation of these factors (increased or decreased vs other populations). According to these data, articles were excluded if no factor was found related to SO and no group with both sarcopenia and obesity was present, not excluded before but finally not in agreement with the selection criteria.

2.3. Data items

As multiple terms could be used for describing a common factor or could be sum up with one general name, one term was chosen and used for all the factors related. The complete list of factors and the terms finally chosen are available in supplementary material (Table S1).

2.4. Analysis of factors identified

Iterations of the factors found were analyzed to classify them according to their frequency in the literature. Different types of factors were identified: protective factors, risk factors, comorbidities and also treatment strategies. Factors were gathered in 4 categories (lifestyle factors, clinical conditions, biological factors and psychosocial factors) irrespective of their types. An additional analysis was performed to check the different clinical conditions in whom SO was investigated. When articles did not mention a specific clinical status and are not related to aging as people are younger than 65 years old, SO was mentioned as the clinical condition.

2.5. Evaluation of identified factors

In order to evaluate the relevance of the factors in SO, we asked a panel of experts. The multiprofessional panel consisted of 14 experts from all around the world whom the field of research is directly linked to SO (Table S2). A questionnaire was sent to the experts for evaluation of the factors. Identified factors were considered by the experts in order to highlight the most important factors for establishing a phenotype of SO. Using the form, factors were classified. For each factor, each expert gave a score (from 0 to 10). A factor with the score 10 was highly relevant to be included in the SO phenotype whereas a score of 0 meant that the factor should not be considered. During the first round, experts were also able to suggest other factors that were not previously identified in the

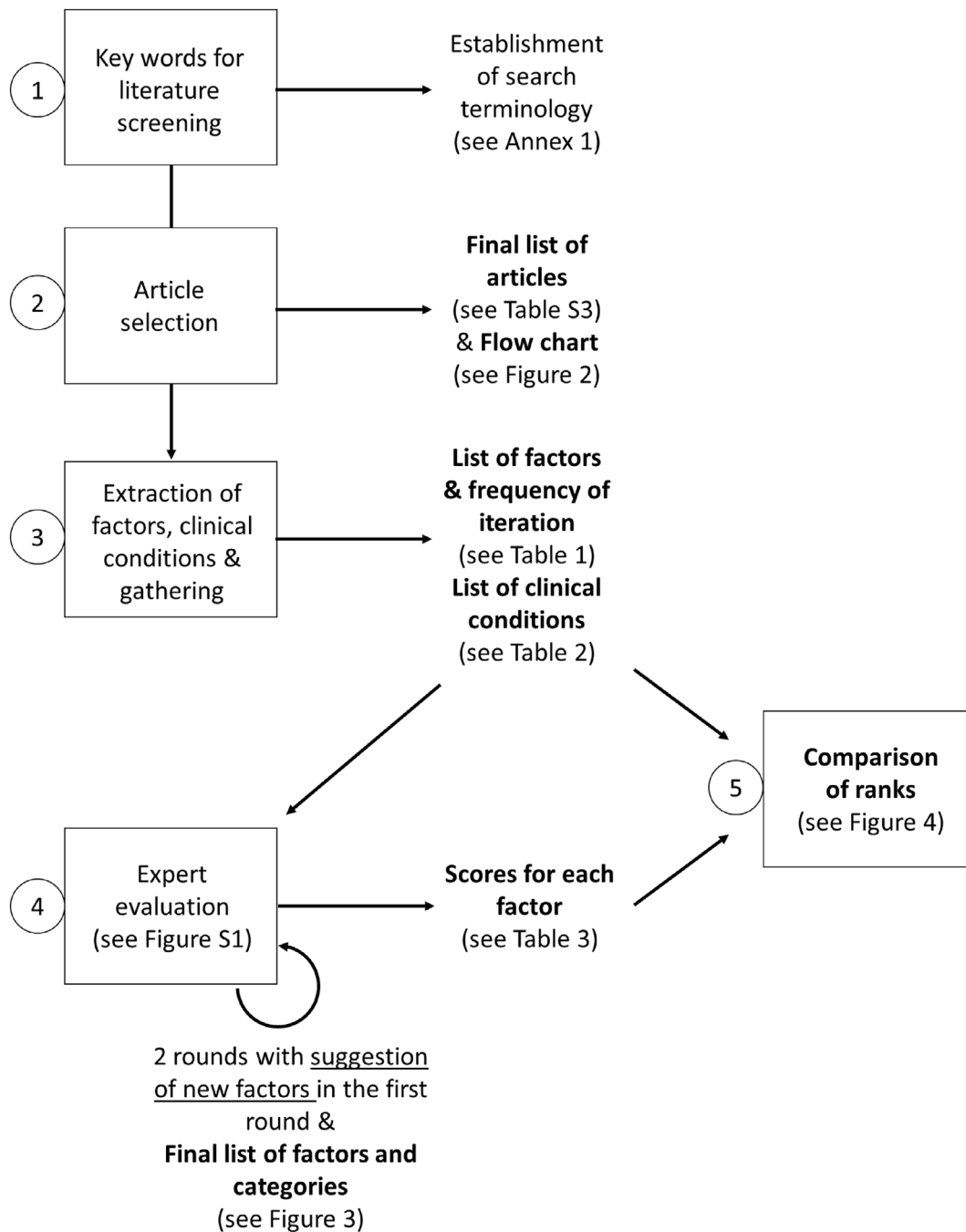


Fig. 1. Methodology.

literature. On the second round, all the experts gave a new score for the factors, including also the factors suggested in the first round. All the factors were then classified according to the standard normal distribution of the individual scores obtained.

2.6. Statistical analysis

Results were expressed as numbers and percentages - N (%) - for categorical variables. The evaluation of factors related to SO were standardized (subtracted by the mean and divided by the standard deviation) to reduce the evaluative differences between experts' ranking. Frequency of factors in literature was compared to the experts' evaluation by categorizing the frequency in 4 groups: not

found in literature, low frequency (1–9 times), moderate frequency (10–19 times) and high frequency (20 and more).

3. Results

3.1. Selection of sources of evidences

The search yielded 7,095 articles (see flow chart in Fig. 2). After duplicate removal, 4,746 articles remained. The first phase of exclusion based on abstracts and titles, language, article type, population studied and presence of a combination of sarcopenia and obesity, led to the inclusion of 919 articles. By reading the full text, 679 articles were excluded mainly because no SO groups and/

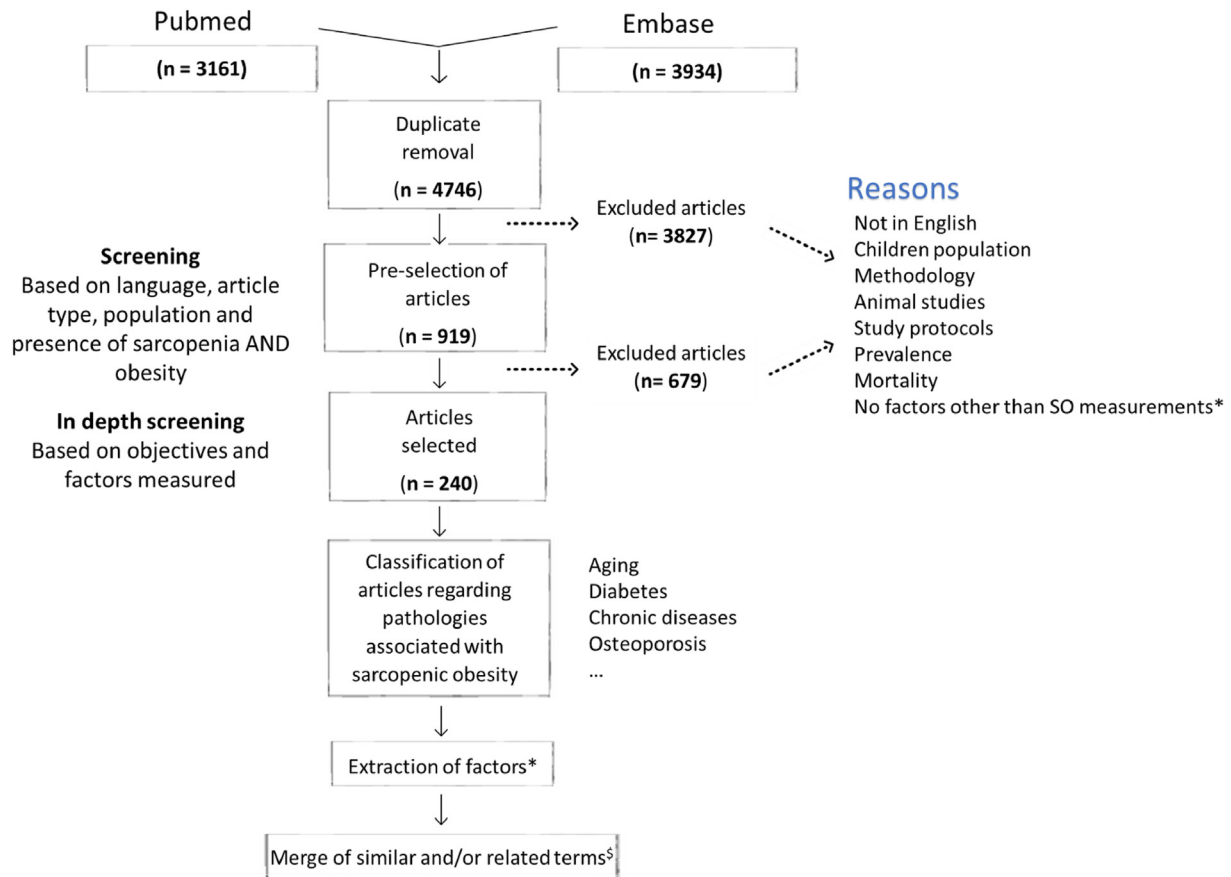


Fig. 2. Flow chart of scientific article selection for the identification of factors significantly associated with SO.

Screening process of articles.

⁵ When gathering the factors, several can be the same but with different spelling or have the same meaning. In order to simplify the final list, common terms were grouped under only one term.

*Measurements of parameters focused on obesity (BMI, percent fat, ...) and sarcopenia (muscle mass, quality and function) are not considered as factors as they are already included in the definition of sarcopenic obesity (SO). We were focusing on factors associated with SO not on the definition of SO.

or no factors other than SO measurements were found. Two hundred and forty articles remained. These were observational, cohort and intervention studies. Based on these, diseases and clinical conditions were registered before extraction of the factors related to SO. The complete list of articles included is available in supplementary material (Table S3).

3.2. Synthesis of results

- List of factors related to SO

From articles, 619 factors were mentioned as significantly associated with SO. To avoid redundancy and to facilitate the analysis, these factors were gathered in more general terms to reach a final list of 39 factors extracted from the literature (Table 1). Insulin resistance, dyslipidemia, exercise training and inflammation were the most frequent factors cited as related to SO. Then hypertension and spontaneous physical activity were also frequently associated with SO. Each other factor represented less than 4% of the total number of factors. Some factors are always or mostly described as positively associated with SO (e.g. insulin resistance, dyslipidemia, inflammation, osteopenia, aging, etc.), or negatively associated with SO (e.g. exercise training, spontaneous physical activity, sleep, smoking). However, the positive or negative relation with SO was controversial for some factors (growth factors and hormones, lipids, secreted muscle biomarkers). Fifteen out of

17 articles depicted a positive association of dietary proteins, amino acids and derivatives or a negative association of lower protein intake with SO.

- Clinical conditions related to SO

Articles were classified regarding the clinical conditions of subjects included in the studies (Table 2). Globally, most of patients included were older than 65 years old and were mentioned as “aging”. This clinical condition represented 126 out of 240 articles. Forty one studies were not linked with any specific clinical condition other than sarcopenic obesity and represented 13.4% of the total number of articles. Then the frequency decreased below 10% (diabetes, osteoporosis, cardiovascular diseases, postmenopausal status, arthritis, chronic kidney diseases, non-alcoholic fatty liver disease, respiratory diseases) and below 2% (endocrine disorders, cancer, cirrhosis, hormone-dependent cancer, chronic diseases, colorectal cancer, human immunodeficiency virus, intestinal disorders, liver diseases, muscular dystrophy, neurological disorders).

3.3. Evaluation of the factors by a panel of experts

- Categorization of the factors

All the factors are presented in Fig. 3. Four categories were created: lifestyle factors, clinical conditions, psychosocial factors and biological factors. In the final list, history of weight cycling,

Table 1
Frequency of factors associated with SO.

Factors	N (%)	Positive association N (%)
Insulin resistance	50 (11.2%)	46 (92.0%)
Dyslipidemia	43 (9.6%)	36 (83.7%)
Exercise training	30 (6.7%)	1 (3.3%)
Inflammation	28 (6.3%)	25 (89.3%)
Hypertension	27 (6.0%)	26 (96.3%)
Spontaneous physical activity	24 (5.4%)	0 (0.00%)
Diabetes	18 (4.0%)	17 (94.4%)
Proteins	17 (3.8%)	2 (11.8%)
Liver diseases	16 (3.6%)	13 (81.2%)
Growth factors & hormones	15 (3.4%)	7 (46.7%)
Psychological status (depression)	15 (3.4%)	15 (100%)
Chronic kidney disease	14 (3.1%)	14 (100%)
Vitamin D status (low)	14 (3.1%)	14 (100%)
Unbalanced diet	10 (2.2%)	7 (70.0%)
Osteopenia	9 (2.0%)	9 (100%)
Social status (low)	9 (2.0%)	8 (88.9%)
Alcohol	8 (1.8%)	3 (37.5%)
Lipids	8 (1.8%)	3 (37.5%)
Energy intakes	7 (1.6%)	2 (28.6%)
Secreted muscle biomarkers	7 (1.6%)	4 (57.1%)
Sleep (quality and time)	7 (1.6%)	0 (0.0%)
Adipokines	6 (1.3%)	6 (100%)
Arthritis	6 (1.3%)	6 (100%)
Respiratory diseases	6 (1.3%)	6 (100%)
Smoking	6 (1.3%)	0 (0.00%)
Cancer treatment	5 (1.1%)	5 (100%)
Genetic variation	5 (1.1%)	4 (80.0%)
Micronutrients	5 (1.1%)	0 (0%)
Aging	4 (0.9%)	4 (100%)
Ethnic origin	4 (0.9%)	3 (75%)
Sex (male)	4 (0.9%)	2 (50.0%)
Myosteatosis	4 (0.9%)	4 (100%)
Heart failure	3 (0.7%)	3 (100%)
Perinatal environment (low quality)	3 (0.7%)	3 (100%)
Serum prealbumin/albumin (low)	3 (0.7%)	3 (100%)
Hemoglobin	2 (0.5%)	2 (100%)
Quality of life (low)	2 (0.5%)	2 (100%)
Surgery	2 (0.5%)	2 (100%)
Antioxidant status (oxidative stress)	1 (0.2%)	1 (100%)

Factors found in the literature were classified from the more frequent to the rarest (number of times or in percent of total number of factors - i.e. 447 -). In the last column, positive association with sarcopenic obesity (as found in literature) was also reported for each factor. In this column, the percentage is based on the frequency of the second column (e.g. 46/50 on the first line).

Cushing's syndrome, aging, bariatric surgery, orthopedic surgery, poor oral health, antidepressive therapies, health literacy and gut microbiota were factors suggested during the first round of evaluation and were evaluated during the second round.

- Global analysis

Each expert evaluated all the factors (see Fig. S1 representing individual answers) and the results are displayed in Table 3. Spontaneous physical activity, energy intake and proteins were the three most important factors to the experts. Exercise training as intervention, aging, unbalanced diet and inflammation were rated as relevant factors to consider. Factors related to psychosocial status (in purple) were not considered important and some biological factors were suggested as not relevant (serum prealbumin/albumin, antioxidant status, genetic variation and hemoglobin). Regarding the additional factors suggested by at least one of the experts, the overall panel did not rate these factors as the most important factors for SO development except for history of weight cycling.

- Comparison of expert opinions and literature

Table 2
Clinical conditions associated with SO in the selected articles.

CLINICAL conditions	N ^a (%)
Aging	126 (41.0%)
Diabetes	20 (6.5%)
Osteoporosis	18 (5.9%)
Cardiovascular diseases	17 (5.5%)
Postmenopausal status	15 (4.9%)
Arthritis	13 (4.2%)
Chronic kidney diseases	12 (3.9%)
Non-alcoholic fatty liver disease	12 (3.9%)
Respiratory diseases	9 (2.9%)
Endocrine disorders	4 (1.3%)
Cancer	3 (1%)
Cirrhosis	3 (1%)
Hormone-dependent cancer	3 (1%)
Chronic diseases	2 (0.7%)
Colorectal cancer	2 (0.7%)
Human Immunodeficiency Virus	2 (0.7%)
Intestinal disorders	2 (0.7%)
Liver diseases	1 (0.3%)
Muscular dystrophy	1 (0.3%)
Neurological disorders	1 (0.3%)

^a The total number is higher than the number of total articles as some articles are related to two or more clinical status (e.g. aging and diabetes). % expressed the percentage of the total number of clinical conditions found. Forty one studies were not linked with any specific clinical condition other than sarcopenic obesity, representing 13.4% of the total number of clinical conditions registered.

A comparison of the expert evaluation and the literature was performed by splitting the factors in four categories (Fig. 4). Overall, the higher frequency in the literature was not related to a more positive evaluation by the experts. Energy intake, myosteatosis and quality of life which were not commonly reported in the literature were considered as important by the experts (3rd, 8th and 12th positions, respectively). Inversely, some factors were rated as less important but were found frequently in the literature: chronic kidney disease, dyslipidemia and hypertension, (respectively 41st, 42nd, 44th positions).

4. Discussion

In this review, we were able to highlight 39 factors found in the literature, completed with 11 factors additionally suggested by the experts. These factors could be very helpful in the detection of patients at risk of SO considering lifestyle factors but also, biological components, specific diseases and psychosocial factors.

4.1. Factors in the literature

In order to better define the SO-related phenotype, the aim of this study was to investigate the available data in the literature to establish an exhaustive list of factors related to SO and propose them to a panel of experts working in the field for validation. We firstly set up a list of factors from which the most frequent ones were related to obesity-related metabolic dysfunctions (insulin resistance, dyslipidemia, inflammation, hypertension, diabetes) and sedentary lifestyle (exercise training, spontaneous physical activity). This could be notably explained by the fact that some of these factors are commonly included in routine measurements when obese patients are included in research protocols and can be easily evaluated in blood samples (e.g. quantification of total cholesterol, high- or low-density lipoproteins for dyslipidemia). Some are also related to obesity comorbidities such as fatty liver diseases [6] and type 2 diabetes [7,8]. The low frequency (less than 3%) of other factors could be explained by the following reasons: (i) more difficulties to be assessed (e.g. myosteatosis, secreted muscle

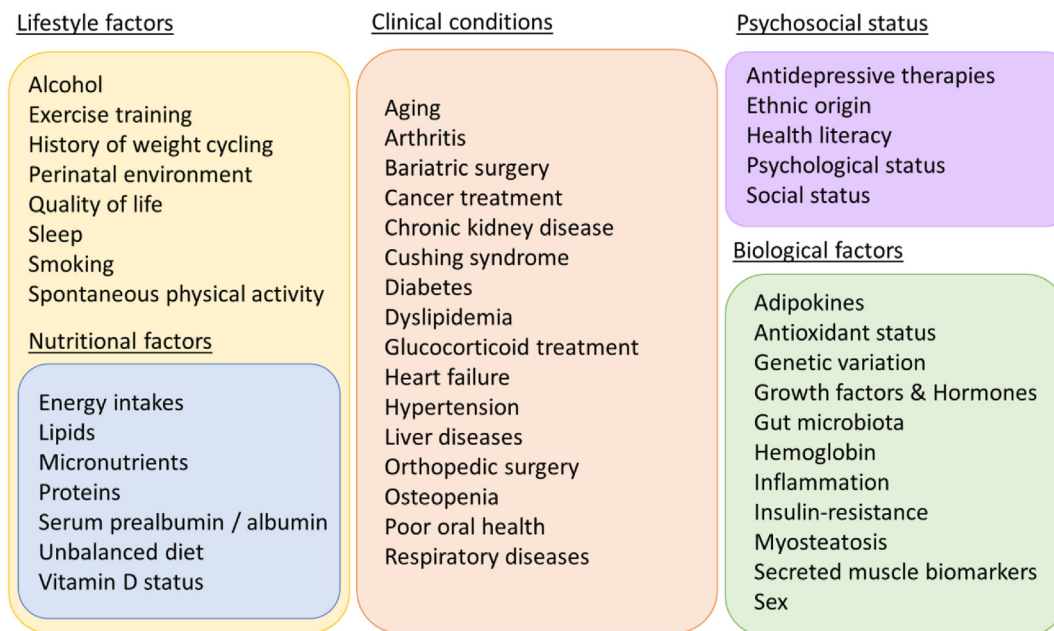


Fig. 3. Final list of factors evaluated by the experts. (From the left to the right) History of weight cycling, Cushing syndrome, Aging, Bariatric surgery, Orthopedic surgery, Poor oral health, Antidepressive therapies, Health literacy and Gut microbiota were suggested by the experts in the first round of evaluation. Others were found in the literature.

biomarkers, genetic variation), (ii) more difficulties to be exhaustively/precisely estimated (e.g. diet composition and psychosocial status by questionnaires, antioxidant status), (iii) not generally considered related to SO due to lack of evidence and/or by low statistical power due to population size and confounders. Additionally, evidence on nutrition and muscle aspects has only been developed very recently (i.e. sarcopenia definition) and may participate to the low number of studies investigating their role in the timeline of our analysis (2000–2021).

To further analyze the results from the literature, clinical conditions were also considered. As primary sarcopenia is defined as an age-related loss of muscle mass and function, most of the articles were focused on people aged over 65 years without a specific clinical disorder. The remaining articles were related to a wide variety of clinical disorders, pointing out that secondary sarcopenia, mostly during illness or chronic diseases, should be considered for building the SO-associated phenotype. As mentioned in Donini et al., 2022 [3], these pathophysiological situations could be a cause of SO and might be considered in the screening of SO as risk factors for sarcopenia, but also as aggravating progression factors after SO diagnosis.

Even if some factors were frequently found to be associated with SO, controversies still exist on their positive or negative association with the disease. For dyslipidemia and insulin resistance, the majority of the articles reported a positive link but some found negative association [9–13]. As these two dysregulations could be related to lower muscle response to insulin, it might be stated that the positive link should be the most plausible but further studies should be necessary to clearly conclude. More recently, higher triglyceride levels were associated with SO in males but not in females [14]. Difference between sexes could partially explain the discrepancies.

For the less frequently cited factors, further studies appear to be necessary to confirm the potential link with SO onset. Indeed, alcohol consumption was positively related to SO [15–17] or negatively [18–21]. Such discrepancies might be partially explained by sex-specific factors [22]. Discrepancies were also found for the

association of sex, social status and quality of life with SO development as some articles detected a higher risk in males [23,24] or females [25,26] and in the presence of poor social status [18–20,26–29], in people living in urban area [30], married individuals [20] or in white collar subgroup [31].

4.2. Factors/clinical conditions less frequently cited but of particular importance in SO development

As mentioned above, SO could be a consequence of a specific disease. We found very few articles analyzing the risk of SO linked to several diseases that are known to induce a loss of muscle mass and function. The severity of non-alcoholic fatty liver disease is linked to SO compared to patients without SO [32]. In chronic kidney disease, even if the SO prevalence is lower than that of sarcopenia, patients are also at risk of SO. As mentioned by Barreto Silva et al., high total and central body adiposity contribute to sarcopenia through a bi-directional relationship with reduced physical activity and unbalanced diet in these patients [33]. The proportion of overweight and obese individuals with human immunodeficiency virus has strongly increased because of the impact of antiretroviral therapy leading to metabolic disease and increased ectopic fat accumulation in liver and skeletal muscles [34]. Attention should also be given to cancer patients as it has been shown that several types of cancer (oropharyngeal, lung, liver, pancreas, and gastrointestinal) could be linked to higher risk of SO [35]. Globally, many diseases could lead to a reduced physical activity and/or an unbalanced diet increasing significantly the loss of muscle mass also in patients who are overweight or obese and might be considered as a SO risk factor.

In all the various clinical situations linked to SO, it might be of particular importance to address the role of myosteatorsis and low muscle density in the development of SO as literature is scarce on this [36]. The panel of experts agreed on its particular importance. In our research, one article mentioned a larger muscle mass but a reduced muscle quality associated with SO [37]. Other papers also described an association between myosteatorsis and SO [38–42].

Table 3
Evaluation of factors by the panel of experts.

FACTORS EVALUATED	mean	SD
Spontaneous physical activity	1.41	0.46
Proteins	1.37	0.47
Energy intake	1.37	0.63
Exercise training	1.27	0.78
Aging	1.22	0.70
Unbalanced diet	1.18	0.47
Inflammation	1.06	0.41
Myosteatosis	0.98	0.68
Insulin resistance	0.96	0.64
History of weight cycling	0.72	0.60
Diabetes	0.64	0.51
Quality of life	0.49	0.9
Vitamin D status	0.36	0.51
Growth factors & Hormones	0.36	0.57
Secreted muscle biomarkers	0.19	0.78
Social status	0.09	0.48
Psychological status	0.07	0.55
Adipokines	0.05	0.81
Bariatric surgery	0.00	0.9
Lipids	-0.04	0.76
Sleep	-0.05	0.75
Health literacy	-0.13	0.69
Cancer treatment	-0.15	0.76
Arthritis	-0.17	0.64
Heart failure	-0.19	0.66
Liver diseases	-0.22	0.62
Osteopenia	-0.22	0.74
Micronutrients	-0.22	0.59
Ethnic origin	-0.29	0.57
Glucocorticoid treatment	-0.29	0.98
Respiratory diseases	-0.30	0.92
Sex	-0.30	0.80
Orthopedic surgery	-0.34	0.71
Poor oral health	-0.35	0.7
Antidepressive therapies	-0.36	0.96
Gut microbiota	-0.45	0.65
Chronic kidney disease	-0.57	0.87
Dyslipidemia	-0.61	0.71
Serum prealbumin / albumin	-0.67	0.75
Hypertension	-0.69	0.84
Cushing syndrome	-0.74	0.97
Perinatal environment	-0.85	0.95
Smoking	-0.90	0.57
Alcohol	-0.97	0.85
Antioxidant status	-1.03	0.46
Genetic variation	-1.15	0.47
Hemoglobin	-1.24	0.88

Table 3
(continued)

Standardized normal distribution of factors according to the score obtained when evaluated by the experts. Factors in bold type were suggested by the experts and were not previously found in the literature as significantly associated with SO.

*Surgery was divided in orthopaedic and bariatric surgery, as suggested by experts.

(In order of appearance) Aging, History of weight cycling, Bariatric surgery, Health literacy, Orthopedic surgery, Poor oral health, Antidepressive therapies, Gut microbiota and Cushing syndrome were suggested by the experts in the first round of evaluation. Others were found in the literature.

Background colour of each factor depict the categories defined in figure 4: lifestyle factors (yellow) including nutritional factors (blue), clinical conditions (orange), psychosocial factors (purple) and biological factors (green).

Gut dysbiosis could be another parameter involved in SO. We did not find articles on this aspect even if dysbiosis has been linked to obesity, sarcopenia and age separately [43–45]. Similarly, the panel of experts did not consider it as an important factor likely because of the lack of literature in the research field of SO or because of the difficulty to include it in clinical assessment, as could be the case for myosteatosis.

4.3. Other factors related to SO or protecting from SO

Few studies were focused on the treatment of SO except for physical activity (spontaneous exercise or training activities) and nutritional interventions [46,47]. When investigated, physical activity was always positively associated with an improvement of body composition, through loss of body fat and/or increase of muscle mass or function. Only one study focused on the pharmacological treatment by liraglutide, a glucagon-like peptide-1 receptor agonist, reporting preserved muscle mass despite loss of body fat [48].

Preventive and treatment strategies against SO based on diet are lacking in the literature and existing articles reported differential results regarding the link between food quality and prevention of SO. Even if a majority of articles depicted protective effect of protein and derivatives on SO development, two studies found higher intakes in SO group compared to sarcopenia group [49] and compared to people without sarcopenia, expressed as % of energy [50]. Smith et al. [51] showed that fish oil supplementation could slow down the decline in muscle mass and function in older adults. Da Boit et al. described an increased muscle function in older women but not in men [52] after receiving fish oil supplements. Conversely, eicosapentaenoic acid (a very long chain omega-3 polyunsaturated fatty acid) was found to be associated with higher intramuscular adipose tissue and arachidonic acid (omega-6 polyunsaturated fatty acid) associated to smaller muscles [53]. In the same study, linoleic acid (omega-6 polyunsaturated fatty acid) was associated with lower intramuscular adipose tissue. The impact of carbohydrate intakes was also controversial as some articles reported a lower or higher intake with SO. Benton et al. found that higher carbohydrate intakes were associated with higher strength, both in upper and lower body in overweight elderly people [54].

More recently, Park et al. suggested that adequate energy intake that meets requirements is more likely to be effective as a major prevention and treatment goal for sarcopenia, whereas physical activity guidelines should be prioritized in the case of SO [55]. Thus, future work should further study the role of nutrition and specific diet interventions in the development or prevention of SO.

Randomized controlled trials are needed to clearly demonstrate their role.

Very few articles were focused on psychosocial evaluation. Even if depression is known to be associated with obesity [56,57], evidences are lacking in SO. A recent systematic review on depressive disorders and SO found large variability in assessment methods leading to heterogeneous results [58].

4.4. Limitations of the present review and future steps

Our study has some limitations. The analysis was performed only with articles written in English and before the publication of the SO definition consensus [3]. This milestone would have a crucial impact on future works and might lead to a better understanding of the disease and the factors associated. We did not consider the variability in cut-off values used between the studies for the definition of SO. However, it might have a weak effect on our results as we focused on other factors than body composition and muscle strength and function. The analyses depicted a high variability of factors' types: some are negatively correlated to SO and could be considered as protective factors (i.e. exercise training in intervention studies), meaning they could be risk factors if there is a lack of practice or if a poorer level is observed in the targeted population (i.e. quality of life). All of the factors identified can thus be considered in clinical practice either as deleterious or as protective regarding patient's conditions. Furthermore, other factors can be closely related to treatment strategies (i.e. exercise training, protein, essential fatty acid intakes) or comorbidity (i.e. insulin resistance) that lead to difficulties to summarize the global findings. The factors gathered together are sometimes too heterogeneous like the secreted muscle biomarkers or the hormones and growth factors analyzed. Taken individually, these articles gave interesting results which will be helpful for profiling individuals at risk of SO and targeting them for SO development prevention but their frequency is too low to definitely conclude on their role. Even if this analysis is based on a high number of studies, some of them originated from the same population or cohorts emphasizing some factors. However, even considering the same cohort, some studies found different results mainly because of inclusion/exclusion criteria or cut-offs applied.

Factors found in literature were classified by the experts but it was not possible to propose a restrictive number of key factors as we were not able to perform statistical analyses and decipher which factors are relevant or not. However, we could hypothesize that obese patients in clinical practice accumulating factors found related to SO development could lead to higher risk of SO. The strength of the factors in the development of SO could be

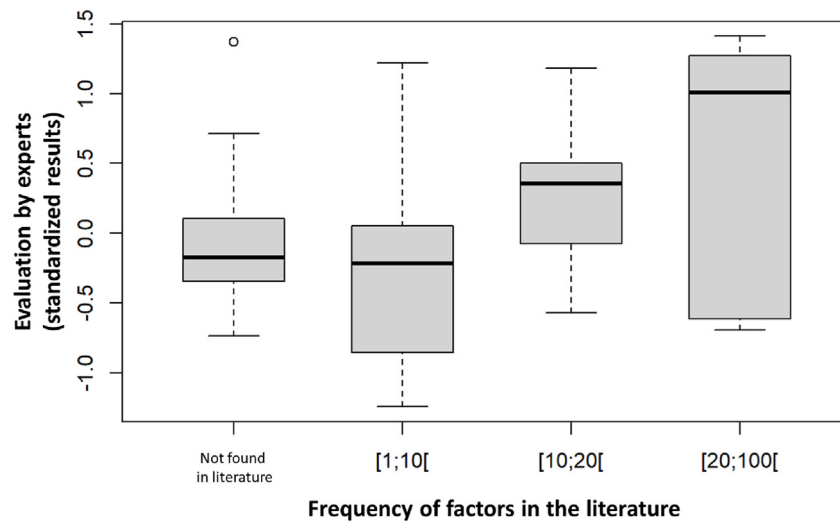


Fig. 4. Link between the frequency of factors and their evaluation by experts.

By splitting the factors according to their frequency in literature (1–9 times, 10–19 times, 20–99 times or not found in the literature) and the evaluation by the experts (scores were standardized), the graph represents the link between literature and expert evaluation. Overall, the most frequent factors are also the factors obtaining a better score in the evaluation despite variability between factors.

determined in the future, especially by studying longitudinal cohorts as it has been done in the recent article of Gortan Capellari et al. in the context of the MoMa epidemiological study. They found insulin resistance and plasma ghrelin profile to be predictive SO risk factors independent of age, sex and BMI [59].

5. Conclusion

With this review based on 20 years scientific literature, focusing on identifying all the potential factors already reported as related to SO development, top 5 factors (insulin resistance, dyslipidemia, exercise training, inflammation and hypertension) are positively or negatively related to obesity. These factors were mostly found in aging but a large number of clinical conditions were found to be associated with SO development. The variety of clinical situations may affect the pathological process and may explain the variability of factors found associated with SO. The experts' evaluation highlighted different factors as top 5 was spontaneous physical activity, proteins, energy intake, exercise training and aging. Further studies are needed to test the contribution of these factors associated with SO among the population overtime or in randomized controlled trials to demonstrate causality.

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Conflict of interest

The authors have no competing interests to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clnu.2024.04.033>.

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