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The Position Statements of the Sarcopenia Definition and Outcomes Consortium

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ABSTRACT

BACKGROUND. To develop an evidence-based definition of sarcopenia, the Sarcopenia Definition and Outcomes Consortium (SDOC) crafted a set of position statements informed by literature review and SDOC's analyses of 8 epidemiologic studies, 6 randomized clinical trials, 4 cohort studies of special populations, and 2 nationally representative population-based studies.

METHODS. Thirteen position statements related to the putative components of sarcopenia definition – informed by the SDOC analyses and literature synthesis - were reviewed by an independent International Expert Panel (Panel) iteratively and voted on by the Panel during the Sarcopenia Position Statement Conference. Four position statements related to grip strength, three to DXA-derived lean mass, four to gait speed, and two summary statements.

RESULTS. The SDOC analyses identified grip strength – either absolute or scaled to measures of body size – as an important discriminator of slowness. Both low grip strength and low usual gait speed independently predicted falls, self-reported mobility limitation, hip fractures, and mortality in community-dwelling older adults. Lean mass measured by dual-energy x-ray absorptiometry (DXA) was not associated with incident adverse health-related outcomes in community-dwelling older adults with or without adjustment for body size.

CONCLUSIONS. The Panel agreed that both weakness defined by low grip strength and slowness defined by low usual gait speed should be included in the definition of sarcopenia. These position statements offer a rational basis for an evidence-based definition of sarcopenia. The analyses that informed these position statements are

summarized in this article and discussed in accompanying articles in this issue of the Journal.

Key words: Sarcopenia, lean mass cut-points, grip strength cut-points, mobility disability, consensus definition of sarcopenia

INTRODUCTION

The lack of a consensus definition of sarcopenia as a biomarker that can help identify older adults at risk for mobility disability and other adverse health outcomes has limited the ability of clinicians to diagnose and treat this condition and hindered the development of function promoting therapies (1). Many investigators, professional societies and organizations around the world have proposed various definitions of sarcopenia (2-14), but these definitions have largely been based on expert opinion. A Foundation for the National Institutes of Health (FNIH)- supported initiative derived cutpoints for lean mass and grip strength based on the analysis of largely healthy older adults (5), but did not evaluate the cutpoints for their ability to predict patient-important clinical outcomes, such as falls, fractures, and mortality. Consequently, an evidence-based definition of sarcopenia has been lacking.

In 2016, the National Institute on Aging (NIA) and the Foundation for the National Institutes of Health (FNIH) funded the Sarcopenia Definitions and Outcomes Consortium (SDOC, the Consortium), a collaboration among content experts and many cohort studies and clinical populations, to develop evidence-based cutpoints for lean mass and strength to identify persons at risk for mobility disability and other adverse health outcomes, such as falls, self-reported mobility limitation, hip fractures, and death. The SDOC assembled a large body of data from epidemiologic studies, clinical trials, and special populations and applied data-driven analytical approaches to generate the cutpoints. The preliminary findings of the analyses were presented at a meeting that took place on October 2, 2017 in Bethesda, MD (1) and included SDOC members, additional content experts from around the world, and the program staff from the NIA

and FNIH. In addition to specific recommendations on the future direction of the research and the analytical approach, the expert attendees offered several recommendations to advance the goal of turning the analytical findings into a consensus definition of sarcopenia (1). First, it was recommended that SDOC establish an independent International Expert Panel (The Expert Panel) to review the final analytical findings and a synthesis of the published evidence. Second, it was recommended that SDOC develop a set of position statements informed by the analytical findings and literature synthesis. Third, expert attendees urged SDOC to have the position statements and the supporting evidence reviewed and voted on by the Panel in a Consensus Conference in the Fall of 2018.

To implement these recommendations of the October 2017 meeting (1), The SDOC held a Sarcopenia Position Statement Conference in Boston, MA in November 2018. Prior to the Conference, draft Position Statements related to the putative components of the sarcopenia definition were developed by the SDOC team based on literature review and SDOC analyses of the data from 8 epidemiologic studies, 6 randomized clinical trials and 4 cohort studies of special populations, and 2 nationally representative population-based studies. A summary of the analyses and the position statements were presented to the Panel and other content experts and stakeholders. These 13 position statements that were reviewed by the Panel, and the evidence that formed the basis of these positions are summarized in this article, and are described in detail in a series of linked articles in this issue of the Journal (15-19).

METHODS

The Analytic Approach

The detailed methods and results of the analyses are presented in several accompanying manuscripts in this issue of the Journal (15-19) and are described only briefly here. The SDOC team assembled 8 observational studies that included 18,831 community-dwelling older adults (13,683 men and 5,148 women), 8 carefully characterized clinical populations (6 randomized trials and 2 cohort studies of patients with hip fracture and HIV), and 2 nationally representative population-based cohorts (the Health and Retirement Survey n = 7,370 with 3,170 men and 4,200 women; and the National Health and Aging Trends Survey n = 5,614 with 2,460 men and 3,154 women) (20-40). Among 18,831 community-dwelling older adults in the 8 observational studies, 3,143 (17%) had self-reported mobility limitation defined as any difficulty walking 2-3 blocks or climbing 10 steps.

The SDOC team assembled a comprehensive set of 36 candidate sarcopenia variables related to DXA-derived body composition measures and grip strength. In the epidemiologic cohorts, the lean mass measurements by DXA were harmonized across studies and calibrated to NHANES standard using validated equations (41). We also evaluated the impact of body size using allometric scaling (42); neither harmonization nor allometric scaling, however, had substantial effects on the results.

The candidate variables were assessed for their ability as discriminators for slowness (defined as usual walking speed < 0.8 m/sec) cross-sectionally in two parallel analyses. Receiver operating characteristic (ROC) and the associated area-under-the-

ROC-curves (AUC) from logistic regression were used to screen several putative sarcopenia variables derived from grip strength, lean mass, body size and their combinations against the outcome of slowness,. In addition, these variables were also entered into Classification and Regression Tree (CART) models to identify those variables that most strongly discriminated those with slowness from those without, and to derive cutpoints for these variables as discriminators of slowness.

Using cutpoints for lean mass and grip strength identified by the CART and ROC/AUC models, we assessed whether the candidate sarcopenia variables were associated with adverse clinical outcomes such as mortality, falls, self-reported mobility limitation and hip fracture using proportional hazards and logistic regression. In addition, we determined the prevalence of weakness defined by the cutpoints derived from the CART and ROC/AUC analyses and evaluated the sensitivity and specificity of these cutpoints in clinical populations, randomized trials, and in nationally representative samples from NHATS and HRS.

The International Expert Panel

The SDOC convened an independent International Expert Panel that included content experts from around the world, and representatives of pharmaceutical companies, major professional societies, and patient advocacy groups (**Table 1**). The potential financial or professional conflicts disclosed by the panelists were reviewed (**Supplemental Table 1**). Members of the Expert Panel were not involved in the development of the SDOC analysis plan or in the analyses.

The Process of Position Statement Development, Vetting, and Approval

The SDOC established 3 task forces consisting of 2 or 3 SDOC members each to assemble the analytical results, perform a literature review, and develop proposals for position statements for consideration by the Expert Panel. The SDOC Team synthesized the analytical findings and literature review to craft 13 position statements that were grouped in four categories: statements related to grip strength (4 statements), to lean mass measured using dual energy X-ray absorptiometry (DXA) (3 statements), to gait speed (4 statements), and summary statements (2 statements).

The Expert Panel reviewed the analytical findings and literature evidence presented by the SDOC Task Forces In conference calls between May and November 2018, and provided comments and suggestions. The interactive discussions between the Expert Panel and the SDOC Task Forces enabled a comprehensive review of the Position Statements and multiple revisions based on the Expert Panel's feedback.

The Sarcopenia Position Statement Conference was held on November 13, 2019 in Boston, MA, and was attended by the SDOC investigators, the Expert Panel, and other content experts and stakeholders from around the world. During the Conference, after discussion of the position statements in which all conference attendees took part, the Expert Panel voted on each of the 13 position statements. Each Expert Panel member voted to approve or disapprove each position statement on a scale of 1 to 9 (1-3 approve; 4-6 uncertain; 7-9 disapprove). The Expert Panel could indicate uncertainty about a Position Statement in one of two ways: an average score of 4 to 6 or substantial dispersion of scores - some panelists voting 1 to 3, some voting 7 to 9. After the November 2018 Conference, these position statements were posted on a website for a

4-week comment period. A summary of the supporting evidence and the discussion are provided below.

RESULTS

Supporting Evidence for Position Statements Related to Grip Strength

The CART analyses identified grip strength – either absolute or scaled to measures of body size – as an important discriminator of slowness. Low grip strength, with or without standardization to weight or BMI, was a predictor of adverse health outcomes, such as falls, self-reported mobility limitation, hip fracture, and mortality in older adults. Weakness, defined by the grip strength cut-points, was common among older Americans. The sensitivity and specificity of these metrics as discriminators of slowness, as well as the proportion of individuals below the diagnostic cutpoints (prevalence) varied by sex and co-morbidity status. In general, the grip strength cut-points to define weakness in women had higher sensitivity and lower specificity than in men. The performance of grip strength cutpoints to define weakness differed substantially in hip fracture and HIV cohorts than in epidemiologic studies of community-dwelling individuals, indicating that the performance of the cut-points may vary with the study population.

Discussion Related to Grip Strength

The advantages and disadvantages of using grip strength in the definition of sarcopenia were discussed. Grip strength can be measured easily and reliably, and equipment for measuring grip strength is inexpensive and portable. However, the devices and the procedures used for measuring grip strength vary in different countries;

therefore, standardization of the equipment and the procedure for measuring grip strength is necessary for application of cutpoints across regions. Although grip strength is cross-sectionally associated with lower extremity strength, the lower extremity strength is a more important contributor to slowness (44). However, few large epidemiologic studies have included data on rigorously measured lower extremity strength; furthermore, measurement of lower extremity strength requires specialized equipment and may be difficult to perform in a clinic setting. Non-muscle factors such as arthritis, pain, depression, and subject motivation and effort could influence grip strength measurement. The SDOC analyses used grip strength at one time point consistent with clinical practice where the clinicians often rely on a single measurement at the time of patient encounter.

Voting Results and Strength of Agreement for Position Statements Related to Grip Strength

The Expert Panel expressed strong agreement with position statements 1 to 4 and unanimously approved these statements (Figure 1).

Supporting Evidence for Position Statements Related to DXA-Derived Lean mass

The position statements 5, 6 and 7 related to lean mass were informed by the SDOC analyses, literature review, and meta-analyses of studies published from 1998 to 2018 (e.g., 44-45). DXA-derived lean mass was harmonized across different models and manufacturers of scanners to the NHANES standard. The harmonization of DXA-derived lean mass did not make a significant difference in the cut-points.

The SDOC team considered scaling factors including body mass, body surface area, height, body fat, percent fat mass, BMI, and regional lean mass. The team used proportional ratios, allometric scaling, and regression residuals to derive scaling factors. Because all scaling approaches produced similar results, only the unscaled variables were used in the CART analyses in favor of simplicity.

In the CART analyses, body composition measures (e.g. BMI, lean mass by DXA or body fat) did not emerge as important discriminators of slowness.

The SDOC team reviewed several published meta-analyses that evaluated the relationship between lean mass and adverse health outcomes (e.g., 44-45). These meta-analyses used composite measures of sarcopenia that included walking speed and grip strength or combined data from studies that used disparate methods for assessment of lean mass such as DXA, bioelectrical impedance, and computerized tomography. To address the limitations of the published meta-analyses, the SDOC researchers conducted an additional meta-analysis of DXA-derived lean mass and its relationship to disability, physical function, mortality, and falls in a smaller carefully selected subset of published studies. However, the odds ratios relating lean mass alone to these 4 outcomes were around 1, consistent with the findings of our analyses.

Discussion Regarding DXA-Derived Lean Mass

Because muscle mass has historically been viewed as an important component of sarcopenia, there was disagreement amongst the panelists about excluding lean mass from the definition of sarcopenia. Lean mass has been traditionally measured by DXA as an approximation of muscle mass; the analytical results were based on DXA-

derived lean mass and may not apply to all methods of measuring muscle mass. It is possible that other more accurate measures of skeletal muscle mass may be more robustly associated with health outcomes and may be utilized in the future. Regardless of whether lean mass should be included in a definition of sarcopenia, there was agreement amongst the panelists that DXA-derived lean mass measures were not good predictors of mobility disability or other health-related outcomes, such as falls, hip fracture, and mortality.

Voting Results and Strength of Agreement for Position Statements Related to Lean Mass

The Expert Panel expressed strong agreement with position statements 5 and 6 but expressed some uncertainty about statement 7 (**Figure 1**).

Supporting Evidence for Position Statements Related to Gait Speed

Usual gait speed declines with aging. Since there is ample data in the literature regarding the usefulness of gait speed as a predictor of many relevant outcomes in older adults including physical disability, hospitalization, fall-risk, and death (45-48), the SDOC did not aim to define new gait speed cutpoints. In the SDOC analysis, low gait speed was significantly associated with mortality, falls, and IADL disability, regardless of grip strength and body size, consistent with previous reports. In general, both low grip strength and low usual gait speed were independently associated with adverse health outcomes (increased risk of falls, self-reported mobility limitation and mortality).

Discussion Related to Gait Speed

Many factors influence gait speed; muscle strength is an important but only one of many determinants of gait speed. Gait speed varies with age, sex, race/ ethnicity, and disease condition. Gait speed can be measured in a clinical setting, but may vary depending on how it is measured highlighting the need for standardizing the procedures for measuring gait speed.

Voting Results and Strength of Agreement for Position Statements Related to Gait Speed

The Expert Panel expressed strong agreement with position statements 8, 9 and 11. Statement 10 had good agreement with a few members expressing some uncertainty.

Discussion Related to Summary Position Statements

The Panel noted some caveats to the Summary Statements 12 and 13. First, these position statements are formulated for community dwelling adults; how they apply to persons with acute or subacute muscle loss due to cancer or sepsis or to hospitalized acutely ill persons is not known. The Panel noted that although frailty and sarcopenia may have some overlapping features such as decreased muscle strength, they are distinct conditions and that these Position Statements do not apply to frailty or cachexia. Although the grip strength and gait speed cut-points may help define sarcopenia, they may not necessarily be responsive to some types of interventions depending on the mechanism of action of the therapeutic intervention. The Expert Panel discussed whether weakness and slowness represent different stages of the condition and whether older adults who have both weakness and slowness have a more advanced

stage of the condition than those who have low grip strength (weakness) but not low gait speed (slowness).

Voting Results and Strength of Agreement for Summary Position Statements

Statement 13 had strong agreement from the expert panel and statement 12 had good agreement with a few members expressing some uncertainty. The uncertainty was related to the exclusion of DXA-derived lean mass from the definition.

SYNTHESIS AND CONCLUSIONS

The SDOC Position Statements on sarcopenia - vetted and approved by an external, independent International Expert Panel - offer a rational basis for an evidence-based definition of sarcopenia. Several unique attributes of the SDOC processes and Position Statements distinguish them from some other efforts to develop a consensus definition of sarcopenia. First, these Position Statements and the cutpoints described in the linked manuscripts are evidence-based rather than opinion-based: they were derived from the analyses of data from one of the largest assemblies of observational studies that included large numbers of older adults with mobility complaints. Second, the proposed cutpoints were evaluated based on their ability to predict patient-important, incident health outcomes of public health importance: mobility limitation, mortality, falls, and hip fractures. Both low grip strength and low gait speed were generally predictive of adverse health outcomes. The performance characteristics of cut-points – sensitivity, specificity, predictive value – were evaluated in community-dwelling older adults, and in special populations enrolled in randomized clinical trials of function promoting therapies and special clinical populations (e.g., persons with hip fracture or HIV-infection), as well as two large nationally representative population-based studies. The SDOC process of generating the Position Statements facilitated consensus generation while maintaining transparency because it enabled the panelists to express disagreement and their level of uncertainty. The iterative nature of the Expert Panel's review of the Position Statements and the supporting analyses and literature synthesis during multiple conference calls over several months leading up to the conference enabled panel's input to be incorporated into the final Position Statements.

The performance characteristics of these cutpoints vary with age, race/ethnicity, comorbid conditions and population. Therefore, sex-specific cutpoints derived in these analyses should be evaluated in diverse populations, including clinical populations with specific conditions. The estimates of prevalence of weakness, slowness or sarcopenia based on these cutpoints in various populations would be a valuable guide to public health policy, to pharmaceutical drug-development, and in clinical practice to encourage lifestyle intervention.

There was agreement that a risk model to predict mobility disability and other patient-important outcomes that integrates these position statements; takes into account age, sex, and race/ethnicity; and is useful to patients, clinicians and researchers is a priority research need. Inevitably, the cutpoints derived from these analyses will be refined over time as they are evaluated prospectively as outcomes or enrollment criteria in randomized trials and observational studies and as new data become available. The national efforts to generate guidelines for high cholesterol and high blood pressure offer useful historical precedence for the nascent SDOC initiative. The cholesterol guidelines published by the Adult Treatment Panel (ATP) of the National Cholesterol Education Program (NCEP) (50-51) and the Joint national Commission (JNC) guidelines for the treatment of hypertension (52-53) have undergone multiple revisions over many decades. Analogously, the transformation of SDOC into a sustainable organization based on the ATP and JNC models will enable continual refinement of the risk models and generation of progressively updated guidelines for the diagnosis, treatment and prevention of sarcopenia in the general population, and in older adults with specific conditions.

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Table 1. International Expert Panel

Chairperson of the International Expert Panel
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Vice Dean of Medicine, University of Southampton
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Suzette Pereira, PhD.
Senior Research Scientist, Strategic Research
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Laura Schaap, PhD
Faculty of Science, Nutrition and Health
Free University Amsterdam

Jean Woo, MD, PhD
Henry G Leong Research Professor of Gerontology and Geriatrics
Director, CUHK Jockey Club Institute of Ageing
Director, SH Ho Centre for Gerontology and Geriatrics
The Chinese University of Hong Kong

Table 2. The Approved Position Statements

Grip strength

1. Muscle weakness in older adults can be conveniently defined using grip strength.
2. Muscle weakness, as defined by low grip strength, is a predictor of adverse health-related outcomes such as mobility limitation, falls, ADL disability, and mortality in community dwelling older adults.
3. Muscle weakness, as defined by low grip strength, should be included in the definition of sarcopenia.
4. The performance characteristics of a sex-specific cut-point for low grip strength may vary by age, race, disease condition and other factors.

Lean mass by DXA

5. Appendicular lean mass measured by dual-energy x-ray absorptiometry (DXA) – either absolute or after scaling for body size – is not a good predictor of adverse health-related outcomes such as mobility limitation, falls, ADL disability, and mortality in community dwelling older adults.
6. The highly variable risk associations found between appendicular lean mass by DXA and adverse health-related outcomes in community dwelling older adults limit the utility of lean mass assessed by DXA as a predictor or prognostic risk factor for adverse health-related outcomes.
7. Lean mass measured by DXA should not be included in the definition of sarcopenia.

Gait speed

8. Slowness, defined by low usual gait speed, is a predictor of adverse health-related outcomes, such as self-reported mobility limitation, falls, ADL disability, hospitalization and mortality in older adults.
9. Strength is one of the many factors that influence usual gait speed.
10. Usual gait speed is an indicator of walking ability and should be included in the definition of sarcopenia.
11. The performance characteristics of a cut-point for low usual gait speed may vary by age, sex, race, disease condition and other factors.

Summary statements

12. Low grip strength and low usual gait speed independently predict adverse health-related outcomes such as mobility limitation, falls, ADL disability and mortality in community dwelling older adults.

13. Both weakness defined by low grip strength and slowness defined by low usual gait speed should be included in the definition of sarcopenia.