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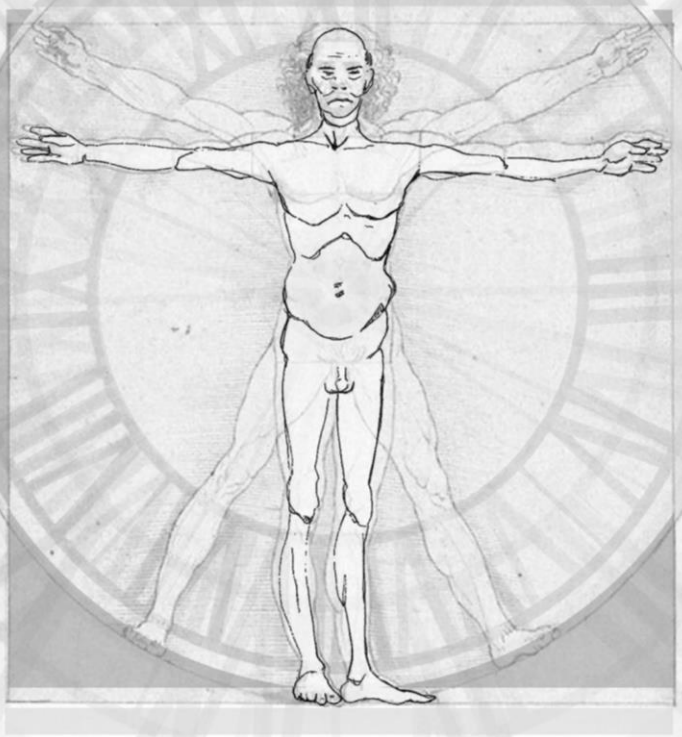

CONTRIBUTION À L'ÉTUDE DE LA SARCOPÉNIE
DÉFINITION, DIAGNOSTIC ET CONSÉQUENCES

CONTRIBUTION TO THE STUDY OF SARCOPENIA
DEFINITION, DIAGNOSIS AND OUTCOMES

Thèse présentée en vue de l'obtention du grade
de Docteur en Sciences de la Santé publique

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PUBLIC HEALTH EPIDEMIOLOGY AND HEALTH ECONOMICS

fnrs LA LIBERTÉ DE CHERCHER

La vieillesse est si longue, qu'il ne faut pas la commencer trop tôt …

Benoîte Groult

REMERCIEMENTS

Etant de nature très gourmande, je me permets une métaphore culinaire en comparant l'écriture des remerciements de ma thèse au fait de poser la « cerise sur le gâteau ». Amener le point final à un travail de quatre années me procure à la fois un sentiment libérateur (enfin terminé !) et nostalgique (la fin d'un travail passionnant, exaltant et enivrant au quotidien) ...

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Charlotte

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RÉSUMÉ

INTRODUCTION ET OBJECTIFS

La sarcopénie, qui s'est vue très récemment attribuer un code nosologique par la Classification Internationale des Maladies (ICD-10-CM), est caractérisée par une faible masse musculaire couplée à une fonction musculaire limitée. Depuis la première apparition de ce terme dans la littérature scientifique en 1989, la sarcopénie a suscité un intérêt croissant auprès de la communauté scientifique et médicale. Même si plusieurs initiatives de consensus ont vu le jour ces dernières années, il n'existe toutefois toujours pas de définition opérationnelle universelle de la sarcopénie, ce qui complique son évaluation épidémiologique. Les recherches menées dans le cadre de cette thèse de doctorat ont pour ambition d'apporter une contribution aux recherches menées dans le domaine de la sarcopénie. En effet, le terme « sarcopénie » est relativement récent dans la littérature scientifique, ce qui explique que plusieurs aspects potentiellement pertinents concernant l'évaluation de la sarcopénie en termes de santé publique n'aient toujours pas été investigués ou n'aient été que superficiellement abordés. Dans le cadre de cette thèse de doctorat, différentes recherches ont été développées avec l'objectif de contribuer aux recherches menées sur la sarcopénie, principalement au niveau de sa définition, de son diagnostic et de l'identification de ses conséquences.

MATÉRIEL ET MÉTHODES

La première partie consiste en la réalisation d'une revue systématique de la littérature et d'une méta-analyse visant à synthétiser les conséquences cliniques de la sarcopénie telle que diagnostiquée selon une définition opérationnelle particulière, celle proposée par l'European Working Group on Sarcopenia in Older People (EWGSOP).

La deuxième partie présente les données obtenues à partir de la cohorte SarcoPhAge (*Sarcopenia and Physical impairments with advancing Age*). L'étude SarcoPhAge est constituée de sujets âgés ambulants de plus de 65 ans résidant en Province de Liège. Chez tous ces sujets, recrutés entre juin 2013 et juin 2014 à la Polyclinique Lucien Brull de Liège, un dépistage complet de la sarcopénie, suivant le modèle proposé par l'EWGSOP, a été réalisé. Cette étude a pour objectif d'évaluer la prévalence de la sarcopénie dans cette population, l'incidence de la sarcopénie au cours du temps et les paramètres cliniques et physiques liés à la sarcopénie. Bien que l'étude SarcoPhAge soit initialement prévue pour suivre les participants durant 5 années, dans cette seconde partie, nous ne présentons que le design de

l'étude, les caractéristiques des sujets lors de leur inclusion dans l'étude et les conséquences indésirables associées à la sarcopénie après 2 ans de suivi.

La troisième partie présente les résultats de deux études réalisées sur la population SarcoPhAge visant à évaluer l'effet de l'utilisation de différents outils de diagnostic ou de différentes valeurs seuils de diagnostic (tels que proposés par l'EWGSOP) sur la prévalence mesurée de la sarcopénie.

Enfin, la quatrième partie aborde le développement et la validation du questionnaire SarQoL® (*Sarcopenia & Quality of Life*), un questionnaire de qualité de vie spécifique à la sarcopénie. Ce questionnaire, initialement développé et validé en français a également fait l'objet d'une traduction et d'une validation en anglais.

RÉSULTATS

Dans la première partie de cette thèse, nous avons ainsi montré que la sarcopénie, telle que définie par l'EWGSOP, est associée à un risque plus élevé de mortalité (OR : 3,60 (IC 95 % 2,96 – 4,37)) et de limitations fonctionnelles (OR : 3,03 (IC 95 % 1,80 – 5,12)). Deux études rapportent également un risque de chute augmenté chez les sujets sarcopéniques et une étude rapporte une incidence augmentée d'hospitalisations. Les effets de la sarcopénie sur l'incidence de fractures et sur la durée de séjours hospitaliers semblent toutefois moins évidents : seule la moitié des études prospectives incluses dans notre revue systématique a analysé ces conséquences et montré une association significative. En se basant uniquement sur des études prospectives et sur l'utilisation de l'algorithme de diagnostic proposé par l'EWGSOP comme définition de la sarcopénie, nous n'avons pas pu identifier d'autres conséquences de la sarcopénie.

Dans le cadre de l'étude SarcoPhAge, 534 participants ont été recrutés. Parmi ceux-ci, 73 ont été diagnostiqués sarcopéniques (prévalence de 13,7 %). Les résultats observés dans l'étude SarcoPhAge après deux années de suivi corroborent l'association entre la sarcopénie et la mortalité avec un OR brut retrouvé dans notre étude de 3,65 (IC 95 % 1,41 – 9,49) ainsi qu'entre la sarcopénie et l'incidence d'hospitalisation avec un OR brut de 2,75 (IC 95 % 1,34 – 5,63). Aucune association entre la sarcopénie et l'incidence de chutes et de limitations fonctionnelles à 2 ans n'a toutefois été retrouvée.

Dans la troisième partie, nous avons pu mettre en lumière l'effet que pouvait avoir l'utilisation d'outils différents pour mesurer la masse musculaire, la force musculaire et la performance physique sur la mesure de prévalence de la sarcopénie. En effet, l'utilisation de l'un ou l'autre outil entraînerait une prévalence de la sarcopénie pouvant varier de 8,4 à 27,6 %. De plus, nous avons également établi l'effet que pouvait avoir l'utilisation de différentes valeurs seuils de diagnostic, également pour les

mesures de masse musculaire, de force musculaire et de performance physique, sur la mesure de prévalence de la sarcopénie. Cette fois, les résultats indiquent une prévalence pouvant varier de 9,25 à 18,0 % selon les valeurs seuils utilisées.

Enfin, la quatrième partie de cette thèse reporte les résultats du développement d'un questionnaire de qualité de vie spécifique à la sarcopénie, le *SarQoL®*. Ce questionnaire, initialement développé en français, a été validé au sein des participants de l'étude SarcoPhAge. Les résultats reportent la capacité du SarQoL® à discriminer les sujets sarcopéniques par rapport aux non sarcopéniques, les premiers présentant systématiquement une qualité de vie inférieure. De plus, les analyses de validation ont indiqué une bonne cohérence interne, une bonne fiabilité test-retest, une bonne validité de construit et aucun effet de plancher ni de plafond. Le questionnaire SarQoL® a également été traduit et validé en anglais, lors d'un séjour de recherche réalisé à l'étranger au sein de la *MRC Epidemiology Unit* of Southampton, UK. Les analyses de validation de cette version anglaise ont été effectuées sur les participants de la Hertfordshire Cohort Study, UK. Les qualités psychométriques de la version anglaise du SarQoL® reflétaient celles de la version française.

CONCLUSION

L'évaluation épidémiologique de la sarcopénie pourrait indéniablement être facilitée par le développement d'une définition unique et de critères de diagnostics précis et adaptés non seulement au type de population mais également au cadre de diagnostic visé. Les recherches menées dans cette thèse ont le mérite d'apporter des éléments supplémentaires dont les experts peuvent s'enrichir pour développer cette définition clé universelle. Elles pourraient également inciter au développement d'études cliniques dans le domaine de la sarcopénie et à la mise en place de stratégies préventives ou thérapeutiques. En effet, au vu de la prévalence de la sarcopénie et des conséquences cliniques et socio-économiques qui y sont attribuées, la sarcopénie est indiquée, par certains auteurs, comme un fléau pour la santé publique. Ainsi, toute tentative visant à réduire l'incidence de la sarcopénie et de ses conséquences potentielles sur la santé et la qualité de vie devrait être largement encouragée.

SUMMARY

INTRODUCTION AND OBJECTIVES

Sarcopenia, which has recently been recognized as an independent condition by the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Code, is characterized by a progressive and generalized loss of muscle mass and muscle function with advancing age. The term "sarcopenia" was firstly introduced in 1989 and this was the starting point of an ever-growing interest from the scientific and medical community. Currently, several definitions of sarcopenia have been proposed but, unfortunately, there is yet no universal consensus for an operational definition of sarcopenia, which is an important issue for its epidemiological evaluation. The researches carried out during this doctoral thesis aimed to contribute to the field of researches in sarcopenia. Indeed, because the term "sarcopenia" is quite recent in the scientific literature, several potentially relevant aspects of its assessment, in a Public health point of view, have only been superficially assessed or not assessed at all. In this doctoral thesis, various researches have been developed to further contribute to the definition, the diagnosis and the identification of consequences of sarcopenia.

MATERIAL AND METHODS

The first part consists of a systematic review and meta-analysis performed to summarize the clinical consequences of sarcopenia, diagnosed with the operational definition proposed by the European Working Group on Sarcopenia in Older People (EWGSOP).

The second part of this thesis presents results of the SarcoPhAge study (*Sarcopenia and Physical impairments with advancing Age*). The SarcoPhAge study is a cohort study of ambulatory subjects aged 65 years or older, living in the Province of Liège. These subjects, recruited between June 2013 and June 2014, underwent a complete screening for sarcopenia, based on the model proposed by the EWGSOP. This study aimed to assess the prevalence of sarcopenia in these subjects, the incidence of sarcopenia across time and the clinical and physical components linked to sarcopenia. The SarcoPhAge study has been designed for a 5-year period. However, in this thesis, only the design of the SarcoPhAge study as well as baseline data and 2-year adverse consequences of sarcopenia are presented.

In the third part, results of two additional studies performed on the SarcoPhAge population are presented. These studies aimed to assess the impact of the use of different tools and different cut-off limits in the diagnosis of sarcopenia on the prevalence of sarcopenia.

Finally, the last part is dedicated to the development and validation of the SarQoL® questionnaire (*Sarcopenia & Quality of Life*), a quality of life questionnaire specific to sarcopenia. This questionnaire, firstly developed in French, has also been translated in English.

RESULTS

In the first part of this doctoral thesis, we showed, through a meta-analysis, a higher rate of mortality among sarcopenic subjects (pooled OR of 3.60 (95 % CI 2.96 - 4.37)) as well as a higher rate of functional decline (pooled OR of 3.03 (95 % CI 1.80 - 5.12)). A higher incidence of falls was also found in 2 studies and a higher incidence of hospitalization was found in one study. The impact of sarcopenia on the incidence of fractures and the length of hospital stay was less clear (only 1/2 studies showed an association for both outcomes). When restricting only to prospective studies in which a diagnosis of sarcopenia was performed with the definition proposed by the EWGSOP, no other consequences of sarcopenia could be identified.

Among the 534 subjects recruited for the SarcoPhAge study, 73 were diagnosed sarcopenic, which represents a prevalence of 13.7 %. Results over 2 years of follow-up were consistent with the above systematic review since we found a crude OR of 3.65 (95 % CI 1.41 – 9.49) for the association between sarcopenia and mortality. We also found a crude OR of 2.75 (95 % CI 1.34 – 5.63) for the association between sarcopenia and the risk of hospitalization. No association between sarcopenia and either the incidence of falls or functional limitations after 2 years was however found.

In the third part we showed that prevalence of sarcopenia is highly dependent on the diagnostic tools used. Estimated prevalence of sarcopenia varied from 8.4 % to 27.6 % depending on the tools used for the assessment of muscle mass, muscle strength and physical performance. We also showed that prevalence of sarcopenia varies widely depending on the cut-off points used for the diagnosis. Prevalence of sarcopenia varied from 9.25 % to 18.0 % depending on the cut-offs values chosen.

Finally, in the last part, results about the development and validation of the SarQoL® questionnaire are reported. This questionnaire, initially developed in French, has been validated across the SarcoPhAge population. The psychometrics properties analyses showed first that the questionnaire discriminates sarcopenic subjects from non-sarcopenic ones. Indeed, sarcopenic subjects showed a systematic lower quality of life. The results of the validation of the questionnaire also showed a high internal consistency, a good test-retest reliability, a good construct validity and no floor or ceiling effects. The SarQoL® questionnaire was also translated in English during a 6-month internship in the *MRC Epidemiology Unit* of Southampton, UK. The validation analyses were performed on the

participants of the Hertfordshire Cohort Study, UK. Psychometric properties of the English version of the SarQoL® were consistent with the French one.

CONCLUSION

The epidemiological assessment of sarcopenia could undeniably be improved by the development of one unique operational definition of sarcopenia including clear diagnosis criteria. The researches presented in this doctoral thesis bring some key elements that could be used by experts willing to develop this single universal definition. The results presented here could also be an incentive for further development of clinical studies in the field of sarcopenia and the implementation of preventive and therapeutic strategies. Because of the high prevalence of sarcopenia and its armful clinical consequences, some authors indicate sarcopenia as a burden for public health. Therefore, any initiative led to reduce the incidence of sarcopenia and its potential consequences on public health and quality of life should be encouraged.

PRÉAMBULE

Résultat à la fois des progrès sociaux, sanitaires et technologiques, la tranche de la population des plus de 65 ans ne cesse d'augmenter à travers le monde. Si aujourd'hui, nous comptons environ 600 millions de personnes de plus de 65 ans dans le monde, vers 2050, nous devrions en compter quelque 2 milliards (Organisation Mondiale de la Santé, OMS). L'espérance de vie à la naissance ne cesse également d'augmenter et se situe aujourd'hui, au sein des pays industrialisés, autour de 80 ans. Le phénomène de vieillissement entraîne de nombreux changements dans la composition corporelle des individus et, parmi ces changements, une perte de masse musculaire squelettique est notée. En effet, dès l'âge de 20 ans, on observe une diminution progressive de la taille et du nombre de fibres musculaires entraînant une perte de masse musculaire d'environ 30 % à l'âge de 80 ans[1,2]. Au-delà de certains seuils, cette perte de masse musculaire est considérée comme trop importante. Ce phénomène, associé à une perte de force musculaire et/ou à une diminution substantielle des capacités physiques, est appelé « sarcopénie ».

Aujourd'hui, il n'existe pas encore de définition opérationnelle de la sarcopénie universellement acceptée. Plusieurs définitions ont cependant été proposées et les plus récentes intègrent à la fois les concepts de masse et de fonction musculaire. La sarcopénie, ayant récemment obtenu un code nosologique dans la Classification Internationale des Maladies (CIM) et pouvant donc désormais être reconnue comme une maladie[3] et non plus uniquement comme un syndrome gériatrique, serait donc définie par une masse musculaire affaiblie couplée à une faiblesse au niveau de la fonction musculaire.

Le terme « sarcopénie » est relativement récent dans la littérature scientifique et a, de ce fait, connu un intérêt croissant particulièrement au cours des 15 dernières années. Cet intérêt se marque notamment par une augmentation des publications scientifiques : en effet, les recherches sur PubMed comprenant le mot-clé « sarcopenia » ne comptaient que 115 publications en 2000, 1000 en 2010 et ont progressivement atteint le seuil des 4300 en 2016. Même si ce nombre paraît élevé en première intention, il reste sensiblement faible lorsqu'il est comparé à d'autres sujets de recherche en lien avec les pathologies musculo-squelettiques (exemples : environ 73 000 publications pour le mot clé « osteoporosis », environ 70 000 publications pour le mot clé « osteoarthritis »). Bien que cette littérature s'étoffe de manière substantielle depuis quelques années, plusieurs aspects pertinents concernant l'évaluation de la sarcopénie en termes de santé publique n'ont toujours pas été investigués.

L'objectif de cette thèse de doctorat consiste donc à enrichir les recherches menées sur la sarcopénie, principalement au niveau de sa définition, de son diagnostic et de l'identification de ses conséquences cliniques, par la réalisation de quatre projets de recherche. Un résumé des

résultats de ces quatre recherches sera présenté dans la partie « SYNTHÈSE DES RÉSULTATS PRINCIPAUX » de ce manuscrit.

Dans le cadre de cette thèse de doctorat, 11 articles scientifiques ont été rédigés (*10 publiés dans des journaux internationaux à comité de relecture, 1 soumis pour publication*). Les résultats de ces articles seront présentés dans les parties « INTRODUCTION GÉNÉRALE » et « SYNTHÈSE DES RÉSULTATS PRINCIPAUX » de ce manuscrit (Table 1). Les versions intégrales de ces articles sont disponibles en annexes.

Table 1. Publications relatives à la thèse de doctorat « Contribution à l'étude de la sarcopénie : définition, diagnostic et conséquences »

Auteurs	Titre	Référence	Statut	Annexe
Partie INTRODUCTION GÉNÉRALE				
C. Beaudart, R. Rizzoli, O. Bruyère, J-Y. Reginster, E. Biver	Sarcopenia: Burden and challenges for Public Health	Archives of Public Health. 2014 Dec 18;72(1):45.	**Publié**	1
C. Beaudart, J-Y. Reginster, J. Petermans, O. Bruyère	Qualité de vie du patient sarcopénique: apport de l'étude liégeoise SarcoPhAge	Gériatrie et Psychologie Neuropsychiatrie du Vieillissement. 2015 Dec;13(4):391-5.	**Publié**	2
C. Beaudart, F. Buckinx, V. Rabenda, S. Gillain, E. Cavalier, J. Slomian, J. Petermans, JY. Reginster, O. Bruyère	The effects of vitamin D on skeletal muscle strength, muscle mass and muscle power: a systematic review and meta-analysis of randomized controlled trials	The Journal of Clinical Endocrinology and Metabolism. 2014 Nov;99(11):4336-45.	**Publié**	3
C. Beaudart, E. McCloskey, O. Bruyère, M. Cesari, Y. Rolland, R. Rizzoli, I. Araujo de Carvalho, J. Amuthavalli Thiyagarajanm, I. Bautmans, MC. Bertière, ML. Brandi, N. Burlet, E. Cavalier, F. Cerreta, A. Cherubini, R. Fielding, E. Gielen, F. Landi, J. Petermans, JY. Reginster, M. Visser, JA. Kanis C. Cooper	Sarcopenia in daily practice: Assessment and Management	BMC Geriatrics. 2016 Oct 5;16(1):170.	**Publié**	4
Partie SYNTHÈSE DES RÉSULTATS PRINCIPAUX				
C. Beaudart, M. Zaaria, F. Pasleau, J.Y. Reginster, O. Bruyère	Impact of sarcopenia on health outcomes: a systematic review		**Soumis**	5
C. Beaudart, JY. Reginster, J. Petermans, S. Gillain, A. Quabron, M. Locquet, J. Slomian, F. Buckinx, O. Bruyère	Quality of life and physical components linked to sarcopenia: The SarcoPhAge study	Experimental Gerontology. 2015 Sep;69:103-10.	**Publié**	6
C. Beaudart, JY. Reginster, J. Slomian, F. Buckinx, N. Dardenne, A. Quabron, C. Slangen, S. Gillain, J. Petermans, O. Bruyère	Estimation of sarcopenia prevalence using various assessment tools	Experimental Gerontology. 2015 Jan;61:31-7.	**Publié**	7
C. Beaudart, JY. Reginster, J. Slomian, F. Buckinx, M. Locquet, O. Bruyère	Prevalence of sarcopenia: the impact of different diagnostic cut-off limits	Journal of Musculoskeletal and Neuronal Interactions. 2014 Dec;14(4):425-31.	**Publié**	8
C. Beaudart, E. Biver, JY Reginster, R. Rizzoli, Y. Rolland, I. Bautmans, J. Petermans, S. Gillain, F. Buckinx, J. Van Beveren, JM. Jacquemain, P. Italiano, N. Dardenne, O. Bruyère	Development of a self-administrated quality of life questionnaire for sarcopenia in elderly 65 years and older: the SarQoL®	Age Ageing. 2015 Nov;44(6):960-6.	**Publié**	9
C. Beaudart, JY Reginster, R. Rizzoli, Y. Rolland, I. Bautmans, E. Biver, J. Petermans, S. Gillain, N. Dardenne, O. Bruyère.	Validation of SarQoL®, a specific health-related quality of life questionnaire for sarcopenia	Journal of cachexia, Sarcopenia and Muscle. (2016). doi:10.1002/jcsm.12149	**Publié**	10
C. Beaudart, MH. Edwards, C. Moss, JY. Reginster, R. Moon, C. Parsons, C. Demoulin, E. Dennison, O. Bruyère, C. Cooper	English translation and validation of the SarQoL®, a quality of life questionnaire specific for sarcopenia	Age and Ageing	**Publié**	11

INTRODUCTION GÉNÉRALE

1. EVOLUTION DES DÉFINITIONS DE LA SARCOPÉNIE

Le terme « sarcopénie » (du grec, signifiant littéralement « sarkos = chair » et « penia = perte ») a été introduit la première fois en 1989 par Irwin Rosenberg[4] pour décrire une perte involontaire de masse musculaire squelettique avec l'avancée en âge. Sur base de ce concept, Baumgartner[5] fut le premier à développer une définition opérationnelle de la sarcopénie. En sommant la masse musculaire squelettique des quatre membres, il définit la sarcopénie par *une masse musculaire appendiculaire divisée par la taille au carré inférieure à deux déviations standard par rapport à la masse musculaire squelettique appendiculaire* d'un groupe de référence constitué d'adultes âgés de 18 à 40 ans faisant partie de la Rosetta Study[5]. Baumgartner choisit, dans son approche, de diviser la masse musculaire appendiculaire par la taille au carré, en se basant sur le principe qu'il existe une forte corrélation entre la masse musculaire corporelle et la taille des sujets. Il utilise cette définition pour la première fois dans le cadre de la New Mexico Aging Process Study (NMAPS)[5] dans laquelle les résultats indiquent que la prévalence de la sarcopénie augmenterait avec l'âge mais également que la sarcopénie serait associée à un plus haut taux d'incapacités fonctionnelles. Cette étude fut parmi les premières à démontrer l'effet potentiel de la sarcopénie sur la santé publique.

Toutefois, la communauté scientifique s'est rapidement rendue compte qu'un élément important n'était pas pris en compte dans cette définition, telle qu'elle était proposée. En effet, plusieurs études longitudinales ont progressivement montré une dégradation de force musculaire accélérée par rapport à la perte de masse musculaire avec l'avancée en âge. De ce fait, bien que la masse musculaire soit un déterminant non négligeable de la force musculaire[6,7], la perte de masse musculaire liée à l'avancée en âge ne peut toutefois que partiellement expliquer la perte de force musculaire. De plus, une méta-analyse[8] a montré que la faiblesse musculaire, définie par une faible masse musculaire combinée à une faible fonction musculaire, avait un pouvoir prédictif d'invalidités physiques et de limitations fonctionnelles supérieur au concept de faible masse musculaire seul. Il semble donc qu'une définition de la sarcopénie n'incluant qu'une mesure de masse musculaire soit par conséquent insuffisante pour identifier des sujets âgés présentant une faiblesse musculaire cliniquement significative. Plusieurs groupes d'experts[9–14] se sont ainsi penchés sur cette problématique et ont tenté de développer des critères diagnostics consensuels pour la sarcopénie avec l'idée communément partagée que le diagnostic de la sarcopénie devrait inclure à la fois le principe d'une faible masse musculaire mais également le principe d'une faible fonction musculaire, identifiée soit par une faible force musculaire soit par une performance physique affaiblie. Bien que différentes définitions de la sarcopénie aient ainsi émergé au gré des découvertes scientifiques, il n'existe actuellement toujours aucune définition opérationnelle de la sarcopénie *universellement* acceptée.

Les caractéristiques de plusieurs de ces définitions opérationnelles ont été synthétisées dans le cadre d'une publication que nous avons réalisée en collaboration avec le Service des Maladies Osseuses de l'Hôpital Universitaire de Genève, en Suisse[15] (version intégrale de l'article disponible en annexe 1) (Table 2).

La proposition de définitions opérationnelles et consensuelles par ces regroupements d'experts constitue indéniablement une véritable avancée dans le domaine de la sarcopénie. Toutefois, il est important de noter qu'à notre connaissance, aucune des définitions actuellement proposées n'a été validée de manière robuste pour son habilité à prédire des évènements indésirables liés à la perte de masse et de fonction musculaire comme l'invalidité physique, les fractures, les chutes, l'hospitalisation ou encore, la mortalité.

Table 2. Définitions opérationnelles de la sarcopénie (adaptée de Beaudart *et al.*[15])

Critères		**Masse musculaire**	**Fonction musculaire**		
			Force musculaire		**Performance physique**
Baumgartner[5]	Sarcopénie	ALM/ ht² < 2 SD de la moyenne de jeunes adultes sains	/		/
European Society for Clinical Nutrition and Metabolism Special Interest Groups (ESPEN-SIG)[14]	Sarcopénie	Pourcentage de masse musculaire < 2 SD de la moyenne de jeunes adultes du même sexe et de la même origine ethnique (individus âgés de 18 à 39 ans et faisant partie de la cohorte NHANES III)	/		Vitesse de marche : < 0,8 m/s Ou performance physique réduite dans l'un des tests fonctionnels proposés dans le « comprehensive geriatric assessment »
European Working Group on Sarcopenia in Older People (EWGSOP)[9]	Sarcopénie	ALM/ht² - Hommes : ≤ 7,23 kg/m² - Femmes : ≤ 5,67 kg/m²	Force de préhension - Hommes : < 30 kg - Femmes : < 20 kg	OU	Vitesse de marche : < 0,8 m/s
	Sarcopénie sévère			ET	
International Working Group on Sarcopenia (IWGS)[10]	Sarcopénie	ALM/ht² - Hommes : ≤ 7,23 kg/m² - Femmes : ≤ 5,67 kg/m²	/		Vitesse de marche : < 1 m/s
Society of Sarcopenia, Cachexia and Wasting Disorders[11]	Sarcopénie avec mobilité fonctionnelle limitée	ALM/ht² > 2 SD en dessous de la moyenne de jeunes adultes sains âgés de 20 à 30 ans de la même origine ethnique	/		Vitesse de marche : ≤ 1 m/s Ou distance de marche < 400 m durant le test de 6 minutes de marche
Foundation of NIH Sarcopenia Project[12]	Faiblesse musculaire et faible masse musculaire	ALM_{BMI} - Hommes : < 0,789 - Femmes : < 0,512	Force de préhension - Hommes : < 26 kg - Femmes : < 16 kg		/

ALM/ht² = rapport de la masse musculaire appendiculaire sur la taille au carré (ALM pour *Appendicular Lean Mass*) ; ALM_{BMI} = rapport de la masse musculaire appendiculaire sur l'indice de masse corporelle (BMI pour *Body Mass Index*); SD = écart type (SD pour *Standard Deviation)*

Parmi les définitions opérationnelles proposées figure celle publiée en 2010 par l'European Working Group on Sarcopenia in Older People (EWGSOP)[9]. Cette définition résulte d'un consensus obtenu par des représentants de quatre organisations Européennes : *The European Geriatric Medicine Society*, *The European Society for Clinical Nutrition and Metabolism*, *The International Association of Gerontology and Geriatrics—European Region* et *The International Association of Nutrition and Aging*. L'EWGSOP[9] recommande ainsi de définir la sarcopénie par une faible masse musculaire couplée soit à une faible force musculaire soit à une faible performance physique. Différents outils de mesure et différents seuils, en dessous desquels ces critères sont considérés comme trop faibles, sont proposés par ces experts pour les mesures de la masse musculaire, de la force musculaire et de la performance physique. L'EWGSOP[9] est actuellement le seul groupe à suggérer 3 degrés conceptuels de la sarcopénie : la pré-sarcopénie, la sarcopénie et la sarcopénie sévère (Table 3).

Table 3. Degrés de sarcopénie définis par l'EWGSOP (adaptée de Cruz-Jentoft *et al.*[9])

Degrés	Masse musculaire	Force musculaire		Performance physique
Pré-sarcopénie	↓			
Sarcopénie	↓	↓	Ou	↓
Sarcopénie sévère	↓	↓		↓

L'EWGSOP[9] a, par ailleurs, développé un algorithme de diagnostic de la sarcopénie (Figure 1).

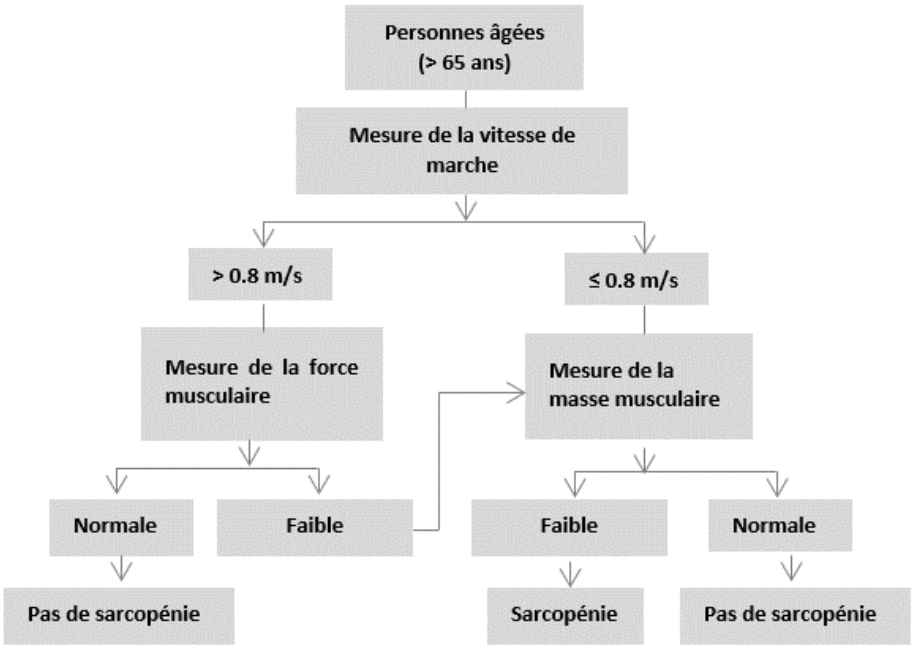


Figure 1. Algorithme suggéré par l'EWGSOP pour diagnostiquer la sarcopénie chez des sujets âgés de 65 ans et plus (adaptée de Cruz Jentoft *et al.*[9])

Par la facilité d'application de son algorithme et par le fait que cette approche permette d'apprécier la sévérité de la sarcopénie – ce qui est utile tant en recherche épidémiologique que dans la pratique clinique quotidienne – les recherches menées dans le cadre de cette thèse de doctorat se sont basées sur la définition proposée par l'EWGSOP[9] pour établir un diagnostic de sarcopénie.

2. DIAGNOSTIC DE LA SARCOPÉNIE

Le diagnostic de la sarcopénie se réalise à l'aide d'outils permettant de mesurer la masse musculaire, la force musculaire et la performance physique. Une large gamme de techniques peut être utilisée pour mesurer ces trois différentes composantes de la sarcopénie[16], telle que définie par l'EWGSOP[9]. Ces différentes techniques ont pu être listées dans le cadre d'une enquête réalisée récemment par l'Unité de Recherche en Santé publique, Epidémiologie et Economie de la Santé (URSAPES) de l'Université de Liège[17]. Un total de 255 cliniciens provenant de 55 pays différents a pris part à cette enquête avec pour objectif d'identifier les techniques les plus largement utilisées pour un diagnostic clinique de la sarcopénie.

2.1. La masse musculaire appendiculaire

La masse musculaire peut être mesurée par trois techniques d'imagerie médicale : la tomographie par ordinateur (CT scan), l'imagerie par résonance magnétique (IRM) et l'absorptiométrie biphotonique à rayons X (DXA pour *Dual Energy X-ray Absorptiometry*). Le CT scan et l'IRM sont actuellement les techniques de référence, dites « gold standard ». En effet, ces méthodes permettent de séparer la masse graisseuse des autres tissus du corps et ainsi d'obtenir des images et mesures très précises de la masse musculaire. Toutefois, les coûts importants et la difficulté d'accès à ces équipements limitent leur utilisation en recherche et dans la pratique clinique[18,19].

De ce fait, la technique alternative la plus largement utilisée pour mesurer la masse musculaire appendiculaire est la DXA. Cette technique, démontrant une excellente corrélation par rapport aux méthodes de référence, permet de distinguer la graisse, la densité minérale osseuse et la masse maigre par la transmission à travers le corps de rayons X à haute et basse énergies[20,21]. De plus, elle présente l'avantage d'exposer le patient à des rayonnements limités, contrairement au CT-scan. Toutefois, la DXA, à la différence du CT-scan et de l'IRM, ne permet pas de différencier la masse graisseuse intramusculaire, ce qui limite donc l'évaluation de la qualité du muscle[22]. Toutefois, malgré cette limitation, la DXA reste considérée comme la procédure de choix pour l'évaluation de la masse musculaire en recherche et dans la pratique clinique. Pour le diagnostic de la sarcopénie, une mesure de masse musculaire appendiculaire (ALM pour *Appendicular Lean Mass*) est généralement réalisée en sommant la masse musculaire des quatre membres. Un indice de masse musculaire squelettique est ensuite obtenu (SMI pour *Skeletal Muscle Index*) en divisant l'ALM par la taille du sujet au carré (ALM/ht^2)[9,10] ou par l'indice de masse corporelle (ALM/IMC)[12]. Dans le papier de consensus défini par l'EWGSOP[9], deux valeurs seuils sont proposées pour définir la sarcopénie. La première, proposée par Baumgartner *et al*.[5], se base sur les résultats d'une étude de population composée de 883 sujets âgés

vivant au Nouveau Mexique. Les auteurs ont comparé les résultats de SMI de cette population par rapport à un jeune groupe de référence et ont ainsi défini une faible masse musculaire par une diminution de deux déviations standard de l'ALM/ht^2 par rapport au groupe jeune de référence, ce qui mène aux valeurs seuils de 7,26 kg/m² pour un homme et 5,50 kg/m² pour une femme. En dessous de ces seuils, la masse musculaire appendiculaire est ainsi considérée comme trop faible. La seconde valeur seuil disponible dans l'article publié par l'EWGSOP[9] est proposée par Newman *et al*.[23]. Ces auteurs ont réalisé une étude de cohorte observationnelle de 2984 sujets âgés de 70 à 79 ans vivant dans 4 districts des Etats-Unis. Newman *et al*.[23] ont utilisé une autre approche pour le diagnostic de la sarcopénie et ont défini, arbitrairement, le 20ème percentile, ajusté sur le sexe, comme valeur seuil de diagnostic pour la sarcopénie. Les valeurs seuils retenues par cette étude sont de 7,25 kg/m² pour les hommes et de 5,67 kg/m² pour les femmes.

En dehors des techniques d'imagerie médicale, d'autres méthodes proposées par l'EWGSOP[9] existent pour mesurer la masse musculaire. Parmi celles-ci, on note l'impédancemétrie bioélectrique (BIA pour *Bioelectrical Impedance Analysis*), méthode portative, peu coûteuse, facile d'utilisation permettant d'obtenir des estimations du volume de masse graisseuse et de masse maigre par une analyse segmentaire multifréquence réalisée au moyen d'électrodes tactiles placés en différents points du corps. La précision de cet outil est toutefois parfois remise en question et des équations d'ajustement sont souvent nécessaires pour obtenir des mesures plus proches de celles obtenues par DXA[24–26]. Enfin, la masse musculaire peut également être estimée par de simples mesures anthropométriques comme par exemple, la circonférence du mollet, la circonférence de l'avant-bras, ou encore l'épaisseur du pli cutané de la partie médiane du bras[9,16,27,28].

2.2. La force musculaire

Il existe également différentes méthodes pour mesurer la force musculaire.

En recherche ainsi qu'en pratique clinique, c'est généralement la mesure de la force de préhension qui est utilisée pour définir la force musculaire. En effet, cette mesure, démontrant une très bonne reproductibilité inter- et intra-examinateur(s) dans le cadre où elle est réalisée selon un protocole standardisé, semble fortement corrélée avec la force et la puissance musculaire des membres inférieurs ainsi qu'avec la force d'extension du genou[29,30]. La force de préhension se mesure par le biais d'un dynamomètre. Le dynamomètre de référence pour cette mesure est le dynamomètre de Jamar ou tout dynamomètre hydraulique similaire. Toutefois, les patients présentant un diagnostic avancé d'arthrose digitale, par exemple, peuvent utiliser, par facilité, un dynamomètre pneumatique, comme le vigorimètre de Martin[31]. Ce vigorimètre se présente sous la forme d'une poire souple, disponible en trois tailles, qui facilitera la mesure de la force de préhension dans ces cas particuliers. Différentes

valeurs seuils sont présentées dans la littérature pour caractériser une faiblesse musculaire, se situant entre 16 et 20 kg pour une femme et entre 26 et 30 kg pour un homme[12,32–34]. Bien que des valeurs seuils existent pour définir une faible force musculaire, les protocoles de mesure de la force de préhension ne sont pas toujours les mêmes au sein des différentes études. Cela entraîne une certaine variabilité dans les résultats et rend, par ailleurs, les comparaisons entre études difficiles. Pour contrer ce problème, certains auteurs ont tenté de développer une approche standardisée de mesure de la force de préhension[35]. Ces conditions standards sont définies comme suit : position assise du sujet dans un siège standard avec les avant-bras reposant sur les bras de la chaise ; six mesures de force musculaire doivent être réalisées, 3 de chaque côté ; le sujet doit être encouragé à serrer le dynamomètre le plus fort possible durant 3 à 5 secondes pour chacune des mesures ; le meilleur des six résultats est reporté comme résultat final.

La force musculaire peut également être définie par la force musculaire des membres inférieurs et, plus fréquemment, la force des quadriceps. Cette mesure pourra être effectuée grâce à l'utilisation d'un dynamomètre ou par la réalisation de tests de force comme, par exemple, le test du lever de chaise qui consiste en la mesure du temps nécessaire à un sujet pour se relever 5 fois de suite d'une chaise sans l'utilisation de ses bras comme appui. Dans certaines études, la force musculaire est également mesurée par le débit expiratoire de pointe[9,16,27]. On note toutefois que peu de recherches cliniques ont été réalisées pour mesurer la validité de cette mesure par rapport à des mesures de référence. De ce fait, dans le cadre du diagnostic de la sarcopénie, l'EWGSOP[9] recommande plus volontiers l'utilisation de la force de préhension pour mesurer la force musculaire.

2.3. La performance physique

Il existe également une multitude de tests pour mesurer la performance physique. Les plus couramment utilisés par les cliniciens dans le cadre d'un diagnostic de la sarcopénie, sont, selon notre enquête[17], la mesure de la vitesse de marche, le test du « Short Physical Performance Battery » (SPPB), le test du « Get Up and Go » ou du « Timed Up and Go » et le « Stair Climb Power Test ». On note toutefois que la mesure de la vitesse de marche et le test du SPPB sont les deux tests recommandés par l'EWGSOP[9]. Le test de la vitesse de marche est un test généralement très bien accepté, à la fois par les participants mais également par les chercheurs et cliniciens[36]. Ce test ne requiert aucun autre équipement qu'un sol plat dépourvu d'obstacle. Lorsque la vitesse de marche est mesurée sur 4 mètres, ce qui est la distance recommandée par l'EWGSOP[9] pour le diagnostic de la sarcopénie, les hommes et les femmes présentant une vitesse de marche inférieure à 0,8 m/s sont considérés comme ayant une performance physique faible[34]. La valeur seuil de 1 m/s sur 6 mètres de marche a également été proposée par deux groupes d'experts européens, l'*International Working Group on Sarcopenia*[10] et la *Society*

of Sarcopenia, Cachexia and Wasting Disorders[11] en se basant sur une étude publiée par Cesari *et al*.[37] en 2005, incluant 3047 sujets âgés et montrant que les sujets présentant une vitesse de marche inférieure à 1 m/s présentaient significativement plus de conséquences indésirables pour la santé telles que des limitations fonctionnelles et une incidence plus élevée d'hospitalisations.

La vitesse de marche peut être mesurée seule comme indicateur de performance physique mais peut également être mesurée dans un ensemble de tests constituant le « Short Physical Performance Battery (SPPB) ». Le SPPB est un test composite mesurant à la fois la vitesse de marche, l'équilibre et la capacité à se relever 5 fois d'une chaise. Ce test présente une bonne corrélation par rapport à un test de marche de 400 mètres[38]. De plus, un groupe d'experts a recommandé son utilisation dans les études cliniques chez des personnes âgées fragiles[11]. Les participants présentant un score au SPPB test inférieur à 8 points sont considérés comme ayant une faible performance physique[39].

2.4. Applicabilité de ces méthodes en recherche et en pratique clinique quotidienne

Il semble clair que certaines de ces techniques sont plus facilement applicables en recherche qu'en pratique clinique. En effet, dans sa pratique courante, le médecin ne dispose pas toujours du temps et des outils adaptés à la réalisation d'un diagnostic complet de la sarcopénie. Nous avons donc, en collaboration avec l'*European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, Frailty and Sarcopenia (ESCEO),* organisé un Groupe de Travail, réuni dans l'objectif de pouvoir fournir une classification de ces différents outils de mesure de masse musculaire, de force musculaire et de performance physique selon leur applicabilité en recherche et en pratique clinique[27] (version intégrale de l'article disponible en annexe 4) (Table 4). Le classement de ces différents outils a été réalisé en tenant compte de leur facilité d'application, de leur complexité d'utilisation et de leur coût.

Table 4. Applicabilité des différents outils utilisés dans le cadre du diagnostic de la sarcopénie en recherche et en pratique clinique (adaptée de Beaudart *et al*.[27])

	Applicable dans des centres de recherche	Applicable dans des centres cliniques spécialisés	Applicable dans des centres de soins primaires
Evaluation de la masse musculaire			
DXA	+++	+++	+
Mesures anthropométriques	+	++	++
CT-scan	+++	++	+
MRI	+++	++	+
BIA	++	++	+
Evaluation de la force musculaire			
Force de préhension	+++	+++	+++
Force des membres inférieurs	+++	++	+
Test du lever de chaise	+	+	++
Evaluation de la performance physique			
Vitesse de marche	+++	+++	+++
Test du Timed Up and Go	++	+	+
Test d'équilibre	+	+	+
Test de 6 minutes de marche	++	+	+
Test de marche de 400 mètres	++	+	+
Test de montée d'escaliers	++	+	+
Test SPPB	+++	++	+

Nb. Le groupe d'experts a choisi d'attribuer à chaque outil soit +++ (outil le plus recommandé), ++ (outil recommandé comme meilleure alternative à l'outil idéal), ou + (outil le moins recommandé).

2.5. Application pratique pour nos recherches

Dans le cadre des recherches originales menées dans cette thèse, nous avons privilégié la mesure de masse musculaire par DXA, la mesure de force musculaire par force de préhension au moyen d'un dynamomètre hydraulique et la mesure de performance physique par le SPPB test et par la vitesse de marche. Ces outils, à la fois recommandés par l'EWGSOP[9] et largement utilisés dans la littérature scientifique, présentent en effet un excellent score d'applicabilité dans un cadre de recherche.

3. LA SARCOPÉNIE, UN SUJET DE RECHERCHE PERTINENT EN SANTÉ PUBLIQUE …

Nous avons tenté de montrer, dans le cadre d'une revue de la littérature publiée dans les « *Archives of Public Health* » réalisée en collaboration avec le Service des Maladies Osseuses de l'Hôpital Universitaire de Genève[15] (version intégrale de l'article disponible en annexe *1*), l'importance de la sarcopénie en termes de santé publique. Elle démontre en effet une *prévalence actuelle et future élevée* ainsi que des *conséquences cliniques, économiques et sociales importantes*. On note également que la prise en charge actuelle de la sarcopénie est rendue compliquée par l'*absence de traitement reconnu* pour la sarcopénie.

3.1. De par sa prévalence actuelle et future élevée

La prévalence mesurée de la sarcopénie peut varier considérablement selon l'âge, le sexe et la provenance de la population étudiée. Récemment, Cruz-Jentoft *et al.*[40] ont réalisé une revue systématique visant à synthétiser les données de prévalence de la sarcopénie disponibles dans la littérature scientifique. Ils reportent une prévalence pouvant varier de 1 à 29 % dans une population de sujets âgés ambulants, avec une prévalence encore plus élevée au sein de populations hospitalisées ou institutionnalisées. D'une manière générale, on observe une augmentation de la prévalence de la sarcopénie avec l'âge. Les données ne semblent pas consensuelles concernant la variation éventuelle de la prévalence de la sarcopénie en fonction du sexe mais certaines études ont observé une plus haute prévalence chez les hommes, en particulier dans les tranches d'âge les plus élevées[41,42]. Il semblerait également que la prévalence de la sarcopénie soit plus faible chez les populations présentant une couleur de peau foncée[43] et plus élevée dans les populations Asiatiques[41,44,45], chez les sujets ayant un faible indice de masse corporelle[46–48], ou encore ayant un plus faible niveau éducationnel[49].

On note également que la prévalence de la sarcopénie semble, assez logiquement, dépendante de la définition utilisée pour le diagnostic de cette dernière. En 2013, Batsis *et al.*[50] ont mesuré la prévalence de la sarcopénie au sein d'un échantillon de 4984 sujets âgés de plus de 60 ans et ont trouvé une prévalence pouvant varier de 7 à 94 % selon la définition utilisée. Une seconde étude, réalisée en 2013[51] a également cherché à mesurer le degré de concordance entre différentes définitions mais également différentes valeurs seuils de diagnostic au niveau de la mesure de masse musculaire. Ainsi, on retrouve, au niveau des résultats, une prévalence chez les hommes variant de 0 à 20,8 % pour les moins de 60 ans, variant de 0 à 31,2 % pour les sujets âgés de 60 à 69 ans et variant entre 0 et 45,2 % pour les plus de 70 ans. Chez les femmes, on retrouve une prévalence variant de 0 à 15,6 % pour les moins de 60 ans, 0 à 21,8 % pour les femmes âgées de 60 à 69 ans et enfin, de 0 à 25,8 % pour les plus de 69 ans. Très récemment, une équipe de Toulouse[52] a également publié des données de prévalence

de la sarcopénie au sein d'une population de 2725 femmes de plus de 75 ans présentant des antécédents de fracture de la hanche[52]. Une fois de plus, à travers les définitions utilisées pour diagnostiquer la sarcopénie, les auteurs ont trouvé une forte variation de la prévalence, s'étendant de 3,3 à 20,0 %. On note également que seuls 3,1 % des participantes ont été diagnostiquées de manière consensuelle par l'ensemble des définitions.

La coexistence de plusieurs définitions opérationnelles de la sarcopénie utilisant des critères de diagnostic différents entraîne indéniablement de larges variations dans la mesure de la prévalence de la sarcopénie. Une difficulté supplémentaire réside dans le fait qu'au sein d'une même définition consensuelle, différents outils ou différentes valeurs seuils de diagnostic sont parfois proposés. Par conséquent, l'utilisation d'une même définition, mais d'outils ou de valeurs de diagnostic différents, pourrait donc également mener à une variation de la prévalence mesurée.

Récemment, une étude visant à évaluer la prévalence future de la sarcopénie a été réalisée au sein de l'URSAPES de l'Université de Liège[53]. L'objectif de cette étude consistait à estimer la prévalence future de la sarcopénie en fonction des différents critères proposés par l'EWGSOP[9] utilisés pour diagnostiquer la sarcopénie. Les résultats principaux révélés par cette étude sont les suivants (Figure 2) :

- En utilisant les critères proposés par l'EWGSOP[9] entrainant la plus *haute* mesure de prévalence de la sarcopénie, il semblerait que le nombre d'individus atteints de sarcopénie augmenterait, en Europe, de 19 740 527 en 2016 à 32 338 990 en 2045 (soit une augmentation de 63,8 %). Cela correspondrait à une augmentation de la prévalence de la sarcopénie de 20,2 % en 2016 à 22,3 % en 2045.
- En utilisant les critères proposés par l'EWGSOP[9] entrainant la plus *faible* mesure de prévalence de la sarcopénie, il semblerait que le nombre de sujets atteints de sarcopénie augmenterait, en Europe, de 10 869 527 en 2016 à 18 735 173 en 2045 (soit une augmentation de 72,4 %). Cela correspondrait à une augmentation de la prévalence de la sarcopénie de 11,1 % en 2016 à 12,9 % en 2045.

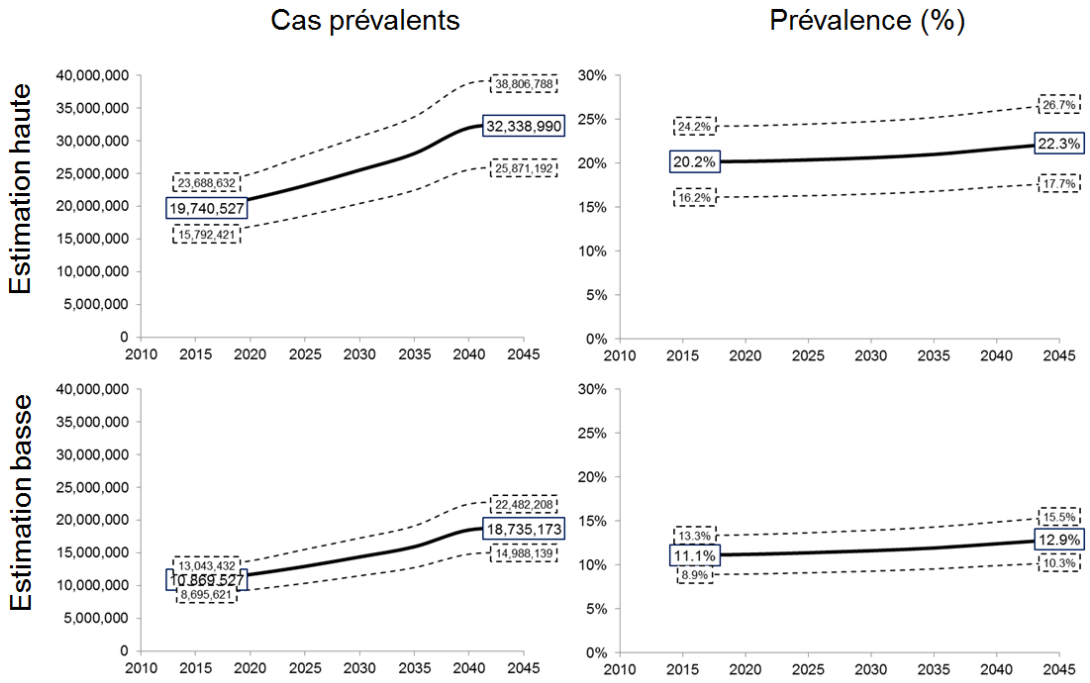


Figure 2. Estimation de la prévalence future de la sarcopénie en Europe (la ligne en pointillés du haut correspond aux données des femmes, la ligne en pointillés du bas correspond aux données des hommes, la ligne pleine correspond au total) (adaptée de Ethgen *et al*.[53])

Ces résultats, hypothétiques et suggérés en l'absence de mise en place de toute forme de stratégie préventive et thérapeutique, soulignent, une fois de plus, l'importance de ce phénomène en termes de santé publique.

3.2. De par ses conséquences cliniques importantes et son effet sur la qualité de vie

La littérature scientifique réfère un large nombre de conséquences de la sarcopénie. Parmi ces conséquences, on retrouve le développement d'incapacités physiques, l'augmentation de la fréquence d'admissions en maison de repos, l'incidence plus élevée de dépression, de chutes, de fractures, d'hospitalisations, une augmentation du nombre de jours d'hospitalisation, et même, un risque accru de mortalité[39,45,47,54–60]. Cela entraîne inévitablement une augmentation des nécessités de soins dans ce groupe de la population et, par conséquent, une augmentation des dépenses de santé liées à ces soins, autant à domicile qu'en ambulatoire. Actuellement, les seules données économiques disponibles dans le domaine de la sarcopénie datent de 2000 et rapportent que les coûts directs de la sarcopénie aux Etats-Unis s'élèveraient annuellement à $ 18,5 milliards, $ 10,8 milliards chez les hommes et $ 7,7 milliards chez les femmes. Ce montant ne représente pas moins de 1,5 % du total des dépenses de santé aux Etats-Unis[61]. Toutefois, on peut soulever que les conséquences directement attribuables à la sarcopénie restent difficiles à établir. En effet, les différentes études reportant ces conséquences

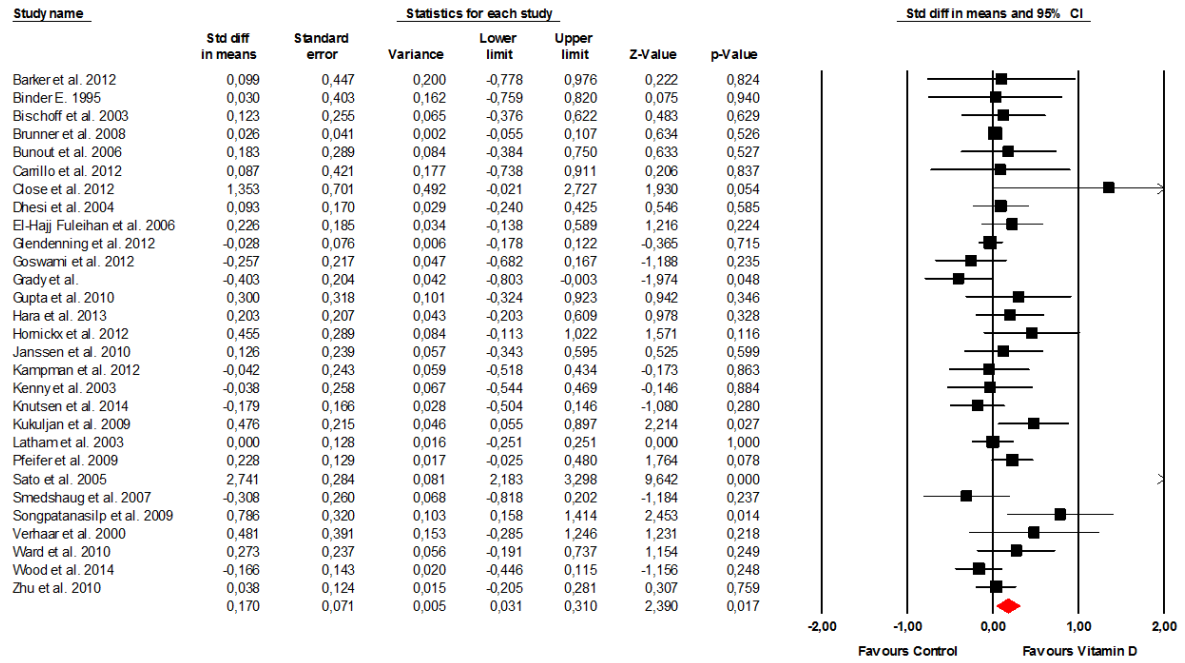
n'utilisent pas toujours les mêmes critères de diagnostic pour la sarcopénie. De ce fait, certaines des conséquences précitées semblent vraisemblablement être davantage reliées au processus de perte de masse musculaire isolé, ou au processus de perte de fonction musculaire isolé qu'à la condition de sarcopénie elle-même. De plus, ces différentes conséquences ne sont pas toujours identifiées par une étude prospective. En effet, dans certains cas, seule une association transversale a été observée. Dès lors, le terme « association » devrait être préféré au terme « conséquences ».

Actuellement, très peu de recherches ont été menées pour évaluer l'effet que pourrait avoir la sarcopénie sur la qualité de vie des sujets[62]. Nous avons récemment publié une revue dans le journal « *Gériatrie et psychologie neuropsychiatrique du vieillissement* »[63] (version intégrale de l'article disponible en annexe 2) qui reporte les résultats de 5 études observationnelles s'étant intéressées à la qualité de vie de sujets atteints de sarcopénie. Ces études semblent toutefois hétérogènes en termes de résultats avec, d'une part, des résultats indiquant une qualité de vie diminuée dans cette population pour certains domaines tels que la fonction physique, la mobilité et la vitalité ; et, d'autres part, des études ne montrant aucune association identifiée entre sarcopénie et qualité de vie. On note que ces études ont utilisé des questionnaires de qualité de vie génériques pour mesurer l'association entre la sarcopénie et la qualité de vie (Short-Form 36 [SF-36[64]] et EuroQol five dimensions questionnaire [EQ-5D[65]]). Ces questionnaires, par définition, traitent de l'ensemble des domaines pouvant affecter la qualité de vie des personnes, de tout âge, pour toute pathologie et ne semblent, par conséquent, pas toujours adaptés pour des situations cliniques spécifiques telles que la sarcopénie[63]. Avant la réalisation de nos travaux, aucun questionnaire spécifique n'était en fait disponible dans la littérature, ce qui pouvait limiter la mesure de qualité de vie dans cette population.

3.3. De par ses potentiels thérapeutiques encore trop faiblement investigués

Dans leur évaluation économique de la sarcopénie, Janssen *et al*.[61] ont identifié qu'une réduction de 10 % de la prévalence de la sarcopénie pourrait mener à une économie de $ 1,1 milliard par an aux Etats-Unis. Il est toutefois intéressant de noter qu'actuellement, à notre connaissance, aucune campagne de santé publique ou campagne de prévention n'est menée ou n'a été menée avec pour objectif de réduire la prévalence de la sarcopénie. Pourtant, même si les investigations menées sur ce sujet restent encore insuffisantes, différentes démarches préventives peuvent néanmoins être entreprises dans ce domaine. En effet, actuellement, on note deux grands axes thérapeutiques potentiels de la sarcopénie. Le premier axe est l'activité physique et le second, la nutrition. Une récente revue systématique[40] a effectivement mis en lumière le rôle des interventions à base d'activité physique (exercices de résistance, de marche, d'équilibre, programme de renforcement musculaire

progressif, etc.) pour augmenter la force musculaire et améliorer la performance physique de sujets âgés. Les résultats suggèrent également que la combinaison de différents programmes d'activité physique pourrait améliorer davantage ces paramètres musculaires. On note toutefois qu'aucune de ces études n'a inclus de sujets atteints de sarcopénie. Il est donc difficile de savoir si les effets observés dans ces études seraient maintenus dans une population de sujets sarcopéniques. La nutrition a également été suggérée comme un axe thérapeutique ou préventif potentiel dans le domaine de la sarcopénie. Une alimentation saine et équilibrée pourrait donc être un facteur clé dans le maintien d'une bonne santé musculaire. Toutefois, d'après la même revue systématique publiée par Cruz-Jentoft *et al*.[40] en 2014, il ne semble pas y avoir de preuve solide apportée par la littérature scientifique quant à l'amélioration des paramètres musculaires suite à une supplémentation nutritionnelle seule. Seuls certains effets de la créatine, des acides aminés essentiels et de la beta-hydroxy beta-methylbutyrate (HMB) sur la fonction musculaire de sujets âgés ont été retrouvés dans certaines études randomisées contrôlées. Bien qu'aucune étude n'ait encore évalué les effets d'une supplémentation en vitamine D sur la fonction musculaire de sujets sarcopéniques, une récente méta-analyse que nous avons réalisée au sein de l'URSAPES de l'Université de Liège[66] (version intégrale de l'article disponible en annexe 3) a toutefois montré le potentiel thérapeutique de la vitamine D dans ce domaine. En effet, les résultats de cette méta-analyse suggéraient une amélioration faible mais significative de la force musculaire suite à une supplémentation en vitamine D dans une population de sujets jeunes et âgés (Figure 3). Par ailleurs, les effets d'une supplémentation en vitamine D semblaient significativement supérieurs chez les sujets de plus de 65 ans par rapport aux sujets plus jeunes. Les preuves restent encore toutefois trop faibles pour établir des recommandations cliniques et de santé publique solides dans le domaine de la sarcopénie.



Heterogeneity : Q-value 125.37 ; Df(Q) 28 ; p-value 0.001; I^2 : 77.67

Figure 3. Effets d'une supplémentation en vitamine D sur la force musculaire. Résultats poolés de 29 RCTs[66]

La combinaison d'une intervention d'activité physique et de supplémentation nutritionnelle a également fait l'objet de plusieurs recherches. En 2015, Denison *et al*.[67] ont par ailleurs publié une revue systématique visant à synthétiser les effets d'études combinant une intervention d'activité physique à une supplémentation nutritionnelle sur différents paramètres musculaires (masse musculaire, force musculaire, performance physique). Ces études n'étant pas directement réalisées sur des sujets sarcopéniques, suggèrent que l'addition d'une supplémentation nutritionnelle ne semble pas démontrer d'effets supplémentaires à ceux procurés par l'activité physique. Nous avons eu l'occasion de mettre à jour cette revue systématique, en collaboration avec la *MRC Epidemiology Unit* de Southampton, United-Kingdom (UK), qui a dès lors inclus 38 études randomisées contrôlées. A l'exception de la créatine qui semble renforcer les effets de l'activité physique et ainsi, améliorer les paramètres de masse musculaire et de force musculaire de manière significativement plus élevée chez les sujets bénéficiant, en plus de l'activité physique, de cette supplémentation nutritionnelle, aucun autre supplément diététique ne semble ressortir des analyses.

Actuellement, il n'existe pas de médicament enregistré ou commercialisé ayant pour cible thérapeutique la sarcopénie. Toutefois, différentes molécules sont actuellement en cours de développement au sein d'industries pharmaceutiques. Sur consultation de la base de données GlobalData, 23 études cliniques sont actuellement en cours de réalisation dont deux en Phase IV, deux en Phase III et plus de la moitié en Phase II. Parmi les molécules évaluées en étude de phase III et IV,

nous retrouvons le cholécalciférol, l'allopurinol, la leucine et la créatine monohydrate. Aucune étude de grande envergure n'a toutefois encore été menée dans ce domaine.

OBJETS DE RECHERCHE

A la lumière des éléments soulevés dans l'introduction générale de cette thèse, nous identifions, entre autres, certains points pertinents à évaluer pour enrichir et renforcer les recherches de santé publique menées dans le domaine de la sarcopénie :

- ✓ Les conséquences cliniques à court, moyen et long termes de la sarcopénie telle que définie par l'EWGSOP[9] ne sont pas clairement identifiées dans la littérature ;
- ✓ Tenant compte du fait que la définition consensuelle de l'EWGSOP[9] est relativement récente, encore peu d'études de large envergure utilisant cette définition pour diagnostiquer la sarcopénie ont été menées. Des études de cohorte additionnelles comprenant des sujets de plus de 65 ans mériteraient d'être menées afin de valider cette définition comme étant prédictive d'évènements indésirables ;
- ✓ La définition de l'EWGSOP[9] propose différents outils pour mesurer la masse musculaire, la force musculaire et la performance physique. Il n'existe pas encore d'étude publiée permettant de mesurer l'effet de l'utilisation des différents outils proposés sur la prévalence de la sarcopénie ;
- ✓ La définition de l'EWGSOP[9] propose différentes valeurs seuils pour identifier une faible masse musculaire, une faible force musculaire et une faible performance physique, les trois composantes de la sarcopénie. Il n'existe pas encore d'étude publiée permettant de mesurer l'effet de l'utilisation de ces différentes valeurs seuils sur la prévalence de la sarcopénie ;
- ✓ Peu de données concernant l'effet de la sarcopénie sur la qualité de vie existent. Cela tient principalement du fait qu'il n'existe pas de questionnaire de qualité de vie spécifique dans le domaine de la sarcopénie.

Afin d'investiguer ces différents points et ainsi contribuer à l'avancée des recherches dans le domaine de la sarcopénie, plusieurs recherches, constituant donc cette thèse de doctorat, ont été menées. Les articles scientifiques relatifs à ces recherches seront présentés de manière résumée dans la partie « SYNTHÈSE DES RÉSULTATS PRINCIPAUX ». Leurs versions intégrales sont disponibles dans la partie « ANNEXES ». Ces différents articles scientifiques ont été organisés, pour cette thèse de doctorat, en quatre parties :

La **PREMIÈRE PARTIE** consiste en la réalisation d'une revue systématique et méta-analyse visant à synthétiser les conséquences de la sarcopénie telle que diagnostiquée selon la définition de l'EWGSOP[9]. Ces conséquences seront exclusivement tirées d'études prospectives. La **DEUXIÈME PARTIE** présente les données que nous avons obtenues à partir de la cohorte SarcoPhAge (*Sarcopenia and Physical impairments with advancing Age*). L'étude SarcoPhAge est une étude constituée de sujets ambulants âgés de plus de 65 ans. Chez tous ces sujets, un diagnostic complet de la sarcopénie, en

suivant le modèle proposé par l'EWGSOP[9], a été réalisé. Cette étude a pour objectif d'évaluer la prévalence de la sarcopénie dans cette population, l'incidence de la sarcopénie au cours et temps ainsi que les potentiels paramètres cliniques et physiques liés à la sarcopénie. Bien que l'étude SarcoPhAge soit initialement prévue pour suivre les participants durant 5 années, dans ce second chapitre seront uniquement présentés le design de l'étude SarcoPhAge, les caractéristiques des sujets lors de leur inclusion dans l'étude et les conséquences indésirables associées à la sarcopénie après 2 ans de suivi. La **TROISIÈME PARTIE** présentera les résultats de deux études réalisées sur la population SarcoPhAge visant à évaluer l'effet de l'utilisation de différents outils de diagnostic ou de différentes valeurs seuils de diagnostic (tels que proposés par l'EWGSOP[9]) sur la prévalence de la sarcopénie. Enfin, la **QUATRIÈME PARTIE** abordera le développement et la validation du questionnaire SarQoL®, un questionnaire de qualité de vie spécifique à la sarcopénie. Ce questionnaire, initialement développé et validé en français a également fait l'objet d'une traduction et d'une validation en anglais.

SYNTHÈSE DES RÉSULTATS PRINCIPAUX

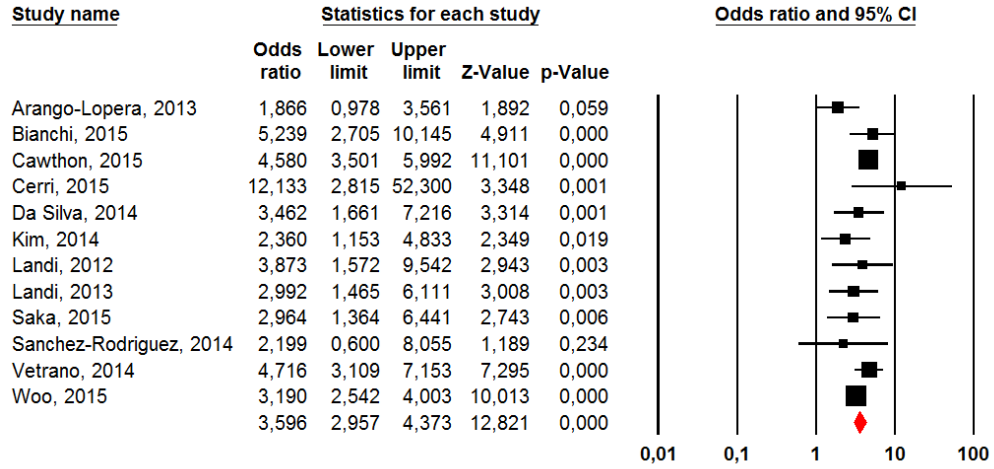
1. REVUE SYSTÉMATIQUE SUR LES CONSÉQUENCES DE LA SARCOPÉNIE

Plusieurs conséquences de la sarcopénie sur la santé sont actuellement reportées au sein d'études épidémiologiques. Cependant, ces conséquences énumérées ne sont pas toujours établies par des études prospectives. D'autre part, l'absence de consensus pour définir la sarcopénie, malgré de nombreuses initiatives de groupes d'experts, rend difficile l'établissement d'un lien de cause à effet entre la sarcopénie et ses conséquences défavorables, ce qui constitue un frein à la reconnaissance de la sarcopénie en tant qu'entité clinique à part entière. L'objectif de notre recherche consiste à établir une liste claire des conséquences de la sarcopénie provenant uniquement d'études *prospective*s ayant utilisé exclusivement une définition unique de la sarcopénie, à savoir la *définition de l'EWGSOP*[9], pour le diagnostic de la sarcopénie.

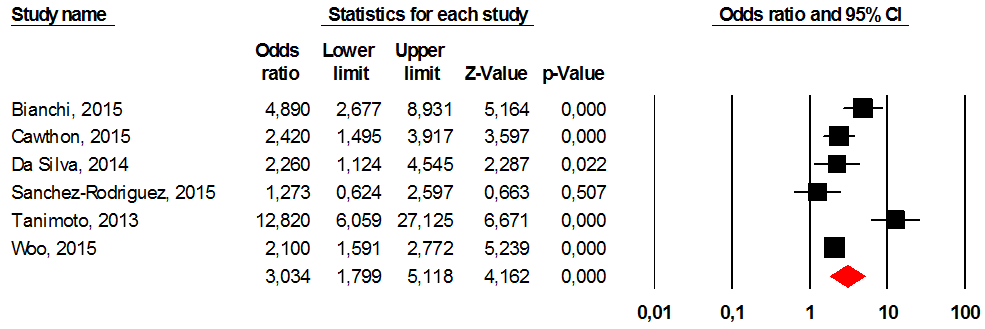
Pour ce faire, nous avons appliqué une stratégie de recherche bibliographique aux bases de données suivantes : MEDLINE, EMBASE, Cochrane Database of Systematic Review, ACP Journal Club, Database of Abstracts of Reviews of Effects (DARE), Allied and Complementary Medicine (AMED). Une recherche manuelle a également été effectuée sur base de la bibliographie d'études pertinentes sur le sujet. Aucune limite de temps n'a été appliquée. Une première sélection des études identifiées par la stratégie de recherche, sur base uniquement de la lecture du titre et de l'abstract a été réalisée indépendamment par deux chercheurs. Le texte intégral de chacun des articles a ensuite été relu et les articles ont été sélectionnés sur base des critères d'inclusion suivants : études prospectives, hommes et femmes de plus de 65 ans avec un diagnostic de la sarcopénie réalisé selon les critères de l'EWGSOP[9], présentation des résultats concernant au moins une conséquence de la sarcopénie. Tout désaccord concernant l'inclusion ou l'exclusion d'une étude a été résolu par discussion et obtention d'un consensus entre deux chercheurs indépendants. La qualité individuelle de chaque étude prospective incluse dans la revue systématique a été mesurée par la *Newcastle-Ottawa Scale* (NOS). Une méta-analyse a été réalisée pour les conséquences extraites d'au minimum 3 études individuelles. L'ampleur de l'effet a ainsi été exprimé en *Odds Ratio* (OR) avec son *intervalle de confiance à 95 %* (IC 95 %).

Après élimination des doublons entre les bases de données, un total de 772 références a été obtenu suite à l'application de la stratégie de recherche sur les différentes bases de données. Parmi ces références, 17 ont été incluses dans la revue systématique. Le nombre de participants variait de 99 à 6658 sujets et la durée de suivi variait de 3 mois à 9,8 ans. Parmi ces 17 études prospectives, 12 ont évalué l'impact de la sarcopénie sur la mortalité. Dix de ces études sur 12 ont conclu à une augmentation du risque de mortalité dans la population des sujets sarcopéniques, en comparaison aux

non sarcopéniques. Ces résultats ont été poolés par la réalisation d'une méta-analyse et indiquent un OR de 3,60 (IC 95 % 2,96 – 4,37), montrant un risque de mortalité associé à la sarcopénie (Figure 4A). Des analyses en sous-groupes ont également été réalisées afin d'identifier un éventuel effet de l'âge, de la qualité des études et de la durée de suivi des études sur les résultats. Il en ressort que seul l'âge entraîne une différence de résultats, avec un risque de mortalité associé à la sarcopénie significativement plus élevé chez les sujets de 79 ans ou plus comparé aux sujets plus jeunes. La sarcopénie semblait également être associée à un déclin fonctionnel. En effet, 5 études sur 6 ont reporté une association significative entre la sarcopénie et un déclin fonctionnel. Ces résultats, poolés par méta-analyse, indiquent un OR de 3,03 (IC 95 % 1,80 – 5,12) (Figure 4B). Deux études reportent également un risque de chute augmenté chez les sujets sarcopéniques et une étude reporte une incidence augmentée d'hospitalisations. Enfin, deux études se sont intéressées à l'association entre sarcopénie et risque de fracture et deux autres à l'association entre sarcopénie et durée du séjour d'hospitalisation. On note que les résultats sont mitigés avec seulement une étude sur deux montrant une association significative entre la sarcopénie et ces conséquences.



A. Mortality and sarcopenia
Heterogeneity Q-value 16.05; df(Q) 11; p-value 0.14; I^2 31.4



B. Functional disability and sarcopenia
Heterogeneity Q-value 27.99; df(Q) 5; p-value <0.001; I^2 82.1.

Figure 4. Association entre la sarcopénie et la mortalité (A) ainsi qu'entre la sarcopénie et le déclin fonctionnel (B)

Un article scientifique rapportant les résultats de cette recherche a été soumis pour publication. La version intégrale de cet article, tel qu'il a été soumis le 06 septembre 2016, est disponible en annexe 5.

2. DESIGN, DESCRIPTION ET RÉSULTATS DE L'ÉTUDE SARCOPHAGE [42]

L'étude SarcoPhAge (*Sarcopenia and Physical impairment with advancing Age*) est une étude longitudinale incluant des sujets ambulants de plus de 65 ans résidant en province de Liège. Les objectifs de l'étude SarcoPhAge sont d'évaluer, par l'utilisation de l'algorithme de diagnostic proposé par l'EWGSOP[9], la prévalence de la sarcopénie, l'incidence de la sarcopénie au cours du temps, mais également de mesurer l'évolution à court et moyen termes de certains paramètres physiques et cliniques des participants afin d'identifier d'éventuelles composantes cliniques reliées à la sarcopénie ainsi que l'effet que peut avoir la sarcopénie sur ces composantes.

L'étude SarcoPhAge a débuté en juin 2013. Durant une année, un total de 534 participants ont été recrutés dans différents Services de la Polyclinique Lucien Brull à Liège (gériatrie, métabolisme de l'os et du cartilage, rhumatologie, centre de réhabilitation gériatrique) mais également par des annonces dans la presse. Tous ces participants ont été reçus individuellement en rendez-vous pour une durée de 45 minutes à 1 heure au cours duquel des données sociodémographiques, anamnestiques et cliniques ont été recueillies. Pour réaliser un diagnostic de la sarcopénie, l'algorithme proposé par l'EWGSOP[9] a été utilisé. Ainsi, la masse musculaire a été mesurée par absorptiométrie biphotonique à rayons X (DXA), la force musculaire a été évaluée par la force de préhension et mesurée par un dynamomètre hydraulique et, enfin, la performance physique a été évaluée par le test SPPB. Différentes variables ont également été recueillies telles que la consommation de tabac et d'alcool, la nécessité de disposer d'une aide à la marche, les antécédents de fractures et d'hospitalisation, la consommation de médicaments, les comorbidités, le statut cognitif (Mini Mental State Examination[68]), le statut nutritionnel (Mini-Nutritionnal Assessment[69]), le niveau de dépendance (échelles de Katz[70] et de Lawton[71]), la présence de trouble dépressif (Geriatric Depression Scale[72]), la qualité de vie (questionnaires génériques Short-Form 36[73] et EQ-5D[65]), la fatigue (Mobility-Tiredness Scale[74]), le risque de chute (tests de Tinetti[75] et Timed Up and Go[76]), la fragilité (critères de Fried[77]) et le débit expiratoire de pointe. Ensuite, annuellement, tous ces examens ont été renouvelés auprès de notre échantillon d'étude.

Lors de la première année d'étude, un total de 534 sujets ont ainsi été recrutés pour l'étude (60,5 % de femmes, âge moyen de 73,5 ± 6,16 ans). Sur cette population, 73 sujets ont été diagnostiqués sarcopéniques, ce qui représente une prévalence de 13,7 % (Figure 5). La prévalence de la sarcopénie chez les hommes était de 11,8 % alors qu'elle était de 14,9 % chez les femmes. La prévalence de la sarcopénie semble augmenter avec l'âge, atteignant même les 44,0 % chez les hommes après l'âge de 80 ans.

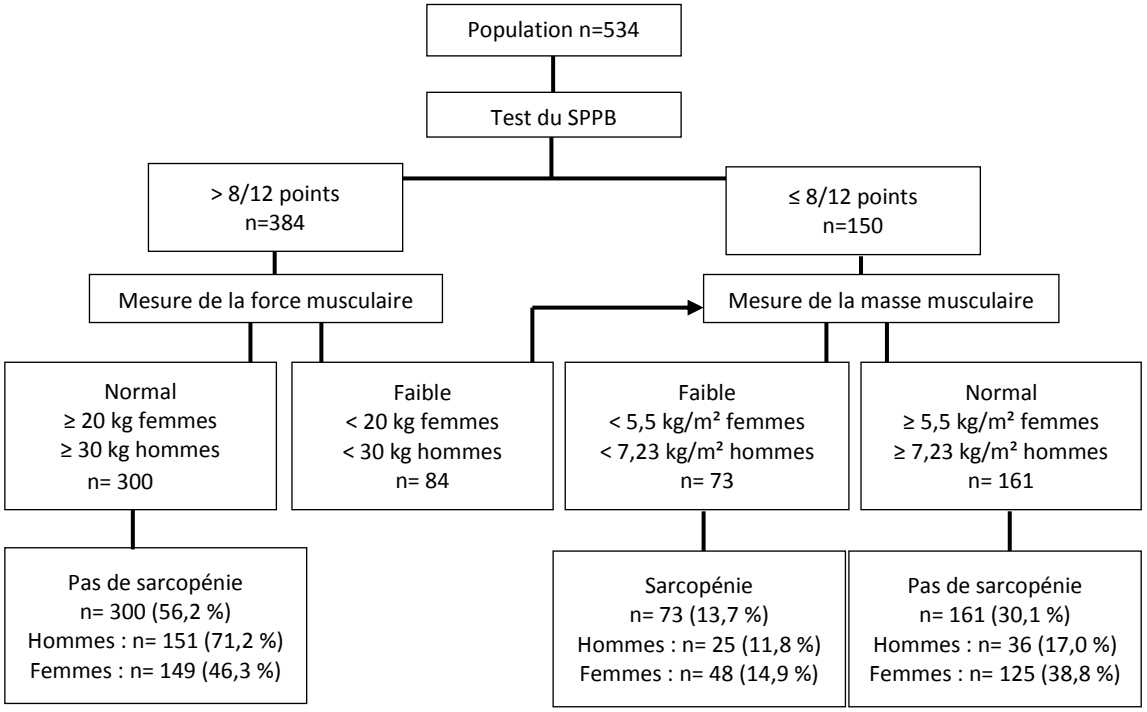


Figure 5. Diagnostic de la sarcopénie dans l'étude SarcoPhAge selon l'algorithme proposé par l'EWGSOP (adaptée de Beaudart *et al.*[42])

Les sujets diagnostiqués sarcopéniques étaient significativement plus âgés que les non sarcopéniques ($p < 0,001$), présentaient un plus faible indice de masse corporelle (IMC) ($p < 0,001$) et des indices anthropométriques plus faibles (p-valeurs < 0,001). Ils prenaient également plus de médicaments ($p = 0,01$), présentaient plus de comorbidités ($p = 0,003$), utilisaient plus souvent une aide à la marche ($p = 0,02$), présentaient un plus haut taux d'hospitalisation endéans l'année précédant le diagnostic ($p = 0,03$) et étaient également plus souvent dans un état de malnutrition ($p < 0,001$). Enfin, les sujets diagnostiqués sarcopéniques semblaient également avoir un moins bon statut cognitif ($p < 0,001$). L'association de la sarcopénie avec la qualité de vie et certaines composantes physiques a été mesurée en ajustant les analyses sur ces différences de caractéristiques cliniques observées entre les deux groupes. Après ajustement, les sujets atteints de sarcopénie présentaient une qualité de vie diminuée par rapport aux sujets non sarcopéniques au niveau du domaine de la fonction physique du SF-36 ($p = 0,001$), semblaient plus dépendants dans certaines activités de la vie quotidienne (ménage $p = 0,02$, habileté à gérer ses finances $p = 0,01$), étaient plus souvent dans un état de fragilité ($p = 0,03$), présentaient un plus haut risque de chute (Timed Up and Go $p = 0,025$) mais également une réduction au niveau de la vitesse de marche ($p = 0,001$), du débit expiratoire de pointe ($p = 0,01$), de la masse musculaire ($p = 0,006$) et de la masse graisseuse ($p < 0,001$).

La présentation du design de l'étude SarcoPhAge ainsi que les caractéristiques des sujets à l'inclusion ont été publiés au sein du journal « Experimental Gerontology » (Facteur d'impact 3,48) (*Beaudart, C. et al. Quality of life and physical components linked to sarcopenia: The SarcoPhAge study. Experimental Gerontology. 2015 Sep;69:103-10.).* La version intégrale de l'article est disponible en annexe 6.

Un total de 336 sujets a été revu après deux ans de suivi (évaluation T2), soit 62,9 % de l'effectif total. Parmi les 198 sujets n'ayant pas participé à cette évaluation T2, nous notons 20 décès (3,74 % de l'échantillon total) et 59 incapacités physiques de se représenter à l'examen (11,0 % de l'échantillon total) pour des raisons diverses (hospitalisations, institutionnalisations, perte de mobilité, comorbidités importantes, etc.). Nous déplorons une perte de 12 sujets due à l'impossibilité de contacter ces derniers (2,24 % de l'échantillon total). Par ailleurs, nous observons un taux de refus à se présenter à cette évaluation T2 assez élevé : 107 participants n'ont ainsi pas reconduit leur accord pour continuer la recherche (20,0 % de l'échantillon total) pour des raisons évoquées assez variées (manque d'intérêt pour l'étude, refus de se déplacer, etc.).

Sur les 73 sujets diagnostiqués sarcopéniques lors de leur entrée dans l'étude, 9 sujets se sont déclarés incapables de continuer l'étude dans le courant de ces deux années de suivi (12,3 %) et 7 sujets sont décédés (9,59 %). Une incidence significativement plus élevée de décès a été observée chez les sujets sarcopéniques en comparaison aux non sarcopéniques (2,82 % chez les non sarcopéniques, p = 0,005) avec un OR brut de 3,65 (IC 95 % 1,41 - 9,49) et un OR ajusté sur l'âge, le nombre de médicaments et le nombre de comorbidités de 4,00 (IC 95 % 1,51 – 10,6).

Sur les 73 sujets diagnostiqués sarcopéniques lors de leur inclusion dans l'étude, seuls 33 ont été revus après 2 années de suivi. Au cours de ces deux années de suivi, une incidence d'hospitalisations de 52,9 % a été observée chez les sujets sarcopéniques contre 29,0 % chez les sujets non sarcopéniques (p = 0,004). Un OR brut de 2,75 (IC 95 % 1,34 - 5,63) a ainsi été observé. L'OR était de 2,61 (IC 95 % 1,18 - 5,76) après ajustement sur l'âge, le nombre de comorbidités et le nombre de médicaments couramment consommés. Aucune différence significative entre les deux groupes concernant l'incidence de chutes (p = 0,63), de fractures (p = 0,34) ou de déclin fonctionnel (évalué par une diminution substantielle de la vitesse de marche[78] (p = 0,34), du SPPB test[78] (p = 0,63) et de la vitesse de réalisation du test de lever de chaise[79] (p = 0,63)) n'a toutefois été reportée.

Sur les 336 sujets analysés en T2, 54 sujets ont été diagnostiqués sarcopéniques (16,0 %). Sur ces 54 sujets sarcopéniques, 24 l'étaient déjà lors de l'inclusion dans l'étude (T0). On observe ainsi une incidence de 30 nouveaux sarcopéniques au cours des 2 années de suivi. On constate également que,

parmi les 33 sarcopéniques diagnostiqués à l'inclusion dans l'étude et revus en consultation T2, 9 sont passés à un statut de non sarcopénie après deux années de suivi (Figure 6).

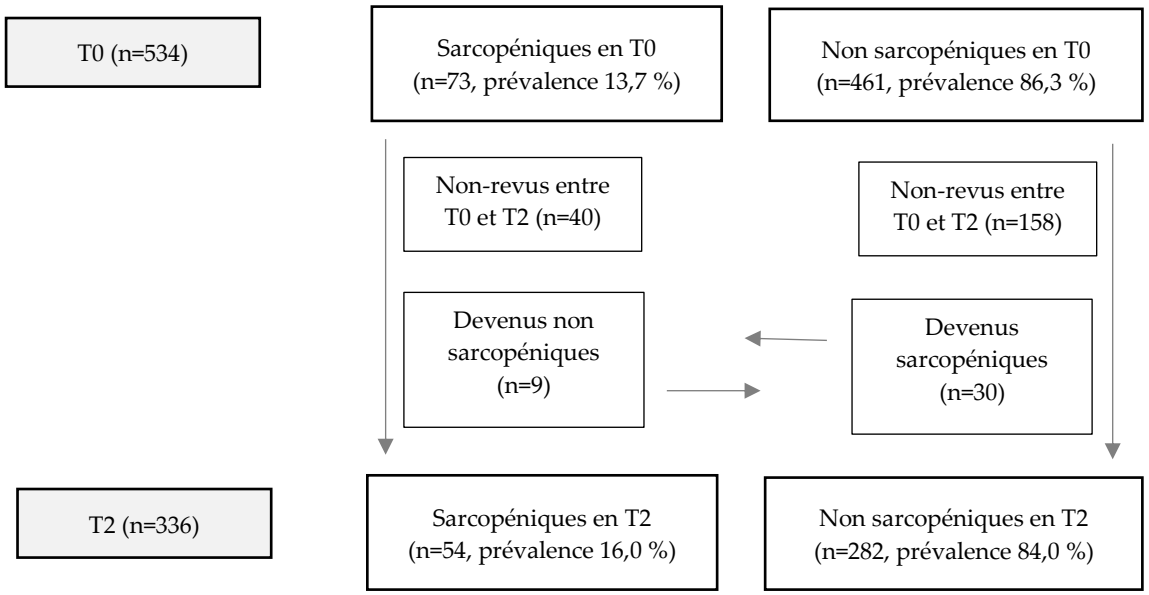


Figure 6. Evolution du statut de sarcopénie entre T0 et T2

3. PRÉVALENCE DE LA SARCOPÉNIE SELON DIFFÉRENTS CRITÈRES DE DIAGNOSTIC

3.1. Prévalence de la sarcopénie selon l'utilisation de différents outils de diagnostic[80]

Comme expliqué précédemment, il n'existe actuellement pas de recommandation concernant les outils à utiliser pour évaluer la masse musculaire, la force musculaire et la performance physique, les trois composantes de la sarcopénie. En effet, l'EWGSOP[9] propose plusieurs outils différents pour mesurer chacune de ces composantes. Dans une étude transversale, nous avons comparé la prévalence de la sarcopénie en fonction des différents outils de diagnostic utilisés.

Cette étude a donc été menée sur un sous-groupe de la population SarcoPhAge. Pour mesurer la masse musculaire, la force musculaire et la performance physique, nous avons à chaque fois utilisé deux outils de diagnostic différents. Pour la masse musculaire, nous avons utilisé l'absorptiométrie biphotonique à rayons X (DXA) et l'impédancemétrie bioélectrique (BIA) ; pour la force musculaire, nous avons utilisé un dynamomètre hydraulique (DH) et pneumatique (DP) ; pour la performance physique, nous avons utilisé le test du Short Physcial Performance Battery (SPPB) et la vitesse de marche (UGS). Huit définitions ont ainsi été établies (Table 5).

Pour ce faire, 250 sujets recrutés au sein de la Polyclinique Lucien Brull à Liège dans le cadre de la cohorte SarcoPhAge ont été inclus dans cette étude (62,8 % de femmes, âge moyen de 74,1 ± 6,4 ans). En fonction de la définition utilisée, la prévalence de la sarcopénie variait de 8,4 % (définitions BIA-HD-UGS et BIA-HD-SPPB) à 27,6 % (définitions DXA-PD-UGS et DXA-PD-SPPB) (Table 5).

Table 5. Estimation de la prévalence de la sarcopénie en fonction de 8 méthodes de diagnostic (adaptée de Beaudart *et al*.[80])

	Prévalence de la sarcopénie
DXA – HD - UGS	14 %
DXA – HD - SPPB	14,8 %
DXA – PD - UGS	27,6 %
DXA – PD - SPPB	27,6 %
BIA – HD - UGS	8,4 %
BIA – HD - SPPB	8,4 %
BIA – PD - UGS	17,2 %
BIA – PD - SPPB	17,2 %

Concernant la masse musculaire, les résultats indiquent que la BIA surestime celle-ci en comparaison à la DXA. En effet, la moyenne de prévalence de la sarcopénie avec la BIA était de 12,8 % alors qu'elle était de 21,0 % en utilisant la DXA. De plus le SMI moyen de la population s'élevait à 6,08 kg/m² chez les femmes et 7,93 kg/m² chez les hommes lorsque celui-ci était mesuré par la DXA et de 7,63 kg/m² pour les femmes et 9,66 kg/m² pour les hommes lorsque celui-ci était mesuré par la BIA. Pour la force musculaire, le dynamomètre pneumatique diagnostiquerait deux fois plus de sujets sarcopéniques que le dynamomètre hydraulique (moyenne de prévalence de sarcopénie avec DP = 22,4 % ; moyenne de prévalence de sarcopénie avec DH = 11,4 %). En utilisant le dynamomètre hydraulique, la force de préhension moyenne des participants était de 27,5 kg alors qu'elle n'était que de 12,2 kg en utilisant le dynamomètre pneumatique, soit une différence observée de 15,3 kg. Finalement, aucune différence de prévalence de la sarcopénie n'a été observée en comparant la vitesse de marche au test SPPB (moyenne de prévalence avec SPPB = 17,0 % ; moyenne de prévalence avec UGS = 16,8 %). Nous avons également comptabilisé les sujets diagnostiqués sarcopéniques à travers les 8 définitions. Sur les 250 sujets recrutés pour l'étude, 173 n'étaient diagnostiqués sarcopéniques par aucune des 8 définitions alors que 18 l'étaient par l'ensemble des 8 définitions. Les 4 définitions utilisant la DXA pour la mesure de masse musculaire ont diagnostiqué, de manière concordante, 17 sujets sarcopéniques. En revanche, les 4 définitions utilisant la BIA pour la mesure de masse musculaire ne semblaient concordantes que pour le diagnostic de 3 sujets sarcopéniques. Cette distribution de diagnostic à travers les définitions est visuellement représentée par la Figure 7.

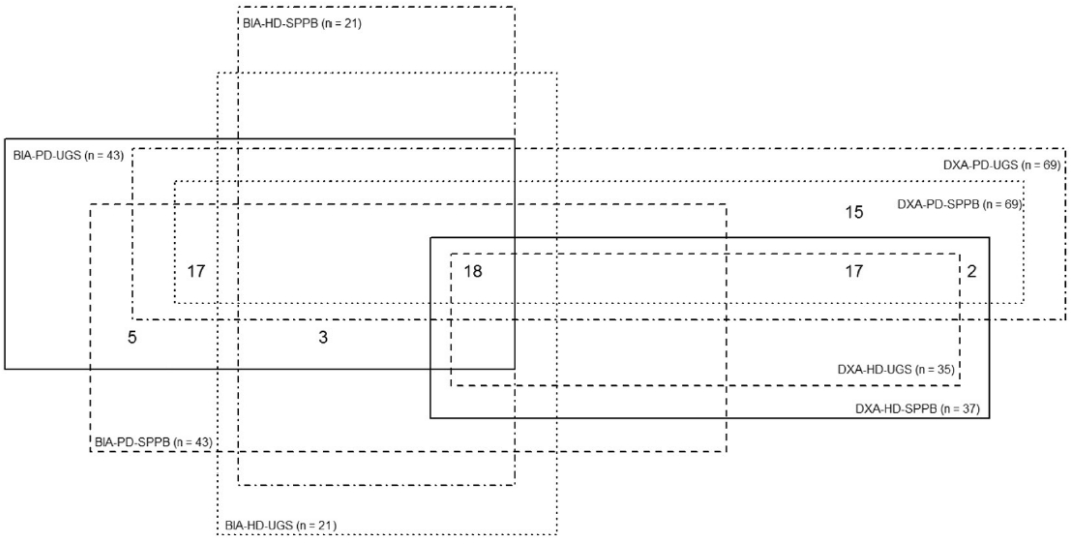


Figure 7. Nombre de sujets diagnostiqués sarcopéniques selon les 8 définitions[80]

Cet article a été publié au sein du journal « Experimental Gerontology » (Facteur d'impact 3,48) (*Beaudart, C. et al. Estimation of sarcopenia prevalence using various assessment tools. Experimental Gerontology. 2015 Jan;61:31-7).* La version intégrale de cet article est disponible en annexe 7.

3.2. Prévalence de la sarcopénie selon l'utilisation de différentes valeurs seuils de diagnostic[81]

Dans l'article de consensus proposé par l'EWGSOP[9], différentes valeurs seuils de diagnostic sont suggérées pour définir une faible masse musculaire appendiculaire, une force musculaire limitée ainsi qu'une faible vitesse de marche. L'objectif de notre recherche est d'évaluer la variation de la prévalence de la sarcopénie en fonction de l'utilisation de ces différentes valeurs seuils.

Cette étude a été menée sur un sous-groupe de la population SarcoPhAge. La masse musculaire appendiculaire (MM) des participants a été mesurée par un examen d'absorptiométrie biphotonique à rayons X, la force musculaire (FM) par un dynamomètre hydraulique et la vitesse de marche (VM) a été calculée sur une distance de 4 mètres. Deux différentes valeurs seuils de diagnostic, proposées par l'EWGSOP[9], ont été comparées pour chacune des variables (Table 6).

Table 6. Diagnostic de la sarcopénie : valeurs seuils suggérées par l'EWGSOP (adaptée de Beaudart *et al.*[81])

<table>
<tr><th>Masse musculaire (MM) : valeur seuil 1</th><th>Masse musculaire (MM) : valeur seuil 2</th></tr>
<tr><td>Hommes : 7,26 kg/m2
Femmes : 5,50 kg/m2</td><td>Hommes : 7,25 kg/m2
Femmes : 5,67 kg/m2</td></tr>
<tr><th>Force musculaire (FM) : valeur seuil 1</th><th>Force musculaire (FM) : valeur seuil 2</th></tr>
<tr><td rowspan="2">Hommes : < 30 kg
Femmes : < 20 kg</td><td>Hommes :
IMC ≤ 24 : ≤ 29 kg
IMC 24,1–26 : ≤ 30 kg
IMC 26,1–28 : ≤ 30 kg
IMC > 28 : ≤ 32 kg</td></tr>
<tr><td>Femmes :
IMC ≤ 23 : ≤ 17 kg
IMC 23,1–26 : ≤ 17,3 kg
IMC 26,1–29 : ≤ 18 kg
IMC > 29 : ≤ 21 kg</td></tr>
<tr><th>Vitesse de marche (VM) : valeur seuil 1</th><th>Vitesse de marche (VM) : valeur seuil 2</th></tr>
<tr><td rowspan="2">< 0.8 m/s</td><td>Hommes :
Taille ≤ 173 cm : < 0,65 m/s
Taille > 173 cm : < 0,76 m/s</td></tr>
<tr><td>Femmes :
Taille ≤ 159 cm : < 0,65 m/s
Taille > 159 cm : < 0,76 m/s</td></tr>
</table>

Huit critères de diagnostic ont ensuite été établis :

- A : MM valeur seuil 1, FM valeur seuil 1, VM valeur seuil 1,
- B : MM valeur seuil 1, FM valeur seuil 1, VM valeur seuil 2,
- C : MM valeur seuil 1, FM valeur seuil 2, VM valeur seuil 1,
- D : MM valeur seuil 1, FM valeur seuil 2, VM valeur seuil 2,
- E : MM valeur seuil 2, FM valeur seuil 1, VM valeur seuil 1,

- F : MM valeur seuil 2, FM valeur seuil 1, VM valeur seuil 2,
- G : MM valeur seuil 2, FM valeur seuil 2, VM valeur seuil 1,
- H : MM valeur seuil 2, FM valeur seuil 2, VM valeur seuil 2.

Pour cette étude, 400 sujets ont été recrutés au sein de la Polyclinique Lucien Brull à Liège (60,7 % de femmes, âge moyen de 73,8 ± 6,2 ans). La prévalence de la sarcopénie variait de 9,25 % à 18,0 % en fonction des valeurs seuils utilisées. L'utilisation de la première ou de la seconde valeur seuil pour la masse musculaire entraîne une importante variation de la prévalence de la sarcopénie (12,6 % versus 16,1 % respectivement). Pour la force musculaire, l'utilisation d'une valeur seuil dépendante de l'IMC semble restreindre le nombre de sujets diagnostiqués sarcopéniques (16,1 % avec la valeur seuil générale versus 11,6 % avec celle dépendante de l'IMC). Pour la vitesse de marche, les résultats suivent la même tendance : 14,8 % des sujets ont été diagnostiqués sarcopéniques avec l'utilisation de la valeur seuil générale versus 12,9 % avec l'utilisation de la valeur seuil spécifique au sexe et à la taille des sujets. Nous avons également stratifié les résultats en fonction du sexe et de l'âge des participants. D'une manière générale, il semble que la variation de la prévalence de la sarcopénie soit principalement attribuable aux femmes. En effet, cette prévalence varie de 6,58 % à 20,2 % chez les femmes, en fonction du critère de diagnostic choisi, alors qu'elle ne varie que de 13,4 % à 14,7 % chez les hommes (Figure 8). Concernant l'âge, on observe également une plus grande différence de prévalence chez les femmes. La prévalence de la sarcopénie chez les femmes varie de 1,18 % (critère D) à 7,06 % (critère E) dans la catégorie d'âge 65-69 ans alors qu'elle varie de 16,7 % (critère D) à 38,1 % (critère E) dans la catégorie ≥ 80 ans. Etant donné la variation de prévalence observée en fonction de l'utilisation de l'une ou l'autre méthode diagnostique, nous avons également vérifié les différences de caractéristiques des femmes diagnostiquées sarcopéniques à travers les 8 critères de diagnostic. Aucune différence significative n'a été observée à l'exception de la vitesse de marche qui était significativement supérieure chez les femmes diagnostiquées sarcopéniques avec la méthode D en comparaison aux méthodes E ($p = 0,039$) et F ($p = 0,035$).

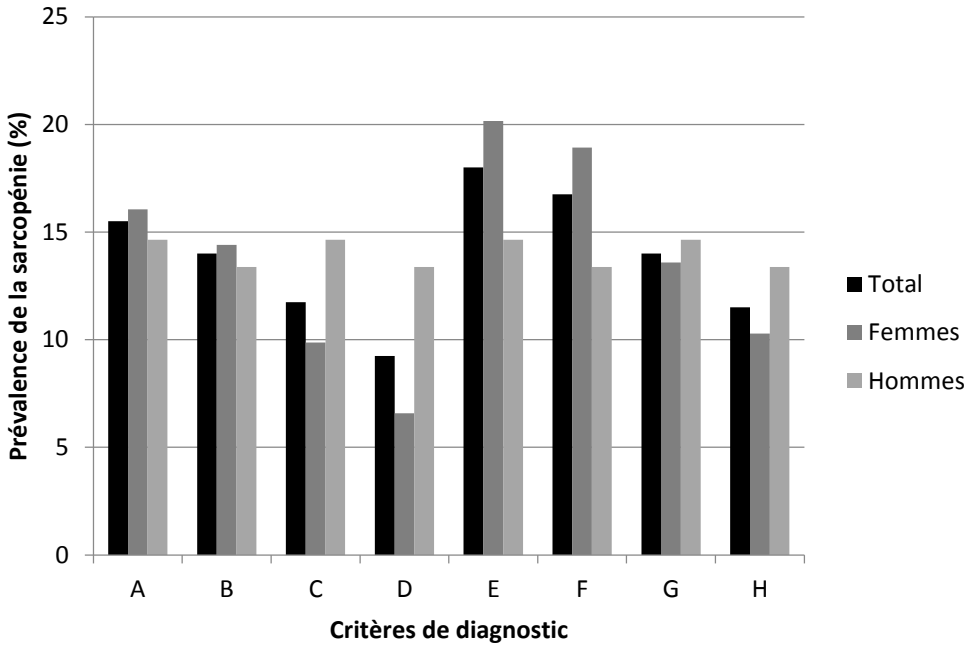


Figure 8. Prévalence de la sarcopénie selon 8 critères de diagnostic (adaptée de Beaudart *et al*.[81])

Cette recherche a été publiée au sein du journal « Journal of Musculoskeletal and Neuronal Interactions » (Facteur d'impact 1,60) (*Beaudart, C. et al. Prevalence of sarcopenia: the impact of different diagnostic cut-off limits. Journal of Musculoskeletal and Neuronal Interactions. 2014 Dec;14(4):425-31).* La version intégrale de cet article est disponible en annexe 8.

4. QUALITÉ DE VIE ET SARCOPÉNIE

4.1. Développement et validation du SarQoL®, un questionnaire de qualité de vie spécifique à la sarcopénie[82,83]

Au vu des conséquences associées à la sarcopénie, soulevées à travers la revue systématique et méta-analyse que nous avons réalisée, ses répercussions sur la qualité de vie semblent être implicites. Les données actuellement présentes dans la littérature sont toutefois relativement pauvres et hétérogènes. En effet, l'effet de la sarcopénie sur la qualité de vie est actuellement étudié au moyen de questionnaires de qualité de vie génériques. Ces questionnaires, par définition, traitent de l'ensemble des domaines pouvant affecter la qualité de vie des personnes, de tout âge, pour toute pathologie. La proportion de questions spécifiques à la sarcopénie est donc restreinte dans ce type de questionnaire. Ainsi, par exemple, une thérapeutique axée dans le domaine de la sarcopénie ne pourrait, dans l'hypothèse où celle-ci serait efficace, n'entraîner une amélioration de l'état de santé que pour ces quelques questions concernées par la sarcopénie et le score total de qualité de vie du questionnaire pourrait n'être que très peu modifié. Or, dans un questionnaire spécifiquement développé pour la sarcopénie, toutes les réponses aux questions pourraient être susceptibles de varier suite à une intervention thérapeutique efficace. Puisqu'il n'existait encore aucun questionnaire de qualité de vie spécifique à la sarcopénie, l'objectif de notre étude a donc consisté à développer et valider un tel questionnaire, le SarQoL® (*Sarcopenia & Quality of Life* questionnaire).

Le questionnaire SarQoL® a été développé selon 4 étapes successives : 1. Génération des items par la réalisation d'une revue systématique sur le sujet, par l'interview de sujets atteints de sarcopénie et par la distribution d'un questionnaire semi-structuré à des experts de la sarcopénie ; 2. Réduction des items par les experts et par un échantillon de sujets atteints de sarcopénie ; 3. Développement des questions en partenariat avec l'ensemble des experts ; 4. Pré-test du questionnaire auprès d'un échantillon de sujets atteints de sarcopénie.

Un total de 46 sujets a été inclus dans la phase de développement du SarQoL®. La population avait un âge moyen de 76,3 ± 6,51 ans et 73,8 % des sujets étaient des femmes. Lors de la première phase, celle de la génération des items, un total de 180 items a été identifié. Suite à la réalisation d'une première réunion avec les experts, ce listing a été réduit à 136 items, par la suppression d'items redondants, non clairs ou douteux. La phase de réduction des items a ensuite permis d'identifier 55 items pour le questionnaire (Figure 9). Le questionnaire SarQoL® est donc composé de 55 items, répartis en 7 domaines de qualité de vie, retranscrits sous forme de 22 questions. Les 7 domaines identifiés sont les suivants : santé physique et mentale, locomotion, composition corporelle, fonctionnalité, activités de la

vie quotidienne, activités de loisir et peurs. Le pré-test du questionnaire indique que le SarQoL® se complète facilement, en 10 minutes environ, de manière indépendante.

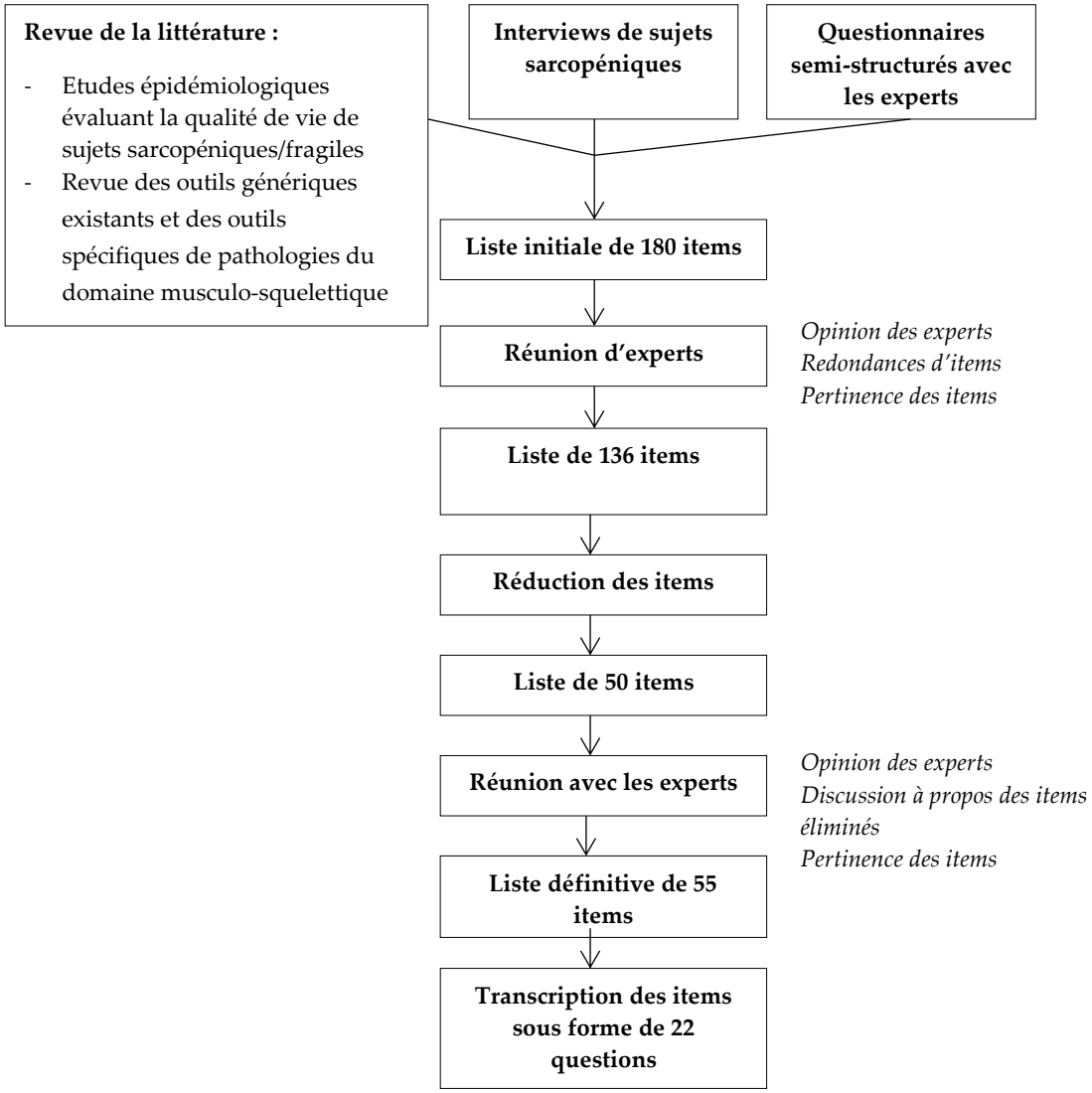


Figure 9. Développement du questionnaire SarQoL® (adaptée de Beaudart *et al*.[82])

Cette recherche a été publiée au sein du journal « Age and Ageing » (Facteur d'impact 4,20) (*Beaudart, C. et al. Development of a self-administrated quality of life questionnaire for sarcopenia in elderly subjects: the SarQoL®. Age Ageing. 2015 Nov;44(6):960-6).* La version intégrale de l'article est disponible en annexe 9.

La validation du questionnaire SarQoL® a ensuite été réalisée en analysant ses différentes propriétés psychométriques. Premièrement, la puissance discriminative du SarQoL®, ou la capacité du questionnaire à démontrer une différence de qualité de vie entre les sujets sarcopéniques et les non sarcopéniques, a été mesurée par une régression logistique. La cohérence interne, ou l'homogénéité des différentes dimensions du questionnaire, a été mesurée par l'α de Cronbach. Nous avons également mesuré la corrélation de chaque domaine du SarQoL® avec le score total du SarQoL®. La validité de construit a été mesurée par la validité divergente et convergente. Trois questionnaires supplémentaires ont été distribués aux participants, le SF-36[64], l'EQ-5D[65] et le Mobility T-test[84]. Des corrélations de Spearman ont été mesurées entre le SarQoL® et chacun de ces trois questionnaires afin de vérifier l'hypothèse selon laquelle le SarQoL® était corrélé fortement avec certains construits similaires à celui-ci et faiblement avec certains construits éloignés de celui-ci. La fiabilité test-retest après un intervalle de 2 semaines a été évaluée par un coefficient de corrélation intraclasse (ICC). Enfin, les effets de plancher et de plafond, soit le nombre de réponses minimales et maximales obtenues par la population répondant au SarQoL®, ont été mesurés.

Un total de 296 sujets d'un âge médian de 73,3 (P25 – P75 : 68,9 – 78,6) ans a été inclus dans la phase de validation du questionnaire. Parmi ces sujets, 43 ont été diagnostiqués sarcopéniques. Après ajustement sur l'âge et l'IMC, le score total (sur 100) du questionnaire SarQoL® pour les sujets sarcopéniques était significativement inférieur au score des sujets non sarcopéniques (54,7 (P25 – P75 : 45,9 – 66,3) pour les sarcopéniques versus 67,8 (P25 – P75 : 57,3 – 79,0) pour les non sarcopéniques, OR = 0,93 (IC 95 % 0,90 - 0,96)). Un coefficient α de Cronbach de 0,87 a été obtenu pour le questionnaire, indiquant une bonne cohérence interne. L'ensemble des domaines du SarQoL® sont positivement corrélés avec le score total du SarQoL® ($p < 0,001$ pour tous les domaines). Le questionnaire SarQoL® est également significativement corrélé, comme attendu, avec certains domaines des questionnaires SF-36 (fonction physique, vitalité et santé générale) et EQ-5D (score total de l'EQ-5D, question reliée aux activités courantes de la vie quotidienne) ainsi qu'avec le score total du Mobility T-test. De plus faibles corrélations ont été observées entre le SarQoL® et la question de l'EQ-5D reliée à la douleur et l'inconfort. Une bonne fiabilité test-retest a également été observée, avec un ICC de 0,91 (IC 95 % 0,82 – 0,95). Enfin, aucun effet de plancher ou de plafond n'a été identifié.

Le premier questionnaire de qualité de vie spécifique à la sarcopénie a ainsi été développé par l'URSAPES de l'Université de Liège, en collaboration avec le Service des Maladies Osseuses de l'Hôpital Universitaire de Genève. Le questionnaire SarQoL®, développé en français, est valide, cohérent et fiable et peut, de ce fait, être recommandé dans un cadre de recherche ou dans un cadre clinique. La sensibilité au changement du questionnaire SarQoL® doit toutefois encore être évaluée.

Cette recherche a été publiée au sein du journal « Journal of Cachexia, Sarcopenia and muscle » (Facteur d'impact 7,41) (*Beaudart, C. et al. Validation of SarQoL®, a specific health-related quality of life questionnaire for sarcopenia. Journal of Cachexia, Sarcopenia and Muscle (2016). Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/jcsm.12149).* La version intégrale de l'article est disponible en annexe 10.

4.2. Traduction et validation du SarQoL® en anglais[85]

Dans le but de rendre le SarQoL® plus accessible et d'augmenter ainsi son utilisation internationale, la traduction de ce questionnaire dans d'autres langues que le français a semblé nécessaire. L'objectif de la présente étude a donc consisté à traduire le SarQoL® en anglais et à valider les propriétés psychométriques de cette version anglaise.

La traduction du questionnaire a été réalisée selon 5 étapes. La première étape consistait à traduire le questionnaire du français vers l'anglais par deux traducteurs, indépendamment l'un de l'autre. Ces traducteurs étaient bilingues anglais et français et avaient pour langue maternelle l'anglais. Lors de la seconde étape, les deux traducteurs ont comparé leurs traductions et se sont mis d'accord pour produire une « version 1 » du questionnaire traduit. L'étape 3, ou étape de rétro-traduction, consistait à traduire cette version 1, cette fois-ci, de l'anglais vers le français, toujours par deux traducteurs, indépendamment l'un de l'autre. Ces deux rétro-traducteurs étaient également tous les deux bilingues et avaient pour langue maternelle le français. Lors de la quatrième étape, l'ensemble des traducteurs (les deux traducteurs initiaux ainsi que les deux rétro-traducteurs) se sont réunis avec un expert en méthodologie et un expert de la langue anglaise. Les rétro-traductions ont été discutées lors de cette réunion et l'ensemble des experts se sont accordés sur une « version 2 » du questionnaire. La dernière étape a consisté en un pré-test du questionnaire ainsi traduit afin d'arriver, après d'éventuelles adaptations, à la version anglaise « finale » du SarQoL®.

Le questionnaire SarQoL® a été traduit sans difficulté majeure. Un pré-test a été réalisé sur 10 sujets anglophones.

La validation de la version anglaise du SarQoL® a été réalisée sur des participants de la Hertfordshire Cohort Study, UK (Figure 10) lors d'un séjour de recherche réalisé à l'étranger au sein de la *MRC Epidemiology Unit* of Southampton, UK. La même méthodologie que celle utilisée pour la validation de la version originale du SarQoL® a été entreprise pour la validation du SarQoL® en anglais. Dans un premier temps, le questionnaire SarQoL® a été envoyé à l'ensemble de la population par courrier postal afin de mesurer la validité du questionnaire à discriminer les sujets sarcopéniques des non sarcopéniques mais aussi sa cohérence interne et ses potentiels effets de plancher et de plafond. Un second courrier a ensuite été envoyé afin de mesurer la validité de construit et la validité test-retest. Idéalement, ces deux dernières analyses de validité doivent être réalisées sur des sujets sarcopéniques. Toutefois, au sein de la Hertfordshire Cohort Study, seuls 14 sujets étaient diagnostiqués sarcopéniques selon la définition proposée par l'EWGSOP[9]. Un minimum de 50 sujets étant nécessaires pour ces analyses, selon les recommandations[86], nous avons décidé d'utiliser des valeurs

seuils différentes de celles classiquement proposées par l'EWGSOP[9] pour le diagnostic de la sarcopénie. Ces valeurs seuils modifiées nous ont permis d'identifier 93 sujets présentant non pas une sarcopénie mais une « faiblesse musculaire ».

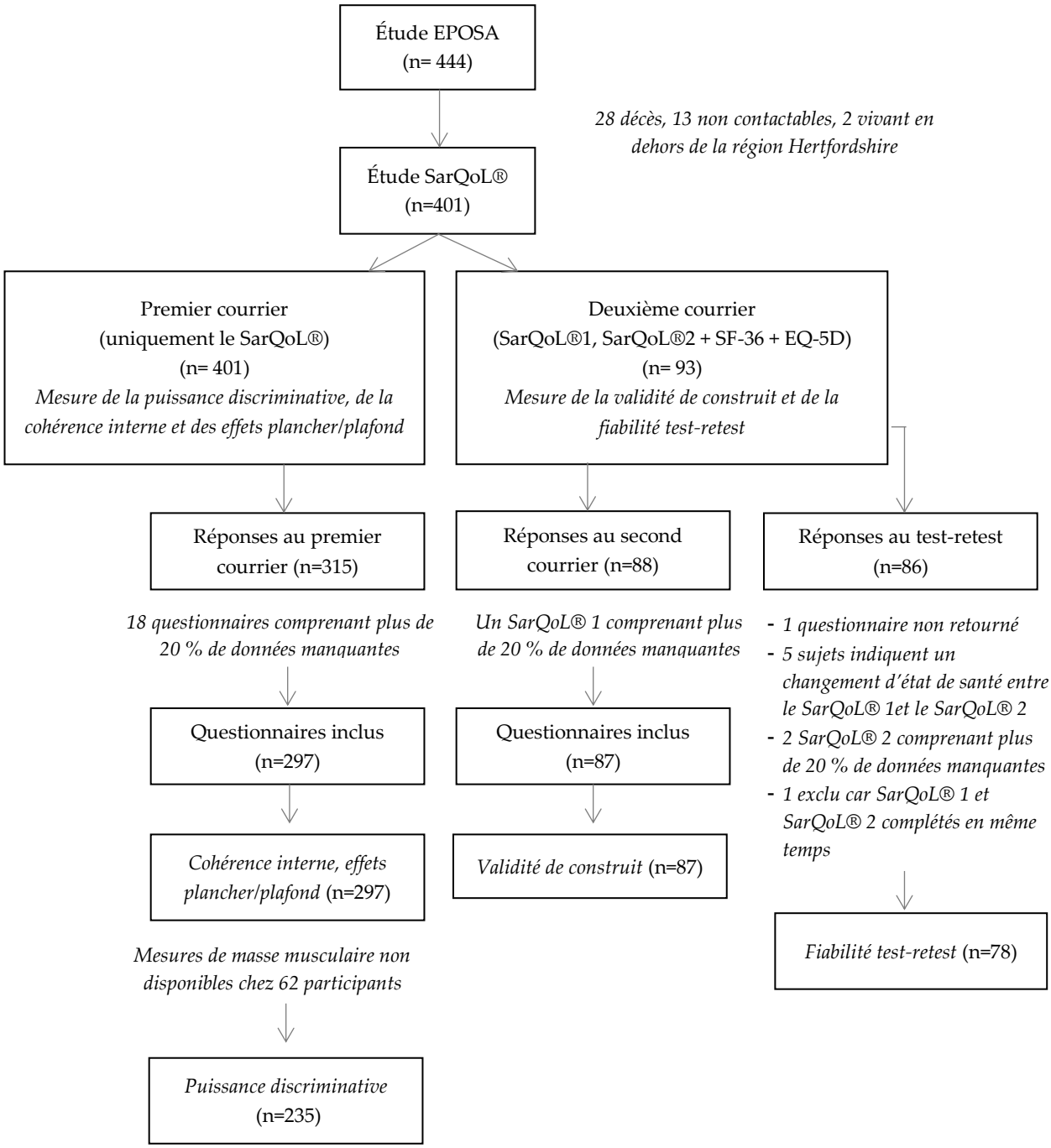


Figure 10. Validation de la version anglaise du SarQoL® au sein de la Hertfordshire Cohort Study (adaptée de Beaudart *et al*.[85])

Dans la première étape de la validation, le questionnaire a été envoyé aux 401 participants. Un total de 315 sujets a complété le questionnaire. Après exclusion des questionnaires présentant plus de 20,0 % de données manquantes, 297 questionnaires ont été utilisés. La population totale comprenait

ainsi 137 femmes et 160 hommes d'un âge moyen de 79,5 ± 2,62 ans. Les résultats ont indiqué une bonne validité discriminante de la version anglaise du SarQoL® (score de qualité de vie inférieur pour les sujets sarcopéniques, p = 0,01), une bonne cohérence interne (α de Cronbach de 0,88) et aucun effet plancher ou de plafond. Lors de la seconde étape, le questionnaire a été envoyé aux 93 participants présentant une faiblesse musculaire. Après exclusion des questionnaires présentant plus de 20,0 % de données manquantes, 87 questionnaires ont été inclus dans l'analyse. Les résultats indiquent une excellente fiabilité test-retest (ICC de 0,95, IC 95 % : 0,92 – 0,97) ainsi qu'une bonne validité de construit. La table 7 reprend les résultats des analyses de validation effectuées.

Table 7. Synthèse des résultats de validation de la version anglaise du SarQoL®

Puissance discriminative	→ Bonne puissance discriminative entre les sujets sarcopéniques et non sarcopéniques (61,9 ± 16,5 versus 71,3 ± 12,8, p = 0,01)
Validité de construit	→ Fortes corrélations trouvées avec les domaines reliés à la mobilité (EQ-5D), à la réalisation d'activités de la vie quotidienne (EQ-5D), à la vitalité (SF-36) et aux fonctionnalités physiques (SF-36). → Faibles corrélations trouvées avec les domaines reliés à l'anxiété (EQ-5D), la santé mentale (SF-36), les problèmes sociaux (SF-36) et les soins personnels (EQ-5D).
Cohérence interne	Alpha de Cronbach de 0,88 →Excellente cohérence interne
Fiabilité test-retest (intervalle de 2 semaines)	ICC de 0,95, IC 95 % 0,92 - 0,97 → Excellente fiabilité test-retest
Effets de plancher et de plafond	Aucun

Une version validée du questionnaire SarQoL® en anglais est désormais disponible et peut être utilisée pour évaluer l'effet de la sarcopénie sur la qualité de vie. Avant la réalisation de cette étude, le SarQoL® n'avait encore été validé que dans une seule et unique cohorte, la cohorte SarcoPhAge. La réalisation de cette étude permet ainsi une seconde validation. Les données psychométriques indiquent que la version anglaise du SarQoL® est valide, fiable et cohérente.

Cette recherche a été acceptée pour publication le 29 septembre 2016 au sein du journal « Age and Ageing » (Facteur d'impact 4,20). Les preuves de l'article sont disponibles en annexe 11.

DISCUSSION GÉNÉRALE

1. IMPACTS GÉNÉRAUX DE NOS RECHERCHES

La réalisation de cette thèse a permis de contribuer à l'étude de la sarcopénie principalement au niveau de sa définition, de son diagnostic et de l'étude de ses conséquences.

1.1. Contribution à la définition de la sarcopénie

Les recherches menées dans le domaine de la sarcopénie ont évolué de manière indéniable au cours de ces dernières années. Toutefois, il règne toujours un « flou » persistant autour du concept même de la sarcopénie. Ce flou pourrait partiellement s'expliquer par le fait qu'il n'existe toujours pas de définition opérationnelle de la sarcopénie mondialement acceptée. Plusieurs définitions opérationnelles[9–14] coexistent et le choix d'en utiliser une plutôt qu'une autre est généralement argumenté par les chercheurs/cliniciens/industriels. Ces différentes définitions ne se contredisent pas mais diffèrent bien souvent sur un ou plusieurs points ; un critère de diagnostic jugé non nécessaire par certaines définitions, jugé indispensable par d'autres ou encore des outils de mesure proposés différents, des valeurs seuils de diagnostic différentes, etc. Il a toutefois déjà été montré que l'utilisation de l'une ou l'autre définition influence la prévalence de la sarcopénie[50,52]. L'évolution souhaitée des recherches dans le domaine de la sarcopénie ne pourra pas s'effectuer si une standardisation n'est pas obtenue. Toutefois, la problématique de la définition de la sarcopénie la plus pertinente à utiliser reste un débat ouvert. En effet, à ce jour, aucune définition opérationnelle proposée n'a réellement réussi à se « dégager » des autres. Une des caractéristiques communes des différentes définitions proposées est leur caractère récent. De ce fait, très peu de données existent déjà sur la validité de ces définitions à prédire des évènements indésirables à court, moyen ou long terme. L'étude SarcoPhAge peut permettre, entre autres, de tenter de fournir une validation complémentaire à une de ces définitions, celle proposée par l'EWGSOP[9]. Nos résultats préliminaires indiquent en effet que les sujets sarcopéniques diagnostiqués selon les recommandations fournies par l'EWGSOP[9] auraient un risque de décès et d'hospitalisation à deux ans significativement supérieur aux sujets non sarcopéniques. La revue systématique réalisée dans le cadre de cette thèse et se focalisant uniquement sur les conséquences de la sarcopénie lorsque celle-ci est diagnostiquée selon l'algorithme proposé par l'EWGSOP[9] permet également de valider cette définition comme étant prédictive de décès[54,58,87–93] et de déclin fonctionnel[45,87,91,92,94]. Les effets observés sur les chutes[91,95] et l'incidence d'hospitalisation[87] restent toutefois actuellement insuffisants pour conclure à une association. A notre connaissance, hormis la revue systématique que nous avons réalisée, il n'existe pas d'autre synthèse de la littérature s'étant intéressée aux conséquences de la sarcopénie, diagnostiquée selon une autre définition. Or, une avancée non négligeable qui pourrait être opérée dans le domaine de la sarcopénie, serait d'identifier

si, parmi la kyrielle de définitions opérationnelles proposées, l'une de ces définitions serait davantage prédictive d'effets indésirables que les autres. Une étude prospective, très récemment publiée[96], a été réalisée dans ce sens puisqu'elle évaluait la capacité de 9 définitions opérationnelles de la sarcopénie à prédire l'incidence de chutes. Le risque de chute observé semble dépendant de la définition utilisée puisque, en fonction de celles-ci, un risque relatif (RR) variant entre 0,61 (IC 95 % 0,24 – 1,55), lorsque la définition utilisée est celle du FNIH[12] et 1,82 (IC 95 % 1,24 - 2,69), lorsque la définition utilisée est celle de l'EWGSOP[9], a été trouvé. Cela renforce la complexité à disposer de plusieurs définitions de la sarcopénie dans la littérature scientifique.

Dernièrement, on observe une remise en question du concept même de sarcopénie et, plus particulièrement, de l'utilité d'incorporer une mesure de masse musculaire dans son diagnostic. Or, à l'origine du terme, c'est la masse musculaire elle seule qui permettait le diagnostic de la sarcopénie[5]. Plusieurs études ont ainsi récemment mis en évidence une absence de relation statistiquement significative entre la masse musculaire et l'incidence d'effets cliniques indésirables[97–99]. Alors qu'une faible force musculaire ainsi qu'une performance physique affaiblie ont à plusieurs reprises été suggérées comme prédictives d'un déclin fonctionnel, de chutes ou encore d'incapacités physiques, la valeur prédictive d'une faible masse musculaire est plus difficilement démontrée[100–105]. Ceci a été supporté par une très récente étude suggérant que définir la sarcopénie uniquement sur base de la force musculaire serait plus prédictif de conséquences indésirables sur la santé, telles que les chutes et la détérioration de l'équilibre et de la mobilité, que les définitions actuellement proposées, incluant une mesure de masse musculaire[106]. Aujourd'hui, la relation entre masse musculaire, force musculaire et performance physique reste, en effet, toujours ambigüe. A l'inverse, d'autres études ont plutôt suggéré que la mesure de la vitesse de marche comme marqueur de performance physique aurait un intérêt limité dans le diagnostic de la sarcopénie[12,87]. Un diagnostic de la sarcopénie reposant sur une faible masse musculaire couplée à une faible force musculaire seulement serait en effet tout aussi prédictif du risque de déclin fonctionnel et de mortalité que le diagnostic complet, proposé par l'EWGSOP[9], intégrant également une mesure de performance physique. De plus, et ceci principalement dans des populations fragiles institutionnalisées ou hospitalisées, la mesure de performance physique, par l'intermédiaire de la mesure de la vitesse de marche ou par la réalisation du SPPB test, se démontre parfois difficilement applicable en raison des limitations fonctionnelles ou autres handicaps fonctionnels de certains patients. Cette réflexion a été intégrée par la « Foundation for the National Institutes of Health Sarcopenia Project" (FNIH)[12] qui propose maintenant une définition opérationnelle de la sarcopénie intégrant uniquement les concepts de masse et de force musculaire.

Une réflexion additionnelle amenée par cette thèse en ce qui concerne les difficultés gravitant autour de la définition de la sarcopénie est que les définitions actuellement proposées ne se personnalisent pas en fonction du « cadre de diagnostic ». En effet, en recherche ou en pratique clinique, les moyens logistiques et financiers sont différents, les populations sont différentes et les objectifs de diagnostic le sont aussi. Ainsi, le diagnostic de la sarcopénie devrait probablement être dépendant du cadre dans lequel il est appliqué. Il pourrait donc être opportun de disposer d'une définition « opérationnelle » consensuelle, à utiliser dans un cadre de recherche ou dans le cadre d'études cliniques menées dans le domaine de la sarcopénie mais également de disposer d'une définition « clinique » qui serait applicable dans le cadre d'une pratique clinique courante. Une initiative proche de cette idée a été menée par le Groupe de Travail Sarcopénie d'ESCEO, dont certains membres de l'URSAPES de l'Université de Liège font partie[27] (version intégrale de l'article disponible en annexe 4). Ce groupe d'experts propose ainsi, pour le cadre clinique, des techniques de dépistage visant à identifier des sujets étant à risque de sarcopénie en alternative à un diagnostic clinique complet impliquant une mesure de masse musculaire, de force musculaire et de performance physique, pouvant parfois être difficilement réalisable dans le cadre d'une consultation clinique de routine. La méthode du « Red Flag » est ainsi proposée ; méthode qui consiste en une liste de facteurs « d'alerte » que les cliniciens pourraient être susceptibles d'observer ou d'évaluer chez leurs patients. Si plusieurs facteurs d'alerte sont identifiés par le clinicien, un examen de diagnostic plus spécifique pourra par la suite être mené. Récemment, le questionnaire SARC-F[107] a également été développé dans l'objectif d'identifier facilement des sujets à risque de sarcopénie. Cette méthode, cette fois-ci recommandée par le groupe d'experts et non pas directement développée par celui-ci, consiste en un questionnaire simple de 5 questions investiguant les potentielles difficultés éprouvées par les patients dans les domaines de la force musculaire, de la marche, de la capacité à se relever d'une chaise sans assistance, de la montée d'escaliers et investiguant également le nombre de chutes présentées sur une année. Un score est alors attribué à chacun de ces domaines avec un score supérieur ou égal à 4 indiquant un risque accru de sarcopénie. Il est toutefois important de préciser que ce questionnaire semble démontrer une haute spécificité mais une faible sensibilité à l'égard du diagnostic de la sarcopénie[108]. Dans le même ordre d'idée, il pourrait s'avérer intéressant de développer un algorithme équivalent, par exemple, au FRAX®[109] dans le domaine de l'ostéoporose. Le FRAX® est un outil développé par l'OMS qui permet, à partir de données cliniques observées et de facteurs de risque individuels, d'évaluer le risque de fractures des patients. Ainsi, le développement d'un tel outil dans le domaine de la sarcopénie, reposant toujours sur des mesures cliniques (exemple : masse musculaire, fonction musculaire) combinées également à des facteurs de risque définis (exemple : âge, sexe, chute(s) et hospitalisation(s) antérieure(s), etc.), pourrait permettre d'identifier les patients à risque de sarcopénie. Des seuils

d'intervention thérapeutique pourraient ainsi être définis. Un processus thérapeutique serait, dès lors, limité aux patients présentant les risques d'évènements de santé les plus élevés.

1.2. Contribution au diagnostic de la sarcopénie

Lorsque des recherches sont menées dans le domaine de la sarcopénie, il est certes important de tenir compte de l'effet que peut avoir l'utilisation de l'une ou l'autre définition opérationnelle de la sarcopénie mais également de l'effet que peut avoir l'utilisation de l'un ou l'autre outil de mesure de masse musculaire, de force musculaire ou de performance physique ou de l'une ou l'autre valeur seuil de diagnostic. Une originalité importante de cette thèse est d'avoir pour la première fois mis en lumière cet aspect.

Au sein de la définition de l'EWGSOP[9] mais également dans la littérature scientifique en général[16], plusieurs outils sont proposés pour mesurer les trois composantes de la sarcopénie, c'est-à-dire la masse musculaire, la force musculaire et la performance physique. Nous avons pu montrer, à travers l'étude présentée dans la partie « SYNTHÈSE DES RÉSULTATS PRINCIPAUX – TROISIÈME PARTIE » de cette thèse, l'effet très important que pouvait avoir l'utilisation de l'un ou l'autre outil de diagnostic sur la mesure de la prévalence de la sarcopénie. Ainsi, une prévalence pouvant varier de 8,4 à 27,6 % est observée selon les outils de diagnostic utilisés. Certaines études[50,110] avaient déjà montré l'effet que pouvaient avoir certains critères de diagnostic ou certaines définitions de la sarcopénie sur la prévalence de cette dernière mais, à notre connaissance, notre étude est la première à présenter l'effet que peut entraîner l'utilisation d'outils de diagnostic différents, au sein de la même définition, sur la prévalence de la sarcopénie. On note également que, comme discuté dans le point précédent, ces différents outils ne sont toutefois pas toujours applicables à l'ensemble des cadres de diagnostic. On obtient vraisemblablement des mesures plus précises de la masse musculaire lorsque celle-ci est évaluée au moyen d'outils d'imagerie médicale (MRI, CT-scan, DXA) mais la réalisation de ces examens en pratique clinique courante n'est pas facile. Nous avons mené, au sein de l'URSAPES de l'Université de Liège, une enquête visant à définir les outils de diagnostic les plus largement utilisés en pratique clinique[17]. Les résultats de cette enquête, menée auprès de 255 cliniciens provenant de 55 pays à travers les 5 continents montrent que, parmi les cliniciens interrogés, 53,3 % mesurent la masse musculaire de leurs patients âgés de 65 ans ou plus en pratique courante, 54,5 % mesurent la force musculaire et 71,4 % mesurent la performance physique. Les outils les plus couramment utilisés pour mesurer ces paramètres sont, respectivement, les données anthropométriques, telles que la circonférence du mollet (57,9 %) pour la mesure de la masse musculaire, le dynamomètre hydraulique (66,4 %) pour la mesure de la force musculaire et la vitesse de marche (63,3 %) pour la mesure de la

performance physique. Ce type d'enquête permet également de tenir compte de paramètres de faisabilité lors de la proposition d'une définition opérationnelle de la sarcopénie en pratique clinique.

En plus des différents outils disponibles pour les mesures des composantes de la sarcopénie, une difficulté supplémentaire est que, pour chaque outil, plusieurs valeurs seuils de diagnostic sont également proposées. Il est important de noter que ces valeurs seuils ont été établies à partir de différentes études individuelles. Pour la mesure de masse musculaire par DXA, par exemple, on retrouve deux valeurs seuils différentes proposées dans l'article de consensus de l'EWGSOP[9]. En effet, les experts ont identifié ces deux valeurs seuils dans la littérature sur base de deux études différentes : une réalisée sur une population de 883 hommes et femmes hispaniques pour laquelle la valeur seuil a été définie comme étant inférieure à deux déviations standard par rapport aux mesures d'un groupe jeune et sain de référence[5] ; l'autre réalisée sur une population de 2976 sujets âgés de 70 à 79 ans vivant aux Etats-Unis pour laquelle la valeur seuil a été définie comme inférieure au 20ème percentile de cette population de sujets âgés[23]. Ainsi, le groupe d'experts reporte l'existence de plusieurs valeurs seuils établies à partir de ces études mais n'incorpore pas le fait que l'utilisation de l'une ou l'autre valeur seuil pourrait avoir un impact sur le diagnostic de la sarcopénie. Il était a priori évident que le fait de proposer différentes valeurs seuils allait mener à une variation dans le diagnostic de la sarcopénie mais, jusqu'à la publication de nos résultats, aucune étude n'avait encore évalué cela de manière quantitative.

La validation d'outils de diagnostic et de valeurs seuils de diagnostic est un enjeu important, tant en recherche qu'en clinique. En effet, l'utilisation de critères inappropriés à la population cible peut mener à une sur- ou une sous-estimation de la prévalence de la sarcopénie, ce qui peut mener à des conséquences non négligeables en recherche mais également dans le cadre d'une pratique clinique. En effet, en identifiant une population sarcopénique différente selon l'utilisation de l'un ou l'autre critère, les caractéristiques des sujets atteints de sarcopénie et les associations observées entre la sarcopénie et certains paramètres de santé seront également vraisemblablement différents. Dans un cadre clinique, cela peut engendrer le risque d'entreprendre une prise en charge non nécessaire pour un patient faux positif et donc non sarcopénique ou, à l'inverse, de priver de prise en charge un patient faux négatif et qui serait donc pourtant sarcopénique. Ainsi, les chercheurs et les cliniciens, en plus de devoir effectuer un choix parmi la kyrielle de définitions opérationnelles proposées, doivent également poser un choix concernant les outils de diagnostic et les valeurs seuils proposées au sein de ces définitions, en sachant pertinemment bien que leurs choix influenceront leurs résultats.

Par conséquent, identifier les outils et les valeurs seuils les plus pertinents pour le diagnostic de la sarcopénie serait vraisemblablement un pas important mené dans ce domaine. Une technique pour y

arriver pourrait consister à identifier les outils et les valeurs seuils les plus prédictifs d'évènements indésirables. L'étude SarcoPhAge devrait nous permettre, à terme, d'obtenir de tels résultats. Ainsi une comparaison de chaque valeur seuil proposée et de chaque outil de mesure de masse musculaire, de force musculaire et de performance physique proposé sera réalisée quant à leur capacité à prédire des évènements indésirables tels que l'invalidité physique, l'hospitalisation, l'institutionnalisation, la chute, la fracture, la durée de séjour durant une hospitalisation, ou encore, le décès. Ces données ne seront probablement pas suffisantes pour établir une définition unique et claire mais elles pourraient pour le moins apporter des données scientifiques supplémentaires que les groupes d'experts, tentant d'établir une définition opérationnelle consensuelle universelle de la sarcopénie, pourraient utiliser.

1.3. Contribution à l'identification des conséquences de la sarcopénie

Comme susmentionné, un des projets de cette thèse consistait à réaliser une revue systématique et une méta-analyse permettant d'identifier les conséquences de la sarcopénie, lorsque celle-ci est diagnostiquée selon une définition bien précise, celle de l'EWGSOP[9]. Au-delà du fait d'apporter un poids supplémentaire à cette définition en l'indiquant comme étant prédictive de différents évènements indésirables, la prise de connaissance par les cliniciens des résultats de cette revue systématique pourrait également les sensibiliser à l'importance du diagnostic et à la prise en charge précoce de la sarcopénie en pratique courante. Dès le stade préliminaire de sarcopénie – autrement nommé par les experts de l'EWGSOP[9] « pré-sarcopénie » – et donc, dès l'observation d'une diminution de masse musculaire, des démarches préventives pourraient être entreprises afin d'éviter l'apparition d'une sarcopénie et d'évènements indésirables y étant associés. Dans une démarche autant de santé publique que socio-économique, il serait avantageux de réduire l'incidence de ces effets indésirables et donc, d'entreprendre des démarches préventives le plus précocement possible.

L'identification des conséquences de la sarcopénie, peut également s'avérer particulièrement utile dans le cadre d'études cliniques menées dans le domaine de la sarcopénie. En effet, lorsqu'une étude clinique est programmée dans le but de tester l'efficacité d'un programme thérapeutique ou d'un nouveau produit pharmaceutique ou non-pharmaceutique sur la sarcopénie, il est nécessaire de définir des « critères d'évaluation ». Bien souvent, les programmes thérapeutiques dans lesquels les produits seront principalement testés pour leur efficacité à améliorer la masse musculaire, la force musculaire et la performance physique des sujets, soit directement les composantes de la sarcopénie. Toutefois, il est probablement préférable de mener une étude clinique pour tester des traitements quant à leur efficacité à réduire les évènements indésirables de la sarcopénie. Ainsi, un traitement qui améliorerait non seulement la masse musculaire, la force musculaire et/ou la performance physique mais qui, de surcroit, démontrerait sa capacité à réduire les chutes, les fractures, le déclin fonctionnel,

le risque d'hospitalisation, les durées d'hospitalisation ou encore la mortalité, serait d'un intérêt majeur, et se justifierait tout particulièrement aux yeux de la santé publique et des agences réglementaires comme l'European Medicines Agency (EMA). Toujours dans ce cadre, les informations majeures fournies par notre méta-analyse sont les odds ratios permettant de définir l'ampleur de l'impact de la sarcopénie sur la mortalité et le déclin fonctionnel. Si des chercheurs ou industriels décident de mener une étude interventionnelle dans ce domaine, avec pour objectif de montrer un effet de leur thérapeutique sur l'un de ces évènements indésirables, cette mesure d'impact pourrait servir à mesurer la taille d'échantillon nécessaire à montrer un effet significatif de cette intervention si celui-ci existe. Il n'est pas toujours facile de disposer de ces données dans la littérature scientifique et la réalisation d'une méta-analyse démontre, dans ce cas, un intérêt tout particulier.

Une autre manière de démontrer l'intérêt d'une thérapeutique est de montrer qu'elle peut également améliorer la qualité de vie des patients. La qualité de vie, définie par l'OMS comme étant "*la perception qu'a un individu de sa place dans l'existence, dans le contexte de la culture et du système de valeurs dans lesquels il vit en relation avec ses objectifs, ses attentes, ses normes et ses inquiétudes* », est ainsi considérée comme une mesure subjective de l'effet d'une maladie ou d'un traitement sur les domaines physiques, psychologiques et sociaux ainsi que sur le bien-être d'un individu. La mesure de la qualité de vie est devenue de plus en plus importante en recherche et en pratique clinique au cours des trois dernières décennies. De plus en plus d'études randomisées contrôlées et d'études observationnelles intègrent en effet la qualité de vie comme critère d'évaluation secondaire. De plus, un nombre conséquent d'interventions sont maintenant réalisées avec pour principal objectif d'améliorer la qualité de vie des sujets. Sur base d'une récente enquête du Centre Fédéral d'Expertise (KCE), il semblerait effectivement que les citoyens belges portent leur préférence aux nouveaux traitements qui améliorent avant tout la qualité de vie[111]. Il apparaît donc essentiel, dans le cadre du développement de stratégies thérapeutiques et préventives ciblant la sarcopénie, de disposer d'un outil permettant d'évaluer l'effet et l'efficacité de ces stratégies sur la qualité de vie des sujets. C'est dans cet esprit que nous avons décidé de développer le questionnaire spécifique SarQoL®.

Cet outil a tout d'abord été développé en français au sein de la cohorte SarcoPhAge. Bien qu'il n'existe pas de guidelines strictes concernant le développement de questionnaires de qualité de vie, nous avons suivi des recommandations et des étapes préalablement utilisées par d'autres auteurs pour le développement d'outils spécifiques de qualité de vie[112–117]. Différents experts mais également différents sujets sarcopéniques ont été inclus directement dans l'ensemble des étapes du développement du SarQoL®. Les analyses de validation semblent indiquer de bonnes qualités psychométriques à ce questionnaire, dont l'utilisation peut dès lors être recommandée aussi bien en

recherche qu'en clinique. Toutefois, la sensibilité au changement du SarQoL® n'a pas encore été évaluée, ce qui peut actuellement limiter son utilisation dans le cadre d'essais thérapeutiques. En effet, on attend de ce type de questionnaire de pouvoir à la fois fournir une évaluation épidémiologique de la qualité de vie d'une population mais également d'être sensible au changement et ainsi, d'être répondant à un éventuel traitement. A ce jour, le questionnaire SarQoL® n'a pas encore été testé au sein d'une étude clinique pour cette qualité.

L'European Medicines Agency (EMA), qui coordonne et supervise le développement de nouveaux médicaments tant à usage humain que vétérinaire, recommande l'utilisation de Patient Reported Outcome Measures (PROMs) qui permet de mesurer l'effet d'un traitement directement détectable par le patient. Ces PROMs peuvent être mesurés, par exemple, par des questionnaires de qualité de vie. Le questionnaire SarQoL® pourrait ainsi à l'avenir, être utilisé par les industriels souhaitant développer un médicament dans le domaine de la sarcopénie. Lorsqu'une étude clinique est menée par une industrie européenne dans le but d'évaluer l'efficacité et la sécurité d'un nouveau médicament, celle-ci est amenée à suivre les recommandations en matière d'études cliniques dressées par cette agence réglementaire. Actuellement, il n'existe pas de guidelines dressés par l'EMA pour la sarcopénie. Cela peut en partie expliquer les raisons pour lesquelles peu d'études cliniques sont actuellement menées dans ce domaine. Récemment, le groupe de travail « sarcopenia » de l'ESCEO a suggéré des recommandations pour le développement d'études cliniques visant à tester des médicaments à visée préventive ou curative de la sarcopénie[118]. Par la réalisation d'une étude randomisée contrôlée, réalisée en double aveugle, le critère d'évaluation principal proposé par ce groupe de travail pourrait donc être l'amélioration de la survie, un bénéfice détectable par le patient (amélioration des capacités fonctionnelles ou de la qualité de vie) ou encore, une diminution du risque de développer une conséquence liée à la sarcopénie (par exemple, une incapacité fonctionnelle). Ce document, récemment publié, pourrait servir de motivation à l'EMA pour développer des recommandations officielles à suivre lorsqu'une entreprise pharmaceutique ou agro-alimentaire planifie une étude clinique dans ce domaine. La revue systématique couplée à une méta-analyse que nous avons réalisée dans le cadre de cette thèse pourrait éventuellement servir de base aux industriels pour définir les critères d'évaluations principaux et secondaires à prendre en considération dans leurs études cliniques. En fonction des critères d'évaluation choisis, ils pourraient donc établir un nombre minimal d'individus à inclure dans les études de phase III, en se basant sur les résultats de la méta-analyse que nous avons réalisée.

2. PERSPECTIVES DE RECHERCHE

La finalisation des différents projets de cette thèse ouvre les portes à la réalisation de nouveaux projets.

2.1. Perspectives de recherche sur l'étude SarcoPhAge

L'étude SarcoPhAge est un projet longitudinal ; les résultats reportés dans cette thèse ne concernent que les deux premières années de suivi de cette cohorte. Cette cohorte est toutefois initialement prévue pour être suivie durant 5 années. Grâce à ce suivi prospectif à plus long terme, différentes analyses majeures dans le domaine de la sarcopénie pourront être entreprises. Premièrement, nous avons pour objectif de mesurer la capacité des différentes définitions opérationnelles de la sarcopénie à prédire divers évènements indésirables. Nous avons effectué les mesures cliniques nécessaires pour pouvoir appliquer au sein de notre étude pas moins de 8 définitions opérationnelles de la sarcopénie[5,9–12,14,119,120], comprenant à la fois des définitions intégrant uniquement la notion d'une réduction de la masse musculaire[5,119,120], mais également des définitions intégrant en plus la notion de fonction musculaire diminuée[9–12,14]. Comme déjà abordé dans cette discussion, une étude récemment publiée[96] s'est déjà intéressée à la capacité de ces différentes définitions à prédire le risque de chute. Toutefois, la cohorte SarcoPhAge s'intéresse à un nombre important d'évènements indésirables. En plus de ceux identifiés par la réalisation de notre revue systématique (pour rappel, le déclin fonctionnel, la mortalité, les chutes, les fractures et l'hospitalisation), nous aurons également la possibilité de vérifier la capacité de ces différentes définitions à prédire des évènements tels que l'entrée en maison de repos, le déclin cognitif, l'incidence de troubles dépressifs, mais également à identifier l'évolution de la qualité de vie, de l'état nutritionnel, des paramètres biologiques, de la tension artérielle et des paramètres osseux. Ces données originales n'ont pas encore été reportées dans la littérature. Toujours dans cet esprit, nous aurons l'opportunité de tester la capacité de différentes valeurs seuils proposées au sein de la définition de l'EWGSOP[9], mais également proposées au sein d'autres définitions opérationnelles, à prédire ces mêmes évènements indésirables. En effet, nous pouvons observer une large disparité parmi les valeurs seuils de diagnostic proposées et nous avons pu voir dans nos recherches que cela avait une influence importante sur la mesure de la prévalence de la sarcopénie. Enfin, nous pourrons également identifier la capacité de certains outils à prédire l'ensemble de ces évènements indésirables. En effet, pour l'étude SarcoPhAge, la masse musculaire a systématiquement été mesurée à l'aide de deux outils différents (la DXA mais également la BIA), la force musculaire a également été mesurée par deux dynamomètres différents (un dynamomètre hydraulique et un dynamomètre pneumatique)

et, enfin, la performance physique a été mesurée à la fois par la vitesse de marche sur 4 mètres, mais également par la réalisation du Short Physical Performance Battery test.

Au sein de l'étude SarcoPhAge, nous avons également, en plus d'une mesure de force musculaire des membres supérieurs, réalisé une mesure de force musculaire des membres inférieurs. La force musculaire des membres inférieurs, et plus fréquemment la force des quadriceps, peut être mesurée par différents dynamomètres. La force *isométrique* pourra ainsi être mesurée via, par exemple, l'utilisation d'un dynamomètre portatif (exemple, le MicroFET 2, récemment validé par l'URSAPES de l'Université de Liège au sein d'une population de sujets âgés résidant en maison de repos[121]) et sera représentée par la résistance maximale exercée sur ce dynamomètre. Le dynamomètre *isocinétique*, quant à lui, autorise une mesure de force en conditions dynamiques (modes concentriques et excentriques par exemple). Il s'agit d'un mouvement à vitesse constante : l'opérateur choisit ainsi une vitesse de mouvement et non une charge. L'originalité du concept réside dans l'adaptation instantanée de la résistance à la force développée par le sujet testé. Ce type d'effort garantit une contraction musculaire maximale durant l'intégralité du mouvement et est, par conséquent, un reflet plus proche de la fonction musculaire exercée dans les gestes fonctionnels quotidiens. Toutefois, la mesure de la force isocinétique requiert l'utilisation d'appareils de mesures très sophistiqués et onéreux limitant parfois son utilisation en recherche et en pratique clinique. De plus, cette mesure est plus chronophage que la mesure de la force isométrique. Pour ces raisons, dans le cadre de l'étude SarcoPhAge, nous n'avons pu réaliser de mesure de force isocinétique. Néanmoins, la force isométrique des quadriceps a été mesurée par le dynamomètre MicroFet2. Certains auteurs suggèrent, pour alléger le diagnostic de la sarcopénie, qu'une simple mesure de force des quadriceps pourrait remplacer la mesure de force de préhension et de performance physique, cette première étant largement prédictive d'incapacités fonctionnelles et de limitations de la mobilité[106,122]. De plus, la force des quadriceps semble être reliée à la capacité de réaliser l'épreuve du lever de chaise[123], à l'équilibre[124] et à la vitesse de marche[125]. Bien que la mesure de la force de préhension présente un intérêt et qu'elle soit potentiellement complémentaire à la force des quadriceps, on peut cependant considérer que cette dernière mesure reste plus proche des conditions d'autonomie des sujets. Les données de force isométrique récoltées dans le cadre de l'étude SarcoPhAge pourront ainsi être exploitées dans le cadre de la définition de la sarcopénie mais également quant à leur capacité à prédire des évènements indésirables.

Dans le cadre de notre cohorte SarcoPhAge, nous avons également réalisé des prélèvements sanguins chez une importante partie des sujets. Trois prélèvements ont actuellement été réalisés : un lors de l'inclusion dans l'étude, un après 1 an de suivi et le dernier lors de la 2ème année de suivi. Ils sont

actuellement stockés à -80 degrés. Des prélèvements ont été obtenus pour tous les participants consentant à la réalisation d'une prise de sang et se présentant à l'évaluation à jeun. Dans la littérature, plusieurs marqueurs biologiques ont déjà été investigués pour leur association avec la sarcopénie. Les plus largement investigués sont les marqueurs inflammatoires. En effet, des taux élevés de marqueurs inflammatoires tels que l'Interleukine-6 (IL-6) ont été associés à des évènements indésirables liés à la sarcopénie, tels qu'un déclin fonctionnel, une limitation de la performance physique[126,127] ou encore un risque plus élevé d'hospitalisation ou de décès[128]. D'autres résultats suggèrent que le facteur de nécrose tumorale alpha (TNF-α), l'IL-6 ainsi que la protéine C réactive seraient négativement corrélés avec la masse musculaire, la force musculaire et la performance physique[129–131]. Une large étude longitudinale[132] confirme ces résultats en reportant une perte de force musculaire après 5 ans plus importante chez des sujets présentant des taux élevés de ces marqueurs inflammatoires. L'implication de plusieurs hormones dans la sarcopénie, telles que la déhydroépiandrostérone sulfate, la testostérone et l'insuline growth factor 1 a également été suggérée à travers plusieurs études épidémiologiques[66,133–136]. On note, par ailleurs, également une implication de l'hémoglobine, ou l'anémie serait associée à une plus faible force musculaire, performance physique et à des incapacités fonctionnelles[137,138] ; de l'albumine, pour laquelle des concentrations faibles seraient associées à un déclin plus important de la masse musculaire[139] ; et de la créatinine urinaire[140]. D'autres marqueurs prometteurs ont été récemment identifiés et pourraient représenter des paramètres particulièrement utiles dans le domaine de la sarcopénie car ils sembleraient corrélés de manière plus directe aux changements musculaires. Parmi ces marqueurs, on note le peptide N-terminal du procollagène de type 3 (P3NP), l'Irisine, l'Activine A (AA), ou encore la myostatine (MYO). Par ailleurs, l'équipe du Pr. Etienne Cavalier du Département de Chimie Médicale du CHU de Liège a récemment réalisé une étude visant à évaluer la validité de certains de ces marqueurs dits « prometteurs ». Ainsi, le profil de 6 marqueurs a été analysé afin d'évaluer leur coefficient de variation, leur stabilité dans le temps, leurs valeurs de référence et la clairance rénale. Alors que trois de ces marqueurs (ostéoglycine (OGN), protéine transmembranaire 19 (TMEM19) et Irisine) se sont montrés invalides lors des premières étapes de test (manque de sensibilité, coefficient de variation supérieur à 15 %), l'analyse de l'AA, MYO et P3NP révèle que seuls les marqueurs P3NP et AA sont influencés par la fonction rénale des patients et que les marqueurs AA et MYO sont stables à 6 mois alors que le P3NP ne se démontre stable que durant 1 mois. Peu de données valides sont actuellement disponibles dans la littérature concernant l'ensemble de ces marqueurs biochimiques. L'étude SarcoPhAge pourra donc contribuer aux recherches menées dans ce domaine en apportant des informations supplémentaires sur les potentielles relations observées entre ces différents marqueurs biochimiques et la sarcopénie.

2.2. Perspectives et recherches associées sur le questionnaire SarQoL®

Plusieurs perspectives de recherche concernant le questionnaire SarQoL® sont également envisagées.

Comme indiqué dans les résultats de cette thèse, le SarQoL® a été préalablement développé en français et validé dans une population de sujets sarcopéniques francophones. Les analyses de validation révèlent que le questionnaire est cohérent, valide, fiable, ne présente pas d'effets de plancher et de plafond et discrimine les sujets sarcopéniques des sujets non sarcopéniques. Toutefois, nous n'avons pas eu l'opportunité de tester la « sensibilité au changement » du questionnaire SarQoL®. En effet, les données de validation sont transversales. On note toutefois que le SarQoL® sera administré chaque année aux participants de l'étude SarcoPhAge dans le but d'obtenir des données prospectives et de pouvoir interpréter les résultats du SarQoL® face à la variation de l'état de sarcopénie au cours du temps, ou à la variation de masse musculaire, de force musculaire ou de performance physique. Dans le cadre de collaborations que nous avons développées au cours des quatre dernières années, le questionnaire SarQoL® est actuellement utilisé au sein d'une cohorte Suisse à Genève et d'une cohorte française à Toulouse dans l'objectif de fournir une validation supplémentaire à cet outil. En effet, actuellement la version française du SarQoL® n'a été validée que dans une population unique, celle de l'étude SarcoPhAge. Une validation supplémentaire permettrait de renforcer les données obtenues et de disposer de données de sensibilité face au changement supplémentaires.

Lors des présentations de nos résultats au sein de congrès internationaux, nous nous sommes rapidement rendu compte de la nécessité de développer une version anglophone du questionnaire dans le but de rendre celui-ci plus accessible. Dans le cadre d'un séjour effectué au sein de la *MRC Epidemiology Unit* of the University of Southampton, UK, nous avons donc procédé à la traduction et validation d'une version anglaise du questionnaire. Les résultats de l'analyse de validation, réalisée sur les participants de la Hertfordshire Cohort Study, UK, indiquent de toutes aussi bonnes qualités psychométriques par rapport à la version française. Bien que la population d'étude soit différente de celle de SarcoPhAge, le questionnaire semble toujours discriminant pour la sarcopénie, valide, fiable et cohérent. Ces données sont encourageantes pour la réalisation de prochaines traductions en langues étrangères. Depuis la publication relative au développement du questionnaire SarQoL®[82], l'URSAPES de l'Université de Liège a été contacté par pas moins de 12 équipes de recherche intéressées par la traduction du SarQoL® dans leur langue nationale. Ainsi, la traduction du SarQoL® a déjà été réalisée en Néerlandais, Italien, Grec, Roumain, Allemand, Espagnol, Hongrois et Polonais. D'autres

traductions, comme l'Ukrainien, le Portugais, le Tchèque et le Thaï sont également en cours. Ceci permet indéniablement d'augmenter l'utilisation internationale du SarQoL®.

Toujours dans le but d'augmenter la visibilité et l'utilisation de ce questionnaire, nous avons également développé un site Internet www.sarqol.org et une application Smartphone, lancée en juin 2016. Le site SarQoL®, lancé en août 2015, a déjà été visité plus de 5400 fois.

Le questionnaire SarQoL® est un questionnaire auto-administré comprenant 55 items traduits sous la forme de 22 questions. Ce questionnaire nécessite en moyenne 10 à 15 minutes de remplissage. Afin de faciliter son utilisation par, entre autres, des médecins généralistes ou spécialistes désireux de s'informer sur la qualité de vie de leurs patients, nous prévoyons de réaliser une version courte du SarQoL® (la *Short-Form SarQoL*®). Ce projet est inscrit dans le cadre d'une collaboration que nous avons développée avec le « Department of Health Services Research » de l'Université de Maastricht.

CONCLUSION

La sarcopénie est un concept en constante évolution, et ce, depuis la genèse du terme « sarcopenia » en 1989. Reconnue désormais comme une véritable maladie, la sarcopénie a très probablement encore de belles années de recherche scientifique devant elle. Une des premières étapes semblant essentielle à l'évolution de ce concept est d'aboutir à une définition universellement acceptée de la sarcopénie mais également à une standardisation de la mesure des concepts de la sarcopénie. L'évaluation épidémiologique de la sarcopénie pourrait indéniablement être facilitée par le développement d'une définition unique et de critères de diagnostics précis et adaptés non seulement au type de population mais également au cadre de diagnostic visé. Les recherches menées dans cette thèse ont le mérite d'apporter des éléments supplémentaires dont les experts peuvent s'enrichir pour développer cette définition clé universelle. Elles pourraient également inciter au développement d'études cliniques dans le domaine de la sarcopénie et à la mise en place de stratégies préventives ou thérapeutiques. En effet, au vu de la prévalence de la sarcopénie et des conséquences cliniques et socio-économiques qui y sont attribuées, la sarcopénie est indiquée, par certains auteurs, comme un véritable fléau pour la santé publique. Ainsi, toute tentative visant à réduire l'incidence de la sarcopénie et ses conséquences potentielles sur la santé et la qualité de vie des sujets en étant atteints devrait être largement encouragée.

LISTE DES ABRÉVIATIONS

AA	Activine A	**IC 95 %**	Intervalle de confiance à 95 %
ALM	Appendicular Lean Mass	**ICC**	Coefficient de Corrélation Intraclasse
AMED	Allied and Complementary Medicine	**IL-6**	Interleukine-6
BIA	Biolectrical Impedance Analysis	**IMC**	Indice de masse corporelle
BMI	Body Mass Index	**IRM**	Imagerie par résonance magnétique
CIM	Classification Internationale des maladies	**IWGS**	International Working Group on Sarcopenia
CT-scan	Tomographie par ordinateur	**KCE**	Centre Fédéral d'Expertise
DARE	Database of Abstracts of Reviews of Effects	**MM**	Masse musculaire
DH	Dynamomètre hydraulique	**MYO**	Myostatine
DP	Dynamomètre pneumatique	**NMAPS**	New Mexico Aging Process Study
DXA	Absorptiométrie biphotonique à rayons X	**NOS**	Newcastle-Ottawa Scale
EMA	European Medicines Agency	**OGN**	ostéoglycine
EQ-5D	EuroQol five dimensions questionnaire	**OMS**	Organisation mondiale de la santé
ESCEO	European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, Frailty and Sarcopenia	**OR**	Odds Ratio
ESPEN-SIG	European Society for Clinical Nutrition and Metabolism – Special Interest Group	**P3NP**	Pro-Collagène de type 3
EWGSOP	European Working Group on Sarcopenia in Older People	**PD**	Dynamomètre pneumatique
FDA	Food Drug Agency	**PROMs**	Patient Reported Outcome Measures
FM	Force musculaire	**SarcoPhAge**	Sarcopenia and Physical impairments with advancing Age
FNIH	Foundation for the National Institutes of Health	**SarQoL**	Sarcopenia & Quality of Life
FNRS	Fonds de la Recherche Scientifique	**SF-36**	Short-Form 36
HD	Dynanomètre hydraulique	**SMI**	Skeletal Muscle Index
HMB	Beta-hydroxy beta-methylbutyrate	**SPPB**	Short Physical Performance Battery

T0	Temps 0, inclusion	**UK**	United Kingdom
TMEM19	Protéine transmembranaire 19	**URSAPES**	Unité de Recherche en Santé publique, Epidémiologie et Economie de la Santé
TNF-α	Facteur de nécrose tumorale alpha	**VM**	Vitesse de marche
TUG	Timed up and Go	**WOMAC**	Western Ontario and McMaster Universities Osteoarthritis Index
UGS	Vitesse de marche		

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ANNEXES

TABLE DES ANNEXES

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COMMENTARY Open Access

Sarcopenia: burden and challenges for public health

Charlotte Beaudart[1,2*], René Rizzoli[3], Olivier Bruyère[1,2,5], Jean-Yves Reginster[1,4] and Emmanuel Biver[3]

Abstract

Sarcopenia, operationally defined as the loss of muscle mass and muscle function, is a major health condition associated with ageing, and contributes to many components of public health at both the patient and the societal levels. Currently, no consensual definition of sarcopenia exists and therefore it is still a challenge to establish the actual prevalence of sarcopenia or to establish the direct and indirect impacts of sarcopenia on public health. Anyway, this geriatric syndrome represents a huge potential public health issue because of its multiple clinical and societal consequences. Moreover, all these aspects have an impact on healthcare costs both for the patient and the society. Therefore, the implementation of effective and broadly applicable preventive and therapeutic interventions has become a medical and societal challenge for the growing number of older persons affected by sarcopenia and its disabling complications.

Keywords: Sarcopenia, Public health, Epidemiology, Consequences, Diagnosis

Background

Thanks to social, health and technological progress, the proportion of older people in the age pyramid is increasing all over the world. According to the World Health Organisation, in 2050 there should be at least 2 milliards of people aged 65 years or older, compared to 600 million today. The life expectancy is also increasing and is estimated around 80 years in industrial countries [1]. The aging process is responsible of many changes in body composition including a loss of skeletal muscle mass. From the age of 25, there is a progressive decrease in the size and number of muscle fibres resulting in a loss of about 30% of muscle mass at the age of 80 [2]. Beyond some defined threshold, this age-related loss of muscle mass is characterized as abnormal. To characterize this phenomenon, the term "sarcopenia" was firstly introduced by Irwin Rosenberg [3]. The definition of sarcopenia was then enriched with scientific and technological advances and gradually evolved to incorporate the notions of decreased muscle mass [4], then of decreased muscle function (low muscle strength or low physical performance) [5-11]. These definitions differ from each other in regards to muscle mass indicators (ratio of appendicular lean mass over height squared, ALM/ht^2, or over body mass index, ALM_{BMI}), the cutpoints for slow gait speed and whether or not they include a measure of weakness (Table 1). However, there is actually no universal consensus for an operational definition of sarcopenia, which is an important issue for public health.

A wide range of techniques can be used to measure the different components of sarcopenia [12]. Three techniques can be used for the measurement of appendicular lean mass: body imaging techniques, bio impedance analysis and anthropometry measures. In research, the two gold standards are the computed tomography (CT-scan) and the magnetic resonance imaging (MRI). However, because of the high costs and the limited access to this kind of equipment, the European Working Group on Sarcopenia in Older People (EWGSOP) [8] recommends in clinical practice, first the use of either dual energy X-ray absorptiometry (DXA) or, as a portable alternative to DXA, the bioelectrical impedance analysis (BIA). Despite their easy use in clinical practice, the anthropometric measures are not recommended for the diagnosis of sarcopenia because these measures are not validated in older people and are, therefore, vulnerable to error. Several techniques are also available for the measurement of

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Table 1 Proposed operational definitions of sarcopenia

Criteria		Muscle mass		Muscle function		
				Muscle strength		Physical performance
Baumgartner criteria [4]	Sarcopenia	ASM/ ht^2 > 2 SD below young healthy mean		x		x
European Society for Clinical Nutrition and Metabolism Special Interest Groups (ESPEN-SIG) [7]	Sarcopenia	Percentage of muscle mass ≥2 SD below mean in young adults of the same sex and ethnic background (individuals aged 18–39 years in the NHANES III cohort)		x		Gait speed: <0.8 m/s or Reduced performance in any functional test used for comprehensive geriatric assessment
European Working Group on Sarcopenia in Older People (EWGSOP) [8]	Sarcopenia	ALM/ht^2		Grip strength	OR	Gait speed: <0.8 m/s
		- Men: ≤7.23 kg/m^2		- Men: <30 kg		
	Severe sarcopenia	- Women: ≤5.67 kg/m^2		- Women: <20 kg	AND	
International Working Group on Sarcopenia (IWGS) [9]	Sarcopenia	ALM/ht^2		x		Gait speed: <1.0 m/s
		- Men: ≤7.23 kg/m^2				
		- Women: ≤5.67 kg/m^2				
Society of Sarcopenia, Cachexia and Wasting Disorders [10]	Sarcopenia with limited mobility	ALM/ht^2 > of 2 SD below the mean of healthy persons aged 20–30 years of the same ethnic group		x		Gait speed: ≤1.0 m/s or Walking distance < 400 m during a 6-min walk
Foundation of NIH Sarcopenia Project [11]	Weakness and low lean mass	ALM_{BMI}		Grip strength		x
		- Men: <0.789		- Men: <26 kg		
	Slowness with weakness and low lean mass	- Women: <0.512		- Women: <16 kg	AND	Gait speed: ≤0.8 m/s

ASM/ ht^2 = ratio of appendicular skeletal muscle mass over height squared; ALM/ht^2 = ratio of appendicular lean mass over height squared; ALM_{BMI} = ratio of appendicular lean mass over body mass index; SD standard deviation.

muscle strength. Three techniques could potentially be used for the diagnosis of sarcopenia: handgrip strength, knee flexion or knee extension strength and the measurement of peak expiratory flow. In clinical research, the handgrip strength is the most widespread method. Indeed, this method does not require any special equipment, has been documented as a good marker of physical performance among community-dwelling older people and is well correlated with leg strength [13,14]. Finally, the physical performance can be measured by the "short physical performance battery test (SPPB)", by the "usual gait speed" or by the "timed up and go test" or "stair climb power test". The EWGSOP [8] recommends the use of either the usual gait speed, measured on a 4-meter distance or the SPPB test [15] which is a composite measuring walk speed, balance and the ability to stand up 5 times from a chair. Different cut-offs have been developed by the EWGSOP for each variable and could be applied for the diagnosis of sarcopenia. Recently, the Foundation of NIH Sarcopenia Project proposed recommendations for cut-off points for weakness and low lean mass definitions aiming to provide an operational definition for sarcopenia. It was recommended to assess muscle strength by grip strength with cutpoints <26 kg in men and <16 kg in women, and low lean mass by appendicular lean mass adjusted to BMI, with respective cutpoints <0.789 kg/m^2 and <0.512 kg/m^2 [16].

Given the variability in the definitions of sarcopenia, it is still a challenge to establish the actual prevalence of sarcopenia according to age and gender and to assess the direct and indirect impacts of sarcopenia on public health. The aim of this review is to discuss, both broadly and specifically, the public health implication of sarcopenia and its association with objectives health-related outcomes such as falls, fractures, admission in nursing homes or mortality.

Discussion

Epidemiology of sarcopenia

Sarcopenia is very common in older people. Currently it is still a public health challenge to establish a prevalence of sarcopenia. Indeed, this estimated prevalence depends on the type of studied population. A large number of studies have assessed the prevalence of sarcopenia within a cohort of adult subjects and this estimated prevalence could range from 0.1% to 85.4% according to patients' characteristics [17-22]. Globally, a higher prevalence of sarcopenia is often observed in men, in elderly subjects, in subjects living in nursing home, in subjects having a low body mass index but also in subjects having a low educational level. The prevalence of sarcopenia seems also to differ according to ethnicity. Indeed, a higher prevalence of sarcopenia is observed in Asian people and a lower prevalence is observed in people with dark skin compared to Caucasian people. Recently, a systematic review [23] on the prevalence of sarcopenia has been published. It indicates that the prevalence of EWGSOP-defined sarcopenia is 1-29% for older adults living in community. The differences in prevalence seem attributable to the age of the population and the methods of assessment used but also to the cut-offs used for the diagnosis.

Prevalence of sarcopenia could also differ depending on the definitions used for the diagnosis of sarcopenia, as recently highlighted in the comparison of the FNIH criteria with the International Working Group and the European Working Group for Sarcopenia in Older Persons [11]. In 2013, Batsis et al. [24] compared eight definitions of sarcopenia and found a prevalence ranging from 4.4% to 94% across definitions. In 2013, Bijlsma et al. found that the prevalence of sarcopenia with different diagnostic criteria ranged from 0% to 20.8% in the lowest age category (below 60 years), from 0% to 31.2% in the middle (60 to 69 years) and from 0% to 45.2% in the highest (above 70 years) [25]. As expected, studies using muscle mass as single criterion of diagnosis revealed a higher prevalence of sarcopenia than studies based on the EWGSOP consensus algorithm. The choice of cut-off limits applied could also influence the prevalence of sarcopenia. This is confirmed in a study (performed in our Department, in press) showing that the prevalence of sarcopenia can vary from 9.25% to 18% depending on the cut-offs used. This same study also shows the importance of the diagnostic tool chosen for the measurement of muscle mass, muscle strength and physical performance. Depending on the tool used, the prevalence of sarcopenia can range from 8.4% to 27.6%.

Sarcopenia is also often related to multiple pathologies and comorbidities which can also compromise the measurement of its prevalence. Some authors are actually interested in sarcopenia in combination with another health issue, like osteoporosis, osteopenia, obesity, type II diabetes mellitus, breast cancer, etc. The prevalence of sarcopenia is systematically higher in subjects presenting another health condition than in healthy subjects. Sarcopenia could be, in this case, considered as one consequence of this health problem.

This confused state and the current impossibility of establishing a clear prevalence of sarcopenia makes comparisons between studies difficult and thus represents an important public health issue. Moreover, the various values for the prevalence of sarcopenia found across studies are probably associated with different characteristics of sarcopenic subjects which could compromise the implementation of pertinent therapeutic strategies in the field of sarcopenia.

Consequences of sarcopenia: Indirect impact on public health

Many consequences of sarcopenia are prognostic indicators of public health burden, such as the development of

physical disability, nursing home admission, depression, hospitalization, and even mortality [26]. In particular, sarcopenia is associated with poor physical performance, functional decline and physical disability [22,26]. Sarcopenia predicts loss of independence for daily life activities in elderly men and women [27,28], and also affects gait speed or regularity. Leg lean mass has been identified as an independent predictor of the level of mobility impairment assessed by the SPPB test [29]. Ability to walk is an obvious determinant of subsequent disability, mortality, and health care costs [30]. Sarcopenia is also associated with falls, a well known issue regarding the risk of fracture and disabilities (odds ratio for fall in the sarcopenia group relative to the normal group: 4.42 (95% CI 2.08-9.39) in men and 2.34 (95% CI 1.39-3.94) in women) [31].

Sarcopenia is also associated with many comorbidities which have a major impact on public health. As occurring concomitantly with age-related bone loss, sarcopenia coexists with osteoporosis and may increase fracture risk, potentially directly via crosstalk between muscle and bone tissues [32,33] and indirectly via increase of risk of falling [34,35]. Most of endocrine diseases (diabetes, hypogonadism, hypercortisolism…) as well as obesity, or chronic kidney disease [34], are associated with sarcopenia independently of age-related muscle loss, which may be an underlying mechanism by which chronic diseases cause physical disability [36].

In this context, sarcopenia is also associated with greater risk of hospitalization [37] and is highly prevalent among older adults admitted to acute care wards [38] or in nursing homes [39]. Sarcopenia is also a predictor of bad outcomes in patients who undergo major general or vascular surgery [40] or with serious illness, such as in transplantation or cancer outcome [41,42]. All these health-related consequences of sarcopenia are supposed to alter quality of life in these patients [43].

Importantly, several studies indicate that sarcopenia and indicators of alterations of muscle strength (such as grip strength, walking speed, chair rises, or standing balance) predict future mortality in middle-aged and older adults [21,44]. Sarcopenia is also associated with short- and long-term mortality in hospitalized patients [38], or in nursing home elderly residents [45].

Taken together, these data highlight how sarcopenia may impact various public health components, at the patient level with higher rate of disabilities, loss of independence, bad comorbidities outcome, institutionalization or mortality, but also at the societal level, contributing to major healthcare and dependence costs in disabled sarcopenic elderly (Figure 1). However, none of the proposed operational definitions of sarcopenia demonstrated its superiority to be predictive of these health-related "hard" outcomes, such as fractures, falls, admission in nursing homes, or mortality. Future researches are clearly needed in this field to clarify which operational definition of sarcopenia should be integrated in clinical practice to diagnose and target sarcopenia and its impact on public health.

Public health costs of sarcopenia

Disability is associated with an increased risk of hospitalization and nursing home placement, increased home healthcare and, obviously, health care expenditure. Given the effect of sarcopenia on disability, public health costs of sarcopenia are expected to be high. Currently, economic data on sarcopenia are very poor. Only one study has currently reported the healthcare costs of sarcopenia in the United States [46]. Those estimates have taken into consideration the direct costs of sarcopenia which raised, in 2000, to $18.5 billion, $10.8 billion in men and $7.7 billion in women. These costs are represented by hospitalization, nursing home admissions and home healthcare expenditure. In 2000, this amount represented about 1.5% of total health expenditure in the United States. It must be added that, in addition to disability, sarcopenia is associated with multiple comorbidities and may also have effect on osteoporosis [47], obesity [48] and type II diabetes mellitus [49]. Whith these comorbidities associated healthcare costs taken into account, the economic burden of sarcopenia may probably be even more important than reported in the study of Janssen [46]. This study is currently unique and, until now, no reliable economic assessment of sarcopenia has been performed in Europe.

Despite this lack of other economical assessment, several studies have however looked at the relationship between sarcopenia and different area of expenditure such as hospitalization or nursing home admission. In the United kingdom, one study has shown that, in comparison with patients without sarcopenia, those diagnosed with sarcopenia presented a mean length stay in hospital significantly higher (mean of 13.4 ± 8.8 days for sarcopenic subjects versus 9.4 ± 7 days for non-sarcopenic subjects; $p = 0.003$) [50]. The association between sarcopenia and hospitalization was examined in another study [37] showing a significant association between low muscle density (RR 1.5, 95% CI 1.2-1.7) and grip strength (RR 1.5, 95% CI 1.3-1.8) with hospitalization. Lean mass was however not associated with risk of hospitalization.

Although some studies have shown a higher risk of institutionalization among frail people [51-53], regarding sarcopenia specifically, no study has currently assessed the relationship between sarcopenia and nursing home admissions [54].

Sarcopenia is also associated with other healthcare costs area such as loss of productivity, reduced quality of live and loss of autonomy but also with psychological

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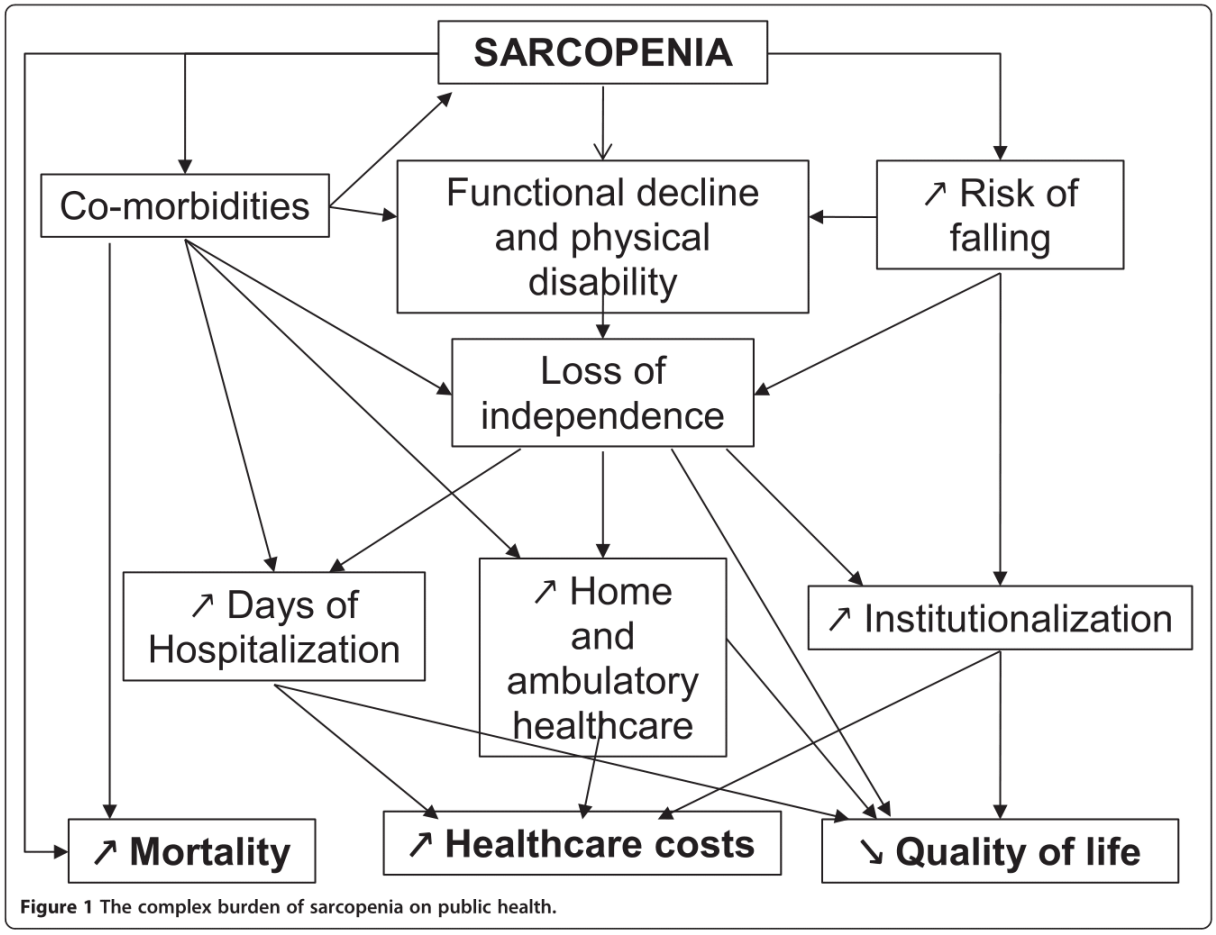

Figure 1 The complex burden of sarcopenia on public health.

problems. However, these indirect costs of sarcopenia have never been quantified, neither in the US, nor in Europe.

In their assessment of healthcare costs of sarcopenia in the United States, Janssen et al. [46] also examined the effect that reduced prevalence of sarcopenia would have on healthcare expenditure, through for example pharmacological treatment, public health campaigns, physical activity intervention,. They found that a 10% reduction in the prevalence of sarcopenia would result in saving $1.1 per year in the US. In a public health context, this potential economic saving is important. In comparison with osteoporotic fractures, for which the economic costs are similar [55] and for which numerous public health campaigns are organized aiming at reducing their occurrence, it is startling to note that, for sarcopenia, no public health campaigns are directly aimed at reducing the prevalence of this important geriatric syndrome. Because the number of older people is increasing all over the world, health policy decision-makers should consider some money investment in sarcopenia prevention and treatment to ensure important future savings.

Targeting sarcopenia: potential impact on public health

Obviously there is currently no consensual operational definition of sarcopenia. This age-related condition has numerous consequences in public health, illustrated with relevant hard clinical outcomes such as falls, fractures, hospitalisations, institutionalizations, mortality. These consequences directly induce high personal, social and health care systems costs, which will most certainly increase steadily with population ageing. The implementation of effective and broadly applicable preventive interventions has become a medical and societal challenge for the growing number of older persons affected by sarcopenia and its disabling complications. Identifying and targeting the determinants of sarcopenia is a necessary first step to limit its impact on public health (Figure 1). In addition to the identification of the determinants of skeletal muscle loss, research strategies will have to include a lifecourse approach focused on factors associated with peak muscle mass and strength, such as birth weight [56] and early nutrition [57]. Nutritional interventions may influence sarcopenia, in particular diets rich in proteins and antioxidant

nutrients, as well as vitamin D or omega-3 fatty acids supplements. Various exercise-related interventions (resistance exercise training, gait, balance, coordination and functional exercises) have been tested, targeting muscle strength, physical function, the risk of falls and balance in older people [58]. Potent pharmaceutical therapies have been proposed, such as hormone therapies (growth hormone, testosterone, selective androgen receptor modulator dehydroepiandrosterone, estrogen), angiotensin converting enzyme inhibitors, ghrelin agonists, but with up to now, little convincing effects or with presenting adverse side effects [58]. One of the most promising approaches may be the inhibition of myostatin, a regulator of muscle development and growth [59,60]. It is likely that combining lifestyle, nutritional, pharmacological and physical interventions is the most promising strategy. Clinical trials are currently conducted in this direction, such as the DoHealth study, which combines vitamin D, omega-3 fatty acids and physical exercise for the prevention of diseases at older age (ClinicalTrials.gov Identifier: NCT01745263). The cost-benefit ratio of these interventions will have to be assessed in health economic models based on health care utilization and incidence of chronic diseases. However, a gap persists regarding assessment of specific health conditions related to sarcopenia, as fracture has become the relevant outcome to evaluate interventions targeting osteoporosis. Validation of specific, objective and reproducible outcomes or tools is a necessary step before considering the development of interventions targeting sarcopenia and likely to be recognized both by the scientific and medical community and regulatory agencies.

Conclusion

Sarcopenia has become a major health condition associated with ageing, and contributes to many components of public health at both the patient and the societal levels. It interferes with the incidence and prognosis of many comorbidities, and obviously increases health care utilization. It is a determinant of loss of independence, leading to institutionalizations or prolonged hospitalizations. All these aspects increase healthcare costs for the society, and affect quality of life and mortality of sarcopenic patients. With the improvement of life expectancy and the consensual previsions of marked increase of the proportion of older people, it is urgent to consider the economic and societal burden of sarcopenia, and to implement interventions to prevent and treat sarcopenia in the ageing population.

Abbreviations

ALM: Appendicular lean mass; MRI: Magnetic resonance imaging; EWGSOP: European working group on sarcopenia in older people; DXA: Dual energy X-ray absorptiometry; BIA: Bioelectrical impedance analysis; SPPB: Short physical performance battery.

Competing interests

The authors declare that they have no competing interests.

Authors' contribution

OB, JYR and RR conceived the study. CB and EB drafted the manuscript and OB helped to draft the manuscript. All authors read and approved the final manuscript.

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Synthèse

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Qualité de vie du patient sarcopénique : apport de l'étude liégeoise SarcoPhAge

Quality of life of sarcopenic patients: contribution of the SarcoPhAge study

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Résumé. Les conséquences de la sarcopénie sur la qualité de vie sont difficiles à évaluer et, de ce fait, sont relativement mal étudiées. Les rares travaux évaluant la qualité de vie des sujets atteints de sarcopénie utilisent des questionnaires génériques tels que le SF-36 ou l'EQ-5D. En utilisant ces outils dans l'étude SarcoPhAge, une cohorte liégeoise comprenant 534 sujets de 65 ans et plus, il est suggéré que la qualité de vie est diminuée au niveau de la fonction physique chez les sujets sarcopéniques. Les questionnaires génériques ne permettent cependant pas de couvrir de manière exhaustive tous les domaines de dysfonctions potentiellement observés chez le sujet sarcopénique. Or, il n'existe actuellement pas de questionnaire de qualité de vie validé et spécifique de ce syndrome gériatrique. Il serait donc utile de disposer d'un tel outil spécifique à la sarcopénie qui permettrait d'évaluer prospectivement la qualité de vie de sujets sarcopéniques, mais également de rendre compte de l'efficacité et de la pertinence de nouvelles stratégies thérapeutiques et préventives développées dans ce domaine.

Mots clés : sarcopénie, qualité de vie, SarcoPhAge

Abstract. *The consequences of sarcopenia on quality are difficult to evaluate and consequently are quite poorly studied. The few studies assessing the quality of life in sarcopenic subjects currently use generic quality of life questionnaires such as SF-36 and EQ-5D. The SarcoPhAge study, conducted on a cohort developed in Liège including 534 subjects of 65 years or older, suggested that sarcopenic subjects present a significant worse quality of life in the domains of physical function compared to non-sarcopenic subjects. Generic tools do not cover exhaustively all the areas of potential dysfunction concerned in this geriatric syndrome. Yet, there is no specific and validated quality of life questionnaire for sarcopenia. It would be useful to have at our disposal a sarcopenia specific quality of life questionnaire to assess not only the prospective quality of life of sarcopenic subjects but also to assess the efficacy and the relevance of new therapeutic and preventive strategies developed in the field of sarcopenia.*

Key words: *sarcopenia, quality of life, SarcoPhAge*

État des lieux

Au niveau du muscle strié squelettique de l'être humain il existe, à partir de l'âge de 25 ans, une diminution progressive de la taille et du nombre de fibres musculaires entraînant une perte moyenne de masse musculaire d'environ 30 % à l'âge de 80 ans [1]. Toutefois, avec l'avancée en âge, certaines personnes présentent une perte de masse musculaire anormalement importante. Pour définir ce phénomène, le terme « sarcopénie » fut pour la première fois utilisé en 1989 par Rosenberg *et al.* [2]. Aujourd'hui, il n'existe toujours pas de définition universelle consensuelle de la sarcopénie. Toutefois, récemment, un groupe européen, l'*European working group on sarcopenia in older people* (EWGSOP), a défini la sarcopénie par une diminution de la masse musculaire appendiculaire associée soit à une diminution de la force musculaire, soit à une diminution de la performance physique [3]. Ce groupe a aussi développé un algorithme de diagnostic de ce syndrome gériatrique (*figure 1*). La sarcopénie sévère, quant à elle, est définie lorsque les trois critères sont rencontrés : présence d'une masse musculaire affaiblie, d'une force musculaire affaiblie et d'une performance physique affaiblie. La sarcopénie peut être associée à diverses pathologies concomitantes comme, par exemple l'ostéoporose, l'obésité mais également un certain nombre de maladies endocriniennes (diabète, hypogonadisme, hypercortisolisme, etc.) [4, 5].

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Aujourd'hui, la prévalence de la sarcopénie reste toujours difficile à établir. Elle varie en effet selon la définition utilisée pour diagnostiquer la sarcopénie, selon les caractéristiques de la population étudiée, selon les outils utilisés pour le diagnostic ou encore, selon les seuils utilisés pour le diagnostic [6-9].

Les conséquences de la sarcopénie en matière de santé publique sont nombreuses. En effet, celle-ci entraîne entre autres, des incapacités fonctionnelles menant à un plus grand risque de chutes et de fractures, une perte d'indépendance dans les activités de la vie quotidienne, une altération de la mobilité mais également un plus grand risque d'hospitalisation ou d'entrée en institution, ainsi que de la dépression [10]. Au vu des conséquences physiques et mentales associées à la sarcopénie, ses répercussions sur la qualité de vie semblent être implicites. Les données présentes dans la littérature actuellement sont toutefois relativement pauvres et hétérogènes [11]. Puisqu'il n'existe à ce jour pas de questionnaire de qualité de vie spécifique à la sarcopénie, les quelques études évaluant la qualité de vie chez des sujets atteints de cet état utilisent donc des questionnaires génériques tels que le Short-Form 36 (SF-36) ou encore l'EuroQoL 5-dimension (EQ-5D). Ces questionnaires qui, par définition, traitent de l'ensemble des domaines pouvant affecter la qualité de vie des personnes, de tout âge, pour toute pathologie ne semblent toutefois pas toujours adaptés pour des situations cliniques spécifiques telles que la sarcopénie. En 2012, Silva Netto *et al.* [12] ne notaient en effet pas de différence significative entre les sujets sarcopéniques et les sujets non-sarcopéniques au niveau de l'ensemble des domaines de qualité de vie du SF-36 (fonction physique, fonction sociale, limitations fonctionnelles, limitations émotionnelles, santé mentale, vitalité, douleur physique, santé générale). Ceci est confirmé par Yadav *et al.* [13] qui ont montré que, sur base du questionnaire SF-36, les sujets sarcopéniques (n = 47) présentaient un score moyen physique (PCS : *physical composite score*) de 30 et un score moyen mental (MCS : *mental composite score*) de 52 versus respectivement un score de 31 et un score de 48 pour les non-sarcopéniques (n = 165) (p = 0,88 et p = 0,20, respectivement). En revanche, Morishita *et al.* [14] ont observé en 2012, dans une étude portant sur 164 patients, une qualité de vie significativement diminuée chez les sujets sarcopéniques au niveau de la fonction physique (p = 0,022), de la douleur physique (p = 0,016) et de la vitalité (p = 0,012). Les autres domaines du SF-36 ne différaient par contre pas entre les sarcopéniques et les autres. Une autre étude a mesuré la qualité de vie des sujets sarcopéniques en utilisant le questionnaire EQ-5D [15]. Dans ce travail, les sujets sarcopéniques semblaient présenter plus de problèmes de mobilité (p < 0,001), plus de problèmes pour prendre soin d'eux-mêmes (p = 0,001), plus de problèmes pour réaliser les activités de la vie quotidienne (p < 0,001) et plus de problèmes de dépression ou d'anxiété (p = 0,001).

On note toutefois que ces études n'utilisent pas l'algorithme de diagnostic de la sarcopénie proposé par l'EWGSOP et largement utilisé depuis lors dans les études épidémiologiques. Ainsi, dans les études rapportées plus haut, la sarcopénie est généralement définie par une masse musculaire affaiblie, le paramètre de fonction musculaire (force musculaire ou performance physique) n'étant de ce fait pas considéré pour la définition de la sarcopénie. De plus, l'âge moyen de la population étudiée dans ces différentes études était inférieur à 65 ans. À ce jour, nous n'avons pas identifié d'étude mesurant la qualité de vie chez des sujets sarcopéniques de plus de 65 ans.

Données de l'étude SarcoPhAge

L'étude SarcoPhAge (*Sarcopenia and physical impairment with age*) est une cohorte liégeoise prospective

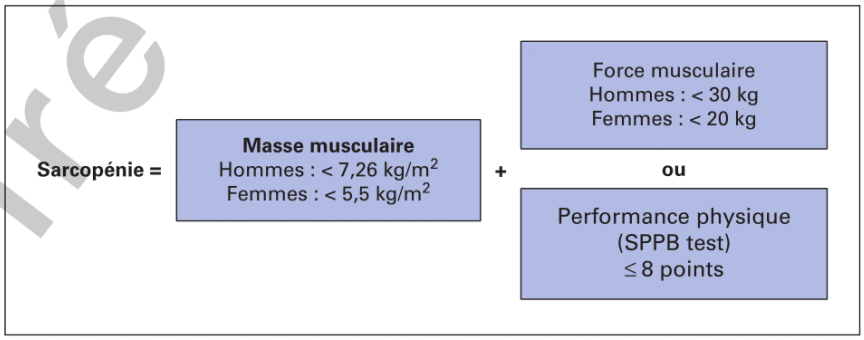

Figure 1. Algorithme de diagnostic de la sarcopénie (EWGSOP).
Figure 1. *EWGSOP-suggested algorithm for sarcopenia.*

Tableau 1. Qualité de vie dans la sarcopénie – données de l'étude SarcoPhAge.
Table 1. *Quality of life in sarcopenia - results of the SarcoPhAge study.*

	n	Tous (n = 534)	Sarcopéniques (n = 73)	Non-sarcopéniques (n = 461)	p-valeur*
SF-36					
SF-36 fonction physique (%)	526	63,4 ± 26,7	52,0 ± 29,2	65,2 ± 25,9	0,001
SF-36 fonction sociale (%)	526	69,3 ± 24,1	66,7 ± 27,9	69,8 ± 23,5	0,94
SF-36 limitations fonctionnelles (%)	526	55,2 ± 41,2	52,5 ± 42,7	55,8 ± 40,9	0,37
SF-36 limitations émotionnelles (%)	526	59,4 ± 41,5	58,2 ± 41,3	59,6 ± 41,5	0,32
SF-36 santé mentale (%)	526	60,7 ± 19,3	58,8 ± 20,1	61,0 ± 19,2	0,90
SF-36 vitalité (%)	526	50,7 ± 18,3	48,2 ± 18,1	51,1 ± 18,3	0,48
SF-36 douleur physique (%)	526	55,6 ± 25,5	52,3 ± 29,6	56,2 ± 24,8	0,23
SF-36 santé générale (%)	526	57,7 ± 18,3	53,6 ± 20,2	58,4 ± 18,0	0,64
EQ-5D	534	0,64 ± 0,24	0,61 ± 0,26	0,65 ± 0,24	0,58
EQ-VAS (%)	534	69,4 ± 17,4	67,7 ± 17,4	69,7 ± 17,4	0,20

*p-valeur ajustée sur l'âge, le sexe, l'indice de masse corporelle, le statut cognitif, le statut nutritionnel, le nombre de comorbidités, et le nombre de médicaments couramment consommés.
**p-value adjusted on age, sex, body mass index, cognitive status, nutritional status, number of comorbidities and number of current drugs.*

composée de sujets volontaires de 65 ans et plus [16]. Entre juin 2013 et juin 2014, 534 sujets d'un âge moyen de 73,5 ± 6,16 ans, ont été recrutés. Le diagnostic de la sarcopénie reposait sur la définition de l'*European working group on sarcopenia in older people* [3]. La masse musculaire a été mesurée par absorptiométrie biphotonique à double énergie (DXA), la force de préhension a été mesurée par un dynamomètre hydraulique et la performance physique a été mesurée par le test du *Short physical performance battery*. Outre un diagnostic de la sarcopénie, différentes variables ont été recueillies : indice de masse corporelle, données anthropométriques, comorbidités, médicaments, consommation d'alcool ou de tabac, degré de dépendance (échelle de Katz [17] et de Lawton [18]), état nutritionnel (*Mini nutritional assessment* [19]), état cognitif (*Mini mental state examination* [20]), dépression (*Geriatric depression scale* [21]), risque de chute (Tinetti [22] et *Timed up and go* [23]), état de fatigue (*Mobility-tiredness scale* [24]), vitesse de marche sur 4,5 mètres, vitesse maximale du souffle (débitmètre de pointe) mais également, la qualité de vie. La qualité de vie des patients a été évaluée par le questionnaire SF-36 [25] mais également par le questionnaire EQ-5D [26] et EQ-VAS [26, 27].

Parmi les 534 sujets recrutés, 73 ont été diagnostiqués sarcopéniques, ce qui représentait une prévalence de 13,7 %. Chez les hommes, la prévalence s'élevait à 11,8 % et chez les femmes, celle-ci s'élevait à 14,9 %. Sur base du questionnaire SF-36, les sujets sarcopéniques présentaient une qualité de vie au niveau du domaine de la fonction physique significativement plus faible que les sujets non-sarcopéniques (52,0 ± 29,2 % pour les sujets sarcopéniques, versus 65,2 ± 25,9 % pour les non-sarcopéniques, p = 0,001 après ajustement sur l'âge, le sexe, l'indice de masse corporelle, le statut cognitif, le statut nutritionnel, le nombre de comorbidités et le nombre de médicaments couramment consommés). Aucune autre différence significative n'était observée entre les deux groupes pour le domaine de la fonction sociale, des limitations dues à des problèmes physiques, des limitations dues à des problèmes émotionnels, de la santé mentale, de la vitalité, de la douleur physique ou encore, de la santé générale. Un score moyen au questionnaire EQ-5D de 0,61 ± 0,26 était observé chez les sujets sarcopéniques, versus 0,65 ± 0,24 chez les non-sarcopéniques. La différence n'était cependant pas significative (p = 0,58). De plus, sur base de l'échelle EQ-VAS, qui consiste en une auto-évaluation de la qualité de vie générale sur une échelle graduée de 0 à 100, les sujets sarcopéniques ne semblaient pas présenter une qualité de vie significativement plus faible que les sujets non-sarcopéniques (67,7 ± 17,4 % sur l'échelle VAS pour les sarcopéniques versus 69,7 ± 17,4 % pour les non-sarcopéniques, p = 0,20) (*tableau 1*).

La sarcopénie sévère, c'est-à-dire la présence à la fois d'une masse musculaire, d'une force musculaire et d'une performance physique affaiblies, a été diagnostiquée chez 32 sujets, ce qui représente une prévalence de 5,99 %. En comparaison aux non-sarcopéniques, toujours après ajustement sur les variables potentiellement confondantes (âge, sexe, indice de masse corporelle, statut cognitif, statut nutritionnel, nombre de comorbidités et nombre de médicaments couramment consommés), les sarcopéniques sévères démontrent une qualité de vie significativement diminuée pour 3 des 8 domaines du SF-36 : fonction physique (p < 0,001), fonction sociale (p = 0,023) et santé générale (p = 0,026). Aucune différence n'était toutefois observée pour les résultats du questionnaire EQ-5D et de l'échelle EQ-VAS.

En comparaison aux études déjà publiées, l'étude SarcoPhAge confirme que seuls certains domaines spécifiques de qualité de vie semblent être affectés dans la sarcopénie.

Questionnaire spécifique de qualité de vie

Les conséquences de la sarcopénie sur la qualité de vie sont difficiles à évaluer et, de ce fait, sont relativement mal étudiées. Depuis quelques années, le concept de qualité de vie est de plus en plus intégré comme une mesure de résultat, tant par les industriels que par les chercheurs. Sur base d'une récente enquête du KCE, il semblerait que les citoyens portent préférence aux nouveaux traitements qui améliorent avant tout la qualité de vie [28]. Il apparaît donc essentiel, dans le cadre de développement de stratégies thérapeutiques et préventives ciblant la sarcopénie, de disposer d'un outil permettant d'évaluer l'impact et l'efficacité de ces interventions sur la qualité de vie des sujets, ce qui n'est malheureusement pas le cas actuellement.

En effet, récemment, un groupe de travail de la *European society for clinical and economical aspects of osteoporosis, osteoarthritis and musculoskeletal disorders* (ESCEO) visant à évaluer la qualité de vie dans le domaine de la fragilité et de la sarcopénie [11], a attiré l'attention sur les limites de l'utilisation de questionnaires de qualité de vie dits « génériques » pour évaluer la qualité de vie des sujets sarcopéniques. Les questionnaires génériques, par définition, traitent de l'ensemble des domaines pouvant affecter la qualité de vie des personnes, de tout âge, pour toute pathologie [29]. La proportion de questions spécifiques à la sarcopénie est donc restreinte dans ce type de questionnaire. Ainsi, une thérapeutique axée dans le domaine de la sarcopénie n'entraînera une amélioration de l'état de santé que pour ces quelques questions concernées par ce syndrome et le score total de qualité de vie du questionnaire ne sera pas sensiblement modifié. Or, dans un questionnaire spécifiquement développé pour la sarcopénie, toutes les réponses aux questions sont susceptibles de varier suite à une intervention thérapeutique. Le score total de qualité de vie sera donc, par conséquent, autrement modifié. L'article du groupe d'experts ESCEO [11] vise donc à mettre en évidence l'absence, mais également le besoin d'avoir à disposition un questionnaire de qualité de vie spécifique à la sarcopénie. La recherche s'intéressant de plus en plus à ce syndrome gériatrique, il semble maintenant nécessaire de disposer de tels outils pour pouvoir évaluer l'efficacité des interventions visant à améliorer non seulement l'état de santé de sujets atteints de sarcopénie, mais également leur qualité de vie.

Points clés

- Les conséquences de la sarcopénie sur la qualité de vie sont difficiles à évaluer et, de ce fait, sont relativement mal étudiées.
- Dans l'étude SarcoPhAge, les sujets sarcopéniques présentent une qualité de vie au niveau du domaine de la fonction physique significativement plus faible que les sujets non-sarcopéniques.
- Les données actuelles sont évaluées au moyen de questionnaires de qualité de vie générique. Il n'existe en effet pas de questionnaire de qualité de vie validé et spécifique de ce syndrome gériatrique.
- Le développement d'un questionnaire spécifique pourrait permettre à la fois d'évaluer transversalement et prospectivement la qualité de vie de sujets atteints de sarcopénie, mais également de rendre compte de l'efficacité et de la pertinence de nouvelles stratégies thérapeutiques et préventives développées dans le domaine de la sarcopénie.

C'est dans cet esprit que le Département des sciences de la Santé publique de l'Université de Liège travaille au développement d'un questionnaire de qualité de vie spécifique à la sarcopénie. Pour développer une première version du questionnaire, quatre étapes successives ont été suivies. La première étape consistait à générer des items sur base d'une revue systématique de la littérature, d'entretiens semi-directifs avec des sujets sarcopéniques et d'un questionnaire semi-directif destinés à des experts dans le domaine de la sarcopénie ; la seconde étape consistait à diminuer cette liste d'items afin d'en conserver les plus pertinents ; la troisième étape consistait à développer les questions à partir de la liste définitive d'items ; enfin, la quatrième étape consistait en un pré-test du questionnaire ainsi développé auprès de sujets atteints de sarcopénie afin d'en vérifier la lisibilité et la compréhension. La première version de ce questionnaire auto-administré, le questionnaire SarQoL (*Sarcopenia and quality of life*) comporte 55 items transcrits sous forme de 22 questions [30]. La vérification des propriétés psychométrique du SarQoL (fidélité test-retest, cohérence interne, validité convergente, validité divergente, effets de plancher et de plafond) est actuellement en cours de réalisation.

Conclusion

Avec ce questionnaire, nous espérons ainsi pouvoir renforcer les connaissances de la sarcopénie en matière de qualité de vie. Le questionnaire SarQoL pourra

ainsi permettre à la fois d'évaluer transversalement et prospectivement la qualité de vie de sujets atteints de sarcopénie, mais également de rendre compte de l'efficacité et de la pertinence de nouvelles stratégies thérapeutiques et préventives développées dans le domaine de la sarcopénie.

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ORIGINAL ARTICLE

Endocrine Research

The effects of vitamin D on skeletal muscle strength, muscle mass and muscle power: a systematic review and meta-analysis of randomized controlled trials

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Context There is growing evidence that vitamin D plays a role on several tissues including skeletal muscle.

Objective To summarize with a meta-analyse the effects of vitamin D supplementation on muscle function.

Data sources A systematic research of randomized controlled trials, performed between 1966 and January 2014 has been conducted on Medline, Cochrane Database of Systematics Reviews, Cochrane Central Register of Controlled and completed by a manual review of the literature and congressional abstracts.

Study selection All forms and doses of vitamin D supplementation, with or without calcium supplementation, compared with placebo or control were included. Out of the 225 potentially relevant articles, 30 randomized controlled trials involving 5615 individuals (mean age: 61.1 years) met the inclusion criteria.

Data extraction Data were extracted by two independent reviewers.

Data synthesis Results revealed a small but significant positive effect of vitamin D supplementation on global muscle strength with a standardized mean difference (SMD) of 0.17 ($p=0.02$). No significant effect was found on muscle mass (SMD 0.058; $p=0.52$) or muscle power (SMD 0.057; $p=0.657$). Results on muscle strength were significantly more important with people who presented a 25-hydroxyvitamin D level <30 nmol/L. Supplementation seems also more effective on people aged 65 years or older compared to younger subjects (SMD 0.25; 95% CI 0.01 to 0.48 versus SMD 0.03; 95% CI -0.08 to 0.14).

Conclusions Vitamin D supplementation has a small positive impact on muscle strength but additional studies are needed to define optimal treatment modalities, including dose, mode of administration and duration.

Vitamin D, or calciferol, is a liposoluble prohormone available in two forms: vitamin D_2 and vitamin D_3. Many studies suggest that vitamin D is essential for bone health because of its role in the regulation of calcium and phosphate homeostasis (1). Currently, there is growing evidence that low serum concentration of 25-hydroxyvi-

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Abbreviations:

tamin D (25[OH]D) is also associated with many non-skeletal disorders such as cardiovascular diseases, inflammation, infectious diseases, etc., (2). Moreover, vitamin D seems to play also a role on several tissues including skeletal muscle (3). Indeed, a recent review (4) developed four lines of evidence to support the role of vitamin D in muscle health. First, muscle manifestations such as proximal muscle weakness, diffuse muscle pain and gait impairments are defined to be well-known clinical symptoms of vitamin D deficiency (5–10). Second, a vitamin D receptor has been localized on muscle tissue (11). Third, several observational studies suggest a positive relationship between serum level of vitamin D and muscle function. Fourth, regarding the findings listed above, many researchers decided to investigate the effects of vitamin D supplementation on muscle function but results remains controversial. Consequently two different meta-analyses that computed results of studies assessing the effects of vitamin D supplementation on muscle strength have been conducted in 2011. The first one (12), based on only three studies and focused only on people aged 65 and older, suggests that vitamin D supplementation could improve muscle strength. The second one (13), based on 12 studies and conducted on elderly subjects with baseline 25[OH]D concentration greater than 25 nmol/L, suggests no association between vitamin D supplementation and muscle strength. Because of the opposite results of these two meta-analyses, which focused only on specific groups of population and included a relatively restricted number of studies, it is difficult to conclude whether vitamin D supplementation has an effect on muscle strength for the global population. Moreover, muscle functions are not limited to muscle strength but comprises also muscle mass and muscle power and to date, no systematic review or comprehensive meta-analysis has addressed the role of supplementation of vitamin D on muscle mass and muscle power.

Vitamin D could be a simple and widely applicable public health intervention, especially in the field of musculoskeletal diseases. In view of the promising but inconclusive early results, a systematic meta-analysis that would summarize the results of randomized controlled trials assessing the effect of vitamin D supplementation on muscle function could be of a great public health interest. The main objective of this meta-analysis is therefore to compute results of randomized controlled studies performed on global population to assess the effect of vitamin D supplementation on muscle function, including muscle strength, muscle mass and muscle power.

Materials and Methods

Search strategy

In concordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (14), we conducted a detailed literature search in English to identify all studies performed between 1966 and January 2014 assessing the effects of vitamin D supplementation on the muscle function. The following electronic databases were searched: Medline, Cochrane Database of Systematics Reviews and Cochrane Central Register of Controlled Trials. The search strategy and MeSH search terms used are detailed in Appendix 1. Additional studies were identified by a manual search of bibliographic references of extracted articles and existing reviews, by contacting experts in the field and by a manual search in the gray literature including abstracts presented from 2011 to 2013 in major meetings of nutrition, geriatrics and bone research.

Study selection

Two authors (CB and FB) made independently an initial screening of the titles and abstracts. They subsequently examined the full texts of the articles remaining after the initial screening stage to determine whether the studies met the inclusion criteria. All differences of opinion regarding selection of articles were resolved through discussion and consensus. In both rounds of

Table 1. Inclusion criteria

	Inclusion criteria
Design	Randomized controlled studies
Langage	English
Participants	Humans, no age restriction
Intervention	Supplementation of vitaminD (all doses and all forms), no length of follow-up restriction
Comparator	Placebo or another standard treatment. The control group must be comparable to the treated group with the exception of vitamin D supplementation
Mesures	measure of muscle strength, muscle mass or muscle power before and after intervention for both groups
Date	From 1966 to January 2014

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title/abstract and full text review, studies were included according to some specific inclusion criteria (Table 1).

Studies were excluded if they were reviews, trials that were not randomized, duplicated studies, animal studies, studies that did not use a placebo or a control group or used vitamin D as part of a complex nutritional supplementation regimen.

Methodological quality assessment

We used the system developed by Jadad (15) to evaluate methodological quality. Two authors (CB and FB) independently assessed the quality of trials. The Jadad score can range from zero to five. Studies were considered of excellent quality if their Jadad score reached five, of good quality if their score was three or four and of poor quality if their score was one or two.

Data extraction

Articles selected for full review had the following data extracted : authors, date of publication, country where the study was realized, sample size, number and percentage of female included, mean age, age range and type of population, before and after serum concentration of 25[OH]D, percentage of the subjects that completed the study, length of intervention, details of the interventions for the control and treated groups, type of vitamin D supplementation, mode of administration, treatment adherence, physical measure, measurement techniques and results.

Muscle strength was defined as the amount of force a muscle can produce and was measured by grip strength, quadriceps muscle strength and leg extension strength. Muscle mass was defined as the total of body lean mass measured by Dual Energy X-Ray Absorptiometry. Finally, muscle power was defined as the maximum force that a muscle or muscle group can generate in a minimum amount of time and was measured by leg peak power.

We paid particular attention to missing data. In order to include a maximum of studies in our meta-analysis, we systematically contacted authors or coauthors when information was missing in the full-text paper.

When the same study reported multi measures of muscle strength, we deliberately chose to report, in the meta-analysis, only one of these results. We reported, in priority, the result of grip strength if available, followed by the result of quadriceps strength and, finally the result of the leg extension strength. Moreover, when one study managed three different groups to assess the difference between a placebo and two doses of vitamin D, we inserted arbitrary in the meta-analysis the results of the group supplemented with the higher dose of vitamin D.

Grading of Recommendations Assessment Development and Evaluation (GRADE) was used to assess the quality of the evidence. The strength of the evidence for each outcome measurement was classed into one of four categories: high, moderate, low and very low (16).

Statistical analysis

To provide a comparison between outcomes reported by the different studies, effect size as standardized mean difference with 95% CIs was assessed for each outcome.

Regarding the supplementation protocols heterogeneity, since participant demographics and clinical settings differed greatly between studies, we assumed the presence of heterogeneity a priori, and we used random effects models (17). Results were examined for heterogeneity using Cochran's Q statistic and the I^2 statistic was used to quantify total variation across studies attributed to heterogeneity rather than sampling error (18).

Five meta-regressions were performed on baseline 25[OH]D levels, 25[OH]D levels changes during study, age, length of study and vitamin D dose to assess the effects of these different variables on the treatment effect. For doses-analyses, we excluded studies with intramuscular (IM) supplementation, with a direct supplementation of an active form of vitamin D (Alfacalcidol, 1·25 dihydroxyvitamin D) or with vitamin D_2.

Subgroups analyses were prespecified to assess whether the treatment effect was modified by one or more of eight different clinical characteristics (baseline 25[OH]D concentration, clinical settings, age, supplementation action, sex, length of intervention, dose of supplementation, study quality). A test of interaction was done on all subgroups to establish if the difference in effect size between subgroups was statistically significant.

Potential publication bias was explored by means of a funnel plot. We used the Begg's adjusted rank correlation test and the Egger's regression asymmetry test to detect publication bias.

For all results, a two-sided p value of 0.05 or less was considered as significant. All analyses were performed using the software package Comprehensive Meta Analysis, Biostat v2.

Results

Study characteristics

A total of 225 records were found in our initial search, restricted to 222 after removing duplicate studies. During the titles and abstracts screening stage, 165 of them were excluded. During the full-text review, 11 studies were identified as presenting incomplete or missing data. We contacted the authors of those studies and obtained the required data for nine of them. Consequently, during the full-text articles reviews, we excluded only two studies for incomplete data, instead of nine. After the full-text review, a total of 30 randomized controlled trials remained (Figure 1) (19–48). Out of them, 29 trials reported muscle strength as outcome (19–39, 41–48), six trials reported muscle mass as outcome (23, 24, 27, 38, 40, 47) and five reported muscle power as outcome (19, 24, 34, 36, 46).

Characteristics of the 30 studies are presented in Table 2. Out of those 30 randomized controlled trials involving 5615 participants, 72% were women and the mean age of the subjects was 61.1 (range: 10–99 years). Vitamin D_3 was used in 22 studies (19–25, 27–29, 31, 33–41, 43, 47) and vitamin D_2 in four studies (26, 42, 46, 48). Alfacalcidol was used as supplementation in three studies (32, 44, 45) and 1.25 dihydroxyvitamin D in one other (30). In 14 different studies(19, 25–27, 29, 30, 33, 37, 39, 42, 43, 45–47), participants received vitamin D-only supplementation whereas in the 16 other trials(20–23, 28, 31, 32, 34–36, 38, 40, 41, 44, 48), they received combined vitamin D and calcium supplementation.

Only one study supplemented the participants with an IM injection (26). All other studies used an oral supple-

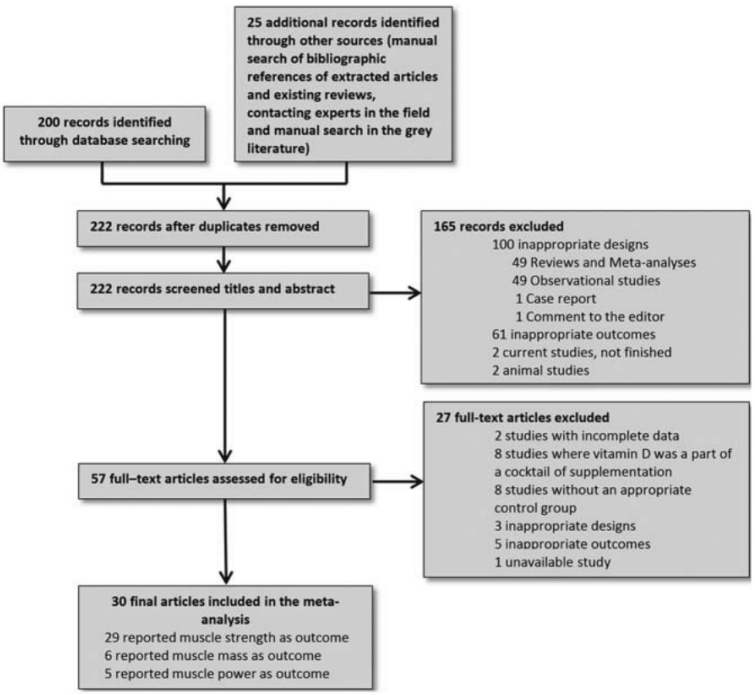

Figure 1. Flowchart of literature search

mentation. Treatment duration lasted from one to 60 months.

Regarding the study quality assessment, a median score of 4 out of 5 points (P25 3; P75 5; mean 3.9 points) on the Jadad scale was found, reflecting that the studies were overall of good quality (Table 5, Supplementary Files).

Muscle strength

Out of the 30 randomized controlled trials, 29 involving 5533 subjects, reported muscle strength measures. Results show that vitamin D supplementation has a small but significantly positive effect on global muscle strength with a standardized mean difference (SMD) of 0.17 (95% CI 0.03 to 0.31; $P = .02$) (Figure 2A). We note however that heterogeneity is significant (Q-value = 125.4; $P < .001$; I^2 77.7%). Among the 29 randomized controlled trials, 16 studies reported grip strength results (21–23, 27–31, 34–37, 46, 47) and 19 studies reported lower limb muscle strength results (19–21, 23–26, 30, 31, 33, 34, 36, 38, 39, 41, 44–46, 48). Regarding the individual type of strength, results shows no significant effect of vitamin D supplementation on grip strength (SMD 0.01; 95% CI −0.06 to 0.07; $P = .87$), but a significant positive effect on lower limb muscle strength (SMD 0.19; 95% CI 0.05 to 0.34; $P = .01$).

Subgroup analyses

Table 3 summarizes results of subgroups analyses. Supplementation of people who presented a 25[OH]D level < 30 nmol/L resulted in a significant higher improvement of their muscle strength compared to those who presented a 25[OH]D level ≥ 30 nmol/L ($P = .02$). Moreover, we also found higher SMDs for people who demonstrated an increase of their 25[OH]D concentration of at least 25 nmol/L within the duration of the study. This observation was confirmed by a meta-regression showing a significant association between changes in 25[OH]D concentration and changes in muscle strength (slope 95%CI = 0.01 (0.00;0.01)); $P = .01$) (Figure 3, Supplementary Files). We note that, in subgroups analyses, we only found a significant intergroup difference for people who presented a change of their 25[OH]D concentration of more than 50 nmol/L within the duration of the study compared to others ($P < .01$).

Vitamin D supplementation on people aged 65 years or older resulted in a significant improvement of muscle strength (SMD 0.25; 95% CI 0.01 to 0.48) whereas supplementation of younger did not (SMD 0.03; 95% CI −0.08 to 0.14). Intergroup difference is however nonsignificant ($P = .13$). In line with these results, we found that people institutionalized or hospitalized presented a greater standardized mean difference compared to community-dwellers (SMD 0.45 vs 0.05; $P < .01$). We also found that studies with a methodological quality above 4 points resulted in a significant improvement of muscle strength with a SMD of 0.22 (95% CI 0.03 to 0.41), whereas studies of lower quality did not (SMD 0.07; 95% CI −0.13 to 0.26).

Except for an apparent greater effect of vitamin D supplementation on muscle strength for only-women and only-men studies compared to mixed studies, we did not find any other significant difference between analyzed subgroups.

Muscle mass

Regarding the muscle mass, six studies have been included in the meta-analysis (23, 24, 27, 38, 40, 47) (Figure 2 B).

The pooled SMD for vitamin D supplementation on muscle mass is 0.058 ($P = .52$) suggesting that vitamin D has no significant effect on muscle mass. Heterogeneity is not significant ($P = .395$).

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Table 2. Study and participants characteristics

Study, year	N (women, %)	Participants	Mean age (years)	Baseline 25[OH]D (nmol/liter)	Study duration (months)	Supplementation	Type of vitamin D	Dose of vitamin D (IU)	Outcome	25[OH]D after treatment (nmol/liter)	Trial quality*
Barker 2012(19)	20 (50)	Active males and females	28.6 (18–45)	80.4	1	Vit D only	D_3	4000 IU/day	Strength Power	126.3	3
Binder 1995(20)	25 (36)	Institutionnalized	87.9 (NR)	56.8	2	Vit D + Ca	D_3	100000 IU once + 50 000 IU/week	Strength	81.6	2
Bischoff 2003(21)	62 (100)	Geriatric care	85.3 (63–99)	29.8	3	Vit D + Ca	D_3	800 IU/day	Strength	65.4	5
Brunner 2008(22)	2364 (100)	Postmenopausal women	62.4 (50–79)	NR	60	Vit D + Ca	D_3	400 IU/day	Strength	NR	4
Bunout 2006(23)	48 (90)	Community-dwelling	77 (≥70)	31.8	9	Vit D + Ca	D_3	400 IU/day	Strength Mass	64.4	5
Carrillo 2013(24)	23 (52)	Overweight and obese adults	26.1	48.2	3	Vit D + Ca	D_3	4000 IU/day	Strength Mass Power	83.4	3
Close 2012(25)	10 (0)	Healthy adults	NR	NR	2	Vit D only	D_3	5000 IU/day	Strength	NR	4
Dhesi 2004(26)	139 (78)	Ambulatory fallers	76.8 (≥65)	25.8	6	Vit D only	D_2	600000 IU once	Strength	43.7	5
El-Hajj Fuleihan 2006(27)	117 (100)	Healthy children and adolescents	13.3 (10–17)	34.9	12	Vit D only	D_3	2000 IU/day	Strength Mass	94.8	5
Glendenning 2012(28)	686 (100)	Older postmenopausal women	76.7 (>70)	NR	3	Vit D + Ca	D_3	150000/3months	Strength	NR	3
Goswami 2012(29)	86 (100)	Young Asian students	21.8 (NR)	23.2	6	Vit D only	D_3	60000/week during 6 weeks + 60000 twice/month during 4 months	Strength	74.63	5
Grady 1991(30)	98 (54)	Community-dwelling	79.1 (70–97)	62.9	66	Vit D only	1·25$[OH]_2$D		Strength	NR	3
Gupta 2010(31)	40 (40)	Healthy volunteers	31.55 (20-40)	23.2	6	Vit D + Ca	D_3	60000 IU/week (8 weeks) + 60000 IU/months (4 months)	Strength	56	4
Hara 2013(32)	94 (100)	Postmenopausal osteoporotic women	67.7 (55–75)	45.7	4	Vit D + Ca	1-hydroxycholecalciferol	1 μg/day	Strength	NR	3
Hornikx 2010(33)	49 (24)	COPD patients	68 (≥50)	42.4	3	Vit D only	D_3	100000 IU/month	Strength	127.3	3
Janssen 2010(34)	70 (100)	Geriatric care	80.8 (≥65)	34.4	6	Vit D + Ca	D_3	400 IU/day	Strength Power	77.2	4
Kampman 2012(35)	68 (71)	Multiple sclerosis ambulatory patients	40.5 (18–50)	56.4	22	Vit D + Ca	D_3	20000IU/week	Strength	123.2	5
Kenny 2003(36)	60 (0)	Community-dwelling	76.5 (65–87)	62.4	6	Vit D + Ca	D_3	1000 IU/day	Strength Power	87.1	5
Knutsen 2014(37)	146 (75)	Healthy immigrants	37.5 (18–50)	27	4	Vit D only	D_3	1000 IU/day	Strength	52	5
Kukuljan 2009(38)	89 (0)	Community-dwelling	61 (50–79)	80.6	18	Vit D + Ca	D_3	800 IU/day	Strength Mass	NR	2
Latham 2003(39)	243 (53)	Geriatric care	79.5 (77–81)	42.4	6	Vit D only	D_3	300000 IU once	Strength	59.9	5
Manios 2009(40)	82 (100)	Postmenopausal women	61.3 (55–65)	NR	12	Vit D + Ca	D_3	300 IU/day	Mass	NR	2
Pfeifer 2009(41)	242 (74.5)	Community-dwelling	76.5 (70–94)	54.5	20	Vit D + Ca	D_3	800 IU/day	Strength	84	4
Sato 2005(42)	96 (100)	Women after stroke	74.1 (NR)	24.5	24	Vit D only	D_2	1000 IU/day	Strength	83.4	5
Smedshaug 2007(43)	60 (65)	Institutionnalized	82.4 (NR)	46.6	12	VIt D only	D_3	400 IU /day	Strength	70.4	3
Songpatanasilp 2009(44)	42 (100)	Postmenopausal women	70.7 (65–84)	24.3	3	Vit D + Ca	1-hydroxycholecalciferol		Strength	NR	5
Verhaar 2000(45)	27 (100)	Geriatric care	75.7 (≤70)	18.2	6	Vit D only	1-hydroxycholecalciferol		Strength	27.8	1
Ward 2010(46)	72 (100)	Healthy children and adolescents	13.8 (12–14)	18.0	12	Vit D only	D_2	150000 IU/3 months	Strength Power	56	5
Wood 2014(47)	196 (100)	Postmenopausal women	63.8 (60–70)	33.8	12	Vit D only	D_3	1000IU/day	Strength Mass	75.7	4
Zhu 2010(48)	261 (100)	Community-dwelling	76.9 (70–90)	44.7	12	Vit D + Ca	D_2	1000 IU/day	Strength	60	5

NR = Not reported

** Quality evaluation was conducted using Jadad criteria*

Muscle power

Five studies reported results on muscle power (19, 24, 34, 36, 46). The meta-analysis of these five studies does not show a significant result of vitamin D supplementation on muscle power (Figure 2C). No heterogeneity has been found in this meta-analysis ($P = .94$).

GRADE Analysis

Our GRADE analysis showed a moderate evidence quality for muscle strength. The main reason for the reduced level of evidence is the small sample size in some studies and the presence of heterogeneity in this meta-analysis. Regarding muscle mass and muscle power, our GRADE analysis showed a low level of evidence. This is mainly due to the restricted number of studies included in this meta-analysis but also to the small number of subjects in some of these studies. Future researches on muscle strength, muscle mass and muscle power are likely to have an important impact on our confidence in the estimate of effect and are likely to change this estimate (Table 4).

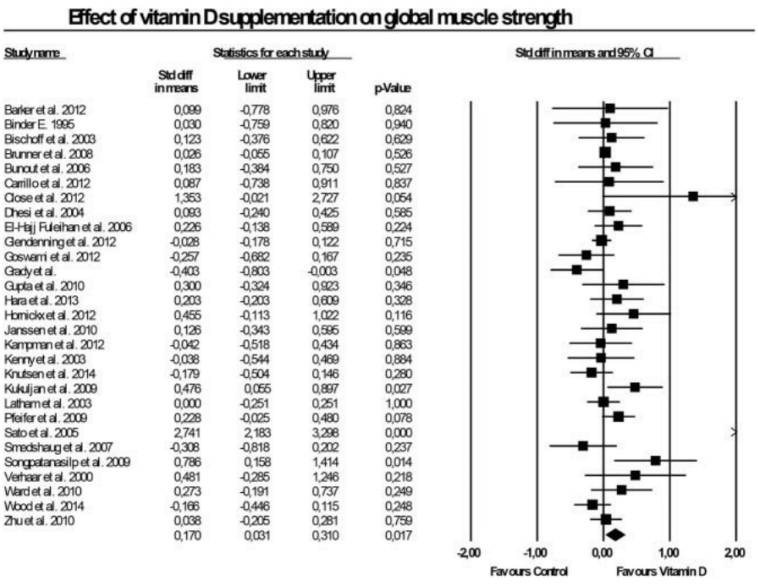

Figure 2. Effect of vitamin D supplementation on global muscle strength (A), muscle mass (B) and muscle power (C) (*A) Heterogeneity : Q-value 125.37; Df(Q) 28; p-value 0.001; I^2 : 77.67* (*B) Heterogeneity : Q-value 5.17; Df(Q) 5; p-value 0.39; I^2 3.34* (*C) Heterogeneity : Q-value 0.76; Df(Q) 4; p-value 0.94; I^2 0.00%*

Discussion

Principal findings

The aim of this meta-analysis was to assess the effect of vitamin D supplementation on muscle function. Pooled results from the 29 identified randomized controlled trials have shown a small but positive significant effect of vitamin D supplementation on muscle strength. These results could be of a great public health interest because of the well-known correlation between, on one hand, low muscle strength and, on the other hand, functional impairments (49, 50), affected quality of life (QOL) (51) and mortality (52).

Positive effects on muscle strength are especially observed on lower limb muscles. These results are interesting insofar they can explain the significant effect of vitamin D on falls observed in three different meta-analyses (53–55). Indeed, quadriceps strength is recognized to be a significant predictor of incident falls (56).

Concerning muscle mass and muscle power, no significant effect of vitamin D was found. However, only six studies for muscle mass and five studies for muscle power with a total of only 538 and 245 subjects have been included respectively in the meta-analysis on muscle mass and muscle power. Given this small number of included studies, results must be interpreted with caution. Sufficient good quality studies are lacking to enable a clear assessment of the impact of vitamin D on muscle mass and muscle power.

Comparison with previous studies

Our findings can be compared to results of the meta-analyses of Stockton et al (13) and Muir et al (12), but several methodological differences between their meta-analyses and ours can be observed. We have found a larger number of studies, thus provided a bigger sample and hence more representative results. Indeed, when data were missing in the paper, we systematically contacted authors or coauthors of the paper to obtain these data, which enabled us to include 30 studies in our meta-analysis, instead of 3 for Muir et al (12) and 12 for Stockton et al (13). Contrary to Stockton et al (13), we also

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Table 3. Subgroups analyses

	Subtotal (n)	Number of studies	SMD (95%CI)	p-value
Serum 25(OH)D concentration				
< 30nmol/liter	710	9	0.47 (-0.07; 1.01)	0.02
≥ 30nmol/liter	1763	17	0.06 (-0.05; 0.16)	
Clinical settings				
Community-dwelling	4901	21	0.05 (-0.04; 0.15)	<0.01
Institutionalized or hospitalized	632	8	0.45 (-0.16; 1.07)	
Age				
< 65 yr	3221	11	0.03 (-0.08; 0.145)	0.13
≥ 65 yr	2302	17	0.25 (0.01; 0.48)	
Supplementation				
Vitamin D alone	1359	14	0.06 (-0.01; 0.13)	0.7
Vitamin D + calcium	4174	15	0.25 (-0.08; 0.59)	
Sex				
Women only	4173	13	0.29 (0.01; 0.05)	0.21
Men and women	1201	13	0.02 (-0.10; 0.15)	
Men only	159	3	0.38 (-0.17; 0.93)	
Length of intervention				
< 26 weeks	1157	10	0.13 (-0.06; 0.33)	0.72
≥ 26 weeks	4376	19	0.17 (-0.01; 0.36)	
Dose of supplementation				
< 1600 IU/day	3337	10	0.04 (-0.08; 0.15)	0.90
≥ 1600 IU/day	1367	11	0.02 (-0.08; 0.13)	
Change of 25(OH)D concentration				
< 25 nmol/liter	904	8	0.06 (-0.07; 0.20)	0.23
≥ 25 nmol/liter	1335	15	0.27 (-0.04; 0.57)	
< 50 nmol/liter	1783	17	0.06 (-0.04; 0.15)	<0.01
≥ 50 nmol/liter	456	6	0.56 (-0.24; 1.36)	
Quality of studies				
< 4 points	1171	10	0.07 (-0.13; 0.26)	0.42
≥ 4 points	4362	19	0.22 (0.03; 0.41)	

SMD = Standardized Mean Difference

Table 4. Evidence quality and recommendation grade

Outcome	Nb. of studies	Study design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Evidence quality
Muscle strength	29	RCT	No serious	Serious[a]	Serious[b]	No serious	Not assessed[c]	Moderate
Muscle mass	6	RCT	No serious	No serious	Serious[b]	No serious	Not assessed[c]	Low
Muscle power	5	RCT	No serious	No serious	Serious[b]	No serious	Not assessed[c]	Low

[a] A significant heterogeneity was observed in this meta-analysis. [b] wide confidence intervals around the estimate of the effect were observed for most studies. [C] not assessed because of methodological issues (high heterogeneity observed in the meta-analysis on muscle strength and limited number of studies included in the meta-analyses on muscle mass and muscle power)

decided to exclude studies that used vitamin D as part of a complex nutritional supplementation regimen because of the impossibility to report only effects of vitamin D. Moreover, unlike these two authors, when a study presented results of two different measurements of muscle strength, we decided to report only one of these results to avoid an artificial increase of the statistical power in the meta-analysis.

Regarding subgroup analyses, like Stockton et al (13), we have found a possibly greater effect of vitamin D supplementation in subjects with a baseline 25[OH]D level below 30 nmol/L.

Although for bone health, vitamin D seems more efficient when combined with calcium, we have found no significant difference between a simple supplementation of vitamin D and a supplementation of vitamin D combined with calcium. The role of calcium on muscle func-

tion is yet not clear but this result does not seem to suggest an additional effect of calcium on muscle strength.

Regarding the age subgroup, we suggest a possible better effect on subjects aged 65 years or older. Moreover, effect on muscle strength seems also more important in frail people compared to community-dwelling people. These results could be an incentive to perform interventional studies with vitamin D in the field of older people's musculoskeletal diseases, such as sarcopenia.

Strength and limitations

We have used the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (14) to perform our research, to ensure as much as possible a good quality to our research. Thanks to a rigorous research of published and unpublished studies, and thanks to the contact we have made with authors or coauthors when information was missing in the full-text paper, we have included a higher number of studies in our meta-analysis than other authors (12, 13). We have defined clear inclusion criteria and have carefully ensured that the treated group was strictly comparable to the control group, with the exception of vitamin D supplementation. The 30 randomized controlled trials identified with this method and included in the meta-analysis showed a median score of quality of 4 out of 5 points, reflecting a high methodological quality.

Our study has also some limitations. Despite our efforts to include all potentially interesting studies in our meta-analysis, we have been obliged to exclude two studies because their authors did not answer our request for more information. Even if it is not the case for the meta-analysis on muscle mass and muscle power, we found a significant heterogeneity in the meta-analysis on muscle strength. This could be explained by the large number of studies included in the meta-analysis and by the variability observed between the different protocols of supplementation. However, we have presumed this heterogeneity in the statistical methodology and used a random effect model in our analyses. We also regret to be unable to find any dose effect in this meta-analysis but this is probably due, once again, to the variability of the different protocols of supplementation across studies. To avoid an artificial increase of the statistical power in the meta-analysis, we have arbitrary chosen to report only the result of the group supplemented with the higher dose of vitamin D. This choice was however not determinative in view of the nonsignificant results of the dose-effect meta-regression. Regarding the study quality assessment, we have to acknowledge that, despite its large use, the Jadad score is not perfect and that another quality scale could have been used. Moreover, because of the limited number of studies included in the meta-analyses on muscle mass and muscle power and because of the high heterogeneity observed in the meta-analysis on muscle strength, we were unable to measure the potential publication bias by the Begg's adjusted rank correlation and the Egger's regression asymmetry tests (57). Finally, only six studies were included in the muscle mass analysis and five in the muscle power analysis. This number is quite small and more good quality studies are needed to make a clear statement about the effect of vitamin D supplementation on these variables.

Conclusion

Based on the studies included in this meta-analysis, vitamin D supplementation has a small but positive impact on global muscle strength, more specifically on lower limb. These results could have a positive public health interest, especially in the field of musculoskeletal diseases. However, no impact was found on muscle mass and muscle power. Our meta-analysis suggests that vitamin D could improve muscle strength but additional studies are needed to define optimal treatment modalities, including dose, mode of administration and duration.

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Take-home points: This systematic review and meta-analysis summarises results from 30 randomized controlled trials assessing effect of vitamin D supplementation on muscle function on the general population providing the most comprehensive synthesis on this issue so far.; Vitamin D supplementation has a small but significant positive effect on global muscle strength, but no effect on muscle mass and muscle power.; Effects may be more important with people presenting a baseline 25[OH]D concentration lower than 30 nmol/L, with people institutionalised or hospitalized and with people aged 65 years or older.

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Sarcopenia in daily practice: assessment and management

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Abstract

Background: Sarcopenia is increasingly recognized as a correlate of ageing and is associated with increased likelihood of adverse outcomes including falls, fractures, frailty and mortality. Several tools have been recommended to assess muscle mass, muscle strength and physical performance in clinical trials. Whilst these tools have proven to be accurate and reliable in investigational settings, many are not easily applied to daily practice.

Methods: This paper is based on literature reviews performed by members of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) working group on frailty and sarcopenia. Face-to-face meetings were afterwards organized for the whole group to make amendments and discuss further recommendations.

Results: This paper proposes some user-friendly and inexpensive methods that can be used to assess sarcopenia in real-life settings. Healthcare providers, particularly in primary care, should consider an assessment of sarcopenia in individuals at increased risk; suggested tools for assessing risk include the Red Flag Method, the SARC-F questionnaire, the SMI method or different prediction equations. Management of sarcopenia should primarily be patient centered and involve the combination of both resistance and endurance based activity programmes with or without dietary interventions. Development of a number of pharmacological interventions is also in progress.

Conclusions: Assessment of sarcopenia in individuals with risk factors, symptoms and/or conditions exposing them to the risk of disability will become particularly important in the near future.

Keywords: Sarcopenia, Daily practice, Assessment, Management, Tools

Background

The term sarcopenia was first coined by Rosenberg et al. in 1989 [1] as a progressive loss of skeletal muscle mass with advancing age. Since then, the definition has expanded to incorporate the notion of impaired muscle strength and/or physical performance. Currently, several definitions of sarcopenia have been proposed [2–10] but no consensus has yet been reached. Depending on the definition used, the prevalence of sarcopenia is reported to be up to 29 % for older community-dwelling adults and up to 33 % for individuals living in long-term care institutions [11, 12]. Sarcopenia is associated with morbidity and mortality from linked physical disability, falls, fractures, poor quality of life, depression and hospitalization [13–19].

Current research is focusing on nutritional exercise/activity based and other novel interventions for improving the quality and quantity of skeletal muscle in older people. Some studies demonstrated that resistance training combined with nutritional supplements can improve muscle function [11, 20–22]. A number of pharmacological interventions are in development but no single agent has been shown to be clinically effective, without unwanted effects, in maintaining or increasing skeletal muscle mass or function. With the prospect of effective interventions, the identification and assessment of sarcopenia will become

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particularly important to prevent disability and other negative health outcome in the near future.

The challenge in clinical practice will be in the assessment of sarcopenia to identify those who might benefit most from these interventions. Among the l current definitions of sarcopenia [3, 7, 8], there is a general agreement on the need for muscle mass measurement with varying recommendations on the roles of muscle strength assessment and/or physical performance. Currently, several well validated tools exist to measure these parameters, which have been reviewed recently [18, 23, 24]. Whereas they have been used for sarcopenia case finding in the research setting, their use is not always feasible in daily clinical practice. The purpose of this paper is to discuss different approaches in the assessment of sarcopenia and potential management strategies in clinical practice.

Methods

As in previous initiatives and publications [25–35], the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) working group on frailty and sarcopenia consists of clinical scientists and experts in the field of musculoskeletal diseases. Different members of the ESCEO working group were asked to prepare a review of the literature on 1) the general tools for the assessment of sarcopenia, both in research and in clinic (CC); 2) the assessment of physical performance in daily practice (MC); 3) the role of imaging in the diagnosis of sarcopenia in daily practice (MV); 4) the role of biochemical markers in the diagnosis of sarcopenia in daily practice (EC) and 5) the role of primary versus secondary care physicians in the evaluation of sarcopenia (AC). A brief summary of the management of sarcopenia in daily practice was also proposed and discussed. Randomized controlled studies, prospective studies, systematic reviews and meta-analyses published before September 2015 were searched on PubMed and Embase using the following search terms : 1) Sarcopenia, Clinical, Evaluation, Assessment, Management; 2) Physical function, Physical performance, Gait, Walk, Walking, Strength; 3) Elderly, Muscle mass, Sarcopenia, Dual x-ray absorptiometry/DXA/DEXA, Computer tomography/CT, Magnetic resonance imaging/MRI, Bioelectrical impedance/BIA; 4) Frailty, Sarcopenia, Biomarker, Biochemical marker, and 5) Primary care, Specialist care, Secondary care, Sarcopenia, Management, Screening, Questionnaire. Additional studies were identified by a manual search of bibliographic references of relevant articles and existing reviews. Each member prepared a list of the most important papers based on their review of the literature and then made a set of preliminary recommendations. The subsequent step was a face-to-face meeting for the whole group to make amendments and discuss further recommendations. The plan of the manuscript was also discussed and shared conclusions were reached. The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties.

Results

How to assess sarcopenia in clinical practice?

Despite a relatively large number of tools being available to measure muscle mass, muscle strength and physical performance [36, 37], some of them are likely to be of greater validity and utility for the assessment of sarcopenia in clinical practice than in clinical research and are summarised in Table 1. Whereas some biochemical markers of muscle metabolism (e.g. activin, n-terminal propeptide of procollagen III and myostatin) are being investigated for their ability to indicate muscle mass or strength, current data suggest that it is premature to recommend their use in daily practice [38].

Table 1 Applicability of the existing tools for the assessment of muscle mass, muscle strength and physical performance in research and clinical settings

	Applicable in research settings	Applicable in specialist clinical settings	Applicable in primary care settings
Assessment of muscle mass			
DXA	+++	+++	+
Anthropometric measurements	+	++	++
CT-scan	+++	++	+
MRI	+++	++	+
BIA	++	++	+
Assessment of muscle strength			
Handgrip strength	+++	+++	+++
Lower limb muscle strength	+++	++	+
Repeated chair stands test	+	+	++
Assessment of physical performance			
Gait speed	+++	+++	+++
Timed Up and Go test	++	+	+
Balance test	+	+	+
6-min walk test	++	+	+
400 m walk test	++	+	+
Stair climb test	++	+	+
SPPB test	+++	++	+

SPPB Short Physical Performance Battery

Nb. The group has chosen to attribute to each tool +++ (best recommended tool) or ++ (best alternative tool) or + (less recommended tool) based on the availability and the costs of the tool, the required time for the examination and the availability of robust cut-off points

There are currently a number of approaches to the definition of sarcopenia in clinical practice [3, 7, 36]. However, these are usually more suited to research studies than wider clinical practice. Additionally, some of the available methodologies for the assessment of sarcopenia utilise methods for measuring muscle mass, strength and physical function that are more suited to secondary care, than primary care settings. We therefore tabulated our preferences according to feasibility, complexity, required time for the examination, availability of robust cut-off points and cost, in each of these three contexts: research, specialist settings and primary care (Table 1).

Assessment of muscle mass

The widespread use of magnetic resonance imaging (MRI) and computed tomography (CT) scan for the non-invasive assessment of muscle mass [39] is limited in primary care settings by difficulties in access, costs, the lack of portable equipment and the requirement of highly specialized personnel.

Dual-energy x-ray absorptiometry (DXA) is a well-established, low-radiation technique used to assess body composition and provides reproducible estimates of appendicular skeletal lean mass [40, 41]. It is acknowledged that the accuracy of DXA for assessing muscle mass in people of different ages and different pathological conditions may vary. Moreover, DXA (in contrast to CT-scan and MRI) cannot assess intra-muscular fat, which turns out to be of increasing importance in terms of the quality of muscle and associations with clinical outcomes. Bearing these limitations in mind, DXA is still considered as the procedure of choice for routine clinical assessment. Using DXA, appendicular skeletal lean mass (ALM) is measured as the sum of the non-bone and non-fat mass of the four limbs. To adjust for body size, a skeletal muscle index (SMI) is derived as ALM/height^2. Thresholds of SMI at two standard deviations below the mean SMI of young male and female reference groups have been proposed as gender-specific cut-off points for sarcopenia. This results in two thresholds, proposed by the EWGSOP [3], the first of 5.5 kg/m^2 for women and 7.26 kg/m^2 [8] for men and the second of 5.67 kg/m^2 for women and 7.25 kg/m^2 for men [42], depending on the reference group on which these cut-off have been established. Using a different approach, the FNIH sarcopenia project [7] has also recently defined cut-offs for appendicular lean mass adjusted for body mass index (BMI), giving values of < 0.512 for women and < 0.789 for men. However, it should be pointed that these cut-offs might also be modified according to ethnicity [43].

If clinicians have no access to DXA, they can use anthropometric measurements. Indeed, a recent survey [44] showed that anthropometric data are currently the most widely used methods in clinical practice (57.5 % of clinicians that measure muscle mass in their practice use anthropometric data) followed by DXA (45.9 %). Several anthropometric measurements exist (i.e. body mass index, calf circumference, mid-upper arm circumference and skinfold thickness). Moreover, mid-arm muscle and calf circumferences have been shown to be correlated with appendicular muscle mass and reflect both health and nutritional status and predict performance, health and survival in older people [45–47]. However, with advancing age, changes in the distribution of fat and loss of skin elasticity are such that circumference and skinfold measures incur a loss of accuracy and precision in older people [47, 48]. Some studies suggest that an adjustment of anthropometric measurements for age, sex or BMI results in a better correlation with DXA-measured lean mass [49–51]. Anthropometric measurements are simple clinical prediction tools that can be easily applied for sarcopenia since they offer the most portable, commonly applicable, inexpensive and non-invasive technique for assessing size, proportions and composition of the human body [50]. However, their validity is limited when applied to individuals due to large prediction errors and because cut-off points, to identify low muscle mass, still need to be defined. Therefore, if a patient is identified as at risk of having sarcopenia by anthropometric measurements, an additional measurement of muscle mass with DXA would still be recommended.

Finally, bio-electrical impedance analysis (BIA) is a method which estimates the volume of fat and lean body mass based on the relationship between the volume of a conductor and its electrical resistance. The method is not expensive, requires no specialized staff and is relatively easy to use in clinical practice, both on ambulatory subjects or on hospitalized patients. Moreover, reference values have been established for older individuals [3]. Even if the method's accuracy has been challenged and has been reported to overestimate muscle mass and underestimate fat mass [52–54], it is possible to use some adjustment equations to obtain valid measurements [55].

In summary, we would propose assessing primarily muscle mass by DXA, if this tool is available, and if not, anthropometry measurements can easily be used, in primary care settings, as a first screening of patients with low muscle mass. These patients can then be referred for an additional evaluation in specialist clinical settings.

Assessment of muscle strength

Handgrip strength appears to be the most widely used method for the measurement of muscle strength. A recent survey indicated that clinicians, both from the fields of geriatric medicine and rheumatology, prefer the use of grip strength over chest press and lower limb isokinetic

dynamometry as a measure of overall muscle strength [44]. In general, isometric handgrip strength shows a good correlation with leg strength [56] and also with lower extremity power, knee extension torque and calf cross-sectional muscle area [15, 57]. The measurement is easy to perform, inexpensive and does not require a specialist trained staff. Standardized conditions for the test [58] include seating the subject in a standard chair with their forearms resting flat on the armchairs. Clinicians should demonstrate the use of the dynamometer and show that gripping very tightly registers the best score. Six measures should be taken, 3 with each arm. Ideally, the patients should be encouraged to squeeze as hard and as tightly as possible during 3–5 seconds for each of the 6 trials; usually the highest reading of the 6 measurements is reported as the final result. The Jamar dynamometer, or similar hydraulic dynamometer, is the gold standard for this measurement. However, for patients with advanced arthritis, the design of this dynamometer may be a limitation [59]. A pneumatic dynamometer, such as the Martin vigorimeter, may be a good alternative. With this device, patients try to squeeze rubber balls (available in three sizes) with the same protocol as that used for the Jamar dynamometer. A variety of thresholds of grip strength have been proposed to characterize low muscle strength, ranging from 16 to 20 kg for women and 26–30 kg for men [7, 15, 60, 61]. Lower limb muscle strength, most frequently of the quadriceps, can also be measured. Commercial dynamometers can enable isometric and/or isokinetic measurements of strength. Even if these measurements are feasible in frail people [62, 63], they are often limited in clinical practice by their relative expense, the need to purchase dedicated equipment, the lack of trained staff and limited data in older populations. However, the repeated chair stand test, which is a timed test requiring participants to rise from a chair without using their arms and return to the seated position, consecutively, for five times, has been shown to be able to provide a reasonably reliable and valid indication of lower body strength [64].

In summary, we would recommend to measure muscle strength by handgrip strength in clinical practice (Table 1). *For primary care settings where the availability of a handgrip dynamometer is not systematic, the repeated chair stand test could be used as an alternative measure of muscle strength.*

Assessment of physical performance

The most widely used tool in clinical practice for the assessment of physical performance is the gait speed measurement, employed by almost two-thirds (63.3 %) of clinicians that assess physical performance (among 255 clinicians who took part in an international online survey; 87.8 % of medical doctors with geriatrics (57.6 %) and rheumatology (18.8 %) as major fields of interest) [44]. The test is highly acceptable for participants and health professionals in clinical settings [65]. No special equipment is required as it only needs a flat floor devoid of obstacles. In the 4-m gait speed test, which is recommended by the EWGSOP for the assessment of sarcopenia, men and women with a gait speed <0.8 m/s are described as having a poor physical performance [15]. The average extra-time added to the consultation by measuring the 4-metre gait speed was only 95 ± 20 s.

Gait speed can be performed alone or as part of a test battery, the most popular of which is the Short Physical Performance Battery (SPPB). The SPPB is a test scored to a maximum of 12 points comprising an assessment of gait speed (over 3–4 m), a balance test and a repeated chair stand test. These tests focus on lower extremity function, as the latter has been shown to correlate with mobility, disability and patient outcomes including hospitalization, institutionalization, and mortality. The SPPB takes about 10 min to complete [66]. Participants presenting a score ≤8 points have been described as having a poor physical performance [3].

Other standalone tests can be performed to assess physical performance. In the Timed Up and Go (TUG) test, individuals are asked to rise from a standard armchair, walk to a marker 3 m away, turn, walk back and sit down again. The 6-min walk distance or 400 m walk time can be used to measure aerobic capacity. The stair climb power test also shows good correlation with other measures of leg power and physical performance, but is mostly restricted to use in research settings [67].

In summary, we would propose that physical performance is primarily assessed in clinical practice by measuring gait speed. The SPPB test may be limited by the time of administration but might also be useful to identify men and women with low physical performance (Table 1).

The role of primary care physicians

In view of the current lack of a consensus concerning the definition of sarcopenia and also of the practical issues related to time constraints and limited access to assessment tools in the primary care setting, the group believes that the role of primary care physicians should be to identify patients who are at risk of sarcopenia and to refer them to specialists in the field. Some interesting methods that might be suitable for screening purpose are presented in the following section.

Consideration of possible sarcopenia should be undertaken in older individuals (e.g. > 65 years) with signs or symptoms suggestive of the condition both in primary care and in specialized clinical settings. Several methods can be proposed to perform a simple, rapid and inexpensive

identification of those at risk. However, none of them has received an extensive validation, and therefore further research in this area is urgently needed.

The red flag method

The purpose of the red flag method is to understand, during a standard medical consultation (or health assessment) the clinical presentation of individuals with particular regard to physical manifestations of sarcopenia such as general weakness or loss of muscle mass. The subject can also be asked about symptoms such as loss of weight, loss of muscle strength, loss of energy, falls, etc. (Table 2). An assessment of nutrition habits should also be performed to check, for example, if the subject has sufficient protein intake. The Mini-Nutritional Assessment could also be used for a rapid and easy assessment of malnutrition or, at least, risk of malnutrition [68]. Finally, clinicians can also assess physical activity. Indeed physical inactivity or high levels of sedentary behaviour may be considered a red flag. If the screening identifies any red flag suggesting the presence of sarcopenia, more sophisticated assessment procedures of sarcopenia can be implemented. Red flags have been identified through reviewed papers identified by members of the group and are presented in Table 2.

The SARC-F questionnaire

The SARC-F questionnaire [69] was developed as a possible rapid screening test for sarcopenia. This questionnaire could enable healthcare providers to quickly and easily assess the risk of sarcopenia during a standard health consultation. The subject is asked 5 questions addressing strength, assistance in walking, rising from a chair, stair climbing and falls. Each component is scored from 0 to 2 points, giving a global score of the SARC-F between 0 and 10 points. A score ≥ 4 points is reported to be predictive of sarcopenia and poor outcomes and could be a trigger for a more detailed assessment of sarcopenia.

Despite a questionable sensitivity [70], the SARC-F questionnaire is considered as one of the best available tools to be used in primary care for raising awareness of the diagnosis of sarcopenia. Similarly to the red flag method, a result ≥ 4 for the SARC-F questionnaire could be an incentive to send the subject to a complete assessment of sarcopenia.

Table 2 The Red Flag method

	Red flags
Clinician's observation	General weakness of the subject
	Visual identification of loss of muscle mass
	Low walking speed
Subject's presenting features	Loss of weight
	Loss of muscle strength, in arms or in legs
	General weakness
	Fatigue
	Falls
	Mobility impairment
	Loss of energy
	Difficulties in physical activities or activities of daily living
Clinician's assessment	Nutrition
	Body weight
	Physical activity

Nb. Red flags have been identified through reviewed papers identified by members of the group

Prediction of low muscle mass according to age and BMI

Recently, a study [71] has been performed with the purpose to identify predictors of low skeletal muscle mass in older adults toward development of a practical clinical assessment tool for use by clinicians to identify individuals requiring DXA screening for muscle mass. For this purpose, ALM was calculated from DXA scans and SMI defined as the ratio of ALM divided by height in square centimetres. Older participants (from 65 to 85 years) were classified has having low muscle mass if their SMI was 1 standard deviation below the mean SMI of young adults. This model was validated on a sample of 200 subjects of the NHANES population. Results of the validation analysis revealed that age and BMI were strongly associated with a low SMI and may be an informative predictor in the primary care settings. Consequently, two models were proposed, one for men and one for women and consist of two tables presenting the probability of low muscle mass by age and BMI. In a 200-person validation, the model sensitivity was 81.6 % for men and 90.6 % for women and the model specificity was 66.1 % for men and 66.2 % for women.

Anthropometric prediction equation in combination with a measure of muscle function

Other authors developed gender specific anthropometric equations, based on age, weight, BMI values, to estimate appendicular skeletal muscle mass [72]. To validate these prediction equations, muscle mass was assessed using DXA in three cohorts of older Australian subjects [72] (appendicular skeletal muscle mass prediction equation: $10.05 + 0.35(\text{weight}) - 0.62(\text{BMI}) - 0.02(\text{age}) + 5.10$ (if male)). The results showed a strong correlation between the equations and the muscle mass measured using DXA, with an adjusted R^2 of 0.869. In a subsequent research the prediction equations were evaluated in combination with assessment of hand grip strength as a screening method to identify older patients who should undergo DXA evaluation for sarcopenia. The best strategy to reduce the number of DXA was to apply the equation

first, to assess hand grip strength in those with low estimated muscle mass and to proceed to DXA only in individuals with low grip strength [50].

Prediction of sarcopenia using age, handgrip strength and calf circumference

In 2014, Ishii et al. [73] developed a new screening tool for sarcopenia in a sample of almost 2000 autonomous community-dwelling older subjects in Japan. Sarcopenia was defined on the basis of low muscle mass measured by BIA and either low muscle strength characterized by handgrip or low physical performance characterized by slow gait speed. Using a database including demographic variables, albumin, chronic diseases, physical activity information and anthropometric measurements, the authors developed a gender specific model including three variables, i.e. age, handgrip strength and calf circumference. Based on the model, the authors constructed a gender specific score chart that had an excellent discrimination ability, with an area under the curve of 0.939 for men and 0.909 for women. The formula to calculate the scores are as follows: score in men, 0.62 x (age-64) – 3.09 x (grip strength –50) – 4.64 x (calf circumference –42); score in women, 0.80 x (age-64) – 5.09 (grip strength –34) – 3.28 x (calf circumference – 42). The corresponding probabilities of sarcopenia were calculated as: probability in men, $1 / [1 + e^{-(\text{sum score}/10-11.9)}]$; probability in women, $1/[1 + e^{-(\text{sum score}/10-12.5)}]$. This model still requires further validation in independent cohorts, before its use in clinical practice can be promoted.

How to manage sarcopenia in daily practice?

Identification of comorbidities

Sarcopenia is frequently found in association with comorbidities, e.g. osteoporosis, osteopenia, obesity, type II diabetes mellitus, breast cancer, etc. [74, 75]. In such cases, sarcopenia may be considered as a secondary consequence of the co-existing pathological condition. The impact of management of these conditions (e.g. better diabetic control, reduction of inflammatory status, or weight loss in obesity due to an energy-restricted diet) on the accompanying sarcopenia is unclear [76].

Physical activity

Physical activity interventions and progressive resistance training have been suggested to have a predominant effect on muscle strength, muscle mass and physical performance in older people [77].

However, so far, studies mainly focusing on well-defined sarcopenia with standardization of the physical intervention are still missing. Hence, it is still difficult to give a patient-specific physical activity prescription for the management of sarcopenia. However, healthcare providers can nevertheless give some general recommendations in order to improve other common conditions in older adults (WHO recommendation: http://www.who.int/dietphysicalactivity/factsheet_olderadults/en/). Moreover, in their review, Cruz Jentoft at al [11]. forwarded two recommendations regarding the management of physical activity interventions in older people. First, to obtain an impact on muscle function, the duration of the intervention should be for at least 3 months. Second, supervised resistance exercise or multicomponent/combined exercise programs should be recommended for frail or sedentary community-dwelling people.

Nutrition

Although nutrition is considered as a major point for the management of sarcopenia, evidence of the effect of nutrition on muscle function is often derived from short-term studies in specifically selected sample and large clinical trials are still lacking. Currently, there is no robust evidence for nutritional recommendations for subjects with sarcopenia.

However, even if randomized controlled trials are inconsistent regarding the effects of protein supplementation on muscle function, several observational studies have suggested that maintaining adequate protein intake may help preserve muscle mass and strength in both adults and older people [78, 79]. Bauer et al. [80] recommended increasing protein intake to 1.2 g/kg body weight/day either by diet or by protein supplementation in older adults because of blunted muscle protein synthetic response and blunted post-prandial inhibition of muscle protein breakdown (anabolic resistance). Frail older adults or older who have acute or chronic diseases need higher dietary protein (i.e. 1.2–1.5 g/kg body weight/d) [80]. Recent evidence suggests that the recommended dietary allowance for protein is inadequate in older people [81]. Some other nutritional supplements, such as β-hydroxy β-methylbutyrate, creatine and vitamin D have been suggested to have an effect on muscle function. Indeed, β-hydroxy β-methylbutyrate supplements appear to increase muscle mass whilst its effects on muscle strength and physical performance are inconsistent [11, 20, 21]. Supplementation with creatine, protein or leucine combined with resistance exercises seems to have a positive impact on muscle mass, muscle strength and physical performance [22, 82, 83]. Finally, a recent meta-analysis has suggested that vitamin D supplementation could increase lower limb muscle strength [84]. Based on this evidence, dietary protein caloric intake, protein quality, as well as the vitamin D status of older individuals could be checked by clinicians and/or dieticians and individual prescription of nutritional supplements could be considered.

Pharmacological management

Currently, no drug is registered for the treatment of sarcopenia. However, several new chemical entities are

Table 3 Pharmacological agents in development with potential for treating sarcopenia

Mechanism of action	Drug name	Drug Developer	Indication sought	Study phase
I. Myostatin Antagonists				
Activin receptor trap	ACE-031	Acceleron	Duchenne muscular dystrophy	Phase 3 (trial terminated early)
Myostatin antibody	REGN-1033	Regeneron/Sanofi	Sarcopenia	Phase 2
	LY-2495655	Eli Lilly	Hip arthroplasty	Phase 2
			Elderly Fallers	
			Cancer Cachexia	
	PF-06252616	Pfizer	Inclusion body myositis	Phase 1
Activin receptor inhibitor	Bimagrumab (BMY338)	Novartis	Sarcopenia	Phase 2 and 3
			Hip fracture	Phase 2
			Cancer and COPD cachexia	
II. Selective Androgen Receptor Modulators	Enobasarm (Ostarine)	GTx	Cancer Cachexia	Phase 3 (did not meet primary endpoint)
III. Skeletal Troponin Activators	Tirasemtiv	Cytokinetics	ALS	Phase 2,3
	CK-2017357		Myasthenia Gravis	

currently at various stages of development. These are summarized in Table 3 with their potential future indications and their current phase of development.

Discussion and general consensus

The ESCEO Experts group agreed on some general recommendations to be implemented in clinical practice:

- Several tools are currently available for the measurement of muscle mass, muscle strength and physical performance, with a potential use for the diagnosis and follow-up of sarcopenia but they are not fully adapted for widespread use in clinical daily practice. The recommended tools for the diagnosis of sarcopenia in specialist clinical practice are DXA for the measurement of appendicular muscle mass, grip strength for the measurement of muscle strength and gait speed for the measurement of physical performance. Thresholds previously recommended in the literature can be applied to distinguish normal from abnormal;
- Healthcare providers, particularly in primary care, should consider an assessment of sarcopenia in individuals at increased risk; suggested tools for assessing risk include the SARC-F questionnaire, the SMI method or different prediction equations based on anthropometric data associated with the measurement of handgrip strength, although all of them require further validation;
- Whereas further studies are required to provide a full evidence-based guidance to clinicians, current management can include physical activity advice, particularly progressive resistance training, treatment and prevention of vitamin D deficiency and adequate energy and dietary protein intake.

The Expert group also emphasizes the importance of education and increased awareness of clinicians to the potential deleterious outcomes of sarcopenia.

Conclusions

Physicians and other health professionals have an important role to play in the assessment and management of sarcopenia to reduce its impact on individuals' well-being, the development of disability, and on health resources utilization.

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HEALTH OUTCOMES OF SARCOPENIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Objective: The purpose of this study was to perform a systematic review to assess the short-, middle- and long-term consequences of sarcopenia.

Methods: Prospective studies assessing the consequences of sarcopenia were searched across different electronic databases (MEDLINE, EMBASE, EBM Reviews, Cochrane Database of Systematic Reviews, EBM Reviews ACP Journal Club, EBM Reviews DARE and AMED). Only studies that used the definition of the European Working Group on Sarcopenia in Older People to diagnose sarcopenia were included. Study selection and data extraction were performed by two independent reviewers. For outcomes reported by three or more studies, a meta-analysis was performed. The study results are expressed as odds ratios (OR) with 95% CI.

Results: Of the 772 references identified through the database search, 17 were included in this systematic review. The number of participants in the included studies ranged from 99 to 6658, and the duration of follow-up varied from 3 months to 9.8 years. Eleven out of 12 studies assessed the impact of sarcopenia on mortality. The results showed a higher rate of mortality among sarcopenic subjects (pooled OR of 3.596 (95% CI 2.96-4.37)). The effect was higher in people aged 79 years or older compared with younger subjects (p=0.02). Sarcopenia is also associated with functional decline (pooled OR of 6 studies 3.03 (95% CI 1.80- 5.12)), a higher rate of falls (2/2 studies found a significant association) and a higher incidence of hospitalizations (1/1 study). The impact of sarcopenia on the incidence of fractures and the length of hospital stay was less clear (only 1/2 studies showed an association for both outcomes).

Conclusion: Sarcopenia is associated with several harmful outcomes, making this geriatric syndrome a real public health burden.

INTRODUCTION

The term sarcopenia was first coined by Rosenberg et al. in 1989[1] to define a progressive loss of muscle mass with advancing age. This very first definition included only the notion of muscle mass. However, with time, the definition has expanded to incorporate the notion of muscle function, including reduced muscle strength and/or physical performance. Currently, several definitions of sarcopenia have been proposed[2–10], but no worldwide consensus has yet been reached. It is important to note that sarcopenia is now recognized as an independent condition by an ICD-10-CM code[11].

Currently, some potential consequences of sarcopenia on individual health and public health[12] have been suggested, including physical disabilities, depression, decreased quality of life, nursing home admission and even death. However, it is not always clear whether these consequences were determined from longitudinal studies or simply from cross-sectional studies, in which case it would be incorrect to define these health issues as "consequences"; they would be more appropriately called "associations". Moreover, it appears that the consequences of sarcopenia can vary according to the operational definition used for the diagnosis of sarcopenia. For example, Bishoff-Ferrari[13] compared the ability of different operational definitions to predict falls. It appears that the relative risk (RR) of falls for sarcopenia patients could vary from 1.82 (95% CI 1.24-2.69) to 0.61 (95% CI 0.24-1.55) depending on the definition used to diagnose sarcopenia.

To avoid ambiguity surrounding the interpretation of the consequences of sarcopenia and move gradually, it would be interesting to identify the consequences of sarcopenia related to one unique definition of sarcopenia. A couple of years ago, the European Working Group on Sarcopenia in Older People[3] reached a consensus and defined sarcopenia as a progressive and generalized loss of muscle mass and muscle function (muscle strength or physical performance) with advancing age. To reinforce its validity, this recent operational definition still needs to show its ability to predict the clinical outcomes of sarcopenia.

The aim of this research is therefore to identify all short-, middle- and long-term consequences of sarcopenia, as defined by the European Working Group on Sarcopenia in Older People (EWGSOP)[3], specifically reported in prospective studies.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement has been followed for all steps of this research.

Literature search

The electronic databases MEDLINE, EMBASE, EBM Reviews, Cochrane Database of Systematic Review, EBM Reviews ACP Journal Club, EBM Reviews Database of Abstracts of Reviews of Effects (DARE) and Allied and Complementary Medicine (AMED) were searched for cohort studies assessing the clinical and health consequences of sarcopenia. No date limit was applied. The search strategy and search terms used for this research are detailed in Table 1. Additional studies were identified through a manual search of the bibliographic references of relevant articles and existing reviews.

Study selection

In the initial screening stage, two investigators independently reviewed the title and abstract of each of these references to exclude articles irrelevant to the systematic review. Rigorous inclusion criteria were adhered to (Table 2). In the second step, the two investigators independently read the full texts of the articles that were not excluded in the initial stage, then selected the studies that met the inclusion criteria. All differences of opinion regarding the selection of articles were resolved through discussion and consensus.

Studies dealing with sarcopenia associated with cancer cachexia or neurological diseases, any malignant disease, inflammatory or autoimmune diseases, corticosteroids for systemic use and obesity were excluded.

Data extraction

Data were extracted independently by two reviewers according to a standardized data extraction form. The following data were extracted: authors; journal name; year of publication; country; objective of the study; socio-demographic data (country, type of population, sex ratio, mean age); sample size; design (length of intervention, number of groups, description of groups); tools used to assess muscle mass, muscle strength and physical performance; reported prevalence of sarcopenia; outcomes; conclusion; presence of conflicts of interest; and potential funding.

To include as many studies as possible in our systematic review, we systematically contacted authors or co-authors when information was missing in the full-text paper.

Methodology quality assessment

The assessment of methodological quality was performed independently by two reviewers using the Newcastle-Ottawa Scale (NOS). A quality score was calculated based on three categories: group selection (four items), comparability between groups (one item), and outcome and exposure

assessment (3 items). A maximum of one point could be awarded for each item in the group selection and outcome and exposure assessment categories. A maximum of two points could be awarded for comparability. Thus, the maximum possible score was nine points, which represented the highest methodological quality. Studies were considered high quality if they scored above the median of seven points. Disagreements between the reviewers were discussed until consensus was reached.

Synthesis of the results

The findings were evaluated in a descriptive manner based on the information provided by each of the included studies. For outcomes reported by three or more studies, a meta-analysis was performed. Study results were expressed as odds ratios (OR) with 95% CI. When available, adjusted ORs were reported. Otherwise, crude ORs were computed from the available results in the paper. We decided to use/compute ORs instead of HRs because HRs were not available for all studies and were impossible to compute with the data available in the different papers. When one study reported results for different time points, we decided to include only the results for the longest follow-up point. To evaluate the impact of individual studies on the overall results, we performed a one-way sensitivity analysis by omitting one study at a time and then repeating the analysis.

Since participant demographics and clinical settings differed among studies, we assumed the presence of heterogeneity a priori. Therefore, we used a random-effects model to pool the results. We assessed heterogeneity using the χ_2-test of heterogeneity and the I^2 measure of inconsistency. Moreover, analyses of subgroups based on the clinical setting (community-dwelling, hospitalized and institutionalized people), NOS score (according to the median quality), age (according to the median age), length of follow-up (according to the median length of follow-up) and the tool used to measure muscle mass (Dual-Energy X-Ray Absorptiometry (DXA), Bioelectrical impedance analysis (BIA) or anthropometric measurements) were performed. A test of interaction using a mixed-effects model was performed for all subgroups to establish whether the difference in effect size among subgroups was statistically significant.

Potential publication bias was explored by means of a funnel plot. We used the Egger's regression asymmetry test to detect publication bias.

For all results, a two-sided p value of 0.05 or less was considered significant. All analyses were performed using the software package Comprehensive Meta Analysis, Biostat v2.

RESULTS

Search strategy

A total of 1026 studies were identified through electronic database searches. Among these studies, we were able to remove 254 duplicates. Therefore, 772 articles were screened for title and abstract by two independent reviewers. Only 16 studies met the inclusion criteria, but two of these studies described the same results. As a result of a manual search of the bibliographies of pertinent papers, we were able to identify two additional studies. Therefore, 17 prospective studies assessing the outcomes of sarcopenia, defined according to the EWGSOP guidelines, were included in this systematic review (Figure 1).

Included studies

All of these studies (characteristics presented in Table 3) were quite recent since they were published between 2012 and 2015. Most of the studies were performed in Europe (9/17 studies[14–22]), while 5 were performed in America (2 in USA, 3 in South America) [23–27], and 3 were performed in Asia[28–30]. All of the studies included subjects aged 60 years or older; 11 studies included community-dwelling older people[16,17,20,24–30], 4 included hospitalized subjects[14,15,19,22], and 2 involved nursing home residents[18,21]. Only one study included only men[27]; all of the others were mixed-gender studies, with the percentage of women varying between 48.9%[30] and 75%[18]. The number of participants ranged from 99[15] to 6658[26], and the duration of follow-up varied from 3 months[15,19,22] to 9.8 years[27]. Sarcopenia was diagnosed according to the algorithm proposed by the EWGSOP. Muscle mass was measured using bioelectrical impedance analysis (BIA) in the majority of studies (7/17 studies[14,15,18–20,22,28]), followed by anthropometric measurements (6/17 studies[16,17,21,23–25]) and, finally, by Dual-Energy X-ray Absorptiometry (DXA) (4/17 studies[26,27,29,30]). Muscle strength was measured using handgrip strength in all of studies except for one[30], which used an isokinetic device. Finally, only one study used the Short Physical Performance Battery (SPPB)[30] test to measure physical performance; all other studies used gait speed. The prevalence of sarcopenia varied from 4.3% in a population of ambulatory community-dwelling men[27] to 73.3% among nursing home residents in Turkey[21].

The studies reported results for approximately 6 different types of consequences: mortality (12 studies[14–16,18–21,23,25,27,29,30]), functional decline (7 studies[15,20,22,24,27–29]), falls (2 studies[17,27]), fracture (2 studies[26,27]), length of hospital stay (2 studies[22,29]) and hospitalization (1 study[20]).

Mortality

A total of 12 studies reported results for mortality[14–16,18,20,21,23,25,27,29,30].

One study scored 5/9[15] on the NOS, 7 scored 7/9[14,16,19,20,27,29], 3 scored 8/9[18,23,30] and one scored 9/9[21], indicating excellent quality. The population was composed of ambulatory community-dwelling subjects in 7 of these studies[16,20,23,25,27,29,30], hospitalized subjects in 3 studies[14,15,19] and nursing home residents[18,21] in the two last. A higher risk of mortality was found for sarcopenic subjects compared with non-sarcopenic ones in 10/12 studies. In one[31] of these studies, the results were only significant for sarcopenic men and not for sarcopenic women. A meta-analysis was performed to compute the results of these different studies. Because we contacted the authors or co-authors when information was missing from the full-text paper, we were able to obtain the ORs of all studies. An overall OR of 3.596 (95% CI 2.96-4.37) was found, indicating a higher risk of mortality for sarcopenic subjects compared with non-sarcopenic ones (Figure 2A). Egger's regression analysis showed that publication bias was not present (p=0.80). The results of the subgroup analyses are available in Table 4. A significant difference in effect was found only for age, with a significantly higher association between sarcopenia and mortality in subjects aged 79 years or older (OR 4.42 (95% CI 3.60 – 5.42)) compared with younger subjects (OR 3.09 (2.49 – 3.84); p=0.02).

Functional decline

Seven studies[15,20,22,24,27–29] reported results regarding the association between sarcopenia and the incidence of functional disability. However, two individual studies[15,22] reported similar results for a similar population for the outcome of functional decline. We decided to keep the most recent study in our analysis. Therefore, only 6 studies were analyzed for this outcome (1 with an NOS score of 6/9[22], 4 with an NOS score of 7/9[20,24,27,29], 1 with an NOS score of 8/9[28]). Five out of these 6 studies found a significantly greater decline of function (assessed using the ADL-Katz scale[20,24,28], the IAD-Lawton scale[20,24,28], the Barthel Index[22] and self-reported functional limitations[27,29]) in sarcopenic subjects compared with non-sarcopenic subjects. However, in one of these studies[29], the association was significant only for men and not for women. The pooled results indicated a higher risk of functional disability for sarcopenic subjects compared with non-sarcopenic ones (pooled OR 3.03 (95% CI 1.80- 5.12)). No publication bias was found for this meta-analysis (p=0.37). The results of the subgroup analyses are available in Table 3. No effect of age, length of follow-up or of tool used to measure muscle mass was found.

Falls

Two studies[17,27] (both with a score of 7/9 on the NOS) reported results for the association between sarcopenia and the incidence of falls. One of these studies was performed on 260 community-dwelling individuals with a mean age of 86.7±5.4 years who were followed for 2 years to determine the incidence of falls[17]. The second study was performed on 5828 ambulatory community-dwelling individuals for whom the incidence of falls was recorded 3 times per year for 1 year. Both studies found a significant association between sarcopenia and the incidence of falls. In the first study[17], 27.3% of the sarcopenic subjects fell at least one time, compared with 9.8% of the non-sarcopenic ones ($p<0.001$). A crude HR of 3.45 (95% CI 1.68-7.09) was reported. The HR was still significant in a fully adjusted model (adjusted for age, gender, cognitive impairment, ADL impairment, sensory impairments, body mass index, depression, physical activity, cholesterol, stroke, diabetes, number of medications, and reactive C protein) that resulted in an HR of 3.23 (95% CI 1.25 – 8.29). In the second study[27], the authors found a higher risk of recurrent falls (at least 2 falls in one year) for sarcopenic subjects, with a significant OR equal to 2.38 (95%CI 1.75-3.23) when adjusted for age.

Fractures

Two studies[26,27] followed sarcopenic subjects to assess the incidence of fractures. The first study[26], which had an NOS score of 6/9, followed 5544 elderly men and 1114 women living in the community for 9 years and 8 years, respectively. The studies defined 4 groups: subjects with normal bone mineral density (BMD) and no sarcopenia, subjects with normal BMD but with sarcopenia, subjects with low BMD but no sarcopenia and, finally, subjects with low BMD and sarcopenia. The authors found a significantly higher incidence of all types of fractures in the sarcopenic subjects compared with the non-sarcopenic subjects only when the sarcopenic subjects also presented with low BMD. The HRs varied from 3.75 (95% CI 2.64-5.32) for men to 2.8 (95% CI 1.72-4.58) for women in the crude model and from 3.79 (95% CI 2.65-5.41) for men and 2.27 (95% CI 1.37-3.76) for women in the multivariable adjusted model. The results followed the same trend when traumatic fractures were excluded from the analyses. The second study[27], which had an NOS score of 7/9, followed 5934 ambulatory community-dwelling men to determine the incidence of hip fracture and did not report any association between sarcopenia and the incidence of hip fractures (OR adjusted for age and BMD 1.17 (95% CI 0.71-1.93)).

Length of hospital stay

Two studies[22,29] followed sarcopenic subjects to assess the impact of sarcopenia on the length of stay during hospitalization. The first study[22], which had an NOS score of 6/9, included 99

hospitalized elderly men and women aged 84.6±6.6 years. The authors did not report a significant difference in the length of hospital stay in a referral acute care unit between the sarcopenic patients (19.5 ± 16.3 days) and the non-sarcopenic patients (15.0 ± 9.9 days; p=0.179). In contrast, the second study[29], which had an NOS score of 7/9, followed 3999 community-dwelling elderly men and women for 7 years and found a significantly higher percentage of sarcopenic men than non-sarcopenic men had a hospital stay longer than 20 days during follow-up. An adjusted OR (for age, education, COPD, diabetes mellitus, hypertension, heart disease, current smoker, MMSE, and depression) of 1.84 (95%CI 1.32-2.58) was found. No such difference was found for women.

Hospitalization

Only one study[20], with a score of 7/9 on the NOS scale, followed sarcopenic subjects to assess the impact of sarcopenia on the incidence of hospitalization. A total of 538 community-dwelling elderly subjects aged 77.1±5.5 years were followed for a median of 55 months. Among the sarcopenic subjects (there was a 10.2% prevalence of sarcopenia), 60% were hospitalized during the follow-up versus 48% of the non-sarcopenic subjects. The risk of hospitalization was higher in sarcopenic subjects, with a crude HR of 1.57 (95% CI 1.09-2.26) and a fully adjusted HR (adjusted for age, gender, comorbidities, BMI, education, and hemoglobin) of 1.57 (95% CI 1.03-2.41).

DISCUSSION

The purpose of this systematic review and meta-analysis was to present and evaluate the clinical and socio-economic consequences of sarcopenia. A clear synthesis of the outcomes of sarcopenia was lacking in scientific literature. To avoid confounding consequences that were only related to low muscle mass or low muscle function separately with consequences that were directly attributable to sarcopenia itself, which is now defined by both reduced muscle mass and limited muscle function, we decided to focus on definitions that included both of these concepts. However, since various proposed operational definitions could lead to differences in the ability to predict an outcome, only one definition was included in this systematic review (i.e., the EWGSOP definition).

No fewer than 17 prospective studies were included in our systematic review and meta-analysis. Across these studies, we identified 6 different types of outcomes. The most studied consequence of sarcopenia is mortality. Indeed, 12 studies reported data for mortality, and 10 suggested a significant relationship between sarcopenia and mortality. Because of the high number of studies focusing on this outcome, we were able to perform a meta-analysis, which indicated that sarcopenia patients faces a 4 times higher risk of mortality than non-sarcopenic subjects. The results did not vary according to

the settings of the participants (community dwelling versus hospitalized subjects versus nursing home residents) or to the length of follow-up. Only age seems to have an impact on the results; as expected, there was a higher association of mortality with sarcopenia among subjects aged 79 years or older. Recently, another meta-analysis[32] that aimed to assess the association between sarcopenia and mortality was published; however, the authors did not focus on a unique definition and therefore also included studies that used only muscle mass-based definitions of sarcopenia. Nevertheless, they also found a significantly higher risk of mortality in sarcopenic subjects compared with non-sarcopenic subjects, with an HR of 1.87 (95% CI 1.61-2.18). It must be pointed out that no difference has been observed regarding the definition used for sarcopenia; a higher risk of mortality was found for sarcopenic subjects regardless of the definition used for the diagnosis. Another well-studied outcome of sarcopenia across the scientific literature is functional decline. Six out of 7 studies reporting functional decline as an outcome of sarcopenia showed a significant association. It has been suggested that sarcopenic subjects have a 3 times higher risk of functional decline or functional disability compared with non-sarcopenic subjects. Significant heterogeneity was found in this meta-analysis, probably because of the different methods used to measure functional decline (the ADL-Katz scale[20,24,28], the IAD-Lawton scale[20,24,28], the Barthel Index[22] and self-reported functional limitations[27,29]). This heterogeneity was presumed and, for this reason, we decided to use a random effects model and to perform some subgroup analyses. It should be noted that neither the age of the participants, the length of follow-up nor the tool used to measure muscle mass seemed to interact with the observed association between sarcopenia and functional decline. Four other types of consequences (i.e., the incidence of falls, the incidence of hospitalization, the incidence of fractures and the length of hospital stay) were also identified across the 17 included studies. However, the limited number of studies reporting these outcomes did not allow us to perform meta-analyses. We did not find any other reported consequences of sarcopenia in the literature based on our search strategy. It is regrettable that there are still no available regarding the consequences of sarcopenia, as defined by the EWGSOP, on quality of life. Some transversal data are available[33–36], but we did not identify any prospective studies on this topic. However, this lack is probably because, before last year, no specific quality of life questionnaire for sarcopenia was available in the literature. In 2015, a specific health-related quality of life questionnaire for sarcopenia was developed and validated by our team[37]. It should be very interesting to obtain prospective data about quality of life and its impact on individuals with sarcopenia.

Several operational definitions of sarcopenia are currently proposed in the scientific literature. Although the definition proposed by the EWGSOP is one of the most widely used in current epidemiological studies, it still needs to obtain scientific validation and be recognized as able to

predict the health and clinical outcomes of sarcopenia. The present systematic review provides key elements favorable to this validation. Indeed, the majority of studies identified by this systematic review showed an association between sarcopenia, as defined by the EWGSOP, and health-related clinical outcomes.

With the exception of mortality and functional decline, for which we have a substantial number of scientific papers, there are few epidemiological studies assessing the association with other outcomes. However, our systematic review draws on the state of the art and opens doors for the development of future prospective studies. For the development of these future studies, it is important to follow some standardization regarding the definition of sarcopenia used for the diagnosis. Indeed, some studies suggest that the use of different definitions of sarcopenia has a substantial impact on its reported prevalence and outcomes[13,38]. However, it should be noted that even if the tools used to define sarcopenia have been suggested to have an important impact on the prevalence of sarcopenia[39,40], the results of our meta-analysis suggest that the impact on health-related outcomes is more limited.

This study was the first to present a list of the consequences of sarcopenia based on a systematic review. We searched in multiple electronic databases to identify a maximum possible number of studies that would meet our inclusion criteria. An important strength to highlight is that we contacted several authors of studies to obtain the data needed to compute ORs and information that was missing from the published papers. We obtained replies from 6 authors, which allowed us to include these studies in the meta-analysis. Nevertheless, this study has some limitations, particularly in the quantitative synthesis of results. Indeed, because some heterogeneity was found in the way that results were reported across studies (i.e., some authors reported HRs, some crude and some adjusted on confounding parameters, while others authors reported ORs, some crude and some adjusted), we decide to use ORs because we were able to compute ORs using the incidence data available in the papers. With this method, however, we most often reported crude ORs, which did not take into account some potential confounding factors. Moreover, there was considerable variation in the length of follow-up across studies, which can also have an impact on the results. The shortest length of follow-up was three months, while the longest was 9.8 years, which can influence the accuracy for estimating the risk of mortality or functional decline. However, we tried to take this parameter into account by performing subgroup analyses. The results did not show any effect on the length of follow-up, mortality, or functional decline. Notwithstanding the aforementioned limiting factors of this research, we believe that these findings can serve as a worthy reference for researchers and clinicians in their future evaluation of sarcopenia. Given its consequences, sarcopenia can be considered an important public health problem, and preventive and therapeutic interventions deserve to be further

developed. The results can also serve the industry by defining an outcome point for clinical studies and assessing sample sizes for clinical trials. Furthermore, they can serve as a basis for future decision making regarding the health care system.

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Table 1. Search strategy

1. Sarcopenia/
2. Sarcopeni$.tw
3. Ewgsop.tw
4. Exp cohort studies/
5. Cohort stud$.tw
6. Cohort analy$.tw
7. Follow-up stud$.tw
8. Longitudinal stud$.tw
9. Prospective stud$.tw
10. Observational stud$.tw
11. or/1-3
12. or/4-10
13. And/11-12

Table 2. Inclusion criteria

Design	Prospective studies (with at least two prospective evaluations)
Participants	Human, middle-aged and elderly men and women
Diagnosis of sarcopenia	Based on the EWGSOP definition (presence of low muscle mass + either low muscle strength or low physical performance (low gait speed or low SPPB test)).
Outcome	Report of at least one outcome of sarcopenia
Language	English

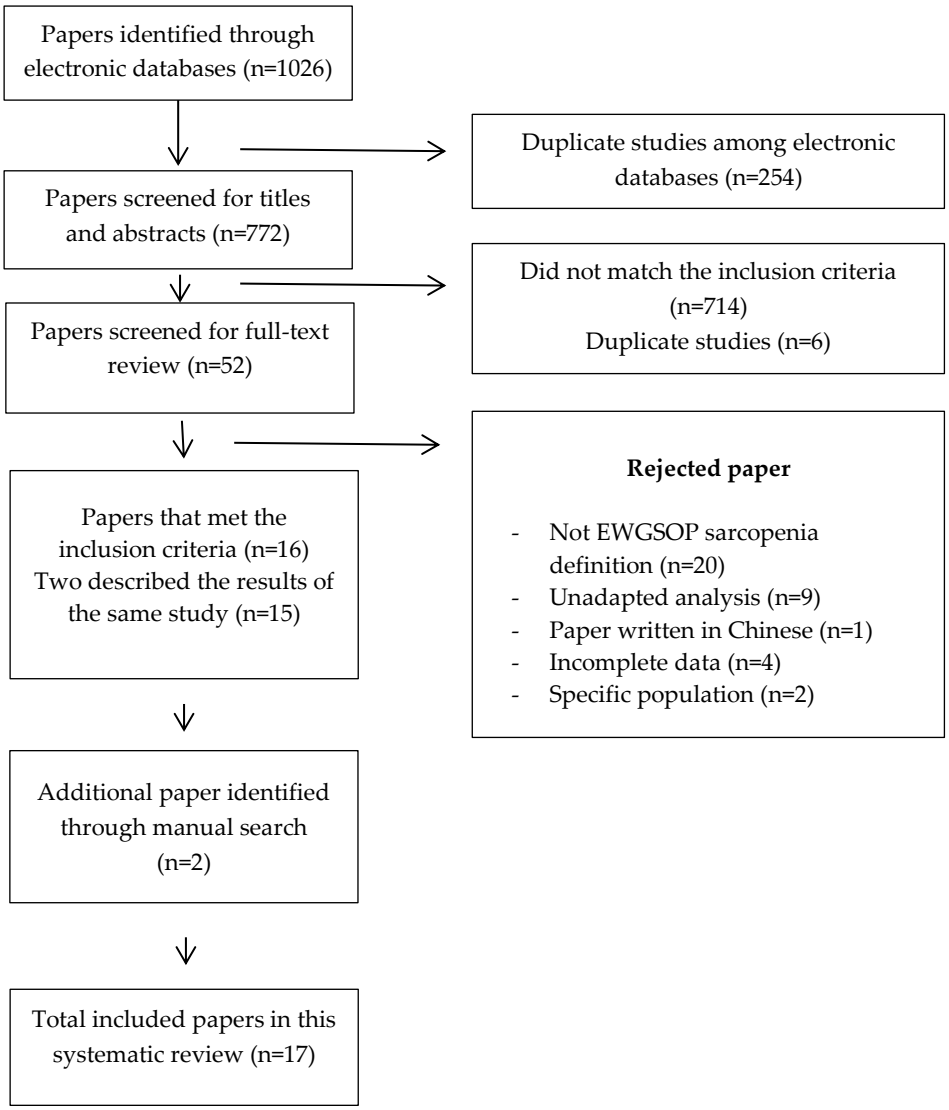
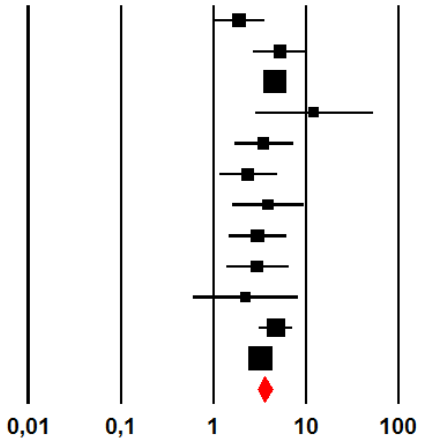


Figure 1. Search strategy

Figure 2. Mortality (A) and functional decline (B) as outcomes of sarcopenia

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Arango-Lopera, 2013	1,866	0,978	3,561	1,892	0,059
Bianchi, 2015	5,239	2,705	10,145	4,911	0,000
Cawthon, 2015	4,580	3,501	5,992	11,101	0,000
Cerri, 2015	12,133	2,815	52,300	3,348	0,001
Da Silva, 2014	3,462	1,661	7,216	3,314	0,001
Kim, 2014	2,360	1,153	4,833	2,349	0,019
Landi, 2012	3,873	1,572	9,542	2,943	0,003
Landi, 2013	2,992	1,465	6,111	3,008	0,003
Saka, 2015	2,964	1,364	6,441	2,743	0,006
Sanchez-Rodriguez, 2014	2,199	0,600	8,055	1,189	0,234
Vetrano, 2014	4,716	3,109	7,153	7,295	0,000
Woo, 2015	3,190	2,542	4,003	10,013	0,000
	3,596	2,957	4,373	12,821	0,000

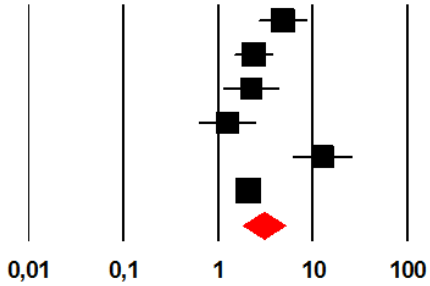


2A. Mortality and sarcopenia

Heterogeneity Q-value 16.05; df(Q) 11; p-value 0.14; I^2 31.4

* All ORs were crude ORs.

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Bianchi, 2015	4,890	2,677	8,931	5,164	0,000
Cawthon, 2015	2,420	1,495	3,917	3,597	0,000
Da Silva, 2014	2,260	1,124	4,545	2,287	0,022
Sanchez-Rodriguez, 2015	1,273	0,624	2,597	0,663	0,507
Tanimoto, 2013	12,820	6,059	27,125	6,671	0,000
Woo, 2015	2,100	1,591	2,772	5,239	0,000
	3,034	1,799	5,118	4,162	0,000



2B. Functional disability and sarcopenia

Heterogeneity Q-value 27.99; df(Q) 5; p-value <0.001; I^2 82.1.

* Only the OR reported in the Cawthon et al. study was age-adjusted. All other ORs were crude.

Table 3. Study characteristics

First author's name	Sociodemographic data 1.Country 2. Type of population 3. Sex ratio 4. Mean age	Sample size	Design 1.Time of follow up 2. Number of groups 3. Description of groups	Tool used to assess muscle mass	Tool used to assess muscle strength	Tool used to assess physical performance	Prevalence of sarcopenia	Outcomes	NOS quality assessment
da Silva, 2014a[23]	Brazil Community-dwelling adults Age ≥ 60 years Age: 69.6 ± 0.6 years Women: 59.5%	1149	5 years (mean follow-up of 4.19 ± 0.4 years) Two groups: Sarcopenic Non-sarcopenic	Anthropometric equation: Lee equation	Hand-held dynamometer	Gait speed determined by the walk test of the SPPB (4 m)	15.4%	Mortality	8
da Silva, 2014b[24]	Brazil Community-dwelling adults Age ≥ 60 years Age: 68.9 ± 0.4 years Women: 56.5%	328	4 years Two groups: Sarcopenic Non-sarcopenic	Anthropometric equation: Lee equation	Hand-held dynamometer	Gait speed determined by the walk test of the SPPB (4 m)	13.4%	Functional disability	7
Vetrano, 2014[14]	Italy Hospitalized patients Age ≥ 65 years Age: 80.8 ± 7 years Women: 56%	In-hospital mortality: 770 1-year mortality: 650	1 year Two groups: Sarcopenic Non-sarcopenic	BIA	Hand-held dynamometer	Gait speed (4 m)	28%	Mortality (in hospital, one-year mortality)	7
Sanchez-Rodriguez, 2014[15]	Spain Hospitalized patients Age ≥ 75 years Age: 84.6 ± 6.6 years (range: 76 to 80.5 years) Women: 61,6%	99	3 months Two groups: - Sarcopenic - Non-sarcopenic	BIA	Hand-held dynamometer	None	46.5%	Mortality Functional status	5
Sánchez-Rodríguez, 2015[22]	Spain Hospitalized patients Age ≥ 70 Age: 84,1 ± 8,5 years Women: 62 (62%)	100	3 months Two groups: - Sarcopenic - Non-sarcopenic	BIA	Hand-held dynamometer	Gait speed (4 m)	58%	Functional status Length of stay	6

Tanimoto, 2013[28]	Japan Community-dwelling elderly Age: ≥ 65 Age: Men: 73.3 ± 5.9 years / Women: 73.1 ± 6.2 years Women: 63,4% (471)	716	2 years Three groups: - Sarcopenic - Intermediate - Non-sarcopenic	BIA	Hand-held dynamometer	Gait speed (5 m)	9.36%	Functional disability	8
Arango-Lopera, 2013[25]	Mexico Community-dwelling elderly Age: ≥ 70 Age: 78.5 ±7 years Women: 53.3%	345	3 years Two groups: Sarcopenic Non-sarcopenic	Calf circumference	Hand-held dynamometer	Gait speed	33.6%	Mortality	7
Landi, 2013[16]	Italy Frail octogenarians living in the community Age: 80 to 85 years Age: 82.2 ± 1.4 years Women: 131 (66.5%)	197	7 years Two groups: Sarcopenic Non-sarcopenic	Mid-arm muscle circumference (MAMC)	Handgrip dynamometer	Gait speed (4 m)	21.8%	Mortality	7
Landi, 2012a[17]	Italy Community-dwelling individuals Age: ≥ 80 Age: 86,7 ± 5.4 years Women: 177 (68%)	260	2 years Two groups: - Sarcopenic - Non-sarcopenic	Mid-arm muscle circumference (MAMC)	Handgrip dynamometer	Gait speed (4 m)	25.4%	Fall	7
Landi, 2012b[18]	Italy Elderly adults living in a nursing home Age: ≥ 70 Age: 84.1 ± 4.8 years Women: 91 (75%)	122	6 months Two groups: - Sarcopenic - Non-sarcopenic	BIA	Handgrip dynamometer	Gait speed (4 m)	32.8%	Mortality	8
Cerri, 2015[19]	Italy Elderly adults hospitalized with malnutrition or at risk of malnutrition Age: ≥ 65 years Age: (years) 84.2 ± 7.1 (range: 66-100) Women: 61 (59.2%)	103	3 months Three groups: Sarcopenic Non-sarcopenic Uncertain diagnosis	BIA	Handgrip dynamometer	Gait speed (4 m)	21.4%	Mortality	7

Woo, 2015[29]	China Community-living elderly adults Age: ≥ 65 years Mean age: 75,4 years Women: 246 (55.2%)	Varying between 1872 and 4000, depending on the outcome	4 -10 years, depending on the outcome of interest Two groups: Sarcopenic Non-sarcopenic	DXA	Handgrip dynamometer	- Gait speed (6 m) - Chair stands	9.02%	Mortality Functional disability Length of stay	7
Bianchi, 2015[20]	Italy Community-dwelling elderly adults Age: ≥ 65 years Age: 77.1 ± 5.5 Women: 288 (53.5%)	538	55 months (median of follow-up) Three groups: - Sarcopenic - Pre-sarcopenic - Non-sarcopenic	BIA	Handheld dynamometer	Gait speed (4 m)	10.2%	Mortality Hospitalization Functional disability	7
Chalhoub, 2015[26]	USA Community-living elderly adults Age: ≥ 65 years Mean age: 76.8 years Women: 16.7% (1114) Men: 5544	6658	Men (MrOS): 9 years Women (SOF): 8 years 4 groups: - Normal BMD, No sarcopenia - Normal BMD, Sarcopenia - Low BMD, No sarcopenia - Low BMD, Sarcopenia	DXA	Dynamometer	Gait speed (6 m)	5.57%	Fractures	6
Saka, 2015[21]	Turkey Nursing home residents Age: ≥ 65 years Mean age: 78.0 ± 7.9 years (65–101) Women: 49% (199)	402	1 year 4 groups: Sarcopenia - MN/MR - Sarcopenia - MN/MR + Sarcopenia + MN/MR - Sarcopenia + MN/MR +	Anthropometric measurements: - Calf circumference - Mid-upper arm circumference	Handheld dynamometer	Gait speed (4 m)	73.3%	Mortality	9
Cawthon, 2015[27]	USA Ambulatory community-dwelling men Age: ≥ 65 years Mean age: 76.6 years 100% men	Varying between 3726 and 5934, depending on the outcome	9.8 years Two groups: - Sarcopenic - Non-sarcopenic	DXA	Handgrip strength	- Gait speed (6 m) Average of two trials - Chair stands	4.3 %	Mortality Falls Fractures Functional limitations	7
Kim, 2014[30]	Korea Community-dwelling older adults Age: ≥ 65 years Mean age: 73.6 years Women: 48.9% (272)	556	6 years Two groups: - Sarcopenic - Non-sarcopenic	DXA	Isokinetic device at an angular velocity of 60°/s	SPPB score	ASM/ht2 : 8.8% ASM/wt : 26%	Mortality	8

Table 4. Subgroup analyses

	Number of studies	OR (95% CI)	p-value
Mortality			
Clinical settings			
Community	7	3.39 (2.65 – 4.33)	0.63
Hospital	3	4.73 (2.46 – 9.12)	
Nursing home	2	3.32 (1.84 – 5.98)	
Age			
≤ 79 years	6	3.09 (2.49 – 3.84)	0.02
> 79 years	6	4.42 (3.60 – 5.42)	
Length of follow-up			
≤ 36 months	6	3.31 (2.17 – 5.07)	0.23
> 36 months	6	3.72 (3.02 – 4.60)	
NOS score			
≤ 7 points	8	3.75 (2.90 – 4.84)	0.38
> 7 points	4	3.04 (2.07 – 4.48)	
Tool used for muscle mass measure			
BIA	4	4.84 (3.47-6.74)	0.06
DXA	4	3.58 (2.73-4.63)	
Anthropometric measures	4	2.67 (1.84-3.87)	
Functional decline			
Age			
≤ 75 years	3	3.79 (1.36 -10-6)	0.52
> 75 years	3	2.52 (1.26 – 5.03)	
Length of follow-up			
≤ 51.5 months	3	3.31 (0.87 – 12.55)	0.79
> 51.5 months	3	2.75 (1.75 – 4.31)	
Tool used for muscle mass measure			
BIA	3	4.24 (2.87-6.27)	0.29
DXA	3	2.18 (1.74-2.74)	

Nb. Subgroup analyses for clinical settings and NOS score could not be performed for functional decline given the limited number of studies for these groups (one unique study with a NOS score ≤ 7 and one unique study performed with hospitalized subjects).

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Quality of life and physical components linked to sarcopenia: The SarcoPhAge study

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ABSTRACT

Introduction: The SarcoPhAge project is an ongoing longitudinal study following community-dwelling elderly subjects with the objective to assess some health and functional consequences of sarcopenia. The sarcopenia diagnosis algorithm developed by the European Working Group on Sarcopenia in Older People (EWGSOP) and used in the present study needs further validation through cross-sectional and longitudinal studies. The aim of the present study is to assess, using this algorithm, the prevalence of sarcopenia and the clinical components linked to this geriatric syndrome.
Methods: Participants were community dwelling subjects aged 65 years or older. To diagnose sarcopenia, we applied the definition of the EWGSOP. Muscle mass was measured by dual-energy X-ray absorptiometry, muscle strength by a hydraulic dynamometer and physical performance by the SPPB test. Large amounts of socio-demographic, anamnestic and clinical data were collected in all subjects.
Results over one year: 534 subjects were recruited for this study (60.5% of women, mean age of 73.5 ± 6.16 years), among whom 73 subjects were diagnosed sarcopenic, which represents a global prevalence of 13.7%. Prevalence was 11.8% in men and 14.9% in women. Sarcopenic subjects were older; had a lower Body Mass Index, lower calf, waist, wrist and arm circumferences; presented more cognitive impairments (Mini-Mental State Examination), more comorbidities; were more often malnourished; and consumed more drugs. After adjustment for age, BMI, cognitive status, nutritional status, number of comorbidities and number of drugs, sarcopenic subjects had a worse physical health-related quality of life (SF-36) for the domain of physical functioning, were at higher risk of falls (Timed Up and Go test), were more frail (Fried), presented more often tiredness for the achievement of activities of daily living (Mobility-test), presented less fat mass and obviously less lean mass. Sarcopenic women were also more dependent for housekeeping and handling finances (Lawton scale) than non-sarcopenic ones.
Conclusion: Sarcopenia seems to be associated with many harmful clinical components making this geriatric syndrome a real public health burden. Follow-up data of the SarcoPhAge study will be helpful to assess the outcomes of sarcopenia based on the EWGSOP diagnosis algorithm and its different proposed cut-offs.

1. Introduction

Sarcopenia is defined as a geriatric syndrome characterised by a progressive decrease in skeletal muscle mass, resulting in loss of strength and function. This term was firstly introduced by Rosenberg in 1989 (Rosenberg, 1997) and this was the starting point of many researches and attempts to establish a clinically applicable definition. Unfortunately, there is actually no universal consensus for an operational definition of sarcopenia, which is an important issue for public health (Beaudart et al., 2014b). Indeed, this confused state makes comparisons between studies difficult and epidemiological evaluation unclear. Several cross-sectional and longitudinal studies exist in the field of sarcopenia (Akune et al., 2014; Landi et al., 2013; Legrand et al., 2013; Patel et al., 2013; Smoliner et al., 2014; Vetrano et al., 2014b; Volpato et al., 2013; Volpato et al., 2014) in order to assess the clinical components of sarcopenia but each of these studies is focused on restricted clinical characteristics. Based on this observation, the objective of our study, which is called the SarcoPhAge study, is to assess the prevalence of sarcopenia and the relationship between sarcopenia and a large amount of socio-demographic, clinical and physical components such as anthropometric data, civil status, level of education, comorbidities, use of drugs, alcohol consumption, physical activity, nutritional status, dependence in activity of daily living,

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cognitive status, depression, risk of falls, quality of life, tiredness, fat mass and also bone health. The SarcoPhAge study is an ongoing longitudinal study following community-dwelling elderly subjects. In the present paper, we lay out the methodological protocol of our study but also the cross-sectional results that compared clinical characteristics of sarcopenic subjects to non-sarcopenic subjects, diagnosed by the definition of the European Working Group on Sarcopenia in Older People (EWGSOP), in order to identify the clinical components linked to sarcopenia.

2. Methods

2.1. Population

The SarcoPhAge (Sarcopenia and Physical impairment with advancing Age) study is a 5-year prospective longitudinal study of Belgian voluntary subjects aged 65 years and older. The subjects were recruited in different departments (e.g. osteoporotic centre, geriatric centre, rheumatic centre, rehabilitation centre) from an outpatient clinic in Liège, Belgium, but also by means of press advertisement. There were no selection criteria on health or demographic characteristics except for subjects with an amputated limb or with a BMI above 50 kg/m^2 who were excluded from this research. All patients gave informed consent and the study was approved by the Ethics Committee of the University Teaching Hospital of Liège (number 2012/277).

Between June 2013 and June 2014, 534 subjects were recruited in the SarcoPhAge study. We included a maximum of subjects during this 1-year period of recruitment, and did not calculate a required sample size because we did not develop any hypotheses. All subjects were interviewed by a clinical research assistant (CRA) for a mean time of 45 min to gather socio-demographic and anamnestic data. Clinical characteristics of each patient were collected to perform a complete diagnosis of sarcopenia.

2.2. Diagnosis of sarcopenia

The definition of the European Working Group on Sarcopenia in Older People (EWGSOP) (Cruz-Jentoft et al., 2010) was applied for the diagnosis of sarcopenia. According to these experts, sarcopenia is characterised by a low muscle mass plus either low muscle strength or low physical performance, defined by the cut-off discussed by the EWGSOP. Muscle mass, muscle strength and physical performance were measured in all the subjects.

2.2.1. Muscle mass

Appendicular lean mass was measured by dual-energy X-ray absorptiometry (DXA) (Hologic Discovery A, USA). We used this technique, recommended by the EWGSOP (Cruz-Jentoft et al., 2010), because computed tomography and magnetic resonance imaging, considered as gold standards in this field, are limited in their use by high costs and concerns about radiation exposure. On the contrary, DXA, which is a method able to distinguish lean tissues from fat and bone mineral, has the advantage of exposing patients to minimal radiation. All whole-body scans were carried out by the same technician and the device was calibrated daily by scanning a spine phantom. Appendicular skeletal muscle mass (ASM) was obtained by adding skeletal muscle mass of both arms and legs. A skeletal muscle mass index (SMI), which is used for the diagnosis of sarcopenia, was calculated by dividing the ASM by the height squared. The proposed cut-offs of 7.26 kg/m^2 for men and 5.5 kg/m^2 for women (Baumgartner et al., 1998) were used.

2.2.2. Muscle strength

As recommended by the EWGSOP (Cruz-Jentoft et al., 2010), we measured subjects' handgrip strength to determine their muscle strength. Therefore, we used a hydraulic dynamometer (acquired from Saehan Corporation, MSD Europe Bvba, Belgium), calibrated at the beginning of the study for 10, 40 and 90 kg, that subjects had to squeeze as hard as possible three times with each hand (dominant and non-dominant). We used the highest result out of the six measurements recorded in our analysis (Roberts et al., 2011). For the diagnosis of sarcopenia, we used the recommended cut-offs of 30 kg for men and 20 kg for women.

2.2.3. Physical performance

For the physical performance, we used the Short Physical Performance Battery (SPPB) test. This test is composed of three separate tests: balance, 4-metre gait speed and chair stand tests. A score between 0 and 4 is assigned for each test, and the 3 tests are weighted equally. As suggested, the cut-off for the diagnosis of sarcopenia for this test, is a score of 8 points or less out of a maximum of 12 points (Guralnik et al., 2000). Gait speed is also proposed by the EWGSOP (Cruz-Jentoft et al., 2010) as a tool to assess physical performance. Given the fact that gait speed is one of the components of the SPPB test, we chose to use the SPPB test as diagnostic tool.

2.3. Clinical characteristics

2.3.1. Anamnestic data

Subjects were asked about their alcohol consumption (yes/no), smoking habits (yes/no), if they were consulting a physiotherapist (yes/no), using walking assistance (yes/no), had a prevalent fracture (yes/no) and had been hospitalized in the previous year (yes/no). The number of drugs and self-reported comorbidities were also collected. Drugs were then classed into 20 domains defined by the "Centre Belge d'Information Pharmacothérapeutique (CIPB)".

2.3.2. Anthropometric measurements

Weight at the nearest 0.1 kg, height at the nearest 0.1 cm, and calf, waist, wrist and arm circumferences at the nearest 0.1 cm were measured.

2.3.3. Activity of daily living (Katz, Lawton)

Subjects' functional limitations in activity of daily living (ADL) were assessed by the Katz scale (Katz et al., 1963) and the Lawton scale (Lawton and Brody, 1969). The Katz scale measures the independence of the subject in 6 basic and instrumental activities of daily living: bathing, dressing, toileting, transferring to and from a bed or chair, continence and feeding. A score ranging from 1 to 4 is attributed for each item depending on how independent the individual is when performing the activity. Higher score indicates higher dependence in ADL activities. The Lawton Scale (IADL) was used to assess individual performance in the following activities: using the telephone, using transportation, shopping, food preparation, housekeeping, laundry, taking medications on time, and handling finances. Score can range from 0 point to 8 points for women and from 0 point to 5 points for men (activities of food preparation, housekeeping and laundry were not calculated). Higher score indicates higher independence in IADL activities.

2.3.4. Cognitive and depression scale

Cognitive function was assessed with the Mini-Mental State Examination (MMSE) (Tombaugh and McIntyre, 1992) which consists of a brief 30-point questionnaire. A maximum score of 30 is attainable by a person without any neuropsychological impairment.

The 15-item Geriatric Depression Scale (Yesavage et al., 1982) was used to assess the level of depression of each individual. A score equal or less than 5 indicates no depression, a score between 6 and 10 indicates mild to moderate depression and a score between 11 and 15 indicates severe depression.

2.3.5. Nutritional status

Nutritional status of individuals was assessed by the Mini-Nutritional Assessment (MNA) (Guigoz et al., 1996). This test comprises two parts: a screening part followed by an assessment part. If the score obtained for the screening part was of 12 points or more on a total of 14 points, the subjects was classified as well-nourished and did not need to complete the assessment part. When subjects presented a screening score of 11 points or less, the assessment part had to be completed. The full evaluation is scored on 30 points. A score of 24 points or more indicates that the subjects is well-nourished, a score between 17 and 23.5 points indicates a risk of malnutrition and a score lower than 17 points indicates malnutrition.

2.3.6. Physical frailty

Physical frailty was diagnosed on the basis of the five FRIED criteria: weakness (dynamometer-measured grip-strength below established cut-off based on gender and BMI), low gait speed (walking speed measured on 4.5 m distance below established cut-off based on gender and height), low physical activity (self-reported time spent in physical activity in the past seven days based on the Minnesota scale below established cut-off based on sex), exhaustion (self-reported exhaustion measured by two items from the Center for Epidemiologic Studies Depression scale) and weight loss (self-reported unintentional weight loss of more than 4.5 kg in the past year) (Fried et al., 2001). The aggregate frailty score was calculated as the sum of the five component scores, ranging from 0 to 5. Subjects with a score of 0 or 1 were categorized as non-frail, with a score of 2 as pre-frail, and with a score of 3 to 5 as frail.

2.3.7. Quality of life

We assessed quality of life by using 1) the Short-Form 36 questionnaire (SF-36) (Ware and Sherbourne, 1992), composed of 36 items measuring 8 health-related quality of health domains (physical functioning (PF), role limitation due to physical problems (RP), bodily pain (BD), general health (GH), vitality (VT), social functioning (SF), role limitation due to emotional problem (RE), and mental health (MH)) scored on a scale from 0 (worst quality of life) to 100 (best quality of life) using the standard SF-36 scoring algorithms; 2) the EuroQoL 5-dimension (EQ-5D) (Rabin and de Charro, 2001), which records the level of self-reported problems according to five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). A single-index value is calculated with a score range from 1 (perfect health) to 0 (death) (Cleemput, 2010); and 3) the EQ visual analogue scale (EQ-VAS) (Brooks, 1996; Rabin and de Charro, 2001), which records the patient's self-rated health on a scale ranging from 0 (worst imaginable health) to 100 (best imaginable health).

2.3.8. Tiredness

Fatigue following daily-life activities was estimated using the Mobility-Tiredness scale (Mob-T) (Avlund et al., 1993) specifically tailored to measure tiredness during daily activities in elderly persons. High scores indicate less fatigue.

2.3.9. Grip work

Grip work, or fatigue resistance test (Bautmans et al., 2011), was measured with a hydraulic handgrip dynamometer (acquired from Saehan Corporation, MSD Europe Bvba, Belgium). Subjects were asked to squeeze the dynamometer as hard as possible and to maintain the pressure until grip strength dropped to 50% of its maximum record. The grip work, or the total effort produced during this test was calculated by the following formula: Grip Work = (Grip Strength (kg) × 0.75) × Fatigue Resistance (min).

2.3.10. Risk of falls

Risk of falls was measured using the Tinetti (1986) and the Timed Up and Go (TUG) tests (Podsiadlo and Richardson, 1991). The Tinetti test consists of two subtests: a balance test (9 items scored on 16 points) and a gait test (7 items scored on 12 points). A total score of more than 24 points indicates low risk of falls, a score between 19 and 24 points indicates moderate risk of falls and a score of less than 19 points indicates severe risk of falls. For the TUG test patients were asked to stand up from a chair, walk to a marker 3 m away, turn around, walk back and sit down again. A time of more than 14 s suggests a high risk of falls.

2.3.11. Peak flow meter

Peak expiratory flow rate was measured with a Mini-Wright's peak flow meter. For this test, subjects were instructed to breathe in as much as possible and to blow into the instrument rapidly and forcefully. The test was repeated twice and the highest result, expressed in litre/min, was used for analysis.

2.3.12. Bone mineral density

BMD measurements, using DXA technology (Hologic QDR Delphi (S/N) 70249), were obtained at the level of the hip (both total and femoral neck) and the lumbar spine (L2–L4) in subjects recruited in the osteoporotic centre.

2.4. Statistical analysis

Continuous data are presented as mean ± Standard Deviation (SD). Qualitative variables were reported as absolute and relative frequencies (%).

A global presentation of all subjects' baseline characteristics was performed and the sarcopenic subjects' characteristics were compared to other subjects using a univariate analysis. Student's or Chi squared tests were therefore used.

Difference between quality of life and physical evaluation in sarcopenic and non-sarcopenic were explored by a multivariate analysis. A logistic regression has been performed on sarcopenia status and variables that presented a $p < 0.01$ in univariate analysis were included in the model. Analyses were adjusted on age and sex but also on BMI, cognitive status (MMSE), nutritional status (MNA), number of drugs and number of comorbidities. Variables were checked for multicollinearity.

Data analysis was performed using the software Statistica 9.1. Results were considered statistically significant when 2-tailed p values were less than 0.05.

3. Results

3.1. Prevalence of sarcopenia

A total of 534 subjects were recruited for this study (60.5% of women; mean age of 73.5 ± 6.16 years (Table 1)). Based on the EWGSOP algorithm, 73 subjects were diagnosed sarcopenic, which represents a global prevalence of 13.7% (Fig. 1). Prevalence in men was 11.8% and prevalence in women was 14.9%.

Prevalence of sarcopenia increases with age (Fig. 2). Between the age of 65 and 69 years ($n = 192$), a total of 12 subjects were diagnosed sarcopenic. For this age range, the prevalence of sarcopenia in women and men is comparable (16.7% versus 16%, $p = 0.94$). Between 70 and 79 years ($n = 234$), 36 subjects were diagnosed sarcopenic. The prevalence rises to 27.1% for women versus 20% for men ($p = 0.25$ between men and women). After the age of 80 ($n = 108$), 25 subjects were diagnosed sarcopenic. The sex-relationship is inverted, with 44% of sarcopenia in men compared to 29.2% in women ($p = 0.20$).

3.2. Characteristics of the SarcoPhAge population

The 73 subjects diagnosed with sarcopenia were significantly older than the rest of the population (Table 1). They also presented a lower BMI ($p < 0.001$) and lower anthropometric data ($p < 0.001$ for wrist,

Table 1
Baseline anamnestic, sociodemographic and clinical characteristics of the SarcoPhAge population.

	n	All (n = 534)	Sarcopenia (n = 73)	No sarcopenia (n = 461)	p-Value
Age	534	73.5 ± 6.16	77.1 ± 7.03	72.9 ± 5.82	<0.001
Sex	534				
Women		322 (60.3)	48 (65.7)	274 (59.4)	0.32
Civil status	533				
Married		311 (58.2)	38 (52.0)	273 (59.2)	0.59
Single		32 (5.99)	5 (6.85)	27 (5.85)	
Other status		190 (35.6)	29 (39.75)	161 (34.9)	
Level of education	534				0.21
Without qualification		11 (2.06)	2 (2.74)	9 (1.95)	
Primary school		60 (11.2)	8 (10.9)	52 (11.3)	
Secondary school		266 (49.8)	42 (57.5)	224 (48.6)	
Post-secondary education		189 (35.4)	20 (27.4)	169 (36.7)	
Doctoral		8 (1.5)	1 (1.37)	7 (1.52)	
Walking assistance	534				0.02
Yes		47 (8.80)	12 (16.4)	35 (7.59)	
Smoking					
Yes		50 (9.36)	10 (13.7)	40 (8.68)	0.17
Alcohol consumption					
Yes		263 (49.2)	29 (39.7)	234 (50.8)	0.08
1-year prevalent hospitalization					
Yes		152 (28.5)	23 (31.5)	129 (27.9)	0.03
Number of concomitant diseases	534	4.34 ± 2.50	5.14 ± 2.72	4.21 ± 2.44	0.003
Number of drugs	534	5.81 ± 3.47	6.79 ± 3.14	5.66 ± 3.50	0.01
Anthropometric data					
Height	534	163.3 ± 9.72	161 ± 9.5	163.7 ± 9.72	0.03
Weight	534	71.4 ± 16.0	59.4 ± 10.3	73.3 ± 15.9	<0.001
BMI	534	26.6 ± 4.77	22.8 ± 2.9	27.2 ± 4.74	<0.001
Calf circumference	534	34.8 ± 3.72	31.5 ± 2.74	35.3 ± 3.59	<0.001
Waist circumference	309	94.5 ± 13.3	86.2 ± 12.2	95.8 ± 13.1	<0.001
Wrist circumference	534	16.7 ± 1.60	15.8 ± 1.37	16.9 ± 1.58	<0.001
Arm circumference	534	27.9 ± 3.50	25.1 ± 2.73	28.4 ± 3.40	<0.001
MMSE score	534				
25–30 points		488 (91.4)	58 (79.4)	430 (93.3)	<0.001
21–24 points		32 (5.99)	11 (15.1)	21 (4.55)	
≤20 points		14 (2.62)	4 (5.48)	10 (2.17)	
Mini-Nutritional Assessment	534				
Well-nourished		67 (12.5)	20 (27.4)	47 (10.2)	<0.001
Risk of malnutrition		457 (85.6)	48 (65.7)	409 (88.7)	<0.001
Malnutrition		10 (1.87)	5 (6.85)	5 (1.08)	<0.001
Depression (/15 points)	526	4.06 ± 5.47	4.99 ± 3.97	3.91 ± 5.66	0.13
Short Minnesota – leisure activities	534				
Kcal/week women		993.5 ± 1151.6	1106.8 ± 1289.7	973.8 ± 1127.2	0.46
Kcal/week men		1220.1 ± 1281.2	844.3 ± 1736.1	1268.2 ± 1208.3	0.11

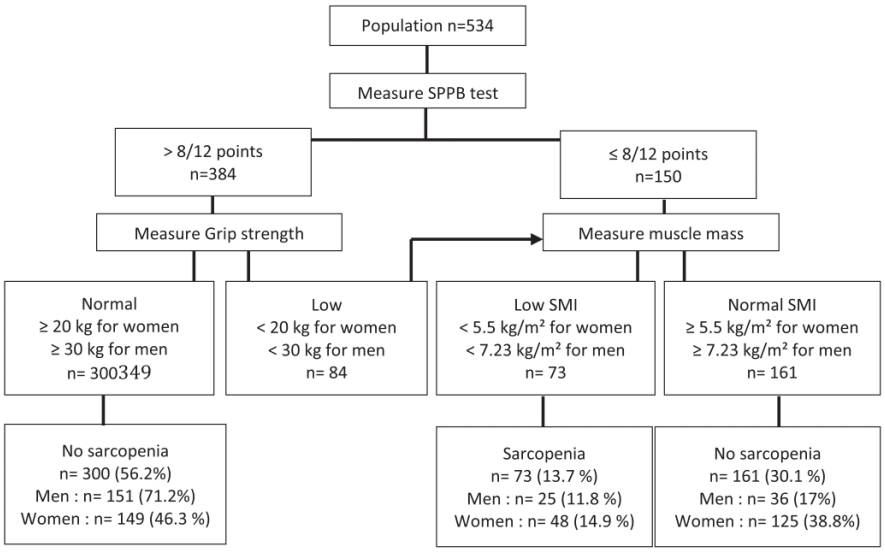

Fig. 1. Diagnostic of sarcopenia according to the EWGSOP' suggested algorithm.

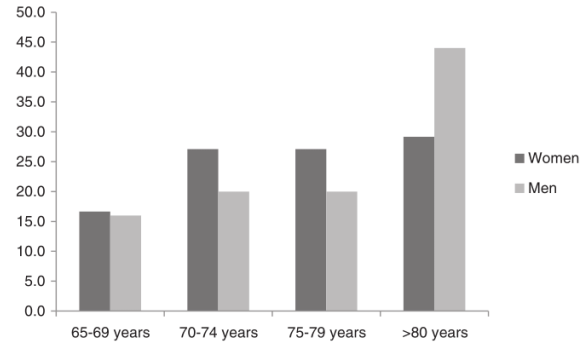

Fig. 2. Prevalence of sarcopenia (%) stratified by age and sex. Number of subjects per category: 65–69 years, n = 192 (women = 120, men = 72); 70–74 years, n = 136 (women = 81, men = 55); 75–79 years, n = 98 (women = 60, men = 38); >80 years, n = 108 (women = 61, men = 47).

calf, waist and arm circumferences). They also needed more often a walking assistance (0.02). Sarcopenic subjects took a mean of 6.79 ± 3.14 regular drugs versus 5.66 ± 3.50 for non-sarcopenic subjects ($p = 0.01$). They also took significantly more drugs acting on the respiratory system ($p < 0.001$), on the nervous system ($p = 0.008$) but also drugs for fever and pain ($p = 0.046$), for osteoarticular diseases ($p = 0.02$) and anaesthetic drugs ($p = 0.01$). Sarcopenic subjects presented a higher number of comorbidities (5.14 ± 2.72 versus 4.21 ± 2.44, $p = 0.003$). They presented significantly more respiratory troubles ($p = 0.01$), kidney troubles ($p = 0.025$) and dizziness ($p = 0.018$). Sarcopenic subjects presented a higher rate of hospitalization the year before the visit (31.5% for sarcopenic subjects compared to 27.9% for non sarcopenic subjects, $p = 0.03$) and were also significantly more malnourished ($p < 0.001$) or more at risk of malnutrition ($p < 0.001$). MMSE score was significantly lower in sarcopenic subjects compared to the others ($p < 0.001$).No difference was found between groups regarding sex, level of education, civil status, smoking, consumption of alcohol, depression or level of leisure activities.

3.3. Quality of life and physical components linked to sarcopenia

After adjustment for age, sex, BMI, cognitive status (MMSE), nutritional status (MNA), number of drugs and number of comorbidities, a sarcopenia-related decrease of quality of life in physical function ($p = 0.001$) was found using the SF-36 questionnaire. No differences in the quality of life were found for the other domains of the SF-36 questionnaire or for the EQ-VAS scale ($p = 0.20$) and the EQ-5D ($p = 0.58$).

Sarcopenic subjects do not seem more dependent than non sarcopenic subjects in the activities of daily living. Indeed, they presented a global score of 6.77 ± 1.56 points in the Katz scale versus 6.42 ± 1.14 for the non-sarcopenic subjects (p adjusted = 0.62). Regarding the IADL, the total score of the Lawton scale was 6.96 ± 1.65 points for sarcopenic women versus 7.46 ± 1.23 points for non-sarcopenic women ($p = 0.20$). However, sarcopenic women seem more dependent for some of the IADL. It was mainly housekeeping ($p = 0.02$) and the ability to handle finances ($p = 0.01$) which were the IADL significantly worse for sarcopenic women than for non-sarcopenic ones. They declared that they preferred to leave the management of finances to their husband or children. Regarding men, sarcopenic men do not seem more dependent in the different IADL than non-sarcopenic men.

In the sarcopenic population, 34.2% of subjects were also diagnosed as frail and 47.9% as pre-frail versus respectively 12.6% and 47.9% in the non-sarcopenic population ($p = 0.03$ and $p = 0.81$ respectively).

All other physical tests results were significantly worse for the sarcopenic subjects than for the non-sarcopenic ones (higher risk of falls assessed by the TUG test, lower gait speed, lower results at the peak expiratory flow, lower grip resistance, higher tiredness during mobility activities, longer time necessary to rise 5 times from a chair).

As expected, and after adjustment for age, sex, BMI, cognitive status, nutritional status, number of drugs and number of comorbidities, sarcopenic subjects presented less total lean mass ($p < 0.001$) than others. Relative fat mass was also lower in sarcopenic subjects but absolute fat mass was not (34.2% versus 34.9%). No differences were found between sarcopenic and non-sarcopenic subjects regarding BMD (g/cm^2) of lumbar spine ($p = 0.55$), hip ($p = 0.95$) and femoral neck ($p = 0.99$). These parameters have only been assessed in part of the population (Table 2).

Among our population, 28.1% (150 subjects) presented a SPPB test lower or equal to 8 points distributed as follows: 46 subjects in the sarcopenic group (63%) and 104 in the non-sarcopenic group (22.6%). In the global population, 34.6% had a grip strength below the gender specific cut-off points. In the sarcopenic group, this proportion rose to 83.6% versus 26.9% in the non-sarcopenic group. Because the diagnosis of sarcopenia depends mainly on the SMI cut-off, it is not surprising that all sarcopenic subjects presented a SMI below the cut-off proposed by the EWGSOP. However, in the non-sarcopenic group, 78 subjects (16.9%) also presented a reduced SMI value but were not diagnosed sarcopenic because of their higher value for grip strength or for the SPPB test (Table 3).

4. Discussion

In the baseline evaluation of the SarcoPhAge study, we assessed the prevalence of sarcopenia and the clinical components linked to sarcopenia among community-dwelling older people using the EWGSOP algorithm (Cruz-Jentoft et al., 2010) for the diagnosis of sarcopenia. We found a global prevalence of sarcopenia of 13.7% (14.9% in women, 11.8% in men), which is slightly higher than the prevalence found in the BELFRAIL study (Legrand et al., 2013), another prospective, observational, Belgian population-based cohort study that found a prevalence of sarcopenia of 12.5%. The 288 subjects included in the BELFRAIL study were globally older than our population (84.8 ± 3.6 years), and therefore we could have expected a lower prevalence in our cohort. However, even if they used also the EWGSOP algorithm (Cruz-Jentoft et al., 2010) for the diagnosis of sarcopenia, they did not use the DXA, but a bioelectrical impedance analysis (BIA) to measure the body composition of subjects. In the scientific literature, we found that this method is known to underestimate muscle mass (Sillanpaa et al., 2014) compared to DXA and hence, could lead to an overestimation of the prevalence of sarcopenia. Indeed, even if the EWGSOP have adapted the cut-off used for the diagnosis of sarcopenia when using BIA instead of DXA, these cut-offs were generated in an Asian population (Chien et al., 2008) which may be different from a European population. Moreover, several types of BIA devices exist and a recent study has shown that these cut-offs are probably device-dependent (Beaudart et al., 2014a, 2015). We note however that the difference in prevalence between the BELFRAIL study and our study is small and that, at the exception of age, clinical characteristics of subjects in the two cohorts are relatively similar. A recent well-conducted systematic review (Cruz-Jentoft et al., 2014) assessed the prevalence of sarcopenia across studies and found that, when diagnosed with the EWGSOP algorithm, the prevalence can range from 1 to 29% for older adults living in community depending on country, age and assessment method. As in our study, most of the studies included in the review showed that prevalence of sarcopenia is increasing with age and no gender-effect of sarcopenia is noticed in any of them. Our results confirm these observations. We also note that prevalence of sarcopenia can be dependent on the cut-off used for the diagnosis. Indeed, in the definition of the EWGSOP (Cruz-Jentoft et al., 2010), several cut-offs are proposed for muscle mass, muscle strength and physical performance. A recent study (Beaudart et al., 2014a,b) suggested a high impact of these cut-offs on the estimated prevalence of sarcopenia.

Table 2
Quality of life and physical evaluation of the SarcoPhAge population.

	n	All (n = 534)	Sarcopenia (n = 73)	No sarcopenia (n = 461)	p-Value[a]
Quality of life					
SF-36 PF (%)	526	63.4 ± 26.7	52.0 ± 29.2	65.2 ± 25.9	0.001
SF-36 SF (%)	526	69.3 ± 24.1	66.7 ± 27.9	69.8 ± 23.5	0.94
SF-36 RF (%)	526	55.2 ± 41.2	52.5 ± 42.7	55.8 ± 40.9	0.37
SF-36 RE (%)	526	59.4 ± 41.5	58.2 ± 41.3	59.6 ± 41.5	0.32
SF-36 MH (%)	526	60.7 ± 19.3	58.8 ± 20.1	61.0 ± 19.2	0.90
SF-36 VT (%)	526	50.7 ± 18.3	48.2 ± 18.1	51.1 ± 18.3	0.48
SF-36 BP (%)	526	55.6 ± 25.5	52.3 ± 29.6	56.2 ± 24.8	0.23
SF-36 GH (%)	526	57.7 ± 18.3	53.6 ± 20.2	58.4 ± 18.0	0.64
EQ-5D	534	0.64 ± 0.24	0.61 ± 0.26	0.65 ± 0.24	0.58
EQ-VAS (%)	534	69.4 ± 17.4	67.7 ± 17.4	69.7 ± 17.4	0.20
KATZ total score (6–24 points)	534	6.47 ± 1.21	6.77 ± 1.56	6.42 ± 1.14	0.62
Lawton score	534				
Women total (1–8 points)		7.38 ± 1.31	6.96 ± 1.65	7.46 ± 1.23	0.20
Men total (1–5 points)		4.78 ± 0.68	4.40 ± 1.26	4.83 ± 0.55	0.14
Frailty (FRIED score)	534				
Non-frail		195 (36.5)	13 (17.8)	182 (39.5)	0.11
Pre-frail		256 (47.9)	35 (47.9)	221 (47.9)	0.81
Frail		83 (15.5)	25 (34.2)	58 (12.6)	0.03
Tiredness					
Mobility-test (6 points)	526	4.47 ± 1.82	3.77 ± 1.79	4.58 ± 1.79	0.03
WHOQOL F2.2 (/5 points)	526	2.71 ± 0.93	2.79 ± 0.92	2.69 ± 0.93	0.97
WHOQOL F2.4 (/5 points)	526	2.66 ± 1.02	2.76 ± 1.08	2.64 ± 1.01	0.86
Grip work (kg × s)	534	421.3 ± 349.6	262.1 ± 168.1	446.7 ± 364.1	<0.001
Peak flow meter (L/min)	289	299.9 ± 145.7	206.4 ± 95.5	312.7 ± 146.9	0.01
Risk of falls					
Tinetti gait (/16 points)	534	15.5 ± 1.61	14.7 ± 2.3	15.6 ± 1.43	0.26
Tinetti walk (/12 points)	534	11.2 ± 1.75	10.4 ± 2.3	11.3 ± 1.61	0.14
Tinetti total (/28 points)	534	26.7 ± 3.26	25.1 ± 4.23	26.9 ± 3.01	0.25
Timed Up and Go (s)	534	11.6 ± 5.47	14.8 ± 7.62	11.1 ± 4.87	0.025
Gait speed (m/s)	534	0.98 ± 0.29	0.82 ± 0.28	1.00 ± 0.28	0.001
Time to raise 5 times of a chair (s)	500	14.6 ± 4.55	16.6 ± 4.51	14.3 ± 4.49	0.006
Total lean mass (kg)	534	44.9 ± 10.9	37.8 ± 7.58	46.1 ± 11.0	<0.001
Total fat mass (kg)	534	25.5 ± 8.35	21.1 ± 6.69	26.3 ± 8.38	<0.001
Total fat mass (%)	534	34.8 ± 7.37	34.2 ± 7.3	34.9 ± 7.38	0.11
BMD (g/cm^2)					
Lumbar spine	154	0.97 ± 0.19	0.95 ± 0.2	0.98 ± 0.19	0.55
Hip	154	0.80 ± 0.12	0.75 ± 0.12	0.81 ± 0.13	0.95
Femoral neck	154	0.68 ± 0.10	0.65 ± 0.12	0.69 ± 0.1	0.99

Only total lean mass (kg), total fat mass (kg) and total fat mass (%) were adjusted only on age, sex, Mini-Mental State Examination, Mini-Nutritional Assessment, number of drugs and number of comorbidities.

[a] p-Value adjusted for age, sex, Body Mass Index, Mini-Mental State Examination, Mini-Nutritional Assessment, number of drugs and number of comorbidities.

Unfortunately, no consensus on the most relevant cut-off is actually available.

In our study, we found, that BMI was lower in sarcopenic subjects than in non-sarcopenic subjects. This observation is consistent with previous works (Akune et al., 2014; Da Silva et al., 2014; Kim et al., 2014; Landi et al., 2013; Landi et al., 2012; Legrand et al., 2013; Smoliner et al., 2014; Vetrano et al., 2014a; Volpato et al., 2014) and quite expected in so far that sarcopenic subjects presented a lower amount in muscle mass. In line with these results, all anthropometric data (calf, waist, wrist and arm circumferences) seemed also lower in sarcopenic subjects. Malnutrition is also more often present in sarcopenic subjects. In 2014, Da Silva et al. (2014) also used the MNA questionnaire in their

Table 3
Characteristics linked to the diagnosis of sarcopenia.

	n	All (n = 534)	Sarcopenia (n = 73)	No sarcopenia (n = 461)	p-Value[a]
SPPB cut-off	534				
SPPB > 8 points		384 (71.9)	27 (37.0)	357 (77.4)	<0.001
SPPB ≤ 8 points		150 (28.1)	46 (63.0)	104 (22.6)	
Grip strength maximum (kg)	534				
Women		21.8 ± 6.72	17.8 ± 7.51	22.5 ± 6.8	<0.001
Men		38.7 ± 9.5	27.1 ± 6.38	40.3 ± 8.7	<0.001
Grip strength cut-off	534				
Grip strength > 20 or 30 kg		349 (65.3)	12 (16.4)	337 (73.1)	<0.001
Grip strength < 20 or 30 kg		185 (34.6)	61 (83.6)	124 (26.9)	
SMI kg/m^2	534				
Women		6.1 ± 1.01	5.06 ± 0.38	6.28 ± 0.98	<0.001
Men		7.91 ± 1.1	6.41 ± 0.45	8.11 ± 1.00	<0.001
SMI cut-off	534				
SMI > 7.26 or 5.5 kg/m^2		383 (71.7)	0 (0.00)	383 (83.1)	<0.001
SMI < 7.26 or 5.5 kg/m^2		151 (28.3)	73 (100.0)	78 (16.9)	

[a] p-Value adjusted for age, sex, Body Mass Index, Mini-Mental State Examination, Mini-Nutritional Assessment, number of drugs and number of comorbidities.

population and found a prevalence of malnutrition of 8.1% for sarcopenic subjects compared to 0.9% in non-sarcopenic subjects. These results are comparable to those we found.

Sarcopenic subjects also presented more comorbidities and consumed more drugs. These results are of a great interest in regards of public health to lighten the economic burden of sarcopenia. Up to now, no European economic data are available for sarcopenia but in the United States the health care costs related to sarcopenia are estimated at about $ 18.5 billion, being 1.5% of total health care expenditure (Janssen et al., 2004). Given the fact that sarcopenia is itself an adverse outcome of ageing and of multiple diseases, it is also a risk for other adverse events (Taekema et al., 2010). For drug consumption, our results are consistent with the studies of Smoliner et al. (2014) and of Volpato et al. (2013) regarding the number of drugs consumed. They are inconsistent with the one of Landi et al. (2012) who found no significant difference regarding the number of drug consumed by sarcopenic subjects living in nursing home.

To our knowledge, only a handful of studies assessed the risk of falls in sarcopenic subjects. In our study, we found a higher risk of falls for sarcopenic subjects compared to non-sarcopenic subjects, assessed by the Timed Up and Go test. Falls are associated with walking speed and, in our study, sarcopenic subjects presented a significant reduced gait speed compared to non-sarcopenic subjects. Moreover, physical performance, one of the components of sarcopenia, can be assessed either by the SPPB test or by the walking speed. As these two tests seem highly correlated (Beaudart et al., 2014a,b), and that the SPPB test in our study was significantly associated with sarcopenia, it was expected to find a lower gait speed in sarcopenic subjects. Falls are predictive of hospitalization, institutionalisation, disability and death (Gillain et al., 2014) which points sarcopenia as one important geriatric syndrome to care about.

Given the various impacts of sarcopenia on physical health, quality of life of subjects affected by this syndrome is very likely to be deteriorated. By now, few studies have reported data concerning quality of life for sarcopenic subjects. Patel et al. (2013), in 2013, reported a reduced quality of life in the domain of physical function and general health for sarcopenic subjects living in the UK. This confirmed a previous study (Sayer et al., 2006) showing a significant association between quality of life and grip strength. Our study highlighted also a quality of life for physical function significantly reduced for sarcopenic subjects. These results are in line with the conclusions of Rizzoli et al. (2013) who draw attention to the limits of the use of a generic quality of life questionnaire for assessing quality of life in sarcopenic subjects. Only specific domains, such as mobility or physical function, are concerned in sarcopenia and a specific tool seem necessary to assess the real impact of sarcopenia on quality of life.

This study has a number of strengths. It is not only conducted on a large sample of community dwelling-subjects, but it also takes into account a really large number of socio-demographic, anamnestic and physical variables. Therefore, the SarcoPhAge study may offer robust longitudinal evaluations on sarcopenia. Moreover, we used the EWGSOP algorithm for the diagnosis of sarcopenia, which offers the possibility of relevant comparisons with other lately published studies. Furthermore, unlike most of other studies in which muscle mass was measured with a portative device, the BIA, we used the DXA to measure muscle mass of subjects. Thereby the issue, still discussed that BIA could overestimate muscle mass and that the cut-off applied by the EWGSOP for BIA could be device-dependent has been avoided. Finally, we respected the most recent guidelines for the assessment of muscle strength, as this assessment is still often open to debate. Our study is unfortunately limited in its external validity because of the non-representativeness of our sample. The sample is mainly composed of voluntary subjects which can limit the extrapolation of our results to all women and men in Belgium. Moreover, given the low prevalence of sarcopenia, we only had 73 subjects with sarcopenia in our study. In some age categories, for example 80 years and older, we only have 25 sarcopenic subjects. This number could be low for the representativeness of our results. Another limitation, which may affect future longitudinal results, is that we do not measure lower limb muscle strength. One more limitation is that, the cut-offs proposed by the EWGSOP (Cruz-Jentoft et al., 2010) and used in our study for the diagnosis of sarcopenia, are derived from specific non-Belgian populations study. However, even if the clinical characteristics of the subjects included in these populations are probably different from the clinical characteristics of our subjects, we note that both populations are composed of elderly subjects. We also note that the cross-sectional design of our study allows the establishment of some associations between sarcopenia and physical components but unfortunately does not allow to find cause–effect relationship. Longitudinal studies are necessary to state on such a type of relationship.

5. Conclusion

Sarcopenia seems to be associated with many clinical components making this geriatric syndrome a potential public health burden. Given the ceaseless evolution of its definitions, prospective studies are still failing to both draw up a list of consequences of sarcopenia on health and find predictors of sarcopenia. Moreover, the challenge of choosing the appropriate cut-offs for the diagnosis of sarcopenia remains. A longitudinal study, such as ours, could come up with cut-off criteria for muscle mass, muscle strength and gait speed, which would be the most predictive of functional decline and should therefore be used for the diagnosis of sarcopenia.

Conflict of interest

None.

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Author contribution

CB, OB, JYR and JP conceived the study and the protocol. CB, AQ, ML, and JS were in charge of patients' recruitment and collected all data. SG helped in the recruitment of subjects and provided clinical support. FB helped in the management of data and CB performed statistical analyses. CB wrote the paper and is primarily responsible for the final content. All authors read and approved the final manuscript.

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Estimation of sarcopenia prevalence using various assessment tools

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ABSTRACT

Background: Sarcopenia is defined as a progressive and generalized loss of muscle mass with either a loss of muscle strength or a loss of physical performance but there is no recommendation regarding the diagnostic tools that have to be used. In this study, we compared the prevalence of sarcopenia assessed using different diagnostic tools.
Methods: To measure muscle mass, muscle strength and physical performance, we used for each outcome two different diagnostic tools. For muscle mass, we used Dual Energy X-Ray Absorptiometry (DXA) and bioelectrical impedance analysis (BIA); for muscle strength, we used a hydraulic dynamometer and a pneumatic dynamometer; for physical performance we used the Short Physical Performance Battery test (SPPB test) and the walk speed. Eight diagnostic groups were hereby established.
Results: A total of 250 consecutive subjects were recruited in an outpatient clinic in Liège, Belgium. Estimated prevalence of sarcopenia varied from 8.4% to 27.6% depending on the method of diagnosis used. Regarding muscle mass, BIA systematically overestimated muscle mass compared to DXA (mean estimated prevalence with BIA = 12.8%; mean prevalence with DXA = 21%). For muscle strength, the pneumatic dynamometer diagnosed twice more sarcopenic subjects than the hydraulic dynamometer (mean estimated prevalence with PD = 22.4%; mean estimated prevalence with HD = 11.4%). Finally, no difference in prevalence was observed when the walking speed or the SPPB test was used. A weak overall kappa coefficient was observed (0.53), suggesting that the 8 methods of diagnosis are moderately concordant.
Conclusion: Within the same definition of sarcopenia, prevalence of sarcopenia is highly dependent on the diagnostic tools used.

1. Introduction

Sarcopenia is an aging-related condition defined by a progressive and generalized loss of muscle mass and function (Baumgartner et al., 1998; Cooper et al., 2012). This geriatric syndrome, now recognized as a major clinical problem for older people, is an increasing public health issue in our society. Indeed, sarcopenia is associated with some adverse clinical outcomes such as physical impairment, limitation of mobility, decreased quality of life, increased risk of falls, hospitalization and mortality (Lauretani et al., 2003; Janssen, 2006; Visser et al., 2005; Janssen et al., 2002; Rantanen, 2003; Lang et al., 2010; Rizzoli et al., 2013) but also with major co-morbidities such as type 2 diabetes, obesity and osteoporosis (Sayer et al., 2005).

The definition of sarcopenia has been largely modified since the term "sarcopenia" was firstly introduced by Rosenberg in 1989 (Rosenberg, 1997). Originally, definitions of sarcopenia were based on decreased muscle mass only. Progressively, a qualitative dimension was added to focus on decreases in muscle strength and physical performance. These definitions have obviously a major impact on the assessment of the prevalence of the disease. Recently, Bijlsma et al. (Bijlsma et al., 2013) assessed the impact of these different definitions on the prevalence of sarcopenia and showed that it ranged from 0% to 45.2% depending on the definition used.

Recently the progress has been made in this field with the practical and consensual clinical definition of sarcopenia developed by the European Working Group on Sarcopenia in Older People (EWGSOP) (Cruz-Jentoft et al., 2010). According to this European consensual definition, sarcopenia is defined by the presence of low skeletal muscle mass and either low muscle strength or low muscle performance.

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However, the EWGSOP does not recommend the use of specific tools to measure muscle mass, muscle strength and physical performance (Cooper et al., 2013). Indeed, the EWGSOP suggests two different methods to assess muscle mass in clinical practice (i.e. the Dual Energy X-Ray Absorptiometry (DXA) and the bio-electrical impedance analysis (BIA) but also two methods to assess the physical performance (i.e. the "Short Physical Performance Battery" test and the usual gait speed). The muscle strength is referenced to be assessed by the handgrip strength but no recommendation is given regarding the tools to be used for this measurement. However, the use of different diagnostic tools may lead to different prevalences of sarcopenia and may therefore have important consequences on clinical researches and development of therapeutic strategies. To our knowledge, no study has yet assessed the variation in prevalence of sarcopenia depending on the different tools used to measure the variables of muscle mass, muscle strength and physical performance. Therefore, through this cross-sectional study, we aim to assess the impact of the use of these different diagnostic tools on the estimated prevalence of sarcopenia.

2. Methods

2.1. Study population

Subjects were recruited consecutively in an outpatient clinic in Liège, Belgium in an osteoporotic and geriatric department but also by means of press advertisement. Volunteers had to be over 65 years old and had to read and sign an informed consent after being informed of the objectives and methods of the research. Subjects with an amputated limb, with a BMI above 50 kg/m^2 or wearing an electronic implant were excluded from the research.

The study was approved by the Ethics Committee of the University Teaching Hospital of Liège.

All subjects enrolled in this study were interviewed to gather their socio-demographic data and anamnesis. Anthropometric measurements (weight at the nearest 0.1 kg, height at the nearest 0.1 cm, calf, wrist and arm circumferences at the nearest 0.1 cm) as well as clinical measurements (walking speed, nutritional status with the "Mini-Nutritional Assessment", quality of life with the "Short-Form 36", cognitive status with the "Mini-Mental State Examination (MMSE)", depression with the "Geriatric Depression Scale", dependence in daily living activities with the "Lawton scale" and gait and body balance with the "Tinetti test") were also collected.

2.2. Diagnosis of sarcopenia

The definition of the EWGSOP was applied for this research (Cruz-Jentoft et al., 2010). According to these experts, sarcopenia diagnosis is based on the documentation of low muscle mass plus either low muscle strength or low physical performance.

Each variable was measured with 2 different tools, as presented in the following sections.

2.2.1. Assessment of appendicular muscle mass

We used the following two techniques to assess appendicular muscle mass.

Dual Energy X-Ray Absorptiometry (DXA) exams were performed with a Hologic Discovery A (Hologic, Inc., USA) device. This whole-body scan is able to distinguish fat, bone mineral and lean tissues and exposes the patient to minimal radiation. All evaluations were carried out by the same technician and the device was calibrated twice a week by scanning a spine phantom. Appendicular skeletal lean mass (ASM) was determined as the sum of the mass of the four limbs. Skeletal muscle mass index (SMI) was calculated by dividing appendicular lean mass by height squared. The cut-off informed by the EWGSOP group (Cruz-Jentoft et al., 2010) for the diagnosis of sarcopenia is fixed at 7.26 kg/m^2 for men and 5.5 kg/m^2 for women (Baumgartner et al., 1998). To find this cut-off, Baumgartner et al. (1998) developed in 1998 a population-based survey of 883 elderly subjects and compared results of body composition with a data set including 229 young subjects aged 18–40 years (Gallagher et al., 1997). They defined cut-off values for sarcopenia based on comparison of the distribution for muscle mass in young subjects versus elderly people. With this technique, they defined a SMI two standard deviations below the mean SMI of young male and female reference groups as the gender-specific cut-off point for sarcopenia. Sarcopenia, diagnosed using this approach, was significantly associated with disability and was independent of ethnicity, age, comorbidity, health behaviors and fat mass.

Bio-electrical impedance analysis (BIA) was performed with an InBody S10, Biospace device (Biospace Co., Ltd, Korea/Model JMW140). This non-invasive and easy to use method estimates the volume of fat and lean body mass based on the relationship between the volume of a conductor and its electrical resistance. Volunteers were seated on a chair and tactile electrodes were placed at 8 points on the body. All bio-electrical impedance analyses were carried out by the same technician. Cut-off criteria for sarcopenia, when using bio-electrical impedance analysis, were 8.87 kg/m^2 for men and 6.42 kg/m^2 for women (Chien et al., 2008), as recommended by the EWGSOP. These cut-offs were defined based on the comparison of a group of 302 individuals aged 65 years and older for the distribution of muscle mass with a group of 200 young subjects aged 18–40 years. Using a SMI of 2 standard deviations or more below the normal sex-specific means for young persons, they found a cut-off of 8.87 kg/m^2 for men and 6.42 kg/m^2 for women.

2.2.2. Assessment of muscle strength

We also used two types of dynamometer to assess handgrip strength, a pneumatic and a hydraulic dynamometer.

The hydraulic dynamometer used was a Hydraulic Hand Dynamometer, Saehan Corporation (MSD Europe Bvba, Belgium) and the pneumatic dynamometer used was a Squeeze Dynamometer, Saehan Corporation (MSD Europe Bvba, Belgium). Both dynamometers were calibrated for 10, 40 and 90 kg by the firm at the beginning of the recruitment period.

Subjects were asked to grip the two dynamometers as hard as they can three times with each hand. The maximum of the six measurements was recorded as the result, as recently recommended by Roberts (Roberts et al., 2011). We used the cut-off points for the diagnosis of sarcopenia, defined by the EWGSOP group (Cruz-Jentoft et al., 2010): 30 kg for men and 20 kg for women. These cut-offs were found by Lauretani et al. (2003) based on 1030 subjects aged 20–102 years. They found that 20 kg for women and 30 kg for men were the two thresholds that best discriminates subjects with mobility limitations. The EWGSOP also presented a BMI-dependant cut-off where cut-off points for subjects presenting a lower BMI are lower than those for subjects with a higher BMI (Fried et al., 2001). Given that the EWGSOP definition did not reach an international consensus regarding the cut-off to use for the diagnosis, we arbitrarily chose to use the cut-off of Lauretani et al. (2003).

2.2.3. Assessment of physical performance

We used the following two different methods to assess physical performance in our population, as recommended by the EWGSOP group.

The SPPB test is a composite of three separate tests: balance, 4-meter gait speed and chair stand tests. Each test is weighted equally with a score between 0 and 4 points. Sarcopenia diagnosis cut-off for this test, scored on 12 points, is below or equal to 8 points (Guralnik et al., 2000).

Usual gait speed was assessed by timing subjects asked to walk a 4-meter distance, at a comfortable speed. The cut-off point for a 4-meters course is set at 0.8 m/s (Lauretani et al., 2003). They chose this cut-off because, in their population of 1030 subjects aged 20–102 years, this

value corresponds to the lowest quintile threshold of the speed distribution.

3. Definition

Based to these 2 muscle mass measurements, 2 muscle strength measurements and 2 physical performance measurements, we established 8 diagnostic methods of sarcopenia. These methods are summarized in Table 1 and were used in our analysis.

4. Statistical analysis

Patients were defined as sarcopenic, or not, according to each of these eight diagnostic methods. Then, we estimated the percentage of sarcopenic subjects for each diagnostic method. Afterwards, the degree of concordance between each method was calculated and recorded in a frequency table. For each tool, we assessed the percentage of subjects distributed below the tools respective cut-off. The agreement between tools for identifying subjects below the cut-off was tested by Cohen's kappa coefficient; the closer the value to 1, the better the concordance. Scatter plots for each tool of diagnosis have also been performed to allow a visual representation of the distribution of subjects across the different cut-off points. Each point of the scatter plot corresponds to one individual. Several individuals can present the same value of measurement and are placed on the same line along the x-axis. The agreement between diagnostic methods was also assessed by Cohen's kappa coefficient.

We analyzed the differences in subject's characteristics according to the 8 diagnostic methods. Quantitative variables were expressed as mean ± standard deviation (SD) and qualitative variables were reported as absolute and relative frequencies (%). Each clinical characteristic was analyzed by a regression or an ordinal logistic model in order to assess if there was a difference between the patients defined sarcopenic by a method and those who weren't defined as sarcopenic by this method. Each method of diagnosis was considered as a binary variable (1 = patient was considered as sarcopenic, 0 = patient was not considered as sarcopenic). The p-value in the table is the overall p-value of the regression model whereas the asterisk (*) indicates the significant variables, in other words, the methods of diagnosis for which the patients considered as sarcopenic showed a clinical characteristic statistically different from those who weren't defined as sarcopenic by this method.

Analyses were performed using the SAS statistical package (version 9.3 for windows) and R statistical software (version 2.15 for windows). Results were considered statistically significant at the 5% critical level ($p < 0.05$).

Table 1
Estimated prevalence of sarcopenia according to the eight diagnosis method (for all population and stratified by sex).

	Number of subjects diagnosed as sarcopenic (prevalence) Total population	Prevalence of sarcopenia
DXA–HD–UGS	35	14%
DXA–HD–SPPB	37	14.8%
DXA–PD–UGS	69	27.6%
DXA–PD–SPPB	69	27.6%
BIA–HD–UGS	21	8.4%
BIA–HD–SPPB	21	8.4%
BIA–PD–UGS	43	17.2%
BIA–PD–SPPB	43	17.2%

DXA: Dual Energy X-Ray Absorptiometry; BIA: bio-electrical impedance analysis; HD: hydraulic dynamometer; PD: pneumatic dynamometer; UGS: usual gait speed; SPPB: Short Physical Performance Battery.

5. Results

5.1. Subject characteristics

250 subjects were recruited over a 6-month period in our outpatient clinic in Liège, Belgium. Most recruited patients were women (62.8%) and the mean age of the population was 74.1 ± 6.4 years.

5.2. Prevalence of sarcopenia according to diagnostic tools

The estimated prevalences of sarcopenia using the 8 methods of diagnosis are presented in Table 1. General prevalence of sarcopenia ranges from 8.4% with methods BIA–HD–UGS and BIA–HD–SPPB to 27.6% with methods DXA–PD–UGS and DXA–PD–SPPB.

Regarding muscle mass, it seems that BIA systematically overestimates muscle mass compared to DXA. Indeed, the mean sarcopenia estimated prevalence is 12.8% when using BIA, and 21% with DXA, and the mean appendicular muscle mass divided per height squared (ALM/ht^2) is 6.08 kg/m^2 for women and 7.93 kg/m^2 for men when assessed with DXA, and 7.63 kg/m^2 for women and 9.66 kg/m^2 for men with BIA.

For muscle strength, the pneumatic dynamometer diagnosed on average twice more sarcopenic subjects than the hydraulic dynamometer. The mean estimated prevalence with pneumatic dynamometer is 22.4% while the mean estimated prevalence with hydraulic dynamometer is 11.4%. When using the hydraulic dynamometer, the mean maximal strength of subjects is 27.5 kg but when using pneumatic dynamometer, the mean strength is 12.2 kg, which represents a difference of 15.3 kg.

Finally, no difference in prevalence was observed between the usual gait speed and the SPPB test. The mean estimated prevalence using usual walking speed is 16.8% and 17% when using the SPPB test. Results shows the same prevalence of sarcopenia for definitions DXA–PD–UGS and DXA–PD–SPPB, for definition BIA–HD–UGS and BIA–HD–SPPB and for definition BIA–PD–UGS and BIA–PD–SPPB, which means that in these three cases, estimated prevalence of sarcopenia is not dependant on the method used to measure physical performance.

5.3. Concordance between tools

Distribution of subjects across the different cut-off points for these tools has also been represented on scatter plots (Supplementary files, Fig. 2A, B and C). Regarding muscle mass, results indicate that 28.4% of subjects (27.9% of men and 28.6% of women) were distributed below the EWGSOP suggested cut-off when using DXA versus 17.6% when using BIA (26.9% of men, 12.1% of women). Kappa value for the concordance between BIA and DXA is 0.48 (CI 95%: 0.35–0.60).

For muscle strength, when using the hydraulic dynamometer, 34.8% of subjects (19.3% of men, 43.9% of women) were below the cut-off points versus 94.4% with the pneumatic dynamometer (92.5% of men, 95.5% of women). The concordance between the hydraulic dynamometer and the pneumatic dynamometer is low with a kappa value of 0.048 (CI 95%: 0.01–0.08). Moreover, compared to cut-off points of the hydraulic dynamometer, those of the pneumatic dynamometer should be decreased at 8 kg for women and 12 kg for men to reach the same percentage of subjects distributed below the value.

Finally, for physical performance, 23.2% of subjects (18.3% of men, 26.3% of women) were below the cut-off point of 0.8 m/s for gait speed and 20.4% below the cut-off of 8 points for the SPPB test (8.6% of men, 27.4% of women). Concordance between the SPPB test and the usual gait speed is strong with a kappa value of 0.72 (CI 95%: 0.61–0.82).

5.4. Concordance between methods of diagnosis

Table 2 shows the concordances between definitions. Concordance between methods DXA–PD–UGS and DXA–PD–SPPB, between methods BIA–HD–UGS and BIA–HD–SPPB and between methods BIA–PD–UGS and BIA–PD–SPPB is 1, which represents a perfect concordance. This

Table 2
Concordance between the eight methods of diagnosis.

	DXA–HD–UGS	DXA–HD–SPPB	DXA–PD–UGS	DXA–PD–SPPB	BIA–HD–UGS	BIA–HD–SPPB	BIA–PD–UGS	BIA–PD–SPPB
DXA–HD–UGS		0.97 (0.92–1.0)	0.60 (0.48–0.71)	0.60 (0.48–0.71)	0.60 (0.44–0.76)	0.60 (0.44–0.76)	0.36 (0.21–0.52)	0.36 (0.21–0.52)
DXA–HD–SPPB			0.63 (0.51–0.74)	0.63 (0.51–0.74)	0.58 (0.42–0.73)	0.58 (0.42–0.73)	0.35 (0.19–0.50)	0.35 (0.19–0.50)
DXA–PD–UGS				1	0.31 (0.19–0.43)	0.31 (0.19–0.43)	0.52 (0.40–0.65)	0.52 (0.40–0.65)
DXA–PD–SPPB					0.31 (0.19–0.43)	0.31 (0.19–0.43)	0.52 (0.40–0.65)	0.52 (0.40–0.65)
BIA–HD–UGS						1	0.61 (0.47–0.76)	0.61 (0.47–0.76)
BIA–HD–SPPB							0.61 (0.47–0.76)	0.61 (0.47–0.76)
BIA–PD–UGS								1

DXA: Dual Energy X-Ray Absorptiometry; BIA: bio-electrical impedance analysis; HD: hydraulic dynamometer; PD: pneumatic dynamometer; UGS: usual gait speed; SPPB: Short Physical Performance Battery.

means that the measure of physical performance with either the "Short Physical Performance Battery test" or the "usual walking speed" does not change the estimated prevalence of sarcopenia. The higher concordance is observed between DXA–HD–UGS and DXA–HD–SPPB (kappa coefficient of 0.97). Indeed, only two more subjects were diagnosed as sarcopenic when using the SPPB test instead of the usual gait speed for the physical performance measurement. The lowest kappa coefficient is observed between definition DXA–PD–UGS or DXA–PD–SPPB, using DXA to measure muscle mass and pneumatic dynamometer to measure muscle strength and definition BIA–HD–UGS or BIA–HD–SPPB, using BIA for muscle mass and hydraulic dynamometer for muscle strength. A weak overall kappa coefficient is observed (coefficient 0.53, 95% CI 0.18–0.89), which means that, globally the 8 definitions are moderately concordant.

We also numbered the subjects diagnosed as sarcopenic across the eight different diagnostic methods (Table 3). On the 250 subjects recruited for the study, 173 did not have sarcopenia according to any definition while 18 subjects were diagnosed sarcopenic by all the eight definitions. 17 subjects were diagnosed sarcopenic with only the four definitions using DXA to measure muscle mass while only 3 subjects were diagnosed as sarcopenic with the only four definitions using BIA. This distribution is represented visually in Fig. 1.

5.5. Clinical characteristics of sarcopenic subjects

We also decided to analyze sarcopenic subject's characteristics in the different subgroups. Results are presented in Table 4.

Age is significantly higher in subjects who were diagnosed sarcopenic by method DXA–HD–UGS ($p < 0.001$) and by method BIA–HD–UGS or BIA–HD–SPPB ($p = 0.034$) compared to non-sarcopenic subjects. BMI was lower in subjects who were diagnosed sarcopenic by method DXA–PD–UGS or DXA–PD–SPPB ($p < 0.001$). For subjects with sarcopenia detected by method DXA–PD–UGS or DXA–PD–SPPB, calf, arm and wrist circumferences were also lower ($p = 0.0025$, 0.012 and <0.001 respectively). MMSE was higher for subjects with sarcopenia diagnosed by method DXA–HD–UGS ($p < 0.001$) but was lower for those diagnosed sarcopenic by method DXA–HD–SPPB ($p < 0.001$). Subjects with sarcopenia diagnosed by method BIA–HD–UGS or BIA–HD–SPPB had higher walking speed ($p = 0.0042$) but a lower Tinetti value for walk ($p = 0.053$) than those who were not diagnosed by this method ($p = 0.0042$). Fat mass was lower for patients with sarcopenia detected by method BIA–PD–UGS or BIA–PD–SPPB ($p = 0.016$). No statistical association was found between methods of diagnosis and walking aid, number of drugs, number of comorbidities, nutritional status, Lawton scale, depression scale, quality of life and Tinetti scale for balance.

6. Discussion

Within the same definition of sarcopenia, recommended by the EWGSOP, estimated prevalence of sarcopenia seems highly dependent on the diagnostic tools used to measure the three variables: muscle mass, muscle strength and physical performance. Indeed, we found important differences of measured prevalence of sarcopenia whether BIA or DXA and whether a pneumatic dynamometer or a hydraulic dynamometer was used. On the contrary, whether the SPPB test or the usual gait speed is used to measure the physical performance, it does not result in a difference of prevalence. We also found significant differences regarding the clinical characteristics of sarcopenic subjects diagnosed with these methods. If the clinical characteristics of sarcopenic subjects are different depending on the tools used for the diagnosis of sarcopenia, the long-term clinical consequences of sarcopenia may also differ and therefore therapeutical strategies will not be easily evaluated and implemented. The identification of the most pertinent tools for the diagnosis of sarcopenia could therefore be of a great clinical and public health interest.

A wide range of techniques can be used to assess appendicular lean mass. Even if computed tomography (CT scan) and magnetic resonance imaging (MRI) are considered to be the gold standard in research, the EWGSOP suggests the use of Dual Energy X-Ray Absorptiometry (DXA) and bio-electrical impedance analysis (BIA) in clinical use because of their lower cost and larger availability. BIA is known to underestimate fat mass and overestimate muscle mass (Faria et al., 2014; Sillanpaa et al., 2014). Despite the recommended adaptation of cut-off for BIA, in our study, the overestimation of lean mass with the BIA device InBody S10 compared to DXA was much larger than expected, resulting in a

Table 3
Distribution of subjects according to the eight diagnostic methods.

DXA–HD–UGS	DXA–HD–SPPB	DXA–PD–UGS	DXA–PD–SPPB	BIA–HD–UGS	BIA–HD–SPPB	BIA–PD–UGS	BIA–PD–SPPB	Number	Frequency
0	0	0	0	0	0	0	0	173	69.2
1	1	1	1	1	1	1	1	18	7.2
0	0	1	1	0	0	1	1	17	6.8
1	1	1	1	0	0	0	0	17	6.8
0	0	1	1	0	0	0	0	15	6.0
0	0	0	0	0	0	1	1	5	2.0
0	0	0	0	1	1	1	1	3	1.2
0	1	1	1	0	0	0	0	2	0.8

DXA: Dual Energy X-Ray Absorptiometry; BIA: bio-electrical impedance analysis; HD: hydraulic dynamometer; PD: pneumatic dynamometer; UGS: usual gait speed; SPPB: Short Physical Performance Battery.

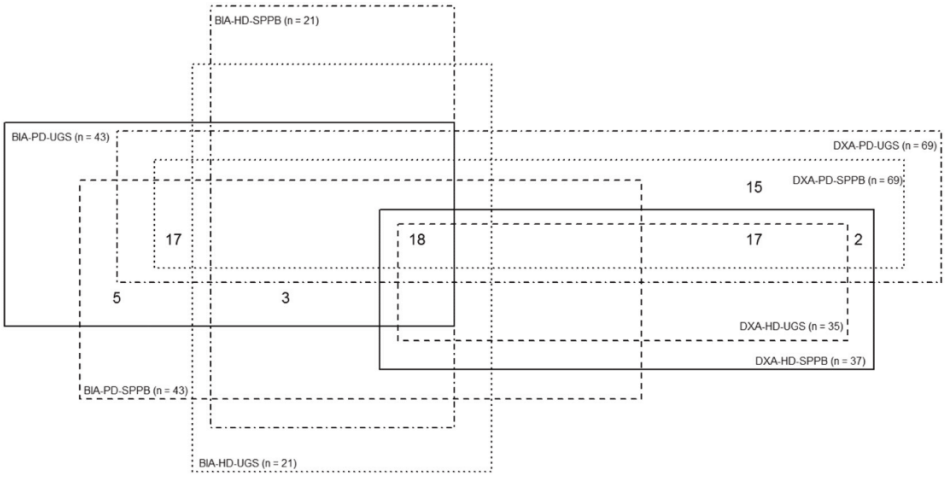

Fig. 1. Number of subjects diagnosed as sarcopenic according to the eight definitions. DXA: Dual Energy X-Ray Absorptiometry; BIA: bio-electrical impedance analysis; HD: hydraulic dynamometer; PD: pneumatic dynamometer; UGS: usual gait speed; SPPB: Short Physical Performance Battery.

high difference of prevalence of sarcopenia whether BIA or DXA was used. These results suggest that the adaptation of BIA cut-offs should be device dependant. Indeed, all types of BIA devices are probably not equal to each other. The device used to determine the cut-off discussed on the EWGSOP paper is a Maltron system (Maltron Bioscan 920, Rayleigh, UK) and our device is a InBody S10 Biospace device (Biospace Co., Ltd, Korea/Model JMW140). These two devices were based on the same method of measurement of muscle mass, i.e. the estimation of body composition using the difference of conductivity of the various tissues due to the difference of their biological characteristics. However, the Maltron system performed the analyses with an operating frequency of 50 Hz while for the InBody S10 system, a total of 30 impedance measurements are obtained using 6 different frequencies (1 kHz, 5 kHz, 50 kHz, 250 kHz, 500 kHz, 1000 kHz). The fact that we used a different device than the one used to establish the cut-off points of the EWGSOP could explain our results. Interestingly, all types of commercially available BIA devices present differences in technical characteristics, such as the frequency used for the analysis. Researchers must be careful when they choose their tool to measure muscle mass and must make sure that this tool is validated against DXA for the diagnosis of sarcopenia.

EWGSOP also reviewed several methods to measure muscle strength. Because of its low cost, easy use and large availability,

Table 4
Clinical characteristics of sarcopenic subjects according to the eight diagnostic methods.

	DXA–HD–UGS (n = 35)	DXA–HD–SPPB (n = 37)	DXA–PD–UGS (n = 69)	DXA–PD–SPPB (n = 69)	BIA–HD–UGS (n = 21)	BIA–HD–SPPB (n = 21)	BIA–PD–UGS (n = 43)	BIA–PD–SPPB (n = 43)	Total n	p-Value
Age (years)	78.6 ± 6.3	78.0 ± 6.6	76.0 ± 6.5	76.0 ± 6.5	80.0 ± 7.0[a]	80.0 ± 7.0[a]	77.0 ± 7.4	77.0 ± 7.4	250	<0.0001
Sex										
Women	23 (65.7)	25 (67.6)	43 (62.3)	43 (62.3)	10 (47.6)	10 (47.6)	19 (44.2)[a]	19 (44.2)[a]	250	0.021
BMI (kg/m^2)	23.2 ± 2.4	23.4 ± 2.8	23.4 ± 2.8[a]	23.4 ± 2.8[a]	22.8 ± 2.7	22.8 ± 2.7	23.1 ± 3.2	23.1 ± 3.2	250	<0.0001
Walking aid										
Yes	6 (17.1)	6 (16.2)	7 (10.3)	7 (10.3)	5 (23.8)	5 (23.8)	7 (16.7)	7 (16.7)	250	0.17
Calf circumference (cm)	31.5 ± 2.6	31.7 ± 2.7	32.0 ± 2.6[a]	32.0 ± 2.6[a]	31.1 ± 2.7	31.1 ± 2.7	31.7 ± 2.7	31.7 ± 2.7	248	<0.0001
Arm circumference (cm)	25.1 ± 2.9	25.1 ± 2.8	25.6 ± 3.1[a]	25.6 ± 3.1[a]	24.5 ± 2.9	24.5 ± 2.9	25.3 ± 3.0	25.3 ± 3.0	248	<0.0001
Wrist circumference (cm)	15.8 ± 1.5	15.8 ± 1.4	16.1 ± 1.8[a]	16.1 ± 1.8[a]	16.3 ± 1.7	16.3 ± 1.7	16.3 ± 1.4	16.3 ± 1.4	248	0.0006
Drugs (nbr)	6.9 ± 2.7	6.8 ± 2.8	6.2 ± 2.9	6.2 ± 2.9	6.8 ± 2.4	6.8 ± 2.4	5.5 ± 2.7	5.5 ± 2.7	250	0.083
Comorbidities (nbr)	4.5 ± 2.5	4.6 ± 2.4	4.0 ± 2.3	4.0 ± 2.3	4.2 ± 2.1	4.2 ± 2.1	3.8 ± 1.9	3.8 ± 1.9	250	0.39
Mini-Nutritional Assessment										
Well nourish	24 (68.6)	26 (70.3)	50 (72.5)	50 (72.5)	13 (61.9)	13 (61.9)	31 (72.1)	31 (72.1)		
Risk of malnutrition	9 (25.7)	9 (24.3)	17 (24.6)	17 (24.6)	6 (28.6)	6 (28.6)	10 (23.3)	10 (23.3)		
Malnutrition	2 (5.7)	2 (5.4)	2 (2.9)	2 (2.9)	2 (9.5)	2 (9.5)	2 (4.6)	2 (4.6)	250	0.043
MMSE (/30 points)	26.9 ± 2.1[a]	26.5 ± 2.6[a]	27.2 ± 2.3	27.2 ± 2.3	26.5 ± 2.4	26.5 ± 2.4	27.3 ± 2.1	27.3 ± 2.1	250	0.0001
Lawton scale										
Men (/5 points)	4.2 ± 1.1	4.2 ± 1.1	4.5 ± 0.9	4.5 ± 0.9	4.2 ± 1.2	4.2 ± 1.2	4.5 ± 0.9	4.5 ± 0.9	93	0.11
Women (/8 points)	7.0 ± 1.3	7.1 ± 1.3	7.4 ± 1.1	7.4 ± 1.1	6.6 ± 1.2	6.6 ± 1.2	7.21 ± 1.1	7.21 ± 1.1	157	0.30
Geriatric Depression Scale (points)	4.4 ± 4.1	4.4 ± 4.0	3.7 ± 3.5	3.7 ± 3.5	4.7 ± 4.3	4.7 ± 4.3	3.8 ± 3.5	3.8 ± 3.5	244	0.54
SF-36 (/100)	59.9 ± 19.9	60.6 ± 19.6	65.0 ± 18.4	65.0 ± 18.4	57.4 ± 22.0	57.4 ± 22.0	64.1 ± 18.9	64.1 ± 18.9	244	0.12
Walk speed (m/s)	0.82 ± 0.32	0.83 ± 0.32	0.96 ± 0.29	0.96 ± 0.29	0.71 ± 0.34[a]	0.71 ± 0.34	0.91 ± 0.33	0.91 ± 0.33	249	<0.0001
Tinetti										
Balance (/16)	14.7 ± 2.3	14.8 ± 2.2	15.3 ± 1.7	15.3 ± 1.7	14.2 ± 2.7	14.2 ± 2.7	15.1 ± 2.1	15.1 ± 2.1	248	0.064
Walk (/12)	10.7 ± 2.1	10.7 ± 2.1	11.3 ± 1.7	11.3 ± 1.7	10.0 ± 2.1[a]	10.0 ± 2.1[a]	11 ± 1.8	11 ± 1.8	248	0.025
Fat mass (kg)	21.7 ± 8.0	21.7 ± 7.8	21.7 ± 6.8	21.7 ± 6.8	20.2 ± 9.7	20.2 ± 9.7	19.9 ± 7.9[a]	19.9 ± 7.9[a]	250	<0.0001

DXA: Dual Energy X-Ray Absorptiometry; BIA: Bio-electrical impedance analysis; HD: hydraulic dynamometer; PD: pneumatic dynamometer; UGS: usual gait speed; SPPB: Short Physical Performance Battery.

[a] Significant covariate.

handgrip strength is the suggested method, as also confirmed by another expert group (Cooper et al., 2013). Grip strength is usually assessed by means of a dynamometer, but different types of dynamometers currently exist. Some authors already compared a hydraulic dynamometer (Jamar) and a pneumatic one (Martin Vigorimeter) (Desrosiers et al., 1995; Li et al., 2010) and found a high correlation between the two device for measuring grip strength. Different types of pneumatic dynamometers currently exist and we chose the Squeeze Dynamometer because unlike the Martin Vigorimeter, results are expressed in kilograms and offered us thereby a pertinent comparison with the hydraulic dynamometer. However, in our study, contrary of the pre-cited authors, the pneumatic dynamometer diagnosed about twice more sarcopenic subjects than the hydraulic dynamometer. Our primary hypothesis was that the two devices do not measure the same muscle characteristic. Indeed, the pneumatic dynamometer is a pressure measure implying a pseudo-dynamic movement as opposed to the static strength measure of the hydraulic one. Previous published results showing a high correlation between the two types of dynamometer (Desrosiers et al., 1995; Li et al., 2010) are not favorable to this hypothesis, but the tested tools are not exactly those that we used in the present study. The different available pneumatic dynamometers do not seem identical in measuring grip strength and, consequently, authors must be careful when they chose a dynamometer for their researches. We can also note that, even if the calibration was performed by the company at the beginning and at the end of the recruitment period, a minor risk of inaccurate calibration remains. Complementary researches are needed to determine the most appropriate dynamometer, in this context, by identifying for example the group of diagnosed sarcopenic subjects presenting the most serious or the most important long term consequences. The choice of the cut-off can also be a point of concern. Indeed, the EWGSOP suggested two cut-off points for the diagnosis of sarcopenia regarding muscle strength, an absolute cut-off value of 20 kg for women and 30 kg for men, and a BMI-dependent cut-off. As no consensus has yet been reached about which cut-off has to be used for the diagnosis of sarcopenia, we chose the absolute values. In the meantime, we have shown that the prevalence of sarcopenia can range from 9.25% to 18% according to which cut-off from the EWGSOP definition has been used for the diagnosis (Beaudart et al., in press). The absence of strict cut-off criteria for the diagnosis of sarcopenia is currently pointed out as a limit of the EWGSOP definition.

Even if many tests of physical performance are available, EWGSOP recommends using the Short Physical Performance Battery (SPPB) test and the usual gait speed for the diagnosis of sarcopenia. According to our results, it seems that the two methods are relatively concordant. In the literature, there are as many studies using the SPPB as studies using the usual gait speed. It seems easier to use the usual gait speed but some authors defend the fact that the SPPB overviews more aspects of physical performance. We did not find a significant difference of estimated prevalence between both methods. Moreover, definitions A and B presented a kappa concordance equal to 0.97 and the concordance was perfect between other definitions assessing physical performance with SPPB or with usual gait speed.

7. Conclusion

This research reveals high differences of measured prevalence of sarcopenia depending on the diagnostic tools used. A consensus regarding the tools that must be used in the context of diagnosing sarcopenia is essential in order to make studies comparable. Regarding the measurement of muscle mass, we found a high difference in the prevalence of sarcopenia whether Dual Energy X-Ray Absorptiometry or bioelectrical impedance analysis was used. This result suggests that a pondered formula should be developed for each type of bio-electrical impedance analysis device. Concerning muscle strength, results of prevalence were discordant whether a pneumatic dynamometer or a hydraulic dynamometer was used. Future researches are needed to identify the most appropriate dynamometer to use in the context of sarcopenia. Finally, regarding physical performance, the two tools recommended by the EWGSOP do not influence the estimated prevalence of sarcopenia and seem both appropriate for the diagnosis. Validation of diagnostic tools is a crucial issue in clinical research. Indeed, unappropriated tools can lead to an over- or underestimation of prevalence of sarcopenia, with consequences that could be important, from a public health point of view. For example, the risk would be to give an unnecessary treatment to a false positive subject (i.e. without sarcopenia) and to deprive a false negative patient (i.e. with sarcopenia) of effective treatment.

Author's contributions

CB, OB, JP and JYR designed the study. CB, CS, AQ, JS and FB recruited the subjects and collected the data. CB and ND performed statistical analyses and interpreted data with OB and SG. All authors commented on the drafts and approved the final draft. CB is the manuscript's guarantor.

Declaration of interest

The authors indicate that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.exger.2014.11.014.

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Original Article

Hylonome

Prevalence of sarcopenia: the impact of different diagnostic cut-off limits

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Abstract

Introduction: In the definition of the European Working Group on Sarcopenia in Older People (EWGSOP), different cut-off limits are proposed for appendicular lean mass, muscle strength and gait speed. Therefore we aimed to examine the variation in prevalence of sarcopenia obtained with these cut-off limits. **Materials and Methods:** Subjects aged 65 years and older were recruited in an outpatient clinic in Belgium and screened for sarcopenia using the EWGSOP definition. Appendicular lean mass was measured by Dual Energy X-Ray Absorptiometry, muscle strength by a hydraulic handgrip dynamometer and gait speed was measured on a 4-meter distance. Two different cut-off points proposed by the EWGSOP were examined for each variable and 8 diagnostic methods were thereby established. **Results:** 400 subjects were recruited for this study. Prevalence of sarcopenia varied from 9.25% to 18% depending on the cut-offs applied. When stratified by sex, it seems that the variation in prevalence of sarcopenia was mainly attributable to women. This prevalence ranged from 6.58% to 20.2% for women and only from 13.4% to 14.7% for men. **Conclusion:** Prevalence of sarcopenia varies widely depending on the EWGSOP cut-off points applied for women. This may limit clinical researches and development of therapeutic strategies in the field of sarcopenia.

Keywords: Sarcopenia, Prevalence, EWGSOP, Cut-off, Diagnosis

Introduction

One of the consequences of aging consists of decreases in muscle mass[1]. This phenomenon has been described for the first time in 1989 by Irwin Rosenberg as "sarcopenia"[2]. Over the last decade, definitions of sarcopenia, among researchers, have varied and have been conflicting[3,4]. In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) published their recommendations for a clinical definition and consensual diagnosis criteria of sarcopenia[5]. They defined sarcopenia as a progressive and generalized loss of skeletal muscle mass and strength, or physical performance, with a risk of adverse outcomes such as physical disability, poor quality of life and death[5-9].

Prevalence of sarcopenia is difficult to establish. Indeed, this prevalence can differ depending on the characteristics of the studied population. A higher prevalence is often observed in subjects living in nursing home, in elderly subjects, in subjects having a low body mass index but also in subjects having a low educational level[10,11-13]. The prevalence is also depending on the definition used for the diagnosis of sarcopenia. In 2013, Batsis et al.[14] compared eight definitions of sarcopenia and found a prevalence ranging from 4.4% to 94% across definitions. As expected, studies using muscle mass as single criterion of diagnosis came up with a higher prevalence of sarcopenia than studies based on the EWGSOP consensus algorithm. Interestingly, since 2010, most of the studies have used the EWGSOP consensus to define sarcopenia[5]. This is an epidemiological great step that allows a more meaningful comparison between studies. However, within this consensual definition, different cut-off points are recommended for the diagnosis of sarcopenia in regards of the measurement of muscle mass, muscle strength and gait speed[5]. Two options, for each variable (skeletal muscle mass index, muscle strength and physical performance including more specifically gait speed), are actually suggested to define sub-normal values.

The authors have no conflict of interest.

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It is normal to expect that the use of different cut-off limits will lead to differences in the estimation of the prevalence of sarcopenia. To the best of our knowledge, no cross-sectional study has yet assessed the difference in prevalence of sarcopenia depending on the specific cut-off limits discussed by the EWGSOP[5]. In this cross-sectional study, our aim was to explore how the different cut-offs could affect the prevalence of sarcopenia in a population of subjects aged 65 years and older but also in this population stratified by age and by sex.

Materials and Methods

Study subjects

The present study was conducted on subjects aged 65 years or older, selected from July 2013 to June 2014, who were either consulting an outpatient clinic specialised in bone, cartilage and muscle in Liège, Belgium or recruited by press advertisements. These subjects were enrolled in the SarcoPhAge cohort, which is a Belgian 5-year prospective cohort.

Subjects had to read and sign an informed consent after being informed of the objectives and methods of the research. There were no selection criteria on health or demographic characteristics except for subjects with an amputated limb or with a BMI above 50 kg/m² who were excluded from this research.

The study was approved by the Ethics Committee of the University Teaching Hospital of Liège, Belgium.

Clinical characteristics

All subjects were interviewed by a clinical research assistant for a mean time of 45 minutes. The clinical research assistant collected sociodemographic, anamnestic and clinical data such as civil status, level of education, actual income, living at home or at another place, walking aids if any, comorbidities and drugs use. Anthropometric measures such as height, weight and calf, wrist and arm circumferences were also collected. The clinical research assistant also gathered information on the cognitive function (Mini-Mental State Examination), the limitation in instrumental activities of daily living (Lawton scale), the nutritional status (Mini Nutritional Assessment), the quality of life (Short-Form 36) and the depression (Geriatric Depression Scale).

Diagnosis of sarcopenia

We used the definition of the EWGSOP for the diagnosis of sarcopenia[5]. According to the experts of this working group, sarcopenia diagnosis is based on documentation of low muscle mass plus either low muscle strength or low physical performance. An overview of the different cut-off criteria for sarcopenia, which includes muscle mass, muscle strength and gait speed, is given in Table 1.

Muscle mass

Appendicular lean mass was measured by Dual-Energy X-Ray Absorptiometry (DXA) (Hologic Discovery A, USA). We used this technique, recommended by the EWGSOP, because computed tomography and magnetic resonance imaging, considered as the gold standards in this field, are limited in their use by high costs and concerns about radiation exposure. On the contrary, DXA, which is a method able to distinguish lean tissues from fat and bone mineral, has the advantage of exposing patients to minimal radiation. All whole-body scans were carried out by the same technician and the device was calibrated twice a week by scanning a spine phantom. Appendicular skeletal muscle mass (ASM) was obtained by adding skeletal muscle mass of both arms and legs. A skeletal muscle mass index (SMI), which is used for the diagnosis of sarcopenia, was calculated by dividing the ASM by the height squared. For the diagnosis of sarcopenia, two cut-offs were discussed in the EWGSOP report for this SMI. Based on reference groups derived from a population-based survey of 883 elderly Hispanic and non-Hispanic white men and women living in New Mexico, the first cut-off point raises at 7.26 kg/m² for men and 5.5 kg/m² for women[15]. This cut-off was defined by the EWGSOP at two standard deviations (SD) below the mean reference value, which was, in this case, healthy young adults living in Mexico. The second cut-off proposed is based on a group of 2976 subjects aged 70 to 79 years living in four districts of the United States and is defined as under the 20th percentile of the SMI of this population[16]. To be diagnosed sarcopenic, the SMI must be below 7.25 kg/m² for men and 5.67 kg/m² for women.

Muscle mass: cut-off 1	Muscle mass: cut-off 2
Men: 7.26 kg/m²	**Men:** 7.25 kg/m²
Women: 5.5 kg/m²	**Women:** 5.67 kg/m²
Muscle strength: cut-off 1	**Muscle strength: cut-off 2**
Men: <30 kg	**Men:**
	BMI ≤24: ≤29 kg
	BMI 24.1-26: ≤30 kg
	BMI 26.1-28: ≤30 kg
	BMI >28: ≤32 kg
Women: <20 kg	**Women:**
	BMI ≤23: ≤17 kg
	BMI 23.1-26: ≤17.3 kg
	BMI 26.1-29: ≤18 kg
	BMI >29: ≤21 kg
Gait speed: cut-off 1	**Gait speed: cut-off 2**
<0.8 m/s	**Men:**
	Height ≤173 cm: <0.65 m/s
	Height >173 cm: <0.76 m/s
	Women:
	Height ≤159 cm: <0.65 m/s
	Height >159 cm: <0.76 m/s

Table 1. Overview of cut-off criteria for the diagnosis of sarcopenia.

Muscle strength

As recommended by the EWGSOP, we measured subjects' handgrip strength to determine their muscle strength.Therefore,

Methods	Muscle mass	Muscle strength	Physical performance
A	Cut-off 1	Cut-off 1	Cut-off 1
B	Cut-off 1	Cut-off 1	Cut-off 2
C	Cut-off 1	Cut-off 2	Cut-off 1
D	Cut-off 1	Cut-off 2	Cut-off 2
E	Cut-off 2	Cut-off 1	Cut-off 1
F	Cut-off 2	Cut-off 1	Cut-off 2
G	Cut-off 2	Cut-off 2	Cut-off 1
H	Cut-off 2	Cut-off 2	Cut-off 2

Table 2. Eight methods of diagnosis of sarcopenia issued from the EWGSOP report.

we used a hydraulic dynamometer (Saehan Corporation, MSD Europe Bvba, Belgium) that subjects had to grip as hard as possible three times with each hand (dominant and non-dominant). For our analysis, we used the highest result out of the six measurements recorded[17]. For the diagnosis of sarcopenia, we also used the two different cut-offs discussed in the EWGSOP report. The first cut-off has been suggested by Lauretani et al.[7] based on a study of a cohort of 1030 Italian subjects aged 20-102 years and raises at 30 kg for men and 20 kg for women. The second cut-off depends on subjects' Body Mass Index (BMI). Four quartiles of grip strength depending on the subjects' BMI have been defined from of a cohort of 5317 subjects aged 65 years or older studied by Fried et al.[18]. Rationally, cut-off points issued from subjects presenting a lower BMI are below those issued from subjects with a higher BMI.

Physical performance

The third variable needed for the diagnosis of sarcopenia, physical performance, can be measured either by gait speed, expressed as meter/seconds, or by the Short Physical Performance Battery test, which is a composite test scored on 12 points. In the present study, we used the gait speed as criteria for the diagnosis of sarcopenia. Subjects had to walk a 4-meter course at their usual gait speed. Time taken to execute this walk was recorded and expressed as meter per second. Once again, two different cut-off points are discussed in the EWGSOP report for the gait speed. Also based on the results of Lauretani et al.[7], the first cut-off point for the diagnosis of sarcopenia raises at 0.8 m/s, both for women and men. The second cut-off is sex-and-height-dependent, which means it is different for men and women and it increases with their height. This second cut-off is based on the quartiles groups defined in the cohort of Fried et al.[18].

Diagnosis method

According to the EWGSOP[5], sarcopenia is defined as follow: (low muscle mass AND (low muscle strength OR low gait speed)). With 2 cut-off points available for each of the three components of sarcopenia, we defined 8 methods of diagnosis of sarcopenia, as given in Table 2.

Clinical characteristics	Men (n=157)	Women (n=243)
Age	74±6.4	73.8±6.2
Antropometric data		
Height (cm)	172±6.6	157.3±6.77
Weight (kg)	81.7±16.2	64.1±12.6
Body Mass Index (kg/m²)	27.6±4.88	25.9±4.57
Calf circumference (cm)	36.1±3.82	33.8±3.56
Waist circumference (cm)	101.7±12.1	89.1±12.9
Wrist circumference (cm)	18.1±1.54	16.1±1.69
Arm circumference (cm)	28.8±3.51	27.4±3.75
Number of diseases	4.23±2.55	4.54±6.27
Number of drugs	5.71±3.51	6.27±3.6
MMSE score (/30 points)	27.8±2.15	27.5±3.19
Lawton score (/5 points for men; /8 points for women)	4.76±0.70	7.29±1.35
Mini-Nutritional Assessment		
Well-nourished	136 (86.6)	193 (79.4)
Risk of malnutrition	19 (12.1)	44 (18.1)
Malnutrition	2 (1.27)	6 (2.47)
Quality of life SF-36 (%)	63.4±17.1	57.6±19.2
Depression (/15 points)	3.39±3.05	4.29±3.6
Total lean mass (kg)	55.6±9.33	37.9±5.69
Total fat mass (kg)	24.8±8.36	25.7±8.69
Diagnosis component of sarcopenia		
Gait speed (m/s)	1.02±0.29	0.93±0.28
Grip strength maximum (kg)	38.4±9.81	21.2±6.44
Skeletal Muscle Index kg/m²	7.91±1.17	6.06±1.02

Table 3. Clinical characteristics of subjects.

Statistical analysis

Continuous data are presented as mean ± SD. Categorical data were summarized as count and percentage.

Baseline differences between men and women were tested using a Student's t-test. Prevalence of sarcopenia was assessed according to each diagnosis method, as described in Table 2. After assigning the status of sarcopenic or not to each individual, the study population was stratified by sex and age (65-69 years, 70-74 years, 75-79 years and 80 years and older). The

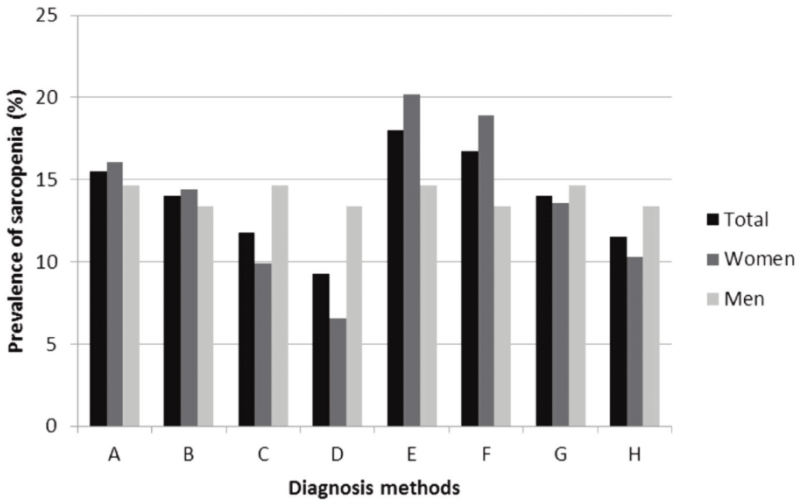

Figure 1. Prevalence of sarcopenia according to the eight diagnosis method, globally and stratified by sex.

difference in women characteristics dependant of the diagnosis method was tested with a Student's t-test.

All analyses were executed with the software Statistica 9.1. Results were considered statistically significant when 2-tailed p values were less than 0.05.

Results

A total of 400 subjects aged 65 years and older participated at this study. Out of them, 243 were women, which represent 60.7% of the population. Mean age was 73.8±6.2 years for women and 74±6.4 years for men. BMI was significantly higher in men than women (27.6 kg/m^2 versus 25.9 kg/m^2) as well as arm circumference (28.8 cm versus 27.4 cm), wrist circumference (18.1 cm versus 16.1 cm) and calf circumference (36.1 cm versus 33.8 cm). Men also presented a higher global quality of life than women (63.4 % versus 57.6 %) and a lower level of depression (3.39 points versus 4.29 points). Regarding body composition, men subjects presented a mean of 24.8±8.36 kg of fat mass which was not significantly different than women (25.7±8.69 kg). Men presented significantly more lean mass than women (55.6 kg versus 37.9 kg) (Table 3).

Globally, total prevalence of sarcopenia, independently from sex, ranged from 9.25% to 18%, depending on the method used for the diagnosis (Figure 1). The lowest prevalence was found with the diagnosis method D and the highest prevalence was found with the diagnosis method E. When stratified by sex, it seems that the variation in prevalence of sarcopenia is mainly attributable to women. Indeed, this prevalence ranged from 6.58% to 20.2% for women and only from 13.4% to 14.7% for men.

When stratified by age (Table 4), there is no difference in prevalence of sarcopenia for men across the diagnosis methods except for men aged between 65 years and 69 years. Indeed, for these men, we found a difference of prevalence imputable to the cut-off used for gait speed. When using the first cut-off of 0.8 m/s, we found a prevalence of sarcopenia of 7.41% but, when using the height-dependant cut-offs, we found a lower prevalence of sarcopenia, reaching only 3.7%. Other cut-off criteria used for muscle mass and muscle strength did not cause differences in the measured prevalence of sarcopenia for men. For women, in the other side, it seems that the cut-off limits used led systematically to a difference in the prevalence of sarcopenia, and this observation is valid across all age strata. In the lowest age category, the prevalence of sarcopenia in women ranged from 1.18% to 4.71% and, in the highest age category, this prevalence ranged from 16.7% to 38.1%.

The strongest impact of the cut-off used for the estimation of the prevalence of sarcopenia is found for muscle strength in women aged 70-74 years. Indeed, the use of a unique cut-off for women's muscle strength leads to an estimation of the prevalence of about 15%, while the use of cut-offs dependent on BMI leads to an estimation of about 5%.

Given this variation in the number of subjects diagnosed with sarcopenia across the different methods, we checked for differences in the sarcopenic women's clinical characteristics between the eight methods used for the diagnosis. No significant difference was found between the different diagnosis criteria except for walk speed which was significantly higher in women diagnosed with method D versus method E (p=0.039) and method F (p=0.035).

Discussion

Different cut-off values are proposed for the diagnosis of sarcopenia, in regards of three measurements: muscle mass,

	65-69 years	70-74 years	75-79 years	≥ 80 years
Men N, (%)				
A	4 (7.41)	6 (16.7)	5 (13.2)	8 (27.6)
B	2 (3.70)	6 (16.7)	5 (13.2)	8 (27.6)
C	4 (7.41)	6 (16.7)	5 (13.2)	8 (27.6)
D	2 (3.70)	6 (16.7)	5 (13.2)	8 (27.6)
E	4 (7.41)	6 (16.7)	5 (13.2)	8 (27.6)
F	2 (3.70)	6 (16.7)	5 (13.2)	8 (27.6)
G	4 (7.41)	6 (16.7)	5 (13.2)	8 (27.6)
H	2 (3.70)	6 (16.7)	5 (13.2)	8 (27.6)
Women N, (%)				
A	4 (4.71)	9 (15.0)	14 (25.0)	12 (28.6)
B	3 (3.53)	9 (15.0)	12 (21.4)	11 (26.2)
C	2 (2.35)	3 (5.00)	11 (19.6)	8 (19.0)
D	1 (1.18)	2 (3.33)	6 (10.7)	7 (16.7)
E	6 (7.06)	10 (16.7)	17 (30.4)	16 (38.1)
F	5 (5.88)	10 (16.7)	16 (28.6)	15 (35.7)
G	4 (4.71)	3 (5.00)	14 (25.0)	12 (28.6)
H	3 (3.53)	2 (3.33)	9 (16.1)	11 (26.2)

Table 4. prevalence of sarcopenia stratified by age and sex.

muscle strength and physical performance. In this study, we assessed the impact of the use of different cut-off limits for the diagnosis of sarcopenia on its estimated prevalence. We found an important variation of the prevalence of sarcopenia depending on the cut-offs used for the diagnosis. The global prevalence of sarcopenia varied from 9.25% to 18% according to the cut-off used.

In men, the use of the different cut-offs does not seem to influence the estimation of the prevalence of sarcopenia. Contrariwise, for women, we found a huge variation of the estimated prevalence of sarcopenia. It is not surprising to see a larger difference in prevalence in women than in men. Indeed, first regarding the measurement of muscle mass, the difference between the two suggested cut-offs is much larger for women than for men. The first cut-off for men reaches 7.26 kg/m^2 for SMI and the second reaches 7.25 kg/m^2, which is a very little difference. This difference is obviously much larger for women since it varies from 5.5 kg/m^2 for the first cut-off to 5.67 kg/m^2 for the second.

In the same vein, the two cut-off criteria proposed for muscle strength are more likely to lead to a difference in the estimated prevalence of sarcopenia for women than for men. Indeed, for men, we can use a unique cut-off which rises at 30 kg or BMI-dependent cut-off. This BMI depend cut-off also raised at 30 kg, or even at 32 kg, at the exception for men presenting a BMI lower or equal to 24 kg/m^2 for whom this cut-off raised at 28 kg. Taking into account that the mean BMI for men in our population was 27.6 kg/m^2, the estimation of the prevalence in our study should not have been influenced by this measurement. For women, on the opposite, the unique cut-off equals 20 kg and the BMI-dependent cut-offs are systematically below this unique cut-off except for women who presented a BMI higher than 29 kg/m^2, which is the case of only 20% of the population of women in our study. Therefore, the estimation of the prevalence of sarcopenia in women, in our study, was noticeably influenced by the muscle strength criteria.

In the literature, one study also assessed the impact of the use of different cut-off criteria on the prevalence of sarcopenia. In 2013, Bijlsma[13] compared the two same cut-offs we used for the measurement of muscle mass and also found no difference in the estimated prevalence of sarcopenia in men but a difference ranging from 2.1% to 3% in women, in other words, by a factor of 1.43. In our analysis, global prevalence for women varied from 11.7% with the first SMI cut-off to 15.7% with the second SMI cut-off. Although the prevalence is higher in our population than in the study of Bijlsma et al.[13], the relative difference is quite the same and varies by a factor of 1.34.

In their study, they also found higher prevalence of sarcopenia with advancing age. This observation is valuable for every study that assesses the prevalence of sarcopenia. It seems that this geriatric syndrome increases with age, as stated in the definition itself. We also found that the older the groups of subjects were the higher the prevalence of sarcopenia was at the exception of the group of men aged 70-74 years which presented a higher prevalence of sarcopenia than the group of 74-79 years. This exception aside, prevalence of sarcopenia increases with age.

Regarding other subjects' characteristics, we did not find any clinical characteristics differences between women diagnosed with the method that leads to the highest prevalence of sarcopenia (20.2%) and women diagnosed with the method that leads to the lowest prevalence of sarcopenia (6.58%). So, even if we observed a large variation in the number of subjects diagnosed with sarcopenia, it is reassuring to note that subjects diagnosed

with one method (set of cut-offs) presented the same clinical characteristics that those diagnosed with another method.

In this study, we sought to quantify the difference in prevalence of sarcopenia obtained with the different cut-off criteria. Because of the cross-sectional design of our study, we were not able to define the most appropriate cut-off for the diagnosis of sarcopenia. Even if the EWGSOP recommends using the normative (i.e. healthy young adults) rather than other predictive reference populations, with cut-off points at two standard deviations below the mean reference value, this group of experts notes that more research is urgently needed in order to obtain good reference values for populations around the world. Regarding the assessment of muscle mass, two cut-offs were suggested by the EWGSOP and used in our study, one defined by Baumgartner et al.[15] and the other defined by Newman et al.[4]. To establish their cut-off, Baumgartner et al.[15] developed a population-based survey of 883 elderly subjects and defined a SMI of two standard deviations below the mean SMI of young male and female reference groups as the gender-specific cut-off points for sarcopenia. In this way, sarcopenia was significantly associated with disability and was independent of ethnicity, age, comorbidity, health behaviours and fat mass. Newman et al.[4] performed an observational cohort of 2984 subjects aged 70-79 years. Newman used a different approach for the diagnosis and chose arbitrarily the gender specific 20th percentile as the cut-off point for the diagnosis of sarcopenia. Using this definition, sarcopenia was associated with poor health, lower activity and impaired lower extremity function in men and specifically with impaired lower extremity function in women.

One of the obvious limits of this study is the comparison of two cut-off points derived from two studies using two different populations. Even if the clinical characteristics of the subjects included in these populations are probably different from the clinical characteristics of our subjects, we note that both populations are composed of elderly subjects. Moreover, these two cut-off limits are suggested by the definition of the EWGSOP for the diagnosis of sarcopenia. So, our study is a first step to quantify the impact of the use of these cut-offs on the prevalence of sarcopenia. Currently, it is still a challenge for public health to establish a clear prevalence of sarcopenia. It seems obvious that the availability of different diagnosis criteria within a consensual definition remains an obstacle to this issue. We still need to establish one unique set of criteria to identify and diagnose subjects with sarcopenia. As second step, future studies should examine which cut-off criteria for muscle mass, muscle strength and gait speed are the most predictive for functional decline or hard clinical outcome such as death, hospitalization, falls, etc. and could therefore be used for the diagnosis of sarcopenia.

In conclusion, the prevalence of sarcopenia for women is depending on the applied cut-off criteria proposed by the EWGSOP. Depending on the cut-offs used for the diagnosis, the prevalence of sarcopenia can be doubled. This observation is true for women, but not for men. Even if the clinical characteristics of diagnosed subjects are not different across the cut-off method used, it is important to take this difference of prevalence into account to compare studies.

Author's contributions

CB, OB and JYR designed the study. CB, ML, JS and FB recruited the subjects and collected the data. CB performed statistical analyses. All authors commented on the drafts and approved the final draft. CB is the manuscript's guarantor.

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Development of a self-administrated quality of life questionnaire for sarcopenia in elderly subjects: the SarQoL

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Abstract

Background: the impact of sarcopenia on quality of life is currently assessed by generic tools. However, these tools may not detect subtle effects of this specific condition on quality of life.
Objective: the aim of this study was to develop a sarcopenia-specific quality of life questionnaire (SarQoL, Sarcopenia Quality of Life) designed for community-dwelling elderly subjects aged 65 years and older.
Settings: participants were recruited in an outpatient clinic in Liège, Belgium.
Subjects: sarcopenic subjects aged 65 years or older.
Methods: the study was articulated in the following four stages: (i) Item generation—based on literature review, sarcopenic subjects' opinion, experts' opinion, focus groups; (ii) Item reduction—based on sarcopenic subjects' and experts' preferences; (iii) Questionnaire generation—developed during an expert meeting; (iv) Pretest of the questionnaire—based on sarcopenic subjects' opinion.
Results: the final version of the questionnaire consists of 55 items translated into 22 questions rated on a 4-point Likert scale. These items are organised into seven domains of dysfunction: Physical and mental health, Locomotion, Body composition, Functionality, Activities of daily living, Leisure activities and Fears. In view of the pretest, the SarQoL is easy to complete, independently, in ~10 min.
Conclusions: the first version of the SarQoL, a specific quality of life questionnaire for sarcopenic subjects, has been developed and has been shown to be comprehensible by the target population. Investigations are now required to test the psychometric properties (internal consistency, test–retest reliability, divergent and convergent validity, discriminant validity, floor and ceiling effects) of this questionnaire.

Keywords: *sarcopenia, quality of life, questionnaire, older people*

Introduction

Sarcopenia is defined by a progressive and generalised loss of muscle mass and function with advancing age [1, 2]. This geriatric syndrome, now recognised as a major clinical problem for older people, is an increasing public health issue in our society [3]. Indeed, sarcopenia is associated with some adverse clinical outcomes such as physical impairment, limitation of mobility, increased risk of falls, hospitalisation and mortality [4–8] but also with major co-morbidities such as type 2 diabetes, obesity and osteoporosis [9].

As of today, the association between sarcopenia and altered quality of life (QoL) has been little studied. Health-related QoL is defined by the World Health Organization (WHO) as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. Although the decline in HR-QoL is intuitively evident for sarcopenic subjects, it is only supported by a few studies showing a significant association between, on one side, decreased grip strength and, on the other side, decreased physical and general health [10–12]. Moreover, QoL in these studies has only been measured through generic QoL questionnaires. However, generic tools may not be able to detect subtle effects of a specific condition on QoL. Consequently, a specific tool would be necessary to assess the impact of sarcopenia on QoL. Even if a large number of disease-specific QoL questionnaires currently exist, none are specific to sarcopenia. In the absence of such a specific tool, the ability to clinically characterise QoL in subjects with sarcopenia, as well as the capacity to assess changes over time in the QoL of these subjects seems compromised. Complete assessment of the benefits of a therapeutic intervention should provide evidence of an impact on patients' HR-QoL.

The aim of this study was to develop a sarcopenia-specific QoL questionnaire, called SarQoL (Sarcopenia Quality of Life), designed for community-dwelling elderly subjects aged 65 years and older. In this paper, we describe the four stages of the development of this specific QoL questionnaire.

Methods

Based on different procedures on how to develop a HR-QoL questionnaire [13–15], but also on experts' recommendations and on many successful studies [16–20], we applied the following four steps to develop our questionnaire (Figure 1):

Step 1. Item generation—based on literature review, sarcopenic subjects' opinion, experts' opinion, focus groups.
Step 2. Item reduction—based on sarcopenic subjects' and experts' relevance ranking.
Step 3. Questionnaire generation—developed during an expert meeting.
Step 4. Pretest of the questionnaire—based on sarcopenic subjects' opinion.

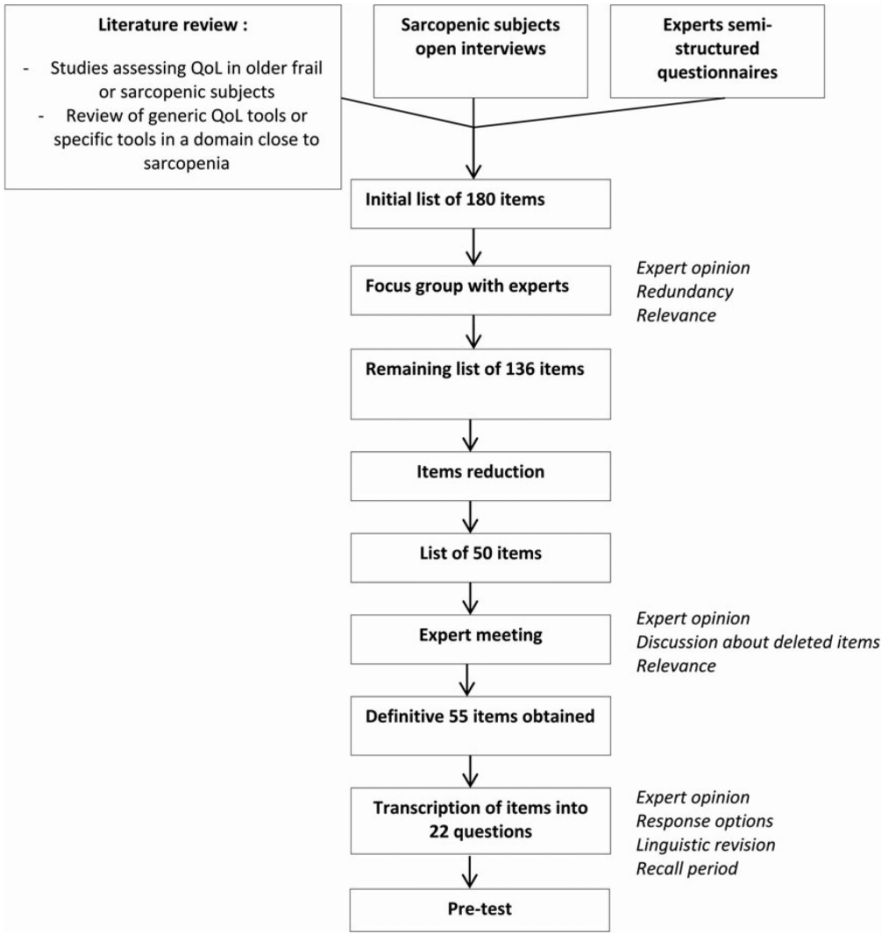

Figure 1. Overview of study procedures.

Language

The SarQoL questionnaire has been developed in French.

Identification of experts

Different experts (eight from Belgium, one from France and two from Switzerland) were included in the development of this questionnaire: three geriatricians (S.G., J.P., Y.R.), three rheumatologist experts in the field of bone and muscle (E.B., J.Y.R., R.R.), one physiotherapist and Professor in Bio-Gerontology and Geriatric Rehabilitation (I.B.), one linguist expert in the French language (J.V.B.), two experts in methodology of questionnaires (M.J., P.I.) and, at last, one statistician (N.D.).

Identification of patient population

We used the definition of the European Working Group on Sarcopenia in Older People (EWGSOP) [21] as criteria for diagnosing sarcopenic subjects. Subjects, aged 65 years and older, were recruited in an outpatient clinic in Liège, Belgium. They are currently enrolled in a 5-year prospective Belgian cohort called SarcoPhAge [22]. Sarcopenia was defined as follows:

- An appendicular lean muscle mass/height^2 (SMI) <5.5 kg/m^2 for women and <7.26 kg/m^2 for men assessed by Dual-energy X-ray absorptiometry.
- A muscle strength <20 kg for women and <30 kg for men assessed by a hydraulic hand dynamometer OR physical performance: ≤8 points for the Short Physical Performance Battery (SPPB) test.

Forty-six community-dwelling sarcopenic subjects were recruited in an outpatient clinic in Liège, Belgium. Inclusion criteria included age ≥65 years, French maternal language and written informed consent obtained. Exclusion criteria were amputated limb and BMI above 30 kg/m^2.

Subjects had to read and sign an informed consent after having been informed of the objectives and methods of the research. The study was approved by the Ethics Committee of the University Teaching Hospital of Liège (number 2013/6).

Step 1: Item generation

Items for the SarQoL were generated in a three-step process. The first step was to draw up, from an exhaustive review of the literature, a comprehensive list of items about QoL in sarcopenia. This list of items was drawn up not only from generic QoL questionnaires intended to either a general population or a population of similar age but also from different studies having assessed the QoL of frail and sarcopenic subjects. This list was then amended after having interviewed five subjects with sarcopenia, in a face-to-face discussion, about how sarcopenia impacts their QoL. All interviews, using open discussion and open-ended questions, were performed by the same clinical researcher (C.B.). During these interviews, sarcopenic subjects described all problems related to sarcopenia that affected their QoL. Answers were transcribed, and a qualitative content analysis of the responses was carried out according to the published methodology [23, 24]. Finally, this list was completed by feedbacks of experts who had received a semi-structured questionnaire, which allowed them to discuss about sarcopenia and its impact on QoL.

Then, the list of items was discussed with the experts in a meeting to reformulate some of them, delete or subdivide others, and, finally, organise them into domains of dysfunction.

Step 2: Item reduction

The aim of this step was to select the most pertinent items to include in the final questionnaire.

To perform this stage, the list of items identified in the generation phase was submitted to 21 sarcopenic subjects, different from those included in Phase 1, and to the experts. They had to grade the relevance of each item on a 4-point Likert scale ranging from '1, not relevant' to '4, extremely relevant'. Then, for each item, we examined its 'frequency' (the proportion of subjects or experts who identified the item as 'extremely relevant') and its importance (the mean importance score based on the Likert scale for this item) and selected items on the basis of the product: frequency × importance. Redundancy of items was also taken into consideration throughout the item reduction process.

Step 3: Development of the questionnaire SarQoL

A focus group was organised with all experts to translate the amended list of items into clear, brief, unambiguous and relevant questions. This meeting also served to define the layout of the questionnaire, the response format and the scoring algorithm. This first version of the questionnaire was submitted to a French linguist to ensure that it was free of any spelling or linguistic errors.

Step 4: Pretest of the questionnaire SarQoL

Once checked by the linguist, the questionnaire was submitted to a sample of 20 sarcopenic patients, different from those included in Stage 1 and Stage 2, to ensure the good understandability of each question and the acceptability of the questionnaire's format. Subjects were invited to express their misunderstanding and to formulate recommendations over the questions. Following this pretest, the second and final version of the questionnaire SarQoL was established.

Statistical analysis

Patient's characteristics are described as median (P25–P75) for continuous variables and count and percentage for categorical variables.

For item reduction, the impact of each item was calculated by multiplying the frequency of an item by its mean importance. This calculation was performed for subjects and for experts separately. The items with an impact of ≥0.5 both for subjects and for experts were selected. Other items were excluded from the list.

All analyses were executed with the software Statistica 9.1.

Results

Patient population

A total of 46 sarcopenic subjects were included in the development of the questionnaire. 78.3% of subjects were women with a mean age of 76.3 ± 6.51 years. Five sarcopenic subjects were included in the phase of items generation, 21 sarcopenic subjects participated in the phase of items reduction and 20 for the pretest. Subjects' characteristics are given in Table 1.

Step 1: Item generation

From the literature review, a first list of 67 items was drawn up. After complementing this list with the open interviews of five sarcopenic subjects and the feedback from the semi-structured questionnaires sent to seven experts (E.B., I.B., S.G., J.P., R.R., J.Y.R., Y.R.), a new list of 180 items was generated. A meeting was then held with all the experts to discuss on the basis of this 180-item list which items had to be deleted because of redundancy, similarity or repetition and which items had to be combined or reformulated. These decisions were made on the basis of consensus agreement between the research team and the experts. At the end of the meeting, the list was reduced to 136 items, structured into eight domains: Physical and Mental Health, Locomotion, Social relations, Body composition, Functionality, Activities of daily living, Leisure activities and Fears.

Step 2: Item reduction

The 136-item list was given to 21 subjects diagnosed sarcopenic and to the experts. Only the items with a frequency × importance product of 0.5 or greater were retained. In three domains, Social relation, Body composition and Fears, no item reached this cut-off point. At this stage, the process reduced the number of items to 48, classified into five domains. Consensus agreement between experts was to keep three items from the domain of Body composition and four items from the domain of Fears and to remove the domain of Social relation from the questionnaire because of its very low score from both patients and experts. The decision of keeping items from the Body composition and Fears domains was based on the fact that the mean rating for these items was >1 for either the experts or the subjects. Following this consensual decision of experts, a final list of 55 items, classified into seven domains was achieved (Table 2).

Step 3: Development of the questionnaire SarQoL

The 55 items were translated into 22 questions during a meeting organised with the experts. The decision regarding the format of questions was made by general consent of the

Table 1. Demographic and clinical characteristics of patients involved in Phase 1, Phase 2 and Phase 4 of the development

	Phase 1: Item generation (n = 5)	Phase 2: Item reduction (n = 21)	Phase 4: Pretest (n = 20)
Age	73.0 (71.0–79.0)	76.1 (71.6–80.1)	75.1 (71.7–80.0)
Sex			
Women	5 (100.0)	13 (61.9)	18 (90.0)
Anthropometric data			
Height (cm)	161.4 (161.0–166.7)	161.3 (156.7–168.1)	157.5 (152.7–162.0)
Weight (kg)	60.3 (50.0–67.5)	58.3 (53.5–61.8)	60.0 (55.2–66.2)
BMI (kg/m^2)	23.1 (17.9–26.0)	22.2 (20.6–23.7)	23.8 (23.2–26.9)
Calf circumference (cm)	33.5 (28.0–33.5)	31.0 (29.5–32.0)	32.0 (30.0–34.2)
Wrist circumference (cm)	15.0 (15.0–15.5)	16.0 (15.0–17.0)	15.5 (15.0–16.5)
Arm circumference (cm)	26.0 (25.0–26.0)	24.5 (23.0–27.0)	26.7 (24.7–27.7)
Civil status			
Married	2 (40.0)	12 (57.1)	12 (60.0)
Divorced	2 (40.0)	3 (14.3)	17 (10.0)
Widow	1 (20.0)	4 (19.0)	4 (20.0)
Single	0 (0.00)	2 (9.52)	2 (10.0)
Level of education			
Without qualification	0 (0.00)	0 (0.00)	0 (0.00)
Primary school	3 (60.0)	2 (9.52)	2 (10.0)
Secondary school	2 (40.0)	11 (52.4)	10 (50.0)
Post-secondary education	0 (0.00)	8 (38.1)	8 (40.0)
Number of diseases	2.0 (2.0–7.0)	5.0 (4.0–8.0)	4.5 (3.0–6.0)
Number of drugs	8.0 (7.0–9.0)	6.0 (5.0–9.0)	6.0 (5.0–10.0)
Gait speed (m/s)	0.95 (0.79–0.97)	0.94 (0.77–1.18)	0.88 (0.78–1.01)
Grip strength maximum (kg)			
Women	24.6 (20.1–25.3)	19.5 (16.0–22.0)	18.0 (16.0–20.5)
Men	–	27.0 (21.5–29.5)	41.7 (38.0–45.5)
SMI (kg/m^2)			
Women	4.97 (4.8–5.3)	5.07 (4.68–5.35)	5.31 (4.76–5.46)
Men	–	6.43 (6.21–6.60)	7.15 (7.10–7.25)

SMI, skeletal muscle index (appendicular lean mass/height^2).

Table 2. Presentation of the final 55 items composing the SarQoL questionnaire

Domains	Items
Physical and mental health	Loss of arm strength
	Loss of leg strength
	Loss of energy
	Muscle pain
	Feeling of muscle weakness
	Feeling of being frail
	Feeling old
	Feeling of being physically weak
Locomotion	Limitation in walking time
	Limitation in number of outings outdoor
	Limitation in walking distance
	Limitation in walking speed
	Limitation in steps length
	Feeling of fatigue when walking
	Need of recovery time when walking
	Difficulties to cross a road fast enough
	Difficulties to walk on uneven grounds
Body composition	Physical change
	Loss of muscle mass
	Weight change (loss or gain)
Functionality	Balance problems
	Falls occurrence
	Loss of physical capacity
	Loss of flexibility
	Climbing one flight of stairs
	Climbing several flight of stairs
	Climbing stairs without a banister
	Stooping
	Crouching or kneeling
	To stand from a sitting position
	Get up from a chair
	To stand up from the floor without any support
	Limitation of movement
	Sexuality
Activities of daily living	Difficulty during light physical effort
	Fatigue during light physical effort
	Pain during light physical effort
	Difficulty during moderate physical effort
	Fatigue during moderate physical effort
	Pain during moderate physical effort
	Difficulty during intensive physical effort
	Fatigue during intensive physical effort
	Pain during intensive physical effort
	Shopping
	Household tasks
	Carrying heavy objects
	Open a bottle or a jar
	Take public transportation
	To get in/out a car
Leisure activities	Change in physical activities
	Change in leisure activities
Fears	Fear of getting hurt
	Fear of not succeeding
	Fear of being tired
	Fear of falling

experts after discussion. The experts proposed a 4-point Likert scale of frequency (often, sometimes, rarely, never) or intensity (a lot, moderately, a bit, not at all) for all questions at the exception of one question. Seven questions were displayed in a table including several items, and other questions were displayed as unique questions. No question uses a recall period. The total scoring of the SaQoL questionnaire ranges from 0 (worst imaginable health) to 100 (best imaginable health). At this stage, the first version of the SarQoL questionnaire was established.

Step 4: Pretest of the questionnaire SarQoL

Finally, the SarQoL questionnaire was pretested on a group of 20 sarcopenic subjects. It took ~10 min to patients to self-administer the questionnaire. No patient reported any difficulty in completing the questionnaire or interpreting the questions. The questionnaire was consequently kept unchanged.

Discussion

In the present study, we report the development of the first specific, self-administrated sarcopenia-related QoL questionnaire, the SarQoL questionnaire. This questionnaire includes 55 items translated into 22 questions rated on a 4-point Likert scale. In view of the pretest, the SarQoL is easy to complete, independently, in ~10 min.

Sarcopenia is associated with the development of physical disability, with nursing home admission, depression, hospitalisation, many co-morbidities, poor physical performance, functional decline, falls and with short- and long-term mortality in hospitalised patients [3]. However, as of today, few studies have assessed the impact of sarcopenia on QoL. In 2012, Kull *et al.* [11] found a reduced QoL in two domains (i.e. physical function and vitality) of the SF-36 questionnaire in sarcopenic subjects. Two other studies found that sarcopenic subjects presented poorer general health and physical functioning scores [12] and presented significantly more problems of mobility, self-care, usual activity and anxiety than non-sarcopenic subjects [25]. Other studies showed an indirect association between sarcopenia and QoL with a significant correlation between reduced grip strength, one of the components of sarcopenia, and reduced QoL in the domains of physical functioning and general health [10, 26]. Another study also showed a correlation between reduced muscle mass in men and reduced general health, assessed with the SF-36 questionnaire [27]. All these results highlight the fact that QoL of subjects suffering from sarcopenia is affected only in specific domains. Even if the SF-36 is widely in use, simple and effective [28], it is acknowledged that this generic tool should be supplemented with disease-specific instruments [29]. There is a need of a specific QoL questionnaire in the field of sarcopenia [8]. This questionnaire should include the physical aspects of the musculoskeletal domains but should also give an even-handed balance to other factors affecting QoL. During the development of the SarQoL, we followed carefully these recommendations and included therefore no less than seven domains of dysfunction: Physical and Mental Health, Locomotion, Body composition, Functionality, Activities of daily living, Leisure activities and Fears.

HR-QoL assessments are obviously important for healthcare providers and regulatory agencies to understand the needs and preoccupation of important segments of the population, such as elderly subjects suffering from sarcopenia. Such a tool could enhance the accuracy of assessments of well-being and physical function, psychological and social implications of sarcopenic subjects. With the future expected development of interventions targeting sarcopenia, this tool will also be useful to measure the effectiveness and relevance of these new therapeutic strategies.

Our study presents several strengths. First of all, we respected guidelines and followed rigorous steps, which have previously been successfully used in many other studies. Next, many experts have been actively involved in the development process; eight clinician experts in the field of sarcopenia, one linguist expert in the French language, two experts in the methodology of questionnaires and one statistician. This large and heterogeneous panel of experts ensured a rigorous methodology, a good use of the French language throughout the questionnaire and a content validity. Moreover, the content validity was also provided by the large range of sources used to generate items and by the inclusion of sarcopenic patients in the two first stages of the development of the questionnaire, the item generation and the reduction of items. Some weaknesses could however be pointed out. First of all, the inclusion of 46 subjects in the development process could be considered as too limited but is in line with the methodology used in other studies [30, 31]. Secondly, these subjects are also enrolled in another study on sarcopenia (the SarcoPhAge study [22]) and might, consequently, be more aware of the impact of sarcopenia given the participant's information and assessments they underwent for the prospective study. We must also note that the majority of the sample is composed of women, which could have some impact on the results. Moreover, in the item generation phase, all included subjects were women. However, the inclusion of subjects in this phase is not formally requested and only ensures a content validity to the questionnaire. Anyway, we acknowledge that if some men would have been included in this phase, it might have resulted in having some items more specific to men added to the list of items generated. Another limitation is that the questionnaire has only been developed with ambulatory community-dwelling subjects and could not be fully adapted to other populations. Finally, only French-speaking subjects were studied, and characteristics of French-speaking Belgian sarcopenic subjects could differ from subjects from other countries.

Future works

Even if the SarQoL questionnaire is now developed, this questionnaire is not yet ready to be used. Indeed, verification of psychometric properties has still to be done and is currently on the way. Future work includes first the development of a scoring algorithm and a factorial analysis of the included questions; second, the analysis of the convergent and divergent validity of the questionnaire, the internal consistency, the test–retest reliability, and the potential ceiling and floor effects.

Key points

- The generic quality of life tools may not detect subtle effects of sarcopenia on quality of life.
- A first version of the SarQoL, a specific quality of life questionnaire for sarcopenic subjects, has been developed.
- The SarQoL has been shown to be comprehensible by the target population.
- Investigations are now required to test the psychometric properties of this questionnaire.

Conflicts of interest

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Validation of the SarQoL®, a specific health-related quality of life questionnaire for Sarcopenia

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Abstract

Background A specific self-administrated health-related quality of life questionnaire for sarcopenia, the Sarcopenia and Quality Of Life (SarQoL®), has been recently developed. This questionnaire is composed of 55 items translated into 22 questions and organized into seven domains of quality of life. The objective of the present work is to evaluate the psychometric properties (discriminative power, validity, reliability, floor and ceiling effects) of the SarQoL® questionnaire.

Methods Sarcopenic subjects were recruited in an outpatient clinic in Liège, Belgium and were diagnosed according to the algorithm developed by the European Working Group on Sarcopenia in Older People. We compared the score of the SarQoL® between sarcopenic and non-sarcopenic subjects using a logistic regression after adjustment for potential confounding variables. Internal consistency reliability was determined using Cronbach's alpha coefficient; construct validity was assessed using convergent and divergent validities. Test–retest reliability was verified after a two-week interval using the intra-class correlation coefficient (ICC). At last, floor and ceiling effects were also tested.

Results A total of 296 subjects with a median age of 73.3 (68.9–78.6) years were recruited for this study. Among them, 43 were diagnosed sarcopenic. After adjustment for potential confounding factors, the total score and the scores of the different dimensions of the SarQoL® questionnaire were significantly lower for sarcopenic than for non-sarcopenic subjects (54.7 (45.9–66.3) for sarcopenic vs. 67.8 (57.3 – 79.0) for non sarcopenic, OR 0.93 (95%CI 0.90–0.96)). Regarding internal consistency, the Cronbach's alpha coefficient was 0.87. The SarQoL® questionnaire data showed good correlation with some domains of the Short-Form 36 (SF-36) and the EuroQoL 5-dimension (EQ-5D) questionnaires and with the mobility test. An excellent agreement between the test and the retest was found with an ICC of 0.91 (95% CI 0.82–0.95). At last, neither floor nor ceiling effects were detected.

Conclusions The SarQoL® questionnaire is valid, consistent, and reliable and can therefore be recommended for clinical and research purposes. However, its sensitivity to change needs to be assessed in future longitudinal studies.

Keywords Sarcopenia; Quality of life; SarQoL®; Psychometric validation; Questionnaire

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Introduction

Sarcopenia is defined by a progressive and generalized loss of muscle mass and muscle function with advancing age.[1,2] Because of its association with many adverse clinical outcomes (e.g. physical impairment, limitation of mobility, increased risk of falls, depression, hospitalization, mortality, etc.),[3–8] sarcopenia is now recognized as a major clinical

problem for older people and as a real public health issue for the society.[9]

However, consequences of sarcopenia on individual quality of life are still poorly understood. One of the main reasons appears to be that studies assessing quality of life in sarcopenia are using generic questionnaires, such as the Short-Form 36 questionnaire (SF-36). Because of the physical and mental consequences associated with sarcopenia,[3–8] the decline of quality of life in sarcopenic subjects is intuitively evident. However, two studies using the SF-36 questionnaire for this purpose failed to show a reduced quality of life in sarcopenic subjects.[10,11] The SF-36 questionnaire has also been used in two other studies[12,13] showing a reduced quality of life in sarcopenic subjects only for some specific domains of quality of life, such as physical function and vitality. The other domains of quality of life did not differ between groups. These results highlight that only some specific domains of quality of life are impacted by sarcopenia and, therefore, generic tools may not be able to detect subtle effects of this specific condition on quality of life.[14] A specific tool could thus be more appropriate to accurately assess the impact of sarcopenia on quality of life.

Recently, the Sarcopenia and Quality of Life (SarQoL®), a specific quality of life questionnaire for sarcopenia, has been developed by our team[15] (Appendix S1, also available on www.sarqol.org). Before using a questionnaire for clinical and research purposes, one has to ensure that the questionnaire has the appropriate psychometric properties for the intended application. The objective of the present work was therefore to evaluate the psychometric properties (discriminative power, validity, reliability, floor and ceiling effects) of this new quality of life measure for sarcopenia. We decided to test the hypothesis that the SarQoL® questionnaire discriminates well the sarcopenic and the non-sarcopenic subjects, presents a good correlation with other questionnaires presenting a similar concept, presents a low correlation with other questionnaires presenting a dissimilar concept, is reliable after a two-week interval, and does not present any floor nor ceiling effect.

Methods

Identification of patient population

Subjects were recruited in an outpatient clinic in Liège, Belgium within the SarcoPhAge cohort (Sarcopenia and Physical impairment with advancing Age),[12] which is a prospective longitudinal study of Belgian voluntary subjects aged 65 years and older. Inclusion criteria included age $\geq$ 65 years and French mother tongue. Subjects with an amputated limb were excluded and, because of the requirements of the device measuring appendicular lean mass (Dual Energy X-Ray Absorptiometry), subjects with a body mass index (BMI) above 30 kg/m^2 were also excluded. Subjects had to read and sign an informed consent after having been informed of the objectives and methods of the research project. The study has been approved by the Ethics Committee of the University Teaching Hospital of Liège (number 2013/6).

To diagnose sarcopenia, we applied the definition of the European Working Group on Sarcopenia in Older People (EWGSOP).[1] Sarcopenia was defined by the following:

- An appendicular muscle mass/height^2 (SMI) $<$ 5.5 kg/m^2 for women and $<$ 7.26 kg/m^2 for men assessed by Dual-Energy X-Ray Absorptiometry and
- A muscle strength $<$ 20 kg for women and $<$ 30 kg for men assessed by a hand dynamometer (acquired from Saehan Corporation, MSD Europe Bvba, Belgium) or a physical performance $\leq$ 8 points for the Short Physical Performance Battery (SPPB) test.

Development of the SarQoL®

The method used for the development of the questionnaire has been described elsewhere.[15] Briefly, the development was articulated in the following four stages: (i) item generation—based on literature review, sarcopenic subjects' opinion, experts' opinion, focus groups; (ii) item reduction—based on sarcopenic subjects' and experts' preferences; (iii) questionnaire generation—developed during an expert meeting; and (iv) pre-test of the questionnaire—based on sarcopenic subjects' opinion.

A total of 43 sarcopenic subjects and 12 experts (three geriatricians, three rheumatologists expert in the field of bone and muscle, one physiotherapist, one epidemiologist, one linguist expert in the French language, two experts in methodology of questionnaires, and one statistician) were involved in the development of the questionnaire.

The final version of the SarQoL® is composed of 55 items translated into 22 questions rated on a 4-point Likert scale. The questionnaire is scored on 100 points. Higher score reflects a higher quality of life. Items are organized into seven domains: domain 1 'Physical and Mental Health' with 8 items; domain 2 'Locomotion' with 9 items; domain 3 'Body Composition' with 3 items; domain 4 'Functionality' with 14 items; domain 5 'Activities of daily living' with 15 items, domain 6 'Leisure activities' with 2 items, and, at last, domain 7 'Fears' with 4 items. It takes approximately 10 min for patients to fill in the questionnaire.

Validation of the SarQoL®

The psychometric properties verification consisted of one discriminative power analysis, and the assessment of reliability

(internal consistency and test–retest reliability), validity (construct validity), and floor and ceiling effects. Because the purpose of the discriminative power analysis is to assess the ability of the questionnaire to differentiate quality of life in regards of sarcopenia status, this analysis has been performed on the whole study population. However, to validate the SarQoL® as a specific tool for measuring quality of life in sarcopenia, all other validation analyses have been performed on the sarcopenia population.

Discriminative power

The ability of the questionnaire to discriminate subjects with different sarcopenia status was assessed by the comparisons between the total score of the SarQoL® questionnaire and between the individual domains scores, for non sarcopenic and sarcopenic subjects. Adjusted logistic regressions were performed for two-group comparison (sarcopenic vs. non sarcopenic subjects). Analyses were adjusted for clinical characteristics, which were significantly different between groups in univariate statistics.

Reliability

Internal consistency. Internal consistency is the estimation of item homogeneity. Internal consistency reliability was determined using Cronbach's alpha coefficient.[16] A value greater than 0.70 indicates a high level of internal consistency.[17] We also tested the impact of each domain on the reliability.

We also assessed the correlation of each domain with the total score of the SarQoL® using Spearman's correlations. A correlation above 0.81 was considered as excellent, between 0.61 and 0.80 as very good, between 0.41 and 0.60 as good, between 0.21 and 0.4 as acceptable, and at last, less than 0.20 as insufficient.[18]

Test–retest reliability. To analyse the test–retest stability of the SarQoL® questionnaire, sarcopenic subjects were asked to fill in the questionnaire a second time after a two-week interval. To avoid finding changes unrelated to the reliability of the questionnaire between the first and the second administration of the SarQoL, participants were asked if they felt any change in their general health (physical and mental health; e.g. sickness, fall, hospitalization, tiredness, etc.) during the past two weeks. Test–retest reliability was only performed among those who reported no change in their general health over this two-week period. The intra-class coefficient correlation (ICC) was used to test the reliability between the first and the retest scores of the total questionnaire and of the individual domains of the SarQoL®. An ICC over 0.7 was considered as an acceptable reliability.[19]

Construct validity

Construct validity was assessed using convergent validity and divergent validity. For the convergent validity, Spearman's correlations were used to evaluate the correlation between the SarQoL® and other questionnaires, which had similar dimensions. Regarding divergent validity, Spearman's correlations were used to evaluate the correlation between the total score of the SarQoL® and other questionnaires, which had different dimensions.

Besides completing the SarQoL® questionnaire, sarcopenic subjects also completed three other questionnaires:

- 1/ the generic Short Form-36 questionnaire[20] which is composed of 36 items measuring eight health-related quality of life domains (physical functioning, role limitation because of physical problems, bodily pain, general health, vitality, social functioning, role limitation because of emotional problem, and mental health) scored on a scale from 0 (worst quality of life) to 100 (best quality of life). The SF-36 questionnaire was used to measure convergent validity between the SarQoL questionnaire and the domains of physical functioning, general health, and vitality;
- 2/ the EuroQoL 5-dimension (EQ-5D) questionnaire[21] which records the level of self-reported problems according to five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Utility score of the EQ-5D questionnaire as well as dimensions of usual activities and mobility has been used to measure the convergent validity with the SarQoL questionnaire. The dimension of pain/discomfort has been used to measure the divergent validity with the SarQoL questionnaire;
- 3/ the Mobility–Tiredness scale which is designed to estimate fatigue following daily life activities for elderly subjects.[22] The scale assessed whether the participants were in need of help to transfer, walk indoors, go outdoors, walk outdoors in nice weather, walk outdoors in poor weather, and climb stairs. Participants who were able to manage the tasks independently were then asked if they felt tired after performing these tasks. Fatigue on these six individual tasks were summed for a total fatigue score (range 0–6), with higher scores indicating higher levels of fatigue. The Mobility–Tiredness scale has been used to measure convergent validity with the SarQoL questionnaire.

Moreover, the participants also had a Mini Mental State Examination (MMSE)[23] which consists of a 30-point questionnaire to assess cognitive function. The score of the MMSE has been used to measure convergent validity with the SarQoL questionnaire.

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Floor and ceiling effects

Floor and ceiling effects were considered to be present when a high percentage of the population had the lowest or the highest score respectively. Floor and ceiling effects higher than 15% were considered to be significant.

Statistical analysis

Normality of quantitative variables was tested by the Shapiro–Wilk test. Because the variables did not present a normal distribution, quantitative variables were expressed as median (P25–P75) and qualitative variables were reported as absolute and relative frequencies (%). Differences of characteristics between sarcopenic and non-sarcopenic subjects were tested with Mann–Whitney *U* test for quantitative variables and with a χ^2 for qualitative variables.

To measure the discriminative power of the questionnaire, a logistic regression model was performed. The model was adjusted for clinical characteristics which were significantly different between groups in univariate analyses (adjusted on age and BMI).

Reliability has been measured by Cronbach's alpha coefficient to test the internal consistency and ICC to test the reliability between the first and the retest scores of the SarQoL® questionnaire. Finally, Spearman's correlations were used to evaluate the construct validity of the SarQoL questionnaire and so, to measure the correlations between the SarQoL® questionnaire and the domains of physical functioning, vitality and general health of the SF-36 questionnaire, the utility score of the EQ-5D questionnaire as well as the questions related to mobility, usual activities, and pain/discomfort of the EQ-5D questionnaire and the Mobility–Tiredness scale.

Analyses were performed using Statistica (version 10 for Windows) and SAS (version 9.3 for Windows; used only for the internal consistency analysis). Results were considered statistically significant at the 5% critical level ($p < 0.05$).

Results

Subjects

A total of 296 subjects with a median age of 73.3 (68.9–78.6) years were recruited. Among them, 169 were women, which represent 57.1% of the population. Based on the algorithm developed by the EWGSOP, 43 subjects (i.e. 28 women and 15 men) were diagnosed sarcopenic. Characteristics of the population and of sarcopenic subjects are presented in *Table* 1.

Sarcopenic subjects were older and had lower BMI (BMI = weight/height^2) than the non-sarcopenic subjects ($p < 0.001$ and $p < 0.001$, respectively). No differences were observed regarding sex, number of concomitant diseases, number or drugs consumed, alcohol consumption, smoking habits, depression, and cognitive function.

All subjects self-completed the questionnaire on a paper format. No clarification has been requested by the subjects.

Discriminative power

Table 2 presents the total score and the individual domains scores of the SarQoL questionnaire for sarcopenic and non-sarcopenic participants.

Sarcopenic subjects presented a quality of life score of 54.7 (45.9–66.3) compared to a score of 67.8 (57.3–79.0) for non sarcopenic participants. The logistic model adjusted for age a BMI showed an OR of 0.93 (95% CI 0.9–0.96) indicating a lower total score for sarcopenic subjects in comparison to non-sarcopenic one (*Table* 3). Moreover, all domains presented scores lower for sarcopenic subjects compared to non-sarcopenic ones. This was confirmed by the logistic analysis model. The discriminant power of the questionnaire is thereby confirmed (*Tables* 2 and 3).

Table 1 Clinical characteristics of the included population

	All (n = 296)	No sarcopenia (n = 253)	Sarcopenia (n = 43)	p-Value*
Age (years)	73.3 (68.9–78.6)	72.4 (68.7–77.7)	77.1 (73.2–82.5)	<0.001
Sex				
Women	169 (57.1)	141 (55.7)	28 (65.1)	0.25
BMI (kg/m^2)	26.8 (23.8–30.1)	27.2 (24.5–30.4)	23.1 (21.1–25.2)	<0.001
Number of concomitant diseases	4.0 (3.0–6.0)	4.0 (3.0–6.0)	4.0 (3.0–6.0)	0.17
Number of drugs	5.0 (3.0–8.0)	5.0 (3.0–8.0)	6.0 (5.0–9.0)	0.07
Alcohol consumption				
Yes	154 (52.0)	135 (53.4)	19 (44.2)	0.27
Smoking				
Yes	27 (9.12)	23 (9.09)	4 (9.30)	0.96
MMSE score (/30 points)	29.0 (28.0–30.0)	29.0 (28.0–30.0)	29.0 (28.0–30.0)	0.36
Depression (/15 points)	2.0 (1.0–5.0)	2.0 (1.0–5.0)	3.0 (2.0–7.0)	0.19

*: p-value between sarcopenia and no sarcopenia.
BMI, body mass index; MMSE, Mini Mental State Examination.

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Table 2 Results of the SarQoL® questionnaire for sarcopenic and non-sarcopenic subjects

	No sarcopenia ($n = 253$)	Sarcopenia ($n = 43$)
Total score	67.8 (57.3–79.0)	54.7 (45.9–66.3)
D1 Physical and Mental Health	63.3 (54.4–76.7)	56.7 (45.6–63.3)
D2 Locomotion	61.1 (50.0–83.3)	52.8 (30.6–66.7)
D3 Body Composition	60.0 (50.0–70.8)	50.0 (41.7–60.0)
D4 Functionality	75.0 (61.5–85.7)	65.4 (53.8–75.0)
D5 Activities of daily living	66.1 (54.5–80.0)	48.3 (40.0–57.7)
D6 Leisure activities	66.6 (33.2–66.7)	50.0 (33.2–66.7)
D7 Fears	87.5 (87.5–100.0)	87.5 (75.0–100.0)

Table 3 Discriminative power of the SarQoL® questionnaire

	Sarcopenia (vs. no sarcopenia)		
	OR	95% CI	*p*-Value*
Total score	0.93	0.90–0.96	<0.001
D1 Physical and Mental Health	0.96	0.94–0.99	0.003
D2 Locomotion	0.97	0.95–0.98	<0.001
D3 Body Composition	0.97	0.95–0.99	0.027
D4 Functionality	0.95	0.93–0.98	<0.001
D5 Activities of daily living	0.93	0.91–0.96	<0.001
D6 Leisure activities	0.97	0.95–0.99	0.013
D7 Fears	0.95	0.91–0.98	0.002

*Adjusted for age and BMI.

Internal consistency

The Cronbach's alpha coefficient of the SarQoL® questionnaire was 0.87. This indicates a high level of internal consistency. When deleting one domain at a time, we found a Cronbach's alpha varying between 0.84 for domain 1 'Physical and Mental Health' to 0.89 for domain 6 'Leisure activities'.

All individual domains were significantly and positively correlated with the total score of the SarQoL® ($p < 0.001$ for all domains) (*Table* 4).

Construct validity

Quality of life did not differ between sarcopenic subjects and non-sarcopenic subjects in terms of utility score assessed with the EQ-5D questionnaire as well as for all the domains of the SF-36 questionnaire at the exception of the domain of physical functioning where the score for sarcopenic subjects (55.0 (35.0–71.25)) was significantly lower than the score of non-sarcopenic subjects (75.0 (50.0–90.0)) ($p = 0.001$).

As expected, the total score at the SarQoL® questionnaire was positively correlated with some domains of the SF-36 questionnaire: physical functioning ($r = 0.49$, $p < 0.001$), vitality ($r = 0.72$, $p < 0.001$), and general health ($r = 0.67$, $p < 0.001$). Good correlations were also found between the total score of the SarQoL® questionnaire and the utility score

Table 4 Results of the correlation between each domain and the total score of the SarQoL® and of the test–retest reliability of the SarQoL® total score and individual domain scores

	Correlation		Test–retest reliability	
	r	*p*-Value	ICC	95% CI
Total score	1	.	0.91	0.82–0.95
D1 Physical and Mental Health	0.78	<0.001	0.84	0.69–0.92
D2 Locomotion	0.84	<0.001	0.65	0.39–0.81
D3 Body Composition	0.56	<0.001	0.52	0.21–0.73
D4 Functionality	0.86	<0.001	0.88	0.78–0.94
D5 Activities of daily living	0.89	<0.001	0.79	0.60–0.89
D6 Leisure activities	0.52	<0.001	0.76	0.55–0.88
D7 Fears	0.58	<0.001	0.42	0.092–0.67

ICC, intra-class correlation coefficient.

of the EQ-5D questionnaire ($r = 0.47$, $p = 0.002$), questions of the EQ-5D questionnaire related to usual activities ($r = -0.57$, $p < 0.001$) but also between the total score of the SarQoL® questionnaire and the Mobility-test questionnaire ($r = 0.77$, $p < 0.001$) which confirmed the convergent validity. A low but significant correlation has been found between the SarQoL® questionnaire and the questions of the EQ-5D questionnaire related to mobility ($r = -0.35$, $p = 0.023$).

For the divergent validity, very low correlations were found between the SarQoL® questionnaire and the MMSE test ($r = 0.02$, $p = 0.89$) but also between the SarQoL® questionnaire and the questions of the EQ-5D related to pain/discomfort ($r = -0.12$, $p = 0.45$).

Test–retest reliability

Among sarcopenic subjects who completed, a second time, the SarQoL® questionnaire after an interval of two weeks, 30 reported no change of health during this period. We found an excellent agreement between the test and retest with an ICC of 0.91 (95% CI 0.82–0.95). Regarding the seven domains, we also found an excellent test–retest reliability for domain 1 'Physical and Mental Health' and for domain 4 'Functionality'. A good reliability was found for domain 2 'Locomotion', domain 5 'activities of daily living', and domain 6 'leisure activities'. Finally, for domain 3 'body composition' and 7 'fears', a low reliability was found with respectively an ICC of 0.52 (95% CI 0.21–0.73) and 0.42 (95% CI 0.09–0.67) (*Table* 4).

Floor and ceiling effects

No sarcopenic subject presented either the lowest score or the highest score at the SarQoL® questionnaire. Consequently, there was neither floor nor ceiling effects.

Discussion

To our knowledge, the SarQoL® questionnaire is the first specific quality of life questionnaire developed for sarcopenia.

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Even if no clear recommendation currently exists for the management of sarcopenia in daily practice, this questionnaire can, however, enhance the accuracy of assessment of well-being and physical function, psychological, and social implications of sarcopenic subjects by clinicians. Moreover, because of the increasing development of therapeutic intervention targeting sarcopenia, this tool can be used to assess the relevance of these interventions and their effectiveness in terms of change in quality of life.

The psychometric property analyses showed first that the questionnaire discriminates between sarcopenic subjects and non-sarcopenic ones. Contrarily to the generic tools, such as the SF-36 and the EQ-5D, the SarQoL® questionnaire is composed exclusively of questions related to sarcopenia. For the development of the questionnaire,[15] literature was carefully searched for items related to sarcopenia. Moreover, several experts coming from various French speaking countries, but also sarcopenic subjects, were asked to define some items of quality of life related to sarcopenia. This list of items was then reduced to the most pertinent ones based on experts' and/or sarcopenic subjects' opinion. The inclusion of sarcopenic subjects at these different steps of development ensured the content validity of the SarQoL® questionnaire. A valid questionnaire implies that the scores obtained by sarcopenic subjects are significantly lower than scores obtained by non-sarcopenic ones, even after adjustment for potential confounding variables. We also measured, in an exploratory analysis, the scores for the severe-sarcopenic subjects (presence of low muscle mass, low muscle strength, and low physical performance).The scores obtained by severe sarcopenic subjects ($n = 16$) were even lower than those obtained by the sarcopenic subjects, which indicates that the SarQoL® questionnaire can capture the severity of sarcopenia.

The results of the validation of the questionnaire also show a high internal consistency. This value is greater than 0.7 and lower than 0.9 which indicates a good internal consistency and a non-redundancy of items.[19] Moreover, it appears that the deletion of one domain at a time did not have a particular impact on the reliability. We also tested the correlation of each domain with the total score, and we found that each domain was positively and strongly correlated with the total score.

Regarding construct validity, we found strong correlation between the SarQoL® questionnaire and the domain of vitality and general health of the SF-36 questionnaire. Because the SF-36 is a quality of life questionnaire, we did not expect very low correlations between any domains of this questionnaire and the SarQoL®. Therefore, we only used the SF-36 questionnaire to measure convergent validity, and we tested only the domains which we hypothesized as having a strong correlation with the SarQoL® because of their potential association with sarcopenia. Regarding the EQ-5D questionnaire, we found a strong correlation with the question related to usual activities but we found a lower correlation than expected with the question related to mobility. However, this question related to mobility in the EQ-5D concerns only walking activity, which may explain why we did not find the expected strong correlation with the SarQoL® questionnaire.

To confirm the reliability of the questionnaire, we measured the test–retest reliability after a two-week interval in 43 sarcopenic subjects. We found an ICC of 0.88 (95% CI 0.77–0.94). When keeping only the 30 sarcopenic subjects than did not report any modification of health between the test and the retest, this ICC increased to 0.91 (95% CI 0.82–0.95), which indicates an excellent test–retest reliability.[19] With the sarcopenic subjects who did not report any change in their health, we found low ICC for domain 3 'Body composition' and domain 7 'Fears'. This could partly be explained by the low number of items included in these domains, 3 and 4 items, respectively. The two-week interval was geared to the subject population. It seems a good compromise between the stability of the measure and the absence of memory bias.

Our study presented some limitations. First, the sensitivity to change of the SarQoL® questionnaire was not assessed. Indeed, as with all developments of health-related quality of life questionnaires, this study is cross sectional, and this parameter can only be tested in a longitudinal study. However, as the subjects included in the present study are part of the SarcoPhAge study,[12] which is a prospective longitudinal study, we will be able, in the future, to record longitudinal data and to correlate the evolution of sarcopenia, or of muscle mass, muscle strength and physical performance of subjects, with the evolution of the SarQoL® score. A second limitation concerned the assessment of the discriminant validity. Indeed, we did not include questionnaires, which would present a totally dissimilar concept other than quality of life. So, we used one question of the EQ-5D questionnaire as well as the MMSE, but it would have been interesting to have a questionnaire exclusively focused on a topic not affected by sarcopenia to assess more appropriately the divergent validity. Finally, our study population was mainly composed of voluntary subjects. These subjects could feel a priori more concerned by muscle disorders than a random sample of the population. This potential bias may have been associated with a decreased score of the non-sarcopenic subjects. We should also acknowledge that the psychometric analyses have only been assessed in the SarcoPhAge cohort, and they should be confirmed in other cohorts to ensure external validity. At the present time, SarQoL® has only yet been developed and validated in French.

Conclusions

The SarQoL® questionnaire, the first specific quality of life questionnaire for sarcopenia, has been developed and has

been shown to be understandable by the target population. The SarQoL® is valid, consistent, and reliable and can therefore be proposed for clinical and research purposes. The questionnaire still needs to be validated regarding the sensitivity to change.

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The authors certify that they comply with the ethical guidelines for authorship and publishing of the Journal of Cachexia, Sarcopenia, and Muscle.[24]

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Online supplementary material

Supporting information may be found in the online version of this article.

Appendix S1. French version of the SarQoL

Conflicts of interest

None declared in relation with this work.

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English translation and validation of the SarQoL®, a quality of life questionnaire specific for sarcopenia

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Abstract

Background: the first quality of life questionnaire specific to sarcopenia, the SarQoL®, has recently been developed and validated in French. To extend the availability and utilisation of this questionnaire, its translation and validation in other languages is necessary.
Objective: the purpose of this study was therefore to translate the SarQoL® into English and validate the psychometric properties of this new version.
Design: cross-sectional.
Setting: Hertfordshire, UK.
Subjects: in total, 404 participants of the Hertfordshire Cohort Study, UK.
Methods: the translation part was articulated in five stages: (i) two initial translations from French to English; (ii) synthesis of the two translations; (iii) backward translations; (iv) expert committee to compare the backward translations with the original questionnaire and (v) pre-test. To validate the English SarQoL®, we assessed its validity (discriminative power, construct validity), reliability (internal consistency, test–retest reliability) and floor/ceiling effects.
Results: the SarQoL® questionnaire was translated without any major difficulties. Results indicated a good discriminative power (lower score of quality of life for sarcopenic subjects, $P = 0.01$), high internal consistency (Cronbach's alpha of 0.88), consistent construct validity (high correlations found with domains related to mobility, usual activities, vitality, physical function and low correlations with domains related to anxiety, self-care, mental health and social problems) and excellent test–retest reliability (intraclass coefficient correlation of 0.95, 95%CI 0.92–0.97). Moreover, no floor/ceiling has been found.
Conclusions: a valid SarQoL® English questionnaire is now available and can be used with confidence to better assess the disease burden associated with sarcopenia. It could also be used as a treatment outcome indicator in research.

Keywords: *older people, sarcopenia, quality of life, translation, validation*

Introduction

Sarcopenia is a syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, functional decline, depression, falls and death [1–13]. Until now, the consequences of sarcopenia on quality of life have been poorly investigated and poorly understood. While there is no consensus over how to measure and monitor health-related quality of life (HRQoL), the most commonly adopted method defined by the World Health Organization (WHO) as individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns [14]. Evaluating the impact of sarcopenia on individuals' HRQoL with a disease-specific tool is important to better detect effect of treatment and observe longitudinal changes of quality of life in subjects suffering from sarcopenia [15]. Until recently, there were no validated specific patient-based instruments for measuring quality of life in those with sarcopenia [16]. Based on these findings, Beaudart et al. [17, 18] developed and validated, in 2015, the SarQoL® (Sarcopenia and Quality of Life, www.sarqol.org), a quality of life questionnaire specific for those diagnosed with sarcopenia composed of 22 questions that can provide more accurate knowledge regarding the impact of sarcopenia on subjects' well-being. The SarQoL® has been developed and validated in French. To extend the availability and utilisation of this questionnaire, its translation and validation in other languages is necessary. The purpose of this study was therefore to translate the SarQoL® questionnaire into English and investigate its main psychometric properties.

Methods

The SarQoL®

The SarQoL® is composed of 22 questions including in total 55 items rated on a 4-point Likert scale (Appendix 1, also available on www.sarqol.org; Supplementary data are available in *Age and Ageing* online). The questionnaire is scored, through a scoring algorithm, on 100 points, with higher scores reflecting a better quality of life. Items are organised into seven domains of HRQoL: domain 1 "Physical and Mental Health"; domain 2 "Locomotion"; domain 3 "Body Composition"; domain 4 "Functionality"; domain 5 "Activities of daily living", domain 6 "Leisure activities" and domain 7 "Fears". The SarQoL® is a self-administrated questionnaire and can be completed in approximately 10 min.

Participants

The study sample composed of men and women from the Hertfordshire Cohort Study (HCS) who agreed to participate in the UK component of the European Project on Osteoarthritis (EPOSA). The HCS and EPOSA study have been described in detail previously [19, 20]. Briefly, in conjunction with the National Health Service Central Registry and the Hertfordshire Family Health Service Association, men and women who were born as singleton births between 1931 and 1939 in Hertfordshire and still lived in the country during the period 1998–2003 were traced. Among them, 592 HCS participants were eligible to participate in EPOSA which started in 2011, of whom 444 (75%) provided written informed consent to participate in the study. The mean age of these 222 women and 222 men was 75.2 (2.6) years. They presented a mean body mass index of 28.1 ± 4.6 kg/m² and 20.9% of them presented two or more chronic diseases. All demographic, health, social and psychological characteristics have been fully described previously [20].

Procedures

English translation of the SarQoL®

The translation was performed according to translation guidelines [2]. Five different phases were followed: (i) the initial translation from French to English by two independent bilingual translators which were English native speakers; (ii) the synthesis of the first two translations to provide a single "version 1" of the translated questionnaire; (iii) the backward translation by two independent bilingual blinded to the original French version and having French as their first language; (iv) an expert committee review to compare the backward translations with the original questionnaire and consent on a "version 2" of the translated questionnaire; (v) the pre-test of the "version 2" of the SarQoL® to ensure good comprehension of each question of the questionnaire and conclude with the "version 3", final version of the English SarQoL®.

Psychometric validation of the English version of the SarQoL®

The methodology applied for the validation of the French version of the SarQoL® was followed and completed in two steps. All of the analyses described below were performed using IMB SPPS Statistics 21.0. Results were considered statistically significant at the 5% critical level ($P < 0.05$).

(1) In the first step, the SarQoL® questionnaire was sent to the whole sample of participants in order to assess the discriminative power of the SarQoL®, its internal consistency and the presence of floor and ceiling effects.
   (A) *Discriminative power* For the discriminative power of the questionnaire, it was assumed that QoL is better in subjects without a diagnosis of sarcopenia compared to subjects diagnosed sarcopenic. We used the definition of the European Working Group on Sarcopenia in Older People (EWGSOP) for the diagnosis of sarcopenia [9]. The EWGSOP recommends using the presence of both low muscle mass and low muscle function (strength or performance) for the diagnosis of sarcopenia.

Therefore, a body composition DXA scan (Hologic Discovery) was performed on participants for assessment of lean mass, a handgrip dynamometer was used for the assessment of muscle strength and gait speed on a 8-feet distance was measured for the assessment of physical performance. An independent sample *T*-test was performed to assess the difference of overall and domain QoL scores between the sarcopenic subjects and the non-sarcopenic subjects.

(B) *Internal consistency* Internal consistency is the estimation of the questionnaire homogeneity. To measure internal consistency, we used Cronbach's alpha coefficient. A coefficient value greater than 0.70 indicates a high level of internal consistency [21]. The impact of each domain on the reliability was also considered. Normality of quantitative variables was tested by the Shapiro–Wilk test. Since scores from the SarQoL® questionnaire were normally distributed, the correlation of each domain with the total score of the SarQoL® was also assessed using Pearson's correlations.

(C) *Floor and ceiling effects* Floor and ceiling effects were defined when a high percentage of the population had the lowest or the highest score, respectively. Floor and ceiling effects higher than 15% were considered to be significant [22].

(2) In a second step, the construct validity and the test–retest reliability of the SarQoL® was determined. These analyses should ideally be performed on subjects with sarcopenia. However, when using the definition of the EWGSOP [9] to identify sarcopenic subjects in the sample, only a restricted number of sarcopenic subjects (n = 14) were identified. This small sample was insufficient to achieve the recommendations; at least 50 subjects are necessary for these validation analyses [22]. Therefore, modified cut-offs from those proposed by the EWGSOP were used to define a larger group of subjects, not with sarcopenia itself, but with a low global "muscle function". The participants were selected by applying the following formula: lowest sex-specific half of appendicular muscle mass + (lowest sex-specific half of muscle strength or lowest half gait speed). With this method, 93 subjects were identified with low "muscle function". The 93 participants received an envelope containing twice the SarQoL® questionnaire (SarQoL® 1 and SarQoL® 2) as well as the generic Short Form-36 questionnaire [23] and the the EuroQoL 5-dimension (EQ-5D) questionnaire [24]. They completed first one SarQoL® as well as the SF-36 and the EQ-5D questionnaires, for the measurement of the construct validity, and were invited to respect a 2-week interval before completing the second SarQoL®, for the measurement of test–retest reliability.

(A) *Construct validity* The construct validity was investigated by measuring using the convergent and divergent validity. The correlation between the SarQoL® and other questionnaires or domains of questionnaires which were supposed to have similar dimension (convergent validity) or different dimension (divergent validity) was assessed. Therefore, beside completing the SarQoL®, the participants were also asked to complete the SF-36 questionnaire [23] which is composed of 36 items measuring 8 HRQoL domains (physical functioning, role limitation due to physical problems, bodily pain, general health, vitality, social functioning, role limitation due to emotional problem and mental health). Additionally participants were also asked to complete the EQ-5D questionnaire [24] which records the level of self-reported problems according to five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), with each dimension having three levels: no problems, some problems and extreme problems. Data of the SF-36 and the EQ-5D questionnaires were not normally distributed and we used therefore Spearman's correlations to measure to correlation of the total score of the SarQoL® with the different scales of the SF-36 questionnaire as well as with the utility score of the EQ-5D questionnaire and the individual domains of the EQ-5D questionnaire.

(B) *Test–retest reliability* The intraclass coefficient correlation (ICC) was used to test the reliability between the first and second questionnaires overall and individual domain scores of the SarQoL®. An ICC over 0.7 was considered as an acceptable reliability [22]. All participants were questioned about having any health change during the past 2 weeks. The results of the participants who did not report any health difference over this 2-week interval were used in analysis.

Results

Translation

The 22 questions of the SarQoL® questionnaire were translated without any major difficulties. Some discussions were however encountered regarding the choice of responses displayed for the 4-likert scale. A pre-test was performed on 10 subjects. Minor changes were consequently made to the questionnaire "version 2". These changes, which did not modify the meaning of the sentences, were mainly related to choice of words used for the 4-Likert scale choices.

Psychometric quality analyses

(1) In the first step, the SarQoL® was sent to a sample of 401 participants of the EPOSA. A total of 315 participants completed the questionnaire; 18 questionnaires (5.7%) comprised more than 20% of missing data and were excluded from analyses. Therefore, 297 questionnaires were used (Figure 1). The population sample was

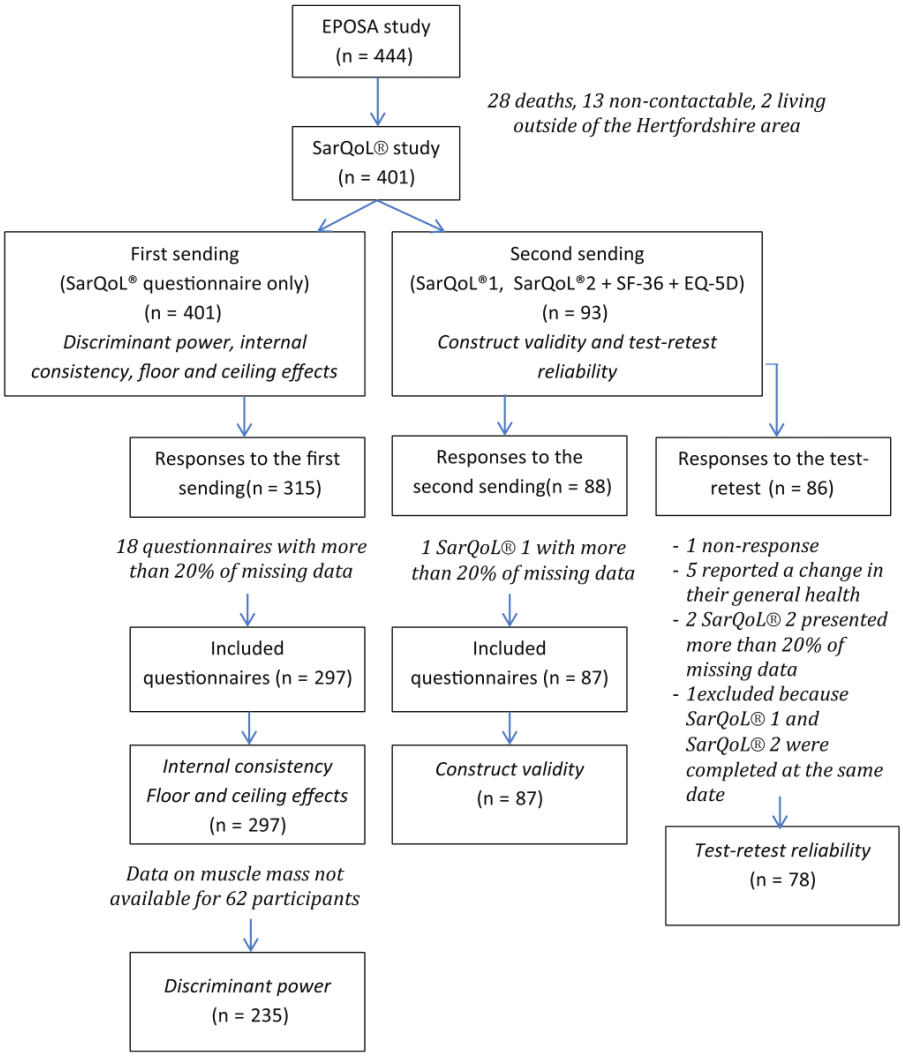

Figure 1. Flowchart of the validation study of the English version of the SarQoL®. SarQoL®1 refers to the first SarQoL® used for the "test" and SarQoL®2 refers to the second SarQoL® used for the retest.

composed of 297 subjects, 137 women (46.1%) and 160 men (53.9%) with a mean age of 79.5 ± 2.62 years.

(A) *Discriminant validity* Data on muscle mass, muscle strength and physical performance were only available for 235 of the 297 respondents. With the criteria and the cut-offs proposed by the EWGSOP [9], a total of 14 subjects were diagnosed sarcopenic. Sarcopenic subjects reported a reduced global quality of life compared to non-sarcopenic subjects (61.9 ± 16.5 versus 71.3 ± 12.8, $P = 0.01$). The domains of physical and mental health, locomotion, functionality and activities of daily living were also lower scored in sarcopenic subjects compared to non-sarcopenic ones (Table 1).

(B) *Internal consistency* A Cronbach's alpha of 0.88 was calculated indicating a high internal consistency. Deleting the domains one at the time, led to Chronbach's alpha values varying between 0.84 (when deleting the domain 5 "Activities of daily living") and 0.89 (for the domain 6 "Leisure activities"). Moreover, all domains showed a significant positive correlation with the total score of the SarQoL® ranging from $r = 0.51$, $P < 0.001$ (domain 6 versus total score of the SarQoL®) to 0.92, $P < 0.001$ (domain 4 versus total score of the SarQoL®) (Table 2).

(C) *Floor and ceiling effects* No subjects presented with the lowest score to the questionnaire (0 point) or the maximal score (100 points). Therefore, no floor neither ceiling effects were found for the questionnaire.

(2) In a second step, the SarQoL® was sent to the 93 participants identified as having a low muscle function. A total of 88 questionnaires were completed. One of the

Table 1. Discriminative power of the SarQoL®

	Sarcopenia (n = 14), mean ± SD	No sarcopenia (n = 221), mean ± SD	P-value
Total score	61.9 ± 16.5	71.3 ± 12.8	0.01
D1 Physical and Mental Health	60.9 ± 15.5	71.1 ± 13.9	0.01
D2 Locomotion	57.1 ± 14.9	65.9 ± 15.9	0.04
D3 Body Composition	70.4 ± 14.9	71.9 ± 13.3	0.70
D4 Functionality	68.0 ± 18.7	76.5 ± 14.1	0.03
D5 Activities of daily living	55.9 ± 25.7	70.6 ± 13.3	0.002
D6 Leisure activities	43.9 ± 16.8	45.1 ± 18.6	0.81
D7 Fears	88.4 ± 12.5	91.3 ± 12.1	0.39

Table 2. Correlations of the total score of the SarQoL® questionnaire with individual domains of the SarQoL®, the SF-36 questionnaire and the EQ-5D questionnaire

	Total score of the SarQoL, r	P-value
SarQoL D1 Physical and Mental Health	0.84[a]	<0.001
SarQoL D2 Locomotion	0.85[a]	<0.001
SarQoL D3 Body Composition	0.61[a]	<0.001
SarQoL D4 Functionality	0.92[a]	<0.001
SarQoL D5 Activities of daily living	0.94[a]	<0.001
SarQoL D6 Leisure activities	0.51[a]	<0.001
SarQoL D7 Fears	0.54[a]	<0.001
Convergent validity		
SF-36 physical functioning	0.82[b]	<0.001
SF-36 role limitation due to physical problems	0.54[b]	<0.001
SF-36 bodily pain	0.55[b]	<0.001
SF-36 general health	0.49[b]	<0.001
SF-36 vitality	0.74[b]	<0.001
EQ-5D utility score	0.58[b]	<0.001
EQ-5D mobility	−0.56[b]	<0.001
EQ-5D usual activities	−0.55[b]	<0.001
Divergent validity		
SF-36 social functioning	0.47[b]	<0.001
SF-36 role limitation due to emotional problem	0.22[b]	0.04
SF-36 mental health	0.29[b]	0.007
EQ-5D, self-care	−0.24[b]	0.032
EQ-5D pain/discomfort	−0.41[b]	<0.001
EQ-5D anxiety/depression	−0.32[b]	0.004

[a]Pearson's correlations (scores of the SarQoL® questionnaire normally distributed).
[b]Spearman's correlations (data of the SF-36 and the EQ-5D questionnaires not normally distributed).

questionnaires comprised more than 20% of missing data and was excluded from analyses. Therefore, construct validity analyses were performed on 87 questionnaires. For test–retest reliability, 78 questionnaires were used for the test–retest reliability analysis (Figure 1).

(A) *Construct validity* Results of construct validity are available in Table 2. As expected, strong/good correlations were found between the SarQoL® and some domains of the SF-36 questionnaire which were supposed to have similar dimensions such as physical functioning (r = 0.82, P < 0.001), vitality (r = 0.74, P < 0.001) and role limitation due to physical problems (r = 0.54, P < 0.001) as well as with the utility score of the EQ-5D questionnaire (r = 0.58, P < 0.001) and the questions of the EQ-5D questionnaire related to mobility (r = −0.56, P < 0.001) and usual activities (r = −0.55, P < 0.001). We found weaker correlations between domains of the SarQoL® which were supposed to have different dimensions such as the domain of mental health (r = 0.29, P = 0.007), and the domain of role limitation due to social problems of the SF-36 questionnaire (r = 0.22, P = 0.04), the questions related to self-care of the EQ-5D questionnaire (r = −0.24, P = 0.032) and the questions related to anxiety of the EQ-5D questionnaire (r = −0.32, P = 0.004).

(B) *Test–retest reliability* Excellent agreement was found between the test and the retest with an ICC of 0.95 (95% CI 0.92–0.97). For individual domains, the lowest ICC was found for domain 6 (ICC of 0.78, 95%CI 0.58–0.88) which is however still considered as acceptable.

Discussion

The SarQoL® is the first developed quality of life questionnaire specific to sarcopenia. Because the SarQoL® has only been developed and validated in French, this study aimed to provide an English version of the SarQoL® questionnaire, validated to be used for research and clinic in English-speaking countries. This research has produced an English version of the SarQoL® which, after transcultural adaptation and validation has proven to be a discriminant, valid and reliable tool to assess quality of life in subjects with sarcopenia.

To provide equivalence between the French and the English version of the SarQoL®, a rigorous translation and cross-cultural adaptation processes was followed. Proof of correctness and equivalence between the two questionnaires was provided by the high internal consistency of the translated questionnaire, by its consistent construct validity and the excellent test–retest reliability observed in results.

The psychometric properties analyses showed that the English version of the questionnaire is able to discriminate the sarcopenic subjects from the non-sarcopenic subjects. General quality of life seems better for the HCS participants compared to the Belgian population (54.7 (45.9–66.3) for the total score of the SarQoL® for Belgian sarcopenic individuals compared to 61.9 ± 16.5 for the HCS population). But in both cases, quality of life of sarcopenic subjects was lower than non-sarcopenic subjects. It has to be pointed that, during the development of the SarQoL® questionnaire, only questions related to sarcopenia have been included. Because each question is related to sarcopenia, it is therefore not surprising to find a lower quality of life for sarcopenic subjects. The English SarQoL® has also been

shown to have a high internal consistency (Cronbach's alpha of 0.88) which is identical to the French version. Moreover, it appears that the deletion of one domain at a time did not have a particular impact on the reliability. The construct validity analyses have also showed that the SarQoL® questionnaire was strongly and significantly correlated with some domains of quality of life which were supposed to have similar dimension, such as mobility, usual activities, vitality, physical functioning and finally physical problems. Because the SarQoL® contains questions specific to sarcopenia and then related to muscle function, these results were expected and can confirm the convergent validity of the SarQoL®. Moreover, we also found low correlations between the SarQoL® and some dimensions such as self-care, anxiety, mental health and social problems, which can confirm that the SarQoL® is divergent with domains that are supposed to be divergent. Finally, the test–retest reliability has been found to be excellent, both for the total score (0.95 (95% CI 0.92–0.97), which is more or less similar to the French version 0.91 (95% CI 0.82–0.95)) and for the individual domains of the SarQoL®. The SarQoL® seems to be stable across time when no health changes occurred.

This study has some limitations. First of all, our sample only comprises 14 sarcopenic subjects which led to alterations to our validation analyses. For the question of feasibility, modified cut-offs for the EWGSOP definition were used to define a larger group of subjects with impaired muscle function. Therefore, this population does not reflect exactly a sarcopenic population but is likely to be those with the lowest muscle function within the study group based on the same characteristics. A second limitation is related to the fact that sensitivity to change could not have been measured in our study given its cross-sectional design. However, we aim to test the sensitivity to change in further analyses when prospective data about muscle mass, muscle strength and physical performance are available for the EPOSA participants.

In conclusion, a valid SarQoL® English questionnaire is now available and can be used with confidence to understand better the burden of disease with sarcopenia and as a treatment outcome indicator in research. Before this study, the SarQoL® questionnaire had only been validated in one unique population study. With this study, we validated it in a second cohort from a different country. The psychometric properties indicated that the English version of the SarQoL® is valid, consistent and reliable which strengthens the evidence that the SarQoL® is a strong and valid tool for the assessment of quality of life in a sarcopenic population. Following the success of this study, we plan to go on to translate and validate the SarQoL® in other languages.

Key points

- The SarQoL® is the first developed quality of life questionnaire specific to sarcopenia.
- The English version of the SarQoL® has been developed and is valid, consistent and reliable.
- An English version of the SarQoL® is available and can be used to better assess the disease burden associated with sarcopenia.

Conflict of interest

C.C. has received consultancy fees and honoraria from Alliance for Better Bone Health, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier, Takeda and UCB. Other authors: none declared.

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Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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