Evaluation of appendicular lean mass using bio impedance in persons aged 80+

Vermeiren, S; Beckwée, D; Vella-Azzopardi, R; Beyer, I; Knoop, V; Jansen, B; Delaere, A; Antoine, A; Bautmans, I; Scafoglieri, A; Gerontopole Brussels Study group

Published in:
Clinical Nutrition

DOI:
10.1016/j.clnu.2018.07.029

Publication date:
2019

License:
CC BY-NC-ND

Document Version:
Accepted author manuscript

Evaluation of appendicular lean mass using bio impedance in persons aged 80+: a new equation based on the BUTTERFLY-study

Vermeiren S [a, b], Beckwée D [a, b, c], Vella-Azzopardi R [a, b, d], Beyer I [a,b,d], Knoop V [a,b], Jansen B [e,f], Delaere A [a,b], Antoine A, Bautmans I [a, b, d] Scafoglieri A [b, g] *On behalf of the Gerontopole Brussels Study group* [h]

[a] Gerontology department and [b] Frailty in Ageing (FRIA) Research department, Vrije Universiteit Brussel (VUB), Laarbeeklaan 103, B-1090 Brussels, Belgium

[c] Rehabilitation Sciences Research Department (RERE), Vrije Universiteit Brussel, Laarbeeklaan 103, B-1090 Brussels, Belgium

[d] Geriatrics department, Universitair Ziekenhuis Brussel (UZ Brussel), Laarbeeklaan 101, B-1090 Brussels, Belgium

[e] Department of Electronics and Informatics ETRO, Vrije Universiteit Brussel (VUB), Pleinlaan 2, 1050 Elsene, Belgium

[f] IMEC Brussel, Vrije Universiteit Brussel (VUB), Pleinlaan 9, 1050 Elsene, Belgium

[g] Experimental Anatomy (EXAN), Vrije Universiteit Brussel (VUB), Laarbeeklaan 103, B-1090 Brussels, Belgium

[h] Members of the Gerontopole Brussels Study group: Ivan Bautmans (FRIA, VUB) *ivan.bautmans@vub.be* , Dominque Verté (Belgian Ageing Studies BAST, VUB) *dominique.verte@vub.ac.be*, Ingo Beyer (Geriatric Medicine department, UZ Brussel) *ingo.beyer@uzbrussel.be*, Mirko Petrovic (ReFrail, UGhent) *mirko.petrovic@ugent.be*, Liesbeth De Donder (Belgian Ageing Studies BAST, VUB) *liesbeth.de.donder@vub.ac.be*, Tinie Kardol (Leerstoel Bevordering Active Ageing, VUB) *mjmkardol@hotmail.com*, Gina Rossi (Clinical and Lifespan Psychology KLEP, VUB) *grossi@vub.ac.be*, Peter Clarys

(Physical Activity and Nutrition PANU, VUB) pclarys@vub.ac.be, Aldo Scafoglieri (Experimental Anatomy EXAN, VUB) aldo.scafoglieri@vub.ac.be, Erik Cattrysse (Experimental Anatomy EXAN, VUB) ecattrys@vub.ac.be, Paul de Hert (Fundamental Rights and Constitutionalism Research group FRC, VUB) paul.de.hert@vub.ac.be, Bart Jansen (Department of Electronics and Informatics ETRO, VUB) bart.jansen@vub.ac.be

Corresponding author

Ivan Bautmans

Gerontology (GERO) & Frailty in Ageing research (FRIA) departments

Vrije Universiteit Brussel (VUB), Laarbeeklaan 103, B-1090 Brussels, Belgium

Email address: *ivan.bautmans@vub.be*

Phone number: +32 2 477 42 07

Abbreviations list

ALM	Appendicular Lean Mass
ALMI	Appendicular Lean Mass Index
BC	Body Composition
BIA	Bioelectrical Impedance Analysis
BMC	Bone Mineral Content
BUTTERFLY	BrUssels sTudy on The Early pRedictors of FraiLtY
CT	Computerized Tomography

DXA	Dual Energy X-ray Absorptiometry
EWGSOP	European Working Group on Sarcopenia in Older People
FFM	Fat Free Mass
FM	Fat Mass
I	Impedance
IWGS	International Working Group on Sarcopenia
LST	Lean Soft Tissue
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
R	Resistance
SMM	Skeletal Muscle Mass
UZ Brussel	Universitary Hospital Brussels
VUB	Vrije Universiteit Brussel
Xc	Reactance

Abstract

Background: To date, the accuracy of bio-impedance (BIA) to assess body composition & sarcopenia in persons aged 80 and over remains unclear.

Objective: We aimed to evaluate the agreement between dual energy X-ray absorptiometry (DXA) and BIA equations to determine lean mass, as well as their suitability to identify sarcopenia.

Design: 174 community dwelling well-functioning persons (83 women, 91 men) aged 80 and over were included. Appendicular lean mass (ALM) was predicted using BIA-based equations available in literature, and compared to DXA outcomes. Through cross-validation and stepwise multiple linear regression, an ALM-formula was generated suitable for this population.

Results: Literature-based BIA equations systematically overestimated ALM. The new prediction formula that we propose for the 80+ is:

ALM=0,827+(0,19*Impedance Index)+(2,101*Sex)+(0,079*Weight); R^2=0,888; SEE=1,450kg

Sarcopenia classification based on our new BIA equation for ALM showed better agreement with DXA (k≥0,454) compared to literature-based BIA equations (k<0,368).

Conclusions: Despite the high correlation between both methods, literature-based BIA equations consistently overestimate ALM compared to DXA in persons aged 80 and over. We proposed a new equation for ALM, reaching higher agreement with DXA and thus improving the accuracy of BIA for this specific age group.

Keywords: body composition, sarcopenia, bioelectrical impedance analysis, dual X-ray absorptiometry, aged 80 and over

Introduction

Body Composition (BC) data provide valuable information and are often used to represent the changes in muscular function associated with ageing (1). One of the most important conditions occurring in an ageing population is sarcopenia, which was initially described by Rosenberg in 1989 (2). Baumgartner was the first to report the prevalence of this phenomenon (3). He defined sarcopenia solely by decreased appendicular skeletal muscle mass, measured by dual energy X-ray absorptiometry (DXA). Nowadays, sarcopenia is a widely studied phenomenon caused by i.a. inflammation, nutritional deficiencies and chronic diseases. This age-related syndrome is known to be highly associated with functional decline, disability and frailty, which highlights the importance of research on this condition (4, 5).

Several working groups defined different consensus based diagnoses of sarcopenia. The European Working Group on Sarcopenia in Older People (EWGSOP) recommended using the presence of both low muscle mass and low muscle function (strength or performance) as diagnostic criteria for sarcopenia whereas the International Working Group on Sarcopenia (IWGS) proposed to use the loss of muscle mass alone or in conjunction with increased fat mass (5-7). Besides the age-related loss of muscle mass, other changes in BC which may be partly responsible for shifts in muscle weakness (such as increasing intramuscular fat) are considered (8). After all, ageing is linked with the redistribution of fat mass to ectopic locations, such as skeletal muscles and liver (9, 10). This awakens the interest in the introduction of fat mass as an alternative definition of sarcopenia, which has been suggested by several researchers (11-13).

Generally accepted methods for the assessment of muscle mass are Magnetic Resonance Imaging (MRI) and Computerized Tomography (CT). Given their reliability and preciseness, they are considered as gold standards (7, 14). However, they come with a high cost and a low

accessibility (15). The use of DXA in order to measure BC, in terms of lean soft tissue, fat mass and bone mineral content of young and older subjects, is widely accepted (16, 17). Despite the fact that some disadvantages have been recognized in literature, it is often used as criterion method (17, 18). However, the DXA instrument is expensive and non-portable, which does not facilitate its use in clinical practice (19). Bioelectrical Impedance Analysis (BIA) may be considered as an interesting option, offering an inexpensive, portable alternative for DXA enabling rapid and accurate estimates of lean mass via prediction formulas. BIA, however, tends to slightly overestimate lean mass (20). Both measurement methods, BIA (21) and DXA (22), are currently being used in the assessment of sarcopenia in the population of older adults.

Several prediction formulas have been developed to determine ALM using BIA (23-25). The prediction formulas found in literature focus on older adults aged 60 or 65 years and over (23, 25) or on a younger cohort (24). BC, however, changes significantly over time, even in the oldest old (26). For this specific age group, no prediction formulas or gender-specific cut-offs for the classification of sarcopenia exist.

The overall aim of this study is to determine the prevalence of sarcopenia in a well-functioning community dwelling population aged 80 and over, by using BIA. We will compare DXA-based and BIA-based ALM data. Subsequently, a new prediction formula for ALM will be created. Next, we will analyze the prevalence of sarcopenia in this population in terms of the EWGSOP cut-offs, by comparing the DXA-measured and BIA-predicted appendicular lean mass index (ALMI). Both existing and newly suggested prediction formulas for ALM are analyzed. Finally, cut-offs for the classification of sarcopenia based on this cohort are evaluated.

1. Materials and Methods

2.1 Study design

Body composition data were collected in the BUTTERFLY study (BrUssels sTudy on The Early pRedictors of FraiLtY), a longitudinal observational cohort study in the oldest old, originating from the Vrije Universiteit Brussel (Belgium). This study was approved by the ethical committee of UZ Brussel (B.U.N. 143201421976). Informed consent was obtained from all participants and the privacy rights of human subjects was observed at all times. For this article, the baseline data were used and cross-sectionally analyzed. The STROBE checklist for cohort, case-control, and cross-sectional studies was used as a reporting guideline (27).

2.2 Setting and Participants

Between February 2015 and April 2017, community dwelling well-functioning adults (male or female) aged 80 years and over were recruited for participation in the BUTTERFLY study. Volunteers were recruited through advertisements on site at the hospital, at the university, via health insurance companies, general practitioners and pharmacies. They were invited at the University Hospital in Jette, Belgium, for an extensive test battery. People underwent standard medical tests (blood analysis, lung and cardiac function control, depression history, assessment of comorbidities etc.), physical tests (body composition, muscle strength and endurance tests, walking speed etc.) and psychosocial tests (questionnaires for social behavior, relationships, cognitive functioning etc.) in order to determine medical, physical and psychosocial capacities.

Participants were allowed to take part in the study if they were aged 80 years or older and if they were able to walk, lived independently at home and if they were mentally fit (MMSE>23/30). Volunteers were excluded if they were recently diagnosed with cancer or if they underwent surgery or any radiotherapy or chemotherapy during the past six months. Also,

in case of a planned surgery, radiotherapy or chemotherapy in the near future, participation in the study was not allowed.

2.3 Variables and measurement methods

Anthropometry

Anthropometry included the measurement of weight, height, waist and hip circumference. Weight was measured using a SECA scale (model 877, type 3) to the closest of 0,1 kg. Height was determined using a measuring rod to the nearest of 0,1 cm, which was incorporated in the SECA balance. Waist and hip circumferences were obtained using a flexible steel measuring tape (Lufkin, W606PM). After complete expiration, waist circumference was measured above the upper most lateral boarder of the ilium. Hip circumference was taken around the widest portion of the buttocks. Both circumferences were measured up to the nearest of 0,1 cm.

Dual Energy X-Ray Absorptiometry

Body composition of the participants was measured using a fan beam whole body DXA device (Hologic 4500 QDR upgraded to Discovery [Bedford, Massachusetts, USA]). The DXA scan machine is able to distinguish fat mass (FM), bone mineral content (BMC) and lean soft tissue (LST) on the basis of tissue density using two X-ray beams with differing energy levels (28, 29). The DXA instrument was calibrated daily using the spine phantom provided by the manufacturer. Additionally, a step phantom calibration was performed on a weekly basis. For standardization purposes of the scans, the files from the original DXA machine were transferred to a computer where they were analyzed using Apex system software version 4.0.2. The scans were blinded and independently processed by two different researchers. The segmentation protocol as described by Scafoglieri et al. was used to uniform measurements (30).

Bioelectrical Impedance Analysis (BIA)

Body composition of the participants was also measured using BIA, a method based on the principle that various human tissues have different conductive and resistive properties at different frequencies of an administered alternating electrical current (31). BIA measures resistance (R) and reactance (Xc) parameters through which appendicular lean mass (ALM), skeletal muscle mass (SMM) and fat-free mass (FFM) can be estimated using different prediction formulas. We used the 50 kHz frequency of the Single-Frequency Bodystat® QuadScan 4000 with long electrodes (ME400). All equation formulas applied in this study were developed using single-frequency BIA, which corresponds to our measurement method.

Participants were positioned in supine position on an examination table with their arms slightly separated from the body and their legs spread. They had to stay in this position for 5 minutes before the BIA measurement could be performed (during these 5 minutes the participants underwent the DXA measurement). The four contact points on the skin were degreased before placing the electrodes on the right hand and foot. Electrodes were placed at the metacarpal-phalangeal joints and the metatarsal-phalangeal joints on the dorsal surface of both right hand and foot.

Regression formulas

For comparison between the obtained DXA data and BIA data, three BIA equation formulas for ALM were used (23-25). All formulas were validated against DXA Hologic. A new regression formula for ALM will be proposed for this specific age group, based on data from our study population.

Table 1: Summary of prediction formulas for ALM

Author	Regression Formula	r	P-value
Kyle et al. 2003	ALM = -4,211+(0,267*H²/R)+(0,095*W)+(1,909*sex)-(0,012*age)+(0,058*Xc)	0,95	< 0,001
Sergi et al. 2015	ALM = -3,964+(0,227*H²/R)+(0,095*W)+(1,384*sex)+(0,064*Xc)	0,94	< 0,001
Scafoglieri et al. 2017	ALM = 4,957+(0,196*H²/R)+(0,06*W)-(2,554*sex)	0,90	< 0,001

DXA = dual energy X-ray absorptiometry; H = height (cm); R = resistance (Ω); W = weight (kg); Xc = reactance (Ω); sex = men: 1, women: 0, r=correlation

2.4 Sarcopenia

EWGSOP composed an algorithm for sarcopenia case findings in older individuals in 2010 (7). This algorithm consists of three consecutive measurements: gait speed, grip strength and muscle mass, each with their own cut-off values. These cut-offs are used for the classification of sarcopenia (7). Since the focus of this study is specifically aimed at appendicular muscle mass, only those cut-offs defined by EWGSOP were used for the classification of sarcopenia. Data from three BIA equation formulas for ALM (Kyle et al., Sergi et al. and Scafoglieri et al.) were each compared to the EWGSOP cut-offs (3, 13, 32). Therefore, our ALM values were subjected to a transformation consisting of a correction for body height (ALM/height²), since cut-off values were presented as appendicular lean mass corrected for height.

2.5 Statistical methods

Statistical analysis was performed using SPSS version 24.0 (2016, SPSS Inc. New York, USA). The Kolmogorov-Smirnov Goodness of Fit test was used to determine the normal distribution of the population. Descriptive statistics of the study population are presented as mean ± standard deviation (SD). Low muscle mass in the characteristics is defined according to Delmonico's cut-offs (32). The values of the BIA equations for the prediction of ALM were compared with

the data obtained by DXA measurements. Since ALM was measured using DXA as a criterion reference, paired samples t-tests and Pearson's correlation coefficients were used in order to establish differences and correlations between measurement methods (33). To determine the 95% interval of the differences between the two measurement methods, limits of agreements were calculated. To visualize the level of agreement between methods, Bland and Altman plots were created. In order to create a new prediction equation for the 80+, first an at random allocation was performed to divide the cohort into two groups: 70% of the sample for validation and 30% for cross-validation (both groups contained an equal proportion of males/females and sarcopenic/non-sarcopenic people). Then, a preliminary equation for ALM was calculated using stepwise multiple linear regression in the 70% group. Independent variables were age, sex, weight, impedance index (height in cm^2/resistance), reactance and waist-hip ratio. Evaluation of the equation was based on multiple correlations (R^2) and standard errors of the estimate (SEE). Cross-validation was performed in the 30% group, including mean differences, correlations and RMS_{error} as statistics. Ultimately, one final equation was calculated for ALM based on the total sample, using stepwise multiple linear regression. Agreement for the classification of sarcopenia by BIA and DXA measurements was performed by using a Cohen's kappa. For interpreting these results, the guidelines provided by Landis & Koch were used (34). To determine gender-specific cut-offs for this age group, we performed a Receiver-Operating-Characteristics (ROC) analysis. For a sensitivity of minimum 95% , which was set a priori in order to minimize the number of false negatives, we aimed for a specificity of minimum 85% to ensure its clinical usefulness.

2. Results

243 2.1 Participants

244 So far, 189 older adults participated in the BUTTERFLY-study. However, not all of them
245 provided all the data needed for the analysis of body composition. Five participants with a
246 pacemaker were excluded from the analysis, as this is a contraindication for performing the
247 BIA-assessment. Ten participants were excluded, since no DXA-scan was performed. One
248 hundred and seventy-four participants (83 women and 91 men, age range 80-95) were finally
249 considered for analysis. Characteristics of the study population as well as the DXA and BIA
250 outcomes are summarized in Table 2. Mean values regarding BMI were 26,4 ± 3,9 kg/m² for
251 women and 27,0 ± 3,2 kg/m² for men. When considering the waist-hip ratio of our population,
252 a mean of 0,90 for women and 0,98 for men was found, which can be considered as obese and
253 overweight, respectively (35). In total, 19,5% of the participants had undergone a total joint
254 replacement (mainly hip or knee arthroplasty), but this explained only 2,4% of the variance in
255 ALM. Low or normal muscle mass was determined according to Delmonico's DXA-based cut-
256 offs for the diagnosis of sarcopenia (Men: <7,25 kg/m2, women <5,67 kg/m²), assigning almost
257 44% of the total population with low muscle mass (32).

258

Table 2: Characteristics of the study population

	Total (n=174)	Men (n=91)	Women (n=83)
General Characteristics			
Age	83,3 ± 3,0	83,3 ± 2,9	83,3 ± 3,0
MMSE (score/30)	27,9 ± 2,0	28,3 ± 1,7	27,3 ± 2,1*
Handgrip strength (kPa)	57,5 ± 17,1	67,5 ± 16,5	46,6 ± 9,2*
Gait speed (m/s)	1,1 ± 0,4	1,1 ± 0,4	1,0 ± 0,2†
Comorbidities	3,5 ± 2,1	3,1 ± 2,1	4,0 ± 2,1†
Arthroplasty (%)	20%	15%	24%
Anthropometrics			
Height (cm)	163,7 ± 8,7	169,2 ± 7,0	157,7 ± 6,0*
Weight (kg)	71,9 ± 12,5	77,5 ± 11,4	65,8 ± 10,6*
BMI (kg/m²)	26,8 ± 3,5	27,0 ± 3,2	26,4 ± 3,9
Waist-Hip ratio	0,94 ± 0,09	0,98 ± 0,07	0,90 ± 0,09*
Dual energy X-ray Absorptiometry			
Lean Mass (kg)	43,9 ± 8,7	50,2 ± 6,4	37,0 ± 4,5*
Appendicular Lean Mass (kg)	18,4 ± 4,3	21,5 ± 3,2	14,9 ± 2,2*
Low muscle mass (n)	76	38	38
Bioelectrical Impedance Analysis			
Resistance (Ω)	488,6 ± 76,5	442,2 ± 52,9	539,5 ± 65,3*
Reactance (Ω)	42,9 ± 9,1	40,4 ± 5,8	45,5 ± 11,1*
Impedance Index (cm²/Ω)	56,8 ± 13,0	65,8 ± 9,8	47,0 ± 8,0*

Mean and standard deviation (SD) are raw data obtained by anthropometrics, DXA scans and BIA values. MMSE=Mini Mental State Examination; kPa=KiloPascal; m/s=meter/second; low muscle mass according to Delmonico et al. (2007); Ω = ohm; *p<0,001; †p<0,05

2.2 Comparison of ALM (DXA vs BIA)

ALM was measured using DXA as a criterion reference. BIA equation formulas from different researchers (Kyle et al., Sergi et al. and Scafoglieri et al.) were used to predict ALM. Means as well as standard deviations of ALM are described in Table 3. High correlations were found

268 between DXA and BIA equations for ALM; 0.93, 0.92 and 0.93 for the equations proposed by
269 Kyle et al., Sergi et al. and Scafoglieri et al., respectively.

270 Mean differences between methods (ALM_{DXA} – ALM_{BIA}) were calculated for each formula
271 (Table 3). The smallest mean difference was found for BIA_{Sergi}: 0,88 kg (95%CI [0,64 to 1,13
272 kg]; p<0,001). The highest mean difference was found using BIA_{Kyle}: 1,94 kg (95%CI [1,67 to
273 2,22 kg]; p<0,001). According to those data, BIA has the tendency to overestimate ALM. To
274 visualize the level of agreement between methods, Bland and Altman plots were created (figure
275 1).

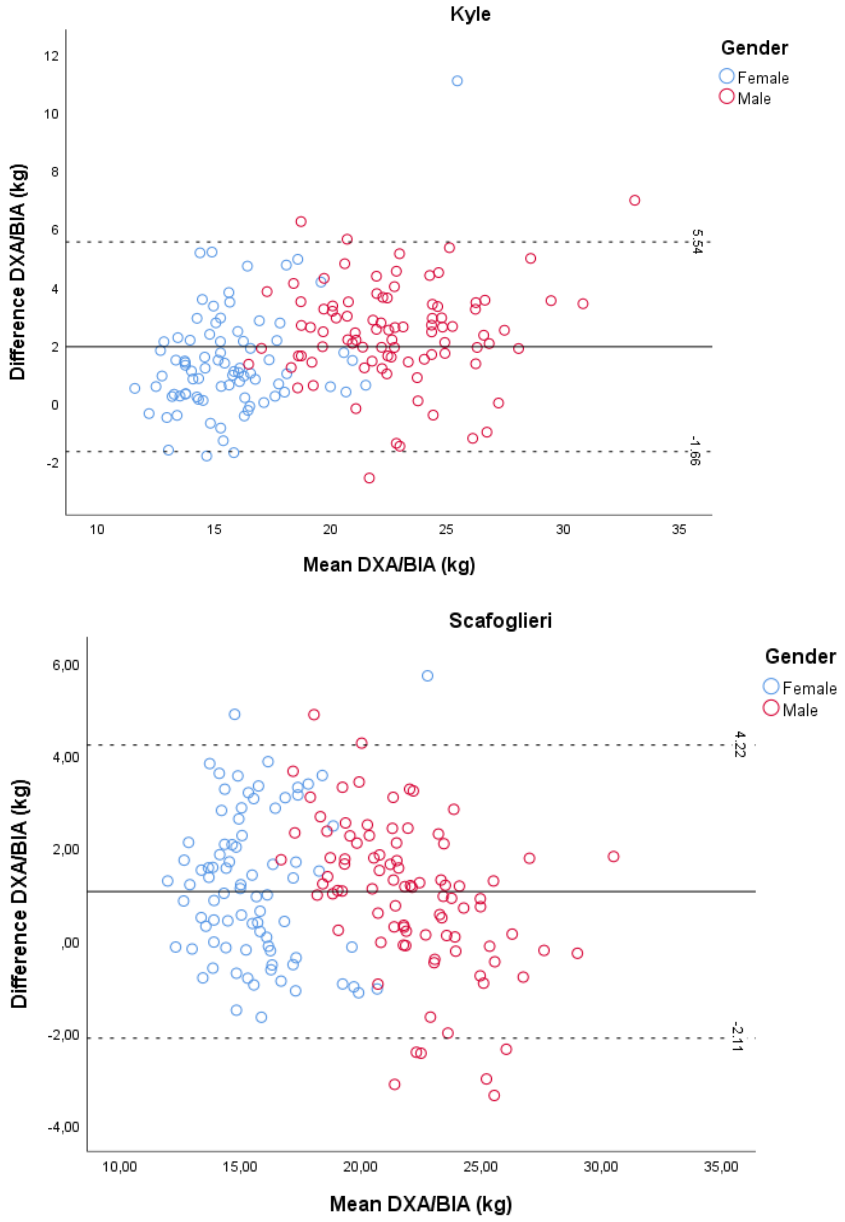
276 **Table 3: Summary of statistics**

Author prediction formula	BIA predicted values (kg)	DXA observed values (kg)	Mean difference (kg) (95% CI)	Limits of agreement (kg)	r
Appendicular Lean Mass					
Kyle et al. 2003	20,3 ± 4,9	18,4 ± 4,3	1,94 (1,67; 2,22)	-1,66; 5,54	0,93*
Sergi et al. 2015	19,3 ± 4,2	18,4 ± 4,3	0,88 (0,64; 1,13)	-2,34; 4,11	0,92*
Scafoglieri et al. 2017	19,5 ± 3,9	18,4 ± 4,3	1,06 (0,81; 1,30)	-2,11; 4,22	0,93*

277 Mean and standard deviations (SD) of observed values by DXA and predicted values by BIA are shown. CI = confidence interval; Limits of
278 agreement were calculated as mean difference ± 1,96 times SD; r = Pearson's Correlation; *p< 0,001

279

Figure 1: Bland and Altman plots: ALM according to DXA and BIA



Bland and Altman plots to show the agreement between DXA and BIA for the measurement of ALM. The solid line represents the mean, dotted lines illustrate the upper and lower limits of agreement.

281

282 2.3 Derivation of a BIA-equation for ALM

283 ***Preliminary equation and cross-validation***

284 After the random allocation of the cohort into two comparable groups (70% and 30%), a preliminary BIA-
285 equation for ALM was calculated using multiple linear regression models. Independent variables were age
286 (years), sex (0=women, 1=men), weight (kg), impedance index (height in cm^2/resistance (Ω)), reactance
287 (Ω) and waist-hip ratio (analysis with waist circumference and hip circumference separately provided the
288 same results). Selected variables for the formula were impedance index, weight and sex.

289 Cross-validation in the 30% group was successful (table 4), with no significant differences between DXA-
290 derived and BIA-observed ALM ($p<0,001$). A low mean difference of 143g was established. It should be
291 noted that in this analysis BIA overestimates ALM compared to DXA.

Table 4: Cross-validated prediction formula

Preliminary BIA-equations (70% of cohort)					**Cross-validation (30% of cohort)**		
	Equation formula	R^2	SEE	p	Mean difference	r	RMS_{error}
ALM	0,684 + (0,175*I) + (0,092*W) + (2,279*S)	0,884	1,477	<0,001	-0,143 (-0,533; 0,247)	0,945*	1,409

ALM = Appendicular Lean Mass, R^2 = Coefficient of determination, SEE = Standard Error of the Estimate, r = Pearson's correlation, RMS_{error} = Root Mean Squared error, I = Impedance index (cm^2/Ω), W = Weight (kg), S = Sex (women=0, men=1), Xc = Reactance (Ω); *p<0,001

Final BIA-equation

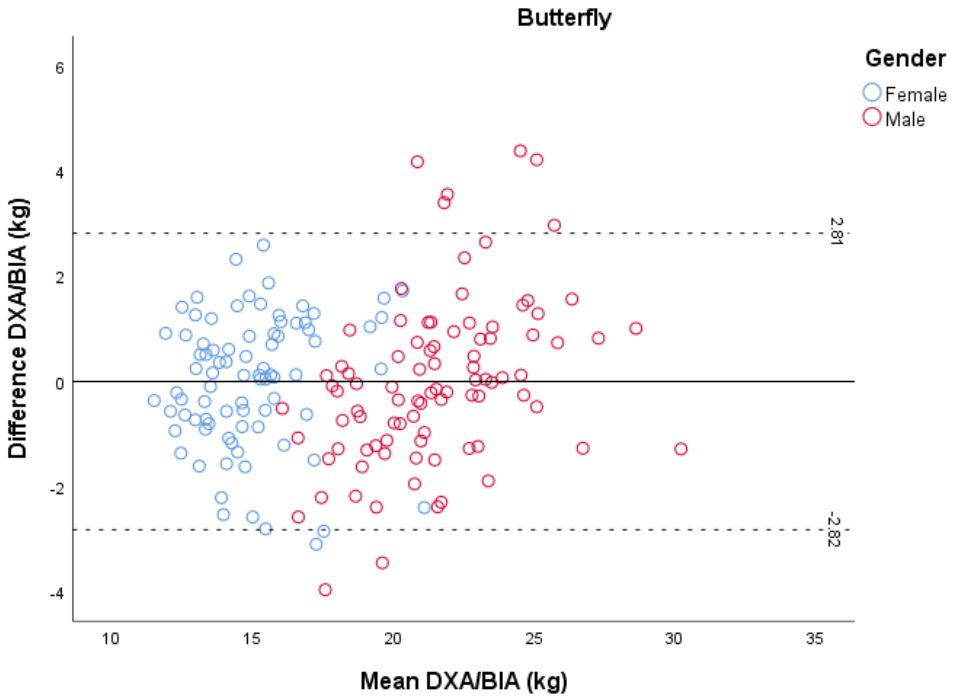
Given the successful cross-validation, a new BIA equation formula for ALM was developed using the whole sample. The impedance index was the most substantial predictor with an R^2 of 0,836. Cumulative R^2 (combined with sex and weight) explained up to 89% of the variability (table 5). Table 5 displays the new prediction formula constructed from the complete sample and figure 2 shows the Bland and Altman plot on the agreement between DXA and $BIA_{Butterfly}$.

Table 5: Final BIA-equation formulas for ALM

	Equation	**R^2**	**SEE**	**p**
ALM	0,827 + (0,19*I) + (2,101*S) + (0,079*W)	0,888	1,450	<0,001

ALM = Appendicular Lean Mass, R^2 = Coefficient of determination, SEE = Standard Error of the Estimate, I = Impedance index (cm^2/Ω), W = Weight (kg), S = Sex (women=0, men=1)

Figure 2: Bland and Altman plot: ALM according to DXA and $BIA_{Butterfly}$



Bland and Altman plot to show the agreement between DXA and $BIA_{Butterfly}$ for the measurement of ALM. The solid line represents the mean, dotted lines illustrate the upper and lower limits of agreement.

2.4 Prevalence and agreement of sarcopenia

Values for ALM originating from the existing and new BIA prediction formulas were corrected for height, according to the standard reference cut-offs for the diagnosis of sarcopenia proposed by EWGSOP, and based on ALM (7). They were then compared to their matching cut-offs in order to diagnose people as either normal or sarcopenic. Results of these comparisons are presented in table 6.

317 **Table 6: Prevalence of sarcopenia by DXA and BIA**

EWGSOP Cut-off	Prevalence of Sarcopenia DXA			Prediction formula BIA	Prevalence of Sarcopenia BIA			Cohen's Kappa
	Total n(%)	Male (n)	Female (n)		Total n(%)	Male (n)	Female (n)	
Baumgartner								
Men: < 7,26 kg/m2 Women: < 5,5 kg/m2	59 (34%)	38	21	Kyle et al (2003)	14 (8%)	9	5	0,228
				Sergi et al (2015)	28 (16%)	23	5	0,368
				Scafoglieri et al (2017)	23 (13%)	17	6	0,307
				BUTTERFLY (2017)	50 (29%)	32	18	0,454
Delmonico								
Men: < 7,25 kg/m2 Women: < 5,67 kg/m2	76 (44%)	38	38	Kyle et al (2003)	17 (10%)	9	8	0,194
				Sergi et al (2015)	31 (18%)	22	9	0,287
				Scafoglieri et al (2017)	26 (15%)	17	9	0,268
				BUTTERFLY (2017)	57 (33%)	31	26	0,507
Newman								
Men: < 7,23 kg/m2 Women: < 5,67 kg/m2	75 (43%)	37	38	Kyle et al (2003)	17 (10%)	9	8	0,198
				Sergi et al (2015)	29 (17%)	20	9	0,241
				Scafoglieri et al (2017)	25 (14%)	16	9	0,335
				BUTTERFLY (2017)	56 (32%)	30	26	0,480

318 Prevalence of sarcopenia according to DXA-measurements and BIA-prediction formulas. Agreement is determined with Cohen's kappa. All kappa's are p<0,001

319 ***DXA***

320 When using Baumgartner's cut-offs, the classification resulted in 59 people (34%) diagnosed as sarcopenic
321 (3). By applying Newman's and Delmonico's cut-offs on the other hand, a larger number of subjects (n=76
322 (44%) and n=75 (43%), respectively) was diagnosed with sarcopenia (table 6) (13, 32).

323 ***BIA existing formulas***

324 For each gender specific cut-off suggested by EWGSOP, the prevalence of sarcopenia based on the existing
325 equation formulas is presented in table 6. According to BIA_{Sergi} and $BIA_{Scafoglieri}$, sarcopenia is more
326 frequent in men. BIA_{Kyle} does not result in differences between males and females, but does show an
327 obviously lower prevalence of sarcopenia than the other formulas.

328 The Cohen's kappa values never exceeded 0.4, which indicates slight to fair agreement (36). The highest
329 agreement was found when comparing ALMI (Appendicular Lean Mass Index) for DXA with BIA_{Sergi}
330 using Baumgartner's cut-off values (k= 0,37). The lowest agreement was found when comparing ALMI for
331 DXA with BIA_{Kyle} using Delmonico's and Newman's cut-off values (k= 0,19). All Cohen's kappa's were
332 significant. ALMI by BIA_{Sergi} classified the highest number of participants as sarcopenic for all three cut-
333 offs. In general, when comparing results from ALMI for DXA with these of BIA, the number of participants
334 diagnosed with sarcopenia was higher for DXA for all three cut-off values.

335 ***BIA BUTTERLFY***

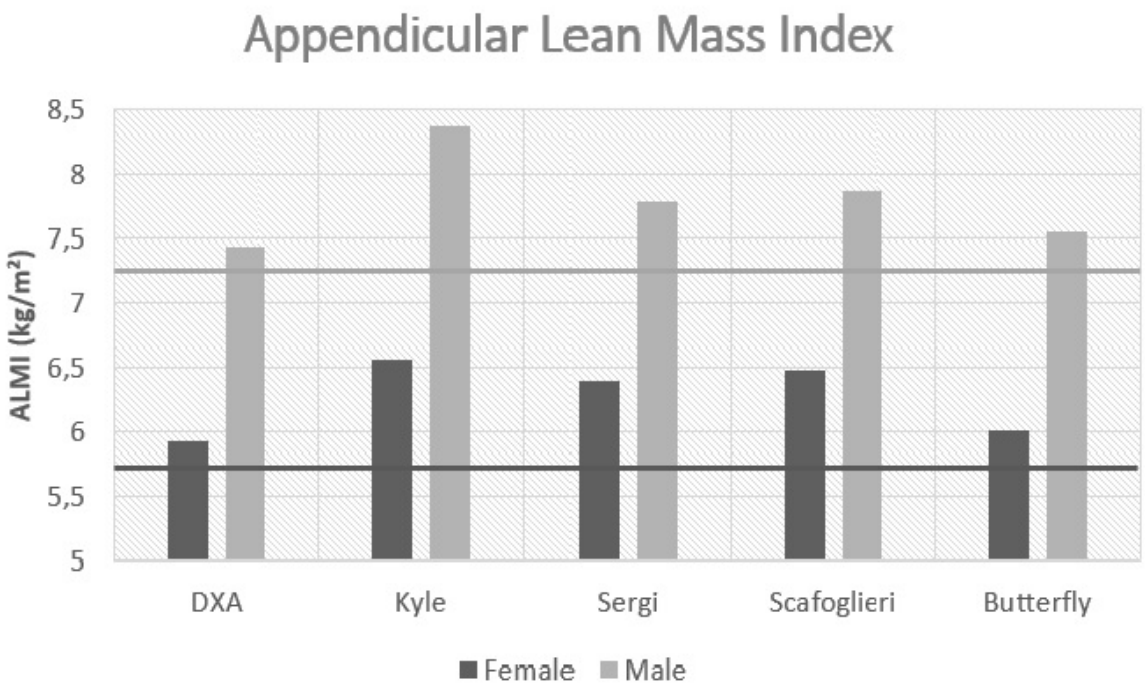
336 With our new prediction formula, a higher prevalence of sarcopenia was established, regardless the
337 EWGSOP cut-off (6). A moderate agreement was established for all cut-offs: Baumgartner k=0,45;
338 Delmonico k=0,51 and Newman k=0,48, implying greater accordance with DXA measurements.

339

340 In figure 3, a comparison is made between DXA, the existing prediction formulas and the newly proposed
341 formula for ALM (Butterfly) corrected for height (kg/m^2). The cut-offs for sarcopenia according to

342 Delmonico et al (2007) are represented by the horizontal lines. DXA measured and $BIA_{Butterfly}$ predicted
343 ALMI show the highest agreement with the suggested cut-offs.
344

345 **Figure 3: Appendicular Lean Mass Index according to DXA and ALM prediction formulas**



346
347 Sex specific bar plots on the mean ALMI observed by DXA and predicted by BIA prediction formulas. ALM was corrected for height (kg/m²). The horizontal
348 lines represent Delmonico's cut-offs for sarcopenia (Men: < 7.25 kg/m2; Women: < 5.67 kg/m2)
349

350 ## 2.5 BIA-based cut-offs for the classification of sarcopenia

351 A Receiver-Operating-Characteristics (ROC) analysis was performed in order to verify whether gender-
352 specific cut-offs for sarcopenia can be proposed. The AUC for women was 0,77 and for men 0,86. For the
353 women in our cohort, with a sensitivity higher than 95%, we reached a specificity of 40% at the cut-off
354 level of 5,49 kg/m². For the male participants, the same level of sensitivity yielded a specificity of 47% at
355 the cut-off level of 6,98 kg/m².

3. Discussion

The main aim of this study was to analyze the prevalence of sarcopenia in a well-functioning community dwelling population aged 80 years and over, by using bio-electrical impedance analysis. Subsequently, the agreement between DXA measured and BIA predicted ALMI data was calculated for the classification of sarcopenia.

This study focuses on a group of older adults aged 80 years and over, a group that is highly underrepresented in terms of research for body composition. Similar studies were mostly performed considering either geriatric (20), hospitalized (37) or younger population groups (38). Therefore, a comparison with previously reported outcomes might appear to be divergent. When describing our participants (table 2), we defined low muscle mass based on the DXA-based cut-offs suggested by Delmonico et al (2007) (32). We chose to apply this cut-off since it implicates the smallest chance for false negatives, which is an important reasoning for clinical practice.

Prediction formulas

In accordance with previous prediction formulas found in literature, certain parameters were suggested to calculate a final prediction formula through stepwise multiple linear regression: age, sex, weight, impedance index, reactance, and waist-hip ratio (23-25). Impedance index, sex and weight were consistently present in all formulas found in literature, as well as in our newly suggested prediction formula.

Despite the high correlations found for DXA measured and BIA predicted ALM, a systematic overestimation by BIA was found, in accordance with existing literature (20, 37, 39). The smallest mean difference was found for BIA_{Sergi}, 0,88 kg (95%CI [0,64 to 1,13 kg]; p<0,001) which can be considered evident since their formula was composed for healthy Caucasian older adults (23). Since the equation of Kyle was composed for a population aged 20 to 94 it might not come as a surprise that this mean difference was the highest of all three (1,94 kg (95%CI [1,67 to 2,22 kg]; p<0,001)) (24). The equation proposed by

379 Scafoglieri et al. was developed for a population with functional limitations. Considering the age of their
380 population (77,6 ± 6,9), the rather low mean difference can be explained (25).

381 *Sarcopenia*

382 Interestingly, there has been some disagreement in literature on the prevalence of sarcopenia. We expected
383 this well-functioning population to be comparable to other investigated robust populations (23). However,
384 our study population showed remarkably more sarcopenic subjects than in some studies (40-42), but less
385 than in other studies (43). Based on the existing prediction formulas, all Cohen's kappa's showed slight to
386 fair agreement (table 6). The highest kappa was found each time when using Baumgartner's cut-offs. It is
387 striking that the EWGSOP cut-offs are much more divergent for women (max. difference of 0,17kg/m²)
388 than for men (max. difference of 0,03kg/m²). This implies that 10% more women are found sarcopenic
389 according to Delmonico's and Newman's cut-offs compared to Baumgartner, by applying the Butterfly
390 ALMI. This is an interesting finding, emphasizing the limitation of applying cut-offs for clinical decision
391 making and the importance of the grey zone around these cut-offs. The strongest agreement for the
392 classification of sarcopenia was found between DXA and $BIA_{Butterfly}$. Nevertheless, no substantial
393 agreement was found for this classification. Given the high age of our study population, heterogeneity might
394 partly explain why these kappa's are not higher. Another explanation might be that EWGSOP cut-offs used
395 to classify into sarcopenic and non-sarcopenic were based on studies using DXA as reference method. BIA-
396 based cut-offs for absolute muscle mass are also made available by EWGSOP, but none for appendicular
397 lean mass (7). This highlights the fact that no BIA-based cut-offs for ALMI have been described for the
398 classification of sarcopenia. Therefore, we performed a Receiver-Operating-Characteristics (ROC)
399 analysis, to verify whether gender-specific cut-offs for sarcopenia can be proposed. Although a fair AUC
400 was found for women (0,77) and for men (0,86), no good cut-offs for clinical practice could be established.
401 Abiding by the sensitivity level which was initially set at 95%, we obtained a low specificity (40% for
402 women, 47% for men). These results are not satisfying in reaching a similar identification of sarcopenia as

DXA. Nevertheless, we should aim for higher agreement when suggesting the use of BIA in clinical practice, to obtain a minimum of false negatives.

The introduction of fat mass or appendicular fat mass might be of added value for the definition of sarcopenia. When looking at the changes in lean and fat mass with ageing, it becomes clear that there is not only a decrease in muscle mass, but also an increase in ectopic and visceral fat, partly emerging in muscle and other organs. Given the importance of fat mass in the assessment of BC by BIA in the context of sarcopenia, and given the previous argumentation on a lack of agreement between the DXA versus BIA based classification of sarcopenia, we want to suggest research on the importance of fat in the identification of sarcopenia in clinical practice. There is an increasing amount of studies on the relation between fat and sarcopenia, in terms of biomarkers or lean/fat proportions (44). Throughout the years, alternative definitions for BMI, such as waist-hip ratio, have been proposed since they are more able to predict visceral fat and possibly associated health risks (45, 46). Furthermore, obesity tends to induce inflammatory processes, which on their turn lead to sarcopenia (47). Combining these findings with the concept of sarcopenic obesity, which was described by Baumgartner et al (48), further research on the relationship between sarcopenia and obesity in our study population is very interesting and clinically relevant (49, 50). Consequently, we want to follow previous research in suggesting alternative definitions for sarcopenia (12, 13).

Strengths and limitations of the study

To our knowledge, this study is the first to suggest a BIA-based ALM prediction formula for the oldest old, encouraging sarcopenia research in this fast growing age group. Focusing on this group, however, might influence generalizability of our results. We suggest further research of the newly obtained prediction formula for ALM in a wider context. In this study, DXA was used as reference method for determining ALM. However, tissue-system level multicomponent models, such as CT and MRI, are considered the gold standards. (7, 14) Unfortunately, we did not have access to those devices. Since the predetermined criterion

reference is DXA, and given the fact that EWGSOP only suggests DXA-validated cut-offs for the classification of sarcopenia based on appendicular skeletal muscle mass, we focused on the available literature-based prediction formulas for ALM. Following this reasoning, we chose not to use a number of published formulas for total skeletal muscle mass. Nevertheless, this might be important for sarcopenia classification.

4. Conclusion

A very high positive correlation (all R ≥0,92) was found for appendicular lean mass obtained by BIA equations compared to DXA. Despite these correlations, a systematic overestimation of ALM was found. A new BIA prediction formula was suggested for ALM, based on our cohort of well-functioning community dwelling adults aged 80 years and over. For all BIA prediction formulas discussed, an underestimation for the prevalence of sarcopenia was observed by comparing DXA to BIA, which was confirmed by the rather low Cohen's kappa values found. Since the EWGSOP cut-offs for ALMI were based on DXA, we suggested BIA-based cut-offs to determine the prevalence of sarcopenia. Unfortunately, those cut-offs did not reach a sufficient level of sensitivity and specificity. Further research to realize good sarcopenia classification based on BIA-derived equations, possibly including reasonings around fat mass, is thus necessary.

Acknowledgements

This study was partly funded by an "Interdisciplinary Research Program" grant (number IRP3) from the research council of the Vrije Universiteit Brussel (VUB).

Statement of authorship

All authors have made substantial contributions to

- The conception and design of the study, or acquisition of data, or analysis and interpretation of data; AND

- Drafting the article or revising it critically for important intellectual content; AND

- Have given their final approval of the version to be submitted.

Authors Contributions

Vermeiren S: 1, 2, 4, 5, 6

Beckwée D: 4, 5

Vella-Azzopardi R: 1, 2

Beyer I: 1, 3

Knoop V: 2

Jansen B: 1, 3

Delaere A: 2, 5

Antoine A: 2, 5

Bautmans I: 1, 3, 4, 5, 6

Scafoglieri A: 1, 3, 4, 5

The Gerontopole Brussels Study group: 1, 3

1. designed research (project conception, development of overall research plan, and study oversight);

2. conducted research (hands-on conduct of the experiments and data collection);

3. provided essential reagents or provided essential materials (contributed by providing constructs, databases, etc, necessary for research);

4. analyzed data or performed statistical analysis;

5. wrote paper (major contribution);

6. had primary responsibility for final content.

Conflict of interest

The authors have no other conflict of interest to declare.

5. References

1. Chien MY, Huang TY, Wu YT. Prevalence of sarcopenia estimated using a bioelectrical impedance analysis prediction equation in community-dwelling elderly people in Taiwan. Journal of the American Geriatrics Society 2008;56(9):1710-5. doi: 10.1111/j.1532-5415.2008.01854.x.

2. Rosenberg IH. EPIDEMIOLOGIC AND METHODOLOGIC PROBLEMS IN DETERMINING NUTRITIONAL-STATUS OF OLDER PERSONS - PROCEEDINGS OF A CONFERENCE HELD IN ALBUQUERQUE, NEW MEXICO, OCTOBER 19-21, 1988 - SUMMARY COMMENTS. American Journal of Clinical Nutrition 1989;50(5):1231-3.

3. Baumgartner RN, Koehler KM, Gallagher D, et al. Epidemiology of sarcopenia among the elderly in New Mexico. American journal of epidemiology 1998;147(8):755-63.

4. Morley JE, Kim MJ, Haren MT, Kevorkian R, Banks WA. Frailty and the aging male. The aging male : the official journal of the International Society for the Study of the Aging Male 2005;8(3-4):135-40. doi: 10.1080/13685530500277232.

5. Fielding RA, Vellas B, Evans WJ, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. Journal of the American Medical Directors Association 2011;12(4):249-56. doi: 10.1016/j.jamda.2011.01.003.

6. Cesari M, Fielding RA, Pahor M, et al. Biomarkers of sarcopenia in clinical trials-recommendations from the International Working Group on Sarcopenia. Journal of cachexia, sarcopenia and muscle 2012;3(3):181-90. doi: 10.1007/s13539-012-0078-2.

7. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age and ageing 2010;39(4):412-23. doi: 10.1093/ageing/afq034.

8. Holmes JD, Andrews DM, Durkin JL, Dowling JJ. Predicting in vivo soft tissue masses of the lower extremity using segment anthropometric measures and DXA. Journal of applied biomechanics 2005;21(4):371-82.

9. Kim TN, Yang SJ, Yoo HJ, et al. Prevalence of sarcopenia and sarcopenic obesity in Korean adults: the Korean sarcopenic obesity study. Int J Obes (Lond) 2009;33(8):885-92. doi: 10.1038/ijo.2009.130.

10. Lang T, Streeper T, Cawthon P, Baldwin K, Taaffe DR, Harris TB. Sarcopenia: etiology, clinical consequences, intervention, and assessment. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2010;21(4):543-59. doi: 10.1007/s00198-009-1059-y.

11. Evans WJ. Skeletal muscle loss: cachexia, sarcopenia, and inactivity. The American journal of clinical nutrition 2010;91(4):1123S-7S. doi: 10.3945/ajcn.2010.28608A.

12. Stenholm S, Harris TB, Rantanen T, Visser M, Kritchevsky SB, Ferrucci L. Sarcopenic obesity: definition, cause and consequences. Current opinion in clinical nutrition and metabolic care 2008;11(6):693-700. doi: 10.1097/MCO.0b013e328312c37d.

13. Newman AB, Kupelian V, Visser M, et al. Sarcopenia: alternative definitions and associations with lower extremity function Journal of the American Geriatrics Society 2003;51(11):1602-9.

14. Lee RC, Wang ZM, Heymsfield SB. Skeletal muscle mass and aging: regional and whole-body measurement methods. Canadian journal of applied physiology = Revue canadienne de physiologie appliquee 2001;26(1):102-22.

15. Heymsfield SB, Adamek M, Gonzalez MC, Jia G, Thomas DM. Assessing skeletal muscle mass: historical overview and state of the art. Journal of cachexia, sarcopenia and muscle 2014;5(1):9-18. doi: 10.1007/s13539-014-0130-5.

16. Smith-Ryan AE, Mock MG, Ryan ED, Gerstner GR, Trexler ET, Hirsch KR. Validity and reliability of a 4-compartment body composition model using dual energy x-ray absorptiometry-derived body volume. Clinical nutrition (Edinburgh, Scotland) 2017;36(3):825-30. doi: 10.1016/j.clnu.2016.05.006.

17. Buckinx F, Reginster JY, Dardenne N, et al. Concordance between muscle mass assessed by bioelectrical impedance analysis and by dual energy X-ray absorptiometry: a cross-sectional study. BMC Musculoskelet Disord 2015;16:60. doi: 10.1186/s12891-015-0510-9.

18. Clarys JP, Scafoglieri A, Provyn S, Louis O, Wallace JA, De Mey J. A macro-quality evaluation of DXA variables using whole dissection, ashing, and computer tomography in pigs. Obesity (Silver Spring, Md) 2010;18(8):1477-85. doi: 10.1038/oby.2009.447.

19. Braulio VB, Furtado VC, Silveira M, Fonseca MH, Oliveira JE. Comparison of body composition methods in overweight and obese Brazilian women. Arquivos brasileiros de endocrinologia e metabologia 2010;54(4):398-405.

20. Reiss J, Iglseder B, Kreutzer M, et al. Case finding for sarcopenia in geriatric inpatients: performance of bioimpedance analysis in comparison to dual X-ray absorptiometry. BMC geriatrics 2016;16(1):52. doi: 10.1186/s12877-016-0228-z.

21. Batsis JA, Mackenzie TA, Barre LK, Lopez-Jimenez F, Bartels SJ. Sarcopenia, sarcopenic obesity and mortality in older adults: results from the National Health and Nutrition Examination Survey III. Eur J Clin Nutr 2014;68(9):1001-7. doi: 10.1038/ejcn.2014.117.

22. Cheng Q, Zhu X, Zhang X, et al. A cross-sectional study of loss of muscle mass corresponding to sarcopenia in healthy Chinese men and women: reference values, prevalence, and association with bone mass. Journal of bone and mineral metabolism 2014;32(1):78-88. doi: 10.1007/s00774-013-0468-3.

23. Sergi G, De Rui M, Veronese N, et al. Assessing appendicular skeletal muscle mass with bioelectrical impedance analysis in free-living Caucasian older adults. Clinical nutrition (Edinburgh, Scotland) 2015;34(4):667-73. doi: 10.1016/j.clnu.2014.07.010.

24. Kyle UG, Genton L, Hans D, Pichard C. Validation of a bioelectrical impedance analysis equation to predict appendicular skeletal muscle mass (ASMM). Clinical nutrition (Edinburgh, Scotland) 2003;22(6):537-43.

25. Scafoglieri A, Clarys JP, Bauer JM, et al. Predicting appendicular lean and fat mass with bioelectrical impedance analysis in older adults with physical function decline - The PROVIDE study. Clinical nutrition (Edinburgh, Scotland) 2017;36(3):869-75. doi: 10.1016/j.clnu.2016.04.026.

26. Baumgartner RN, Stauber PM, McHugh D, Koehler KM, Garry PJ. Cross-sectional age differences in body composition in persons 60+ years of age. The journals of gerontology Series A, Biological sciences and medical sciences 1995;50(6):M307-16.

27. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Annals of internal medicine 2007;147(8):573-7.

28. Pietrobelli A, Formica C, Wang Z, Heymsfield SB. Dual-energy X-ray absorptiometry body composition model: review of physical concepts. The American journal of physiology 1996;271(6 Pt 1):E941-51.

29. Vicente-Rodriguez G, Rey-Lopez JP, Mesana MI, et al. Reliability and intermethod agreement for body fat assessment among two field and two laboratory methods in adolescents. Obesity (Silver Spring, Md) 2012;20(1):221-8. doi: 10.1038/oby.2011.272.

30. Scafoglieri A, Tresignie J, Provyn S, et al. Prediction of segmental lean mass using anthropometric variables in young adults. Journal of sports sciences 2012;30(8):777-85. doi: 10.1080/02640414.2012.670716.

31. Kushner RF. Bioelectrical impedance analysis: a review of principles and applications. Journal of the American College of Nutrition 1992;11(2):199-209.

32. Delmonico MJ, Harris TB, Lee JS, et al. Alternative definitions of sarcopenia, lower extremity performance, and functional impairment with aging in older men and women. Journal of the American Geriatrics Society 2007;55(5):769-74. doi: 10.1111/j.1532-5415.2007.01140.x.

33. Mukaka MM. Statistics corner: A guide to appropriate use of correlation coefficient in medical research. Malawi medical journal : the journal of Medical Association of Malawi 2012;24(3):69-71.

34. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33(1):159-74.

35. Nishida C, Ko GT, Kumanyika S. Body fat distribution and noncommunicable diseases in populations: overview of the 2008 WHO Expert Consultation on Waist Circumference and Waist-Hip Ratio. Eur J Clin Nutr 2010;64(1):2-5. doi: 10.1038/ejcn.2009.139.

36. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. Family medicine 2005;37(5):360-3.

37. Bosaeus I, Wilcox G, Rothenberg E, Strauss BJ. Skeletal muscle mass in hospitalized elderly patients: comparison of measurements by single-frequency BIA and DXA. Clinical nutrition (Edinburgh, Scotland) 2014;33(3):426-31. doi: 10.1016/j.clnu.2013.06.007.

38. Tengvall M, Ellegard L, Malmros V, Bosaeus N, Lissner L, Bosaeus I. Body composition in the elderly: reference values and bioelectrical impedance spectroscopy to predict total body skeletal muscle mass. Clinical nutrition (Edinburgh, Scotland) 2009;28(1):52-8. doi: 10.1016/j.clnu.2008.10.005.

39. Yu SC, Powell A, Khow KS, Visvanathan R. The Performance of Five Bioelectrical Impedance Analysis Prediction Equations against Dual X-ray Absorptiometry in Estimating Appendicular Skeletal Muscle Mass in an Adult Australian Population. Nutrients 2016;8(4). doi: 10.3390/nu8040189.

40. Lera L, Albala C, Sanchez H, et al. Prevalence of Sarcopenia in Community-Dwelling Chilean Elders According to an Adapted Version of the European Working Group on Sarcopenia in Older

601 People (EWGSOP) Criteria. The Journal of frailty & aging 2017;6(1):12-7. doi:
602 10.14283/jfa.2016.117.

603 41. Patel HP, Syddall HE, Jameson K, et al. Prevalence of sarcopenia in community-dwelling older
604 people in the UK using the European Working Group on Sarcopenia in Older People (EWGSOP)
605 definition: findings from the Hertfordshire Cohort Study (HCS). Age and ageing 2013;42(3):378-
606 84. doi: 10.1093/ageing/afs197.

607 42. Volpato S, Bianchi L, Cherubini A, et al. Prevalence and clinical correlates of sarcopenia in
608 community-dwelling older people: application of the EWGSOP definition and diagnostic algorithm.
609 The journals of gerontology Series A, Biological sciences and medical sciences 2014;69(4):438-46.
610 doi: 10.1093/gerona/glt149.

611 43. Janssen I. The epidemiology of sarcopenia. Clin Geriatr Med 2011;27(3):355-63. doi:
612 10.1016/j.cger.2011.03.004.

613 44. Buch A, Carmeli E, Boker LK, et al. Muscle function and fat content in relation to sarcopenia,
614 obesity and frailty of old age--An overview. Experimental gerontology 2016;76:25-32. doi:
615 10.1016/j.exger.2016.01.008.

616 45. Czernichow S, Kengne AP, Stamatakis E, Hamer M, Batty GD. Body mass index, waist
617 circumference and waist-hip ratio: which is the better discriminator of cardiovascular disease
618 mortality risk?: evidence from an individual-participant meta-analysis of 82 864 participants from
619 nine cohort studies. Obesity reviews : an official journal of the International Association for the
620 Study of Obesity 2011;12(9):680-7. doi: 10.1111/j.1467-789X.2011.00879.x.

621 46. de Koning L, Merchant AT, Pogue J, Anand SS. Waist circumference and waist-to-hip ratio as
622 predictors of cardiovascular events: meta-regression analysis of prospective studies. European heart
623 journal 2007;28(7):850-6. doi: 10.1093/eurheartj/ehm026.

624 47. Kim TN, Park MS, Ryu JY, et al. Impact of visceral fat on skeletal muscle mass and vice versa in a
625 prospective cohort study: the Korean Sarcopenic Obesity Study (KSOS). PloS one
626 2014;9(12):e115407. doi: 10.1371/journal.pone.0115407.

627 48. Baumgartner RN. Body composition in healthy aging. Annals of the New York Academy of
628 Sciences 2000;904:437-48.

629 49. Rolland Y, Lauwers-Cances V, Cristini C, et al. Difficulties with physical function associated with
630 obesity, sarcopenia, and sarcopenic-obesity in community-dwelling elderly women: the EPIDOS
631 (EPIDemiologie de l'OSteoporose) Study. The American journal of clinical nutrition
632 2009;89(6):1895-900. doi: 10.3945/ajcn.2008.26950.

633 50. An KO, Kim J. Association of Sarcopenia and Obesity With Multimorbidity in Korean Adults: A
634 Nationwide Cross-Sectional Study. Journal of the American Medical Directors Association
635 2016;17(10):960 e1-7. doi: 10.1016/j.jamda.2016.07.005.

636

637