Interaction of Skeletal and Left Ventricular Mass in Older Adults with Low Muscle Performance

Journal of the American Geriatrics Society

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Journal:	*Journal of the American Geriatrics Society*
Manuscript ID	JAGS-1236-CI-Jun-20.R1
Wiley - Manuscript type:	Clinical Investigation
Date Submitted by the Author:	n/a
Complete List of Authors:	Pelà, Giovanna; University of Parma Department of Medicine and Surgery; University Hospital of Parma Tagliaferri, Sara ; University of Parma Department of Medicine and Surgery Perrino, Felice; University of Parma Department of Medicine and Surgery; University Hospital of Parma Bussolati, Giacomo; University of Parma Department of Medicine and Surgery; University Hospital of Parma Longobucco, Yari; University of Parma Department of Medicine and Surgery Zerbinati, Luna; University of Parma Department of Medicine and Surgery Adorni, Elisa; University of Parma Department of Medicine and Surgery Calvani, Riccardo; Università Cattolica del Sacro Cuore Facoltà di Medicina e Chirurgia, Department of Geriatrics, Neurosciences and Orthopedics; University Hospital Agostino Gemelli, Fondazione Policlinico Universitario Cesari, Matteo; University of Milan, Department of Clinical Sciences and Community Health ; La Fondazione IRCCS Ca' Granda Ospedale Maggiore di Milano Policlinico, UOSD Geriatria Cherubini, Antonio; INRCA-IRCCS, Geriatria, Accettazione Geriatrica e Centro di ricerca per l'invecchiamento Bernabei, Roberto; Università Cattolica del Sacro Cuore Facoltà di Medicina e Chirurgia, Department of Geriatrics, Neurosciences and Orthopedics; University Hospital Agostino Gemelli, Fondazione Policlinico Universitario Di Bari, Mauro; University of Florence, Department of Experimental and Clinical Medicine, Research Unit of Medicine of Aging; University Hospital Careggi, Unit of Geriatrics- Geriatric Intensive Care Unit, Department of Medicine and Geriatrics Landi, Francesco; Università Cattolica del Sacro Cuore Facoltà di Medicina e Chirurgia, Department of Geriatrics, Neurosciences and Orthopedics; University Hospital Agostino Gemelli, Fondazione Policlinico Universitario Marzetti, Emanuele; Università Cattolica del Sacro Cuore Facoltà di Medicina e Chirurgia, Department of Geriatrics, Neurosciences and Orthopedics; University Hospital Agostino Gemelli, Fondazione Policlinico Universitario Lauretani, Fulvio; University of Parma Department of Medicine and

	Surgery; University Hospital of Parma Maggio, Marcello; University of Parma Department of Medicine and Surgery; University Hospital of Parma
Key Words:	Skeletal Muscle Mass, left ventricular mass, SPRINTT study, low physical performance

Interaction of Skeletal and Left Ventricular Mass in older adults with low muscle performance

Running Title: Left ventricular mass and Sarcopenia

Giovanna Maria Pelà, M.D., Ph.D.[a,b], Sara Tagliaferri, Sc.D. Ph.D.[a], Felice Perrino, M.D.[a,b], Giacomo Bussolati, M.D.[a,b], Yari Longobucco, D.S.N.[a], Luna Zerbinati, D.S.N.[a], Elisa Adorni, D.P.T.[a], Riccardo Calvani Sc.D., Ph.D.[c,d], Matteo Cesari, M.D., Ph.D.[e,f], Antonio Cherubini, M.D., Ph.D.[g], Roberto Bernabei, M.D.[c,d], Mauro Di Bari, M.D.[h,i], Francesco Landi, M.D., Ph.D.[c,d], Emanuele Marzetti, M.D., Ph.D.[c,d], Fulvio Lauretani, M.D.[a,b,l] and Marcello Maggio, M.D, Ph.D.[a,b,l].

[a]Department of Medicine and Surgery, University of Parma, Parma, Italy;

[b]University Hospital of Parma, Parma, Italy;

[c]Department of Geriatrics, Neurosciences and Orthopedics, Università Cattolica del Sacro Cuore, Rome, Italy;

[d]Fondazione Policlinico Universitario "Agostino Gemelli" IRCCS, Rome, Italy;

[e]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy;

[f]UOSD Geriatria, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy;

[g]Geriatria, Accettazione Geriatrica e Centro di ricerca per l'invecchiamento. IRCCS INRCA, Ancona, Italy;

[h]Research Unit of Medicine of Aging, Department of Clinical and Experimental Medicine, University of Florence, Firenze, Italy

[i] Unit of Geriatrics - Geriatrics Intensive Care Unit, Department of Medicine and Geriatrics, Careggi Hospital, Firenze, Italy.

[l]Geriatric Clinic Unit, University-Hospital of Parma, Parma, Italy.

Address Correspondence to Giovanna Pelà, Department of Medicine and Surgery, University of Parma, Italy and University Hospital of Parma, via Gramsci 14, 43100 Parma, Italy. *E-mail address*: giovanna.pela@unipr.it

Word count abstract: 289; Word count text: 2955; Tables: 3; Figure: 1.

IMPACT STATEMENT

Older patients with low skeletal muscle mass and physical performance are unique population at high risk of cardiovascular events. We demonstrated for the first time, in this specific population with low

multimorbidity, that left ventricular muscle mass and skeletal muscle mass were positively correlated independently of cardiac output, haemoglobin and body mass index. These findings underline the future need of evaluating and monitoring in parallel left ventricular mass and skeletal muscle mass after proactive interventions including nutrition counseling and resistance exercise. We certify that this work is confirmatory of recent novel clinical research. (Keng et al, JAGS 2019;67:2568-2573).

ABSTRACT

BACKGROUND: It was recently hypothesized the existence of "cardiac-skeletal muscle axis". However, the relationship between skeletal muscle mass (SMM) and left ventricular mass (LVM) has never been investigated in the specific group of older individuals with low skeletal mass and physical performance.

We tested this hypothesis in the SPRINT-T (**S**arcopenia and **P**hysical Frailty **IN** older people: multicomponen**T** Treatment strategies **T**rial) population using LVM as independent variable and SMM as dependent variable.

METHODS: SMM was assessed by DEXA-scan and expressed as Appendicular Muscle Mass (ALM), LVM was estimated through echocardiography. Low ALM was defined according to Foundation for the National Institutes of Health Sarcopenia Project (FNIH) criteria, and Short Physical Performance Battery (SPPB) was used to assess physical performance.

RESULTS: The population consisted of 100 persons (33 men and 67 women), aged ≥ 70 years (mean age 79 ±5) with low ALM and SPPB ranged between 3 and 9 suggestive of physical frailty. Charlson Comorbidity Index median score was 0. Mean values of LVM were 193±67 (g), indexed LVM to body surface area (LVM/BSA) 112±33 (g/m²), and Cardiac Output (CO) 65±19 (l/min). ALM was strongly and positively correlated with LVM (r=0.54602, p<.0001), LVM/BSA (r=0.30761, p<0.002), CO (r=0.49621, p<.0001), BMI (r=0.52461, p<.0001), sex (r=0.77, p<0.001), fat mass (r=0.38977, p<0.0001) and Hb (r=0.26001, p<0.01). In the multivariate analysis, LVM (β 0.019±0.005; p<0.0001), CO (β 0.038±0.016; p=0.019), BMI (β 0.286±0.051; p <0.0001) and Hb (β 0.544 ± 0.175; p=0.0025) remained associated to ALM.

CONCLUSIONS: In a sample of older persons with low muscle mass and physical performance , LVM was positively and significantly correlated with ALM, independently from blood pressure, physical activity, and other potential confounders. Future studies are needed to address the effect of interventions targeting LVM and SMM.

Key words: **skeletal muscle mass; left ventricular mass; low physical performance; SPRINTT study.**

INTRODUCTION

Sarcopenia is considered a primarily age-dependent condition, frequently overlapped with physical frailty,[1] a geriatric syndrome characterized by reduced homeostatic reserve. Both these conditions expose the subject to an increased risk of adverse events, including impaired physical function and disability. [2]

Changes in skeletal muscle mass (SMM) have been associated with cardiovascular diseases.[3-6] In particular, in patients with heart failure, either with reduced or preserved ejection fraction, a loss of SMM contributes to the onset of fatigue and exercise intolerance. Observational studies have also evaluated the relationship between frailty and cardiac function and cardiovascular diseases.[7-10] Patients with physical frailty have a higher prevalence of cardiovascular diseases such as myocardial infarction, angina, and congestive heart failure than well-performing patients.[10] Furthermore, in those patients without a history of cardiovascular disease, frailty was associated with subclinical heart disease i.e., left ventricular hypertrophy (LVH), which is considered a form of preclinical organ damage associated with systolic and diastolic dysfunction.[7-9]

Moreover, it has been demonstrated that, after bed rest or inactivity - well-known risk factors for sarcopenia and physical impairment - cardiac atrophy occurs in both men and women suggesting a common regulation of heart and muscle mass.[11-13]

All these data suggest the utmost important interaction of sarcopenia with cardiac mass during aging. The existence of *cardiac- muscle axis* has been recently hypothesized in older Singapore subjects where a positive and significant relationship was found between skeletal and cardiac ventricular mass.[14] Additionally, although low skeletal muscle mass is considered the other side of the coin, physical impairment ,[2] the combination of these conditions is not routinely assessed during daily clinical practice. Given the unique opportunity to assess a selected cohort of participants enrolled because of low ALM and score of SPPB in the range between 3 and 9 (proxy of physical frailty), we explored the relationship between LVM (independent variable) and SMM (dependent variable) in a group of individuals with these characteristics.

METHODS

Data are from an ancillary study of the **S**arcopenia and **P**hysical f**R**ailty **IN** older people: multi-componen**T** **T**reatment strategies (SPRINT-T) project,[15] a randomized control trial conducted in frail, sarcopenic older subjects aged 70 years and older, to demonstrate the effectiveness of a multicomponent (MCI) intervention based on physical activity, nutritional and technological intervention versus a healthy aging lifestyle education (HALE) program for the prevention of mobility disability.

Inclusion and Exclusion criteria for the Study were detailed elsewhere:[16]

-Men and women aged≥70 years;

-SPPB score between 3 (included) and 9 (included);

-Ability to complete the 400-m walk test within 15 min without sitting down, help from another person, use of a walker, or stopping for more than 1 minute at a time;

-Presence of low muscle mass according to results from a Dual Energy X-Ray Absorptiometry (DEXA) scan. In agreement with the FNIH report 32, low muscle mass will be defined as: Body mass index-adjusted appendicular lean mass (ALM; i.e., the sum of lean mass from both arms and legs): <0.789 in men, and <0.512 in women, OR ii. ALM <19.75 kg in men and <15.02 kg in women;

-Willingness to be randomised to either intervention group and to follow the study protocol.

Exclusion criteria:

-Unable or unwilling to provide informed consent or accept randomisation to either study group;

-Plans to relocate out of the study area within the next 2 years or plans to be out of the study area for more than 6 consecutive weeks in the next year;

-Residence in long-term care;

-Household member enrolled in the study;

-Current diagnosis of schizophrenia, other psychotic or bipolar disorder. Depression is not an exclusion criterion;

-Consumption of more than 14 alcoholic drinks per week;

-Difficulty communicating with the study personnel due to speech, language, or (noncorrected) hearing problems;

-Mini Mental State Examination (MMSE) lower than 24/30;

-Severe osteoarthritis (e.g., awaiting joint replacement) that would interfere with the ability to participate fully in either study arm;

-Cancer requiring treatment in the past 3 years, except for non-melanoma skin cancers or cancers that have an excellent prognosis (e.g., early stage breast or prostate cancer);

-Lung disease requiring regular use of supplemental oxygen;

-Inflammatory conditions requiring regular use of oral or parenteral corticosteroid agents;

-Severe cardiovascular disease (including New York Heart Association [NYHA] class III or IV. The investigators of the Parma SPRINT-T[15-16] site added, at the enrolment of participants, a complete cardiac assessment including clinical evaluation with 12-lead resting Electrocardiogram (ECG) and conventional and Doppler Tissue Echocardiographic (DTE) examination as part of the ancillary protocol to the enrolment of participants.

This ancillary study was submitted to SPRINT-T Scientific Committee and accepted by the Managing Entity, and subsequently approved by AVEN Local ethics committee (*Protocol n.10872)*. Written informed consent was obtained from the participants.

One hundred subjects from those enrolled in the SPRINT-T study in the Frailty Clinic of the University-Hospital of Parma site were selected. Blood pressure (BP) and heart rate (HR) (OMRON 705 IT) were assessed with three consecutive measurements, the data of which were averaged.

Level of physical activity (PA) was assessed by a questionnaire that included detailed information on type, intensity and duration of physical activity.[17]

Whole-body DEXA scans were used to estimate SMM as ALM, and sarcopenia was defined according to the recommendation of the FNIH (ALM/BMI <0.789 in men and <0.512 in women; and/or crude ALM <19.75 Kg in men and <15.02 Kg in women).[18] Fat mass (FM) was also derived from DEXA and expressed in Kg.

Physical Frailty was assessed by SPPB, a battery of three tests with a score in the range between 3 and 9, and this was considered one of the eligibility criteria. Participants in the SPRINT-T trial needed to have sufficient cognitive abilities measured using MMSE, and those participants with MMSE > 24 were included in the study.[19]

Charlson Comorbidity Index (CCI) was used to assess multimorbidity, the median score of CCI was estimated according to Charlson et al.[20]

M-mode, two-dimensional, and Doppler ECHO were performed by an ultrasonography-experienced cardiologist (GP), using a commercially available, multi-hertz sector, 2-4 MHz probe-equipped machine (Vivid S5, GE Healthcare, USA). The interventricular septal (SWT) and posterior (PWT) left ventricular (LV) wall thicknesses, systolic and diastolic (EDD) diameters and volumes, absolute LVM and indexed to body surface area (LVM/BSA) were calculated as previously described.[21] LVH was defined as LVM/BSA of >95g/m^2 in women and >115g/m^2 in men.[22] Relative wall thickness (RWT) was calculated as: (SWT+PWT)/EDD, using the 0.42 cut-off to define eccentric (≤0.42) or concentric (>0.42) remodelling.[22] Simpson's biplane rule-based end-diastolic (EDV) and systolic (ESV) volumes and ejection fraction (EF) were calculated, while Fractional Shortening (FS) was: [(EDV – ESV)/EDV] x 100. Cardiac output was derived by the formula: EDV-ESV.

Mitral inflow pattern was analysed from apical 4-chamber view, and E and A wave and their ratio were considered as peak flow velocity (pv) and time velocity integral (tvi), in order to evaluate the conventional diastolic function. From the same projection, DTE analysis was performed at lateral site and postero-septum of mitral annulus to assess myocardial systolic (S) and diastolic (E', A') waves of LV. The ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity (E/E' ratio) was calculated for the estimation of LV filling pressure.

DEXA scan and cardiological assessment were performed at baseline, within a temporal window of 30 days.

Data are reported as means±SD or numbers and percentage. Factors statistically correlated with ALM, proxy of SMM, were identified using age- and sex-adjusted partial correlation coefficient and Spearman partial rank–order correlation coefficients, as appropriate. Parsimonious models obtained by backward selection from initial fully adjusted models, including age, BMI, systolic BP (SBP), HR, LVM, CO, level of PA, Hb, MMSE and beta-blockers or ACE-inhibitors/angiotensin receptor blockers, were used to identify independent factors of ALM. Sex was not included in the model because the collinearity between LVM and sex ($R=0.51$, $p<0.0001$). A 2-tailed p value<0.05 was considered as statistically significant. SAS 8.2 statistical package was used for all analyses (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Table 1 shows the main characteristics of the study population: 67 were women and 33 men (mean age was 79±5 years). The mean BMI was 27.6 Kg/m² with one third of the sample having BMI value >30 Kg/m². CCI median score was 0, without significant differences between men and women. The mean SBP value was 138±18 mmHg and 70% had a history of hypertension; 12% had coronary artery disease, and 3% had significant cardiac valve disease. No sign of heart failure was detected in any of the patients. With regard to the other comorbidities of the sample, thyroid diseases were reported in 20% and diabetes mellitus in 9%. Forty-one percent of the participants were chronically on β-blockers, 32% on ACE-inhibitors, and 21% on Angiotensin II Receptor Blockers (ARB). Mean values of ALM crude and ALM/BMI and indexed by BMI and SPPB were consistent with the eligibility criteria adopted in SPRINT-T for defining a sarcopenic and physically frail population (Table 1).

The thicknesses of SWT and PW and the LV cavity size, as assessed by diameters and volumes, were in the normal range with males exhibiting greater LV thicknesses and dimensions compared

with females (Supplementary Table). Both LVM and LVM/BSA were higher in men and women, especially in older and hypertensive subjects with a tendency to a geometric remodelling, as evaluated by RWT in both groups (Supplementary Table).

LV systolic function, assessed by EF and FS, was in the normal range as well as CO in the total population, with females showing significantly lower CO and higher EF compared to the male group (Supplementary Table). The mitral inflow pattern showed significant reduction of the E/A ratios in these patients, suggesting an impaired relaxation, confirmed by a lower E' wave from DTE-analysis, which also demonstrated a reduction of S wave without significant differences between the male and female groups (Supplementary Table). E/E' excluded an increased LV filling pressure in our cohort.

ALM was strongly and positively correlated with LVM (r=0.54602, p<.0001), LVM/BSA (r=0.30761, p<0.002), CO (r=0.49621, p<.0001), but also with other structural cardiac parameters such as LV thicknesses, diameters, and volumes (Table 2). In addition, factors associated to ALM included BMI (r=0.52461, p<.0001), sex (r=0.77, p<0.001), FM (r=0.38977, p<0.0001) and Hb (r=0.26001, p<0.01) (Table 2). A negative association was detected between ALM and EF (r=-0.30, p<.0001) and FS (r=-0.27, p<.001), whilst no significant correlation was found with S wave and all diastolic parameters (E/A, E' wave and E/E'). Multivariate analysis confirmed as factors independently associated to ALM, only LVM (β 0.019±0.005; p<0.0001), CO (β 0.038±0.016; p=0.019), BMI (β 0.286 ± 0.051; p<0.0001) and Hb (β 0.544 ± 0.175; p=0.0025) (Table 3). Age, SBP, HR, levels of PA, pharmacological therapy, and MMSE were not significantly associated with ALM.

DISCUSSION

Main results of the present study are the significant correlations between ALM, proxy of SMM, and LVM in older adults with low skeletal muscle mass and physical performance, independently by confounders. ALM was also associated with cardiac output, independently of LVM.

This relationship is not surprising. Sarcopenia shares with cardiovascular disease risk factors, such as age, sedentary lifestyle, obesity, insulin resistance, and metabolic syndrome.[23,24] Sarcopenia is also associated with an increased risk of cardiovascular diseases, as reported by the KNHANES survey.[25]

Recent studies have also shown that sarcopenia is strictly and independently associated with PWV and intima-media thickness, all risk factors of cardiovascular disease.[26]

The link between the cardiac disease and SMM is well-established in heart failure patients who develop secondary sarcopenia due to heart disease.[3-6] Reduced blood oxygenation, physical inactivity and associated increase of inflammatory markers, may induce damage in SMM and cardiac muscle mass. [3-6]

There are indeed few studies on the relationship between skeletal muscle disease, sarcopenia, and cardiac structure and function. We studied this relationship in a specific population of older persons selected because of low muscle mass and physical performance. Interestingly, we found a strong positive association between ALM and LVM and CO (functional and hemodynamic parameter), also independently of LVM (structural cardiac parameter) -i.e. more skeletal mass, more LVM and CO. Our data are consistent with Keng et coworkers who recently demonstrated, among a study sample of Asian older adults without cardiovascular disease, that sarcopenic participants (n=88 subjects aged 74) had smaller LV cavity size and mass than not sarcopenic ones, suggesting the presence of cardio-sarcopenia syndrome.[14] We confirmed this concept here in a different more characterized population (European vs Asian) of older individuals using a more robust technique of DEXA (instead of bioimpedance) to assess body composition.

These results are not in agreement with those presented in two previous studies.[27,28] The first study, conducted in a population of Koreans with an average age of 58 years enrolled in an

epidemiological study, showed that high visceral adiposity and low skeletal muscle mass were independent predictors of LVM.[27] However, the participants of this study were not classified according to sarcopenic status and were relatively young.

The second study, realized in a very large cohort of Korean adults (n=67,106), showed an increased prevalence of both diastolic dysfunction and LVH in the lowest skeletal muscle mass quartile.[28] In our cohort, ALM was positively correlated with LVM, and did not correlate with all diastolic indexes such as E/A, E' wave and E/E'. The different results can be explained by the fact that in the Korean study[28], 70.7% of population attributed to Q1 group were obese (vs 39.0%, 20.7 and 7.1 in Q2, Q3 and Q4 respectively) with a higher proportion of hypertensive (23.1% vs 14.8, 11.6 and 7.7 in Q2, Q3 and Q4 respectively) and diabetic (8.4% vs 5.5, 3.8 and 2.5 in Q2, Q3 and Q4 respectively), well known factors that potentially influence negatively the diastolic function.

Our study is also different from the studies aforementioned for many reasons: the age of the population, ethnicity (Caucasian vs. Asian), and the homogeneity of our sample population, which included only older subjects with low SMM and physical performance.

We should also consider that high LVM is traditionally viewed as clinically unfavourable phenomenon and LVH in hypertensive pathology is associated with greater CV risk and poorer prognosis.[29] The higher incidence of CV, mainly coronary LVH-related events, is justified by the imbalance between increased consumption and insufficient O2 intake available for increased demand.Conversely, it should be also underlined the potential role of LVH as a secondary compensatory mechanism adopted for increasing cardiac work. Examples in this regard include the physiological LVH of the athlete, i.e., the athlete's heart or pathological LVH occurring with the hypertensive heart or aortic stenosis.[30,31]

While physiological LVH allows an increase in cardiac output during sports performance, the pathological LVH ensures the maintenance of a normal cardiac throw, despite the increased after-load.[30] Pathological LVH, in contrast to the physiological one, is associated with both diastolic and

systolic dysfunction, which can be highlighted not with conventional functional indices, such as EF and FS, but with more sophisticated techniques such as DTE and Strain.[32,33]

Consistently, in our study ALM positively correlated with CO and this relationship was also maintained in the multivariate analysis, including LVM as covariate. We cannot exclude that the relationship between exposure and outcome (LVM and SMM) could have been influenced by multimorbidity. In our study sample, there were patients who had heart disease such as CAD, cardiac valve disease, as well as chronic conditions such as hypertension, COPD and thyroid disease. In total, these conditions may account for at least 40% of the study sample. In particular, the increased systolic BP and the high prevalence of hypertensive subjects (70%), could have contributed to increase LV mass; however, this hypothesis was not confirmed in the multivariate analysis.

Moreover, to better clarify the role of multimorbidity, we calculated crude CCI whose median score of 0 (not surprising given the stricted exclusion criteria aforementioned), we evaluated the relationship between CCI and ALM, and the role of CCI in the association between ALM and LVM in the multivariate analysis. CCI was not a significant predictor of ALM ($r=-0.12$, $p=0.22$) and the introduction of CCI in the Backward Analysis did not change the significant relationship between ALM and LVM. Basing on this data, we can assume that multimorbidity had not a relevant impact in this specific sample.

We should acknowledge that our study has two main limitations including the limited number of subjects enrolled and the cross-sectional nature of this study that does not allow drawing conclusions about the nature of the relationship. Moreover, given the strict inclusion criteria and the cohort precisely defined features, the generalization of results for the entire population of the community of older adults deserves further investigation. Additionally, given the collinearity between sex and LVM, we cannot exclude an independent role of sex in determining ALM values. This should be verified in separate groups of males and females with a wider range of ALM values. The relatively low simple size of our group and the narrow dispersion of ALM in both

males and females cannot permit such an analysis and therefore it should be considered as a major limitation of the study.

However, these limitations are offset by important strengths. This is the first time a study investigates the relationship between ALM and LVM in a homogeneous group of both low muscle mass and physical performance. Furthermore, the echocardiographic examinations were performed by a single, experienced operator to limit the variability of the calculation of the LVM - a measure that is affected by both the quality of the images and the experience of the operator.

In conclusion, the present study is the first one that demonstrates a highly significant and positive relationship between ALM and LVM in a cohort of older adults with low muscle mass and physical performance. Our novel findings emphasize the need of studying skeletal and heart in tandem to better address the complexity of aging process.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Dr. Karen Elena Brothers, who critically revised the manuscript.

Financial Disclosure: The present work was funded by a grant from the Innovative Medicines Initiative - Joint Undertaking (IMI-JU 115621).

Conflicts of interest: None declared

Author contributions: GP, FL and MM contributed to the conception and design of the work. All authors contributed to the acquisition, analysis, or interpretation of data for the work. GP performed all echocardiographic examinations and drafted the manuscript. All authors critically revised the manuscript and gave final approval.

Sponsor's role: Some authors of the present work are partners of the SPRINTT consortium, which is partly funded by the European Federation of Pharmaceutical Industries and Associations (EFPIA).

REFERENCES

1. Cruz-Jentoft AJ, Bahat G, Bauer J, et al Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019;48(1):16–31. doi:10.1093/ageing/afy169.
2. Cesari M, Landi F, Vellas B, Bernabei R, Marzetti E. Sarcopenia and physical frailty: two sides of the same coin. Front Aging Neurosci 2014;6:192. doi:10.3389/fnagi.2014.00192.
3. Saitoh M, Ishida J, Doehner W, et al. Sarcopenia, cachexia, and muscle performance in heart failure: Review update 2016. Int J Cardiol 2017;238:5–11. doi:10.1016/j.ijcard.2017.03.155.
4. Adams V, Linke A, Winzer E. Skeletal muscle alterations in HFrEF vs. HFpEF. Curr Heart Fail Rep 2017;14:489-497. doi:10.1007/s11897-017-0361-9.
5. Okita K, Kinugawa S, Tsutsui H. Exercise intolerance in chronic heart failure-skeletal muscle dysfunction and potential therapies. Circ J 2013;77(2):293-300. doi:10.1253/circj.cj-12-123.
6. Seiler M, Bowen T S, Rolim N, et al. Skeletal Muscle Alterations Are Exacerbated in Heart Failure With Reduced Compared With Preserved Ejection Fraction: Mediated by Circulating Cytokines? Circ Heart Fail 2016;9(9):e003027. doi:10.1161/CIRCHEARTFAILURE.116.003027.
7. Gharacholou SM, Tashiro T, Cha SS, Scott CG, Takahashi PY, Pellikka PA. Echocardiographic indices associated with frailty in adults ≥65 years. Am J Cardiol 2015;116(10):1591–1595. doi:10.1016/j.amjcard.2015.08.023.
8. Leibowitz D, Jacobs JM, Gilon D, Lande-Stessman I, Ein-Mor E, Stessman J. Cardiac Structure and Function and Frailty in Subjects Aged 85 and 86 Years. Am J Cardiol 2016;118(5):760–764. doi:10.1016/j.amjcard.2016.06.005.
9. Nadruz W, Jr, Kitzman D, Windham B G, et al. Cardiovascular Dysfunction and Frailty Among Older Adults in the Community: The ARIC Study. J Gerontol A Biol Sci Med Sci 2017;72(7):958–964. doi:10.1093/gerona/glw199.

10. Veronese N, Cereda E, Stubbs B, et al. Risk of cardiovascular disease morbidity and mortality in frail and pre-frail older adults: Results from a meta-analysis and exploratory meta-regression analysis. Ageing Res Rev 2017;35:63–73. doi:10.1016/j.arr.2017.01.003.

11. Kortebein P, Ferrando A, Lombeida J, Wolfe R, Evans WJ. Effect of 10 days of bed rest on skeletal muscle in healthy older adults. JAMA 2007;297(16):1772–1774. doi:10.1001/jama.297.16.1772-b.

12. Perhonen M A, Franco F, Lane LD, et al. Cardiac atrophy after bed rest and spaceflight. J Appl Physiol 2001;91(2):645–653. doi:10.1152/jappl.2001.91.2.645.

13. Dorfman T A, Levine BD, Tillery T, et al. Cardiac atrophy in women following bed rest. J Appl Physiol 2007;103(1):8–16. doi:10.1152/japplphysiol.01162.2006.

14. Keng BMH, Gao F, Teo LLY, et al. Associations between Skeletal Muscle and Myocardium in aging: A syndrome of "Cardio-Sarcopenia"? J Am Geriatr Soc 2019;67:2568-2573. doi:10.1111/jgs.16132.

15. Marzetti E, Cesari M, Calvani R, et al. The "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT) randomized controlled trial: Case finding, screening and characteristics of eligible participants. Exp Gerontol 2018;113:48–57. doi:10.1016/j.exger.2018.09.017.

16. Landi F, Cesari M, Calvani R, et al. The "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT) randomized controlled trial: design and methods. Aging Clin Exp Res 2017;29(1):89–100. doi:10.1007/s40520-016-0715-2.

17. Wareham NJ, Jakes RW, Rennie KL, Mitchell J, Hennings S, Day NE. Validity and repeatability of the EPIC-Norfolk Physical Activity Questionnaire. Int J Epidemiol 2002;31:168–174. doi: 10.1093/ije/31.1.168.

18. Studenski SA, Peters KW, Alley DE, et al. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. J Gerontol A Biol Sci Med Sci 2014;69(5):547–558. doi:10.1093/gerona/glu010.

19. Longobucco Y, Benedetti C, Tagliaferri S, et al. Proactive interception and care of Frailty and Multimorbidity in older persons: the experience of the European Innovation Partnership on Active and Healthy Ageing and the response of Parma Local Health Trust and Lab through European Projects. Acta Biomed 2019;90(2):364–374. doi:10.23750/abm.v90i2.8419.

20. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-383. doi:10.1016/0021-9681(87)90171-8.

21. Pelà G, Crocamo A, Li Calzi M, et al. Sex-related differences in left ventricular structure in early adolescent non-professional athletes. Eur J Prev Cardiol 2016;23(7):777–784. doi:10.1177/2047487315608826.

22. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification. Eur J Echocardiogr 2006;7(2):79–108. doi:10.1016/j.euje.2005.12.014.

23. Kang DO, Park SY, Choi BG, et al. Prognostic Impact of Low Skeletal Muscle Mass on Major Adverse Cardiovascular Events in Coronary Artery Disease: A Propensity Score-Matched Analysis of a Single Center All-Comer Cohort. J Clin Med. 2019;8(5):712. doi:10.3390/jcm8050712.

24. Bahat G, Ilhan B. Sarcopenia and cardiometabolic syndrome: A narrative review. Eur Geriatric Med 2016;7(3):220-223. doi:10.1016/j.eurger.2015.12.012..

25. Bieon CH, Kang KY, Kang SH, NìBae EJ. Sarcopenia is associated with Framingham risk score in the Korean population: Korean National Health and Nutrition examination survey (KNHANES). J Geriatr Cardiol 2015;12:366-372. doi:10.11909/j.issn.1671-5411.2015.04.007.

26. Ochi M, Kohara K, Tabara Y, et al. Arterial Stiffness is associated with low thigh muscle mass in middle-aged to elderly men. Atherosclerosis 2010;212(1):327–332. doi:10.1016/j.atherosclerosis.2010.05.026.

27. Park J, Kim NH, Kim SH, et al. Visceral adiposity and skeletal muscle mass are independently and synergistically associated with left ventricular structure and function: The Korean Genome and Epidemiology Study. Int J Cardiol 2014;176(3):951–955. doi:10.1016/j.ijcard.2014.08.108.

28. Ko BJ, Chang Y, Kang JG, et al. Low relative muscle mass and left ventricular diastolic dysfunction in middle-aged adults. Int J Cardiol 2018;255:118–123. doi:10.1016/j.ijcard.2017.07.089.

29. Levy D, Garrison RJ, Savage DD, Kannel WB. & Castelli WP. Prognostic Implications Of Echocardiographically Determined Left Ventricular Mass In The Framingham Heart Study. N Engl J Med 1990;322(22):1561–1566. doi:10.1056/NEJM199005313222203.

30. Lovic D, Narayan P, Pittaras A, Faselis C, Doumas M, Kokkinos P. Left ventricular hypertrophy in athletes and hypertensive patients. J Clin Hypertens 2017;19(4):413-417. doi:10.1056/NEJM199005313222203.

31. Rader F, Sachdev E, Arsanjani R, Siegel RJ. Left ventricular hypertrophy in valvular aortic stenosis: mechanisms and clinical implications. Am J Med 2015;128(4):344-352. doi:10.1016/j.amjmed.2014.10.054.

32. Pelà G, Bruschi G, Montagna L, Manara M, Manca C. Left and right ventricular adaptation assessed by Doppler tissue echocardiography in athletes. J Am Soc Echocardiogr 2004;17(3):205–211. doi:10.1016/j.echo.2003.12.004.

33. Pelà G, Bruschi G, Cavatorta A, Manca C, Cabassi A, Borghetti A. Doppler tissue echocardiography: myocardial wall motion velocities in essential hypertension. Eur J Echocardiogr 2001;2(2):108–117. doi:10.1053/euje.2000.0057.

FIGURE LEGEND

Figure 1 is depicting the correlation between crude value of ALM and LVM (age- and sex-adjusted model).

Table 1. Characteristics of CARDIO-SPRINTT population (N=100).

VARIABLE	Total	Female	Male
Age (years)	79 ± 5	79 ± 5	80 ± 5
Female n, (%)	67 (67)	67	33
BMI (Kg/m2)	27.6 ± 5.1	27.5 ± 5.5	28.0 ± 4.3
Height (cm)	159 ± 8	155 ± 6	167 ± 7
Weight (Kg)	70 ± 15	65 ± 18	79 ± 13
HR (bpm)	66 ± 11	67 ± 12	65 ± 6
SBP (mmHg)	138 ± 18	138 ± 17	140 ± 20
DBP (mmHg)	80 ± 9	80 ± 9	79 ± 9
24h-SBP (mmHg)	129 ± 13	128 ± 10	130 ± 16
Hb (g/dl)	13.3 ± 1.4	13.0 ± 1.1	14.0 ± 1.9
Smoking n, (%)	8 (8)	4 (6)	4 (12)
Hypertension n, (%)	70 (70)	47 (70)	23 (70)
CAD n, (%)	12 (12)	3(4)	9 (27)
Cardiac valve disease n, (%)	3 (3)	3 (4)	-
COPD n, (%)	9 (9)	3 (4)	6 (18)
Diabetes mellitus	9 (9)	6 (9)	3 (9)
Obesity	30 (30)	20 (30)	10 (30)
Charlson Comorbidity Index, median , IQR	0 [0-1]	0[0-1]	1 [0-2]
Thyroid disease	20 (20)	19 (28)	1 (3)
Beta-Blockers n, (%)	41 (41)	26 (39)	15 (45)
Ace-Inhibitors n, (%)	32 (32)	21 (31)	11 (33)
ARB	21 (21)	14 (21)	7 (21)
ALM (Kg)	17.22 ± 3.73	15.23 ± 2.05	21.28 ± 3.02
ALM/BMI	0.62 ± 0.12	0.56 ± 0.08	0.76 ± 0.07
FM (Kg)	2.57 ± 0.85	2.53± 0.84	2.67 ± 0.86
SPPB	7.06 ± 1.2	7.15 ± 0.1	6.88 ± 1.56
MMSE	27.9 ± 1.7	27.9 ± 1.6	28.0 ± 1.8

Data are expressed as mean ± standard deviation or number of subjects with corresponding percentage or Median and Interquartile Range (IQR). ALM, appendicular lean mass; ALM/BMI, indexed appendicular lean mass; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; FM, Trunk Fat Mass; Hb, haemoglobin; HR, heart rate; MMSE, Mini Mental State Examination; SBP, systolic blood pressure; SPPB, short physical performance battery.

Table 2. Factors related to Appendicular Lean Mass in All Subjects.

Variable	Pearson's correlation r, (p-value)
Clinical data	
FM	0.39 (<0.001)
Age	-0.06 (0.23)
Sex	0.77 (<0.001)
BMI	0.52 (<0.001)
BSA	0.89 (<0.001)
SBP	-0.01 (0.21)
Hb	0.26 (<0.01)
SPPB	-0.06 (0.18)
HR	-0.10 (0.30)
MMSE	0.14 (0.15)
Ace-inhibitors	0.04 (0.72)*
B-blockers	0.24 (0.01)*
ARB	0.03 (0.70) *
Charlson Comorbidity Index	-0.12 (0.22)
Structural LV data	
LVM	0.55 (<0.001)
LVM/BSA	0.31 (0.002)
ESV	0.47 (<0.001)
EDV	0.54 (<0.001)
EDD	0.46(<0.001)
ESD	0.47 (<0.001)
SWT	0.35 (<0.001)
PW	0.34 (<0.001)
Functional LV data	
CO	0.50 (<0.001)
EF	-0.30 (<0.01)
FS	-0.27 (<0.01)
E/A pv	0.02 (0.32)
E/A tvi	0.13 (0.62)
DTE S pv sept.	0.11 (0.18)
DTE S pv lat.	-0.15 (0.25)
DTE E' pv sept.	0.08(0.22)
DTE E'pv lat.	-0.01 (0.27)
E/E'	-0.23 (0.70)

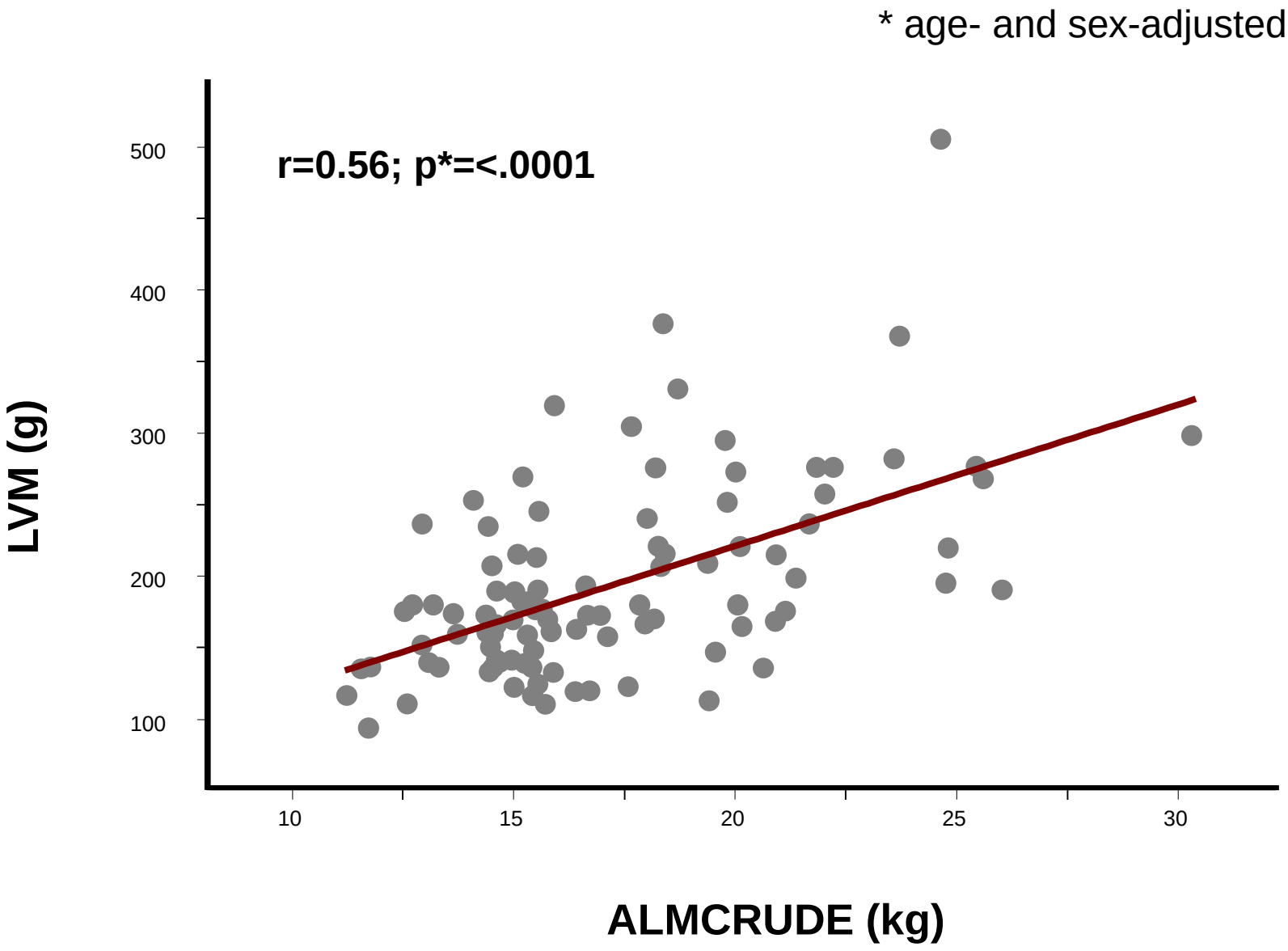
Footnotes: ARB, angiotensin receptor blocker; BMI: body mass index; BSA, body surface area; CO, cardiac output; DTE, Doppler tissue echocardiography; A', end-diastolic myocardial wave; E', proto-diastolic myocardial wave; S, systolic myocardial wave; pv, peak velocity; tvi, time velocity integral; EDD, end-diastolic diameter; EDV, end-diastolic volume; EF, ejection fraction; ESD, end-systolic diameter; ESV, end-systolic volume; FS, fractional shortening; LVM, left ventricular mass; ; MMSE, Mini Mental State Examination ; PW, posterior wall thickness; RWT, relative wall thickness; SWT, septal wall thickness;

* using logistic regression analysis

Table 3. Factors independently related to Appendicular Lean Mass.

VARIABLE	β ± SE	p-value
LVM	0.019 ± 0.005	**<0.0001**
CO	0.038 ± 0.016	0.019
BMI	0.286 ± 0.051	**<0.0001**
Haemoglobin	0.544 ± 0.175	0.0025

The full model obtained by Backward regression analysis included age, heart rate, Mini Mental State Examination, Systolic Blood Pressure; Ace-inhibitors, betablockers, Mean level of Physical Activity from 40 to 60 years old, Charlson Comorbidity Index.


* age- and sex-adjusted
r=0.56; p*=<.0001
LVM (g)
500
400
300
200
100
10
15
20
25
30
ALMCRUDE (kg)

Supplementary Table S1. Left ventricular structural and functional data in CARDIO-SPRINTT Population (N=100)

Variable	Total	Female	Male
EDD (mm)	46.6 ± 6.3	45.0 ± 5.4	49.9 ± 6.8
ESD (mm)	27.8 ± 6.2	26.2 ± 3.9	30.9 ± 8.5
SWT (mm)	9.7 ± 1.5	9.2 ± 1.2	10.6 ± 1.6
PW (mm)	9.3 ± 1.5	8.9 ± 1.3	10.0 ± 1.7
EDV (ml)	95 ± 31	87 ± 22	112 ± 40
ESV (ml)	30 ± 15.9	26 ± 8	38 ± 24
LVM (g)	193 ± 67	169 ± 45	241 ± 79
LVM/BSA	112 ± 33	104 ± 26	128 ± 39
LVH (%)	54 (54)	33 (58)	21 (64)
RWT	0.41 ± 0.07	0.41 ± 0.07	0.41 ± 0.06
FS (%)	40 ± 8	42 ± 6	39 ± 10
EF (%)	69 ± 7	70 ± 5	66 ± 10
CO (ml)	65 ± 19	61 ± 17	74 ± 21
Mitral E pv (cm/sec)	59 ± 17	60.1 ± 17	55.2 ± 15
Mitral E tvi (cm)	10.5 ± 3.1	10.5 ± 3.0	10.6 ± 3.4
Mitral A pv (cm/sec)	82 ± 19	84 ± 20	78 ± 16
Mitral A tvi (cm)	9.4 ± 2.7	9.8 ± 2.8	8.8 ± 2.5
Mitral E/Apv (cm/sec)	0.75 ± 0.35	0.76 ± 0.40	0.72 ± 0.21
Mitral E/A tvi (cm)	1.25 ± 0.93	1.15 ± 0.47	1.46 ± 1.49
DTE S pv (cm/sec)	8.12 ± 2.04	8.30 ± 1.90	7.77 ± 2.28
DTE S tvi (cm)	1.6 1± 0.35	1.65 ± 0.34	1.54 ± 0.37
DTE E' pv (cm/sec)	6.93 ± 2.14	7.11 ± 2.22	6.56 ± 1.97
DTE E' tvi (cm)	0.91 ± 0.14	0.88 ± 0.79	0.98 ± 1.63
DTE A' pv (cm/sec)	11.55 ± 2.93	11.34 ± 2.89	11.98 ± 2.99
DTE A' tvi (cm)	0.93 ± 0.23	0.92 ± 0.23	0.95 ± 0.24
DTE E'/A' pv	0.65 ± 0.37	0.69 ± 0.42	0.58 ± 0.22
DTE E'/A' tvi	1.01 ± 1.04	1.02 ± 0.94	0.99 ± 1.24
E/E'	9.9±4.2	10.1±4.4	9.5±3.9

Data are expressed as mean ± standard deviation. BSA, body surface area; CO, cardiac output; DTE, doppler tissue echocardiography; A', end-diastolic myocardial wave; E', proto-diastolic myocardial wave; S, systolic myocardial wave; pv, peak velocity; tvi, time velocity integral; EDD, end-diastolic diameter; EDV, end-diastolic volume; EF, ejection fraction; ESD, end-systolic diameter; ESV, end-systolic volume; FS, fractional shortening; LVH, left ventricular hypertrophy; LVM, left ventricular mass; ; PW, posterior wall thickness; RWT, relative wall thickness; SWT, septal wall tickness. Values from DTE analysis are the mean of septal and lateral walls.

~~Relationship between~~ Interaction of ~~s~~Skeletal and L~~l~~eft V~~v~~entricular M~~m~~ass in older adults with low ~~physical~~muscle performance ~~skeletal mass and left ventricular mass in sarcopenic and frail older adults.~~

Running Title: Left ventricular mass and Sarcopenia

Giovanna Maria Pelà, M.D., Ph.D.,[a,b] Sara Tagliaferri, Sc.D. Ph.D.,[a] Felice Perrino, M.D.,[a,b] Giacomo Bussolati, M.D.,[a,b] Yari Longobucco, D.S.N.,[a] Luna Zerbinati, D.S.N.,[a] Elisa Adorni, D.P.T.,[a] Riccardo Calvani Sc.D., Ph.D.,[c,d] Matteo Cesari, M.D., Ph.D.,[e,f] Antonio Cherubini, M.D., Ph.D.[g] Roberto Bernabei, M.D.,[c,d] Mauro Di Bari, M.D.,[h,i] Francesco Landi, M.D., Ph.D.[c,d] Emanuele Marzetti, M.D., Ph.D.[c,d] Fulvio Lauretani, M.D.,[a,b,l] and Marcello Maggio, M.D, Ph.D.[a,b,l]

[a]Department of Medicine and Surgery, University of Parma, Parma, Italy;
[b]University Hospital of Parma, Parma, Italy;
[c]Department of Geriatrics, Neurosciences and Orthopedics, Università Cattolica del Sacro Cuore, Rome, Italy;
[d]Fondazione Policlinico Universitario "Agostino Gemelli" IRCCS, Rome, Italy;
[e]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy;
[f]UOSD Geriatria, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy;
[g]Geriatria, Accettazione Geriatrica e Centro di ricerca per l'invecchiamento. IRCCS INRCA, Ancona, Italy;
[h]Research Unit of Medicine of Aging, Department of Clinical and Experimental Medicine, University of Florence, Firenze, Italy
[i] Unit of Geriatrics - Geriatrics Intensive Care Unit, Department of Medicine and Geriatrics, Careggi Hospital, Firenze, Italy.
[l]Geriatric Clinic Unit, University-Hospital of Parma, Parma, Italy.

Address Correspondence to Giovanna Pelà, Department of Medicine and Surgery, University of Parma, Italy and University Hospital of Parma, via Gramsci 14, 43100 Parma, Italy. *E-mail address*: giovanna.pela@unipr.it

Word count abstract: 2889215; ; Word count text: 279529255; Tables: 43; Figure: 1.

IMPACT STATEMENT

~~Frail and sarcopenic~~ O~~o~~lder patients with~~-~~ low skeletal muscle mass and physical performance are unique population at high risk of cardiovascular events. We demonstrated for the first time, in ~~–~~this specific population with low multimorbidity, ~~older frail and sarcopenic patients, t~~ that left ventricular muscle mass and skeletal muscle mass were positively correlated independently of cardiac output, haemoglobin and body mass index. These findings underline the future need of evaluating and monitoring in parallel left ventricular mass and skeletal muscle mass ~~and in the future their changes~~ after proactive interventions including nutrition counseling and ~~–~~resistance exercise. We certify that this work is ~~–~~confirmatory of recent novel clinical research. (Keng et al, JAGS 2019;67:2568-2573).

ABSTRACT

BACKGROUND: It was recently hypothesized the existence of "cardiac-skeletal muscle axis". However, theNo study has fully addressed the relationship between skeletal muscle mass (SMM) and left ventricular mass (LVM) has never been investigated in the specific group of of sarcopenic and frail older individuals with low skeletal mass and physical performancesarcopenic and frail older persons.

We tested this hypothesis in the SPRINT-T (**S**arcopenia and **P**hysical Frailty **IN** older people: multicomponen**T** Treatment strategies **T**rial) population using The aim of the present study was to evaluate the existence of "cardiac-skeletal muscle axis" assessing the relationship between LVM as (independent variable) and SMM as dependent variablein the SPRINT-T (**S**arcopenia and **P**hysical Frailty **IN** older people: multicomponen**T** Treatment strategies **T**rial) population.

METHODS: The population consisted of 100 persons (33 men and 67 women), aged ≥70 years. SMM was assessed by DEXA-scan and expressed as Appendicular Muscle Mass (ALM), LVM was estimated through echocardiography. Low ALM Sarcopenia was defined according to Foundation for the National Institutes of Health Sarcopenia Project (FNIH) criteria, and Short Physical Performance Battery (SPPB) was used to assess physical performance physical frailty basing on Short Physical Performance Battery (SPPB).

RESULTS: The population consisted of 100 persons (33 men and 67 women), aged ≥ 70 years (mean age 79 ±5) with low ALM and SPPB ranged between 3 and 9 suggestive of physical frailty. Charlson Comorbidity Index median score was 0. Mean values of LVM were 193±67 (g), indexed

LVM to body surface area (LVM/BSA) 112±33 (g/m²), and Cardiac Output (CO) 65±19 (l/min). ~~Females showed significantly lower CO and higher ejection fraction (EF) compared to the male group.~~ ALM was strongly and positively correlated with LVM (r=0.54602, p<.0001), LVM/BSA (r=0.30761, p<0.002), CO (r=0.49621, p<.0001), BMI (r=0.52461, p<.0001), sex (r=0.77, p<0.001), fat mass (r=0.38977, p<0.0001) and Hb (r=0.26001, p<0.01). ~~The population consisted of 100 persons (33 men and 67 women), aged ≥70 years with low ALM and SPPB ranged between 3 and 9 suggestive of physical frailty. Mean values of LVM were 193 ± 67 (g), indexed LVM to body surface area (LVM/BSA) 112 ± 33 (g/m²), and Cardiac Output (CO) 65 ± 19 (l/min). Females showed significantly lower CO and higher EF compared to the male group. ALM was strongly and positively correlated with LVM (r=0.54602, p<.0001), LVM/BSA (r=0.30761, p<0.002), CO (r=0.49621, p<.0001), BMI (r=0.52461, p<.0001), sex (r=0.77, p<0.001), FM (r=0.38977, p<0.0001) and Hb (r=0.26001, p<0.01).~~ In the multivariate analysis, LVM (β 0.019±0.005; p<0.0001), CO (β 0.038±0.016; p=0.019), BMI (β 0.286 ± 0.051; p <0.0001) and Hb (β 0.544 ± 0.175; p=0.0025) remained associated to ALM.

CONCLUSIONS: In a sample of older persons with low muscle mass and physical performance ~~sarcopenia and physical frailty~~, LVM was positively and significantly correlated with ALM, independently from blood pressure, physical activity, and other potential confounders. Future studies are needed to address the effect of interventions targeting LVM and SMM.

Key words: **s~~S~~keletal m~~M~~uscle m~~M~~ass~~,~~; left ventricular mass; low physical performance ~~sarcopenia; frailty~~; SPRINTT study.**

INTRODUCTION

~~Current understanding between skeletal muscle mass and the heart is confined to literature that describes alterations in skeletal muscle mass (SMM) and cardiovascular diseases.[1-4] In particular, in patients with heart failure, either with a reduced or preserved ejection fraction, a loss of SMM contributes to the onset of fatigue and exercise intolerance. However, much less is known about the relationship between skeletal mass deficit, i.e., sarcopenia, and cardiac function and structure.~~

~~Sarcopenia is considered a primarily age-dependent condition, characterized by the loss of SMM and strength~~Sarcopenia is considered a primarily age-dependent condition, frequently overlapped with physical frailty,[5] ~~The aforementioned condition is closely related to a level of physical impairment that can lead to disability. The flip side of this assertion is physical frailty,~~ a geriatric syndrome characterized by reduced homeostatic reserve. Both these ~~This~~ conditions exposes ~~s~~ the subject to an increased risk of ~~adverse negative~~ events, ~~including and, as with sarcopenia, the risk of~~ impaired physical function ~~impairment~~ and disability.[6]

Changes in skeletal muscle mass (SMM) have been associated with cardiovascular diseases.[1-4,3-6] In particular, in patients with heart failure, either with reduced or preserved ejection fraction, a loss of SMM contributes to the onset of fatigue and exercise intolerance. Observational studies have also evaluated the relationship between frailty and cardiac function and cardiovascular diseases.[7-10] Patients with physical frailty have a higher prevalence of cardiovascular diseases such as myocardial infarction, angina, and congestive heart failure than well-performing patients.[10] Furthermore, in those patients without a history of cardiovascular disease, frailty was associated with subclinical heart disease i.e., left ventricular hypertrophy (LVH), which is considered a form of preclinical organ damage associated with systolic and diastolic dysfunction.[7-9] ~~These data support the hypothesis that cardiovascular dysfunction plays an important role in the development of frailty and suggests the importance of a cardiac evaluation in frail subjects.~~

Moreover, it has been demonstrated that, after bed rest or inactivity - well-known risk factors for sarcopenia and physical impairment ~~and physical frailty~~ - cardiac atrophy occurs in both men and women suggesting a common regulation of heart and muscle mass.[11-13]

All these data ~~-~~suggest ~~Given the burden of physical disability with aging,~~ the utmost important interaction of ~~the identification of factors contributing to the development of~~ sarcopenia ~~and physical frailty~~ with cardiac mass during aging~~is of utmost importance~~. The existence of *cardiac-muscle axis* has been recently hypothesized in older- Singapore ~~Korean~~ subjects where a ~~se~~ positive and significant relationship was found between skeletal and cardiac ventricular mass.[14] ~~28 Keng (ref). However this association was not independent of confounders frequently encountered in the real multimorbid determinants could influence not only the risk of disability but also affects heart structure and function and, as a consequence, the patientscardiovascular prognosis.~~ Additionally, although low skeletal muscle mass is considered the other side of the coin, ~~-~~physical impairment ~~physical frailty coin~~,[2] the combination ~~-~~of ~~-~~these conditions ~~-~~is ~~-~~not routinely ~~-~~assessed during daily clinical practice.

~~:—~~

~~However,~~ Ggiven the unique opportunity to assess a selected cohort of participants enrolled because of low ALM ~~-~~and ~~-~~score of SPPB ~~short physical performance battery~~ in the range between 3 and 9 (proxy of physical frailty), we ~~However, since no study has specifically~~ explored the relationship between ~~left ventricular mass (~~LVM~~,~~ (independent variable) and SMM (dependent variable) in a group of individuals with these characteristics.~~older people with sarcopenia and physical frailty, we tested this hypothesis in a group of individuals with these characteristics.~~

METHODS

Data are from an ancillary study of the **S**arcopenia and **P**hysical f**R**ailty **IN** older people: multi-componen**T** **T**reatment strategies (SPRINT-T) project,[145] a randomized control trial conducted in frail, sarcopenic older subjects aged 70 years and older, to demonstrate the effectiveness of a multicomponent (MCI) intervention based on physical activity, nutritional and technological intervention versus a healthy aging lifestyle education (HALE) program for the prevention of mobility disability.

Inclusion and Exclusion criteria for the Study were detailed elsewhere:[16]

-Men and women aged ≥ 70 years;

-~~Short Physical Performance Battery (~~SPPB~~)~~ score between 3 (included) and 9 (included);

-Ability to complete the 400-m walk test within 15 min without sitting down, help from another person, use of a walker, or stopping for more than 1 minute at a time;

-Presence of low muscle mass according to results from a Dual Energy X-Ray Absorptiometry (DEXA) scan. In agreement with the ~~Foundation for the National Institutes of Health Sarcopenia Project (~~FNIH~~)~~ report 32, low muscle mass will be defined as: Body mass index-adjusted appendicular lean mass (A~~a~~LM; i.e., the sum of lean mass from both arms and legs): <0.789 in men, and <0.512 in women, OR ii. ~~a~~ALM <19.75 kg in men and <15.02 kg in women;

-Willingness to be randomised to either intervention group and to follow the study protocol.

Exclusion criteria:

-Unable or unwilling to provide informed consent or accept randomisation to either study group;

-Plans to relocate out of the study area within the next 2 years or plans to be out of the study area for more than 6 consecutive weeks in the next year;

-Residence in long-term care;

-Household member enrolled in the study;

-Current diagnosis of schizophrenia, other psychotic or bipolar disorder. Depression is not an exclusion criterion;

-Consumption of more than 14 alcoholic drinks per week;

-Difficulty communicating with the study personnel due to speech, language, or (noncorrected) hearing problems;

-Mini Mental State Examination (MMSE) lower than 24/30;

-Severe osteoarthritis (e.g., awaiting joint replacement) that would interfere with the ability to participate fully in either study arm;

-Cancer requiring treatment in the past 3 years, except for non-melanoma skin cancers or cancers that have an excellent prognosis (e.g., early stage breast or prostate cancer);

-Lung disease requiring regular use of supplemental oxygen;

-Inflammatory conditions requiring regular use of oral or parenteral corticosteroid agents;

-Severe cardiovascular disease (including New York Heart Association [NYHA] class III or IV.

The investigators of the Parma SPRINT-T[14~~5~~-15~~6~~] site added, at the enrolment of participants, a complete cardiac assessment including clinical evaluation with 12-lead resting Electrocardiogram (ECG) and conventional and Doppler Tissue Echocardiographic (DTE) examination as part of the ancillary protocol to the enrolment of participants.

This ancillary study was submitted to SPRINT-T Scientific Committee and accepted by the Managing Entity, and subsequently approved by AVEN Local ethics committee (*Protocol n.10872).* Written informed consent was obtained from the participants.

One hundred subjects from those enrolled in the SPRINT-T study in the Frailty Clinic of the University-Hospital of Parma site were selected. Blood pressure (BP) and heart rate (HR) (OMRON 705 IT) were assessed with three consecutive measurements, the data of which were averaged.

Level of physical activity (PA) was assessed by a questionnaire that included detailed information on type, intensity and duration of physical activity.[16~~7~~]

Whole-body ~~dual energy X-ray absorptiometry (~~DEXA~~)~~ scans were used to estimate SMM as ~~Appendicular Lean Muscle Mass (~~ALM~~)~~, and sarcopenia was defined according to the recommendation of the ~~Foundation for the National Institutes of Health (~~FNIH~~)~~ (ALM/BMI <0.789

in men and <0.512 in women; and/or crude ALM <19.75 Kg in men and <15.02 Kg in women).[178] Fat mass (FM) was also derived from DEXA and expressed in Kg.

Physical Frailty was assessed by ~~Short Physical Performance Battery (~~SPPB~~)~~, a battery of three tests with a score in the range between 3 and 9, and this was considered one of the eligibility criteria. Participants in the SPRINT-T trial needed to have sufficient cognitive abilities measured using ~~Mini Mental State Examination test (~~MMSE~~)~~, and those participants with MMSE > 24 were included in the study.[198]

Charlson Comorbidity Index (CCI)~~Mean score~~ was used to assess multimorbidity, the median score of CCI was estimated according to Charlson et al.~~:~~[20]~~-~~

M-mode, two-dimensional, and Doppler ECHO were performed by an ultrasonography-experienced cardiologist (GP), using a commercially available, multi-hertz sector, 2-4 MHz probe-equipped machine (Vivid S5, GE Healthcare, USA). The interventricular septal (SWT) and posterior (PWT) left ventricular (LV) wall thicknesses, systolic and diastolic (EDD) diameters and volumes, absolute LVM and indexed to body surface area (LVM/BSA) were calculated as previously described.[1921] LVH was defined as LVM/BSA of >95g/m^2 in women and >115g/m^2 in men.[2220] ~~–~~Relative wall thickness (RWT) was calculated as: (SWT+PWT)/EDD, using the 0.42 cut-off to define eccentric (≤0.42) or concentric (>0.42) remodelling.[2220] Simpson's biplane rule-based end-diastolic (EDV) and systolic (ESV) volumes and ejection fraction (EF) were calculated, while Fractional Shortening (FS) was: [(EDV – ESV)/EDV] x 100. Cardiac output was derived by the formula: EDV-ESV.

Mitral inflow pattern was analysed from apical 4-chamber view, and E and A wave and their ratio were considered as peak flow velocity (pv) and time velocity integral (tvi), in order to evaluate the conventional diastolic function. From the same projection, DTE analysis was performed at lateral site and postero-septum of mitral annulus to assess myocardial systolic (S) and diastolic (E', A') waves of LV. The ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity (E/E' ratio) was calculated for the estimation of LV filling pressure.

DEXA scan and cardiological assessment were performed at baseline, within a temporal window of 30 days.

Data are reported as means ± SD or numbers and percentage. Factors statistically correlated with ALM, proxy of SMM, were identified using age- and sex-adjusted partial correlation coefficient and Spearman partial rank–order correlation coefficients, as appropriate. Parsimonious models obtained by backward selection from initial fully adjusted models, including age, BMI, systolic BP (SBP), HR, LVM, CO, level of ~~physical activity~~PA, Hb, MMSE and beta-blockers or ACE-inhibitors/angiotensin receptor blockers, were used to identify independent factors of ALM. Sex was not included in the model because the collinearity between LVM and sex (R=0.51, p<0.0001). A 2-tailed p value < 0.05 was considered as statistically significant. SAS 8.2 statistical package was used for all analyses (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Table 1 shows the main characteristics of the study population: 67 were women and 33 men (mean age was 79±5 years). The mean BMI was ~~higher than~~ 27.6 ~~K~~kg/m² with one third of the sample having BMI value >30 ~~K~~kg/m². CCI median score was 0, without significant differences between men and women. The mean SBP value was 138±18 mmHg ~~high normal~~ and 70% had a history of hypertension; 12% had coronary artery disease, and 3% had significant cardiac valve disease. No sign of heart failure was detected in any of the patients. With regard to the other comorbidities of the sample, thyroid diseases were reported in 20% and diabetes mellitus in 9%. Forty-one percent of the participants were chronically on β-blockers, 32% on ACE-inhibitors, and 21% on Angiotensin II Receptor Blockers (ARB). Mean values of ALM crude and ALM/BMI and indexed by BMI and SPPB were consistent with the eligibility criteria adopted in SPRINT-T for defining a sarcopenic and physically frail population (Table 1).

The thicknesses of SWT and PW and the LV cavity size, as assessed by diameters and volumes, were in the normal range with males exhibiting greater LV thicknesses and dimensions compared with females (Supplementary Table ~~2~~). Both LVM and LVM/BSA were higher in men and women, especially in older and hypertensive subjects with a tendency to a geometric remodelling, as evaluated by RWT in both groups (Supplementary Table~~Table 2~~).

LV systolic function, assessed by EF and FS, was in the normal range as well as CO in the total population, with females showing significantly lower CO and higher EF compared to the male group (Supplementary Table ~~2~~). The mitral inflow pattern showed significant reduction of the E/A ratios in these patients, suggesting an impaired relaxation, ~~–~~confirmed by a lower E' wave from DTE-analysis~~–~~, which also demonstrated a reduction of S wave without significant differences between the male and female groups (~~–~~Supplementary Table~~) – 2)~~. E/E' excluded an increased LV filling pressure in our cohort.

ALM was strongly and positively correlated with LVM (r=0.54602, p<.0001), LVM/BSA (r=0.30761, p<0.002), CO (r=0.49621, p<.0001), but also with other structural cardiac parameters such as LV thicknesses, diameters, and volumes (Table 2~~3~~). In addition, factors associated to ALM included BMI (r=0.52461, p<.0001), sex (r=0.77, p<0.001), FM (r=0.38977, p<0.0001) and Hb (r=0.26001, p<0.01) (Table 2~~3~~). A negative association was detected between ALM and EF (r=-0.30, p<.0001) and FS (r=-0.27, p<.001), whilst no significant correlation was found with S wave and all diastolic parameters (E/A, E' wave and E/E'). Multivariate analysis confirmed as factors independently associated to ALM, only LVM (β 0.019±0.005; p<0.0001), CO (β 0.038±0.016; p=0.019), BMI (β 0.286 ± 0.051; p<0.0001) and Hb (β 0.544 ± 0.175; p=0.0025) (Table 3~~4~~). Age, SBP, HR, levels of ~~physical activity~~PA, pharmacological therapy, and MMSE were not significantly associated with ALM.

DISCUSSION

Main results of the present study are the significant correlations between ALM, proxy of SMM, and LVM in ~~frail and sarcopenic~~ older adults with low skeletal muscle mass and physical performance, independently by confounders. ALM was also associated with cardiac output, independently of LVM.

This relationship is not surprising. S~~Both s~~arcopenia ~~and cardiovascular disease~~ shares with cardiovascular disease ~~common~~ risk factors, such as age, sedentary lifestyle, obesity, insulin resistance, and metabolic syndrome.[2~~13~~,2~~24~~] ~~–~~Sarcopenia is also associated with an increased risk of cardiovascular diseases, as reported by the KNHANES survey.[2~~53~~]

Recent studies have also shown that sarcopenia is strictly and independently associated with ~~indicators of atherosclerosis (such as stiffness,~~ PWV and intima-media thickness, alls~~) that are~~ risk factors of cardiovascular disease~~–~~.[2~~46~~] ~~Our results suggest that both cardiac and skeletal muscle are associated and potentially share the same contributors.~~

The link between the cardiac disease and SMM is well-established in heart failure patients who develop secondary sarcopenia due to heart disease.[3-6~~1~~-4] ~~–In this context, the SMM loss can be attributed to R~~reduced blood oxygenation, physical inactivity and associated increase of inflammatory markers, ~~–~~may induce damage in ~~that can damage both~~ SMM and cardiac muscle mass.[3-6~~1~~-4]

~~Morphological, histological, biochemical, metabolic and energetic analyses, conducted on muscle biopsies, electromyography, spectroscopy and magnetic resonance imaging have shown that in~~

~~chronic heart failure the early onset of fatigue and intolerance to exercise was attributable to a shift from an aerobic to anaerobic metabolism at the muscle level.~~

There are indeed few studies on the relationship between skeletal muscle disease, sarcopenia, and cardiac structure and function. We studied this relationship in a specific population o~~ff frail and sarcopenic~~ older persons selected because of low muscle mass and physical performance. Interestingly, we found a strong positive association between ALM and LVM and CO (functional and hemodynamic parameter), also independently of LVM (structural cardiac parameter) -i.e. more skeletal mass, more LVM and CO.

Our data are consistent with Keng et coworkers ~~that~~who recently demonstrated, among a ~~large~~ study sample of Asian older adults without cardiovascular disease, that sarcopenic participants (n=88 subjects aged 74) had smaller LV cavity size and mass than not sarcopenic ones,~~,~~ suggesting the presence of cardio-sarcopenia syndrome.[2~~147~~] We confirmed this concept here in a different more characterized population (European vs Asian) of older ~~sarcopenic and physical frail~~ individuals ~~,~~ using a ~~Importantly, a~~ more robust technique of DEXA (instead of bioimpedance) ~~was used in our study~~ to assess body composition.

These results are not in agreement with those presented in two previous studies.[2~~75~~,2~~68~~] ~~–~~The first study, conducted in a population of Koreans with an average age of 58 years enrolled in an epidemiological study, showed that high visceral adiposity and low skeletal muscle mass were independent predictors of LVM.[2~~57~~] ~~–~~However, the participants of this study were not classified according to sarcopenic status and were relatively young.

The second study, realized in a very large cohort of Korean adults (n=67~~,~~106), showed an increased prevalence of both diastolic dysfunction and LVH in the lowest skeletal muscle mass quartile.[2~~68~~] ~~–~~In our cohort, ALM was positively correlated with LVM, and did not correlate with all diastolic indexes such as E/A, E' wave and E/E'. The different results can be explained by the fact that ~~However,~~ in the Korean study[2~~86~~], ~~–~~70.7% of population attributed ~~–~~to Q1 group were obese (vs 39.0%, 20.~~-~~7 and 7.~~-~~1 in Q2, Q3 and Q4 respectively) with a~~n~~ higher proportion of hypertensive

(23.1% vs 14.8, 11.6 and 7.7 in Q2, Q3 and Q4 respectively) and diabetic (8.4% vs 5.5, 3.8 and 2.5 in Q2, Q3 and Q4 respectively), well known factors that potentially influence negatively the diastolic function. ~~. These data can justify the different results between our and Korean study.~~

~~However,~~ Oour study is also different from the studies aforementioned ~~previous studies~~ for many reasons: the age of the population, ethnicity (Caucasian vs. Asian), and the homogeneity of our sample population, which included only ~~frail and sarcopenic~~ older subjects with low SMM and physical performance.

~~Keng et coworkers recently demonstrated, among a large study sample of Asian older adults without cardiovascular disease, that sarcopenic participants (n=88 subjects aged 74) had smaller LV cavity size and mass than not sarcopenic, suggesting the presence of cardio-sarcopenia syndrome.[27] We confirmed this concept here in a different more characterized population (European vs Asian) of older sarcopenic and physical frail individuals. Importantly, a more robust technique of DXA (instead of bioimpedance) was used in our study to assess body composition.~~

We should also consider that h~~H~~igh ~~The positive relationship between ALM and~~ LVM is traditionally ~~can be~~ viewed as clinically unfavourable ~~.~~phenomenon ~~. This datum is somewhat of a paradox because it is well-known that~~ and LVH in hypertensive pathology is associated with ~~implies~~ greater CV risk and poorer prognosis.[29~~28~~] ~~–~~The higher incidence of CV, mainly coronary ~~events due to~~ LVH-related events, is justified by the imbalance between increased consumption and insufficient O2 intake available for ~~due to~~ increased demand.

Conversely, ~~However,~~ it should be also underlined the potential role of LVH ~~should be interpreted not only as an energy expenditure but also considered~~ as a secondary compensatory mechanism adopted for increasing cardiac work. Examples in this regard include the physiological LVH of the athlete, i.e., the athlete's heart~~, induced by regular exercise,~~ or pathological LVH ~~secondary to CV~~

~~diseases, such as what~~ occurrings with the hypertensive heart or ~~in cases of~~ aortic stenosis.[29~~29~~,30~~30~~,31]

While p~~P~~hysiological LVH allows an increase in cardiac output during sports performance, ~~while~~ the pathological LVH ensures the maintenance of a normal cardiac throw, despite the increased after-load. [30]~~Therefore, pathological LVH is a positive functional adaptation mechanism in which the heart reshapes itself into a condition capable of normalizing stress and maintaining stroke volume.~~[29~~30~~]

~~It is also well known that~~ Pathological LVH, in contrast to the physiological one, is associated with both diastolic and systolic dysfunction, which can be highlighted not with conventional functional indices, such as EF and FS, but with more sophisticated techniques such as DTE and Strain.[31~~21~~,32~~23~~]

Consistently, i~~I~~n our study~~,~~ ALM positively correlated with CO~~cardiac output,~~ and this relationship was also maintained~~confirmed~~ in ~~by~~ the multivariate analysis, including LVM as covariate. ~~–~~We cannot exclude that the relationship between exposure and outcome (LVM and SMM) could have been influenced by ~~-~~multimorbidity. In our study sample, there were patients who had heart disease such as CAD, cardiac valve disease, as well as chronic conditions such as hypertension, COPD and thyroid disease. In total, these conditions may account for at least 40% of the study sample. In particular, the increased systolic BP and the high prevalence of hypertensive subjects (70%), could have contributed to increase LV mass; however, this hypothesis was not confirmed in the multivariate analysis.

Moreover, to better clarify the role of multimorbidity, we calculated~~-~~ crude ~~Charlson Comorbidity Index~~CCI whose median score of 0 (not surprising ~~–~~given the stricted exclusion criteria aforementioned), we evaluated the relationship between CCI and ALM, and the role of CCI in the association between ALM and LVM in the multivariate analysis.

~~CCI median scoreenbasing on these data, wmoCCIALMCCI~~ CCI was not a significant predictor of ALM (r=-0.12, p=0.22) ~~-~~and ~~-~~the introduction of ~~Charlson Comorbidity Index~~CCI in the Backward

Analysis did not change the significant relationship between -ALM and LVM. Basing on this data, we can assume that multimorbidity had not a relevant impact in this specific sample.

~~Skeletal muscle and heart muscle have many points in common. Both are streaky and composed of sarcoma units, albeit with different characteristics and functions. They have the same embryonic origin, both derived from mesoderm; the heart shares with SMM a large number of genes, mainly those regulating the transcription of contractile and mitochondrial proteins.[34,34] The high number of mitochondria, an expression of high oxidative capacity, testifies to a predominantly aerobic metabolism of these two organs.[34]~~

~~The size of these organs depends on anthropometric characteristics (height, weight and body surface), sex, genetic makeup, and ethnicity.[19, 35-38] The most cardiac and muscular hypertrophy among people of African ethnicity vs. Caucasian ethnicity are examples. [36-39] However, SMM is the force of gravity, while the heart is governed by blood pressure.[40]~~

~~The main strength of this study is the homogeneous sample of frail and sarcopenic older persons enrolled in the study. Furthermore, the echocardiographic examinations were performed by a single, experienced operator to limit the variability of the calculation of the LVM - a measure that is affected by both the quality of the images and the experience of the operator.~~

We should acknowledge that our study has two main l~~L~~imitations including ~~may be~~ the limited number of subjects enrolled and the cross-sectional nature of this study that does not allow ~~to~~ ~~draw~~drawing~~own~~ conclusions about the nature of the relationship. Moreover, given the strict inclusion criteria and the cohort precisely defined features, the generalization of results for the entire population of the community of older adults deserves further investigation. Additionally, given the collinearity between sex and LVM, we cannot exclude an independent role of sex in determining ALM values. This should be verified in separate groups of males and females with a wider range of ALM values. The relatively low simple size of our group and the narrow dispersion of ALM in both males and females cannot permit such an analysis and therefore it should be considered as a major limitation of the study.

However, these limitations are offset by important strengths. ~~to our knowledge,~~ T~~t~~his is the first time a study investigates the relationship between ALM and LVM in a homogeneous group of both low ~~frail and sarcopenic older people.~~ muscle mass and physical performance. Furthermore, the echocardiographic examinations were performed by a single, experienced operator to limit the variability of the calculation of the LVM - a measure that is affected by both the quality of the images and the experience of the operator.

~~Moreover, given the strict inclusion criteria and the cohort precisely defined features, the generalization of results for the entire population of the community of older adults deserves further investigation.~~

~~Since there was collinearity between sex and LVM, we cannot exclude an independent role of sex in determining ALM values. This should be verified in separate groups of males and females with a wider range of ALM values. The relatively low simple size of our group and the narrow dispersion of ALM in both males and females cannot permit such an analysis and therefore it should be considered as a major limitation of the study.~~

~~The increased systolic BP and the high prevalence of hypertensive subjects (70%), related to CV aging process, could have contributed to increase LV mass; however, SBP did not influence the relationship between ALM and LVM in the multivariate analysis.~~

~~In our study we could not demonstrate the existence of other mechanisms to explain the relationship between the muscle heart and SMM. It is well known that SMM has paracrine and endocrine activity that releases modulators for the heart but also for the brain, liver, pancreas, bone and fatty tissue.[41] However, we did not have data on follistatin like 1 (TSTL1), apelin, musclin, fibroblast growth factor 21 (FGF-21), factors released by SMM and exerting beneficial effects on CV system in terms of cardioprotection, vascularization, and optimization of blood pressure.[42]~~

~~The available biobank of SPRINT-T will allow to measure biomarkers and to perform future analyses to test these interesting hypotheses.~~

In conclusion, the present study is the first one that demonstrates a highly significant and positive relationship between ALM and LVM in a ~~frail and sarcopenic cohort of~~ cohort of older adults with low muscle mass and physical performance. Our novel findings emphasize the need of studying skeletal and heart in tandem to better address the complexity of aging process.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Dr. Karen Elena Brothers, who critically revised the manuscript.

Financial Disclosure: The present work was funded by a grant from the Innovative Medicines Initiative - Joint Undertaking (IMI-JU 115621).

Conflicts of interest: None declared

Author contributions: GP, FL and MM contributed to the conception and design of the work. All authors contributed to the acquisition, analysis, or interpretation of data for the work. GP performed all echocardiographic examinations and drafted the manuscript. All authors critically revised the manuscript and gave final approval.

Sponsor's role: Some authors of the present work are partners of the SPRINTT consortium, which is partly funded by the European Federation of Pharmaceutical Industries and Associations (EFPIA).

REFERENCES

1. Cruz-Jentoft AJ, Bahat G, Bauer J, et al Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019;48(1):16–31. doi:10.1093/ageing/afy169.

2. Cesari M, Landi F, Vellas B, Bernabei R, Marzetti E. Sarcopenia and physical frailty: two sides of the same coin. Front Aging Neurosci 2014;6:192. doi:10.3389/fnagi.2014.00192.

~~1.~~3. Saitoh M, Ishida J, Doehner W, et al. Sarcopenia, cachexia, and muscle performance in heart failure: Review update 2016. Int J Cardiol 2017;238:5–11. doi:10.1016/j.ijcard.2017.03.155.

~~2.~~4. Adams V, Linke A, Winzer E. Skeletal muscle alterations in HFrEF vs. HFpEF. Curr Heart Fail Rep 2017;14:489-497. doi:10.1007/s11897-017-0361-9.

~~3.~~5. Okita K, Kinugawa S, Tsutsui H. Exercise intolerance in chronic heart failure-skeletal muscle dysfunction and potential therapies. Circ J 2013;77(2):293-300. doi:10.1253/circj.cj-12-123.

~~4.~~6. Seiler M, Bowen T S, Rolim N, et al. Skeletal Muscle Alterations Are Exacerbated in Heart Failure With Reduced Compared With Preserved Ejection Fraction: Mediated by Circulating Cytokines? Circ Heart Fail 2016;9(9):e003027. doi:10.1161/CIRCHEARTFAILURE.116.003027.

~~5. Cruz-Jentoft AJ, Bahat G, Bauer J, et al Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019;48(1):16–31. doi:10.1093/ageing/afy169.~~

~~6. Cesari M, Landi F, Vellas B, Bernabei R, Marzetti E. Sarcopenia and physical frailty: two sides of the same coin. Front Aging Neurosci 2014;6:192. doi:10.3389/fnagi.2014.00192.~~

7. Gharacholou SM, Tashiro T, Cha SS, Scott CG, Takahashi PY, Pellikka PA. Echocardiographic indices associated with frailty in adults ≥65 years. Am J Cardiol 2015;116(10):1591–1595. doi:10.1016/j.amjcard.2015.08.023.

8. Leibowitz D, Jacobs JM, Gilon D, Lande-Stessman I, Ein-Mor E, Stessman J. Cardiac Structure and Function and Frailty in Subjects Aged 85 and 86 Years. Am J Cardiol 2016;118(5):760–764. doi:10.1016/j.amjcard.2016.06.005.

9. Nadruz W, Jr, Kitzman D, Windham B G, et al. Cardiovascular Dysfunction and Frailty Among Older Adults in the Community: The ARIC Study. J Gerontol A Biol Sci Med Sci 2017;72(7):958–964. doi:10.1093/gerona/glw199.

10. Veronese N, Cereda E, Stubbs B, et al. Risk of cardiovascular disease morbidity and mortality in frail and pre-frail older adults: Results from a meta-analysis and exploratory meta-regression analysis. Ageing Res Rev 2017;35:63–73. doi:10.1016/j.arr.2017.01.003.

11. Kortebein P, Ferrando A, Lombeida J, Wolfe R, Evans WJ. Effect of 10 days of bed rest on skeletal muscle in healthy older adults. JAMA 2007;297(16):1772–1774. doi:10.1001/jama.297.16.1772-b.

12. Perhonen M A, Franco F, Lane LD, et al. Cardiac atrophy after bed rest and spaceflight. J Appl Physiol 2001;91(2):645–653. doi:10.1152/jappl.2001.91.2.645.

13. Dorfman T A, Levine BD, Tillery T, et al. Cardiac atrophy in women following bed rest. J Appl Physiol 2007;103(1):8–16. doi:10.1152/japplphysiol.01162.2006.

14. Keng BMH, Gao F, Teo LLY, et al. Associations between Skeletal Muscle and Myocardium in aging: A syndrome of "Cardio-Sarcopenia"? J Am Geriatr Soc 2019;67:2568-2573. doi:10.1111/jgs.16132.

~~14.~~15. Marzetti E, Cesari M, Calvani R, et al. The "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT) randomized controlled trial: Case finding, screening and characteristics of eligible participants. Exp Gerontol 2018;113:48–57. doi:10.1016/j.exger.2018.09.017.

~~15.~~16. Landi F, Cesari M, Calvani R, et al. The "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT) randomized controlled trial: design and methods. Aging Clin Exp Res 2017;29(1):89–100. doi:10.1007/s40520-016-0715-2.

~~16.~~17. Wareham NJ, Jakes RW, Rennie KL, Mitchell J, Hennings S, Day NE. Validity and repeatability of the EPIC-Norfolk Physical Activity Questionnaire. Int J Epidemiol 2002;31:168–174. doi: 10.1093/ije/31.1.168.

~~17.~~18. Studenski SA, Peters KW, Alley DE, et al. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. J Gerontol A Biol Sci Med Sci 2014;69(5):547–558. doi:10.1093/gerona/glu010.

19. Longobucco Y, Benedetti C, Tagliaferri S, et al. Proactive interception and care of Frailty and Multimorbidity in older persons: the experience of the European Innovation Partnership on Active and Healthy Ageing and the response of Parma Local Health Trust and Lab through European Projects. Acta Biomed 2019;90(2):364–374. doi:10.23750/abm.v90i2.8419.

~~18.~~20. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-383. doi:10.1016/0021-9681(87)90171-8.

~~19.~~21. Pelà G, Crocamo A, Li Calzi M, et al. Sex-related differences in left ventricular structure in early adolescent non-professional athletes. Eur J Prev Cardiol 2016;23(7):777–784. doi:10.1177/2047487315608826.

~~20.~~22. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification. Eur J Echocardiogr 2006;7(2):79–108. doi:10.1016/j.euje.2005.12.014.

~~21.~~23. Kang DO, Park SY, Choi BG, et al. Prognostic Impact of Low Skeletal Muscle Mass on Major Adverse Cardiovascular Events in Coronary Artery Disease: A Propensity Score-Matched Analysis of a Single Center All-Comer Cohort. J Clin Med. 2019;8(5):712. doi:10.3390/jcm8050712.

~~22.~~24. Bahat G, Ilhan B. Sarcopenia and cardiometabolic syndrome: A narrative review. Eur Geriatric Med 2016;7(3):220-223. doi:10.1016/j.eurger.2015.12.012..

~~23.~~25. Bieon CH, Kang KY, Kang SH, NìBae EJ. Sarcopenia is associated with Framingham risk score in the Korean population: Korean National Health and Nutrition examination survey (KNHANES). J Geriatr Cardiol 2015;12:366-372. doi:10.11909/j.issn.1671-5411.2015.04.007.

~~24.~~26. Ochi M, Kohara K, Tabara Y, et al. Arterial Stiffness is associated with low thigh muscle mass in middle-aged to elderly men. Atherosclerosis 2010;212(1):327–332. doi:10.1016/j.atherosclerosis.2010.05.026.

~~25.~~27. Park J, Kim NH, Kim SH, et al. Visceral adiposity and skeletal muscle mass are independently and synergistically associated with left ventricular structure and function: The Korean Genome and Epidemiology Study. Int J Cardiol 2014;176(3):951–955. doi:10.1016/j.ijcard.2014.08.108.

~~26.~~28. Ko BJ, Chang Y, Kang JG, et al. Low relative muscle mass and left ventricular diastolic dysfunction in middle-aged adults. Int J Cardiol 2018;255:118–123. doi:10.1016/j.ijcard.2017.07.089.

~~27. Keng BMH, Gao F, Teo LLY, et al. Associations between Skeletal Muscle and Myocardium in aging: A syndrome of "Cardio-Sarcopenia"? J Am Geriatr Soc JAGS 2019;67:2568-2573. doi:10.1111/jgs.16132.~~

~~28.~~29. Levy D, Garrison RJ, Savage DD, Kannel WB. & Castelli WP. Prognostic Implications Of Echocardiographically Determined Left Ventricular Mass In The Framingham Heart Study. N Engl J Med 1990;322(22):1561–1566. doi:10.1056/NEJM199005313222203.

~~29.~~30. Lovic D, Narayan P, Pittaras A, Faselis C, Doumas M, Kokkinos P. Left ventricular hypertrophy in athletes and hypertensive patients. J Clin Hypertens 2017;19(4):413-417. doi:10.1056/NEJM199005313222203.

31. Rader F, Sachdev E, Arsanjani R, Siegel RJ. Left ventricular hypertrophy in valvular aortic stenosis: mechanisms and clinical implications. Am J Med 2015;128(4):344-352. doi:10.1016/j.amjmed.2014.10.054.

~~30.~~

31.32. Pelà G, Bruschi G, Montagna L, Manara M, Manca C. Left and right ventricular adaptation assessed by Doppler tissue echocardiography in athletes. J Am Soc Echocardiogr 2004;17(3):205–211. doi:10.1016/j.echo.2003.12.004.

32.33. Pelà G, Bruschi G, Cavatorta A, Manca C, Cabassi A, Borghetti A. Doppler tissue echocardiography: myocardial wall motion velocities in essential hypertension. Eur J Echocardiogr 2001;2(2):108–117. doi:10.1053/euje.2000.0057.

~~33. Boengler K, Kosiol M, Mayr M, Schulz R, Rohrbach S. Mitochondria and ageing: role in heart, skeletal muscle and adipose tissue. J Cachexia Sarcopenia Muscle 2017;8(3):349–369. doi:10.1002/jcsm.12178.~~

~~34. Lindskog C, Linné J, Fagerberg L, et al. The Human cardiac and Skeletal Muscle Proteomes defined by transcriptomics and antibody-based profiling. BMC Genomics 2015;16(1):475. doi:10.1186/s12864-015-1686-y.~~

~~35. de Simone G, Devereux RB, Daniels SR, & Meyer RA. Gender differences in left ventricular Growth. Hypertension 1995;26(6 Pt 1):979–983. doi:10.1161/01.hyp.26.6.979.~~

~~36. Drazner MH, Dries DL, Peshock RM, et al. Left ventricular hypertrophy is more prevalent in blacks than in whites in the general population: The Dallas Heart Study. Hypertension 2005;46(1):124–129. doi:10.1161/01.HYP.0000169972.96201.8e.~~

~~37. Araujo AB, Chiu GR, Kupelian V, et al. Lean mass, muscle strength, and physical function in a diverse population of men: a population-based cross-sectional study. BMC Public Health 2010;10:508. doi:10.1186/1471-2458-10-508.~~

38. Pelà G, Li Calzi M, Crocamo A, et al. Ethnicity-related variations of left ventricular remodeling in adolescent amateur football players. Scand J Med Sci Sports 2015;25(3):382–389. doi:10.1111/sms.12238.

39. Demola P, Crocamo A, Ceriello L, et al. Hemodynamic and ECG responses to stress test in early adolescent athletes explain ethnicity-related cardiac differences. Int J Cardiol 2019;289:125–130. doi:10.1016/j.ijcard.2019.04.084.

40. de Simone G, Devereux RB, Kimball T R, et al. Interaction between body size and cardiac workload. Influence on left ventricular mass during body growth and adulthood. Hypertension 1998;31(5):1077–1082. doi:10.1161/01.hyp.31.5.1077.

41. Giudice J, & Taylor JM. Muscle as a paracrine and endocrine organ. Curr Opin Pharmacol 2017;34:49–55. doi:10.1016/j.coph.2017.05.005.

Morley JE. Hormones and Sarcopenia. Curr Pharm Des 2017;23(30):4484–4492. doi:10.2174/1381612823666161123150032.

FIGURE LEGEND

Figure 1 is depicting the correlation between crude value of ALM and LVM (age- and sex-adjusted model).

42.