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Lower muscle tissue is associated with higher pulse wave velocity: a systematic review and meta-analysis of observational study data

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Abstract

Muscle loss and arterial stiffness share common risk factors and are commonly seen in the elderly. We aimed to synthesise the existing literature on studies that have examined this association. We searched electronic databases for studies reporting correlations or associations between a measure of muscle tissue and a measure of arterial stiffness. Meta-analysis was conducted using Fisher's Z-transformed r-correlation (r_Z) values. Pooled weighted r_Z and 95% confidence intervals were calculated in an inverse-variance, random-effects model. Heterogeneity was assessed by the inconsistency index (I^2). Study quality was assessed on a checklist using items from validated quality appraisal guidelines. 1,195 records identified, 21 satisfied our inclusion criteria totalling 8,558 participants with mean age 52 ± 4 years (range: 23-74). Most studies reported an inverse relationship between muscle tissue and arterial stiffness. Eight studies had data eligible for meta-analysis. Muscle tissue was inversely associated with pulse wave velocity in healthy individuals [$r_Z = -0.15$ (95%CI: -0.24, -0.07); $p=0.0006$; $I^2=85\%$; $n=3,577$] and in any population [$r_Z = -0.18$ (-0.26, -0.10); $p<0.0001$; $I^2=81\%$; $n=3,930$]. In a leave-one-out sensitivity analysis, the results remained unchanged. Lower muscle tissue was associated with arterial stiffness. Studies were limited by cross-sectional design. Cardiovascular risk monitoring may be strengthened by screening for low muscle mass and maintaining muscle mass may be a primary prevention strategy.

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Introduction

Sarcopenia describes the progressive loss of muscle mass and function. Whilst there are numerous consensus definitions to identify those with sarcopenia, it is widely accepted that the loss of muscle tissue during ageing can severely impact a person's health. Already, low muscle tissue has been associated with a number of important outcomes of ageing such as falls, fractures, osteoporosis, decreased quality of life and a loss of independence (1). Additionally, as muscle is the largest glucose utilising organ in the body, a loss of muscle tissue may also predispose to an altered glucose metabolism due to a loss in insulin sensitivity (2). Sarcopenia has also been associated with inflammation and cigarette smoking (3, 4). All the above mentioned factors are well-characterised causal influences on the development of cardiovascular (CV) disease, in particular atherosclerotic vascular disease. These observations have lent support to the hypothesis that sarcopenia may be associated with and is a marker of CV disease.

We now understand that much of the CV disease burden, particularly in older people, may be related to so-called "non-traditional" risk factors such as increased arterial stiffness and pulse pressure (5). Arterial stiffness describes the elastic properties of a blood vessel and its ability to expand and contract with pressure changes. Heavily calcified or atherosclerotic vessels change their elastic properties such that they become less compliant (stiffer) and are unable to cope effectively with haemodynamic stresses (6). Increased arterial stiffness augments cardiac workload which may predispose the individual to events such as myocardial infarction or stroke (7).

The gold standard for arterial stiffness measurement is determination of the carotid-femoral pulse wave velocity (PWV) but there is good agreement between other vascular sites such as the brachial-femoral (8). In less compliant vessels, the reflected waveform influences (increases) the systolic blood pressure and the extent of this increase is called the augmentation index (Aix). The pulse pressure (PP) describes the difference in the systolic and diastolic blood pressures. Consistently high PP is indicative of stiffness in the large elastic arteries, in particular the aorta. Overall, arterial stiffness is a simple, validated and independent predictor of cardiovascular morbidity and mortality in hypertension, type 2 diabetes, chronic kidney disease and in elderly populations (8).

Aside from observations that the risk factors for arterial stiffness are also predictive of sarcopenia, there are a number of mechanisms that may directly link the loss of muscle tissue with increased arterial stiffness including inflammatory cytokines, alterations in glucose handling and low physical activity. As such, there is growing observational evidence in humans that low muscle tissue is associated with increased arterial stiffness, however no study exists that has collated this work together and critically analysed the data. Therefore, the aim of this study was to determine if there was an inverse relationship between the amount of muscle tissue and arterial stiffness by way of a

systematic review to survey the literature in this area and where possible, meta-analyse data to quantify the relationship.

Results

Literature search

Database searching identified 2,379 records of which 1,184 were duplicates leaving 1,195 unique records for title/abstract screening. Following screening, 1,160 records were excluded primarily based on the fact the study did not assess an outcome of interest such as PWV, Aix or PP (records excluded on this basis, $n=1,012$) which left 35 records for full-text review. Of these, a further 16 records were excluded mainly because the study did not relate a measure of muscle tissue with arterial stiffness ($n=10$) leaving 19 records left. Snowballing techniques were used in conjunction with hand-searching to identify covert literature. At this stage, we identified a further two articles from hand searching reference lists of full-texts meaning a total of 21 records completely satisfied our inclusion criteria [Figure 1].

Characteristics of study design and patient sampling

Twenty studies were cross-sectional (9-28) and one study was prospective in design but still included baseline cross-sectional data (29). Fifteen studies (10, 11, 13-15, 17-20, 22-26, 28, 29) included a sample of healthy (older or younger) men and women. Three studies sampled participants with type 2 diabetes (T2D) (9, 25, 26), one study selected participants with an ankle-brachial index >0.9 (27); one study selected participants on maintenance haemodialysis (HD) (16); one study selected young healthy astronaut trainees (12) and one study was conducted in patients undergoing occupational therapy for hemiparesis (21). Most studies were conducted in Japanese or Korean populations (15-18, 20-24, 27). Other studies were conducted in USA (12, 19, 28, 29), Brazilian (11), Indian (9), French (10), British (13) and Dutch (14, 25, 26) populations [Table 1].

Quality assessment

All but one study (12) achieved a quality score of at least 5 (out of 10). Six studies were deemed high quality achieving a score greater than 8 (10, 13, 15, 22, 28, 29). Commonly reported items were reporting of study aims and outcomes; reporting important confounding factors such as age, sex and BMI and measuring muscle tissue using validated methods. Inclusion/exclusion criteria, sample generalisability, adjustment analyses for multiple confounding factors, using validated methods to quantify arterial stiffness and identifying study limitations were variously reported (Supplementary table 1).

Sample demographics

Study population varied from a minimum of 10 (12) to 2,272 (29). The average number of participants per study across the included literature was 387 and the total number of participants across all 21 included studies was 8,558. Three studies included only men (10, 12, 20) and two studies included only women (11, 23) and there was an average of 51% males per study and 49% females per study. The lowest mean age was 23 years (19) and the highest was 74 years (29). Mean age for the study sample was not reported in three studies (20, 21, 23) but these reported age ranges. Mean BMI ranged from a minimum 21.9kg/m² (24) to a maximum of 30.2 kg/m² (9). Mean BMI for the sample was not reported in four studies (12, 20, 21, 23) [Table 1].

Assessment of muscle tissue

Most studies reported a measure of muscle mass (9-15, 17, 18, 21-26, 28, 29) (Table 3). Five studies reported measure of muscle cross-sectional area (12, 16, 19, 20, 27). Muscle tissue was predominantly measured as either a whole body assessment (10-13, 15, 21, 22, 29) or as an appendicular assessment (9, 14, 17, 18, 23, 24, 28). Other studies measured muscle tissue or cross-sectional area in specific body regions such as the thigh (16, 19, 20, 27) or trunk (25, 26, 29). Most studies used radiological imaging to determine lean tissue including dual-energy x-ray absorptiometry (DXA) (10, 14, 15, 17, 21, 23-26, 28, 29), computed tomography (CT) (12, 16, 17, 20, 27) or peripheral quantitative computed tomography (pQCT) (19). Other studies utilised bioelectrical impedance analysis (BIA) (9, 11, 13, 18, 22). Assessment of sarcopenia was performed in seven studies (11, 15, 17, 22-24, 29) where in all cases the operational definition consisted of skeletal/appendicular muscle mass relative to height-squared. Six of these studies utilised a cut-point for the definition, including the previously published Baumgartner (30) definition (17, 29) and other user defined cut-points from a reference population (11, 15, 23, 24) [Table 2].

Assessment of arterial stiffness

The majority of studies assessed PWV (9, 10, 13-17, 20-29) other studies assessed PP (11, 19), Aix (18, 19) and one study assessed leg compliance (12) [Table 3]. For studies assessing PWV, eight studies assessed brachial-ankle PWV (15-17, 20, 21, 23, 24, 27); seven studies assessed carotid-femoral PWV (9, 10, 14, 25, 26, 28, 29) and one study assessed carotid-ankle PWV (22).

Relationship between muscle tissue and arterial stiffness

Thirteen studies reported on the relationship between measures of muscle tissue and measures of arterial stiffness (9-16, 19-21, 28, 29) [Table 4]. The majority of these studies reported an r-correlation statistic to describe the strength and direction of the relationship between the amount of muscle tissue and the measure of arterial stiffness (9, 11-13, 15, 16, 19-21, 28, 29). Two studies provided a β -statistic to describe the direction of the relationship between muscle tissue and arterial

stiffness (10, 11, 14). For r-correlations relating muscle to PWV, the magnitude of the statistic ranged from -0.02 (for the correlation between arm mass and PWV) (9) and -0.4795 (trunk mass and PWV) (28) in unadjusted analyses. In adjusted analyses, r-correlations ranged from -0.0082 (arm mass in women and PWV) (29) adjusting for multiple confounding factors, and -0.67 (whole body muscle mass) adjusting for age, bone mineral content, fat mass and intramuscular fat (21). In studies reporting r-correlations for PP one study reported a negative correlation (11) and another reported a positive correlation (19). Calf muscle area was negatively correlated with Aix after adjustment of height and sex in one study (19). In the study evaluating leg compliance, whole body lean mass was positively correlated with compliance whilst calf muscle area was negatively correlated (12). For studies reporting a β -statistic, all three studies reported a negative relationship between muscle mass, peripheral muscle mass and PWV and between skeletal muscle index (SMI) and PP (10, 11, 14). Three studies determined that the relationships were significant in men and not in women (9, 20, 29) and another study determined thigh muscle area was significant in a sample of middle aged to elderly men but was non-significant when the group was stratified into those with type 2 diabetes mellitus and those that did not (20). Overall, only four studies did not report a significant relationship (10, 12-14) between muscle tissue and arterial stiffness. There was a consistent trend across all studies for measures of muscle tissue at various sites in the body to be negatively related to arterial stiffness (mostly PWV) in unadjusted and multiple adjusted analyses.

Meta-analysis of studies reporting correlation statistics

The most complete and consistent data related to the correlation between muscle tissue with PWV which included data from eight studies (9, 13, 15, 16, 20, 21, 28, 29). These data were synthesised into a meta-analysis model. In studies enrolling only healthy participants, muscle tissue was inversely and significantly correlated with PWV ($r_z = -0.15$ and 95% confidence interval = -0.24, -0.07; $p=0.0006$, $n=3577$, five studies) with substantial heterogeneity ($I^2 = 85\%$) [Figure 2]. When data was included from studies enrolling participants from specific patient groups, the results remained similar PWV ($r_z = -0.18$; -0.26, -0.10; $p<0.0001$, $n=3930$, eight studies; $I^2 = 81\%$) [Figure 3]. In sensitivity analyses [Table 5], considering only studies with a mean sample age of 60 years there was data available from two studies (20, 29) and there was a significant negative relationship between muscle tissue and PWV ($r_z = -0.12$; 95% CI: -0.22, -0.01; $p=0.02$, $I^2=85\%$). Similarly, in studies whose mean sample age was <60 years, there was present a significant negative relationship between muscle tissue and PWV ($r_z = -0.22$; 95% CI: -0.35, -0.09; $p=0.0009$, $I^2=72\%$). When the studies were stratified according the imaging modality employed, results were similar whether DXA ($r_z = -0.19$; 95% CI: -0.32, -0.07; $p=0.002$, $I^2=89\%$) or other modalities ($r_z = -0.16$; 95% CI: -0.22, -0.10; $p<0.0001$, $I^2=42\%$, fixed model applied) were used. Finally, in order to examine the potential effect the site of muscle tissue assessment, we stratified the studies according to whether the whole body muscle tissue was assessed ($r_z = -0.11$; 95% CI: -0.20, -0.02; $p=0.02$, $I^2=82\%$) or regional

muscle tissue ($r_z = -0.24$; 95% CI: $-0.34, -0.13$; $p < 0.0001$, $I^2 = 59\%$) and found results similar to other analyses. Finally, we performed a leave-one-out sensitivity analysis and omission of any one study did not alter the final result [Table 6].

Discussion

Sarcopenia, the progressive loss of muscle mass and function, has been associated with CV disease. Arterial stiffness is emerging as an important CV risk factor and given the common risk factors between sarcopenia and arterial stiffness observational studies have demonstrated the concomitant incidence of low muscle mass with increased arterial stiffness. This systematic review and meta-analysis collated results from observational studies which collectively demonstrate that low muscle tissue is consistently associated with increased arterial stiffness. Whilst heterogeneity in terms of study design, population samples and methodology may bias and limit the interpretation of the quantitative meta-analysis component of this review; given the consistent inverse relationship seen across all studies included in this review, there is a biological interaction which may not necessarily be captured statistically due to heterogeneity. For this reason, the present study adds value to the literature as it highlights the need to develop high quality prospective studies conducted in healthy populations using gold-standard techniques to determine if low muscle tissue is both predictive and causative of arterial stiffness.

The causal biological link between low muscle tissue and increased arterial stiffness is only assumed given these data were largely cross-sectional (only one study identified was longitudinal) (29). Therefore, the possible mechanisms by which low muscle tissue may contribute to increased arterial stiffness are unclear. It has also been suggested that increased arterial stiffness proceeds the loss of muscle tissue as heavily calcified and stiff blood vessels may restrict nutrient supply to muscle tissue causing its atrophy. However, there exists a number of pathways common to both muscle loss and increased arterial stiffness including insulin resistance, oxidative stress and inflammation which may offer mechanism insights (31).

Muscle is the largest site of glucose disposal and its loss can impair glucose metabolism which may result in insulin insensitivity/resistance (32). Several human studies suggest that impaired glucose tolerance and insulin resistance adversely affects the mechanical properties of arteries (33). The mechanisms that lead to adverse vascular changes are thought to occur through oxidative stress and endothelial damage. In a Korean cohort, PWV positively correlated with insulin and had higher concentrations of isoprostane 8-epi PGF 2α (an oxidative stress marker) in those with impaired fasting glucose (34). Further, in a hypertensive older adult sample, statin therapy improved the oxidative markers *N*-(epsilon)-carboxymethyl-lysine, Von Willebrand factor and copper/zinc-containing superoxide dismutase. These improvements were correlated with improvements in brachial-ankle

PWV suggesting that oxidative stress precedes increases in arterial stiffness possibly by increasing reactive oxide species (35). Taken together, these studies indicate that impaired glucose metabolism and alterations in oxidative stress at the vascular endothelium directly contribute to vessel compliance and offer a link between how muscle biology may influence the development of arterial stiffness.

Chronic inflammation is another well described mechanism of muscle loss. Inflammatory mediators such as interleukin-6 (IL-6), tumour necrosis factor- α and C-reactive protein can directly affect muscle catabolism and may also act indirectly by lowering growth hormones (36). These inflammatory pathways are shared in the pathogenesis of arterial stiffening. Aortic PWV correlated positively with a number of inflammatory markers such as IL-6, transforming growth factor- β 1, and white blood cell count in dialysis patients (37). Further, osteocalcin, a marker of bone formation produced by osteoblasts, was negatively correlated with aortic PWV after multiple regression. Given osteocalcin's role in bone remodelling, this finding suggests bone biology may influence arterial stiffness and indeed elevated arterial stiffness has been demonstrated in postmenopausal women with osteoporosis (38).

A number of important limitations of the included studies could contribute to the risk of bias. Firstly, the majority of studies were cross-sectional in design. Given that several of these did not adjust for multiple confounders (9, 16, 28), there may be residual confounding in our analysis. Secondly, some studies had small sample sizes [eg. $n=10$ (12)] or the cohort was from a specific patient population [eg. hemiparesis in-patients (21)] and thus their results may not be generalisable. Thirdly, the use of medications was poorly reported and this may potentially impact on blood pressure, blood lipid profile and other risk factors of arterial stiffening. Few studies reported on the amount of objectively measured physical activity undertaken by study participants. This is significant because physical activity is important in maintaining muscle mass and decreasing arterial stiffness by augmenting oxidative stress markers, particularly in older age (39, 40). Finally, for stiffness assessment some studies used oscillometric methods and others employed tonometric methods and similarly there were different methods used to quantify muscle tissue (eg. DXA and CT). There is good agreement between these methods to quantify both arterial stiffness (41) and muscle tissue (42) though these different methods employed across this literature reflects the lack of a standardised approach to measuring arterial compliance and muscle tissue. In attempt to overcome this potential limitation, our sensitivity analyses found similar results when studies were stratified by imaging modality.

The limitations of the present study were that we used aggregate data from a small number of studies. This limited our ability to perform stratified analyses from individual patient data according important confounding factors rather than study-level variables. We also grouped together a

heterogeneous sample of studies (Japanese, European and North American populations). Overall, we attempted to overcome the obvious heterogeneity in study methods by employing random-effects models which offer more conservative effect estimates and in performing a number of sensitivity analyses restricting each analysis to studies of similar methodology or population sample. Specifically, our study may be limited by crude measures of body composition which may not accurately reflect the degree of muscle loss and disability burden across diverse populations (43). Most data were from cross-sectional studies which do not imply causation. We did not restrict our search criteria to exclude interventional studies or other observational studies. Thus, our study highlights the need for more prospective investigations as cross-sectional relationships do not accurately reflect low muscle tissue. We have considered different measures of muscle tissue to all indicate low muscle mass. This is not entirely accurate as differences in muscle cross-sectional area may reflect changes in muscle fibre size as well as fibre atrophy (44). We have also considered different vascular sites such as brachial-ankle and carotid-femoral PWV as measures of arterial stiffness. However, there is good agreement between these measure and we reasoned that in order to maximise the statistical power of our analyses, it was prudent to consider these measurements together rather than conduct separate brachial-ankle or carotid-femoral PWV analyses. Overall, these differences in study methodology highlight the need for a more standardised approach which would ideally involve measurement of aortic PWV and conducted in healthy individuals.

In conclusion, we identified numerous observational studies that reported on the correlation or association of muscle tissue and arterial stiffness. These results suggest that there was a consistent inverse relationship between the amount of muscle tissue and the level of arterial stiffness across diverse population groups. This finding was consistent across several sensitivity analysis accounting for important risk factors of muscle loss and arterial stiffness. Given the lack of prospective data, determination of whether low muscle mass predicts increases in arterial stiffness over time is warranted. Further, it remains to be seen whether improving muscle mass concurrently improves arterial stiffness. Since, arterial stiffness is predictive of CV mortality and events and hence these events could accelerate the transition of people with low muscle mass to greater disability and mortality, this systematic review and meta-analysis suggests it may be useful to consider the cardiovascular health of people with low muscle mass.

Methods:

Study focus

This study was conducted in accordance with the guidelines outlined in the MOOSE statement (Meta-analysis Of Observational Studies in Epidemiology) (45). Studies were eligible if they were observational in design (cross-sectional or longitudinal/prospective), reported a measure of muscle tissue, reported a measure of arterial stiffness and performed a statistical assessment of the relationship between these measures in order to determine the linearity between these measures. Specific exclusion criteria were non-observational studies, animal or cell-based studies, reviews and other meta-analyses and individual case reports. We restricted our analysis to observational studies only as we reasoned that we wanted to be able to establish the natural incidence of both low muscle tissue and increased arterial stiffness. Interventional studies could, depending on the type intervention, potentially alter measures of both arterial stiffness and muscle tissue and thus affect the association between these measures.

Literature search

Records were retrieved by searching MEDLINE (archives from 1966-2016) and EMBASE (1946-2016) databases. Records were identified on the 23rd of February 2016 using a search string detailed in Supplementary Table 1. Titles and abstracts of identified records were screened by a single reviewer (AJR). Reference lists were manually scanned by hand searching. Following title and abstract screening, full text articles were interrogated to determine eligibility for inclusion. For full-texts unavailable publically, attempts were made to obtain these or specific data directly from the authors to ensure eligibility.

Data extraction

Data capture was performed independently by two reviewers (AJR, MNK) with the aid of a data extraction template. The information captured during data extraction was: the name of the first author, year of publication, study design, sample demographics, measurement of muscle tissue and arterial stiffness, statistical analyses employed and study limitations. These data were then tabulated into a format that enabled comparison of relevant study details. Data relating to the relationship between muscle tissue and arterial stiffness were also tabulated.

Quality assessment

Further to data extraction, we performed a quality assessment of studies included in the systematic review. As no standardised quality assessment checklist exists for observational studies reporting on the association between muscle tissue and arterial stiffness, we designed a ten-point semi-quantitative questionnaire using preferred reporting items from MOOSE to judge quality of included studies. Items in our checklist related to study design, generalisability, outcome measurement, statistical analysis and limitations. Items were checked as either “yes”, “no” or

“unclear” and a score of greater than or equal to 8 (yes responses out of 10) was deemed high quality; scores 5-7 were good quality and scores less than or equal to 4 were poor quality (Specific questions are provided in Supplementary Table 2).

Statistical operations

Meta-analysis eligibility:

Studies were included for meta-analysis if they first satisfied the inclusion and exclusion criteria for systematic review and then reported correlation or association statistics (for example Pearson's r correlation coefficient, standardised (β) coefficient, R^2 correlation coefficient or odds ratios) in assessing the relationship between muscle tissue and arterial stiffness. Studies were excluded from meta-analysis, but still kept in the qualitative review, if they reported only descriptive statistics for measures of arterial stiffness according to groups defined on the basis of the amount of muscle tissue (eg. above or below the median amount of muscle tissue). For studies that reported on multiple sites of muscle tissue (eg. leg or arm muscle mass) preference for inclusion in meta-analysis dataset was arbitrarily first given to whole body, then appendicular, then leg, then arm, then trunk measures.

Meta-analysis:

Data was first tabulated into a format that enabled visualisation of group data. In order to pool correlation statistics together, we converted r -correlation coefficients into to the Fisher's z scale using the Fisher's Z transformation: $Z = 0.5 \times \ln\left(\frac{1+r}{1-r}\right)$ and calculated the standard error: $SE = \sqrt{\left(\frac{1}{n-3}\right)}$ (46). The Fisher's Z score and its variance are used in the analysis. These data were then synthesised into an inverse-variance model to determine the pooled weighted r correlation and 95% confidence interval. Heterogeneity was determined by the inconsistency statistic (I^2) where a DerSimonian and Laird random-effects model was applied if I^2 was greater than 50%. A number of sensitivity analyses were performed in order to examine the possible effects of factors that may contribute to muscle loss and arterial stiffness. To assess the effect of age, we divided our analysis into studies with a mean age of ≥ 60 years and studies with a mean age < 60 years and performed the same operations as above. Similarly, though there is good agreement between imaging modalities, to account for potential differences in lean mass measurements we stratified the analysis separating those studies who used DXA and those who used another modality. Finally, whole body muscle mass assessment would best reflect low muscle mass though some studies assessed regional muscle mass such as thigh muscle mass, therefore to investigate the potential effect of imaging site we stratified the analysis into whole body muscle mass assessment and regional muscle mass assessment. Additionally we performed a leave-one-out sensitivity analysis were, sequentially, each study was excluded from the meta-analysis

model in order to determine if the summary effect was overly influenced by any single study (which may be the case for a large study group with smaller studies). All statistical operations were performed using RevMan v5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration 2012) and in consultation with a statistician (MNK).

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Author contributions

AJR designed the study, performed literature searches, data extraction, data analysis, constructed tables and figures and wrote the first draft. MNK Performed data extraction and data analysis. VS provided expert advice on arterial stiffness. PE provided expert advice on muscle biology. DS provided expert advice on muscle biology, contributed to data analysis and table/figure presentation and contributed to manuscript development. All authors reviewed the final draft

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Table 1. Study details and sample demographics

Study & Year	Design	Sample	Country	n	M-F%	Age	BMI (kg/m ²)	T2D	SBP	Inclusion-Exclusion criteria
Abbatecola 2012 (32)	Prospective	Community dwelling older adults	USA	2272	50-50	73.7	27.2	14.30	134.8	No difficulty walking quarter-mile, climbing 10 steps and performing basic activities of living. Free from life-threatening illness
Anoop 2015 (12)	Cross-sectional	T2D	India	168	65-35	50.3	30.15	100	128.7	n/r or unclear
Benetos 2009 (13)	Cross-sectional	Community dwelling older men	France	169	100-0	69.3	27.3	n/r	137	I: >60y, eligible for DXA, no osteoporosis, no CVD, no atrial fibrillation
Coelho 2015 (14)	Cross-sectional	Community dwelling older adults	Brazil	130	0-100	64.3	26.85	4.85	140.4	I: >60y; E: HRT, psychotropic drugs, CVD, pulmonary disease, psychiatric disease, musculoskeletal disorders, at risk of falls
Convertino 1988 (15)	Cross-sectional	Young healthy men	USA	10	100-0	36	n/r	n/r	n/r	E: Taking medications, non-smoking
Corden 2013 (16)	Cross-sectional	Community dwelling adults	UK	221	43-57	40.3	25.5	n/r	120.4	E: CVD, meds for hypertension, DM or cholesterol, pregnant or lactating women
Ferreira 2004 (17)	Cross-sectional	Community dwelling adults	Netherlands	336	48-52	35.6	24.04	n/r	116.2	n/r or unclear
Hong 2014 (18)	Cross-sectional	Community dwelling adults	Korea	452	38-62	53	24.19	n/a	121.9	I: No DM, CVD, hypertension, malignant disease, renal disease, hepatic disease. No meds, alcohol consumption >140g/week, Hepatitis B or C, herbal medication use in previous 6 months
Kato 2011 (19)	Cross-sectional	HD	Japan	161	70-30	61	20.7	n/r	138	E: >80y, advanced cancer
Kim 2011 (20)	Cross-sectional	Community dwelling adults	Korea	510	32-68	53.6	24.38	n/a	121.8	I: No DM, CVD, hypertension, malignant disease, renal disease, hepatic disease. No meds, alcohol consumption >140g/week, Hepatitis B or C, herbal med use in previous 6 months

Lee 2014 (21)	Cross-sectional	Community dwelling older adults	Korea	428	42-58	70.9	24	n/r	132	E: patients with incomplete testing records
Loenneke 2013 (22)	Cross-sectional	Community dwelling adults	USA	27	48-52	23	24.4	n/r	118	I: non-smoker, no CVD or metabolic disturbance
Ochi 2010 (23)	Cross-sectional	Community dwelling middle age to older adults	Japan	496	100-0	n/r	n/r	n/r	n/r	I: free of cerebrovascular events
Okabe 2004 (24)	Cross-sectional	OT in-patients	Japan	24	58-42	n/r	n/r	n/r	n/r	I: Had cerebrovascular event in previous 3 months, physically stable
Sampaio 2014 (25)	Cross-sectional	Community dwelling older adults	Japan	175	48-52	73.6	23.02	11.7	^41.30 %	I: >65y, independent. E: mild cognitive impairment, uncontrolled CVD/metabolic disease, orthopaedic conditions, risk of falls
Sanada 2012 (26)	Cross-sectional	Community dwelling older women	Japan	533	0-100	30-84	n/a	n/r	122.3	I: Free of CVD, not taking beta-blockers or steroids or HRT. Free of chronic disease. Mod PA
Sanada 2010 (27)	Cross-sectional	Community dwelling older adults	Japan	959	50-50	28	21.9	n/r	125.9	I: active and free of CVD. E: use of beta-blockers, steroids, HRT
Snijder 2009 (28)	Cross-sectional	Older men and women with and without diabetes	Netherlands	456	50-50	68.3	26.15	18.7	n/r	n/r or unclear
Snijder 2004 (29)	Cross-sectional	Older men and women with and without diabetes	Netherlands	488	50-50	69	26.4	22	140.7	n/r or unclear
Tabara 2009 (30)	Cross-sectional	ABI>0.9	Japan	407	40-60	68	23.18	11.1	128.9	n/r or unclear
Wohlfahrt 2015 (31)	Cross-sectional	Healthy, non-obese	USA	136	44-56	45	24.3	n/a	114	I: Age 30-65y BMI 18.5-29.9kg/m ² E: liver disease, ESRD, lung cancer, cancer, hypertension, T2D, pregnancy, lactating, excessive adiposity, metabolic diseases, previous

Table 2. Assessment of muscle tissue

Study	Parameter	Region	Modality	Device	Sarcopenia defined	Cut-point
Abbatecola (32)	Muscle mass	Whole body	DXA	Hologic	ASM/h ²	Baumgartner (33)
Anoop 2015 (12)	Muscle mass	Appendicular	BIA	Tanita	n/d	n/a
Benetos 2009 (13)	Muscle mass	Whole body	DXA	Hologic	n/d	n/a
Coelho 2015 (14)	Muscle mass	Whole body	BIA	Tanita	SMI (kg/m ²)	Lower tertile (<15.68kg/m ²)
Convertino 1988 (15)	Muscle mass and CSA	Whole body, calf	Hydrostatic weighing, CT	Siemens	n/d	n/a
Corden 2013 (16)	Muscle mass	Whole body	BIA	InBody	n/d	n/a
Ferreira 2004 (17)	Muscle mass	Trunk and appendicular	DXA	Hologic	n/d	n/a
Hong 2014 (18)	Muscle mass	Whole body and legs	DXA	Hologic	SMI (kg/m ²)	1SD below reference
Kato 2011 (19)	Muscle CSA	Thigh	CT	n/r	n/d	n/a
Kim 2011 (20)	Muscle mass	Appendicular and mid-thigh	DXA, CT	Hologic	ASM/h ²	Baumgartner (33)
Lee 2014 (21)	Muscle mass	Appendicular	BIA	Biospace	n/d	n/a
Loenneke 2013 (22)	Muscle CSA	Femoral	pQCT	Stratec	n/d	n/a
Ochi 2010 (23)	Muscle CSA	Femoral	CT	GE	n/d	n/a
Okabe 2004 (24)	Muscle mass	Whole body and legs	DXA	Hologic	n/d	n/a
Sampaio 2014 (25)	Muscle mass	Absolute	BIA	n/r	SMI (kg/m ²)	n/r
Sanada 2012 (26)	Muscle mass	Appendicular	DXA	Hologic	SMI (kg/m ²)	*Below a median of 6.70
Sanada 2010 (27)	Muscle mass	Appendicular	DXA	Hologic	SMI (kg/m ²)	*Class 1=7.77-6.12; Class 2=6.87-5.46
Snijder 2009 (28)	Lean mass	Trunk and Leg	DXA	Hologic	n/d	n/a
Snijder 2004 (29)	Lean mass	Trunk and Leg	DXA	Hologic	n/d	n/a

Tabara 2009 (30)	Muscle CSA	Femoral	CT	GE	n/d	n/a
Wohlfahrt 2015 (31)	Lean mass	Trunk and appendicular	DXA	GE Lunar	n/d	n/a

*Used a Japanese reference population

Table 3. Assessment of Arterial stiffness

Study	Parameter	Vascular site	Method	Device
Abbatecola (32)	PWV	Carotid-femoral	Doppler (transcutaneous probes)	Park Medical Electronics
Anoop 2015 (12)	PWV	Carotid-femoral	Applanation tonometry	SphygmoCor
Benetos 2009 (13)	PWV	Carotid-femoral	Applanation tonometry	PulsePen
Coelho 2015 (14)	PP	n/a	Oscillometric	Microlife
Convertino 1988 (15)	Leg Compliance*	Calf	Oscillometric	n/r
Corden 2013 (16)	PWV	Aortic arch	Flow waveform analysis	CMRtools (Cardiovascular Imaging Solutions)
Ferreira 2004 (17)	PWV	Carotid-femoral	Volume-plethysmographic apparatus	Komaki
Hong 2014 (18)	PWV	Brachial-ankle	Volume-plethysmographic apparatus	Komaki
Kato 2011 (19)	PWV	Brachial-ankle	Oscillometric	Fukuda Denshi
Kim 2011 (20)	PWV	Brachial-ankle	Volume-plethysmographic apparatus	Komaki
Lee 2014 (21)	Aix	Radial	Pulse Wave Analysis	Omron
Loenneke 2013 (22)	Aix, PP	Radial	Applanation tonometry	SphygmoCor
Ochi 2010 (23)	PWV	Brachial-ankle	Volume plethysmographic apparatus	Omron
Okabe 2004 (24)	PWV	Brachial-ankle	Volume-plethysmographic apparatus	Komaki
Sampaio 2014 (25)	PWV	Carotid-ankle	Oscillometric	Fukuda Denshi
Sanada 2012 (26)	PWV	Brachial-ankle	Volume-plethysmographic apparatus	Komaki
Sanada 2010 (27)	PWV	Brachial-ankle	Volume-plethysmographic apparatus	Komaki
Snijder 2009 (28)	PWV	Carotid-femoral	Oscillometric	Collin Press-Mate
Snijder 2004 (29)	PWV	Carotid-femoral	Oscillometric	Collin Press-Mate
Tabara 2009 (30)	PWV	Brachial-ankle	Oscillometric	Omron
Wohlfahrt 2015 (31)	PWV	Carotid-femoral	Applanation tonometry	SphygmoCor

* Defined as % change in blood volume relative to change in blood pressure

Table 4. Correlations and associations between lean tissue and arterial stiffness

Study	Sample	n	Lean tissue	Outcome	r	R ²	β	p	Adjustments	Meta-analysis
Anoop	Female	58	Right leg	PWV	-0.21	n/r	n/r	0	Unadjusted	*
			Left leg	PWV	-0.23	n/r	n/r	0	Unadjusted	
			Right arm	PWV	-0.07	n/r	n/r	0.55	Unadjusted	
			left arm	PWV	-0.02	n/r	n/r	0.56	Unadjusted	
			trunk	PWV	-0.04	n/r	n/r	0.74	Unadjusted	
	Male	110	Right leg	PWV	-0.16	n/r	n/r	0.09	Unadjusted	*
			Left leg	PWV	-0.18	n/r	n/r	0.05	Unadjusted	
			Right arm	PWV	-0.18	n/r	n/r	0.05	Unadjusted	
			left arm	PWV	-0.18	n/r	n/r	0.04	Unadjusted	
			trunk	PWV	-0.19	n/r	n/r	0.04	Unadjusted	
Benetos		169	Lean mass	PWV	n/r	n/r	-0.25	0.36	Age, fat mass (kg), BMD	
Coelho		130	SMI	PP	-0.7	0.49	-0.226	0.05	Unadjusted	
			SMI	PP	-0.417	0.174	0.98	n/s	Age, metabolic syndrome, smoking, HTN, DM, height, physical function	
Convertino		10	Lean mass	Leg C	0.39	n/r	n/r	0.26	Unadjusted	
			Calf CSA	Leg C	-0.61	0.04	n/r	0.06	Unadjusted	
Corden		221	LMI	PWV	-0.07	n/r	n/r	0.191	Age, sex, MAP, %body fat	*
Hong		552	SMI	PWV	-0.16	n/r	n/r	<0.001	Age	*
Ferreira		336	PLM	PWV		n/r	-0.37	n/r	Sex, height, MAP, body composition, VO ₂ max, Total/HDL, TG, HbA1c, HR	
Kato	All	161	TMA	PWV	-0.18	n/r	n/r	<0.05	Unadjusted	*
	non-DM	127	TMA	PWV	-0.18	n/r	n/r	0.09	Unadjusted	**

Loennecke	DM	34	TMA	PWV	-0.24	n/r	n/r	0.24	Unadjusted	**
		27	Muscle CSA	PP	0.166	n/r	n/r	0.428	Height, sex	
			Muscle CSA	Aix	-0.489	n/r	n/r	0.013	Height, sex	
Ochi	Men	496	Calf CSA	PWV	-0.34	n/r	n/r	<0.001	Weight	*
	Women		Calf CSA	PWV	-0.09	n/r	n/r	0.1	Weight	*
Okabe		24	Muscle mass	baPWV	-0.67	n/r	n/r	<0.01	Age, BMC, fat mass, IMAT	*
				faPWV	-0.627	n/r	n/r	<0.01	Age, BMC, fat mass, IMAT	
Wohlfarht		136	Arm	PWV	-0.424	0.18	n/r	<0.05	Unadjusted	
			Leg	PWV	-0.4	0.16	n/r	n/s	Unadjusted	*
			Trunk	PWV	-0.4795	0.23	n/r	<0.01	Unadjusted	
			Total	PWV	-0.447	0.2	n/r	<0.05	Unadjusted	
Abbetecola	Men	2272	SI	PWV	-0.09	n/r	n/r	0.01	Age, diabetes, site, height, BMI, SBP, PAD, CHD, smoking, IL-6, physical activity, race,	
			arm	PWV	-0.106	n/r	n/r	0.0005	Age, diabetes, site, height, BMI, SBP, PAD, CHD, smoking, IL-6, physical activity, race,	*
			leg	PWV	-0.217	n/r	n/r	0.0003	Age, diabetes, site, height, BMI, SBP, PAD, CHD, smoking, IL-6, physical activity, race,	
	Women		arm	PWV	-0.0082	n/r	n/r	0.6849	Age, diabetes, site, height, BMI, SBP, PAD, CHD, smoking, IL-6, physical activity, race,	*

n.b. data shown in italics were sourced from authors or calculated from published data. ** indicates data was treated separately in meta-analysis.

Abbreviations: Aix = augmentation index; ba = brachial-ankle; BMC = bone mineral content; BMD = bone mineral density; BMI = body mass index; β = Beta coefficient; CHD = coronary heart disease; CSA = cross-sectional area; DM = diabetes mellitus; fa = femoral-ankle; HbA1c = glycated haemoglobin; ; HR = heart rate; HTN = hypertension; IL-6 = interleukin-6; IMAT = intramuscular fat; ; Leg C = leg compliance; LMI = lean mass index, MAP = mean arterial pressure; n/r not reported; PAD = peripheral artery disease; PLM = peripheral lean mass; PP= pulse pressure; PWV = pulse wave velocity; r = r-correlation coefficient; R^2 = R-squared correlation coefficient; SMI = skeletal muscle index, TG= triglycerides TMA = thigh muscle area;

Table 5. Sensitivity analyses

Stratification		Studies (n)	Effect	95%CI	p	I ²
Age	Mean age ≥ 60 y	2 (2768)	-0.12	-0.22, -0.01	0.02	85
	Mean age <60y	5 (1162)	-0.22	-0.35, -0.09	0.0009	72
Imaging modality	DXA	4 (2884)	-0.19	-0.32, -0.07	0.002	89
	Non-DXA	4 (1046)	-0.16	-0.22, -0.10	<0.0001	42
Muscle tissue assessment	Regional	4 (961)	-0.24	-0.34, -0.13	<0.0001	59

Table 6. Leave-one-out sensitivity analysis

Study omitted	n	Fisher transformed r-correlation [95% CI]	p
Okabe 2004	3906	-0.16 [-0.23, -0.08]	<0.0001
Wolhfarht 2015	3794	-0.15 [-0.22, -0.08]	<0.0001
Ochi 2010	3434	-0.17 [-0.25, -0.08]	<0.0001
Anoop 2015	3762	-0.18 [-0.27, -0.09]	<0.0001
Kato 2011	3769	-0.18 [-0.26, -0.09]	<0.0001
Hong 2014	3508	-0.18 [-0.27, -0.09]	<0.0001
Abbatecola 2012	1658	-0.20 [-0.30, -0.10]	<0.0001
Corden 2013	3709	-0.19 [-0.28, -0.11]	<0.0001

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