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Authors: Dallaway, A.*[a,b], Kite, C.[c,d], Griffen, C.[a,b], Duncan, M.[a,e], Tallis, J.[a,e], Renshaw, D.[a], Hattersley, J.[a,b]

Affiliations: [a]Centre for Sport, Exercise and Life Sciences, Faculty of Health and Life Sciences, Science and Health Building, Whitefriars Street, Coventry University, Coventry, CV1 2DS, United Kingdom; [b]Human Metabolic Research Unit, University Hospitals Coventry and Warwickshire, Clifford Bridge Rd, Coventry, CV2 2DX, United Kingdom; [c]School of Life and Health Sciences, Cell and Tissue Biomedical Research Group, Aston University, Aston Triangle, Birmingham, B4 7ET, United Kingdom; [d]Centre for Active Living, University Centre Shrewsbury, University of Chester, Guildhall, Frankwell Quay, Shrewsbury, SY3 8HQ, United Kingdom; [e]School of Life Sciences, Faculty of Health and Life Sciences, Science and Health Building, Whitefriars Street, Coventry University, Coventry, CV1 2DS, United Kingdom

***Corresponding author:** Alexander Dallaway, Centre for Sport, Exercise and Life Sciences, Faculty of Health and Life Sciences, Science and Health Building, Whitefriars Street, Coventry University, Coventry, CV1 2DS, United Kingdom, dallawaa@uni.coventry.ac.uk, Tel: +44 (0) 7849 771844

Abstract

Background: Morphological changes of the lumbar spine muscles are not well characterised with ageing. To further the understanding of age-related degeneration of the lumbar spine musculature, normative morphological changes that occur within the paravertebral muscles must first be established.

Methods: A systematic review and meta-regressions were conducted adhering to PRISMA guidelines. Searches for published and unpublished data were completed in June 2019.

Results: Searches returned 4781 articles. 34 articles were included in the quantitative analysis. Three-level meta-analyses showed age-related atrophy (r = -0.26; 95% CI: -0.33, -0.17) and fat infiltration (r = 0.39; 95% CI: 0.28, 0.50) in the lumbar paravertebral muscles. Degenerative changes were muscle-specific and men (r = -0.32; 95% CI: -0.61, 0.01) exhibited significantly greater muscle atrophy than women (r = -0.24; 95% CI: -0.47, 0.03). Imaging modality, specifically ultrasound, also influenced age-related muscle atrophy. Measurements taken across all lumbar levels revealed the greatest fat infiltration with ageing (r = 0.58, 95% CI: 0.35, 0.74). Moderators explained a large proportion of between-study variance in true effects for muscle atrophy (72.6%) and fat infiltration (79.8%) models.

Conclusions: Lumbar paravertebral muscles undergo age-related degeneration in healthy adults with muscle, lumbar level and sex-specific responses. Future studies should use high-resolution imaging modalities to quantify muscle atrophy and fat infiltration.

Key words: back muscles, lumbosacral region, sarcopenia, muscle degeneration, healthy aging

1. Introduction

Age-related degeneration of skeletal muscle is characterised by intramuscular fat infiltration and a loss of muscle tissue (Cruz-Jentoft et al., 2010; Delmonico et al., 2009; Doherty, 2001; McGregor et al., 2014). These, together with the concomitant loss of muscle force generation (Doherty, 2001; Frontera et al., 2000; Kent-Braun and Ng, 2000), are associated with poor functional outcomes as well as increased risk of morbidity and mortality (Arango-Lopera et al., 2013; Baumgartner et al., 1998; Beaudart et al., 2017; Cruz-Jentoft et al., 2010; Gale et al., 2007; Landi et al., 2013, 2012; Roubenoff and Hughes, 2000; Sayer et al., 2005). Sarcopenia encompasses the interrelationships between deteriorating muscle morphology, physical function and strength (Cruz-Jentoft and Sayer, 2019). Adverse outcomes associated with sarcopenia are a major health concern and socioeconomic burden, resulting in estimated excess annual healthcare costs of £2.5b in the United Kingdom (Pinedo-Villanueva et al., 2019) and $18.5b in the United States (Janssen et al., 2004). Research on sarcopenia has predominantly focused on the systemic loss of muscle and its impact on physical function (Bahat et al., 2016; Batsis et al., 2013). However, a systemic approach to understanding sarcopenia may not be appropriate due to the muscle and location-specific nature of its progression (Abe et al., 2014a; Candow and Chilibeck, 2005). Whilst studies have examined degeneration of the appendicular muscles (Cawthon et al., 2015; Müller et al., 2014; von Haehling et al., 2010; Woo and Leung, 2016) there is a paucity of available research focusing on age-related changes in the trunk musculature. This has been acknowledged by other researchers (Crawford et al., 2016c; Kalichman et al., 2017) despite the importance of paravertebral muscles in the maintenance of spinal health and physical function being increasingly recognised (Crawford et al., 2019; Goubert et al., 2016; Hicks et al., 2005a; Kalichman et al., 2017). Although age is known to influence paravertebral muscle morphology and attempts have been made to characterise degeneration of the paravertebral muscles with the natural ageing process (Burian et al., 2018; Crawford et al., 2016a; Fortin et al., 2014; Kalichman et al., 2017; Lee et al., 2017; Meakin et al., 2013; Shahidi et al., 2017; Valentin et al., 2015) the phenomenon is not fully understood.

The paravertebral muscles (i.e. multifidus, erector spinae, psoas and quadratus lumborum) all contribute to the stability of the lumbar spine (Barr et al., 2005; McGill, 2001; Santaguida and McGill, 1995); although the anatomy and biomechanics of the multifidus demonstrate that it is the most suited to this role (MacDonald et al., 2006; Macintosh and Bogduk, 1986; Moseley et al., 2002; Ward et al., 2009). The larger more superficial muscles surrounding the lumbar region function primarily as torque generators for spinal movement. The psoas acts primarily as a flexor muscle of the hip (Bogduk et al., 1992), the erector spinae function primarily as extensor muscles (Potvin et al., 1991) and the quadratus lumborum brings about lateral flexion although its role in spinal biomechanics is undetermined (Phillips et al., 2008). Senescence of the lumbar paravertebral muscles may have greater functional consequences compared to the appendicular muscles (Eguchi et al., 2017; Hicks et al., 2005b). However, whereas efforts have been made to reach consensus of a reference standard for the measurement of appendicular muscle mass in sarcopenia (Buckinx et al., 2018; Cruz-Jentoft et al., 2019), such efforts have yet to translate to measurements of muscle morphology in the lumbar spine, resulting in disparate methods amongst studies.

Relatively few studies have measured the morphology of all the four main lumbar paravertebral muscles. Indeed, previous systematic reviews focusing on paravertebral muscle degeneration have investigated the morphology of the multifidus and erector spinae without examining the psoas and quadratus lumborum (Fortin and Macedo, 2013; Hebert et al., 2009). Given the different functions of the lumbar paravertebral muscles and their potential for localised degeneration in diseased and healthy populations (Baracos, 2017; Crawford et al., 2016c; Min et al., 2013; Ploumis et al., 2011),

normative features are of interest for each individual muscle surrounding the lumbar spine. Furthermore, there has been limited investigation into both muscle size and quality of the paravertebral muscles. These measurements have been typically performed at a single representative slice in the lumbar region (Burian et al., 2018; Ebadi et al., 2018; Frost and Brown, 2016; Gibbons et al., 1997; Hamaguchi et al., 2016; Hedermann et al., 2018; Hiepe et al., 2015; Ikezoe et al., 2012; Kalafateli et al., 2018; Kim et al., 2017; Maltais et al., 2018; Parkkola et al., 1993b; Rahmani et al., 2019; Watson et al., 2008; Yoshizumi et al., 2014) resulting in cross-sectional areas despite volumetric information being preferable due to its greater association with muscle function (Boom et al., 2008). Inconsistent imaging modalities and image analysis techniques across studies, as well as different measures representing muscle size and quality, also confound comparisons between studies.

The considerable variation in methodological factors across studies makes comparing findings difficult, which has hampered our understanding of changes in lumbar muscle morphology with ageing. A necessary step to better understanding this age-related phenomenon is to conduct a systematic review and meta-analysis. To the authors' knowledge, a quantitative analysis of the research on this topic has not been performed to date. Therefore, bringing together the evidence and accounting for methodological differences will establish a reference for normal age-related degenerative features of lumbar paravertebral muscle morphology and provide recommendations for future studies.

2. Materials and methods

2.1. Protocol and registration

This systematic review was registered on the Prospero International Prospective Register of Systematic Reviews (CRD42018093157) and is reported based on the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009).

2.2. Search methods for identification of studies

To assess the relationship between healthy ageing and changes in muscle morphology, data was sought from eligible studies. Table 1 presents the eligibility criteria for inclusion in this systematic review. Although it can be questioned how baseline data from experimental studies may represent age-related muscle degeneration, in the current study baseline data were treated as cross-sectional observations and deemed eligible provided the inclusion criteria were met. To meet the inclusion criteria for exposure, studies had to show ageing as a generally healthy process, stating that participants were healthy, physically independent and free from disease likely to affect paravertebral muscle morphology (e.g. spondylolisthesis, low back pain, stroke and cancer). This was not exhaustive as shown by the MeSH description for "healthy ageing", and due to the lack of consensus on a definition for healthy ageing (Peel et al., 2004). If a study reported disease cases within an otherwise healthy sample, data was sought for the healthy participants only. If the health status of participants was unclear or ambiguous, confirmation was sought from the author(s).

Table 1 Eligibility criteria for including studies in this systematic review

Inclusion criteria: 1. Study design: observational and baseline data from experimental studies 2. Population: healthy sample including adults older than 40 years of age with an age range of at least ten years. If age is a dichotomous variable, older group's mean age must be greater than 40 years and at least 10 years greater than the younger group's mean age. Longitudinal studies must have a minimum follow-up of 10 years and the sample's mean age must be greater than 40 years at follow-up. 3. Exposure: healthy ageing 4. Comparator: not required. If present, comparison group must meet the inclusion criteria for exposure and have a mean age more than ten years younger than the older group's mean age 5. Expected outcomes: quantitative measures of muscle size (atrophy) or quality (fat infiltration); Imaging modality – magnetic resonance imaging (MRI), computerised tomography (CT) or ultrasound; Lumbar level(s) of measurement – L1-L5/S1; Muscles measured – measurements include psoas, erector spinae, quadratus lumborum and or multifidus
Exclusion criteria: 1. Study design: case series, case reports, preclinical studies, reviews and meta-analyses 2. Population: sample contains no participants aged over 40 years. If age is a dichotomous variable, older group's mean age equal to or less than 40 years or within ten years of the comparison group's age. Longitudinal studies' follow-up period is less than ten years or sample's mean age equal to or less than 40 years at follow-up 3. Exposure: evidence of disease or impairment that is likely to affect lumbar paravertebral muscle morphology 4. Comparator: if reported, comparison group shows evidence of disease or impairment, or has a mean age within ten years of the older group's mean age 5. Outcomes: semi-quantitative and qualitative measures of muscle size or quality; Imaging modality – use of imaging modality other than MRI, CT or ultrasound; Lumbar level(s) of measurement – does not include measurements with L1-L5/S1; Muscles measured – measurements do not include psoas, erector spinae, quadratus lumborum and or multifidus

2.3. Information sources and data extraction

A search strategy was developed by one reviewer (AD) for PubMed (Table 2), which was adapted to the syntax and appropriate subject headings of the other databases. The databases searched were MEDLINE and CINAHL (via EBSCOhost), PubMed, The Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE (via OvidSP). No study design, date or participant demographic restrictions were imposed on the search to ensure literature saturation. An English language restriction was used due to resource limitations. Final searches were completed June 1st, 2019. After initial searches were completed and duplicate records removed (AD), titles and abstracts were screened independently and in duplicate (AD, CG) against the eligibility criteria. Unpublished data and grey literature were sought to ensure a more comprehensive search strategy and reduce the possibility of publication bias (Paez, 2017). Articles not excluded based on title and abstract and deemed relevant progressed to full-text review. Full-text eligibility screening was completed independently by two reviewers (AD, CG) and reasons for exclusion were provided. Disagreements on eligibility were resolved by discussion. Whilst it was planned that unresolved disagreements would be arbitrated independently by a third reviewer (JH), this was never exercised due to the reviewers reaching consensus in all discussions. Where studies were described in multiple publications, the publication with the most comprehensive data was used as the primary reference, excluding the others if the same data were presented. Where multiple publications from the same study but different data were retrieved, all relevant publications were included. If data could not be obtained from the full-text or if clarification was required, authors were contacted by one reviewer (AD). If sufficient data could not be obtained for a study, the study was excluded. Two reviewers (AD, CG) extracted data independently from eligible studies on: study design; sample and comparator information [sample size, gender, mean age, age range, mean body mass index (BMI), ethnicity, additional information

about the setting, definition of health status]; imaging modality; image analysis outcome measures; lumbar level(s) and paravertebral muscle(s) measured; study results including statistical findings and overall conclusions.

Table 2 PubMed search strategy

#1 Paraspinal muscles MeSH Terms
#2 Paraspinal musc* Title/Abstract
#3 Back muscles MeSH Terms
#4 Back musc* Title/Abstract
#5 Multifidus Title/Abstract
#6 Lumbar multifidus Title/Abstract
#7 Lumbar musc* Title/Abstract
#8 Trunk musc* Title/Abstract
#9 Paravertebral musc* Title/Abstract
#10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
#11 Aged MeSH Terms
#12 Aged Title/Abstract
#13 Age Title/Abstract
#14 Aging MeSH Terms
#15 Aging Title/Abstract
#16 Ageing Title/Abstract
#17 Elderly MeSH Terms
#18 Elderly Title/Abstract
#19 Older adult* Title/Abstract
#20 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#21 Atroph* Title/Abstract
#22 Muscular atrophy MeSH Terms
#23 Spinal Muscular Atrophy MeSH Terms
#24 Degenerat* Title/Abstract
#25 Morpho* Title/Abstract
#26 Morphology MeSH Terms
#27 Size Title/Abstract
#28 Attenuation Title/Abstract
#29 Infiltration Title/Abstract
#30 Replacement Title/Abstract
#31 Sarcopen* Title/Abstract
#32 Sarcopenia MeSH Terms
#33 #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32
#34 #10 AND #20 AND #33
#35 Animals MeSH Major Topic NOT Humans MeSH Major Topic
#36 #34 NOT #35

2.4. Assessment of risk of bias in individual studies and study quality

Risk of bias was assessed independently by two reviewers (AD, CK) at the study level using the National Institutes of Health (NIH) Study Quality Assessment Tools. Reviewers used the study rating tools to rate the quality of the study as good, fair or poor. The Risk of Bias Assessment Tool for Nonrandomised Studies (RoBANS) (Kim et al., 2013; Park et al., 2011) was also used (AD, CK) to independently assess risk of bias at the outcome level. A judgement of “low”, “high” or “unclear” was assigned to each question for all included studies. If ratings using the NIH Study Quality Assessment tool or judgements using the RoBANS tool differed between reviewers, reviewers discussed the study in an effort to reach consensus, otherwise a third reviewer (JH) arbitrated disagreements not due to assessor error.

2.5. Synthesis of results and statistical methods

Standardised effect sizes were used in the meta-analysis due to studies using different measurement scales. Pearson's product-moment correlation coefficient (r) was the principal summary measure. For studies reporting ageing as a continuous variable, correlations (r) were transformed into Fisher's z units (z') to approximate normally distributed data. Data were excluded from the meta-analysis when studies used non-parametric statistical tests. For studies that reported ageing as a dichotomous variable, the standardised mean difference (Cohen's d) was calculated. Cohen's d values were then converted into Fisher's z units (Borenstein et al., 2009; Polanin and Snilstveit, 2016). To account for the large variability in spinal-level measurements and different slice orientations, evaluations were categorised into high (L1-L2), mid (L2/3-L3/4), low (L4-L5/S1) and all (combined measurements across high, mid and low levels) lumbar levels. If a study contributed multiple effect sizes, differing only by lumbar level measurements, they were aggregated into appropriate categories. For example, if a study measured psoas cross-sectional area at the L1 and L2, these two effect sizes were aggregated to provide one effect size at the "high" level.

The "metaSEM" package (Cheung, 2014a) was used in the RStudio (RStudio Team (2015). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL http://www.rstudio.com/. Version 1.1.463) environment to perform three-level meta-analyses. Level 1 referred to participants within studies, level 2 (within-study variance) referred to interdependent effects within studies, and level 3 (between-study variance) referred to the studies themselves. This approach allowed us to fully explore the informative differences between outcomes whilst accounting for statistical dependency due to studies contributing multiple effect sizes. The three-level meta-analytical model was also adopted as the dependency between effect-sizes was unknown (Cheung, 2014a, 2014b). Due to the complexity of the data obtained, traditional meta-analytical methods were not appropriate and would have likely artificially reduced variance within and between studies (Cheung and Chan, 2008). Moderators were included in the models to assess their influence on the effect size estimate and to investigate the amount of between-study variance in true effects that could be explained by their inclusion. Categorical moderators included:

1. sex: female*, male;
2. muscle: psoas*, erector spinae, multifidus, quadratus lumborum, combined paraspinals (erector spinae + multifidus), combined paravertebral muscles (all four muscles);
3. level: all*, high, mid, low; and
4. imaging modality: CT*, MRI, ultrasound.

Asterisks denote the reference category. Dummy codes were created for categorical moderators for entry into the meta-regression models.

In addition, age (mean and range) and mean BMI were included as continuous. Continuous covariates were centred, but not standardised, to increase numerical stability. Additionally, random-effects meta-analyses, with effects aggregated within studies, were performed using the R-package "metaphor" (Viechtbauer, 2010) to estimate the robustness of the three-level meta-analyses.

Moderator coefficients and summary effects (z') were transformed back to correlation coefficients (r) with their 95% confidence intervals. Before performing any meta-analyses, a Baujat plot was visually inspected to identify and remove effects that excessively contributed to heterogeneity and the overall result (Baujat et al., 2002). For muscle size, three effect-sizes (Aboufazeli et al., 2018; Hedermann et al., 2018), and for fat infiltration, two effect-sizes (Frost and Brown, 2016; Masaki et

al., 2015) lay away from the majority and were deemed outliers. Sensitivity analyses were performed to explore how the main findings were affected by the removal of studies that: a) did not explicitly state that their sample were healthy and with a normal BMI (18.5-24.9) and b) were rated as fair or poor quality based on the NIH quality assessment tools.

2.6. Investigation of heterogeneity and explained variance in true effects

Heterogeneity within (level 2) and between studies (level 3) was evaluated using the Chi-squared test and I^2 statistic. The I^2 statistic describes the percentage of variability in the point estimates that is due to heterogeneity rather than sampling error (Deeks, 2011). Interpretation of heterogeneity followed Deeks and colleagues' (Deeks, 2011) suggestion that 0-40% might not be important, 30-60% may represent moderate heterogeneity, 50-90% may represent substantial heterogeneity and 75-90% considerable heterogeneity. The percentage of variance in true effects (R^2) explained by the inclusion of moderators was calculated (Konstantopoulos and Hedges, 2009).

2.7. Assessment of risk of bias across studies

To explore publication bias potential, asymmetry was inspected visually using funnel plots and statistically using Egger's regression intercept test (Egger et al., 1997), for which there were a sufficient number of studies. Sutton et al (Sutton et al., 2000) suggest that five studies is usually too few to allow the detection of an asymmetric funnel. Duval and Tweedie's trim and fill test (Duval and Tweedie, 2000) was performed if publication bias was indicated, providing a revised summary point estimate adjusted for publication bias.

3. Results

3.1. Study selection

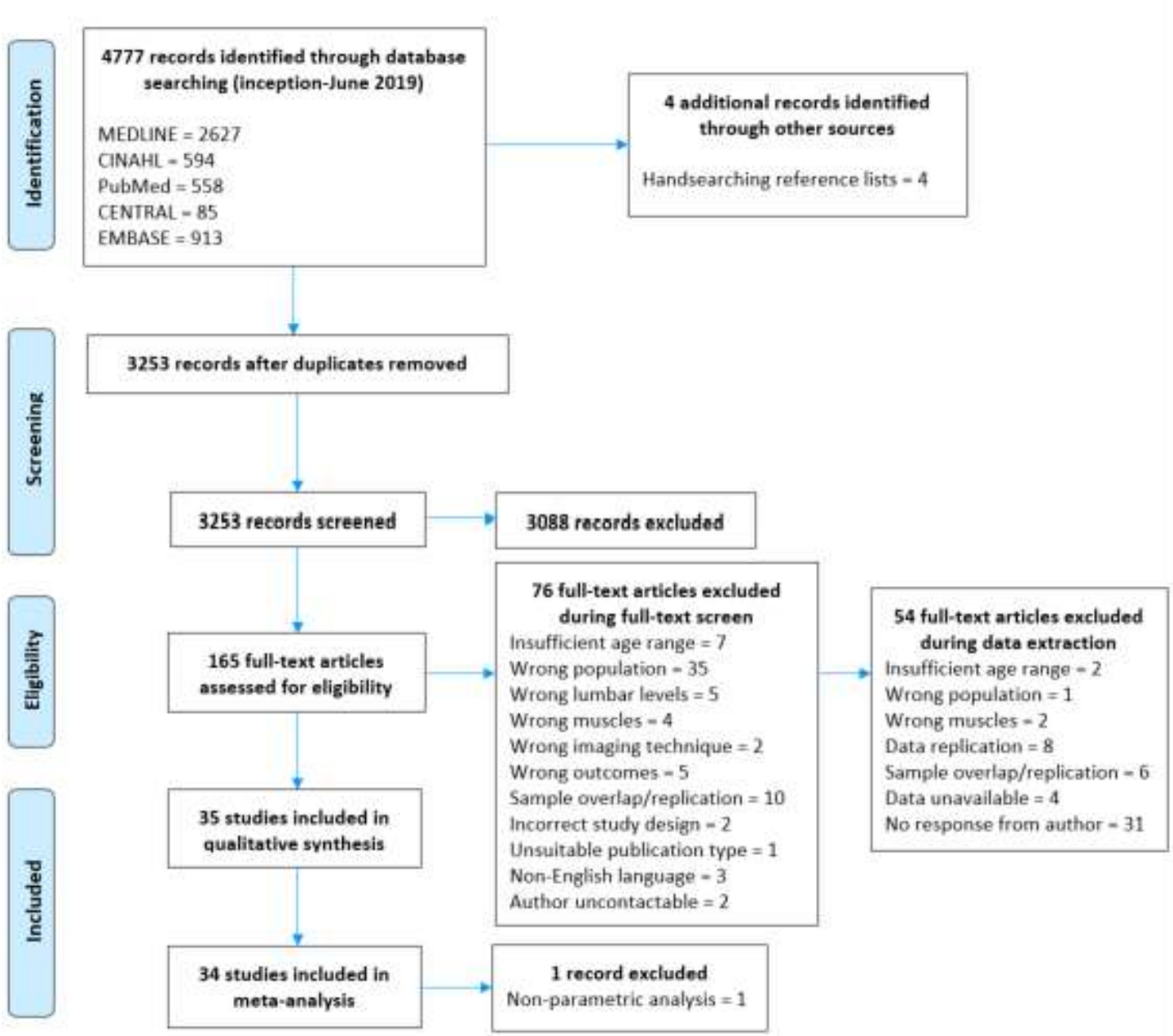

Figure 1 PRISMA flow diagram depicting the selection process for studies

The flow diagram (Fig. 1) presents the study selection process applied in this meta-analysis. Of the 35 studies (Aboufazeli et al., 2018; Anderson et al., 2013, 2012; Bailey et al., 2010; Beneck and Kulig, 2012; Burian et al., 2018; Crawford et al., 2016a; D'Hooge et al., 2012; Danneels et al., 2000; Frost and Brown, 2016; Gibbons et al., 1997; Hamaguchi et al., 2016; Hedermann et al., 2018; Hiepe et al., 2015; Ikezoe et al., 2015, 2012; Johannesdottir et al., 2018; Kim et al., 2017; Lee et al., 2017; Lorbergs et al., 2019; Maltais et al., 2018; Marshall et al., 2011; Masaki et al., 2015; Meakin et al., 2013; Rahmani et al., 2019; Schweitzer et al., 2016; Shadani et al., 2018; Shahtahmassebi et al., 2017; Sions et al., 2017a; Sollmann et al., 2018; Stokes et al., 2005; Thakar et al., 2016; Valentin et al., 2015; Watson et al., 2008; Yoshizumi et al., 2014) included in the qualitative synthesis, 32

reported outcomes for muscle size (n = 5523) and 18 studies reported outcomes for muscle quality (fat infiltration) (n = 3471). These studies comprised of one randomised controlled trial whilst all others adopted observational study designs. Of these, 10 studies originated from North America, 12 from European countries, 11 from Asian countries and 2 from Australia. For studies where separate data by sex were obtained, studies reporting on muscle atrophy with ageing as a continuous variable involved 2860 male and 2430 female participants. Studies comparing muscle size between older and younger groups involved 50 males and 64 females in the older group and 50 males and 69 females in the younger group. For studies reporting on muscle fat infiltration with ageing as a continuous variable, 1615 males and 997 female participants were included. Studies comparing muscle fat infiltration between older and younger groups involved 171 males and 186 females in the older group and 293 males and 209 females in the younger group. Across all studies, age ranged from 18 to 94 years for women, whilst for men age ranged from 18 to 92 years. Women's mean BMI was lower than men's and ranged from 20.5 to 28.0, whereas men exhibited a mean range of 22.2 to 30.4, discounting younger comparison groups. Further details on study design, population characteristics, assessment of health, outcome measures and study quality are presented as a graphical overview in Table 3 for each included study. For the three-level meta-analytical model on age-related muscle atrophy, 29 studies were included giving 144 correlation coefficients. For the three-level model on age-related fat infiltration, 16 studies encompassing 92 correlation coefficients were included.

[nb. Table 3 is provided separately to maintain its readability]

Table 3 Graphical overview of study characteristics

3.2. Assessment of risk of bias in included studies

A risk of bias summary is presented in Fig. 2 with the reviewers' judgements on overall study quality and on each domain included in the graphical overview of study characteristics (Table 3).

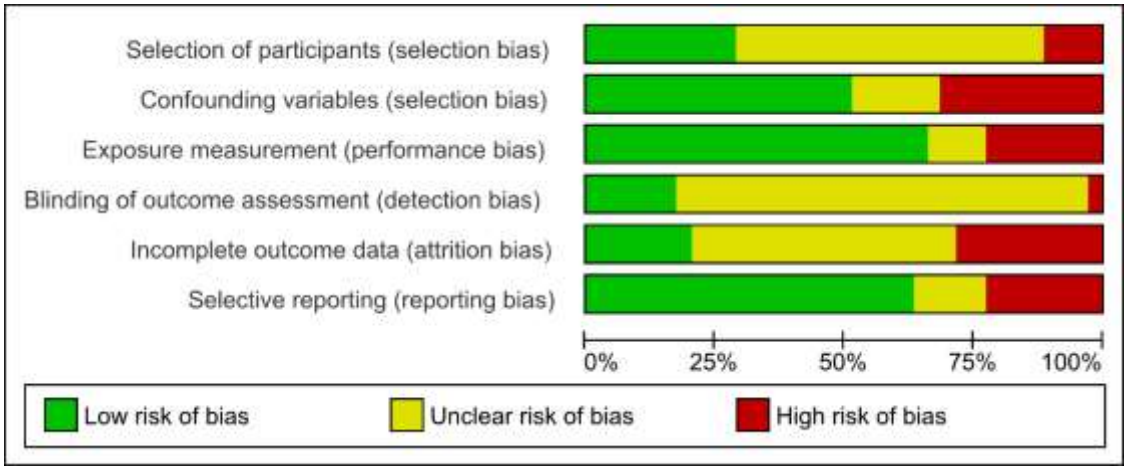

Figure 2 Risk of bias summary: review of authors' judgements on each item from the Risk of Bias Assessment Tool for Nonrandomised Studies (RoBANS) presented as percentages across all included studies

3.3. Overall summary

Random-effects meta-analyses were performed where each study contributed one effect size. The correlation (with its 95% Wald CI's) between healthy ageing and change in lumbar paravertebral muscle size was estimated at r = -0.25 (-0.33, -0.18, $p < 0.001$). For change in intramuscular fat infiltration with ageing, the overall correlation was r = 0.38 (95% CI: 0.27, 0.49, $p < 0.001$). These correlations were similar to those obtained from the three-level meta-analyses (Table 4). To assess the robustness of the three-level models, the null hypothesis: $\tau^2_{(3)} = 0$ was tested. Likelihood-ratio tests for the muscle size model (-2LL (df_1) = 54.6, $p < 0.001$) and muscle quality model (-2LL (df_1) = 56.3, $p < 0.001$) demonstrated that the three-level models were statistically better than the two-level models.

Table 4 Three-level meta-analysis models for age-related muscle atrophy and fat infiltration in the lumbar paravertebral muscles

	No. of studies	No. of effects	Effect size (r)	95% CI	*p*
Three-level muscle atrophy model					
Intercept	29	144	-0.255	-0.333, -0.169	< 0.001
Model summary	Level 2: $\tau^2_{(2)}$ = 0.004 (SE = 0.002), p = 0.05, I^2 = 6.60% (95% LBCI 1.8% 17.5%) Level 3: $\tau^2_{(3)}$ = 0.039 (SE = 0.014), $p < 0.01$, I^2 = 73.97% (95% LBCI 56.3% 86.0%) Q(df_{143}) = 367.44, $p < 0.001$, -2LL(df_{141}) = -26.29				
Three-level fat infiltration model					
Intercept	16	92	0.394	0.278, 0.499	< 0.001
Model summary	Level 2: $\tau^2_{(2)}$ = 0.006 (SE = 0.002), $p < 0.05$, I^2 = 7.54% (95% LBCI 2.4% 20.0%) Level 3: $\tau^2_{(3)}$ = 0.059 (SE = 0.025), $p < 0.05$, I^2 = 79.84% (95% LBCI 61.7% 91.1%) Q(df_{91}) = 411.96, $p < 0.001$, -2LL(df_{89}) = -11.06				

CI = Wald confidence intervals; LBCI = likelihood-based confidence intervals; -2LL = -2 log likelihood

For the random-effects meta-analyses, examination of the I^2 statistic suggested a considerable level of heterogeneity (muscle size model: I^2 = 94%, Q(df_{29}) = 223.5, $p < 0.001$; muscle quality model: I^2 = 98%, Q(df_{16}) = 464.1, $p < 0.001$). To explore potential reasons for heterogeneity, a sub-group analysis was performed by grouping study sample effect sizes by sex. One study analysing muscle size (Yoshizumi et al., 2014) and one analysing muscle quality (Lee et al., 2017) combined sexes in their analysis; these studies were removed from further analyses. For the muscle atrophy model, the random-effects meta-analysis produced summary effects of r = -0.22 (95% CI: -0.31, -0.13, $p < 0.001$) for females and r = -0.32 (95% CI: -0.40, -0.23, $p < 0.001$) for males, which were similar to those obtained in the three-level meta-regression model (Table 5). For the fat infiltration model, the random-effects meta-analysis produced summary effects of r = 0.42 (95% CI: 0.25, 0.57, $p < 0.001$) for females, and r = 0.44 (95% CI: 0.31, 0.55, $p < 0.001$) for males. However, these correlations were considerably less than those obtained from the three-level meta-regression (Table 6).

Substantial heterogeneity was still apparent in both muscle atrophy (females I^2 = 71%, Q(df_{21}) = 48.9, $p < 0.001$; males I^2 = 74%, Q(df_{24}) = 65.3, $p < 0.001$) and fat infiltration (females I^2 = 82%, Q(df_{11}) = 46.9, $p < 0.001$; males I^2 = 82%, Q(df_{12}) = 71.4, $p < 0.001$) random-effect meta-analyses when sub-grouped for sex. The three-level models also revealed greater variance between studies (level 3)

than within studies (level 2) (Table 4), which was supported by rejection of the null hypothesis: $\tau^2_{(2)} = \tau^2_{(3)}$ for both muscle size (-2LL (df_1) = 15.3, $p < 0.001$) and muscle quality (-2LL (df_1) = 14.0, $p < 0.001$) models. This indicates moderators are more likely to exist between than within studies. Therefore, potential moderators (Sex, Muscle, Level, Imaging technique, Mean sample BMI, Mean sample age, Sample age range) were examined using meta-regression to further explore reasons for between-study variance.

3.4. Three-level meta-regression models

The potential differentiating role of moderators on the overall relationship between changes in muscle morphology and ageing in healthy older adults were evaluated using three-level meta-regression. After controlling for other potential covariates that may influence the relationship between the change in muscle size and ageing, males (r = -0.32) differed significantly ($p < 0.01$) with females (r = -0.24). Muscle as a group was approaching significance ($p = 0.06$), whilst the erector spinae (r = -0.32) and quadratus lumborum (r = -0.33) were significant individual muscle moderators ($p = 0.01$ and $p < 0.01$, respectively). There was a significant moderation with the average correlation obtained in studies using ultrasound (r = 0.08, $p < 0.001$); this was reflected in imaging modality reaching significance as a group ($p < 0.01$). Moderators with their regression coefficients are presented in Table 5. The inclusion of all moderators explained 72.6% of between-study variance in true effects (Fig. 3), although the significant moderators alone explained 63.5%.

Table 5 Three-level meta-regression model estimating the moderating effects of Sex (Female = reference category), Muscle (Psoas = reference category), Level (All levels = reference category), Imaging technique (CT = reference category), BMI, mean age, and age range on the relationship between change in paravertebral muscle size and ageing

Moderator	**β**	**SE**	**95% CI**	***P***
Intercept*	-0.24	0.14	-0.47, 0.03	0.02
Male**	-0.08	0.03	-0.14, -0.02	< 0.01
Muscle (ΔLL (df_5) = 10.54, p = 0.06)				
Erector spinae*	-0.08	0.03	-0.14, -0.02	0.01
Multifidus	-0.03	0.06	-0.14, 0.08	0.55
Quadratus lumborum**	-0.09	0.03	-0.15, -0.03	< 0.01
Paraspinals	0.05	0.14	-0.09, 0.19	0.50
Combined paravertebrals	-0.18	0.07	-0.44, 0.10	0.20
Level (ΔLL (df_3) = 1.79, p = 0.62)				
High levels	0.00	0.14	-0.27, 0.28	0.98
Mid levels	-0.07	0.13	-0.32, 0.18	0.59
Low levels	-0.05	0.13	-0.30, 0.21	0.70
Imaging modality** (ΔLL (df_2) = 9.91, p < 0.01)				
MRI	0.13	0.08	-0.02, 0.28	0.09
Ultrasound***	0.32	0.10	0.14, 0.48	< 0.001
BMI	0.00	0.03	-0.06, 0.07	0.95
Mean age	0.02	0.03	-0.04, 0.09	0.49
Age range	-0.03	0.03	-0.09, 0.03	0.28
Level-2 variance	0.002	0.001	-0.001, 0.005	0.23
Level-3 variance	0.011	0.006	-0.002, 0.023	0.09

# of studies = 29, k = 144 correlation coefficients, Q(df143) = 367.44; p < 0.001, -2LL(df127) = -64.58, *< 0.05, **< 0.01, ***< 0.001

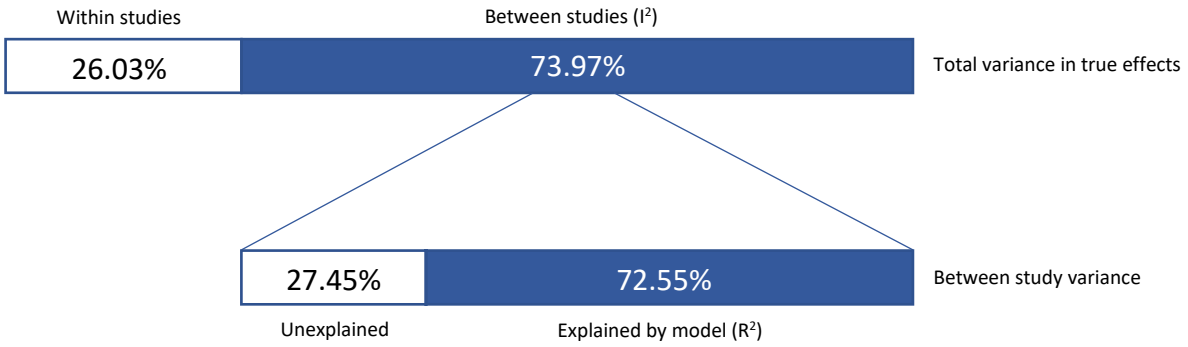

Figure 3 Visual representation of the amount of between-study variance in true effects explained by moderators for the relationship between muscle atrophy and ageing

The overall relationship between intramuscular fat infiltration and ageing was moderated by the selection of paravertebral muscle ($p < 0.001$), after controlling for other potential covariates. Within this group, the erector spinae (r = 0.73), quadratus lumborum (r = 0.68) and paraspinals (r = 0.82) were significant individual moderators ($p < 0.001$). Level of lumbar measurement also made a significant difference in the estimated correlation between fat infiltration and ageing ($p = 0.03$). Measurements at the high (r = 0.12, $p = 0.002$), mid (r = 0.24, $p = 0.012$) and low (r = 0.22, $p = 0.009$) lumbar levels differed significantly with measurements taken across all lumbar levels (r = 0.58). BMI was close to having a significant moderating effect on overall relationship (β = 0.10, $p = 0.08$). Age range of the sample was however significant and had an even greater influence on the relationship between fat infiltration and ageing (β = 0.16, $p < 0.001$). Moderators with their regression coefficients are presented in Table 6. The inclusion of all moderators explained 79.8% of between-study variance in true effects (Fig. 4), although the significant moderators alone explained 65.8%.

Table 6 Three-level meta-regression estimating the moderating effects of Sex (Female = reference category), Muscle (Psoas = reference category), Level (All levels = reference category), Imaging technique (CT = reference category), BMI, mean age, and age range on the relationship between change in paravertebral muscle fat infiltration and ageing

Moderator	β	SE	95% CI	*P*
Intercept***	0.58	0.15	0.35, 0.74	< 0.001
Male	-0.05	0.03	-0.11, 0.02	0.18
Muscle*** (ΔLL (df_4) = 29.59, p < 0.001)				
Erector spinae***	0.15	0.03	0.09, 0.20	< 0.001
Multifidus	0.08	0.08	-0.08, 0.23	0.33
Quadratus lumborum***	0.10	0.03	0.05, 0.16	< 0.001
Paraspinals***	0.24	0.06	0.13, 0.34	< 0.001
Level* (ΔLL (df_3) = 8.85, p = 0.03)				
High levels**	-0.46	0.16	-0.67, -0.18	0.002
Mid levels*	-0.34	0.14	-0.56, -0.08	0.012
Low levels**	-0.36	0.14	-0.58, -0.09	0.009
Imaging modality (ΔLL (df_2) = 1.40, p = 0.50)				
MRI	-0.04	0.10	-0.23, 0.15	0.66
Ultrasound	-0.24	0.20	-0.57, 0.15	0.23
BMI	0.10	0.06	-0.01, 0.22	0.08
Mean age	-0.05	0.06	-0.16, 0.06	0.36
Age range***	0.16	0.04	0.08, 0.25	< 0.001
Level-2 variance	$1e^{-10}$	0.001	-0.002, 0.002	0.99
Level-3 variance	0.012	0.007	-0.001, 0.025	0.08

# of studies = 16, k = 92 correlation coefficients, Q(df91) = 411.96, p < 0.001, -2LL(df76) = -64.83, *< 0.05, **< 0.01, ***< 0.001

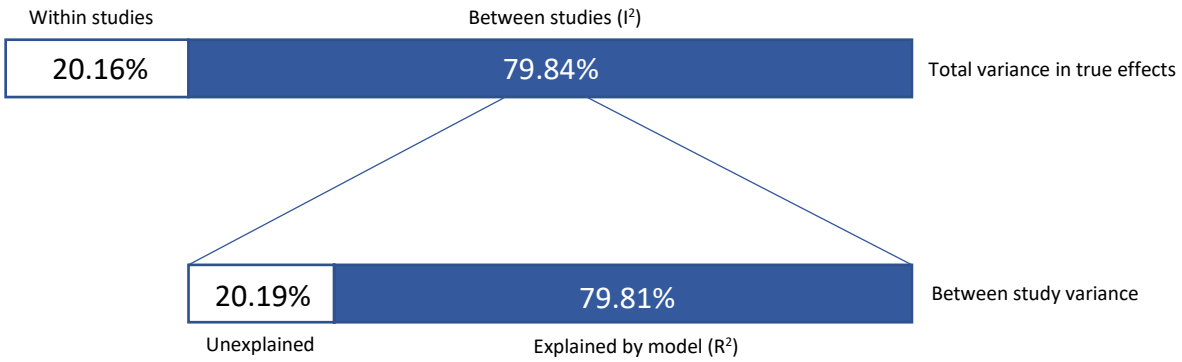

Figure 4 Visual representation of the amount of between-study variance in true effects explained by moderators for the relationship between fat infiltration and ageing

3.5. Risk of bias across studies

For studies assessing muscle size, Egger's regression intercept test (z = 1.41, *p* = 0.16) indicated that publication bias was not present. For studies assessing muscle quality (fat infiltration), visual inspection of the funnel plot (Fig. 5) suggested potential evidence of publication bias, which was consistent with the Egger's regression intercept test (z = -2.03, *p* = 0.04). Due to the asymmetry detected in the funnel plot, Duval and Tweedie's trim and fill test estimated six studies should be added to the right of the mean, which would yield an adjusted point estimate of r = 0.49 (95% CI: 0.39, 0.58) for the relationship between fat infiltration and ageing.

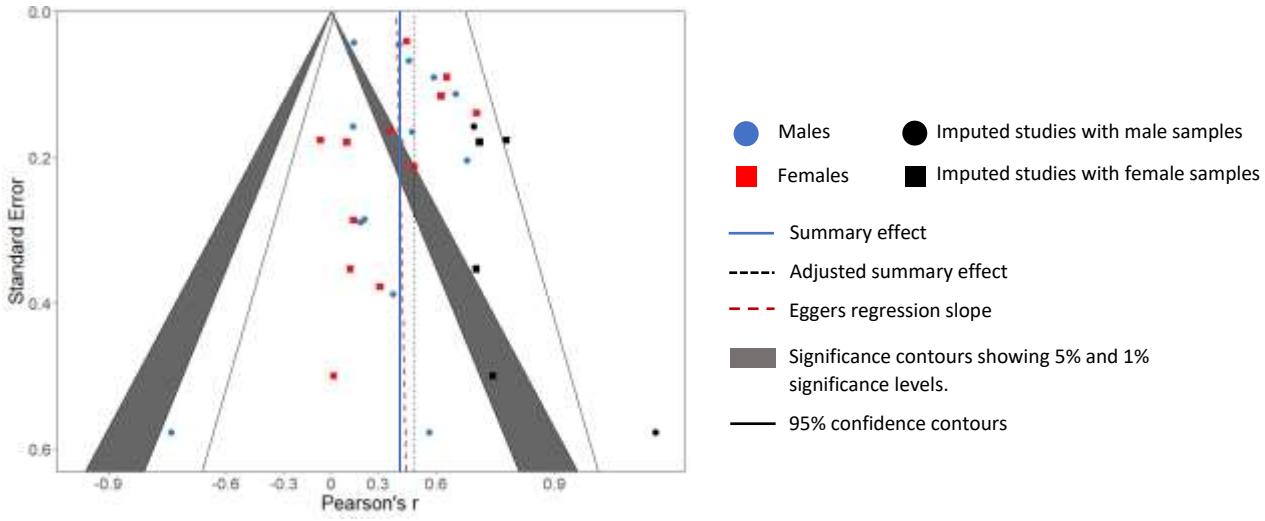

Figure 5 Contour enhanced funnel plot to illustrate potential publication bias for studies assessing muscle quality (fat infiltration)

3.6. Sensitivity analyses

For the relationship between muscle atrophy and ageing, removing studies that did not explicitly state that their sample were "healthy" and had a BMI outside of 18.5-24.9 yielded a lower overall correlation (r = -0.23, 95% CI: -0.36, -0.10, *p* < 0.001), no significant moderators and lower between-study variance (I^2 = 67%) when compared to the original three-level meta-analysis. The inclusion of

moderators explained 100% of the between-study variance in true effects. Removal of fair and poor-quality studies yielded a greater overall effect (r = -0.35, 95% CI: -0.47, -0.22, $p < 0.001$); significant moderators included sex ($p < 0.02$) and mean age of the sample ($p < 0.05$). Between-study variance was also lower in this model ($I^2 = 65\%$) compared to the original three-level meta-analysis, and the inclusion of moderators resulted in an R^2 value of 77%.

For the relationship between fat infiltration and ageing, removing studies that did not explicitly state that their sample were "healthy" or had a BMI outside of 18.5-24.9 yielded a lower overall correlation (r = 0.32, 95% CI: 0.21, 0.43, $p < 0.001$). No moderators were significant in this model, although between-study variance was substantially lower ($I^2 = 17\%$) compared to the original three-level meta-analysis. Removal of fair and poor-quality studies slightly lowered the overall correlation (r = 0.39, 95% CI: 0.18, 0.56, $p < 0.001$). Males ($p < 0.02$), paraspinal muscles ($p < 0.01$), low lumbar levels ($p < 0.05$), ultrasound ($p < 0.02$), BMI ($p < 0.01$) and mean age of the sample ($p < 0.01$) all significantly moderated the relationship between fat infiltration and ageing in the adjusted three-level meta-regression. Muscle ($p < 0.02$) was also retained as a significant moderator group. Between-study variance was lower in this model ($I^2 = 72\%$) compared to the original three-level meta-analysis. Both sensitivity analyses resulted in 100% of the between-study variance in true effects being explained by the inclusion of moderators.

4. Discussion

This is the first study to present a systematic review and meta-analysis on age-related degeneration of the lumbar paravertebral muscles in healthy adults. Given the inconsistent methods and equivocal nature of findings on this topic, this work provides up-to-date evidence on normal age-related changes in the muscles surrounding the lumbar spine and constitutes an important contribution to the literature base to date. The current findings show that the paravertebral muscles undergo degenerative morphological changes as part of healthy ageing in older adults, with increases in fat infiltration more effectual than reductions in muscle size. This suggests that fat infiltration may be a better indicator of age-related decline in the lumbar musculature than muscle atrophy. Indeed, given the predominance of type I fibres in the lumbar paravertebral muscles (Kimura, 2002; Mannion et al., 1997; Ng et al., 1998; Parkkola et al., 1993a; Sirca and Kostevc, 1985) and that type I fibres tend to accumulate fat deposits with age (Choi et al., 2016; Gueugneau et al., 2015) whilst fast-twitch fibres typically exhibit greater atrophy with age (Gueugneau et al., 2015; Lexell et al., 1988; Novotny et al., 2015), it is unsurprising that fat infiltration was the more apparent degenerative feature in the lumbar musculature. Although the findings in this review can be explained by established mechanisms that contribute to the development and morphological expressions of age-related sarcopenia (Bougea et al., 2016; Doherty, 2003; Klitgaard et al., 1990; Larsson et al., 1979; Vettor et al., 2009; von Haehling et al., 2010), confidence in the findings is diminished somewhat by the substantial variance between studies. However, disparate methods and population characteristics amongst studies included in this review were able to explain a large proportion of variance and shed light on which factors play a pivotal role in moderating the age-related changes in lumbar paravertebral muscle morphology.

4.1. Sex differences in muscle atrophy

The relationship between muscle atrophy and ageing differed significantly between males and females but not for fat infiltration. Males exhibited greater lumbar paravertebral muscle atrophy with ageing compared to females. Males possess greater muscle mass than females, therefore having greater potential for atrophy with age (Janssen et al., 2000). However, this may be overly simplistic and not reflect the complex sex-specific mechanisms that drive decrements in muscle morphology associated with sarcopenia (Kirchengast and Huber, 2009; Maggio et al., 2013; Payette et al., 2003). Lifestyle factors, such as physical activity, may influence the sex-specific loss of muscle size. Given that physical activity reduces with ageing equally among men and women (Milanović et al., 2013) and physical activity has been shown to attenuate the loss of lower limb muscle volume in men but not women (Rivera et al., 2016), it is possible that males also experience greater age-related muscle atrophy in other muscles such as those located in the posterior trunk. However, paravertebral muscle size is relatively independent of physical activity level (Dasarathy and Merli, 2016; Fortin et al., 2014). A more likely explanation concerns the sex-specific muscle fibre phenotypes of the lumbar musculature. Males possess a greater proportion of type II muscle fibres in the erector spinae than women (Mannion et al., 2000). Whilst type I fibres are more affected by inactivity and denervation-induced atrophy, type II fibres are more susceptible to the effects of ageing (Wang and Pessin, 2013). Therefore, a greater proportion of type II fibres may predispose men to greater paravertebral muscle atrophy. This is reflected in the current findings where men exhibited greater age-related atrophy than women. However, muscle quality does not appear to be a sex-specific degenerative feature of the lumbar paravertebral muscles.

4.2. Muscle-specific degenerative responses

Muscle as a group significantly moderated the relationship between fat infiltration and ageing and was approaching significance for moderating the relationship between muscle atrophy and ageing. These findings indicate that there is a muscle-specific response in the lumbar musculature. Therefore, selection of paravertebral muscles may be important when evaluating age-related muscle degeneration in the lumbar spine. Atrophy and fat infiltration of the erector spinae and quadratus lumborum showed significantly greater effects with ageing compared to the reference muscle (psoas). The correlation between ageing and fat infiltration in the paraspinals was also significantly greater. Indeed, the paraspinals yielded the greatest estimate of fat infiltration amongst the paravertebral muscles, but exhibited the least amount of age-related atrophy, albeit without reaching significance. There are perhaps two main reasons to explain these findings. The first concerns how the paraspinal muscles' region of interest (ROI) is defined. Measurements of the paraspinals are sometimes preferred due to the difficulty in discerning the erector spinae and multifidus muscle boundaries (Lee et al., 2012). The fascial line between the muscles is used to distinguish the medial border of the erector spinae (Crawford et al., 2017). However, this non-muscular tissue, typically included in paraspinal muscle measurements (Gungor et al., 2015; Lee et al., 2012; Ropponen et al., 2008; Schlaeger et al., 2019), may overestimate fat infiltration especially when fat tissue under the lumbosacral plane has been excluded from the ROI (Berry et al., 2018; Crawford et al., 2017). With advancing age, a redistribution of fat and increase in non-contractile tissue between muscles is observed (Addison et al., 2014). Therefore, it is likely that the greater amount of fat infiltration in the paraspinals is an overestimation and in part caused by the inclusion of age-related increases in non-muscle tissue between the multifidus and erector spinae. This approach may also explain why atrophy is seemingly attenuated in the paraspinals. Increases in non-contractile tissue size between the multifidus and erector spinae may mask age-related muscular atrophy of the paraspinals. However, fat infiltration has been shown to exceed the loss of lean tissue; indicating that intramuscular adipose tissue does not simply replace the space left by muscle atrophy (Manini et al., 2007). As the paraspinal muscles (erector spinae and multifidus) are composed mainly of slow-twitch fibres (JØrgensen et al., 1993; Mannion et al., 1997; Rantanen et al., 1994) that are more vulnerable to fat accretion than atrophy (Choi et al., 2016; Gueugneau et al., 2015), this may also explain why paraspinal muscle size is relatively spared in comparison to compositional changes.

The second explanation concerns functional decline with ageing and low physical activity status in older adults and their effects on muscle morphology. The paraspinal muscles' function, to provide postural support of the lumbar spine and actuate gross trunk movements (Crisco and Panjabi, 1991), may decline with ageing (McGill et al., 1999; Singh et al., 2011). Physical activity also significantly decreases in older age (Morse et al., 2004), which results in the accumulation of intramuscular fat (Goodpaster et al., 2008; Leskinen et al., 2013; Marcus et al., 2010). Therefore, diminished age-related muscle function coupled with physical inactivity is likely to result in atrophy and fat accretion of the paravertebral muscles (Ikezoe et al., 2012; Teichtahl et al., 2015). Indeed, skeletal muscle has been shown to undergo adaptive reductive remodelling in response to both physical inactivity (Fortney et al., 2011; Paddon-Jones et al., 2006) and ageing (Kalichman et al., 2017; Rogers and Evans, 1993; Roubenoff and Hughes, 2000) and given their inter-relationship it is unsurprising that the elderly are susceptible to muscle disuse atrophy (Wall et al., 2013). Narici and Maffuli (Narici and Maffulli, 2010) have suggested that postural muscles are particularly affected by age-related sarcopenia, although this claim warrants further investigation. Deterioration of the paravertebral muscles is likely due to reduced axial loading, as a result of physical inactivity in old age preferentially affecting the antigravity muscles (Ikezoe et al., 2012). Given that paravertebral

muscles are predominantly composed of type I muscle fibres (Kimura, 2002; Mannion et al., 1997; Ng et al., 1998; Parkkola et al., 1993a; Sirca and Kostevc, 1985) that are suited to prolonged tonic activity (Crawford et al., 2016b; Schiaffino and Reggiani, 2011) and this fibre type is susceptible to inactivity atrophy (Wang and Pessin, 2013), less engagement with physical activity is a likely mechanism for muscle atrophy in old age.

Muscles such as the paravertebrals may therefore be more vulnerable to degenerative changes in older age. Indeed, the lumbar musculature is more susceptible to progressive fat infiltration with ageing than the leg muscles (Dahlqvist et al., 2015). However, lower limb muscles appear to experience greater atrophy than the back muscles (Abe et al., 2014b; LeBlanc et al., 1992). This suggests that the postural function of the paravertebrals may attenuate the loss of muscle size, although degenerative changes are still apparent in muscle composition. The results of the current review suggest that the erector spinae and quadratus lumborum, which is frequently overlooked, experience the greatest degenerative changes amongst the lumbar musculature with normal ageing. These muscles in particular should be evaluated when determining age-related changes in the lumbar spine. However, researchers should look to include all of the paravertebral muscles in such evaluations and obtain information on each muscle separately, as degenerative changes are muscle-specific and it is unlikely that any one muscle is representative.

4.3. Lumbar level-dependent fat infiltration

The relationship between ageing and fat infiltration in older adults was significantly moderated by the lumbar level at which paravertebral muscles were measured. Studies evaluating muscles across all lumbar levels showed the greatest degenerative changes with ageing. However, the findings in this review indicate that age-related atrophy of the lumbar paravertebral muscles in healthy older adults is not influenced by the moderating effect of lumbar level. This reveals important methodological considerations as the level of measurement may not be significant for assessing age-related changes in muscle size, but it is of importance for assessing age-related changes in muscle quality. Assessing fat infiltration across all lumbar levels provided the greatest effect size estimate, whilst measurements taken at the high levels (L1-L2) provided the most conservative estimates of muscle quality change (increased fat infiltration) with ageing. Measurements at the mid (L2/3-L3/4) and low (L4-L5/S1) lumbar levels yielded similar small to moderate effect sizes. More importantly, the current findings infer that measurements at the high, mid or low lumbar levels are not representative of the muscle across the whole lumbar region. This finding is supported by the recommendations of Crawford et al. (Crawford et al., 2017), who suggest that a multi-slice approach across all lumbar levels is superior to determine fat proportion within paravertebral muscle. Although more time-consuming, multi-slice approaches show clear benefits compared to more expedient single slice measurements, primarily as fat infiltration and size measurements at a single slice are not representative of the whole lumbar spine (Urrutia et al., 2018). Furthermore, volumetric measures are preferable as they are more meaningful functionally (Boom et al., 2008) and potentially minimise errors associated with postural variations during scanning (Meakin et al., 2013).

4.4. Influence of imaging modality on muscle atrophy

Age-related muscle atrophy was significantly influenced by imaging modality, specifically ultrasound. Ultrasound studies showed that muscle size increased with age in contrast to studies utilising MRI

and CT. This finding contradicts expectations and raises questions about ultrasound as an accurate imaging modality to measure paravertebral muscle atrophy in generally healthy older adults. Discrepant findings between ultrasound and CT/MRI studies may be due to the evaluation of muscle size when defining the ROI. Typically, MRI and CT evaluations do not consider fat infiltration as part of the muscle, whereas ultrasound measurements tend to involve the entire muscle including fat. Not considering the amount of fat infiltration within the muscle could mask reductions in muscle size and lead to spurious results (Elliott et al., 2008). Despite its limitations, the inclusion of fat within the ROI may provide a somewhat useful gross measure of muscle degeneration, whilst excluding regions of fat may demonstrate a more specific measure of muscle quality and potentially degenerative features within the muscle boundaries (Berry et al., 2018). Indeed, skeletal muscle measures derived from ultrasound are less able to distinguish intramuscular fat from muscle and accurate definition of the lumbar paravertebral muscles' boundaries is challenging (Hides et al., 1995; Pressler et al., 2006; Wallwork et al., 2009). MRI and CT provide high resolution images of soft tissues (Hyun et al., 2016). Compared to ultrasound, the superior soft tissue contrast of MRI/CT, particularly MRI (Hu et al., 2011), is thought to improve the visualisation of fascial boundaries (Upadhyay and Toms, 2015). Furthermore, the generally low resolution of ultrasonic images can make discernment of tissue types difficult (Hides et al., 1995). This is particularly troublesome when investigating the deep muscles in the pelvis and trunk; sound is reflected or absorbed by superficial tissue layers which results in deeper muscles lacking sufficient resolution (Pillen, 2010).

Another limitation associated with ultrasound concerns the operator's ability to standardise pressure applied by the transducer to the scan site (Lukaski, 1987). Muscle thickness, as well as subcutaneous adipose tissue, may be affected by excessive pressure (Abe et al., 1994). Therefore, avoiding excessive pressure whilst following a strict imaging protocol is paramount to achieving more accurate measures of muscle morphology when using ultrasound (Dupont et al., 2001). Finally, ultrasound typically has a limited field of view (Sions et al., 2017b), unlike MRI and CT which are capable of imaging the entire lumbar musculature whilst retaining sufficient resolution. Increasing the field of view to capture more of the lumbar musculature may compromise image quality for ultrasound, compounding the limitations stated above. Although imaging modality did not significantly influence the relationship between fat infiltration and ageing, ultrasound again exhibited marked differences with CT and MRI. Therefore, overestimation of muscle size was most likely due to the inclusion of non-contractile tissue (Sions et al., 2017b), whilst the underestimation of fat infiltration was likely a consequence of echo intensity diminishing in deeper muscles of the trunk (Pillen, 2010). Despite ultrasound being acknowledged as a lower cost and portable alternative to assess skeletal muscle morphology in clinical and community settings (Mourtzakis and Wischmeyer, 2014; Stringer and Wilson, 2018), the current findings indicate that studies should use MRI or CT to evaluate age-related atrophy in the lumbar paravertebral muscles.

4.5. Influence of BMI, mean age and age range on muscle degeneration

The continuous covariates did not have a moderating effect on the relationship between ageing and muscle atrophy. However, age range of the sample significantly influenced the relationship between fat infiltration and ageing, and mean BMI of the sample was approaching significance. It seems intuitive that an increase in BMI would increase the amount of fat infiltration in the lumbar paravertebral muscles with ageing. Since increases in BMI are largely attributed to increases in whole-body adiposity (Gallagher et al., 1996), it is likely that the amount of fat infiltrating the paravertebral muscles would also increase. Increasing age range also increased the effect of fat infiltration with ageing. Simply put, as age range increases for a population of healthy older adults,

greater degenerative changes in the paravertebral muscles can be observed. This is reflected in longitudinal observations as small time periods (e.g. 12 months) are likely to highlight only modest age-related changes in muscle morphology (Gibbons et al., 1997; Ikezoe et al., 2015), whereas longer periods (e.g. 15 years) have the potential to exhibit greater changes (Fortin et al., 2014), specifically in fat infiltration.

4.6. Sensitivity analyses

The sensitivity analyses showed that older adults, who are explicitly defined as healthy with a normal BMI, undergo less muscular degeneration in the lumbar region with normal ageing. Furthermore, all moderators were insignificant, suggesting that study level covariates are unable to moderate the relationship between ageing and lumbar paravertebral muscle degeneration in this population. Although samples included from the eligible studies were generally healthy, free from disease and without physical limitations, only 51% of these studies explicitly stated that their sample were healthy in the article. Based on information within articles and correspondence from authors, it is unlikely that the health status of samples between studies differed greatly. However, the sensitivity analyses suggest that older adult participants selected for health (i.e. explicitly defined as healthy with a normal BMI), exhibit less degeneration within the lumbar musculature. Similar discrepancies are seen in the degeneration of the lumbar paravertebral muscles between healthy and diseased populations (Kalichman et al., 2017). Although the samples included in the current review were not from diseased populations, the subtle differences in the definition of health status had a clear influence on age-related muscle atrophy and fat infiltration. Removal of 'poor' and 'fair' quality studies showed that greater atrophy was apparent with ageing. This suggests that good quality studies, most likely through better outcome measurement, are able to detect greater changes in paravertebral muscle size. Caution should be taken with this interpretation due to substantial between-study heterogeneity, although differences in methodologies and study population characteristics can explain most of the variance.

4.7. Limitations

Although this review was comprehensive and systematically rigorous, there were limitations that should be acknowledged. Firstly, data were collated from observational studies and baseline evaluations from experimental studies. Despite being the best available source, observational studies are considered to produce lower quality evidence than experimental studies and include a greater potential risk of bias. Furthermore, all data were collated from cross-sectional observations, making it difficult to ascertain the exact nature of age-related changes in muscle morphology. There is a need for more longitudinal studies directly investigating normative changes in lumbar paravertebral muscle morphology over longer time periods (>10 years). Ill-defined and inconsistent definitions of health status also limited the ability to compare studies. Although 18 studies (51%) explicitly stated that their sample were healthy, many of these studies provided insufficient detail on what constituted as 'healthy'. Furthermore, whilst some studies considered matched controls representative of healthy individuals, caution should be taken with this approach as undetermined phenotypes are likely hidden in the demographics (Määttä et al., 2015). Insufficient selection of participants based on their health status and lack of reporting clarity were substantial limitations. A standardised definition should be adopted to allow comparison between healthy populations as well as with diseased populations. Such advances would provide a reference to facilitate understanding

of spinal disease progression and pain-related expressions of muscle degeneration. Despite large sample sizes present in some studies, it is likely that many of the included data were not sufficiently powered to detect meaningful changes to muscle morphology with ageing; only six studies (17%) provided sample size justifications. It should be recognised that the English language restriction may have also limited the number of articles that were returned, although it was unlikely to result in systematic bias (Morrison et al., 2012). Data regarding physical activity were scarce from the studies included in this review. Although exercise is known to affect muscle morphology (Belavý et al., 2017; Ikenaga et al., 2017; Janssen et al., 2016; Konopka et al., 2018; Manini et al., 2007; Stec et al., 2017), changes in paravertebral muscle morphology are relatively independent of physical activity (Dahlqvist et al., 2015; Dasarathy and Merli, 2016; Fortin et al., 2014). Future studies should consider physical activity level when evaluating age-related degeneration of the lumbar musculature.

4.8. Practical applications

Measurement of muscle morphology is performed as part of sarcopenia diagnostic criteria (Chen et al., 2014; Cruz-Jentoft et al., 2019; Fielding et al., 2011; Studenski et al., 2014). Whilst appendicular skeletal muscle mass is typically measured (Correa-de-Araujo, 2017; Tosato et al., 2017), lumbar (L3) muscle cross-sectional area derived from CT or MRI offers a promising alternative (Golse et al., 2017; Gu et al., 2018; Schweitzer et al., 2015; Shen et al., 2004). However, the current results indicate that measurements derived from a single slice are not representative of the entire lumbar musculature. Volumetric measures across the lumbar are recommended; however, time costs involved in such an approach may not be suited to clinical settings. The choice of muscles should also be considered when investigating changes in lumbar muscle morphology. Whilst analysing each muscle in the lumbar spine would provide the most comprehensive assessment, the erector spinae and quadratus lumborum should be included in measurements as they show significant atrophy and fat infiltration with ageing. Based on the results of this review, MRI and CT are recommended over the use of ultrasound to measure changes in muscle quality and size with ageing. Indeed, MRI and CT are considered gold standard modalities for non-invasive assessment of muscle size (Cesari et al., 2012; Olsen et al., 2005). However, their use is limited in primary care settings by their availability, costs, radiation dosage (CT), inapplicability to persons with implanted medical devices (MRI), and requirement for highly specialised operators (Beaudart et al., 2016; Correa-de-Araujo, 2017). Despite these barriers, the use of high resolution imaging modalities to assess muscle degeneration is expected to become more commonplace in clinical practice (Cruz-Jentoft et al., 2019). Perhaps the greatest advantage of high-resolution imaging modalities is their ability to provide accurate estimates of muscle quality (McGregor et al., 2014). However, this review found numerous measures used in the literature, which makes transference into clinical practice difficult due to a lack of consensus. The importance of muscle quality as a key determinant of muscle function is being increasingly recognised and changes in muscle quality may precede those in muscle size with ageing (Anderson et al., 2016; Correa-de-Araujo et al., 2017; McGregor et al., 2014; Shahidi et al., 2017). Therefore, specific measures of fat infiltration to estimate changes in paravertebral muscle quality may be particularly useful in clinical settings. The findings of this study suggest that any fat infiltration measures derived from high resolution imaging modalities are suitable, although further research is needed to determine the optimal approach for future research and clinical applications. Applying the results from the regression analyses in this review to clinical practice could add to the current clinical perspective. As a measure of magnitude for age-related degeneration in the lumbar paravertebral muscles, correlation coefficients obtained from clinical assessment data can be

compared to the current findings, which may enable identification of abnormal degenerative changes with ageing. However, caution should be exercised due to the wide confidence intervals.

5. Conclusion

This systematic review, for the first time, draws together the extant literature relating to age-related changes in the lumbar musculature. The findings are based on older adults free of diseases or impairments that likely affect paravertebral muscle morphology. This is a necessary first step in furthering our understanding of normative expressions of ageing muscle as well as providing recommendations to establish continuity amongst protocols in future studies. The findings in this review indicate that the paravertebral muscles undergo degenerative changes (atrophy and fat infiltration) with normal ageing. Future studies investigating muscle morphology in the lumbar spine should consider the sex and age range of their sample, look to use MRI/CT to image the paravertebral muscles and analyse all the individual muscles across the entire lumbar region. However, these methodological decisions should not be uniform, rather based on the morphological outcome of interest. In summary, this review will provide a reference for normal age-related changes observed in lumbar paravertebral muscle morphology, which may enable identification of pathological deviations. Furthermore, the practical applications of this meta-analysis will provide guidance to future studies investigating age-related degeneration in the lumbar musculature.

Word count – 7984

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None

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Figure and Table Legend

Table 3 Eligibility criteria for including studies in this systematic review

Table 4 PubMed search strategy

Table 5 Graphical overview of study characteristics (*not provided in text – supplied separately)

Table 4 Three-level meta-analysis models for age-related muscle atrophy and fat infiltration in the lumbar paravertebral muscles

Table 5 Three-level meta-regression model estimating the moderating effects of Sex (Female = reference category), Muscle (Psoas = reference category), Level (All levels = reference category), Imaging technique (CT = reference category), BMI, mean age, and age range on the relationship between change in paravertebral muscle size and ageing

Table 6 Three-level meta-regression estimating the moderating effects of Sex (Female = reference category), Muscle (Psoas = reference category), Level (All levels = reference category), Imaging technique (CT = reference category), BMI, mean age, and age range on the relationship between change in paravertebral muscle fat infiltration and ageing

Fig. 1 PRISMA flow diagram depicting the selection process for studies

Fig. 2 Risk of bias summary: review of authors' judgements on each item from the Risk of Bias Assessment Tool for Nonrandomised Studies (RoBANS) presented as percentages across all included studies

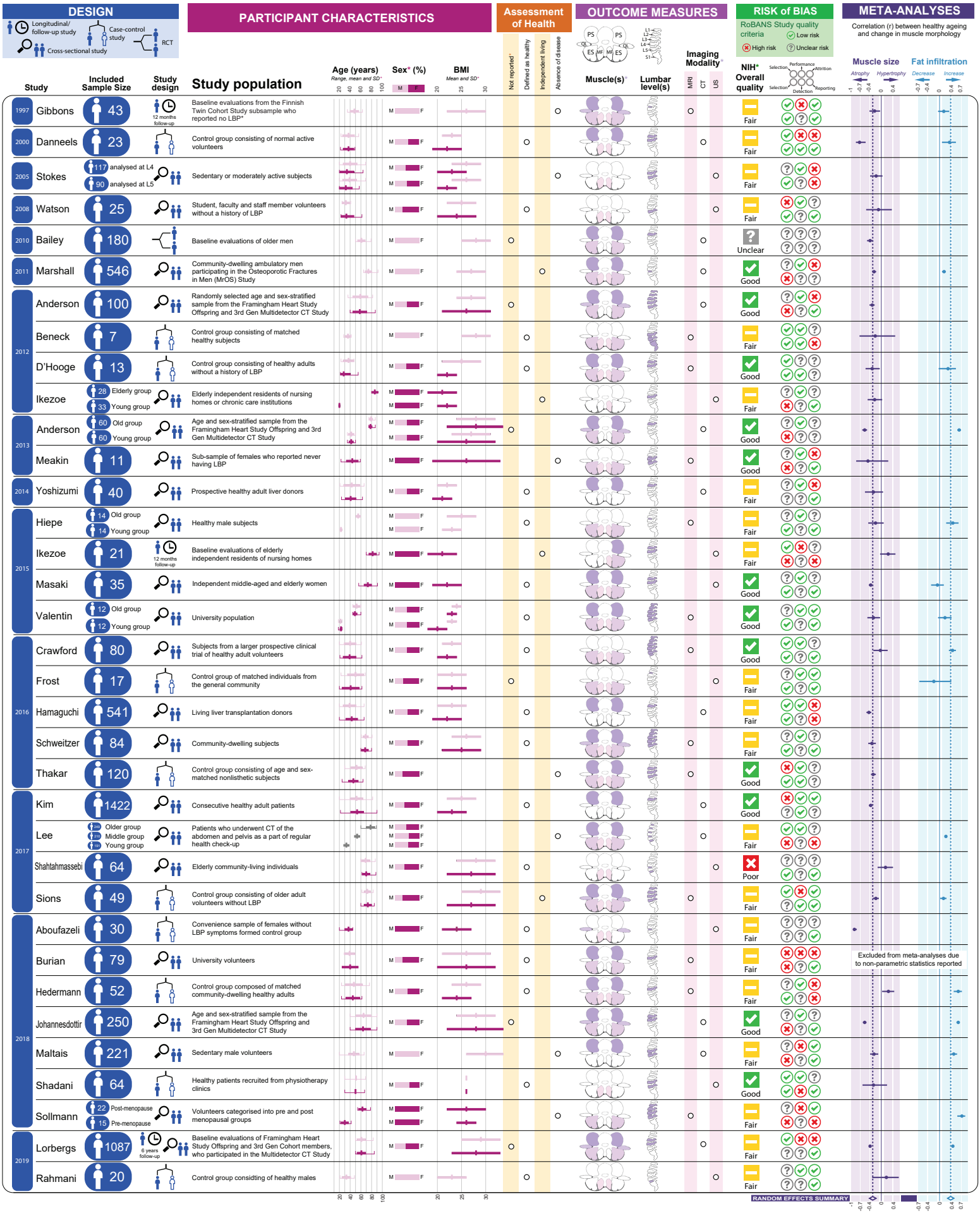
Fig. 3 Visual representation of the amount of between-study variance in true effects explained by moderators for the relationship between muscle atrophy and ageing

Fig. 4 Visual representation of the amount of between-study variance in true effects explained by moderators for the relationship between fat infiltration and ageing

F**ig. 5** Contour enhanced funnel plot to illustrate potential publication bias for studies assessing muscle quality (fat infiltration)

Visual Summary

Graphical overview comparing participant characteristics, evidence quality, risk of bias and findings of the included studies.



*LBP=lower back pain; *SD=standard deviation; *M=male, F=female; *Author(s) confirmed health status; †PS=psoas, QL=quadratus lumborum, ES=erector spinae, MF=multifidus; †MRI=magnetic resonance imaging, CT=computerised tomography, US=ultrasound; *NIH=National Institutes of Health study quality assessment tools