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Novelty bullets: points that summarize the key findings in the work:	• Inclusion of muscle strength and torque of KE and KF data from >15 000 subjects, • Isometric KE and KF strength loss do not accelerate differently between sexes, • Isokinetic 60°s-1 KE torque decline with aging accelerates 25 years earlier in females and female age-related KF peak torqu
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Age and Sex-Related Decline of Muscle Strength Across the Adult Lifespan: A scoping review of aggregated data

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Abstract

Muscle strength is sex-related and declines with advancing age yet, a comprehensive comparative evaluation of age-related strength loss in human females and males has not been undertaken. To do so, segmented piecewise regression analysis was performed on aggregated data from studies published 1990-2018 and available in CINAHL, EMBASE, MEDLINE, and PsycINFO databases. The search identified 5613 articles which were reviewed for physical assessment results stratified by sex and age. Maximal isometric and isokinetic 60°s^{-1} contractions of the KE and KF from 57 studies and 15,283 subject (N=7918 females) had sufficient data reported on females and males for meaningful statistical evaluation to be undertaken. The analysis revealed that isometric KE and KF strength undergo similar rapid declines in both sexes late in the 6th decade of life. Yet, there is an abrupt age-related decline in KE 60°s^{-1} peak torque earlier in females (41.8 years) than males (66.7 years). In the assessment of KF peak torque, an age-related acceleration in strength loss was only identified in males (49.3 years). The results suggest that age-related isometric strength loss is similar between sexes while the characteristics of KE and KF peak torque decline are sex-related which likely explains the differential rate of age-related functional decline.

Novelty

- Inclusion of muscle strength and torque of KE and KF data from >15 000 subjects
- Isometric KE and KF strength loss are similar between sexes
- Isokinetic 60°s^{-1} KE torque decline accelerates 25 years earlier in females and female age-related KF peak torque decline does not accelerate with age

Key words: male, female, sarcopenia, dynapenia, functional independence, isometric, dynamic, quadriceps, hamstring

Background

Aging is associated with decreased muscle strength and power (Dalton et al., 2010; Danneskiold-Samsøe et al., 2009; Jakobi & Rice, 2002; Narici et al., 1991; Vandervoort & McComas, 1986), and attributed as an underlying factor in the increasing prevalence of frailty, and associated mobility limitations in older adults (Bean et al 2003). Internationally age-related mobility and agility disabilities are greater in females compared with males (Mechakra-Tahiri et al., 2012). For example, in Canada 48.4% and 44.3%, of females report mobility and disability difficulties compared to 39.4% and 38.6% of males, respectively (Statistics Canada, 2006). Little consideration has been given to the role of biological sex in age-related strength loss which is an underlying factor of mobility and disability decline and a diagnostic consideration of sarcopenia.

Dynapenia is the term applied to age-related strength loss. The etiology and risk factors associated with dynapenia include reductions in muscle mass, muscle cross-sectional area, muscle quality, muscle fibre numbers, and motor unit remodelling (Baumgartner et al., 1999; Dalton et al., 2010; Foldvari et al., 2000; Frontera et al., 1991; Hunter et al., 2016; Johannesdottir et al., 2018; Lexell, 1997; Piasecki et al., 2018; Vandervoort & McComas, 1986). Collectively, these physiological adaptations also characterise the common syndrome associated with aging: sarcopenia. Operationally defined by the European Working Group on Sarcopenia in Older People as "a progressive and generalised skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability and mortality," (Cruz-Jentoft et al., 2019), sarcopenia contributes to decrements in physical function with advancing age. Sarcopenia, in 2016 was defined as an independent condition with an International Classification of Diseases-10 code, however, most scientists and clinicians remain unaware of the diagnostic tools needed to identify it (Bruyère et al., 2016; Sayer, 2010). While

no longer formally recognized as a separate disorder, dynapenia is the foremost indicator of sarcopenia (Cruz-Jentoft et al., 2019). The age-related adaptations in neural and contractile elements that contribute to sarcopenia are traditionally understudied in females (reviewed in Hunter, 2016; Jakobi et al., 2018), thereby lessening meaningful conclusions on sex-specific mechanisms of age-related functional decline (Butler et al., 2009; Murtagh & Hubert, 2004; Tseng et al., 2014). To better understand functional decline in aging females, it is beneficial to define how male and female strength decreases across the lifespan. Although sarcopenia is a syndrome that encapsulates both loss of strength and function in older age, the term dynapenia will be employed as it describes the primary variable under consideration in this review: strength loss in adults to older adults (Clark & Manini, 2008, 2012).

Cohort studies have reported that females lose absolute as well as relative muscle mass at a slower rate than males (Abe et al., 2014; Gallagher et al., 2017; Lindle et al., 1997; Zamboni et al., 2003), and this observation is as interesting as it is counterintuitive given that older females perform worse on tests of physical function (Butler et al., 2009), and have a higher prevalence of physical disability than males (Murtagh & Hubert, 2004; Tseng et al., 2014). Thereby, creating a conundrum of sorts on whether there is a differential loss of muscle strength between females and males, or whether the higher strength achieved in young males is the greatest factor in maintaining independence in older age. Typically, studies that investigate age-related dynapenia study males and employ linear (Baumgartner et al., 1999; Chin et al., 2012; Hughes et al., 2001; Newman et al., 2003), or curvilinear (Danneskiold-Samsøe et al., 2009; Lindle et al., 1997; Suetta et al., 2019) regression models and have concluded that across muscle groups, strength peaks in young adulthood and generally declines with age (Francis et al., 2017). The curvilinear analyses show a steeper slope in advanced age, indicating that dynapenia accelerates as people

transition from mid-life to older adulthood (Francis et al., 2017). Segmented piecewise regression analysis is unique to these approaches as it enables detection of breakpoints, from aggregated data from many studies, to identify abrupt changes in slope that are indicative of an age threshold when dynapenia may accelerate, and this approach when applied to males and females might facilitate understanding of sex-specific age-related changes.

Isometric and isokinetic contractions are commonly used to assess muscle strength. Isometric maximal voluntary contractions (MVCs) examine the maximum force producing capacity of the neuromuscular system in a fixed position. Isometric leg strength is positively associated with physical function in older adults (Bouchard et al., 2011; Hicks et al., 2012); however, it may not be the most functionally relevant measure as few activities of daily life are performed in a sustained fixed joint orientation. Power and speed, which cannot be measured from an isometric contraction, decline to a greater extent with age compared to maximal strength (Skelton et al., 1994; Thompson et al., 2014; van Driessche et al., 2019), and given the necessity of joint range of motion for functional activity, dynamic contractions require consideration for sex-specific age-related adaptations. Isokinetic dynamometry accounts for these dynamic muscular qualities in the measurement of strength and provides insight into the physiological mechanisms underlying dynamic neuromuscular output (Danneskiold-Samsøe et al., 2009). Though both forms of dynamometry are used to track age-related changes, there are far fewer isokinetic than isometric studies. However, due to its functional relevance to daily movement, isokinetic dynamometry is a more useful tool for measuring age-related sex-specific strength loss to better understand functional decline in older adults.

It is well known that sex and age influence the morphology and control of muscle whereby males and young adults tend to have larger muscles that produce steadier and more

forceful contractions than females and older adults (Behan et al., 2018; Francis et al., 2017; Jakobi et al., 2018). Despite strength being strongly associated with sex, the scientific literature evaluating age-related loss of muscle strength typically evaluates one sex or statistically collapses across sexes and disregards the potential for sex-related differences (Hairi et al., 2010; Kallman et al., 1990). Thus, in order to appreciate sex-related differences in functional ability, an understanding of strength loss between males and females across the entire adult lifespan needs to be ascertained. The objective of this scoping review is to evaluate whether the time-course of dynapenia differs between sexes. This paper reviews previous studies invoking the term gender to describe sex since many studies conflated the terms, although they have inherently different meanings (Institute of Gender and Health, 2019). This evaluation of sex-specific muscle strength loss will provide a time-course that will inform the appropriate timing of interventions to mitigate strength loss in order to preserve functional ability in both aging females and males.

Methods

Study Selection

Relevant studies were identified from the following bibliographic databases: CINAHL (1982–April 2018), EMBASE (1980–April 2018), MEDLINE (1966-April 2018) and PsycINFO (1967– April 2018). All databases were searched using MeSH terms identified in the title, abstract, or key words: (“sex” OR “gender” OR “males and females” OR “men and women”) AND (“age$” OR “aging”) AND (“muscle strength” OR “muscle force” OR “lean body mass”) (Figure 1). After deduplication, the initial search identified 5613 titles from the electronic databases.

Study titles and abstracts were reviewed for the following selection criteria by four authors (KC, EH, GJ, and NN). Articles were excluded if the title or abstract did not meet the following inclusion criteria; (a) published in English, (b) subjects aged 18 years and over, (c) incorporate a male and female comparison (if this was not clear in the abstract, the article was included for further review to determine inclusion), (d) include a healthy population (minimum a healthy control group) (Figure 1). For example, studies examining specific diseases and/or conditions without a healthy control were excluded, and studies that included both males and females but collapsed across sex in the analysis were also removed. Articles were excluded if they met any of the following conditions; (a) published prior to 1990, (b) reported a conflict of interest related to funding support, (c) collapsed across sex for muscle strength results, or (d) did not include a measure of maximal strength for at least one of the following contraction types: knee flexion (KF), knee extension (KE), elbow flexion (EF), elbow extension (EE). To ensure quality of the studies, the main text of the articles that met the inclusion criteria were evaluated between two authors (EH and NN) (Figure 1). Five articles only reported results within figures and these authors were contacted to obtain actual numerical values. The corresponding authors from three of the five studies responded (Beliaeff et al., 2008; Bryant et al., 2007; Koster et al., 2011) to our request and are included in the analysis.

Data Extraction

When the studies were evaluated in detail, eight reported age in decades. The data from these studies were included in the aggregate sample by using the median year of the decade. For example, studies that reported subjects as being in the fourth decade of life (30-39 years) were coded as 35 years of age. All isokinetic MVC data were converted and reported in Newton metres (Nm), and isometric MVC values in Newtons (N). Conversion of Nm to N for the

isometric KE and KF measures was undertaken using a predictive anthropometric equation based upon participant height (Duyar & Pelin, 2003) to yield lever arm length and solve for isometric KE and KF force output at the ankle (N=17). Three community-based studies (Breton et al., 2014; Hisamoto et al., 2005; Tarsuslu-Şimşek & Yanardag, 2017) were not included in the final analysis because they reported isometric MVCs that were >2 standard deviations below age-matched reference values (Danneskiold-Samsøe et al., 2009). The reported studies were stratified into EE, EF, KE, and KF MVC and peak torque by age and sex. The number of isometric and isokinetic upper limb studies that reported strength in both sexes (N=18) was insufficient for statistical evaluation, and thus the analysis was confined to KE and KF. Isokinetic lower limb data for 180°s^{-1} was also considered. Similar to the upper body too little data was available across the lifespan to produce logical outputs; thus, due to insufficient power to produce accurate and physiologically relevant analyses, we have limited our report to isometric and isokinetic 60°s^{-1} KE and KF contractions.

Statistical Evaluation

All analyses were conducted on the mean strength values of females and males, reported in each study. Regression analyses were used to assess age- and sex-related differences, followed by moderated multiple regression analyses to explore age by sex interactions associated with the decline of muscle strength. Subsequently, we employed segmented piecewise regressions within sex to determine whether there were two distinct linear relationships prior to, and following, a sharp change in slope. Segmented piecewise regression models are valuable and informative when analyzing data from multiple studies with varying sample sizes. The sharp changes in slope offer evidence of break points in the trajectory of age-associated loss of muscle strength. Sex-specific differences in the breakpoints (abrupt decline in strength) were assessed using t-tests. All

the analyses were performed for each muscle group (KF, KE) and for both types of contraction (isometric, isokinetic) separately. Alpha levels were set at 0.05. Subject data are presented in Table 1 as they are reported in original citations. The analyses were conducted using the statistical language R (R Foundation for Statistical Computing, Vienna, Austria).

Results

The initial search examined 5613 articles. Following the title and abstract review, the external review process, and quality assessment, results from 57 studies met the inclusion criteria (Table 1). Data evaluated between sexes were from healthy individuals (N=7365 males; N=7918 females) with no known neurological, musculoskeletal, or cardiopulmonary disorders. The statistical analysis was conducted on data reported in studies featuring maximal isometric and isokinetic 60°s^{-1} KE (N=41; N=17) and KF (N=13; N=9) contractions and stratified by age and sex for the reported isometric strength and isokinetic peak torque values. There was a subset of studies (N=34) that reported mean data on more than one muscle group or strength measure. The age ranges analyzed in the final aggregate data encapsulate the normal adult lifespan: isometric KE (20-85yrs) and KF (20-83.1yrs), and isokinetic 60°s^{-1} KE (22-85.9yrs), and KF (22.1-85.9yrs).

Regression analysis did not detect age by sex interactions for isometric KE and KF strength; however, there were main effects of age and sex. Isometric strength was higher in males than females in KE (R^2=0.23, p=1.0e-12) and KF (R^2=0.35, p=4.5e-10). Young adults were stronger than older adults in KE (R^2=0.36, p=5.7e-21) and KF (R^2=0.11, p=1.4e-3) isometric strength. Age by sex interactions were detected for isokinetic KE (ΔR^2= 0.026, F=15.2, df=86, p=1.9e-4) and KF (ΔR^2= 0.019, F=7.44, df=56, p=8.5e-3) contractions. In both muscle groups, male

isokinetic torque declined at a faster rate with age compared to females and is illustrated through original data points (Figures 2C, D).

Segmented piecewise regression analysis detected breakpoints in both sexes for isometric KE and KF, and isokinetic KE (Table 2). The breakpoints in both sets (KE; KF) of isometric data were not different between males (57.2 years; 58.6 years) and females (57.1 years; 57.1 years) ($p>0.05$). In isokinetic KF, a breakpoint was only detected for males (49.4 years). The breakpoint in the isokinetic KE data was significantly lower in females (41.8 yrs) compared with males (66.6 yrs) ($R^2=0.053$, $T=3.2$, $df=178$, $p<0.05$). The only condition where slope was significant before the breakpoint was isometric KE ($p<0.05$) and this was the case in both sexes. Slope was significant after the breakpoint in all contraction types for males ($p<0.05$) but only in isometric ($p<0.05$) and isokinetic KE ($p<0.05$) for females.

Discussion

This scoping review featuring aggregated data sought to investigate sex-specific differences in age-related dynapenia throughout adulthood and into old age. The robust KE and KF data enabled our novel statistical evaluation to be undertaken in these muscle groups; however, it was not possible to apply the analysis to the upper limb or isokinetic contractions other than $60°s^{-1}$ due to the limited number of reports stratified by sex across adult ages. Analysis of the aggregated mean data revealed that males are stronger than females across the adult lifespan and that, in both sexes, isometric KE and KF strength loss abruptly accelerates late in the 6^{th} decade of life. Contrary to isometric, the sex-specific breaking points in dynamic KE strength loss differed between sexes whereby the onset of sudden decline occurs at ~67 years of age in males, and ~25 years earlier in females at ~42 years (Table 2). In dynamic KF, females consistently lose dynamic strength throughout the adult lifespan while males preserve dynamic KF strength until

the onset of rapid decline at ~50 years of age. Data from this sample of 57 studies, directly comparing 7918 females to 7365 males (Table 1) suggests that age-related dynapenia is muscle- and contraction-specific, as well as sex-dependent for the agonist-antagonist pair of KE and KF.

The analysis reveals a distinct acceleration in isometric strength loss in approximately the 6th decade of life, and males appear to lose strength at a faster rate than females (Figure 2): a common observation in lifespan investigations of strength (Gallagher et al., 2017; Lindle et al., 1997; Suetta et al., 2019; Zamboni et al., 2003). This differential rate of decline possibly reflects motoneuron loss in normal healthy aging (Kawamura et al., 1977; Lexell, 1997); however, the sex-specific nature of age-related motor unit remodelling (Piasecki et al., 2016a., Piasecki et al., 2016b) remains to be fully elucidated in humans as an extension of the animal models (Celichowski & Drzymała-Celichowska, 2007; Smart et al., 2019; Swiecicka et al., 2019). For some, the ability to conserve muscle mass by expanding the size of surviving motor units in spite of motoneuron loss may be protective against the functional declines of aging (McPhee et al., 2018; Piasecki et al., 2018). Supporting the position of motoneuron loss, albeit equivocally (Krivickas et al., 2006), some studies have suggested males have a larger proportion of type II muscle fibres (Haizlip et al., 2015; Trevino et al., 2019), yet whether these sex-specific differences at a young age contribute to distinctive rates of strength loss with age remains to be established. However, since the proportion of type II muscle fibres is higher in males than females (Trevino et al., 2019) over a similar timeframe males have relatively more to lose potentially contributing to the greater decline in slope of strength against age following the breakpoints (Francis et al., 2017; Wu et al., 2016).

While the isometric analysis did not reveal sex-specific differences in breakpoints to support the theory that females experience greater functional decline because of earlier strength loss

(Butler et al., 2009; Murtagh & Hubert, 2004; Tseng et al., 2014) it is worth noting that low isometric muscle strength does not entirely predict the severity of sarcopenia in older adults (Cruz-Jentoft et al., 2019). Isokinetic dynamometry studies, which are likely more reflective of changes in physical function (Symons et al., 2004), indicate that females experience rapid onset of dynamic KE peak torque loss earlier than males (Figure 2C). Additionally, the KF peak torque loss is consistent throughout adulthood in females (Figure 2D). The earlier and constant strength loss in these muscles of females, compared with males, is indicative of the sex-specific decline of physical function. Thus, strength training interventions that preserve or ameliorate dynamic strength loss in females should be seriously considered as prehabilitation measures at a relatively younger age than males in order to delay age-related physical disability. The prospect of preserving dynamic torque in older females is promising, as Shaw & Snow (1998) increased KE isokinetic torque nearly 17% in a group of postmenopausal older females, and Bray and colleagues (Bray et al., 2016, 2020) suggested that pre-frail women become less frail following progressive multi-component resistance training. Many studies have described the positive effects of resistance training for healthy older adults (reviewed in Garatachea et al., 2015) and it is widely understood that strength training is beneficial at all stages of adulthood, yet knowing the age at which older adults, especially females, exhibit rapid strength decrements might offer informed motivation for females to exercise at or before critical thresholds of age-related decline. Furthermore, multi-component exercise interventions confer health benefits beyond improved muscle strength. Cardiorespiratory fitness and the ability to perform motor tasks under cognitive load are negatively affected by age (Garatachea et al., 2015; Pereira et al., 2015) and both might be improved, or at least preserved, by exercise training. This combined approach has the potential to delay the progression of sarcopenia and preserve physical function in older adults.

Future research into age-related strength loss should therefore attend to sex-specific differences while monitoring longitudinal changes in strength and in interventions that are undertaken prior to abrupt declines that invariably contribute to reduced physical function. One particularly interesting finding is that females preserve isometric KF strength until mid-life (Figure 2B) but isokinetic KF torque declines linearly from its peak in early adulthood (Figure 2D). These results may be associated with findings of sex-related differences in compartmental leg strength that are present in childhood. The conventional method of measuring hamstrings-to-quadriceps ratio (H:Q) relates peak torque between KF and KE contractions to detect imbalances about the knee in the sagittal plane during isokinetic concentric contractions (Ruas et al., 2019). In a large study of prepubescent children aged 7-12 years (N = 368), males were found to consistently express greater H:Q than females at $60°s^{-1}$ (Holm & Vøllestad, 2008). Other studies investigating H:Q in adults using conventional (de Ste Croix et al., 2017; El-Ashker et al., 2017) and alternative methods, including comparisons of muscle size, angle specific torque, and isometric force (Behan et al., 2018; de Ste Croix et al., 2017; Hannah et al., 2015) between the knee antagonist pairs have found that female H:Q is consistently lower than male. Additionally, when males and females undergo an identical lower body resistance training program, females show significantly greater positive changes in H:Q due to relatively greater increases in concentric isokinetic KF torque (Dorgo et al., 2012). These changes in H:Q are so pronounced that they actually surpass males, and the sex-related trend in H:Q is reversed (Dorgo et al., 2012). The results of the analyses presented herein along with previous reports on sex-related differences in KF performance indicate that females experience accelerated dynamic KF strength loss due to an underlying sex-related difference in knee flexor physiology that is present in children and

persists into adulthood. However, the outlook for female KF strength is positive as they appear to also have better dose-response potential for training this muscle group.

It has been suggested that people experience sarcopenia, as a consequence of declining endogenous estrogen and testosterone (sex hormone) levels in females and males, respectively (Diamanti-Kandarakis et al., 2017; Morley et al., 1997; Philips et al., 1993). Although the endocrine system certainly promotes sexually dimorphic development of body tissues, female estrogen depletion cannot directly explain the present results since the isometric analysis indicated no differences between sexes in the breakpoints, and the female isokinetic KE segmented piecewise regression breaks before the supposed completion of the menopausal transition (Figure 2C). Menopause is frequently suggested to be a primary contributing factor in the development of sarcopenia in females despite the literature being equivocal as to the mechanism and timeframe in which estrogen depletion affects muscle strength (Collins et al., 2019; Elliott-Sale, 2014). In males, testosterone depletion begins as early as the 3rd decade of life (Chu et al., 2008; Diamanti-Kandarakis et al., 2017) which does not explain the sudden declines in strength observed in the 5th, 6th and 7th decades of life (Table 2). Available reports on testosterone depletion in aging males suggest that increasing production of sex-hormone binding globulin attenuates the positive effects of testosterone on muscle strength (Chu et al., 2008; Liu et al., 2007). Although levels of testosterone and circulating DHEAS are well known factors in developing muscle strength and ovarian estrogen decline during menopause might be related to the loss of strength in postmenopausal women (Collins et al., 2019) there is an overall scarcity of information quantifying the progression of sex hormone depletion, and its impact on the aging neuromuscular system of females and males (Decaroli & Rochira, 2017; Diamanti-Kandarakis et al., 2017; Elliott-Sale, 2014; Swiecicka et al., in press). Thus, further study is warranted.

Interestingly, one study included in our analysis that evaluated both females and males, considered sex hormones (estrogens, DHEAS, total testosterone; Gómez-Cabello et al., 2014). In this prospective cohort study Gómez-Cabello and colleagues (2014) used hormones as a confounder in the statistical analysis of physical activity and muscle strength, and suggest that although sex-based hormones are a key factor in altering muscle strength during the ageing process they do not explain the sex-specific differences. Furthermore, sex hormone replacement should not be considered a panacea in preventing age-related physical decline since the understanding of sex hormone interactions upon aging body tissues and their relation to physical function is still unclear. More studies that define the relations between sex hormones and functional muscle groups such as the knee extensors and flexors, would be instrumental in defining factors that contribute to sex-specific strength outcomes in aging.

The major limitation to this statistical analysis is the aggregation of mean data from multiple cross-sectional muscle strength datasets. The data for the different age ranges were from different persons, which confounds age trends with possible cohort differences. This issue is common in cohort research designs (Laursen et al., 2012). However, in the absence of a multi-decade longitudinal study data, the aggregation of data from multiple smaller scale cohort studies provides the best estimate of wider-span trends. While this was the most efficient manner to accrue a sufficient number of data points for segmented piecewise regression analysis, the individual studies do not independently reveal a specific chronological point of age when strength loss will abruptly decline in an average population. Yet, this approach offers an understanding of biological sex-related differences. Most studies have historically evaluated age-related loss of strength exclusively in males or collapsed results across sex to boost statistical power. Since all research evaluated in the present analysis features males and females of the

same age groupings tested under identical conditions, the sex-related differences, or lack thereof, in how dynapenia progresses with age is more robust than when studies employ different testing methods and data from only one sex. A wide array of equipment (commercially available and custom-built dynamometers), joint positions, and testing procedures were used to collect results, and the assessment of voluntary activation was not consistent across studies. For these reasons, the comparative specific age when isometric and dynamic strength loss abruptly accelerates needs to be ascertained experimentally, ideally in a multi-decade longitudinal cohort study. Studies that measure both isometric strength and dynamic torque are few (e.g. (Danneskiold-Samsøe et al., 2009) and even less when comparatives between females and males are also desired.

This scoping review used aggregate data reported in studies that included both main sexes and identified differential rates of dynapenia between sexes across the lifespan. The sheer number of studies returned by our initial database search (Figure 1) makes it apparent that sex and age are strong considerations in understanding the contribution of sarcopenia to functional decline. Yet, only a relatively small fraction (~1%) of the numerous studies stratified results by sex (Table 1). Furthermore, not enough data has been published on the upper body or isokinetic contractions for segmented piecewise regression analyses to be accurately conducted at angular velocities higher than $60°s^{-1}$. Yet, assessing dynapenia in an isokinetic versus isometric contraction of the lower body enables sex-related differences in power and strength loss to become more apparent. Biological sex differences in the diagnosis and management of sarcopenia should be approached from a lifespan perspective to develop timely interventions for aging females and males that preserve physical function.

The authors have no conflicts of interest to report.

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Table 1. Summary of studies that met inclusion criteria.

Study	Male Sample Size	Male Age Groups (Range or Mean ± SD)	Female Sample Size	Female Age Groups (Range or Mean ± SD)	Strength Assessment(s)	Muscle Group(s)	Measurement Device
Andrews et al., 1996	25 26 26	54.0 ± 3.4 66.1 ± 2.9 72.9 ± 2.7	25 29 25	54.6 ± 2.8 64.5 ± 2.9 73.8 ± 3.2	Isometric	EE EF KE KF	Chatillon CSD400C
Backman et al., 1995	10 12 11 10 10 12	17.6 ± 0.6 24.4 ± 3.3 35.1 ± 2.6 43.8 ± 3.5 54.0 ± 3.3 65.6 ± 3.1	10 10 10 13 10 10	17.7 ± 0.6 23.4 ± 2.7 34.8 ± 3.0 43.1 ± 2.8 54.0 ± 2.9 65.4 ± 2.8	Isometric	EF KE KF	Penny & Giles myometer
Beliaeff et al., 2008	201 128 110	69.9 ± 1.4 74.7 ± 1.4 79.8 ± 1.4	181 167 117	69.8 ± 1.4 74.8 ± 1.4 79.6 ± 1.4	Isometric	EF KE	microFET®2
Bijlsma et al., 2013	78	80.7 ± 6.8	119	82.7 ± 7.2	Isometric	KE	Mounted force transducer (ForceLink B.V.)
Björkman et al., 2012	19	79.6 ± 7.6	44	84.7 ± 8.1	Isometric	KE	microFET®2
Bohannon et al., 1996	79	64.3 ± 8.2	77	64.4 ± 8.4	Isometric	KE KF	Chatillon CSD400C

Bohannon, 1997	16 13 15 22 18 22	23.9 ± 3.2 34.2 ± 2.9 44.9 ± 2.6 54.8 ± 3.1 66.2 ± 2.8 73.0 ± 2.7	22 23 21 21 18 20	22.3 ± 2.3 35.1 ± 2.7 44.1 ± 2.4 53.8 ± 2.8 64.8 ± 3.0 73.1 ± 3.1	Isometric	EE EF KE	AccuForce II
Bohannon et al., 2012	10	23.4 ± 1.5	10	23.8 ± 2.3	Isometric	KE	microFET®2
Bouchard et al., 2011	212 261 162	59.5 65.0 80.0	233 253 159	59.5 65.0 80.0	Isometric	KE	Kin-Com MP
Brinkmann, 1996	220	47.0 ± 19.0	273	43 ± 25.0	Isometric	EE EF KE KF	Mounted strain gauge (Interface SM-250)
Bryant et al., 2007	43	60.0 ± 4.0	52	59.0 ± 4.0	Isokinetic	KE KF	Biodex System 2®
Carmeli et al., 2000	7 5	80.1 ± 1.4 83.2 ± 0.9	10 6	81.8 ± 1.6 85.9 ± 1.3	Isokinetic	KE KF	Unspecified Biodex system
Castillo et al., 2015	764	75.1 ± 5.8	977	75.2 ± 6.1	Isometric	KE	Lafayette

Charlier et al., 2015	86 152 360 97 87 13	18-30 30 40-50 50-60 60-70 70<	48 148 249 79 35 7	18-30 30 40-50 50-60 60-70 70<	Isokinetic Isometric	KE	Biodex System 3®
Choquette et al., 2010	439	73.6 ± 0.1	465	74.0 ± 0.1	Isometric	KE	microFET®2
da Boit et al., 2017	13 14	71.5 ± 5.1 69.8 ± 4.0	10 13	70.9 ± 2.6 70.5 ± 3.9	Isometric	KE	Unspecified Biodex system
Danneskiold-Samsøe et al., 2009	10 10 12 10 10 11	27.9 ± 1.2 34.3 ± 2.5 43.8 ± 2.7 54.6 ± 2.0 64.1 ± 2.1 74.8 ± 2.5	18 18 23 18 22 27	26.1 ± 2.2 34.7 ± 2.8 44.4 ± 3.1 55.1 ± 2.9 64.5 ± 3.0 73.1 ± 2.4	Isokinetic	EE EF KE KF	Lido Multi Joint II
Dey et al., 2009	38 38	75.0 ± 0.0 80.0 ± 0.0	49 49	75.0 ± 0.0 80.0 ± 0.0	Isometric	EF KE	Adjustable dynamometer chair
Dorgo et al., 2012	16	23.1 ± 1.6	17	22.1 ± 2.7	Isokinetic	KE KF	Biodex System 3®
Douma et al., 2014	48 51 70 59	20-29 30-39 40-49 50-59	51 39 66 34	20-29 30-39 40-49 50-59	Isometric	EE EF KE KF	microFET®2

Frontera et al., 1991	29	49 ± 4	26	45 ± 4	Isokinetic	EE EF KE KF	Cybex II®
Gómez-Cabello et al., 2014	760	65≤	980	65≤	Isometric	KE	Lafayette
Häkkinen et al., 2001	10 10	42 ± 2 72 ± 3	11 10	39 ± 3 67 ± 3	Isometric	KE	David 200
Harbo et al., 2012	93 total	<30 30-39 40-49 50-59 60-69 70<	85 total	<30 30-39 40-49 50-59 60-69 70<	Isokinetic Isometric	EE EF KE	Biodex System 3 Pro®
Hayashida et al., 2014	51 60	70 75	102 105	65-74 75≤	Isometric	KE	μTas-01
Hicks et al., 2012	419	73.3 ± 6.4	515	74.4 ± 6.8	Isometric	KE	Unidentified handheld dynamometer
Inglis et al., 2013	23	23 ± 3.3	23	23 ± 1.6	Isometric	EF	Mounted load cell (JR3 Inc., Woodland, CA)
Kannus & Beynnon, 1993	143	30.0 ± 4.0	106	29.0 ± 5.0	Isokinetic	KE KF	Cybex II®

Kim et al., 2013	188 51	72.7 ± 7.0 78.7 ± 8.8	188 51	70.6 ± 5.6 76.6 ± 7.6	Isokinetic	KE	Unspecified Biodex system
Kim et al., 2016	260 26	73.66 ± 7.40 79.35 ± 9.19	259 15	73.14 ± 7.03 79.39 ± 8.91	Isokinetic	KE	Unspecified Biodex system
Leyva et al., 2016	161 total	20-29 30-39 40-49 50-59 60-69 70-79	194 total	20-29 30-39 40-49 50-59 60-69 70-79	Isokinetic	KE KF	Biodex System 2®
Mänty et al., 2012	289	75	234	75	Isometric	KE	Adjustable dynamometer chair
Marcell et al., 2014	45	58.6 ± 7.3	20	57.1 ± 8.2	Isokinetic	KE KF	Kin-Com
Mcphee et al., 2014	9 9	22.4 ± 3.1 68.9 ± 4.4	8 10	22.3 ± 1.9 71.1 ± 3.4	Isometric	KE	Force transducer
Meldrum et al., 2007	235 total	20 25 30 35 40 45 50 55 60 65 70	249 total	20 25 30 35 40 45 50 55 60 65 70	Isometric	EE EF KE KF	Quantitative Muscle Assessment system

Molenaar et al., 2013	4 5 4 4 6 1 2	25 35 45 55 65 75 85	5 5 5 5 6 4	25 35 45 55 65 75	Isometric	EF	Mounted strain gauge (Xtran)
Narumi et al., 2017	283 302 382 296 174 189 66	20-29 30-39 40-49 50-59 60-69 70-79 80-89	231 276 342 295 311 372 98	20-29 30-39 40-49 50-59 60-69 70-79 80-89	Isometric	EF	Locomo Scan
Nguyen et al., 2005	660	69.8 ± 6.1	74	70.3 ± 7.4	Isometric	KE	Mounted horizontal spring gauge
Owerkowicz et al., 2016	8	22 ± 0.4	9	22 ± 0.4	Isokinetic Isometric	KE	Biodex System 3®
Phillips et al., 2000	20 20 20 20 20	22.6 ± 2.4 34.0 ± 2.9 43.9 ± 3.1 53.7 ± 3.3 64.5 ± 2.4	20 20 20 20 20	24.2 ± 2.9 35.0 ± 3.4 45.2 ± 3.2 54.5 ± 2.9 63.9 ± 3.0	Isometric	EE EF	Penny and Giles myometer
Rantanen & Heikkinen, 1998	20	80.0 ± 0.0	59	80.0 ± 0.0	Isometric	Elbow Flexion Knee Flexion	Adjustable dynamometer chair

Sahni et al., 2015	1166	60.2 ± 9.3	1509	59 ± 9.3	Isometric	KE	Nicholas hand-held
Samuel & Rowe, 2009	15 14 13	65.7 ± 3.0 73.6 ± 3.2 81.9 ± 1.9	15 15 10	65.2 ± 2.9 73.5 ± 2.8 83.1 ± 2.8	Isometric	KE	Mounted strain gauge
Samuel et al., 2012	10 9	24 ± 4.2 71.2 ± 6.6	10 9	24 ± 2.5 72.4 ± 8.3	Isometric	KE	Mounted strain gauge
Schneider et al., 2016	8 8	27 ± 5 27 ± 5	7 7	24 ± 3 24 ± 3	Isokinetic Isometric	KE KF	Biodex System 2®
Sillanpää et al., 2014	61	75 ± 3.6	74	74.4 ± 3.1	Isometric	KE	Biodex System 3 Pro®
Stoll et al., 2000	253	49.0 ± 17.0	290	47.0 ± 17.0	Isometric	KE KF	Mounted pull gauge
Sunnerhagen et al., 2000	16 20 18 15	44.1 ± 1.5 54.2 ± 1.2 64.2 ± 1.3 73.9 ± 1.5	19 15 27 14	45.1 ± 1.3 55.3 ± 1.6 64.0 ± 1.0 73.9 ± 1.6	Isokinetic	KE KF	Kin-Com
Taş et al., 2017	31	26.3 ± 6.4	36	29.5 ± 8.2	Isokinetic	KE	Biodex System 4®
Tsubaki et al., 2016	157	49.7 ± 19	147	53.9 ± 16.7	Isometric	KE	Mounted load cell (Isoforce GT-300)
Verdijk et al., 2009	29	49 ± 4	26	45 ± 4	Isokinetic	EE EF KE KF	Cybex II®

Ward et al., 2015	896	76.5 ± 2.8	934	76.2 ± 2.8	Isokinetic	KE	Kin-Com
Wee, 2016	28	71 ± 4	28	72 ± 5	Isometric	KE	Lafayette; Unnamed stationary dynamometer
Weeks et al, 2016	26	33.9 ± 11.5	26	33.7 ± 12.6	Isokinetic	KE	Biodex System 4 Pro®
Wu et al., 2016	11 11	23.7 ± 4.2 66.8 ± 3.4	13 9	23.5 ± 3.4 66.1 ± 4.4	Isometric	KE KF	Load cell (Leane International) mounted on a Technogym
Wu et al., 2017	12 13	24.6 ± 2.7 70.1 ± 1.8	13 13	23.4 ± 2.4 69.5 ± 3.2	Isometric	KE KF	Unspecified Biodex system
Yamada et al., 2017	165	74.7 ± 5.2	240	73.8 ± 4.9	Isometric	KE	Mounted strain gauge (TKK5710e)

Table 2. Summary of segmented piecewise regression analysis.

		Male			Female			
Muscle Group	Contraction	Breakpoint (years)	1st Slope	2nd Slope	Breakpoint (years)	1st Slope	2nd Slope	Breakpoint Difference (T-Value)
Knee Extensors	Isometric	57.2	-3.51*	-6.93*	57.1	-2.29*	-5.71*	0.1
	Isokinetic 60°/s	66.6	-1.38	-5.13*	41.8	-0.12	-1.66	3.2†
Knee Flexors	Isometric	58.6	-0.12	-5.9*	57.1	-0.09	-3.54*	0.2
	Isokinetic 60°/s	49.4	-0.15	-1.61*	--	--	--	--

Breakpoint is age expressed in years. The 1st Slope is the slope of the regression before the breakpoint; the 2nd Slope is the slope of the regression after the breakpoint. Slopes are expressed as N/year (isometric) or Nm/year (isokinetic). * denotes significant slope of the regression line at $p \leq 0.05$. † denotes significant difference between sexes in breakpoint age at $p \leq 0.05$.

Figure Captions

Figure 1. Study inclusion exclusion flow chart. N = number of studies.

Figure 2. Liner regression of neuromuscular output (y-axis) and age (x-axis) reported from 57 studies. **(A)** isometric knee extensors (KE), **(B)** isometric knee flexors (KF), **(C)** isokinetic 60°s^{-1} knee extensors **(D)** isokinetic 60°s^{-1} knee flexors (KF). Closed symbols (●) and solid lines indicate males. Open symbols (○) and dashed lines indicate females. N = newtons; Nm = newton meters.

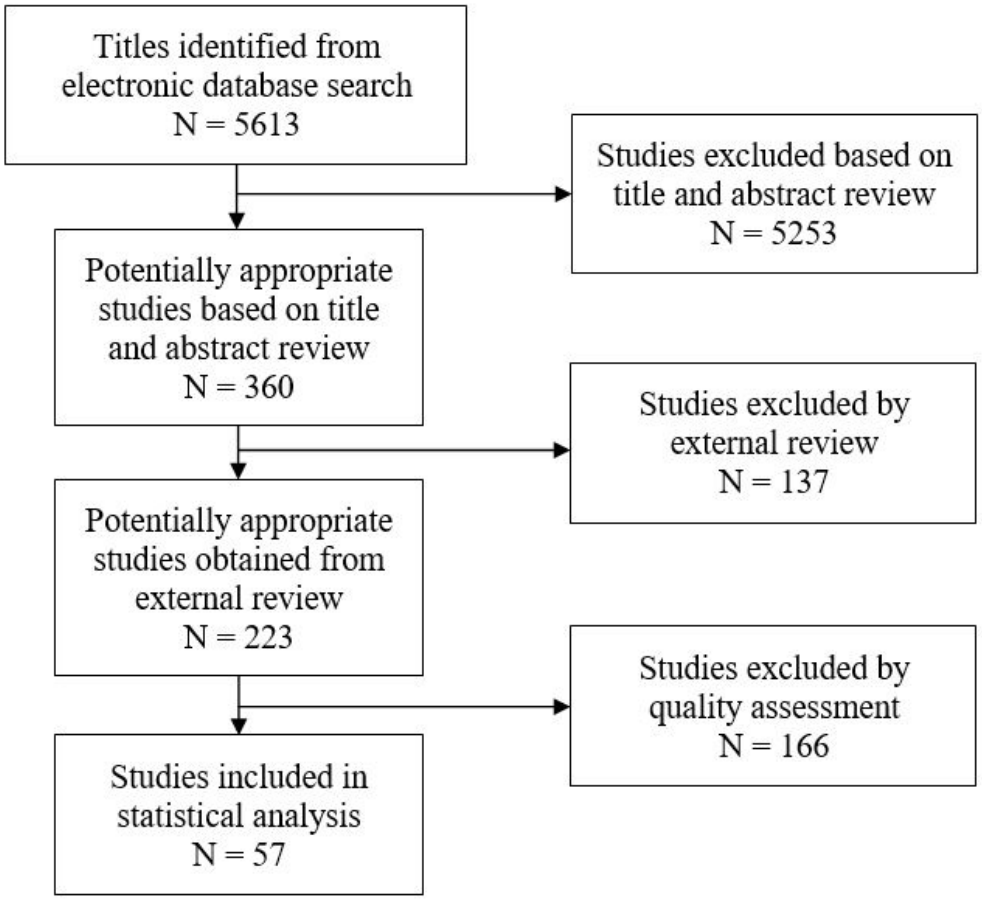

Figure 1: Study inclusion exclusion flow chart. N = number of studies.

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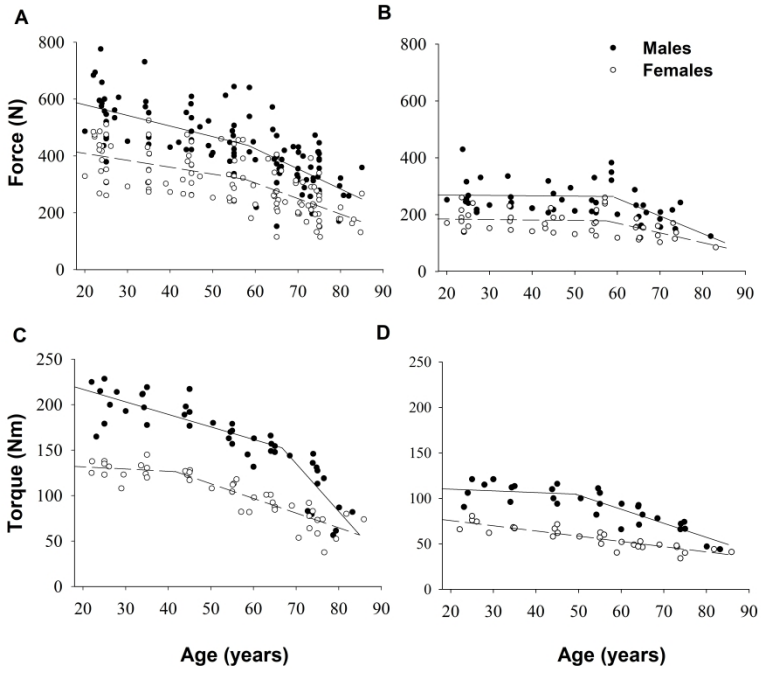

Figure 2: Liner regression of neuromuscular output (y-axis) and age (x-axis) reported from 57 studies. (A) isometric knee extensors (KE), (B) isometric knee flexors (KF), (C) isokinetic 60°s-1 knee extensors (D) isokinetic 60°s-1 knee flexors (KF). Closed symbols (●) and solid lines indicate males. Open symbols (○) and dashed lines indicate females. N = newtons; Nm = newton meters.

279x215mm (600 x 600 DPI)