1   **A new approach to the classification of muscle health: preliminary investigations**

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22 **Abstract**

23 Objective: Upper leg skeletal or lean tissue mass, strength and muscle quality have emerged as time-sensitive

24 indices of muscular health. The aim of this study was to generate a comparative data set based on these indices,

25 in healthy young (n=30, 29.0 ± 3.0 y old) and older (n=32, 58.7 ± 2.8 y old) adults, in order to evaluate their

26 construct validity in establishing cut-points for muscle health. Approach: Whole body and upper leg lean tissue

27 mass was obtained (iDXA[TM]; GE Healthcare, Madison, WI) prior to the assessment of maximal voluntary isometric

28 torque of the knee extensors and flexors (Cybex Isokinetic Dynamometer; Humac Norm, USA). Main Results:

29 Peak isometric upper leg torque showed the greatest age-related difference (-29.0%), followed by muscle quality

30 (-19.1%) and upper leg lean tissue mass (9.8%). Significance: Cut-points based on Z and T-scores generated from

31 the young adult mean suggest muscle quality demonstrates the greatest construct validity toward the aim of

32 classifying the muscular health of adults. Data generated from large, representative and sex-specific samples are

33 required to adequately classify the muscular health of adults.

34 Keywords: muscle quality, lean tissue mass, ageing, sarcopenia

35 **Introduction**

36 The decline in muscular strength and associated reduction in functional capability was thought to be caused by

37 a loss of muscle mass [1]. In an approach similar to that used in bone health, diagnostic criteria for sarcopenia

38 has been based on classifying individuals as having high or low indices of muscle mass relative to a healthy young

39 adult norm [2-6]. For example, sarcopenia has been considered to be a loss of muscle mass in an older adult that

40 is greater than or equal to two standard deviations below the mean value obtained from a representative young

41 adult population. These values are known as T-scores [3, 7]. Using this approach to classify young or older adults

42 muscle or lean tissue mass relative to their age-matched peers produces values known as Z-scores. These studies

43 report a prevalence of sarcopenia between ~9 – 34% in adults >65y and ≥50% in those >80y. Prevalence

44 estimates vary widely depending on the health status and ethnicity of the population sampled. Low relative

45 skeletal muscle mass has been found to be predictive of nursing home admission [7] and perhaps can be

46 considered most predictive of functional decline in older (>70y) populations where relative change in muscle

47 mass is accompanied by relative change in muscle quality [8]. However, low relative skeletal muscle mass may

48 be a less valid tool toward the aim of being able to classify muscle health in healthy adults. This is because

49 changes in muscle strength and muscle quality, starting aged ~40 y [9, 10], occur prior to change in muscle cross-

50 sectional area (CSA) [11, 12]. Furthermore, emerging data is beginning to demonstrate a number of muscular

51 indices which demonstrate more time-sensitive responses to the aging process. For example, the thigh region

52 represents a more sensitive index of age-related change in skeletal mass than the whole body [13] and is also

53 more responsive to therapeutic intervention [14-16]. Within the thigh region, the anterior compartment has

54 been shown to account for the majority of age-related change in terms of skeletal mass [17, 18] and strength as

55 represented by the force generating capacity of the knee extensors [19, 20]. Therefore, it would seem logical

56 that indices of muscle quality are based on knee extensor or combined knee extensor and flexor strength per

57 unit skeletal muscle or lean tissue mass (LTM) [21, 22].

58 In this study, we sought to measure upper leg LTM, maximal voluntary isometric torque of the knee extensors

59 and flexors; and muscle quality (strength per unit tissue) in healthy young (25-35 y) and older (55 – 65 y) adults.

60 The purpose of these measurements was to generate a comparative data set based on time sensitive indices of

61 muscle health. From the young adult mean, cut points can be established where by young and older adult muscle

62 health can be evaluated using Z and T-scores respectively.

63 **Materials and Methods**

64 *Participants and experimental procedures*

65 A convenience sample of healthy young (25 – 35 y) and older (55 – 65 y) adults were recruited via email, poster

66 and word of mouth from the Leeds Beckett University campus community. The age range for younger adults

67 was selected to encompass adults who had reached maturity but were not likely to be subject to age-related

68 muscular change. The age range for older adults was selected to encompass healthy older adults who had not

69 yet retired and were prior to more advanced age-related muscular changes. After receiving a complete

70 explanation of the procedures, benefits and risks of the study, all participants gave their written informed

71 consent. The study was approved by the Research Ethics Committee of Leeds Beckett University (Ref: 12768)

72 and carried out in a manner consistent with the Declaration of Helsinki. Figure 1 illustrates the flow chart of

73 study participants from recruitment to participation. From the 74 respondents, 4 were ineligible due to

74 musculoskeletal conditions of the knee which could have impacted upon the measurement of upper leg

75 strength. Three participants dropped out prior to the study beginning due to personal reasons and 5 participants

76 failed to attend all assessments. The number of participants who completed the study (n=62) was deemed

77 sufficient to demonstrate age-related change based on the work of Lanza et al. [23] and Wu et al. [24] who

78 demonstrated age-related difference in muscle function using sample sizes of 24 and 44 respectively.

79 [**Fig 1.** Study participant flow chart from recruitment to participation]

80 Participants presented to the laboratory where they had an estimate of current physical activity assessed. This

81 was recorded as the type and frequency of active sessions per week using the Bone Specific Physical Activity

82 Questionnaire [25]. This was not a central focus of our investigation rather a method of estimating the relative

83 physical activity status of our young and older participants. Participants then underwent a measure of whole

84 and regional body composition. In an attempt to standardise test conditions and tissue hydration, participants

85 were instructed to refrain from strenuous exercise in the 12-h period before testing and to avoid eating within

86 4 hours of testing. Participants consumed 500 ml of water 1-h prior to testing and were instructed to void and

87 defecate, if required, immediately prior to testing. Body composition analysis was followed by an assessment of

88 maximal voluntary isometric contractions of the knee extensors and flexors.

89 ***Body Composition***

90 Height was measured to the nearest 0.1 cm by using a stadiometer (Seca) and body mass (BM) was measured

91 to the nearest 0.1kg (MC-180MA; Tanita UK Ltd.). Whole body and regional body composition was estimated

92 using Dual-energy X-ray absorptiometry (iDXA™; GE Healthcare, Madison, WI) in accordance with procedures

93 used by Harley et al. (2011). The enCORE system software produced estimates of lean soft tissue, fat and bone

94 mineral content and density for the whole body and specific regions. The thigh, representing upper leg LTM, was

95 measured from the inferior side of the lesser trochanter until the tibiofemoral joint as described in Francis et al.

96 [20].

97 ***Maximal Voluntary Isometric Torque***

98 Maximal voluntary isometric contractions of the knee extensors and knee flexors of the dominant lower limb

99 were assessed using isokinetic dynamometry (Cybex Isokinetic Dynamometer; Humac Norm, USA). The protocol

100 for assessment including warm up, positioning, familiarisation, number of trials and the criteria for acceptance

101 of an MVC has been adapted from and is described in detail in Francis et al. [20]. Muscle quality was expressed

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102   as maximal voluntary isometric knee extensor or combined knee extensor and flexor torque per kilogram upper

103   leg LTM.

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106   *Statistical Analysis*

107   A Shapiro-Wilk test was conducted to assess normality of the data for physical characteristics, number of active

108   sessions per week, body composition, peak torque and muscle quality. Mean and standard deviation (SD) and

109   median and interquartile range (IQR) are reported. Age-related difference between young and older adults were

110   analysed using an independent sample t-test or a Wilcoxon-signed-rank test for normal and non-normal data,

111   respectively. For young adults, Z-scores were defined as ≥1 SD or ≥2 SD below the mean of the height adjusted

112   (ht^2) muscular index. For older adults, T-scores were defined as ≥1 SD or ≥2 SD below the young adult mean of

113   the height adjusted (ht^2) muscular index. Statistical analysis was performed by using PASW Statistics 22.0 for

114   Windows (SPSS, Inc.). Significance (2-tailed) was set at $P < 0.05$ for all analyses.

115   **Results**

116   Sixty-two healthy young (n=30) and older (n=32) adults completed all assessments. All participants had similar

117   physical characteristics and body composition. There was no difference in the number of active sessions young

118   and older adults participated in (Table 1). Young and older adults took part in 15 and 18 different activities

119   respectively. Most frequently reported by young adults were running (n=12), cycling (n=7) and walking (n=10).

120   Older adults mainly participated in walking (n=15), Pilates (n=9) and yoga (n=5). Upper leg LTM was lower in the

121   older adults relative to their younger counterparts but this difference was not seen for whole body LTM. Age-

122   related difference in strength was similar for the knee extensors and flexors. On average, younger adults had

123   29% more upper leg strength relative to older adults (Table 2). As the relative differences in knee extensor and

124   flexor strength were similar between young and older adults so were differences in muscle quality expressed as

125   combined torque or knee extensor torque per kg upper leg LTM (Figure 2; Table 2).

126   A sex-specific sub-analysis was conducted to determine the influence of gender on differences reported.

127   Compared to the younger adults, strength (combined knee extensor and flexor torque) was lower in both men

128 (28.6%) and women (30%) (*P*≤0.02), although women appeared to demonstrate greater strength differences in

129 the knee flexors relative to men (-33.7% (*P*=0.02) *vs.* -18.9% (*P*=0.02)). Upper leg LTM was lower in older women

130 (-14.9%, *P*<0.01) but not in older men (-7.7%, *P*=0.271) relative to their younger counterparts. A greater upper

131 leg LTM difference in women but a similar strength difference in both genders led to a smaller muscle quality

132 (combined strength relative to upper leg LTM) difference in older women compared to older men (-17.5%

133 (*P*=0.019) vs. -21.4% (*P*=0.018)).

134 Based on indices of whole or upper leg LTM none of the younger or older adults had Z or T scores ≥ 2. Knee

135 extensor torque per kg body mass identified a small (n=5; 16.6%) proportion of young adults and a large

136 proportion of older adults (n=13; 40.6%) with Z or T-scores ≥2. Muscle quality expressed as knee extensor torque

137 per kg upper leg LTM identified four (12.5%) older adults with a T-score ≥2 (Table 3).

138 [**Fig 2.** Age-related median difference (16.4%) in muscle quality defined as knee extensor torque per kg upper

139 leg lean tissue mass]

Table 1. Physical characteristics, body composition and activity levels of healthy young (25 – 35y) and older (55-65y) adults[1.]

	Young (n=30)	Older (n=32)	*P*[2]
Age (years)	29.0 ± 3.0	58.7 ± 2.8	
Height (cm)	172.4 ± 10.7	168.0 ± 9.2	0.082
Body mass (kg)	67.7 (23.0)	70.8 ± 13.9	0.704
BMI kg/m^2	24.3 ± 3.9	24.3 (4.8)	0.473
Body Fat (%)	27.0 ± 9.2	27.9 ± 10.5	0.720
LTM (kg)	46.1 (16.5)	46.5 ± 9.7	0.464
Active Sessions (per week)	4.6 ± 1.5	4.6 ± 2.2	0.877

[1]Values are means ± SDs or medians (IQR). No significant differences were found between groups. [2]P values for the difference between young and older groups analysed by independent t test or Mann-Whitney U test.

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Table 2. Upper leg LTM, muscle strength and muscle quality of healthy young (25 – 35y) and older (55-65y) adults[1.]

	Young (n=30)	Older (n=32)	Δ[2]	Δ%	*P[3]*
Upper leg LTM (kg)	5.1 (1.6)	4.6 (1.6)	0.5 (0.2 – 1.3)	9.8%	0.045
Knee extensors (N·m)	227.1 ± 88.2	157.9 ± 58.9	69.2 (18) (31.3 – 107.1)	30.5	0.001
Knee Flexors (N·m)	96.4 ± 38.3	58.3 (43.4)	38.1 (5.7 – 42.1)	39.5	0.007
Combined Torque (N·m)	323.5 ± 122.0	229.8 ± 88.3	93.7 (26.9) (39.9 – 147.6)	29.0	0.001
Muscle quality (combined torque N·m kg^{-1})	58.7 ± 14.6	47.5 ± 13.1	11.2 (3.5) (4.2 – 18.3)	19.1	0.002
Muscle quality (knee extensor torque N·m kg^{-1})	41.1 ± 10.4	32.9 ± 10.0	8.2 (2.6) (3.0 – 13.4)	20.0	0.002

[1]Values are means ± SDs or medians (IQR). No significant differences were found between groups. [2]Differences reported as mean difference (std. error difference), 95% confidence interval (CI) or median difference and 95% bootstrap CI. [3]P values for the difference between young and older groups analysed by independent t test or Mann-Whitney U test.

Table 3. Young adult muscle health classified according to z-scores and older adult muscle health classified according to t-scores.

	Whole body LTM/ht^2	Upper leg LTM/ht^2	Knee Extensor Torque (N·m kg^{-1})	Muscle Quality (knee extensor torque N·m kg^{-1})
Z-Score		Younger Adults n (%)		
1	3 (10 %)	4 (13.3 %)	5 (16.6 %)	10 (33.3 %)
2	-	-	3 (10 %)	-
T-Score		Older Adults n (%)		
1	3 (9.4 %)	12 (37.5 %)	13 (40.6 %)	9 (28.1 %)
2	_	_	9 (28.1 %)	4 (12.5 %)

Discussion

The purpose of this study was to generate a comparative data set of time sensitive indices of muscular health between healthy young and older adults. The main reason for this was to enable calculation of Z and T-scores for young and older adults respectively. These data help to make preliminary suggestions as to the most appropriate muscular indices for the assessment of muscle health in adults. Although upper leg LTM was lower (-9.8%) in older adults it did not identify any older adults as having a T score ≥2. By contrast, knee extensor torque per kg body mass seemed to classify ~69% (n=22) of the older adults at least ≥1 (n=13) or ≥ 2 (n=9) T-scores below the young adult mean. In a group of adults of similar physical characteristics and body composition, this index may only reveal that strength normalised to stature is lower in older adults compared to their younger counterparts. In other words, an index based around muscular strength may be highly sensitive but not very specific and as such may not be able to distinguish between those who have lower muscle strength and those at risk of functional decline. Participants in this study were healthy and physically active, to support the construct validity of the index it might be expected that a greater number of participants would be identified as 1 T-score below the young adult mean rather than 2. To this aim, muscle quality seemed to represent a more appropriate index. The number of older adults classified 1 or 2 T-scores below the young adult mean for muscle quality is more conservative. Furthermore, muscle quality appears to have construct validity in a healthy sample of older adults by classifying a greater number as 1 T-score rather than 2 T-scores below the young adult mean (n= 9 *vs.* n =4).

The discussion around whether these indices can establish an accurate prevalence of 'reduced muscular health' is of course limited by the small size we have used in this preliminary investigation which is not sex-specific. Furthermore, although muscle quality appears to demonstrate greater construct validity, it is difficult to pass comment on the validity of an index without knowing the consequences for functional performance [26]. The results of this study which appear to support muscle quality as a sensitive index of muscle health are interesting considering our group and others have reported muscle strength to better distinguish functional performance compared to muscle quality in older adults [27, 28]. This has led us to question the validity of the muscle quality index as a marker of functional capability [29], particularly given the increase resource required to quantify skeletal mass via imaging methods. It may be that a combination of muscle quality and functional performance is required to develop an index of 'reduced muscular health' that may be predictive of future risk of sarcopenia.

179 Although, not the main focus of our investigation, it is pertinent to comment on the age-related difference in

180 the muscular indices measured and gender differences observed. Comparison of discrete groups of young and

181 older adults with similar physical characteristics, body composition and a similar number of active sessions per

182 week are less frequent in the literature. The advantage of these groups, whilst acknowledging the limitation of

183 the cross-sectional design, is that the main difference between them is age. From our data, upper leg LTM and

184 strength can be estimated as ~3.3% and 10.1% lower per decade of age respectively. These estimates are

185 consistent with the 3 – 6% and 8 – 15% per decade decline in lower limb skeletal muscle or lean tissue and

186 strength reported in the literature [9, 10, 13, 20].

187 Contrary to our hypothesis that the knee extensors would demonstrate a preferential age-related difference

188 relative to the knee flexors, strength differences between both muscle groups in the upper leg were similar. In

189 fact, the median age-related difference in knee flexor torque appeared greater than the mean difference in the

190 knee extensors, although this difference disappeared when torque was combined to represent the upper leg. It

191 is possible that the older adults who appear to have maintained or increased their activity in later life have

192 reduced the preferential difference in knee extensor torque which can be as high as 19-20% per decade in cross-

193 sectional study designs [8, 20]. This interpretation must be considered cognisant that while the older adults

194 complete a similar number of active sessions per week, the predominate mode of exercise is of lower intensity

195 and muscular demand than their younger counterparts (walking (n=15) *vs.* running (n=12)). This more

196 conservative strength difference may go some way to explaining why the age-related difference in muscle

197 quality is at the lower end (6.7 % per decade) of the per decade range (5 – 27% per decade) reported previously

198 [29]. Although these are plausible explanations, Wu et al. [24] report similar results to our study in that strength

199 differences occur at a similar rate (~10% per decade) and evenly between the knee flexors and extensors. The

200 finding of an even difference in strength between the knee extensors and flexors is also consistent with the early

201 work of Frontera et al. [1]. It may be that the preferential difference in knee extensor strength we previously

202 reported is confined to those >50y or specific to women [20]. Although, Frontera et al. [19] also reported a

203 preferential decline in knee extensor strength in a longitudinal analysis, it is in a small sample (n=12).

204 Sub-group analysis by gender revealed that the majority of age-related difference in upper leg LTM was driven

205 by females (-14.9%). The difference between young and older men was not statistically significant (-7.7%,

206 P=0.271). These findings are in agreement with those of Lynch et al. [10] and Janssen et al. [13] who report

207 women to have a greater leg lean or muscle mass decline relative to men between the 3rd and 6th decade

208 respectively. The per decade decline (4.9% (DXA) and 5.7% (MRI)) reported by the authors is similar to that

209 reported in this study (5.0%). The finding that men and women demonstrate a similar difference in leg strength

210 (~30%) with age is in agreement with previous studies. This study appeared to suggest a greater loss of knee

211 flexor torque in women relative to men (-33.7% vs. -18.9%), a finding which has been reported in one other

212 longitudinal study [12]. However, previously we have reported the measurement of maximal voluntary knee

213 flexor torque to be less reliable relative to the measurement of the knee extensors [20]. This may play a role in

214 our study particularly given the small sample used. An even decline in overall lower limb strength for men and

215 women and a greater decline in upper leg LTM for women meant that older women appeared to have a lower

216 difference in muscle quality compared to older men. This gender difference has been reported cross-sectionally

217 and longitudinal in adults in the 7th decade of life [8]. It may also be due to LTM remaining stable in men until

218 age 60y but becoming noticeable different from a young adult in women aged 50y [31]. These gender differences

219 may have had an impact on the Z and T-scores we reported above, however, the 4-older adults classified as

220 having a muscle quality measurement >2SD below the young adult mean were split evenly between genders i.e.

221 2 male and 2 female. Interpretation of the sex-differences in this study must be made cognisant of the small

222 numbers of young men (n=12) and women (n=18) and older men (n=13) and women (n=19). The age-related

223 difference in upper leg LTM, strength and muscle quality are in line with but toward the lower end of the ranges

224 reported in the literature. This is likely due to the relative health of the older adults as indicated by their

225 maintenance of whole body LTM and activity profile. Nonetheless, the differences between young and older

226 healthy adults are still substantial which is in agreement with data demonstrating that not even masters athletes

227 can avoid the age-related decline in muscular health [30]. A strength of the convenience sample used in this

228 study is that all participants were recruited from within a similar community, were healthy, not retired and had

229 a similar number of active sessions per week. This allowed to us to generate a comparative data set where age

230 was the main difference between groups. Our study is limited by a small size and the cross-sectional nature of

231 the design which cannot account for inter-generational differences or a survival bias toward the healthier older

232 adults. Furthermore, our young adult data is not based on a sex-specific mean which may influence the cut-off

233 points identified. Finally, although the number of active sessions per week were similar, younger adults had a

234 preference for activities of higher intensity and muscular demand which could influence the magnitude of

235 difference reported.

236   In summary, this preliminary investigation reported muscle quality as the index of greatest construct validity in

237   the measurement of muscle health when assessed via T-scores. Further work is required in a representative,

238   gender specific sample of healthy adults across a greater number of age ranges. The collection of functional

239   performance data in tandem with such measures is required in order to support the criterion validity of an index.

240   Age-related difference in time-sensitive muscular indices between healthy young and older adults were

241   consistent with the literature although at the lower end of that previously reported. This was perhaps

242   demonstrates the relative health of the sample under investigation.

243   [31]

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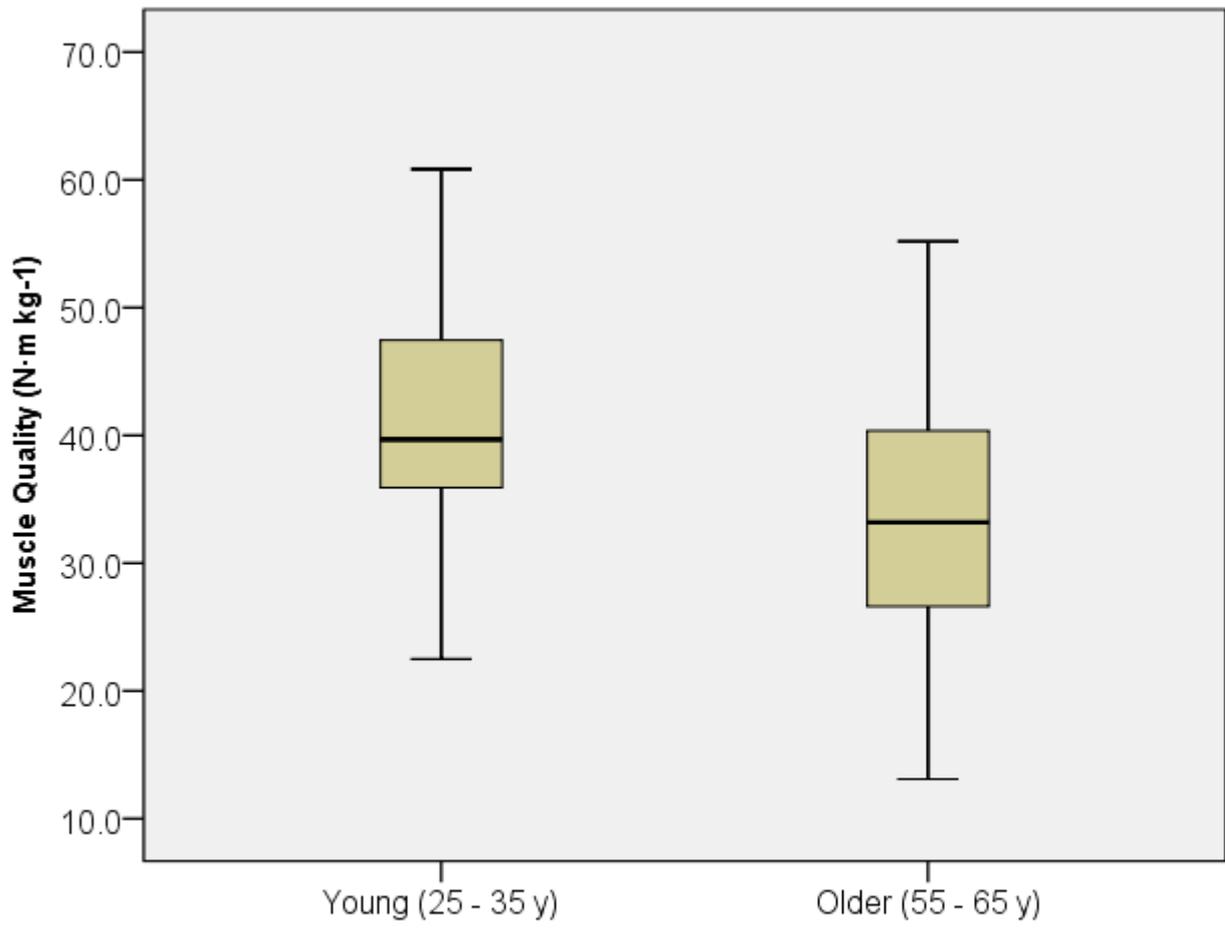353 medical sciences. 1999;54(5):B207-18. Epub 1999/06/11. PubMed PMID: 10362000.

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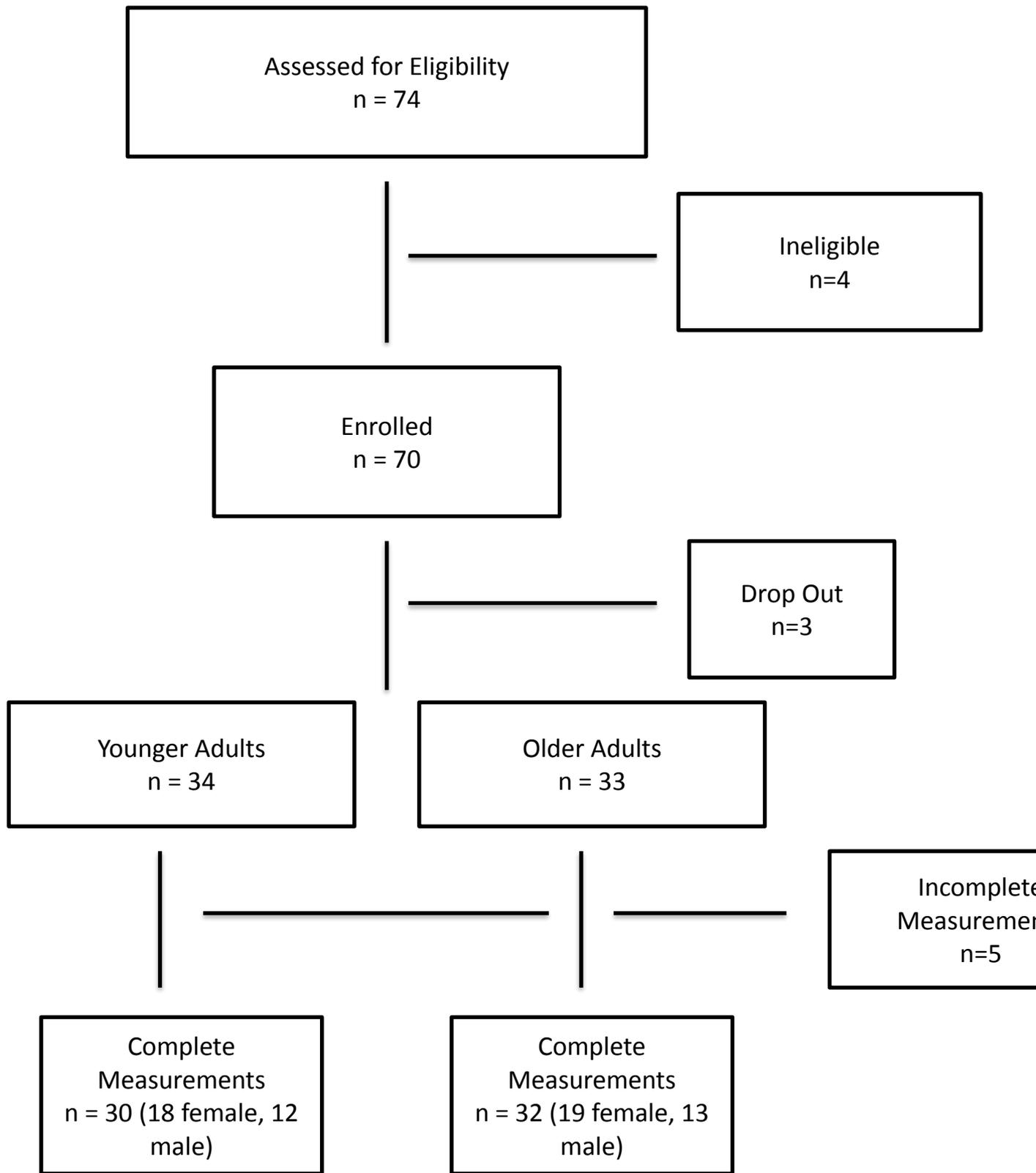
358 **Fig 1.** Study participant flow chart from recruitment to participation.

359
360 **Fig 2.** Age-related median difference (16.4%) in muscle quality defined as knee extensor torque per
361 kg upper leg lean tissue mass.
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