PROSPECTIVE ASSOCIATIONS OF LOW MUSCLE MASS AND FUNCTION WITH 10-YEAR FALLS RISK, INCIDENT FRACTURE AND MORTALITY IN COMMUNITY-DWELLING OLDER ADULTS

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Abstract: *Objectives: Purpose:* To compare the performance of low muscle mass and function with falls risk, incident fracture and mortality over 10 years. *Methods:* 1041 participants (50% women; mean age 63 ± 7.5 years) were prospectively followed for 10 years. Falls risk was measured using the Physiological Profile Assessment, fractures were self-reported and mortality was ascertained from the death registry. Appendicular lean mass (ALM) was assessed using dual energy X-ray absorptiometry. Four anthropometric: (ALM/height^2, ALM/body mass index, ALM/weight×100, a residuals method of ALM on height and total body fat) and four performance-based measures: (handgrip strength, lower-limb muscle strength, upper and lower-limb muscle quality) were examined. Participants in the lowest 20% of the sex-specific distribution for each anthropometric and performance-based measure were classified has having low muscle mass or function. Regression analyses were used to estimate associations between each anthropometric and performance-based measure at baseline and 10-year falls risk, incident fractures and mortality. *Results:* Mean falls risk z-score at 10 years was 0.64 (SD 1.12), incident fractures and mortality over 10 years were 16% and 14% respectively. All baseline performance-based measures were significantly associated with higher falls risk score at 10 years. Low handgrip (RR 1.55, 95% CI: 1.09, 2.20) and ALM/body mass index (RR 1.54, 95% CI: 1.14, 2.08) were the only significant predictors of fracture and mortality respectively. *Conclusions:* Low handgrip strength, a simple and inexpensive test could be considered in clinical settings for identifying future falls and fractures. ALM/ body mass index could be most suitable in estimating 10-year mortality risk, but requires specialised equipment.

Key words: Falls, fracture, mortality, muscle mass, muscle strength, sarcopenia.

Introduction

Ageing is associated with changes in body composition including a decline in muscle mass and function (1). These changes are associated with an increased risk of falls (2), fracture (3, 4), reduced quality of life and death in older people (5). Age-related decline in muscle strength has been directly attributed to loss of muscle mass (6). However, recent evidence suggests that age-associated decline in muscle mass and strength occur at different rates and muscle mass may account for as little as 5% of the decrease in muscle strength (7). Besides, maintaining or improving muscle mass does not prevent age-related decline in muscle strength (1). Given these potential differences, variations may also exist in the associations between low muscle mass and strength and long-term health outcomes among older people. For example, low muscle strength, but not muscle mass, has been shown to be associated with poor mobility, physical disability (8) and mortality over 6 years (5). However, few long-term prospective studies have compared the association of muscle mass, strength and muscle quality in predicting health outcomes such as falls, fracture and mortality in community-dwelling older people. Finding the most valid predictor of important clinical endpoints such as falls risk and fracture is crucial in identifying older

people at risk. Furthermore, it could also help in the design of intervention trials.

This prospective study aims to describe the association of low muscle mass and function with falls risk, incident fracture and all-cause mortality over 10 years in community-dwelling older adults. We hypothesized that low muscle function may be more relevant in predicting 10-year falls risk, incident fracture and all-cause mortality.

Data and Methods

Sample and Study Setting

The Tasmanian Older Adult Cohort (TASOAC) study is a prospective, population-based study primarily aimed at examining the causes and progression of osteoarthritis. Participants aged 50 years and above were selected using a sex-stratified random sampling technique from the electoral roll in Southern Tasmania (population 229,000). A total of 1099 adults (response rate = 57%) consented to participate in the study. Participants were excluded if they had any implants that would prevent them from undergoing an MRI or they were living in a nursing home. Participants who consented to participate in the study were invited to attend a clinic at the Menzies Institute for Medical Research, Hobart, Tasmania

between March 2002 and September, 2004. They were invited for follow–up clinic assessments at 2.5, 5, and 10 years after the initial clinic assessment. The study was approved by the Tasmanian Health and Medical Research Ethics Committee and written informed consent was obtained from all participants.

Baseline measures

Muscle strength measures

Lower-limb muscle strength (kg) was measured simultaneously for both limbs using a dynamometer (TTM Muscular Meter, Tokyo, Japan). Participants stood on the back of a dynamometer platform with their backs against a wall and knee flexed to 115°. A bar was attached to the dynamometer, and participants were instructed to lift the bar using their lower-limbs only to maximum contractile force, whilst maintaining proper head and neck posture. This test assessed the isometric strength of the whole lower-limbs, but predominantly of the quadriceps and hip extensors. Two trials were recorded, with the mean score taken as the criterion value for lower-limbs muscle strength (9). The intra-class correlation coefficient (ICC) for the first and second trial was 0.95 (95% CI: 0.94–0.96). Handgrip strength (psi) was measured using a pneumatic handheld bulb dynamometer (North Coast™ bulb dynamometer; adult 0-30 psi, model no. 70154). Participants were required to grip the bulb and squeeze as hard as possible. Two trials were recorded for the right and left hand and the mean of grip strength both hands was calculated.

Body composition

Body composition was measured using dual energy X-ray absorptiometry (DXA; Hologic Delphi, Hologic, Waltham USA). Appendicular lean mass (ALM), in kilograms, was calculated as the sum of lean mass in the upper and lower limbs. Weight (kg) was measured using electronic scales (Heine, Dover, USA). Height (cm) was measured using the Leicester stadiometer (Invicta, Leicester, UK). Body mass index was calculated as weight (kg) divided by height (m) squared.

Measures of low muscle mass and function

Four measures of low muscle mass (anthropometric measures) and four measures of low muscle function (performance-based measures) were considered. Anthropometric measures were ALM/height^2 (ALMHH$_{LOW}$) (3), ALM /body mass index [BMI] (ALMBMI$_{LOW}$) (10), ALM/weight multiplied by 100 (ALM$_{LOW}$) (11) and the residuals of the linear regression of ALM on height and DXA derived total body fat (ALMR$_{LOW}$) (12). Performance-based measures were handgrip strength (HGS$_{LOW}$), lower-limb muscle strength (LMS$_{LOW}$) (5) , upper-limb muscle quality (UMQ$_{LOW}$), and lower-limb muscle quality (LMQ$_{LOW}$). UMQ$_{LOW}$ was defined as handgrip strength divided by the sum of lean mass in the right and left upper limb and LMQ$_{LOW}$ was defined as lower limb muscle strength divided by the sum of lean mass in the left and

right lower limb (8). Participants in the lowest 20% of the sex-specific distribution for each anthropometric or performance-based measure were classified as having low muscle mass or function (8, 12).

10 year falls risk

Falls risk at 10 years was assessed using the short form Physiological Profile Assessment (PPA) (Prince of Wales Medical Research Institute, Sydney, Australia), a valid and reliable tool used to identify individuals who are at risk of falls (13). The PPA assesses five physiological domains (visual contrast sensitivity, reaction time, knee extension strength, proprioception and postural sway on foam) and a standardized falls risk score is calculated for each individual using these five domains.

Fracture

At each study visit participants were asked to list, by location, any fractures they had since their previous visit. Those who experienced at least one fracture between the baseline and 10-year follow-up assessment were coded as '1' (incident fracture.) and those without any fracture were coded '0' (no incident fracture).

Mortality

Mortality over 10 years was ascertained through national and state death registries. Data on mortality was collected until August 2015.

Data analysis

Linear regression analyses with adjustment for age at baseline were used to estimate the association of low muscle mass and function with 10-year falls risk. Poisson regression was used to estimate incident rate ratios for fracture and mortality over 10 years. Statistical interaction between sex and each measure of muscle mass and function was assessed by a test of significance of a product term. Data was analysed using Stata version 12.

Results

One thousand and ninety-nine participants attended the baseline clinics. Of these, 1041 (63 ± 7.5 years; 50% female) completed all anthropometric and muscle function assessments and were included in our analyses. From baseline to 10-year clinic assessments, 489 (47%) participants were lost to follow-up. Compared to participants retained at the 10-year follow-up assessment, participants lost to follow-up were older (64.5±8.0 [range: 51 – 80.9 years] vs. 61.4±6.6 [range: 51.1 – 79.9 years], P<0.001), had greater number of chronic conditions (1.7±1.5 vs. 1.2±1.2, P<0.001), poorer baseline ALM (24.1±5.3 vs. 24.9±5.3, P=0.025), HGS (11.7±3.0 vs. 12.4±3.0, P<0.001) and LMS (87.8±45.0 vs. 96.8±50.5, P=0.003) than those who completed the 10 year follow-up, but no sex differences were

observed (P= 0.586). Baseline characteristics of the participants are shown in Table 1. The mean age of the participants at baseline was 63±7.5 (range: 51 – 81 years) and the mean fall risk score was 0.16 ± 0.82, indicating a mild increase in risk of falls. At 10 year follow-up assessment, the mean age was 72.1±6.4 (range: 61.9 – 81.9 years) and 52% were female. The prevalence of low muscle mass or function is shown in Table 2. In women, the prevalence ranged from 13% to 23% in 50-59 year olds, 16% to 21% in 60-69 year olds and from 15% to 44% in those aged 70 years and above. In men, the prevalence ranged from 8% to 19%, 17% to 23%, and 23% to 46% in 50-59 year olds, 60-69 year olds and those aged 70 years and above age, respectively. Table 3 shows the associations between each anthropometric and performance-based measures assessed at baseline and 10-year falls risk scores, fracture incidence and mortality over 10 years.

Table 1
Baseline characteristics of participants in the Tasmanian Older Adult Cohort (TASOAC) study (N=1041)

Variables	Mean	SD
Age (years) (range: 51 – 81)	63.0	7.5
Female, n (%)	525	50.4
Height (cm) (range: 141 – 192)	167.1	9.0
Weight (kg) (range: 41.6 – 119.6)	77.8	14.6
BMI (kg/m²) (range: 17.8 – 52.9)	27.8	4.6
BMI category		
Underweight/Normal, n (%)	319	29.0
Overweight, n (%)	477	43.4
Obese, n (%)	303	27.6
Appendicular lean mass (kg) (range: 14.7 – 39.2)	24.5	5.3
Total body fat (%) (range: 4.4 – 54.5)	33.8	8.0
Handgrip strength (psi†) (range: 3.9 –24.3)	12.1	3.0
Lower-limb muscle strength (kg) (range: 7– 256.5)	92.5	49.1
Falls risk z-score, (range: -2.3– 3.6)	0.17	0.82
Total hip BMD (g/cm²) (0.97 – 1.70)	0.97	0.15

Values are mean (SD) unless stated otherwise; †psi: pounds per square inch, BMD bone mineral density, SD standard deviation

Falls risk

The mean falls risk score at 10 year follow up assessment was 0.64 ± 1.12. There was evidence for positive associations between each of the four performance-based measures at baseline and falls risk score at 10 years. The strongest association was found between baseline LMS_{LOW} and 10-year falls risk score (β=0.60, 95% CI: 0.39-0.81, P<0.001). No associations were found for anthropometric measures, or for any interaction between sex and each measures of muscle mass or function.

Fracture

The incidence of fracture over 10 years was 16.8% (n =147). Evidence for an increased risk of 10-year fracture incidence was found only for HGS_{LOW}. The risk of 10-year fracture incidence associated with HGS_{LOW} was modified by sex (P=0.091): where the association was stronger for women (RR 1.63 95% CI: 1.09-2.42, P=0.017) than men (RR 1.46 95% CI: 0.78-2.71, P=0.234).

Mortality

Over the follow-up period, 14% of the participants (94 men and 51 women) died. Increased risk of 10-year mortality was associated with $ALMBMI_{LOW}$ (RR 1.52 95% CI: 1.13 - 2.06, P=0.006). There was no evidence for an association with any other measures of muscle mass or function or for an interaction between sex and other measures of muscle mass or function.

Discussion

This is the first prospective study, to our knowledge, investigating the association between multiple measures of muscle mass and function and falls risk, incident fracture and mortality over 10 years in a large sample of community-dwelling older adults. We found that all performance-based measures at baseline were associated with increased falls risk score at 10 years, but only HGS_{LOW} and $ALMBMI_{LOW}$ were predictive of 10-year fracture incidence and mortality respectively. Importantly, HGS_{LOW} was consistently associated with an increase in falls risk and fracture over 10 years. This finding demonstrates that low handgrip strength alone, a simple and inexpensive procedure, could be considered in clinical settings as a useful screening tool for identifying older adults at risk of falls and fracture. Low muscle mass defined according to ALM adjusted for BMI could be most suitable in estimating 10-year mortality risk in older people, but requires access to specialised equipment.

Increased falls risk score at 10-years was associated with muscle function but not muscle mass. These results are consistent with previous studies (2, 14) and confirm the importance of muscle strength even a decade earlier for predicting falls-risk. Prior studies have also showed that absolute decline in muscle strength and quality, but not muscle mass, are associated with functional limitations and disability – risk factor for falls (8). Muscle strength decreases at a faster rate than muscle mass (7). Even when muscle mass appears preserved, there is evidence of a decline in muscle strength (15), which may be attributable to age-related changes in neuromuscular contributors to strength including decreased motor unit recruitment and increased fatty infiltration of muscle. This rapid age-associated decline in strength may lead to functional limitations at an earlier stage than mass potentially explaining why performance-based measures are superior to anthropometric measures in identifying older adult with higher falls risk over 10 years.

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Table 2
Prevalence of low muscle mass and function at baseline stratified by sex and age (N = 1041)

Low muscle mass / function	Men			Women		
	50-59 years (n=204)	60-69 years (n=200)	≥70 years (n=112)	50-59 years (n=252)	60-69 years (n=173)	≥70 years (n=100)
	n %	n %	n %	n %	n %	n %
Performance-based measures						
LMQ$_{LOW}$	25 (12)	46 (23)	33 (30)	40 (16)	32 (19)	34 (34)
UMQ$_{LOW}$	26 (12)	39 (19)	42 (36)	45 (17)	30 (16)	37 (34)
LMS$_{LOW}$	16 (8)	41 (20)	55 (46)	34 (13)	33 (17)	48 (44)
HGS$_{LOW}$	25 (12)	42 (21)	37 (33)	39 (16)	31 (18)	37 (37)
Anthropometric measures						
ALMHH$_{LOW}$	25 (12)	43 (21)	39 (33)	50 (19)	39 (21)	23 (21)
ALMBMI$_{LOW}$	39 (19)	38 (19)	30 (25)	51 (20)	36 (19)	25 (23)
ALMW$_{LOW}$	34 (16)	35 (17)	38 (32)	36 (14)	38 (20)	38 (34)
ALMR$_{LOW}$	35 (17)	45 (22)	27 (23)	59 (23)	36 (19)	17 (15)

UMQ: upper-limb muscle quality (kg/kg) LMQ: lower-limb muscle quality; (kg/kg) LMS: lower-limb muscle strength (kg) HGS: handgrip strength (psi) ALMHH: appendicular lean mass (ALM)/height^2 (kg/m^2),) ALMBMI: low ALM/body mass index(kg/ kg/m^2) ALMW: ALM / weight * 100 (kg/kg) ALMR: residual of ALM on height and total body fats (kg)

Table 3
Associations between low muscle mass and function at baseline and falls risk at 10-year, incident fractures and mortality over 10 years

Low muscle mass/ function	Cut-point for low muscle mass and function*		Falls risk z-score (n=551)	Fracture n=841)	Mortality (n=1041)
	Male	Female	β (95% CI)	RR (95% CI)	RR (95% CI)
Performance-based measures					
LMQ$_{LOW}$	3.85	1.85	**0.41 (0.19, 0.62)**	0.95 (0.63, 1.43)	1.21 (0.89, 1.64)
UMQ$_{LOW}$	1.08	1.15	**0.29 (0.07, 0.51)**	1.13 (0.78, 1.65)	0.82 (0.59, 1.14)
LMS$_{LOW}$	69.18	26.40	**0.60 (0.39, 0.81)**	0.93 (0.62, 1.40)	1.03 (0.75, 1.42)
HGS$_{LOW}$	10.68	7.54	**0.50 (0.27, 0.73)**	**1.55 (1.09, 2.20)**	0.82 (0.60, 1.12)
Anthropometric measures					
ALMHH$_{LOW}$	8.32	6.64	0.03 (–0.19, 0.25)	0.94 (0.63, 1.41)	1.17 (0.85, 1.66)
ALMBMI$_{LOW}$	0.88	0.60	0.08 (–0.15, 0.32)	1.01 (0.67, 1.53)	**1.54 (1.14, 2.08)**
ALMW$_{LOW}$	29.96	24.36	0.13 (–0.10, 0.35)	1.13 (0.77, 1.67)	1.25 (0.91, 1.72)
ALMR$_{LOW}$	–0.87	–1.82	0.13 (–0.80, 0.34)	1.07 (0.73, 1.57)	1.04 (0.73, 1.48)

*: lowest 20%, Data in bold indicate statistical significance at p<0.05, All analyses are adjusted for age; UMQ: upper-limb muscle quality (kg/kg) LMQ: lower-limb muscle quality; (kg/ kg) LMS: lower-limb muscle strength (kg) HGS: handgrip strength (psi) ALMHH: appendicular lean mass (ALM)/height^2 (kg/m^2),) ALMBMI: low ALM/body mass index(kg/ kg/m^2) ALMW: ALM / weight * 100 (kg/kg) ALMR: residual of ALM on height and total body fats (kg)

HGS$_{LOW}$ was the only measure that provided evidence for an association with 10-year fracture incidence, and this is consistent with a prior study (16). Women had a higher prevalence of fracture (21% vs. 11.8% in men) potentially due to higher prevalence of osteoporosis. Therefore, the stronger associations in women could be explained by low muscle strength and low bone density in women leading to falls related fractures. Contrary to our findings, previous studies have established an association between ALMHH$_{LOW}$ and fracture (17-19). However, these studies were cross-sectional and were conducted among older people admitted to a clinic facility (17-19). The strongest mechanical loads applied to bones are created by muscle contraction (4). Hence, low handgrip strength, a reflection of global muscle weakness of the body

(16), could be a better indicator of 10-year fracture risk than other measures of low muscle mass or function. Interestingly, despite strong correlation (r= 0.77, P < 0.001) between handgrip strength and lower-limb muscle strength in our sample, LMS_{LOW} was not significantly associated with fracture over 10 years. The reason for this observation is not clear.

$ALMBMI_{LOW}$ was the only measure that provided evidence for an association with mortality. Several studies have reported associations between a decline in muscle strength and mortality (5, 20, 21), but conflicting evidence for a decline in muscle mass, with some studies reporting an association (22) and others no association with mortality (5). Lean muscle mass alone may not be predictive of health outcomes, but a combination with other anthropometric indices such as BMI may increase sensitivity. BMI is an established risk factor for diseases including cardiovascular disease, cancer, stroke, and is in itself a strong predictor of all-cause mortality (23). Low BMI is also a strong determinant of transition to sarcopenia (24). It is possible that low muscle mass defined by combining ALM and BMI was the strongest predictor of mortality because BMI conferred additional risk besides consequences of decline in ALM. Furthermore, low ALM relative to BMI is an indication of high body fat percentage (25), hence, the effect of $ALMBMI_{LOW}$ on mortality may potentially be related to obesity rather than sarcopenia.

HGS_{LOW} was the most consistent predictor, being associated with both falls risk and fracture. The predictive validity of handgrip strength as an important marker of health in older people has previously been established (26). The mechanisms underlying why this is the case is not entirely certain (26). Low handgrip strength is potentially a result of chronic conditions such as osteoarthritis, frailty or diabetic neuropathy which are causal risk factors for functional limitation (26). However, recent findings from a sample of over 130, 000 adults from the Prospective Urban Rural Epidemiology study showed that the association between handgrip strength and cardiovascular diseases, cardiovascular death and all-cause mortality was independent of hypertension, diabetes, prior stroke and other co-morbidities (27). This suggests that the mechanism may be independent of chronic health conditions, or alternatively may represent sub-clinical disease and/or, lower levels of social, physical or occupational activity, which increase the risk of clinical disease and disability. Further clinical studies incorporating genetics and environmental factors are warranted to explore why handgrip strength is such a powerful marker of health outcomes (28).

This study has a number of strengths including the 10-year follow-up period, measurement of multiple measures of muscle mass and function and the use of a population-based sample increasing generalizability. A major step in designing an effective intervention is identifying individuals at risk. This prospective population-based study provides evidence for the most appropriate measures of muscle mass and function to identify older people with higher 10-year falls risk, fracture

and mortality. However, this study also has a number of limitations. Firstly, there was 19.2% and 47% missing data for incident fracture and falls risk score respectively. This is a major limitation that could lead to bias in our results. Such missing data is not unexpected in a long-term prospective study involving older people. We performed sensitivity analysis for missing data using multiple imputation to assess the robustness of the falls risk and fracture models assuming the data are missing at random. The results of the analyses were similar to the complete case analyses (supplementary table 1). Secondly, incidence of fracture was self-reported and may be subject to recall bias. However, fractures are a major life event and inaccuracy of recall is unlikely (29). Thirdly, data on the specific cause of death was not available for all the participants, hence, we were unable to perform cause-specific analysis for mortality. Fourthly, grip strength was measured using a pneumatic bulb dynamometer rather than a hydraulic dynamometers (e.g. Jamar), hence cut-points for increased risk of falls and fracture observed in this study may be different for assessments using hydraulic dynamometers. However, previous studies have found high reliability between the two methods (30). Fifthly, physiological assessment of falls risk rather than prospective data on actual falls was used in this study and therefore we cannot be certain whether our findings on associations with falls risk score are representative of incident falls. Nevertheless, the physiological approach to the assessment of falls risk used in the study is not subjected to recall bias (31) and the PPA has been shown to have 75% accuracy in predicting multiple falls among older people (32). On average, our sample was young and overweight. The prevalence of fracture and mortality may have been higher in an 'older' and less overweight population. Lastly, we did not use definitions established for sarcopenia due to our middle-aged and relatively healthy older adult population. For example, previously established cut-points for $ALHMHH_{LOW}$ and $ALMBMI_{LOW}$, proposed by Baumgartner et al (3) and the Foundation for National Institute of Health (FNIH) sarcopenia project would have only classified 4 (men=4; women=0) and 12 (men=10; women=2) participants respectively as having sarcopenia. In contrast we defined cut-points in the lowest 20% of the sex-specific distribution of each anthropometric and performance-based measure which has previously been used as a diagnostic measure for sarcopenia (8, 12). Despite this we still found important associations using this method.

In conclusion, findings from this study suggest that low muscle function defined according to low handgrip strength is associated with increased falls risk and incidence of fracture over 10 years. Diagnostic criteria of low muscle mass and function relevant to clinical settings should be readily available, low cost and predictive of future health outcomes (33). In this respect, defining low muscle function according to low handgrip strength appears to be a promising approach in identifying older people with higher falls and fracture risk over 10 years. Low muscle mass defined according to ALM

adjusted for BMI could be most suitable in estimating 10-year mortality risk in older people, but requires access to specialised equipment.

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