### Title

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**The association of skeletal muscle energetics with recurrent falls in older adults within the Study of Muscle, Mobility and Aging (SOMMA)**

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**Abstract.**

**Background**:     Falls in the older population are a major public health concern. While many physiological and environmental factors have been associated with fall risk, muscle mitochondrial energetics has not yet been investigated.

**Methods:** In this analysis, 835 Study of Muscle, Mobility and Aging (SOMMA) participants aged 70-94 were surveyed for number of falls (total), recurrent falls (2+), and fall-related injuries over the past 12 months at baseline and again after one year. Skeletal muscle energetics were assessed at baseline in vivo using $^{31}$P Magnetic Resonance Spectroscopy (MRS) after an acute bout of exercise (ATPmax) and ex vivo by High Resolution Respirometry (HRR) of permeabilized muscle fibers from the vastus lateralis (MaxOXPHOS).

**Results:** At least one fall was reported in 28.7% of SOMMA participants in the first year of the study, with 12% of older adults reporting recurrent falls (2+). Individuals who experienced recurrent falls had a slower 400m walk gait speed (1.0 ± 0.2 vs. 1.1 ± 0.2, p<.001), reported fewer alcoholic drinks per week in the past year (2.4 ± 4.3 vs. 2.8 ± 4.4, p= 0.054), and took a significantly greater number of medication in the 30 days before their baseline visit (5.6 ± 4.4 vs. 4.2 ± 3.4, p<0.05). A history of falls was reported in 63% of individuals who experienced recurrent falls in the first year of the study compared to 22.8% who experienced one or fewer falls. MaxOXPHOS was significantly lower in those who reported recurrent falls (p=0.008) compared to those with one or fewer falls, but there was no significant difference in ATPmax (p=0.369). Neither muscle energetics measure was significantly associated with total number of falls or injurious falls, but recurrent falls were significantly higher with lower MaxOXPHOS (RR=1.33, 95% CI= 1.02-1.73, p=0.033). However, covariates accounted for the increased risk.

**Conclusions:** Mitochondrial energetics were largely unrelated to fall risk in older adults when accounting for variables, suggesting that the complex etiology of falls may not be related to a single "hallmark of aging" biological pathway.

**Key Words:** Mobility, Mitochondria, Frailty

**Introduction.**

Falls in the older population are a leading cause of morbidity and mortality and represent a worldwide public health concern [1-4]. Falls have consequences beyond physical injury in the older population as they have been associated with reduced quality of life, fear of falling, loss of independence, and institutionalization [5]. According to the CDC, 1 out of 4 individuals over 65 years of age experience a fall each year which result in nearly 30,000 deaths [6]. Understanding the biological factors that increase risk of falls will likely be helpful in developing effective preventive strategies and interventions.

Falling is complex and results from the interaction of multiple risk factors [7-11]. One important fall risk factor is the age-related decline in muscle mass and strength, or sarcopenia, which affects balance, mobility, and physical function [12-17]. Indeed, leg power and strength and physical activity are all associated with falls and modifiable with exercise [18,19]. Mitochondrial dysfunction is a major hallmark of aging, a key contributor to sarcopenia, and has been associated with low leg power and cardiorespiratory fitness, but it is unclear if this association extends to fall risk [20]. As the major energy producing organelle in muscle cells, mitochondria are sensitive to metabolic, inflammatory, and oxidative injury associated with obesity, exercise, and inactivity [21]. Aging is reported to decrease the mitochondria's capacity for oxidative phosphorylation (OXPHOS) and ATP production and increase the production of reactive oxygen species (ROS), particularly in high-energy demand tissue like skeletal muscle [22-24]. Mitochondria are particularly susceptible to oxidative stress as accumulation of ROS further impairs their function through mitochondrial DNA mutations, affecting mitochondrial respiratory chain, and altering membrane permeability and $Ca^{2+}$ homeostasis.[25] The role of mitochondria in sarcopenia and the relationship between muscle function and fall risk has led us to the obvious corollary, that a decline in muscle OXPHOS capacity would result in a greater risk of falls and related injuries.

To examine the role of muscle energetics in fall risk, we analyzed data from the Study of Muscle, Mobility and Aging (SOMMA), using *in vivo* and *in vitro* measures of muscle mitochondrial energetics in 835 older adults over the course of 1 year. Since maximal OXPHOS and ATP generation directly correlate with muscle strength and physical function, [23,26,27] we hypothesized lower muscle energetics will be associated with increased risk of recurrent falls in this population.

**Methods.**

*Study Design and Participants*

SOMMA is an observational multicenter cohort study that recruited community dwelling adults ≥ 70 years from 2 university medical centers between 2019 and 2022. Approval was obtained by institutional review board WIRB-Copernicus Group (WCG IRB) (20180764) prior to initiation of the study [28]. Participants with dementia or active malignancy were excluded from the study. Participants were enrolled if they were able to walk 400 meters or complete a 4-meter walk at a speed ≥ 0.6m/s, climb a flight of stairs, had a BMI < $40kg/m^2$, and had no contraindications to muscle biopsy or magnetic resonance imaging. Individuals on anticoagulants and antiplatelets (except for Aspirin) were excluded. SOMMA obtained MaxOXPHOS and/or ATPmax measurements on 868 of the 879 enrolled participants. Fall data (baseline history, 6 months, and 12 months) was obtained on 835 participants.

*Data Collection*

At baseline, participants were asked to report their recent fall history, or the number of falls they had experienced during the preceding 12 months. Subsequently, fall occurrence was ascertained by questionnaires every 6 months until the end of year one and combined for this analysis. A fall was defined as an unintentional loss of balance resulting in the individual coming into contact with ground or floor or hitting an object like a table or chair. A participant was considered to

have recurrent falls if they had 2 or more falls in the year after baseline (compared with 0 or 1 fall in that time period). Participants who fell were asked about the consequences of the fall and if it resulted in injury. The criteria for an injurious fall was a fall resulting in fractured or broken bone, sprain or strain, bruise or bleeding, hit to or injury of head, or some other unspecified injury. Those with injurious falls were asked if medical attention was sought after the fall, and these falls were subcategorized as serious injuries.

Covariates include clinical site (University of Pittsburgh or Wake Forest University School of Medicine), age, BMI ($kg/m^2$) derived from measured height (stadiometers) and weight (digital scales), and self-reported race and ethnicity (Non-Hispanic White or Racial or Ethnic Minority), self-reported sex, average drinks per week in past 12m, and total number of medications (0 if none taken in past 30 days). Accelerometry data was collected on all 3 orthogonal axes using an ActiGragh GT9X at 80 Hz worn on the non-dominant wrist for 7 full days. Baseline daily activity was assessed as total activity count per 24-hour day (imputed) [27].

*Muscle Mitochondrial Energetics Assessments*

Percutaneous skeletal muscle biopsies of vastus lateralis were performed under local anesthesia. Approximately 10mg of biospecimen was prepared for respiration analysis. Muscle fibers were separated, permeabilized, washed, and placed into Oxygraph 2K (Oroboros Inc., Innsbruck, Austria) respiratory chambers for *ex vivo* assessment of MaxOXPHOS, which represents the maximal oxygen consumption rate in pmol/(s*mg) of permeabilized muscle fibers in the presence of saturating complex I-linked (malate, pyruvate, glutamate) and II substrates (succinate) and ADP. *In vivo* muscle energetics, or ATPmax, which represents the maximal rate of ATP synthesis by oxidative phosphorylation following a ~30 second bout of isometric leg kicking, was assessed via 31P MRS with a 3 Tesla MR magnet (Siemen's Medical System—Prisma (University of Pittsburgh) or Skyra (Wake

Forest University School of Medicine). Detailed mitochondrial protocols have been previously

described [20,29].

*Data Analysis*

Covariates considered in the analysis included age, sex, race (non-Hispanic White vs. racial/ethnic

minority), baseline history of any fall 12 months prior to enrollment, alcohol status (average number

of alcoholic drinks per week in past 12 months), number of prescription drugs (taken in past 30

days), physical activity level (using accelerometry; average total activity count), and leg strength.

Differences in participant characteristics stratified by recurrent falls were assessed using t-tests for

normally distributed data and a Wilcoxon rank-sum test for skewed data, and categorical variables

were assessed by chi-square test, or Fisher's exact test. Kruskal-Wallis Test was used to test the

association between muscle energetics measures and fall frequency and type due to non-normal

distributions for MaxOXPHOS and ATPmax. Negative binomial regression models were used to

examine the association of 1SD decrease in MaxOXPHOS and ATPmax with total, recurrent, and

injurious fall outcomes. Adjusted risk ratios and corresponding 95% confidence intervals were

calculated with significance level p<0.05.

**Results.**

*Participant Characteristics*

     A total of 879 participants aged 70-94 with were enrolled in SOMMA across two clinical

sites, Wake Forest University School of Medicine and the University of Pittsburgh. Of these, 835 (342

were men, and 493 women) had falls data. Covariates considered in this analysis were site, age, BMI,

race/ethnicity, drinks per week over the past 12 months, number of medications taken in past 30

days, history of falls in the past 12 months at baseline, physical activity at baseline, and leg strength

(**Table 1**). Data were stratified by 1 fall or less (0-1) and recurrent falls (2+). After the first year,

28.7% of participants experienced a fall and 12% 2+ falls. Individuals who experienced recurrent falls had a slower 400m walk gait speed and lower muscle strength than those who experienced 1 or no falls. They also reported fewer alcoholic drinks consumed per week in the year before baseline, though this was not significant (p=0.054), and significantly more medications taken in the 30 days before baseline. Of the 100 individuals who reported multiple falls in the first year, 63 (63%) also had a history of falls in the year prior to the start of the study. However, only 167 (22.8%) of the 735 individuals who reported 1 or no falls had a history of falls. Injurious falls were reported in over half (55.1%) of all individuals who had recurring falls and in only 47.1% who had only 1 fall. Serious injuries that required medical intervention were reported in 30.9% of all recurrent fallers, but only 17.9% percent of those who reported only 1 fall.

In this analysis 73% of recurrent fallers experienced an indoor fall and 78.8% an outdoor fall, while only 41.4% of individuals who reported only 1 fall fell indoors compared to 58.6% who fell outdoors. In SOMMA, we found that outdoor falls were reported with a 2.4% higher incidence than indoor falls in women and a 5% higher incidence in men, with women more likely to report an indoor fall (p=0.04) (data not shown). Related to fall injury, more women self-reported having osteoporosis (27.6%) than men (2.6%); and 85.7% of reported fractures (n=21) at baseline were in women (data not shown).

*Lower Ex Vivo Muscle Energetics in Older Adults with More than One Fall.*

To determine if muscle mitochondrial energetics differed in individuals who had reported recurrent falls (2+) or injurious falls, we compared *ex vivo* and *in vivo* muscle energetics measures, MaxOXPHOS and ATPmax, to participants who reported only 1 or no falls (**Figure 1A**), or no injurious falls (**Figure 1B**). MaxOXPHOS was significantly lower (p=0.008) in individuals who reported more

than one fall, but no difference was observed with ATPmax (p= 0.369). There were no differences in muscle energetics in participants who report injurious falls (1+) compared to no injuries.

*No Significantly Greater Risk of Recurrent Falls with Lower Muscle Energetics*

Total number of falls and injurious falls were not associated with changes in muscle energetics (**Figure 1C**), however SOMMA participants had a significant risk of 2 or more falls with lower MaxOXPHOS (RR=1.33, 95% CI= 1.02-1.73, p=0.033), but not ATPmax (RR=1.10, 95% CI= 0.88-1.37). The greater risk of recurrent falls with lower MaxOXPHOS were explained by age, sex, and race, average reported number of alcoholic beverages consumed per week over the past 12 months, number of medications, BMI, physical activity, and baseline history of falls. Leg strength further mediated the risk of recurrent falls due to MaxOXPHOS.

**Discussion.**

In this analysis, 28.7% of participants reported at least one fall and 12% reported 2+ falls during their first year in SOMMA. Those older adults who reported multiple recurrent falls (2+) had significantly lower ex vivo maximal mitochondrial respiration, but not in vivo ATP generation, compared to those who fell once or not at all. The significantly greater risk of recurrent falls due to low muscle energetics was explained by covariates. Recurrent fallers had a modest and borderline-significant (p=0.054) fewer number of alcoholic drinks per week than SOMMA participants who reported 1 or no falls during the course of 1 year. This is interesting as alcohol is known to impair balance in the elderly and increase the risk of falls, however, this might only be applicable in individuals who consume 14 or more alcoholic beverages a week [30]. Conversely, recurrent fallers took a greater number of medications in the 30 days before their baseline visit. There is a general understanding that certain prescription medications or a high number of medications,

polypharmacy, are independent predictors of fall risk [31]. Sex differences in fall risk have also been reported, with 5.6% higher fall risk in women (29.1%) compared to men (23.5%) reported in The English Longitudinal Study of Ageing [1]. However, we observed no significant difference in the number of men and women among SOMMA participants who experienced recurrent falls compared to those who did not, though the occurrence of falls in women was 5.1% higher than in men (data not shown). This is interesting given muscle energetics in women are significantly lower than in men and explain the sex disparity in mobility impairment as we have previously reported [32]. History of falls is a major predictor of future falls [33]. This disparity was clearly observed in SOMMA, with 63% of individuals who reported recurrent falls also having a fall history. However, fall history was not associated with lower muscle energetics (data not shown). Consistent with other reports, physical activity as assessed by actigraphy was not significantly lower in individuals who experienced recurrent falls compared to 1 or fewer falls, however, risky vs. normal activities and fallers vs non-fallers were not assessed [34,35]. This is interesting as physical activity has previously been associated with lower muscle energetics in SOMMA and other studies [27]. Sex differences in physical activity were not accounted for and may be confounding. We have previously reported greater physical activity in women compared to men in SOMMA [32]. SOMMA participants who experienced recurrent falls also had a significantly lower leg strength. Leg power has been previously associated with muscle OXPHOS, which may explain why leg strength moderately attenuated the greater risk of falls due to muscle energetics in this analysis [20].

Falls are a complex, multifactorial, and circumstantial occurrence [1,36,37]. Per other reports, fall incidence appear to depend on fall circumstances, including fall location (e.g., indoors, outdoors), type of activity performed in that location (e.g., recreation, housework), and walking surface (e.g., dry, icy) [37,38]. As confirmed in this analysis, women were significantly more likely to suffer from fall-related injuries compared to men, though obesity, lower muscle strength, and osteoporosis may play a significant role [39]. Due to unreliable self-reporting and possible undiagnosed osteoporosis, we did not account for this covariate in our analysis of injurious falls. However, this suggests injurious

falls may not be associated with muscle energetics due to other physiological factors. In this analysis, we were unable to evaluate any survivorship effect, wherein individuals with the poorest of muscle energetics did not survive to later ages or otherwise become ineligible for this study. These exclusion criteria include dementia, malignancy, an inability to walk 400m, walking speed slower than 0.6m/s, or a BMI>40, each of which is reported to associate with muscle energetics [40,41]. In addition to being healthier than average, only 15.2% of the study cohort belonged to racial or ethnic minorities, limiting the generalizability of the results. Other factors associated with fall risk not assessed here include fear of falling, poor balance, poor vision, knee and joint pain, and hazardous living environment. As fall outcomes were self-reported and not verified, poor memory may have also limited fall recollection.

Consistent with our hypothesis, recurrent fallers had a lower muscle mitochondrial oxygen consumption (MaxOXPHOS) compared to SOMMA participants with 1 or no falls, and a higher risk of falls was significantly associated with lower muscle MaxOXPHOS. However, this was largely explained by covariates, and ATPmax showed no association. These data suggest that falls are multifactorial and that strategies known to improve muscle energetics, such as exercise, could aid in fall prevention, though perhaps indirectly through increased physical activity, lowering BMI, muscle fiber type transitions, etc [42-46]. Indeed, changes in fiber type composition (Type I and Type II) with age may explain why MaxOXPHOS and ATPmax showed disparate associations with fall risk due to their different modes of ATP synthesis (OXPHOS vs. glycolytic) [47]. Other interventions may include reducing the use of unnecessary medications or medications known to affect balance. In conclusion, the capacity of muscle to generate ATP is not independently associated with fall risk, and falls alone may not be a suitable outcome in trials that aim to improve mitochondrial function due to the involvement of other, more direct mediators and confounders, such as muscle strength. Future studies are needed to evaluate the role of muscle mitochondria in these and other mediators of recurrent falls to help us understand the effect of exercise and other mitochondrial interventions in older adults.

**Conflicts of Interest.**

S Cummings and P Cawthon are consultants to Bioage Labs. All other authors report no conflict of interest.

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**Tables.**

**Table 1. Participant Characteristics Stratified by Recurrent Falls (0-1 vs. 2+ falls)**

| Participant Characteristics | N | Overall (N= 835) | 0 - 1 Falls (N= 735) | 2+ Falls (N= 100) | P value |
|---|---|---|---|---|---|
| Site: Pittsburgh | 835 | 406 (48.6) | 361 (49.1) | 45 (45.0) | 0.44 |
| Age, years | 835 | 76.3 ± 5.0 | 76.2 ± 4.9 | 77.3 ± 5.7 | 0.062 |
| Sex: Women | 835 | 493 (59.0) | 429 (58.4) | 64 (64.0) | 0.283 |
| Weight, kg | 835 | 76.1 ± 15.1 | 76.3 ± 15.1 | 74.6 ± 15.1 | 0.312 |
| Body Mass Index (kg/m$^2$) | 835 | 27.5 ± 4.5 | 27.6 ± 4.5 | 27.3 ± 4.9 | 0.582 |
| Racial or Ethnic Minority | 834 | 126 (15.1) | 115 (15.7) | 11 (11.0) | 0.221 |
| Avg Drinks per week in past 12m | 822 | 2.8 ± 4.4 | 2.8 ± 4.4 | 2.4 ± 4.3 | 0.054 |
| Total number of medications | 833 | 4.4 ± 3.5 | 4.2 ± 3.4 | 5.6 ± 4.4 | 0.003 |
| History of fall in year before baseline | 832 | 230 (27.6) | 167 (22.8) | 63 (63.0) | <.001 |
| Total activity counts (x100,000, imputed) | 780 | 1.99 ± 0.6 | 2.00 ± 0.6 | 1.95 ± 0.6 | 0.474 |
| Leg Strength (kg) | 803 | 172.3 ± 60.3 | 174.7 ± 61.4 | 154.5 ± 47.6 | <.001 |
| Gait speed from 400m walk (m/s) | 835 | 1.1 ± 0.2 | 1.1 ± 0.2 | 1.0 ± 0.2 | <.001 |
| At least one fall in year after | 835 | 240 (28.7) | 140 (19.1) | 100 (100.0) | <.001 |

baseline

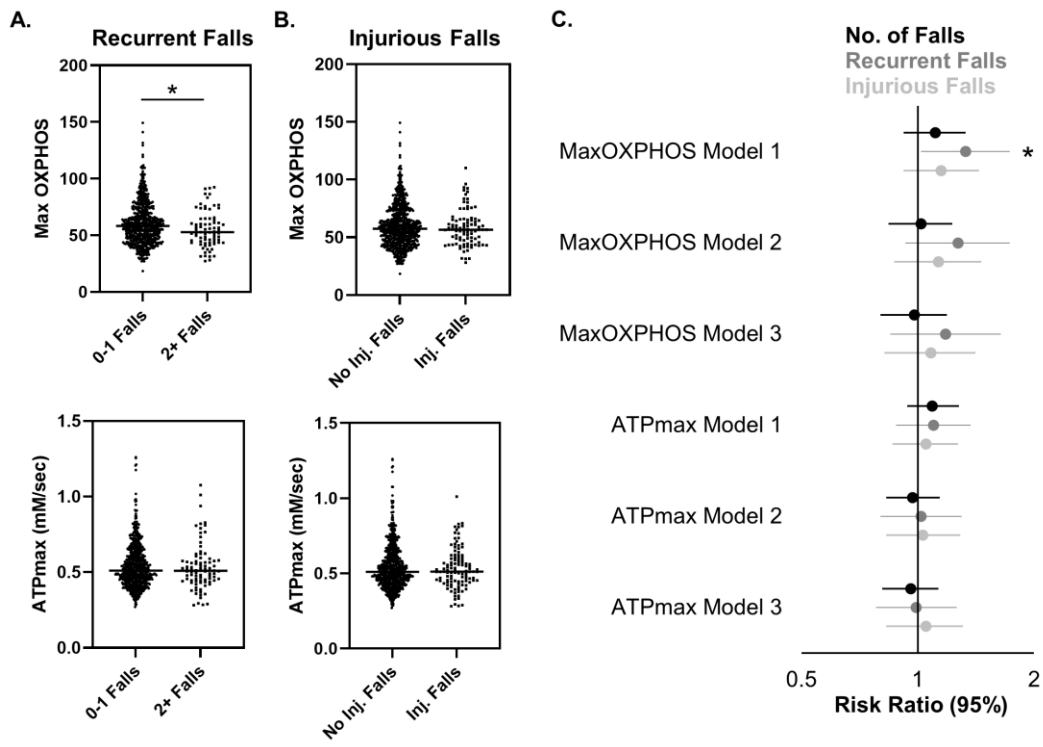| | | | | | |
|---|---|---|---|---|---|
| Any indoor falls in year after baseline | 835 | 131 (15.7) | 58 (7.9) | 73 (73.0) | <.001 |
| Any outdoor falls in year after baseline | 834 | 160 (19.2) | 82 (11.2) | 78 (78.8) | <.001 |
| Injurious fall in year after baseline | 833 | 120 (14.4) | 66 (9.0) | 54 (55.1) | <.001 |
| Serious injurious fall in year after baseline | 832 | 55 (6.6) | 25 (3.4) | 30 (30.9) | <.001 |

Data shown as n(%), mean ± SD.

**Figures Legends**

**Figure 1. Muscle energetics in men and women with recurrent falls. A)** ATPmax and MaxOXPHOS were assessed in SOMMA participants with 0-1 falls (n=735), and 2+ recurring falls (n=100) and **B)** injurious falls (1+)**. C)** A negative binomial regression for total falls, recurrent falls (2+), and injurious falls was performed, and the risk ratio (95% CI) plotted following sequential adjustment for Model 1: Site/technician; Model 2: Model 1 + age, sex, race (white vs. non-white), ETOH status (avg. number of drinks per week in past 12 months), # medications in 30 days before baseline, BMI, total activity counts, and baseline history of falls (y/n); Model 3: Model 2 + Leg strength. A 1SD change in MaxOXPHOS was equivalent to -18.26 pmol/(s*mg), and ATPmax change of -0.15 mM/s. * = p value <0.05.

Figure 1