Statin therapy, muscle function and falls risk in community-dwelling older adults

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Summary

Background: Statin therapy can cause myopathy, however it is unclear whether this exacerbates age-related muscle function declines.

Aim: To describe differences between statin users and non-users in muscle mass, muscle function and falls risk in a group of community-dwelling older adults.

Design: A prospective, population-based cohort study with a mean follow-up of 2.6 years.

Methods: Total 774 older adults [48% female; mean (standard deviation) age = 62 (7) years] were examined at baseline and follow-up. Differences in percentage appendicular lean mass (%ALM), leg strength, leg muscle quality (LMQ; specific force) and falls risk were compared for statin users and non-users.

Results: There were 147 (19%) statin users at baseline and 179 (23%) at follow-up. Longitudinal analyses revealed statin use at baseline predicted increased falls risk scores over 2.6 years (0.14, 95% CI 0.01 to 0.27) and a trend towards increased %ALM (0.45%, 95% CI -0.01 to 0.92). Statin users at both time points demonstrated decreased leg strength (-5.02 kg, 95% CI -9.65 to -0.40) and LMQ (-0.30 kg/kg, 95% CI -0.59 to -0.01), and trended towards increased falls risk (0.13, 95% CI -0.01 to 0.26) compared to controls. Finally, statin users at both baseline and follow-up demonstrated decreased leg strength (-16.17 kg, 95% CI -30.19 to -2.15) and LMQ (-1.13 kg/kg, 95% CI -2.02 to -0.24) compared to those who had ceased statin use at follow-up.

Conclusion: Statin use may exacerbate muscle performance declines and falls risk associated with aging without a concomitant decrease in muscle mass, and this effect may be reversible with cessation.

Introduction

The 1994 Scandinavian Simvastatin Survival Study was the first randomised trial to provide evidence of the benefits of statins (3-hydroxy-3-methylglutaryl coenzyme A, or HMG-CoA reductase inhibitors) for survival in coronary heart disease (CHD) patients.¹ Subsequent clinical trials have demonstrated that statins reduce major coronary events, CHD deaths, requirement for coronary procedures and total mortality, chiefly through lowering concentrations of low-density lipoprotein cholesterol (LDL-C).² Statins are now amongst the most widely used classes of drugs, with annual sales exceeding $12.5 billion in the United States.³ A recent study in Finland demonstrated that the prevalence and incidence of use is highest in those aged 65–74 years, with the largest relative increase in incidence from 1995 to 2005 found in those ≥75 years of age.⁴

A side-effect of statin therapy is myopathy including muscle pain (myalgia) and weakness with or without a concomitant increase in creatine kinase levels.⁵ However, as these symptoms can be non-specific and may not always be reported, it is unclear whether this effect is idiosyncratic or occurs to some extent in most statin users.
Muscle strength is associated with falls, reduced mobility and disability in older adults. Furthermore, longitudinal studies have shown that several measures of muscle strength are predictive of mortality. The possible effects of statin therapy on muscle strength in older adults have not been comprehensively studied. In a small clinical trial participants were able to repeatedly correctly distinguish periods of statin therapy from placebo use, and hip abduction and flexion strength were lower during periods of statin use. However, a study of community-dwelling older males found no association between statin use and functional decline and a recent study of older women found that the development of frailty was similar between statin users and non-users over 3 years.

Given that statin usage and sarcopenia are both common with increasing age, the association between statin use and muscle function in older adults requires clarification. The aim of this longitudinal study was to describe differences between statin users and non-users in muscle mass, muscle function and falls risk in a group of community-dwelling older adults.

Methods

This study was conducted as part of the Tasmanian Older Adult Cohort Study (TASOAC), an ongoing, prospective, population-based study primarily aimed at identifying factors associated with the development and progression of osteoarthritis and osteoporosis in community-dwelling 50- to 80-year-olds. The study was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee, and written informed consent was obtained from all participants.

The cohort consisted of both males and females aged between 50 and 79 years, selected from the roll of electors in southern Tasmania (population 229,000) using stratified simple random sampling without replacement (response rate 57%). The sample was stratified by sex to provide equal numbers of men and women. Institutionalised older adults were excluded. Participants were also excluded due to contraindication for magnetic resonance imaging, as these tests were required to examine osteoarthritis progression.

Enrolled participants attended a clinic for collection of baseline data between March 2002 and September 2004. Follow-up data was collected at a subsequent clinic 2.6 (SD 0.4) years later. A questionnaire recorded participant use of statin medications, including the type and prescribed dosage, at both baseline and follow-up. Medical history including previous diagnosis of cardiovascular disease (CVD) and diabetes, as well as smoking history, were recorded by questionnaire. At both clinics, anthropometric, muscle strength and falls risk data was collected as described below.

Anthropometrics

Height was measured to the nearest 0.1 cm (with shoes, socks and headwear removed) using a stadiometer. Weight was measured to the nearest 0.1 kg (with shoes, socks and bulky clothing removed) using a single pair of electronic scales (Seca Delta Model 707, Bradford, MA) that were calibrated using a known weight at the beginning of each clinic. Individual body mass index [BMI; weight (kg)/height (m²)] was also calculated.

Subjects underwent a whole body scan by dual-energy X-ray absorptiometry (DEXA) using a Hologic Delphi densitometer (Hologic, Waltham, MA, USA), from which soft tissue composition was determined. Participants were excluded from the DEXA scans if their weight exceeded 130 kg (N=3). The analysis provides mass (in grams) of bone mineral content, fat and lean mass of the whole body and compartments including the arms and legs. A further variable of percentage appendicular lean mass (%ALM) was calculated as the sum of lean mass in the arms and legs divided by the sum of lean mass, fat mass and bone mineral content in the arms and legs. This variable was calculated as a means of examining appendicular muscle mass relative to appendicular fat mass, as a high proportion of muscle compared to fat constitutes a more desirable body composition. It has been previously suggested that studies of sarcopenia should consider fat mass when estimating muscle mass of older adults.

Leg strength and muscle quality

At baseline and follow-up, leg strength was measured to the nearest kilogram in both legs simultaneously, using a dynamometer (TTM Muscular Meter, Tokyo, Japan). Participants stood on the back of the dynamometer platform, with back straight against a wall and knees flexed to an angle of 115°. A bar connected by a chain to the dynamometer was held on the front of the thighs. Using only their legs, and keeping the back and neck straight, the participant was then instructed to lift the bar upwards with maximum force. The correct technique was demonstrated by the examiner prior to testing, and can be viewed in Figure 1. This test examines isometric strength, predominantly of the quadriceps and hip extensors.

Two trials were recorded, with the second immediately following the first, and the mean score taken
as the criterion value for leg strength. Intra-class correlation coefficients (ICCs) demonstrated high reproducibility between trials 1 and 2 at both baseline (ICC 0.95, 95% CI 0.94 to 0.96) and follow-up (ICC 0.96, 95% CI 0.95 to 0.97) in the present study. Some participants were excluded from performing the leg strength test as a result of reporting pain or recent surgery. Further participants were excluded from the second trial after experiencing pain in the first trial.

We also calculated leg muscle quality (LMQ—an estimate of specific force) as the magnitude of leg strength from the leg strength test divided by the combined lean mass of the legs from the DEXA scans using the following formula:

\[
\text{LMQ (kg/kg)} = \frac{\text{Leg strength (kg)}}{\text{Left leg lean mass (kg) + Right leg lean mass (kg)}}
\]

**Falls risk**

The Physiological Profile Assessment (PPA; Prince of Wales Medical Research Institute, Sydney, Australia) was used to assess participant falls risk.\(^1\) The PPA examines five physiological domains (vision, reaction time, proprioception, strength and balance) and provides a standardised falls risk score. Falls risk scores less than 0 indicate a low risk of falls, between 0 and 1 indicate a mild risk, between 1 and 2 indicate a moderate risk, and greater than 2 indicate a high risk.

**Physical activity (PA)**

Baseline PA was measured over seven consecutive days following the initial clinic using a pedometer (Omron HJ-003 & HJ-102, Omron Healthcare, Kyoto, Japan). Participants were familiarised with use of the pedometer and were instructed to wear the pedometer on the waistband or belt above their dominant leg. They were also required to complete a pedometer diary recording details including daily step counts and duration of pedometer use. This protocol has been described in greater detail previously.\(^1\)

**Statistics**

Independent \(t\)-tests examined differences between baseline statin-users and non-users for continuous variables, while Yates’ continuity corrections examined proportions of binary variables. The primary outcome variables in this study included the four muscle parameter measures of \%ALM, leg strength, LMQ and falls risk. Due to the known age-related changes and sex differences in muscle mass and strength, multivariable linear regression adjusting for age and sex examined baseline differences in mean values for muscle parameters between statin users and non-users. As the proportion of statin users increased from baseline to follow-up, these analyses were repeated to examine follow-up differences. Box-Cox transformations of outcome variables in cross-sectional analyses (other than falls risk score) were applied so that residuals more closely followed a normal distribution.

Multivariable linear regression analyses examined the associations between statin use and the changes in muscle parameters from baseline to follow-up, adjusting for age, gender, PA, CVD and smoking status, as well as the baseline value for the relevant dependant variable. As statin users were more likely to report a previous diagnosis of CVD and diabetes, regression residuals from the regression of CVD and diabetes on statin use at baseline were used as covariates to avoid over-adjustment. Three comparisons were made in order to examine the effects of statin use at different time points. The first analysis compared muscle parameter changes in baseline statin users to non-users at baseline. The second analysis compared statin users at both baseline and follow-up to all other participants. The third analysis also

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**Figure 1.** Demonstration of the leg strength test with a knee flexion angle of 115°.
examined statin users at both baseline and follow-up, but compared muscle parameter changes to those who reported statin use at baseline and not at follow-up; in other words, those who ceased statin therapy during the study period.

We finally attempted to identify any differences in muscle parameter changes between baseline statin users grouped according to statin agents. Statin users were categorised by the type of statin they reported using, and ANOVA tests controlling for age and gender examined differences in the mean change in muscle parameters.

A $P$-value of $<0.05$ (two-tailed) or a 95% CI not including the null point was considered statistically significant. All statistical tests were performed using Intercooled Stata 9.2 for Windows (StataCorp).

### Results

Of the 1099 participants who attended the baseline clinic, 224 (20%) did not continue at follow-up due to reasons including death, illness, loss of independence or moving away. Total 49 participants at baseline and 52 participants at follow-up were excluded due to incomplete leg strength and DEXA results. Therefore, a total of 774 (48% female) participants were included in the data analyses. The average age of the included participants was 62.0 (SD 7.3) years (range 51–80 years) and there were no significant differences in either age or BMI at baseline between the included participants and those who were excluded due to incomplete data (data not shown).

A total of 147 participants (19.0%) reported use of statins at baseline. Table 1 presents the descriptive statistics for participants at baseline according to statin usage. Statin users were significantly older and trended to be male ($P=0.09$). Statin users had higher body weight and BMI than non-users, but there were no significant differences in body fat percentage. Statin users also averaged significantly lower steps/day than non-users. As expected, statin users were significantly more likely to report a previous diagnosis of CVD, including hypertension, heart attack or thrombosis; and diabetes. There was no difference between statin users and non-users’ self-reported smoking history in the likelihood of having ever smoked, and there was also no difference in the likelihood of being a current smoker (data not shown). Independent $t$-tests revealed no significant differences between statin users and non-users for the muscle parameters of %ALM, leg strength or LMQ; however statin users had significantly greater falls risk scores at baseline.

Table 2 presents cross-sectional associations of statin use with muscle parameters at both baseline and follow-up. Multivariable regressions were used to report the difference in means for muscle parameters between statin users and non-users, after adjustment for age and gender. These analyses revealed that %ALM was significantly lower and falls risk scores were significantly higher in statin users at baseline after adjusting for potential confounders. No differences were observed between groups for the measures of leg strength and LMQ.

Of the 147 participants who reported use of statins at baseline, 136 (92%) also reported use of statins at follow-up (2.6±0.4 years later), while the
remaining 11 participants reported cessation of statin therapy at follow-up. A total of 43 participants who were non-users at baseline reported statin therapy at follow-up, resulting in a total of 179 statin users at follow-up (23%). The associations of statin use with muscle parameter values at follow-up are also presented in Table 2. At follow-up, statin users had significantly lower mean leg strength than non-users after adjusting for age and gender. They also exhibited a trend to lower LMQ and %ALM than non-users.

The results from longitudinal analyses are presented in Table 3. The data are presented as the mean difference in change in the muscle parameters from baseline to follow-up between the specified groups. Analysis 1 compares changes in those who reported statin use at baseline to those who did not, and demonstrates that statin users at baseline had a greater average increase in %ALM, and this difference approached significance ($P=0.055$). The baseline-adjusted mean change in falls risk over 2.6 years was significantly greater for statin users compared to non-users at baseline.

Analysis 2 involved multivariable linear regressions comparing muscle parameter changes in those who reported statin use at both baseline and follow-up to the remainder of the cohort. The baseline-adjusted mean changes in leg strength and LMQ for statin users were 5.02 kg and 0.30 kg/kg lower than the mean changes for the remainder of the cohort, and these differences were significant. Similar to the results demonstrated in analysis 1, statin users at baseline and follow-up had a greater increase in %ALM compared to controls (although not significant) and had a greater mean change in falls risk which approached significance ($P=0.054$).
Adjusting for baseline falls risk score strengthened the effect of the associations observed in analyses 1 and 2, and these associations were not significant when baseline falls risk score was not adjusted for. Further analysis revealed that change in reaction time was the only component of the PPA which demonstrated significant differences in analyses 1 ($P=0.019$) and 2 ($P=0.037$), increasing by around 7 ms more over 2.6 years for statin users than for non-users.

Analysis 3 examined changes in muscle parameters again in those who reported statin use at both baseline and follow-up, and compares these to the changes observed in those who reported statin use at baseline only. The results demonstrated that those who remained on statins from baseline to follow-up had baseline-adjusted mean changes in leg strength and LMQ which were significantly worse ($–16.17 \text{ kg}$ and $–1.13 \text{ kg/kg}$, respectively) than those who ceased statin therapy between baseline and follow-up, after adjustment for confounders.

Finally, we attempted to determine any differences in muscle parameter changes between statin types. Of the 147 baseline statin users in this study, 75 (51%) reported use of simvastatin, 60 (41%) reported use of atorvastatin, and 12 (8%) reported use of pravastatin. After categorising statin users by statin type, ANOVA tests controlling for age and gender revealed no differences in any muscle parameter changes over 2.6 years (data not shown).

**Conclusions**

The results from this longitudinal study suggest that statin therapy may be associated with greater declines in strength and muscle quality, and greater increases in falls risk in the population of community-dwelling older adults. These associations may be reversible as cessation of statin use was associated with a significantly smaller decrease in leg strength and LMQ over 2.6 years than for those who continued statin use. Whilst the observed associations are modest, the associations between statin use and muscle performance require further examination given the high prevalence of statin use amongst the older adult population.

To the best of our knowledge, the present study is the first to provide evidence that statin therapy may have deleterious effects on muscle performance in community-dwelling older men and women. A previous study of community-dwelling older men found no evidence that statin use leads to muscle strength declines, utilising a muscle performance task involving timed chair stands. The differences in results between the present and previous studies may be related to differences in the type of muscle function test performed, the shorter follow-up period of the previous study (1 year) or possibly attributed to the fact that females were included in the present study. The previous study had a similar sample size to the present study ($N=756$); however the sample was from patients receiving primary care from Veteran’s Affairs clinics, which may indicate that these participants had a higher number of comorbidities than those in the present study. This may be reflected in the higher number of statin users they observed ($N=315$). Furthermore, participants in the previous study were of a greater mean age (74 years) than those in the present study (62 years), and it is possible that the deterioration in muscular performance due to sarcopenia progression in very old adults is so pronounced that the effects of statins are undetectable.

Other studies have reported no associations between statin use and functional decline. A large observational study of women older than 65 years ($N>25000$) found no association between statin use and development of frailty over 3 years. This previous study also examined an older age group (65–79 years) and women only. The use of a subjective measure of frailty in the Rand-36 physical function scale, rather than objective measures of muscle function, may explain the lack of observed associations. Amongst 212 participants without peripheral arterial disease in a study of both older men and women, no significant differences were observed for annual decline in muscle performance between statin users and non-users. Once again, the previous study’s participants were older (mean age 70 years) than those in the present study and the differences in results may also be related to the use of walking speed tests in the previous study. It is possible that statin use adversely affects muscle strength as shown in the present study, but not walking performance, which may be under different mechanistic control. While muscle strength plays an important role in walking speed, it is a more automated movement requiring less voluntary control than maximal force tests. This opens the possibility that statin therapy has an indirect effect on strength as a result of neural changes. Decreases in neuromuscular function occur as part of the aging process, and it may be that statin use exacerbates these declines rather than having an effect on muscle fibres, although little evidence exists to support this.

The argument is given weight by the finding that statin users at baseline actually had a greater increase in %ALM over 2.6 years compared to non-users at baseline, which approached
significance (P=0.055). An increase in muscle mass would generally be expected to result in strength improvements, so it is possible that the functional decreases we observed for statin users may be mediated through pathways other than loss of muscle mass, such as some type of neuromuscular decline. Another explanation for this finding could be that a direct measure of muscular lipid content was not used. Inter-muscular adipose tissue (IMAT) and intra-myocellular lipid content (IMLC) are known to increase with age\textsuperscript{21,24} and are associated with reduced strength.\textsuperscript{23,25} It is possible that IMAT, IMLC or a combination of both increased more in statin users from baseline to follow-up, and that this resulted in an apparent increase in muscle mass when calculated by DEXA. Methods which can directly measure IMAT and IMLC should be considered in future studies.

While a greater increase in %ALM for statin users was somewhat unexpected, a previous study has also observed greater muscle hypertrophy in 49 community-dwelling participants (60–69 years old) using statins, following a 12-week resistance training program.\textsuperscript{26} It has also previously been shown in a study of lovastatin that statin use can exacerbate exercise-induced muscle injury.\textsuperscript{27} Riechman et al., argued that statin use may therefore result in muscle hypertrophy if the magnitude of injury and inflammatory response to exercise is related to the hypertrophy through inflammation-related growth factors.\textsuperscript{26} While the present study did not involve an exercise intervention such as those of the previous studies, it is possible that some hypertrophy occurs in statin users following muscle damage resulting from everyday activities, and this may explain the observed increase in %ALM in statin users compared to non-users.

A discrepancy did exist in our findings in that cross-sectional analyses revealed %ALM was significantly lower in statin users, while %ALM actually increased more in statin users in longitudinal analyses. Further research into the effects of statin use on muscle mass is therefore required, and may require more exact methods of quantifying muscle changes such as MRI, as well as the measurement of muscle damage indices.

The PPA is a valid and reliable tool which measures falls risk based on physiological domains of vision, reaction time, proprioception, strength and balance.\textsuperscript{18} The present study uses this instrument to describe associations between statin therapy and falls risk in community-dwelling older adults. We observed that the change in falls risk over 2.6 years was significantly greater for statin users at baseline, and approached significance for statin users at both time points when compared to controls. We further found that these differences were explained by the significantly greater increase in reaction time for the statin users in both comparisons. This association may be due to some deterioration in the muscles used to respond to stimuli in the reaction time test. However, reaction time also requires neural input, and as mentioned earlier, it may be that statin therapy has detrimental neuromuscular effects. While significant, the greater increase in falls risk scores for statin users were modest (~0.15), given that an increase of 1 is required to change fall risk category. Nonetheless, if prolonged statin use was found to further increase falls risk scores, the implications for older adults would be serious.

This study has a number of limitations. First, we relied on self-report of statin use and it is possible that some participants undergoing statin-therapy did not report this. No data was collected regarding compliance amongst statin users, and this may have influenced the observed results. Given the high rates of non-compliance in statin medication users,\textsuperscript{28} it is possible that the deleterious effects of statins on muscle performance were under-estimated. It is also possible that some statin users that ceased therapy at follow-up in this study did so due to myalgia or weakness associated with statin use, however this was not reported. Randomised controlled trials which isolate statin users and non-users, examine statin dosage, and closely monitor compliance and reasons for non-compliance, are required to clarify the associations of statin use and muscle performance.

Secondly, eligible participants may have chosen not to participate in the study due to functional restrictions related to CVD. These participants could be more likely to be statin users and their inclusion may have resulted in differences in the results observed in this study. However, the initial response rate for the TASOAC study was reasonable (57%) and there was a high continuation rate for the follow-up study (81%). Also, the proportion of included self-reported statin users for this age group appears representative of older adults in the general population, based on previously published age-specific statin prescription rates in Australia.\textsuperscript{29}

Thirdly, only a small number of participants (N=11) reported cessation of statin use at follow-up. Studies which compare larger groups of statin users to those who cease statin medication are required in order to clarify whether cessation is associated with improved muscle function. Also, insufficient participants were available to adequately study the effects of different statin types in order to determine whether or not this is a class effect or limited to specific agents. It was only possible to investigate
types of statins which are approved for use in Australia and being prescribed to TASOAC participants, and other types may have differential effects on muscle mass and strength. Research into these statins, and the development of new types which do not cause myalgia or muscle function declines should continue. The US National Lipid Association’s Muscle Expert Panel has previously called for development of statins which do not enter the skeletal muscle, as these would theoretically have no effect on muscle performance.\(^5\)

Finally, it should be pointed out that there is no consensus on a gold-standard for the assessment of sarcopenia. Muscle quality is a relatively new technique which examines the amount of force a muscle group can produce per unit of muscle mass, and has been shown to decline with age.\(^30\) However, a number of different strength tests and muscle mass assessment techniques have been utilised previously to calculate muscle quality. Furthermore, we chose %ALM to quantify muscle mass change in this study in order to assess changes in muscle mass relative to fat change. Other studies have used absolute total lean and appendicular muscle mass, absolute appendicular lean mass as well as appendicular lean mass normalized to height or BMI. Obviously, future studies that use different methods to quantify muscle mass and strength may differ from those observed in the present study.

In conclusion, the results from this study indicate that statin use may exacerbate muscle performance declines and falls risk associated with aging without a concomitant decrease in muscle mass, and this effect may be reversible with cessation.

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### Conflict of interest

None declared.

### References


