Muscle Strength and Sedative Load in Community-Dwelling People Aged 75 Years and Older: A Population-Based Study

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Background. Use of psychotropic and sedative drugs has been associated with impaired muscle strength. Muscle weakness predicts important outcomes for older people including functional disability and mortality. The objective of this study was to investigate if the use of drugs with sedative properties is associated with poorer muscle strength.

Methods. Seven-hundred community-dwelling participants, aged 75 years and older, enrolled in the population-based Geriatric Multidisciplinary Strategy for the Good Care of the Elderly (GeMS) study in 2004 were included in the present analyses. Data on demographics, diagnostics, and drug use were collected during standardized interviews, conducted by trained nurses and verified through medical records. Physiotherapists conducted objective tests of handgrip strength, knee extension strength, and the five repeated chair stands test. Sedative load was calculated using a previously published model for each participant.

Results. Twenty-one percent of the participants (n = 147) had a sedative load of 1–2 and 8% (n = 58) had a sedative load 3 or more. After adjusting for covariates, participants with sedative load more than 0 had poorer performance on grip strength (p = .009), knee extension strength (p = .02), and five chair stands (p = .003) than nonusers of drugs with sedative properties. Increasing sedative load was associated with poorer grip strength.

Conclusions. Use of drugs with sedative properties was associated with impaired muscle strength. Although we adjusted for diagnoses affecting physical function, the possibility of confounding by indication cannot be entirely excluded. Given that muscle strength is predictive of functional disability and mortality, further attention should be directed toward conducting regular reviews of drug therapy and reducing use of sedative drugs.

Key Words: Hypnotics and sedatives—Aged—Muscle strength—Drug utilization.

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Decreased muscle strength represents a threat to independent living and functioning among older people (1,2). Maintenance of adequate muscle strength is vital for activities of daily living (ADLs). Poor muscle strength has been associated with impaired performance in ADLs, instrumental activities of daily living, and with an increased risk of death (2–4). Lower extremity muscle weakness has also been associated with an increased risk of falling (5). Muscle strength predicts functional disability and mortality better than muscle mass (2,3).

Lower limb muscle strength has been associated with the use of sedative and psychotropic drugs (6). The use of sedative drugs such as diazepam has been shown to delay the onset of postural response when posture is challenged by external forces (7). This can be measured as an increased delay in neuromuscular activation and has been associated
with compromised muscle performance (8,9). Use of
sedative drugs has also been associated with lower grip
strength (10,11).

A wide range of drugs have been associated with sedation,
defined as decreased psychomotor functioning and
subjective feelings of drowsiness and sleepiness (12). Older
people are more susceptible to the sedative effects of drugs
than younger adults (13). Sedative and psychotropic drugs
are frequently used among older people in community and
residential aged care settings (14–17). The prevalence of
psychotropic drug use was 19% among community-dwelling
older people in the United States (16). In a Finnish study,
40% of community-dwelling older people used one or more
drugs with sedative properties (15). Concurrent use of mul-
tiple drugs with sedative properties is also common among
older people (15,16,18).

Methods to describe use of multiple drugs with sedative
properties have been developed (19). These methods
provide an opportunity to investigate adverse drug events
related to cumulative exposure to multiple drugs with seda-
tive properties. The Sedative Load Model was designed to
assess the sedative potential of an overall drug regimen and
includes drugs prescribed for intentional sedation and those
prescribed for somatic diseases (20).

The objective of this study was to investigate the associa-
tion between sedative load and objective measures of muscle
strength among community-dwelling older people.

MATERIALS AND METHODS

Study Sample

This study utilized baseline data collected in 2004 as part
of the Geriatric Multidisciplinary Strategy for the Good
Care of the Elderly (GeMS) Study. The GeMS Study was a
randomized comparative study that evaluated a model for
geriatric assessment, care, and rehabilitation (21). The study
sample comprised 1,000 randomly selected people aged
75 years and older (born before November 1, 1928) who
were inhabitants of city of Kuopio, Finland. Of these 1,000
people, 781 provided written informed consent to partici-
pate, 162 refused participation, 2 relocated, and 55 died
before the baseline examination. For those 162 persons who
refused to participate to the study, 71% were women (n =
54) with mean age of 81.5 years (SD 4.2). These match with
participants (69% women, mean age 81.3 with SD 4.6). For
the present study, participants living in institutional care (n
= 81) were excluded. This was because participants living in
institutional care typically have higher exposure to drugs
with sedative properties and different predictors of func-
tional disability compared with those living in community-
dwelling settings (22,23). A total of 700 community-dwelling
participants were included in the present analyses. The
study was approved by the Research Ethics Committee of
the Northern Savo Hospital District, Kuopio, Finland.

Data Collection

Sociodemographic factors, health-related factors such as
comorbidities, and drug use were assessed for each particip-
and during an interview conducted by a trained nurse. Self-
reported drug use and diagnoses were verified using
prescription forms and drug packages, which participants
were asked to bring to the interview, and medical records
from municipal health centers, home nursing services, local
hospitals, and the Kuopio University Hospital.

Sedative Load

Sedative load was calculated according to the Sedative
Load Model (15,20). The model was created by categorizing
all drugs marketed in Finland between 1998 and 2001
according to their sedative potential. The categorization was
based on manufacturers’ summaries of product characteris-
tics and consensus between a psychogeriatrician, a geriatri-
cian, and a physician specialized in pharmacoepidemiology.
The Sedative Load Model considers two groups of drugs.
Drugs in group one included primary sedatives (eg, conven-
tional antipsychotics, anxiolytics, hypnotics, and tricyclic
antidepressants) and were assigned a sedative rating of 2.
Drugs in group two included those drugs with sedation as a
prominent side effect and preparations with a sedating com-
ponent (eg, atypical antipsychotics, selective serotonin
reuptake inhibitors, antiepileptics, opioids, other second-
generation antidepressants) and were assigned a sedative
rating of 1. These ratings were consistent with those used in
previous studies that have employed the Sedative Load
Model (15,18). Only regularly used drugs were considered
when calculating sedative load. Drug use was considered
regular if the drug was being taken daily or at regular inter-
vals (fortnightly or once-a-month for long-acting intramus-
cularly injected antipsychotics). This categorization was
based on each participant’s actual pattern of use rather than
their clinician’s prescribed or intended pattern of use. Only
regularly used drugs were considered when calculating sedative
load. Sedative ratings for all drugs were summed to define
each participant’s sedative load according to the formula:

\[
\text{Sedative load} = \sum_{k=1}^{n} \text{SR}_k,
\]

where \( n \) stands for the number of drugs and \( \text{SR}_k \) indicates
the sedative rating for drug \( k \).

Drug Classification

All drugs with and without sedative properties that were
used by the study participants were classified using the
Anatomical Therapeutic Chemical (ATC) classification system
recommended by the World Health Organization (24). For
the purpose of calculating sedative load, “atypical antipsy-
chotics” were operationally defined as clozapine, quetiapine,
olanzapine, risperidone, ziprasidone, and aripiprazole.
“Conventional antipsychotics” were deemed to include all other drugs in ATC group N05A excluding lithium. “Tricyclic antidepressants” were operationally defined as ATC class N06AA, “selective serotonin reuptake inhibitors” as N06AB, and “other second-generation antidepressants” as moclobemide and N06AX. Benzodiazepines included drugs in ATC groups N05BA and N05CD, and “benzodiazepine-related drugs” zopiclone, zolpidem, and zaleplon as ATC group N05CF. Antiepileptics and opioids were classified as ATC groups N03 and N02A, respectively.

**Sociodemographic and Health-Related Factors**

The Mini-Mental State Examination (MMSE) was utilized to evaluate cognitive function (25). MMSE scores less than 25 were considered indicative of cognitive impairment (26). Each participant’s comorbidities were scored according to a modified version of the Functional Comorbidity Index (FCI (27)), which was developed to predict physical function in older people. The diagnoses that were included in the FCI were arthritis (rheumatoid arthritis and other connective tissue disorders), osteoporosis, asthma/chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, myocardial infarction, Parkinson’s disease, stroke, diabetes mellitus, depressive symptoms (assessed using the Geriatric Depression Scale (28) with Geriatric Depression Scale scores ≥ 5 considered indicative of depressive symptoms), visual impairment, hearing impairment, and obesity (body mass index > 30). Participant self-reported diagnoses were confirmed from medical records and complemented with data obtained from the Finnish National Prescription and Special Reimbursement Registers maintained by the Social Insurance Institution of Finland (29). For the purposes of the analyses, FCI was classified into 3 groups: 0, 1–2, and 3 or more.

Education was categorized into two groups based on self-reported years of education (0–6 and >6 years). Marital status was grouped as married, widowed, divorced, or never-married. Participants were asked if they lived alone or in the same household with other people. Physical activity was assessed using a modified version of the Grimby Scale (30). Participants were categorized as inactive (no other exercise, light walking one to two times a week), moderately active (light walking or other light exercise three or more times a week or moderate exercise one to two times a week), or active (moderate to vigorous exercise several times a week).

**Muscle Strength**

Muscle strength tests were conducted by two trained physiotherapists. The physical function testing was performed between 1 and 2 weeks after the nurse interview. Grip strength was measured using a Saehan dynamometer (Saehan Corporation, South Korea). Participants were allowed to make one maximal effort with both hands and the best result of these attempts was used in the analyses. Grip strength was measured as kilograms.

Maximal isometric knee extension strength was measured in a sitting position using an adjustable dynamometer chair (Good Strength; Metitur Oy, Palokka, Finland). Participants were tested on both legs and allowed to make three maximal efforts and the best result of these six attempts was used in the analyses. Knee extension strength was measured as Newtons.

A modified Five Chair Rise Test (31) was used to assess the ability to perform sit-to-stand and stand-to-sit transfer. Participants were instructed to stand up and sit down five times as fast as possible starting in the sitting position and stopping after the fifth rise. As a modification of the original test, hands were held free on sides and participants were allowed to help with their hands if needed. Performance in the chair stands test was measured as time to do the test in seconds.

**Statistical Analyses**

Health-related and sociodemographic characteristics of the study sample were summarized using means, percentages, and standard deviations. Comparison of these characteristics across different sedative load groups was conducted using chi-square tests for categorical variables and analysis of variance for continuous variables. The Shapiro–Wilk W test was performed to test the normality of continuous variables, and Levene’s test was used to test the equality of variance. As our exposure variable was not normally distributed, we categorized participants into nonusers of sedatives (sedative load = 0), those with a sedative load 1–2, and those with a sedative load 3 or more. Results of the grip strength test and knee extension test were normally distributed. We performed a log10 transformation to improve the normality of the chair stands test. For the chair stands test, the values presented are the back transformed. We then performed unadjusted and adjusted analysis of covariance to compare each user category with muscle strength measures. Adjustments were made for clinically important covariates including age (75–79, 80–84, ≥85 years), gender, education (0–6, >6 years), Grimby Scale (inactive vs moderate and active combined), comorbidities using the modified FCI (0, 1–2, ≥3), and cognitive decline (MMSE < 25). Data analyses were performed using SAS software (version 9.2; SAS Institute, Cary, NC) and SPSS software version 17.0 (SPPS Inc., Chicago, IL).

**RESULTS**

The mean age of the 700 participants was 81.3 (SD 4.6) years (Table 1). The majority of the participants were women (69%, n = 486). The prevalence of depressive symptoms was 8% (n=55), and cognitive impairment was present in 24% (n = 170) of the participants. Twenty-one percent of
Table 1. Characteristics of Study Participants in the GeMS Study

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Sedative Load = 0, n = 495 (%)</th>
<th>Sedative Load = 1–2, n = 147 (%)</th>
<th>Sedative Load ≥ 3, n = 58 (%)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, M (±SD)†</td>
<td>81.3 (4.6)</td>
<td>80.8 (4.4)</td>
<td>82.4 (4.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female</td>
<td>69</td>
<td>66</td>
<td>80</td>
<td>.002</td>
</tr>
<tr>
<td>Living alone</td>
<td>55</td>
<td>54</td>
<td>62</td>
<td>.182</td>
</tr>
<tr>
<td>Education (≤ 6 y)</td>
<td>49</td>
<td>50</td>
<td>50</td>
<td>.173</td>
</tr>
<tr>
<td>MMSE ≥ 25</td>
<td>24</td>
<td>20</td>
<td>30</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>GDS ≥ 5</td>
<td>8</td>
<td>5</td>
<td>12</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive</td>
<td>37</td>
<td>32</td>
<td>45</td>
<td>60</td>
</tr>
<tr>
<td>Moderate</td>
<td>36</td>
<td>38</td>
<td>34</td>
<td>25</td>
</tr>
<tr>
<td>Active</td>
<td>27</td>
<td>30</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>FCI, M (±SD)†</td>
<td>2.6 (1.7)</td>
<td>2.5 (1.7)</td>
<td>2.9 (1.8)</td>
<td>3.4 (1.7)</td>
</tr>
<tr>
<td>Diagnoses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>79</td>
<td>78</td>
<td>80</td>
<td>91</td>
</tr>
<tr>
<td>Dementia</td>
<td>16</td>
<td>12</td>
<td>20</td>
<td>31</td>
</tr>
<tr>
<td>COPD/asthma</td>
<td>9</td>
<td>8</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17</td>
<td>16</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Cancer</td>
<td>18</td>
<td>17</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>17</td>
<td>13</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>Stroke</td>
<td>12</td>
<td>11</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Number of drugs, M (±SD)†</td>
<td>4.9 (3.2)</td>
<td>4.1 (2.7)</td>
<td>6.4 (3.1)</td>
<td>8.6 (3.6)</td>
</tr>
</tbody>
</table>

Notes: Categorical variables were tested with chi square, and continuous variables were tested with analysis of variance. Diagnosis included in the FCI: arthritis (rheumatoid arthritis and other connective tissue disorders), osteoporosis, asthma/COPD, coronary artery disease, congestive heart failure, myocardial infarction, Parkinson’s disease, stroke, diabetes mellitus, depressive symptoms, visual impairment, hearing impairment, and obesity (body mass index > 30). COPD = chronic obstructive pulmonary disease; FCI = Functional Comorbidity Index; GDS = Geriatric Depression Scale; MMSE = Mini-Mental State Examination.

* p Value of comparison between the sedative load groups.
† Continuous variables are presented as means (±SD).

Participants (n = 147) had a sedative load of 1–2 and 8% (n = 58) had a sedative load 3 or more (Table 1). The mean sedative load was 0.67 (SD 1.22). Users of drugs with sedative properties were older (p < .001), more likely to be women (p = .002), to have depressive symptoms (p < .001), and have cognitive impairment (p < .001) than nonusers of drugs with sedative properties. They also had higher number of comorbidities (p < .001). The most frequently used drugs contributing to sedative load were benzodiazepines and related drugs (Table 2).

Unadjusted and adjusted models comparing each of the functional outcomes between participants with different sedative load groups are shown in Table 3. In the unadjusted models, there was a strong relationship between increasing sedative load and poorer performance in grip strength (p < .0001), knee extension strength (p < .0001), and chair stands test (p < .0001). Participants with a sedative load more than 0 had poorer performance in grip strength and chair stands test compared with those with sedative load = 0 (p < .05) when adjusting for age, sex, education, FCI score, MMSE, and the Grimby Scale score (Table 3; Figure 1). In the knee extension strength, significant difference (p < .05) was observed between people with sedative load of 1–2 compared with nonusers of drugs with sedative properties (p = .02). In chair stands test, significant differences were observed between those with sedative load = 0 and those with 1–2 (p = .002) and between those with sedative load = 0 and those with sedative load 3 or more (p = .04). Grip strength showed significant impairment in comparison of those with sedative load 3 or more when compared with either those with sedative load of 1–2 (p = .03) or to those with sedative load = 0 (p = .009).

DISCUSSION

This is the first study to report an association between sedative load and impaired muscle strength. Sedative load was associated with poorer performance in the handgrip strength, knee extension strength, and chair stands test after adjusting for covariates. Higher sedative load was associated with poorer grip strength in adjusted analyses.

Our results were partially consistent with previous studies of psychotropic and sedative drug use (6). Lord and coworkers found an association between psychotropic drug use and impaired quadricep and ankle strength. The Drug Burden Index, a measure of cumulative exposure to drugs with sedative and anticholinergic properties, was associated with lower grip strength and difficulties in performing chair stands (10,11). However, our study differed to that conducted by Lord and coworkers and those using the Drug Burden Index because the Sedative Load Model takes into account use of multiple drugs with sedative properties, does not include anticholinergic drugs, and is not restricted to psychotropic drugs.
Clinical Importance of Findings

In our study, participants with a sedative load less than 0 took more than 17.1 seconds to perform five chair stands. Previous studies have demonstrated that this length of time was predictive of adverse outcomes (32). In a study conducted by Cesari and coworkers, older people who took 17.1 seconds or more to complete five chair stands were at higher risk of developing persistent severe lower extremity limitation and a higher risk of death during follow-up. In our study, clinically meaningful change was also observed in grip strength. Compared with nonusers of sedatives, those with a sedative load 3 or more had 2.9 kg lower grip strength after adjustments for covariates (20.1 vs 17.2 kg).

A recent systematic review of objective measures of physical capability concluded that weaker grip strength is associated with an increased risk of fractures and cognitive decline in most studies (34). The same review reported similar findings in relation to chair stands, although the number of studies examining this parameter was relatively small. Muscle strength is important in cases of sudden perturbations of postural control to prevent falling. It has been shown that the muscle strength required to generate a postural response to prevent falling commonly exceeds muscle strengths measured in older adults (35). Poor performance in grip strength, knee extension strength, and chair stands have been associated with increased risk of death among older people (3,4,32).

The sedative effects of drugs may be pronounced among older people due to age-related change in organ function and body composition, leading to altered pharmacokinetics and pharmacodynamics (36,37). Aging may be associated with reduced hepatic blood flow and a decline in liver size that reduces drug metabolism. Declining renal function may cause an accumulation of drugs that are excreted via the kidneys. A reduction in lean body mass and an increase in the percentage of adipose tissue may result in an increased volume of distribution of lipophilic drugs, such as diazepam. These factors contribute to prolonged elimination half-lives of sedative drugs in older people compared with middle-aged people.

Possible Mechanisms for Association Between Sedative Drugs and Impaired Muscle Strength

Mechanisms by which sedative drugs impair muscle function are not fully understood. However, the mechanisms may include muscle relaxant effects, overall sedation, and slowing of neuromuscular processing in the central nervous system (7,38–40). Drugs acting at GABA receptors may increase intracortical inhibition thereby impairing the ability of the nervous system to activate skeletal muscles (9,41). In a study conducted by Lord and coworkers (6), those taking one or more psychotropic drugs performed poorly in tests of quadriceps and ankle strength. Lord and coworkers found that users of two or more psychotropic drugs performed poorly in tests of reaction time. Cutson

Table 2. Use of Drugs With Sedative Properties Among Participants of the GeMS Study

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Users, % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td></td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>1.7 (12)</td>
</tr>
<tr>
<td>SSRIs</td>
<td>4.6 (32)</td>
</tr>
<tr>
<td>Other antidepressants*</td>
<td>4.1 (29)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td></td>
</tr>
<tr>
<td>Conventional antipsychotics</td>
<td>3.4 (24)</td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td>2.6 (18)</td>
</tr>
<tr>
<td>Benzodiazepines and related drugs</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>8.6 (60)</td>
</tr>
<tr>
<td>Benzodiazepine-related drugs</td>
<td>9.1 (64)</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>1.9 (13)</td>
</tr>
<tr>
<td>Opioids</td>
<td>2.1 (15)</td>
</tr>
<tr>
<td>Other drugs contributing sedative load†</td>
<td>3.9 (27)</td>
</tr>
</tbody>
</table>

Notes: SSRI = selective serotonin reuptake inhibitor.
* Including mianserin, mirtazapine, venlafaxine, moclobemide, trazodone.
† Amitriptyline in combination with chlordiazepoxide or perphenazine, pramipexole, theophylline, pergolide, quinine with psychotropics, cyclizine in combinations, biperiden, clidinium with psychotropics, buspirone, bromhexine.

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Table 3. Unadjusted and Adjusted Analysis of Covariance to Compare Means of Muscle Strength Measures With the Exposure to the Sedative Load Model Exposure

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>SL = 0</th>
<th>SL = 1–2</th>
<th>SL ≥ 3</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grip strength (kg)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>21.3 (20.4–22.2)</td>
<td>17.5 (15.9–19.2)</td>
<td>14.9 (12.2–17.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adjusted</td>
<td>20.1 (19.5–20.8)</td>
<td>19.8 (18.5–21.0)</td>
<td>17.2 (15.1–19.3)</td>
<td>.03</td>
</tr>
<tr>
<td>Knee extension strength</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Newtons)</td>
<td>310.6 (300.0–321.3)</td>
<td>257.2 (236.3–278.0)</td>
<td>267.2 (229.6–304.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>302.2 (294.1–310.2)</td>
<td>280.7 (264.9–296.5)</td>
<td>289.1 (259.6–318.5)</td>
<td>.06</td>
</tr>
<tr>
<td>Adjusted</td>
<td>14.9 (13.4–15.3)</td>
<td>17.5 (16.4–18.7)</td>
<td>16.6 (17.2–20.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Chair stands test (s)*</td>
<td>15.2 (14.7–15.6)</td>
<td>16.8 (15.8–17.8)</td>
<td>16.9 (15.3–18.7)</td>
<td>.003</td>
</tr>
</tbody>
</table>

Notes: Means with 95% confidence intervals are displayed. p Value is for the sedative load variable (2 df). Number of observations for each model: grip strength, unadjusted n = 650, adjusted n = 6 33; knee extension strength, unadjusted n = 535, adjusted n = 525; chair stands test, unadjusted n = 562, adjusted n = 546. SL = sedative load.

*Variable log10 transformed after analysis.
and coworkers (7) found that diazepam delayed muscle activation during balance tests conducted among older people. These results suggest that association between muscle strength and drugs with sedative properties may be associated with reduced mental alertness, neuromuscular coordination, and speed of transmission in the central nervous system. In our study, each participant’s sedative load was calculated only considering regularly used drugs. This meant there were likely to have been no or minimal changes to each participant’s drug regimen in the 1- to 2-week period between the nurse interviews and physical function testing. Combined with the fact elimination half-lives of sedative drugs may be prolonged in older people, it is possible that participants were under the sedative effects of drugs when performing the physical function testing.

The association between sedative drug use and impaired muscle strength may also be due to indirect mechanisms such as disuse atrophy or selective prescribing of sedatives to persons with cognitive impairment. Nevertheless, sedative load more than 0 was still associated with poorer muscle strength after we adjusted our analyses for each participant’s level of physical activity. Sedatives are often prescribed to persons with cognitive impairment, and cognitive impairment has been associated with impaired muscle strength (42). However, our analyses were adjusted for cognitive impairment measured using the MMSE. Nevertheless, as with all observational studies, we cannot exclude the possibility of residual confounding by indication.

While not all adverse drug reactions display a dose–response relationship, based on previous research, we anticipated a dose–response between sedative load and muscle strength (10,11). In this study, increasing sedative load exposure was associated with a decline in grip strength but not with a decline in knee extension strength or increase in time to perform chair stands test. The presence of a dose–response relationship is considered indicative of causality for adverse drug reactions (43). However, given the relatively small sample size of participants with a sedative load of 3 or more, the possible dose–response relationship between sedative load and muscle strength requires further investigation in studies with larger sample sizes.

Although the association between sedative drug use and lowered muscle strength is clinically important, the causality could not be assessed in our cross-sectional design. The association may be explained by sedatives causing impairments in muscle function, either by directly affecting neuromuscular coordination of muscles by the central nervous system (38) or indirectly by causing physical inactivity and

Figure 1. Adjusted means of muscle strength outcome measures according to Sedative Load Model groups. Models are adjusted for age, sex, education, cognitive impairment, the Functional Comorbidity Index score, and physical activity. Chair stands variable is log10 transformed after analyses. Error bars represent standard error. Parenthesis drawn from sedative load (SL) = 0 to SL ≥ 3 represent difference between those two groups.
hence decreased muscle strength. In our study, sedative load more than 0 was still associated with poorer muscle strength after we adjusted for each participant’s level of physical activity. Another explanation could be that sedatives were selectively prescribed to persons with impaired muscle strength. Sedatives are often prescribed to persons with cognitive impairment or with the first symptoms of cognitive decline. Persons with cognitive decline often experience decline in muscle strength (44). If true, this finding raises important concerns regarding the appropriateness of prescribing. This is because the associations between sedative drug use and mobility disability (44), impaired balance (45), decreased muscle strength (6), and difficulties in activities in daily living (44) have previously been reported. Prescribers should be careful not to further enhance decline in muscle strength, cognition, and ADLs caused by the dementing disease process with drugs that have been associated with these adverse drug reactions.

**Practice Implications**

Our findings highlight the important issue of appropriateness of prescribing for older people. This is because of the association between sedatives and mobility limitation (44), impaired balance (45), decreased muscle strength (6), and difficulties in ADLs (44). Use of drugs with sedative properties has previously been associated with an increased risk of falls (46). Sarkisian and coworkers (47) studied modifiable risk factors for functional decline in vigorous and basic ADLs. They concluded that short-acting benzodiazepine use was a modifiable risk factor in clinical practice to prevent functional decline among older people. Our findings highlight the need for thorough and regular review of drug therapy among older people and education of health care providers regarding the potential hazards related to sedative drugs. Our findings also lend support to the importance of conducting additional pharmacoepidemiological research and randomized controlled trials to establish the postmarketing safety and efficacy of drugs routinely used among frail older people (48,49).

**Strengths and Limitations**

Strengths of our study included the use of a population-based sample of older people and the use of interview data that were verified from medical records from health centers, hospitals, and home nursing services. We utilized objective and commonly used tests of muscle strength and physical function. Furthermore, testing was undertaken by trained physiotherapists specialized in the testing of older people. Adjustments were made for comorbidities that have been associated with physical function (27) and also for physical activity level which has been shown to predict physical functioning (50). In addition, sedative load was assessed using a comprehensive and previously published classification of drugs with sedative properties and measured with a scale that describes cumulative exposure to these drugs.

Limitations of our study included the cross-sectional study design which does not allow determination of causality. The study may have limited generalizability to countries with different patterns of prescribing and primary health care systems. However, the population-based sampling strategy means the results are likely to be generalizable to older people in Finland. The drug reimbursement system is the same for all older people across the country (29). In addition, Finland is ethnically homogenous and health care provided by municipalities is organized according to a national framework. Although we adjusted for diagnoses affecting physical function possibility of confounding by indication cannot entirely be ruled out. The FCI is a previously validated index that takes into account medical conditions that have been shown to predict physical function in older persons (27). However, other comorbidities not included in the FCI may also have had impacted the association between sedative load and muscle function. The FCI did not take into account disease severity which also may affect the association between muscle strength and physical function. Although the Sedative Load Model is comprehensive in terms of the drugs that it includes, the model does not include doses of drugs (19), drugs used on an as-needed basis, or past use of drugs with sedative properties.

**Conclusions**

Sedative load was associated with poorer performance in muscle strength tests. There was an association between increasing sedative load and poorer grip strength. Our results highlight the importance of thorough and regular reviews of drugs therapy among older people and education of health care providers regarding the potential hazards related to sedative drugs. Further longitudinal studies are needed to assess the association between sedative load and muscle strength in other populations with differing functional abilities, prescribing cultures, and health care systems.

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