THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2018, Vol. 73, No. 1, 117–122
doi:10.1093/gerona/glx074
Advance Access publication May 6, 2017

OXFORD

Research Article

Polypharmacy as a Risk Factor for Clinically Relevant Sarcopenia: Results From the Berlin Aging Study II

Maximilian König,[1] Dominik Spira,[1] Ilja Demuth,[1,2] Elisabeth Steinhagen-Thiessen,[1,3] and Kristina Norman[1]

[1]Research Group on Geriatrics, [2]Institute of Medical and Human Genetics, and [3]Lipid Clinic and Lipid Apheresis, Charité – Universitätsmedizin Berlin, Germany.

Address correspondence to: Maximilian König, MD, Research Group on Geriatrics, Charité—Universitätsmedizin Berlin, Reinickendorfer Straße 61, 13347 Berlin, Germany. E-mail: koenig.maximilian@charite.de

Received: January 17, 2017; Editorial Decision Date: April 14, 2017

Decision Editor: Stephen Kritchevsky, PhD

Abstract

Background: Sarcopenia affects more than 10% of older adults. Next to age-associated physiologic changes, diseases like diabetes or inflammatory, neurological, malignant and endocrine disorders may contribute to the development of sarcopenia. Likewise, polypharmacy, i.e., multiple drug use, is common among older adults. Although the two conditions frequently co-occur, the association of polypharmacy with sarcopenia has not yet been examined. We investigated the association of polypharmacy and sarcopenia in a large cohort of community-dwelling older adults (60–84 years).

Methods: Thousand five hundred and two participants from the Berlin Aging Study II were included. Polypharmacy was defined as concurrent use of 5 or more drugs (prescription and nonprescription). Body composition was assessed with dual-energy X-ray absorptiometry, and appendicular lean mass (ALM) was calculated as sum of the four limbs' lean mass. Sarcopenia was defined as low ALM-to-body mass index (BMI)-ratio using validated sex-specific cutoffs.

Results: Mean age was 68.7 ± 3.7 years, 50.7% were female. The median (interquartile range) number of drugs was 2 (1–4); 21.1% of subjects reported regular use of ≥5 drugs. Subjects with polypharmacy were more often sarcopenic according to the applied ALM/BMI-cutoffs (16.3% vs 6.9%, $p < 0.001$), with a higher BMI ($p < 0.001$) and lower ALM/BMI ($p < 0.001$), but no significant difference in mean ALM. Notably, polypharmacy was also associated with higher rates of reduced gait speed and exhaustion. Even after multivariable adjustment (sex, age, comorbid conditions and physical activity) polypharmacy was consistently associated with a significantly increased likelihood of sarcopenia (odds ratio = 2.24, 95% confidence interval [CI] = 1.33–3.75).

Conclusion: Polypharmacy is associated with clinically relevant sarcopenia, as assessed by a low ALM/BMI.

Keywords: Pill burden—Frailty—ALM/BMI—Low lean mass

Sarcopenia or low lean mass, respectively, has been recognized as an important medical entity. It is estimated to affect about 10% of people aged 60–70 years and numbers increase sharply for those aged 80 years and older (1–3). Only recently, in an attempt to operationalize sarcopenia, novel criteria for low lean mass have been proposed by the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project, standardizing appendicular lean mass (ALM) to body mass index (ALM/BMI) (4,5). Sarcopenia has a complex, multifactorial etiology. Apart from age-associated physiological changes (poor blood flow, mitochondrial dysfunction, anorexia of aging, loss of motor neuron end plates, loss of anabolic hormones, etc.) (6,7), a multitude of factors have been shown to modulate or promote progressive loss of muscle mass and strength, a process which is often accompanied by gain of fat. Among these are chronic diseases, especially diabetes, neurological, and endocrine disorders as well as malignancies, inflammation and nutritional deficiencies (8), and low physical activity (9). To note, also for certain drugs, detrimental, but also favorable effects on muscle tissue and body composition have been shown (10,11).

In the old, the use of multiple medications (prescription and nonprescription) per day is common (12), and polypharmacy, commonly defined as the concurrent use of five or more drugs (13,14), was found

to be highly prevalent in old populations (12,15). Polypharmacy is tightly linked with chronic illness and multimorbidity, and is in particular associated with specific diseases, which are frequent in the old, such as hypertension, diabetes mellitus, chronic kidney disease, and cardiovascular disease (15). Notably, polypharmacy has also been linked to increased rates of hospitalization, reduced ability to perform instrumental activities of daily living, cognitive impairment, and mortality (16,17). Moreover, it has been shown to be a major risk factor for falls (18). Although sarcopenia and polypharmacy frequently co-occur in older populations, the association of polypharmacy and body composition—and in particular low ALM/BMI—has, however, not yet been addressed. Therefore, the aim of this study was to examine the association between polypharmacy and low lean mass, defined by ALM/BMI-cutoffs as recently proposed by the FNIH Sarcopenia Project, in a large cohort of community-dwelling older adults.

Methods

Study Population

Altogether, 1,502 participants from the Berlin Aging Study II (BASE-II), recruited between 2009 and 2013 were included in this cross-sectional analysis. BASE-II has been described previously in detail (19,20). Briefly, participants were residents of the greater metropolitan area of Berlin, Germany, and were community-dwelling, comparably well-functioning and aged between 60 and 84 years. All participants gave written informed consent and the Ethics Committee of the Charité—Universitätmedizin Berlin approved the study (approval number EA2/029/09).

Polypharmacy

For the analysis of polypharmacy, we used the total medication count, considering scheduled and as-needed medications, as well as prescription and nonprescription drugs, respectively. Nonprescription drugs included over-the-counter medicines and dietary supplements (e.g., omega-3 fatty acids, coenzyme Q10, gingko, chondroitin, crataegus). Participants were asked to bring the medication packets for all drugs used regularly, as well as their medication plan. Study staff reviewed the medication and took a comprehensive medication history (incl. indication, dosage, start, and side-effects). Similar to previous studies, we defined polypharmacy as the regular use of five or more drugs (13,15).

Body Composition/Sarcopenia

Body weight and height were determined by using an electronic weighing and measuring station (seca 764, seca, Hamburg, Germany). BMI was calculated based on weight and height (kg/m^2). Body composition was assessed with dual-energy X-ray absorptiometry (DXA; Hologic QDR DiscoveryTM; Hologic, Inc., Bedford). Total nonbone lean mass was determined from the difference between total lean mass and bone mineral content; and ALM in kg was calculated as sum of the four limbs' lean mass. The definition of sarcopenia was based on low ALM in relation to BMI (ALM/BMI) with the cutoff values suggested by the FNIH Sarcopenia Project (<0.789 in men and <0.512 in women), which are associated with greater weakness and higher likelihood of mobility impairment (5,21,22).

Frailty

Frailty was defined according to the validated definition proposed by Fried *et al.* based on the five criteria unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, and low physical activity (23) with minor adjustments as previously described (22). According to how many criteria were met, participants were ranked as frail (3–5), prefrail (1–2), or not frail (0).

Comorbidities

Extensive cross-sectional data of all participants with respect to sociodemographics, lifestyle, medication, and diagnoses were collected during structured interviews, physical examination, and functional tests. Hypertension was diagnosed if blood pressure was measured >140/90 mm Hg or previously known and diabetes was diagnosed by measured HbA1c >6.5%, fasting glucose >126 mg/dL or 2-hour oral glucose tolerance test >200 mg/dL and/or antidiabetic medication. We used the Rapid Assessment of Physical Activity (RAPA) questionnaire to determine physical activity (24). This instrument records how many times per week and for how long (more/less than 20/30 min per day) the responder carries out light, moderate, or heavy physical activity. A morbidity index, largely based on the categories of the comorbidity index proposed by Charlson (Charlson, 1987), was computed based on self-reported as well as physician-assessed medical diagnoses of diseases, which has been described previously in detail (25,26).

Statistical Analysis

Descriptive data are presented as mean ± standard deviation, median and interquartile range, or total number and percentage (%). Differences between subjects were compared using *t*-test, Mann-Whitney-*U*-Test, chi^2 test or Fishers exact test, where appropriate. Association between sarcopenia as a dichotomous variable, calculated according to sex-specific ALM/BMI-cutoffs, and polypharmacy was further examined with multiple binary logistic regression analysis. Covariates included were either known risk factors for sarcopenia or diseases selected to reflect the most common indications of medication use in BASE-II. Covariates included in the fully adjusted model were: age, sex, joint pain or swelling, osteoporosis, chronic gastritis or gastroesophageal reflux, vitamin D-deficiency, hypothyroidism, liver disease, malignancy, coronary artery disease, COPD, CRP, hypertension, diabetes, low physical activity, current smoking, hyperuricemia, thrombosis or embolism or atrial fibrillation, low-density lipoprotein cholesterol, and estimated glomerular filtration rate (mL/min/1.73 m^2). Polypharmacy was examined as binary variable ("polypharmacy"). In a variant of our regression analysis, single diseases/conditions and laboratory values were replaced by the above-mentioned morbidity index. All analyses were performed using SPSS version 23.0.0.2 (IBM; 1989; 2015). A p value <0.05 was established a priori as level of statistical significance.

Results

Baseline characteristics of all participants (n = 1502) are presented in Table 1. Mean age was 68.7 ± 3.7 years and 50.7% were women. Although the median number of medications (prescription and nonprescription) was two (range 0–15, mean ± SD = 2.8 ± 2.4), about one fifth (21.1%) of study subjects reported regular use of five or more drugs. In total, 8.8% (n = 127) of all subjects were classified as sarcopenic. Split up by sex, men were more frequently affected by sarcopenia than women (11.2% [n = 78] vs 6.6% [n = 49], p = .02). In contrast, we did not find a statistically significant difference in the prevalence of polypharmacy between women and men (22.6%

Table 1. Participant Characteristics According to Polypharmacy Status

	Number of regular drugs†			
	Total sample	<5	≥5	
	n = 1,502	*n* = 1,185 (78.9%)	*n* = 317 (21.1%)	*p* value‡
Age (years)	68.7 ± 3.7	68.5 ± 3.6	69.4 ± 3.9	<.001
Sex (female)	761 (50.7)	589 (49.7)	172 (54.3)	.084
Number of drugs†	2 (1–4)	2 (1–3)	6 (5–7)	<.001
BMI (kg/m^2)	26.8 ± 4.2	26.4 ± 3.9	28.2 ± 4.9	<.001
ALM (kg)	21.2 ± 5.0	21.2 ± 5.0	21.0 ± 5.2	.513
ALM/BMI	0.80 ± 0.18	0.81 ± 0.18	0.76 ± 0.18	<.001
Sarcopenia	127 (8.8%)	78 (6.9%)	49 (16.3%)	<.001
Current smoking*	141 (9.4%)	118 (10.8%)	23 (7.3%)	.160
Systolic blood pressure (mmHg)	147.4 ± 19.2	147.8 ± 19.2	145.8 ± 19.1	.105
Diastolic blood pressure (mmHg)	85.5 ± 10.7	86.0 ± 10.7	83.7 ± 10.8	.001
Total cholesterol (mg/dL)	215.0 ± 39.6	218.3 ± 38.6	202.7 ± 40.6	<.001
HDL-cholesterol (mg/dL)	62.3 ± 17.1	63.2 ± 17.2	58.9 ± 16.4	<.001
LDL-cholesterol (mg/dL)	130.5 ± 35.1	133.6 ± 34.4	118.7 ± 35.7	<.001
GFR_{EPI} (mL/min/1.73 m^2)	76.9 ± 12.1	77.7 ± 11.3	74.1 ± 14.3	<.001
HbA1c (%)	5.6 ± 0.6	5.6 ± 0.5	5.8 ± 0.8	<.001
CRP (mg/L)	1.1 (0.6–2.1)	1.1 (0.6–2)	1.3 (0.7–2.7)	.039
Hemoglobin (g/dL)	13.9 ± 1.1	14.0 ± 1.1	13.6 ± 1.1	<.001
Morbidity index	1 (0–2)	1 (0–2)	2 (1–3)	<.001
Hypothyroidism*	229 (15.6%)	144 (12.4%)	85 (27.7%)	<.001
COPD*	65 (4.3%)	39 (3.3%)	26 (8.1%)	<.001
Osteoporosis*	127 (8.6%)	84 (7.2%)	43 (14.0%)	.001
Coronary artery disease*	60 (4.0%)	25 (2.1%)	35 (11.3%)	<.001
Hypertension	1,162 (77.4%)	885 (74.7%)	277 (87.4%)	<.001
Diabetes	190 (12.7%)	106 (9.0%)	84 (26.8%)	<.001
Frailty				<.001
Prefrail	467 (31.1%)	338 (28.5%)	129 (40.7%)	
Frail	13 (0.9%)	9 (0.8%)	4 (1.3%)	
Vitamin D-deficiency	646 (44.3%)	509 (44.2%)	137 (44.8%)	.457
Low physical activity*	133 (8.9%)	99 (8.4%)	34 (10.9%)	.182

Notes: ALM = appendicular lean mass; BMI = body mass index; ALM/BMI = BMI-adjusted ALM; CRP = C-reactive protein; GFR_{EPI} = glomerular filtration rate computed by Chronic Kidney Disease epidemiology collaboration (CKD-EPI) equation; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; non-HDL-cholesterol = total cholesterol minus HDL-cholesterol; LDL = low-density lipoprotein; COPD = chronic obstructive pulmonary disease. *N* (%), or mean ± standard deviation, or median and interquartile range (IQR).

†Prescription and nonprescription drugs.

*Self-reported.

‡*p* value for test "<5" versus "≥5".

[*n* = 172] vs 19.6% [*n* = 145]; *p* = .150). The average number of drugs was only slightly higher in women, compared to men (3.0 ± 2.4 vs 2.7 ± 2.4, *p* = .038).

Overall, prevalence of polypharmacy, as well as sarcopenia increased stepwise with higher age (Figure 1). However, when stratified for sex, it was notable that in the age-group of 60–69 years, sarcopenia was significantly more frequent in men compared to women (10.8% vs 4.9%, *p* = .001), whereas above 70 years, prevalence of sarcopenia was comparable between men and women (10.5% vs 11.7%, *p* = .390). Likewise, although the prevalence of polypharmacy was constant at ~20% across the examined age spectrum in men, in women, the proportion of polypharmacy increased from 13.7% (60–65 years) to 28.8% (70–75 years) to 57.1% (≥80 years) (*p* < .001 for trend, 5-year age-strata).

When split up according to polypharmacy (<5/≥5 drugs; Table 1), generally, subjects with polypharmacy were marginally older (but without clinical significance; 0.9 years), whereas the sex ratio was well balanced. As expected, subjects with polypharmacy were apparently more morbid than those without polypharmacy, showing a higher prevalence of chronic diseases, e.g., coronary

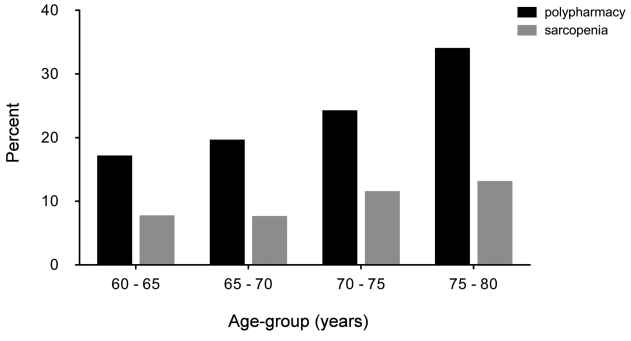

Figure 1. Prevalence of polypharmacy and sarcopenia in BASE-II. Bar graph showing prevalence (in %) of sarcopenia (gray) and polypharmacy (black) by age-strata (60–65; 65–70; 70–75; 75–80 years). Polypharmacy was defined as the concurrent use of 5 or more drugs (prescription and nonprescription) and sarcopenia was determined according to sex-specific cutoffs for the ALM/BMI ratio (low appendicular lean mass in relation to body mass index) as proposed by the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project (5,6).

artery disease, diabetes, hypertension, or osteoporosis, which was reflected also by a significantly higher morbidity index [2 (1–3) vs 1 (0–2); $p < .001$]. On the other hand, diastolic blood pressure was lower (systolic blood pressure only by trend), as well as total- and low-density lipoprotein cholesterol were markedly lower with polypharmacy, most likely indicating the beneficial effects of pharmacotherapy. Interestingly, there were no differences in vitamin D status, current smoking status, and prevalence of self-reported low physical activity.

Regarding parameters of body composition, subjects with polypharmacy were markedly more often sarcopenic as to the applied ALM/BMI-cutoffs (16.3% vs 6.9%, $p < .001$). They had a higher BMI, lower ALM/BMI but showed no statistically significant difference in the unadjusted lean body mass (ALM; Table 1).

Notably, polypharmacy was also associated with higher rates of "reduced gait speed" (15.5% vs 9.9%, $p = .005$) and "exhaustion" (12.6% vs 8.0%, $p = .011$), and there was a significant difference in prevalence of being prefrail or frail between subjects with and without polypharmacy (40.7% vs 28.5% and 1.3% vs 0.8%, $p < .001$, respectively).

Using multiple logistic regression analysis, polypharmacy was confirmed to be associated with a low ALM/BMI even after adjustment for comorbid conditions, sex, age, and clinical parameters (Table 2). This finding was consistent, both, in the analysis of all subjects (odds ratio [OR] = 2.24, 95% confidence interval [CI] = 1.33–3.75), and in sex-stratified analyses (Table 3). Other factors that were independently associated with a low ALM/BMI (in the total population) were higher age, hypertension, diabetes, joint pain/swelling, low physical activity, and estimated glomerular filtration rate.

When we repeated logistic regression analysis, replacing single risk factors/comorbidities by a morbidity index, our finding of a significant and independent association between polypharmacy and sarcopenia could be reproduced for the total population (OR = 2.14, 95% CI = 1.38–3.33, $p = .001$) as well as in sex-stratified analyses (men: OR = 1.86, 95% CI = 1.05–3.32, $p = .034$; women: OR = 2.61, 95% CI = 1.29–5.26, $p = .007$).

Table 2. Logistic Regression for the Association of Polypharmacy and Sarcopenia (Low ALM/BMI)

	Adjusted odds ratio† (95% CI)	*p* value
Polypharmacy	2.24 (1.33–3.75)	.002
Age (years)	1.09 (1.03–1.16)	.006
Low physical activity*	2.00 (1.08–3.70)	.028
Hypertension	3.28 (1.47–7.33)	.004
Diabetes	3.24 (1.96–5.35)	<.001
Joint pain/swelling*	1.66 (1.05–2.60)	.029
eGFR (mL/min/1.73 m^2)	1.02 (1.00–1.04)	.040

Notes: CI = confidence interval; eGFR = estimated glomerular filtration rate, Polypharmacy, ≥5 drugs (reference < 5 drugs); LDL = low-density lipoprotein. Table shows significant factors only.

†Adjusted for age, sex, low physical activity, hypertension, diabetes, vitamin D-deficiency, gastritis/esophageal reflux, hypothyroidism, liver disease (except cirrhosis), atrial fibrillation/deep vein thrombosis/embolism, joint pain/swelling, osteoporosis, coronary artery disease, chronic pulmonary disease, current smoking, hyperuricemia, eGFR, LDL-cholesterol, C-reactive protein, malignancies.

*Self-reported.

Discussion

The results of this cross-sectional study suggest an independent association between polypharmacy and sarcopenia, defined as a low ALM-to-BMI-ratio, as subjects with polypharmacy had a more than twofold higher likelihood of being sarcopenic compared to subjects with a lower drug count.

To our knowledge, this is the first study to investigate and suggest a link between polypharmacy and sarcopenia. The cutoff ≥5 for polypharmacy has been validated many times (13,14) and proven suitable for identifying those at risk for adverse functional outcomes and mortality (14,16,17,27), and is especially helpful as an orientation value in the clinical routine as well as in research. We were now able to show, that polypharmacy, assessed by this commonly used threshold, was independently associated with sarcopenia in a cohort of community-dwelling older adults.

For the definition of sarcopenia, we used the ALM/BMI cutoffs, as recently suggested by the FNIH sarcopenia project, since they have proven suitable to identify those individuals at risk, with clinically relevant weakness and impaired function (4,22), and reflect an individual's adverse lean-to-fat mass ratio (22), rather than just the loss of muscle mass (and/or strength).

As a matter of course, many drugs affect and interfere with various metabolic processes and circulatory homeostasis. In fact, there are several molecular, metabolic, and vascular alterations, which are suspected to play central roles in the development of sarcopenia, that probably also may account for polypharmacy-associated sarcopenia: primarily (drug-induced) mitochondrial dysfunction, but also diminished blood flow, as well as electrolyte, hormonal (6,8), and acid–base disturbances (28). Likewise, for a significant number of commonly prescribed drugs, direct adverse effects on body

Table 3. Logistic Regression for the Association of Polypharmacy and Sarcopenia (Stratified by Sex)

	Adjusted odds ratio† (95% CI)	*p* value
Men		
Polypharmacy	2.09 (1.04–4.21)	.040
Age (years)	1.10 (1.02–1.19)	.018
Low physical activity*	2.23 (1.02–4.89)	.044
Hypertension	7.28 (1.70–31.21)	.008
Diabetes	4.12 (2.18–7.80)	<.001
Joint pain/swelling*	1.65 (0.90–3.01)	.107
eGFR (mL/min/1.73 m^2)	1.03 (1.00–1.06)	.025
Women		
Polypharmacy	2.66 (1.20–5.91)	.016
Age (years)	1.09 (0.99–1.21)	.085
Low physical activity*	1.22 (0.36–4.10)	.746
Hypertension	1.61 (0.57–4.51)	.366
Diabetes	3.14 (1.26–7.84)	.014
Joint pain/swelling*	1.80 (0.86–3.77)	.120
eGFR (mL/min/1.73 m^2)	1.01 (0.97–1.04)	.760

Notes: CI = confidence interval; eGFR = estimated glomerular filtration rate, Polypharmacy, ≥5 drugs (reference < 5 drugs); LDL = low-density lipoprotein. Table shows factors according to Table 2.

†Adjusted for age, low physical activity, hypertension, diabetes, vitamin D-deficiency, gastritis/esophageal reflux, hypothyroidism, liver disease (except cirrhosis), atrial fibrillation/deep vein thrombosis/embolism, joint pain/swelling, osteoporosis, coronary artery disease, chronic pulmonary disease, current smoking, hyperuricemia, eGFR, LDL-cholesterol, C-reactive protein, malignancies.

*Self-reported.

composition are known. Use of proton pump inhibitors has, e.g., been shown to be negatively associated with insulin-like growth factor 1 levels in the InCHIANTI-Study (29). Also, muscle toxicity of statins, glucocorticoids and certain antiepileptic, neuroleptic and antidepressant drugs, as well as potentially detrimental metabolic effects of a variety of drugs (e.g., glucocorticoids, beta blockers, NSAIDS) are well known.

Furthermore, polypharmacy has been associated with poorer nutritional status (30). In this context, medication-associated dysphagia (31) and the role of gastrointestinal side-effects need to be considered. Moreover, other side-effects of the medications used may likely promote adverse redistribution of muscle and fat. For example, the likelihood of being categorized as sedentary has been shown to increase with every additional medication prescribed (32). To that effect, drug-induced orthostatic hypotension may doubtlessly discourage from physical activity, with detrimental effects on body composition (33). Not least, polypharmacy has been identified as a risk factor for under-prescribing (34) and low adherence (35). Deficient medical therapy and only irregular or even sporadic drug intake may have harmful effects on an individual's overall health and hence also on body composition. Furthermore, increasing the number of medications (prescription and nonprescription), exponentially increases the number of combinations of medications, which, in turn, increases the risk of adverse drug reactions and drug–drug interactions (36,37).

As the above examples show, there are several potential mechanisms, which may account for a possible causal association between polypharmacy and sarcopenia. However, we have to point out that the cross-sectional design of our study does not allow any conclusions as to causality, direction of causality, and mechanistic links. Moreover, as we have only analyzed polypharmacy, we cannot determine which medications or drug–drug interactions might account for the observed association. Also, despite careful statistical analysis, in which we included, both single diseases as well as an established morbidity index as covariates, we cannot truly differentiate between the effects of multiple drug use and the effects of underlying diseases on body composition.

Polypharmacy and sarcopenia/body composition are both associated with sex (15,38), which was also evident in our study: First, men were significantly more affected by sarcopenia than women (11.2% vs 6.6%, $p = .02$). Interestingly, the prevalence rate of polypharmacy was almost constant across age in men (~20%), whereas we observed a stepwise increase with advancing age in women, from 13.7% (60–65 years) up to 47.8% (75–80 years). Eventually, this was reflected by a different pattern of associated factors and different effect sizes for women and men in the final regression model (Table 3), as for instance hypertension yielded the highest OR for being sarcopenic in men, but this association was not significant in women.

Sarcopenia and frailty are closely related. Although the present study is the first to link polypharmacy with sarcopenia, prior cross-sectional and longitudinal studies have reported an independent association of polypharmacy with frailty (13,39,40). We likewise found a significantly higher prevalence of frailty-criteria in subjects with, compared to without polypharmacy. This corroborates the preceding findings, e.g., by Gnjidic *et al.* (13), and can serve as an internal validation of the polypharmacy-measure used in this study as well. Polypharmacy not only discriminates well between subjects with low and high risk for sarcopenia, but at the same time between subjects with high and low rates of functional restrictions (e.g., "reduced gait speed" and "exhaustion"), which again underlines the clinical relevance.

The strengths of our study include a large size and well-characterized cohort. Moreover, we believe that one strength of our study was to integrate nonprescription drugs into our analyses, as previous studies have shown that the prevalence of nonprescription medication use was remarkably high, and half of all potential major drug–drug interactions identified, involved a nonprescription medication (12). But our findings are also subject to a number of limitations. Due to the cross-sectional design of the study, we cannot draw any conclusions regarding causality or direction of causality. Moreover, it is in the nature of polypharmacy, that there is no differentiation between drugs with potentially beneficial and such with detrimental effects on body composition. Further longitudinal studies are necessary to confirm whether polypharmacy predicts the development of a low ALM/BMI over time.

Also, it cannot be ruled out that despite good adjustment for comorbidities, our results might still be confounded by e.g., unidentified lifestyle or disease factors.

Conclusion

In summary, we have shown an independent association between polypharmacy and clinically relevant sarcopenia, based on the ALM/BMI-cutoffs defined by the FNIH sarcopenia project.

More studies are required to further elucidate the connection of polypharmacy with sarcopenia.

Funding

This study was supported by the German Federal Ministry of Education and Research under grant number 16SV5536K.

Conflict of Interest

None to declare.

References

1. Landi F, Liperoti R, Fusco D, et al. Prevalence and risk factors of sarcopenia among nursing home older residents. *J Gerontol A Biol Sci Med Sci*. 2012;67:48–55. doi:10.1093/gerona/glr035
2. Cruz-Jentoft AJ, Landi F, Schneider SM, et al. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). *Age Ageing*. 2014;43:748–759. doi:10.1093/ageing/afu115
3. von Haehling S, Morley JE, Anker SD. An overview of sarcopenia: facts and numbers on prevalence and clinical impact. *J Cachexia Sarcopenia Muscle*. 2010;1:129–133. doi:10.1007/s13539-010-0014-2
4. McLean RR, Shardell MD, Alley DE, et al. Criteria for clinically relevant weakness and low lean mass and their longitudinal association with incident mobility impairment and mortality: the foundation for the National Institutes of Health (FNIH) sarcopenia project. *J Gerontol A Biol Sci Med Sci*. 2014;69:576–583. doi:10.1093/gerona/glu012
5. Cawthon PM, Peters KW, Shardell MD, et al. Cutpoints for low appendicular lean mass that identify older adults with clinically significant weakness. *J Gerontol A Biol Sci Med Sci*. 2014;69:567–575. doi:10.1093/gerona/glu023
6. Morley JE, Anker SD, von Haehling S. Prevalence, incidence, and clinical impact of sarcopenia: facts, numbers, and epidemiology-update 2014. *J Cachexia Sarcopenia Muscle*. 2014;5:253–259. doi:10.1007/s13539-014-0161-y
7. Buchmann N, Nikolov J, Spira D, et al. Identifying Sarcopenia in Metabolic Syndrome: data from the Berlin Aging Study II. *J Gerontol A Biol Sci Med Sci*. 2016;71:265–272. doi:10.1093/gerona/glv089

8. Fielding RA, Vellas B, Evans WJ, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. *J Am Med Dir Assoc*. 2011;12:249–256. doi:10.1016/j.jamda.2011.01.003
9. Eibich P, Buchmann N, Kroh M, et al. Exercise at different ages and appendicular lean mass and strength in later life: results from the Berlin Aging Study II. *J Gerontol A Biol Sci Med Sci*. 2016;71:515–520. doi:10.1093/gerona/glv171
10. Rolland Y, Onder G, Morley JE, Gillette-Guyonet S, Abellan van Kan G, Vellas B. Current and future pharmacologic treatment of sarcopenia. *Clin Geriatr Med*. 2011;27:423–447. doi:10.1016/j.cger.2011.03.008
11. Onder G, Penninx BW, Balkrishnan R, et al. Relation between use of angiotensin-converting enzyme inhibitors and muscle strength and physical function in older women: an observational study. *Lancet*. 2002;359:926–930. doi:10.1016/S0140-6736(02)08024-8
12. Qato DM, Wilder J, Schumm LP, Gillet V, Alexander GC. Changes in prescription and over-the-counter medication and dietary supplement use among older adults in the United States, 2005 vs 2011. *JAMA Intern Med*. 2016;176:473–482. doi:10.1001/jamainternmed.2015.8581
13. Gnjidic D, Hilmer SN, Blyth FM, et al. Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. *J Clin Epidemiol*. 2012;65:989–995. doi:10.1016/j.jclinepi.2012.02.018
14. Wimmer BC, Bell JS, Fastbom J, Wiese MD, Johnell K. Medication regimen complexity and polypharmacy as factors associated with all-cause mortality in older people: a population-based cohort study. *Ann Pharmacother*. 2016;50:89–95. doi:10.1177/1060028015621071
15. Aubert CE, Streit S, Da Costa BR, et al. Polypharmacy and specific comorbidities in university primary care settings. *Eur J Intern Med*. 2016;35:35–42. doi:10.1016/j.ejim.2016.05.022
16. Fried TR, O'Leary J, Towle V, Goldstein MK, Trentalange M, Martin DK. Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. *J Am Geriatr Soc*. 2014;62:2261–2272. doi:10.1111/jgs.13153
17. Langeard A, Pothier K, Morello R, et al. Polypharmacy cut-off for gait and cognitive impairments. *Front Pharmacol*. 2016;7:296. doi:10.3389/fphar.2016.00296
18. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. *J Am Geriatr Soc*. 1999;47:30–39. doi:10.1111/j.1532-5415.1999.tb01898.x
19. Bertram L, Böckenhoff A, Demuth I, et al. Cohort profile: the Berlin Aging Study II (BASE-II). *Int J Epidemiol*. 2014;43:703–712. doi:10.1093/ije/dyt018
20. Gerstorf D, Bertram L, Lindenberger U, et al. Editorial. *Gerontology*. 2016;62:311–315. doi:10.1159/000441495
21. Studenski SA, Peters KW, Alley DE, et al. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. *J Gerontol A Biol Sci Med Sci* 2014;69:547–558. doi:10.1093/gerona/glu010
22. Spira D, Buchmann N, Nikolov J, et al. Association of low lean mass with frailty and physical performance: a comparison between two operational definitions of sarcopenia-data from the Berlin Aging Study II (BASE-II). *J Gerontol A Biol Sci Med Sci*. 2015;70:779–784. doi:10.1093/gerona/glu246
23. Fried LP, Tangen CM, Walston J, et al.; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56:M146–M156. doi:10.1093/gerona/56.3.M146
24. Topolski TD, LoGerfo J, Patrick DL, Williams B, Walwick J, Patrick MB. The Rapid Assessment of Physical Activity (RAPA) among older adults. *Prev Chronic Dis*. 2006;3:A118.
25. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383. doi:10.1016/0021-9681(87)90171-8
26. Gerstorf D, Hülür G, Drewelies J, et al. Secular changes in late-life cognition and well-being: towards a long bright future with a short brisk ending? *Psychol Aging*. 2015;30:301–310. doi:10.1037/pag0000016
27. Gómez C, Vega-Quiroga S, Bermejo-Pareja F, Medrano MJ, Louis ED, Benito-León J. Polypharmacy in the elderly: a Marker of Increased Risk of Mortality in a Population-Based Prospective Study (NEDICES). *Gerontology*. 2015;61:301–309. doi:10.1159/000365328
28. Dawson-Hughes B, Castaneda-Sceppa C, Harris SS, et al. Impact of supplementation with bicarbonate on lower-extremity muscle performance in older men and women. *Osteoporos Int*. 2010;21:1171–1179. doi:10.1007/s00198-009-1049-0
29. Maggio M, Lauretani F, De Vita F, et al. Relationship between use of proton pump inhibitors and IGF system in older subjects. *J Nutr Health Aging*. 2014;18:420–423. doi:10.1007/s12603-013-0430-z
30. Heuberger RA, Caudell K. Polypharmacy and nutritional status in older adults: a cross-sectional study. *Drugs Aging*. 2011;28:315–323. doi:10.2165/11587670-000000000-00000
31. Schwemmle C, Jungheim M, Miller S, Kühn D, Ptok M. [Medication-induced dysphagia: a review]. *HNO*. 2015;63:504–510. doi:10.1007/s00106-015-0015-8
32. Heseltine R, Skelton DA, Kendrick D, et al. "Keeping Moving": factors associated with sedentary behaviour among older people recruited to an exercise promotion trial in general practice. *BMC Fam Pract*. 2015;16:67. doi:10.1186/s12875-015-0284-z
33. Hajjar I. Postural blood pressure changes and orthostatic hypotension in the elderly patient: impact of antihypertensive medications. *Drugs Aging*. 2005;22:55–68. doi:10.2165/00002512-200522010-00004
34. Cadogan CA, Ryan C, Hughes CM. Appropriate polypharmacy and medicine safety: when many is not too many. *Drug Saf*. 2016;39:109–116. doi:10.1007/s40264-015-0378-5
35. Pasina L, Brucato AL, Falcone C, et al. Medication non-adherence among elderly patients newly discharged and receiving polypharmacy. *Drugs Aging*. 2014;31:283–289. doi:10.1007/s40266-014-0163-7
36. Field TS, Gurwitz JH, Harrold LR, et al. Risk factors for adverse drug events among older adults in the ambulatory setting. *J Am Geriatr Soc*. 2004;52:1349–1354. doi:10.1111/j.1532-5415.2004.52367.x
37. Johnell K, Klarin I. The relationship between number of drugs and potential drug-drug interactions in the elderly: a study of over 600,000 elderly patients from the Swedish Prescribed Drug Register. *Drug Saf*. 2007;30:911–918. doi:10.2165/00002018-200730100-00009
38. Bjerrum L, Søgaard J, Hallas J, Kragstrup J. Polypharmacy: correlations with sex, age and drug regimen. A prescription database study. *Eur J Clin Pharmacol*. 1998;54:197–202. doi:10.1007/s002280050445
39. Herr M, Robine JM, Pinot J, Arvieu JJ, Ankri J. Polypharmacy and frailty: prevalence, relationship, and impact on mortality in a French sample of 2350 old people. *Pharmacoepidemiol Drug Saf*. 2015;24:637–646. doi:10.1002/pds.3772
40. Gnjidic D, Hilmer SN, Blyth FM, et al. High-risk prescribing and incidence of frailty among older community-dwelling men. *Clin Pharmacol Ther*. 2012;91:521–528. doi:10.1038/clpt.2011.258