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Multimorbidity and risk of falls, fractures, and joint replacements over two decades: Findings from the Hertfordshire Cohort Study

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Aim: To examine the relationship between level of morbidity burden and long-term risk of fractures, falls, and joint replacements in the community-dwelling participants of the Hertfordshire Cohort Study.

Methods: Data were analyzed from 2997 individuals (age 59–73 at baseline). Outcomes (fractures, falls, and lower limb joint replacements) were identified using ICD-10 and OPCS-4 codes from Hospital Episode Statistics data, available from baseline (1998–2004) until December 2018. Number of systems medicated (marker of morbidity level) in relation to risk of outcomes was examined using sex-stratified Cox regression.

Results: Among both men and women, a greater number of systems medicated was related to increased risk of falls ($P < 0.001$) and lower limb joint replacements ($P < 0.003$). More systems medicated was only related to increased risk of fracture among women (P-values for trend of <0.001 among women and 0.186 among men).

Conclusions: Higher morbidity was associated with increased risk of adverse health outcomes related to poor musculoskeletal health, but these relationships varied according to the musculoskeletal outcome studied. Intervention strategies to reduce multimorbidity among middle-aged and older people may hence reduce the burden of musculoskeletal aging. **Geriatr Gerontol Int 2024; ••: ••–••.**

Keywords: fracture, joint replacement, multimorbidity, osteoarthritis, osteoporosis.

Introduction

Multimorbidity is a significant public health problem with a burden that is exacerbated by an aging global population.[1] Previous research has demonstrated that several comorbidities are associated with an increased risk of musculoskeletal conditions such as osteoporosis, sarcopenia, and osteoarthritis (OA).[2–4] According to the Global Burden of Disease Study, approximately 323 million incident cases, 118 000 deaths, and 150 million disability-adjusted life-years were attributable to musculoskeletal disorders in 2019.[5] Much of this burden is due to falls and fractures in later years of life, as osteoporosis and sarcopenia are strongly associated with increased risk of fragility fractures and falls, respectively; in addition, severe OA often requires replacement of the affected joint, resulting in considerable individual and societal costs.[6–8] Hence a detailed understanding of the relationship between the number of comorbidities coexisting in an individual and musculoskeletal health is important to policy-makers and clinicians who wish to reduce this burden.

As noted above, while several studies have highlighted the importance of medical history to the risk of common musculoskeletal conditions of aging, typically this research has focused on an individual comorbidity, rather than on multimorbidity or level of comorbidity burden, and has been restricted to a single musculoskeletal outcome. For example, it has been reported that older adults with conditions such as diabetes,[9] hypertension,[10] chronic obstructive pulmonary disease,[11] and chronic kidney disease[12] are at a higher risk of fracture than the general population. In one of the few studies that considered multimorbidity as a risk factor for

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bone health, a cohort study conducted on community-dwelling older persons in Japan, the authors demonstrated an association between multimorbidity and higher risk of fragility fractures.[13]

A recent study by Zhao and colleagues highlighted associations between possible sarcopenia and multimorbidity among middle-aged and older adults aged >40 years in a Chinese study,[14] while multimorbidity was associated with increased risk of transitioning to worsening frailty states in a study among older Americans.[15] In other work, multimorbidity has been linked to increased likelihood of sarcopenia in large cohorts such as UK Biobank,[16] and also to the progression of muscle aging in the English Longitudinal Study of Ageing (ELSA) cohort.[17]

Likewise, OA is associated with comorbidities, although relationships appear to vary by site. Using a Swedish data registry, researchers reported that hypertension, back pain, gout, allergy, depression, anxiety, and migraine were all associated with increased risk of knee OA diagnosis, while only gastroesophageal reflux disease and back pain were associated with newly diagnosed hip OA, with different relationships observed at weight-bearing and non-weight-bearing sites.[18] Another study reported that 62% of patients in primary care treated for their OA had at least one comorbidity, highlighting the high prevalence of comorbidity burden in this population.[19] A systematic review and meta-analysis on this topic concluded that further research is needed to inform clinical care.[20]

Hence there is a well-established relationship between comorbid condition(s) and musculoskeletal health in later life, although further research has been highlighted as important and necessary. In this study we were specifically interested to understand whether a step change occurred in the relationships between number of comorbidities and risk of musculoskeletal outcomes in a well-phenotyped population. For example, is the relationship graded and linear or non-linear, and does it vary by musculoskeletal outcome? This information may be helpful to clinicians when considering management of musculoskeletal conditions in populations where multimorbidity is common, and to policy-makers planning future healthcare provision.

Methods

The Hertfordshire Cohort Study

The Hertfordshire Cohort Study (HCS) comprises 2997 men and women. Participants were born in Hertfordshire (UK) in 1931–39. In 1998–2004, they attended a home interview and clinic visit for a detailed characterization of their health. The Hertfordshire and Bedfordshire Local Research Ethics Committee granted ethical approval for this study; all participants provided informed consent for researchers to access their medical records in the future and for the investigations they underwent. Further details about this study have been published previously.[21,22]

Ascertainment of participant information at baseline (1998–2004)

A researcher-administered questionnaire was used to gather information about participants' alcohol consumption and smoking habits. For men and unmarried women, occupational social class was determined based on the participant's most recent or current full-time job. For married women, occupational social class was determined based on the husband's occupation. Occupations were then classified according to the 1990 OPCS Standard Occupational Classification (SOC90) unit group for occupation.[23]

Ascertainment of morbidity level at baseline (1998–2004)

Details of prescription and over-the-counter medications currently taken by participants were recorded. These medications were coded according to the British National Formulary into the following systems: cardiovascular; respiratory; gastro-intestinal; endocrine; central nervous; malignant disease and immunosuppression; nutrition and blood; musculoskeletal and joint disease; eye; ear; nose; skin; miscellaneous; and genito-urinary tract. The number of systems each participant was taking medications for was then calculated; this was used as a marker of morbidity level, as has been done previously in the HCS.[24–26] Measures of morbidity burden based on medications taken are commonly used and are strongly associated with adverse health outcomes.[27]

At the baseline clinic, participants' height and weight were measured using a Harpenden pocket stadiometer (Chasmors Ltd, London, UK) and a SECA floor scale (Chasmors Ltd, London, UK), respectively. These measurements were used to calculate body mass index (BMI).

Ascertainment of fractures, falls, and joint replacement events

These events were identified using Hospital Episode Statistics (HES) data; mortality data were also available. Permission to obtain these data from HCS participants from baseline to 31 December 2018 was granted by NHS Digital and the Ethics and Confidentiality Committee of the National Information Governance Board. Linkage of the HCS cohort with HES data has been previously described;[28] the HES data extract for each participant included information relating to hospital admissions, such as diagnoses coded to ICD-10 and medical procedures and operations coded to OPCS-4. Adverse health events included fractures (any), falls, and lower limb joint replacements (hip or knee). These were identified using ICD-10 and OPCS-4 codes as stated in Table 1.

Statistical methods

Participant characteristics at the study baseline (1998–2004) and the health events during follow-up were described using summary statistics. Number of systems medicated in relation to risk of experiencing the following health events were examined using sex-stratified time-to-first-event Cox regression, with death as a censoring event: any fracture, fall, and lower limb joint replacement. For completeness, Cox regression models were implemented with number of systems medicated as a count variable, and then with number of systems medicated treated as a categorical variable, with no systems medicated as the reference category. Stata (release 17.0) was used to conduct the statistical analysis; $P < 0.05$ was regarded as statistically significant. For sensitivity analyses, competing risk models for the hospital-related events were implemented using the Fine–Gray subdistribution hazards model with death as a competing event, and with number of systems medicated treated as a count variable.

Results

Descriptive statistics

Summary statistics for the baseline participant characteristics and the health events experienced during follow-up are shown in Table 2. Mean (SD) age at baseline was 65.7 (2.9) and 66.6 (2.7) years among men and women respectively. The proportion of

Table 1 ICD-10 and OPCS-4 codes used to define fractures, falls, and lower limb joint replacements

Health event	Codes
Any fracture	***ICD-10 codes*** M80: Osteoporosis with pathological fracture M84: Disorders of continuity of bone S22: Fracture of rib(s), sternum and thoracic spine S32: Fracture of lumbar spine and pelvis S42: Fracture of shoulder and upper arm S52: Fracture of forearm S62: Fracture at wrist and hand level S72: Fracture of femur S82: Fracture of lower leg, including ankle S92: Fracture of foot, except ankle T02: Fractures involving multiple body regions T08: Fracture of spine, level unspecified T10: Fracture of upper limb, level unspecified T12: Fracture of lower limb, level unspecified M81: Osteoporosis without pathological fracture M82: Osteoporosis in diseases classified elsewhere M83: Adult osteomalacia M90.7: Fracture of bone in neoplastic disease S02: Fracture of skull and facial bones S12: Fracture of neck T90.2: Sequelae of fracture of skull and facial bones T91.1: Sequelae of fracture of spine T91.2: Sequelae of other fracture of thorax and pelvis T92.1: Sequelae of fracture of arm
Fall	W00-W19: Falls
Lower limb joint replacement (hip and knee replacements)	***OPCS-4 codes*** W37.1 Primary total prosthetic replacement of hip joint using cement W38.1 Primary total prosthetic replacement of hip joint not using cement W39.1 Primary total prosthetic replacement of hip joint not elsewhere classified W40.1 Primary total prosthetic replacement of knee joint using cement W41.1 Primary total prosthetic replacement of knee joint not using cement W42.1 Primary total prosthetic replacement of knee joint not elsewhere classified

men and women with no systems medicated at baseline was 32% and 24%, respectively; 31% of men and 44% of women had two or more systems medicated. During follow-up, 9% of men and 22% of women had a fracture, while 13% of men and 21% of women had a fall. The proportion of men and women who had a lower limb joint replacement during follow-up was 14% and 18%, respectively.

Number of systems medicated and risk of health events during follow-up

Hazard ratios for adverse health events during follow-up per additional system medicated at baseline are presented in Table 3. Among both men and women, a greater number of systems medicated was related to increased risk of falls ($P < 0.001$) and lower limb joint replacements ($P < 0.003$). For example, the hazard ratio (95% confidence interval) for a lower limb joint replacement per additional system medicated was 1.20 (1.08, 1.34) among men and 1.14 (1.05, 1.24) among women (Table 3). More systems medicated was only related to increased risk of fracture among women (*P*-values for trend of <0.001 among women and 0.186 among men). Findings were similar in sensitivity analyses where competing risk analyses were performed (Supplementary Table S1).

Figure 1 graphically illustrates these associations with a reference category of no systems medicated. Graded associations were observed for higher risks of fracture among women as the number of systems medicated increased. In contrast, a threshold effect was observed for falls among men and women, with a higher risk of falls among men and women with at least two systems medicated compared with those who had fewer than two. Similarly, men and women with more than two systems medicated had a higher risk of a lower limb joint replacement compared with those with two or fewer systems medicated.

Discussion

In this study, more systems medicated was associated with higher risks of falls and lower limb joint replacements in both men and women, and higher risk of fracture in women only. These findings suggest that multimorbidity burden, as measured by the number of systems medicated, has important implications for musculoskeletal health among older men and women. These data are important as they demonstrate relationships between number of systems medicated and all three common musculoskeletal conditions of aging in a single community-dwelling cohort followed for 20 years. The thresholding effect seen at two systems medicated

and more than two systems medicated, for falls and lower limb joint replacements respectively, highlights the need to identify these groups and target management appropriately.

This study has several strengths and weaknesses. First, we used data from the HES service for England, which covers all National Health Service (NHS) hospital patients and NHS patients in private hospitals. Participants undergoing privately funded care were excluded from our dataset, as was outpatient care. This limitation may be particularly important for participants who chose to undergo private joint replacements, which is not uncommon in the UK, especially if waiting times are high. The data linkage of our dataset allowed us to follow up our whole cohort, which was all based in Hertfordshire. All our participants were Caucasian, which limits the generalizability of our findings, particularly in the context of the specific geographic location of our study. Finally, it would have been interesting to consider clusters of comorbidities, as some authors have reported, but small numbers of some conditions meant this was not possible.

Table 2 Baseline participant characteristics and health events during follow-up

Participant characteristic [mean (SD), median (lower quartile, upper quartile), or %]	Men ($n = 1579$)	Women ($n = 1418$)
Characteristics at baseline (1998–2004)		
Age (years)	65.7 (2.9)	66.6 (2.7)
BMI (kg/m^2)	27.2 (3.8)	27.6 (4.9)
Ever smoked regularly	67%	39%
High alcohol intake (units per week: >21 men, >14 women)	22%	5%
Social class (manual)	59%	58%
Number of systems medicated		
0	32%	24%
1	37%	32%
2	19%	21%
3 or more	12%	23%
Events during follow-up (ever had)		
Death	36%	26%
Hospital admission	93%	92%
Types of admission during follow-up (ever had)		
Any fracture	9%	22%
Fall	13%	21%
Joint replacements during follow-up (ever had)		
Lower limb joint replacement (hip or knee)	14%	18%

Follow-up period lasted from baseline (1998–2004) until 31 December 2018.

As discussed previously, some studies have considered links between multimorbidity and individual musculoskeletal conditions. Perhaps the most extensive literature relating multimorbidity to musculoskeletal aging has considered relationships with risk of falls. Falls are of course a multifactorial outcome, dependent upon (among other factors) sarcopenia, postural hypotension, visual acuity, and medication such as benzodiazepines. In one study by Yan and colleagues, not only did the authors identify an increasing fall risk with increasing number of comorbidities, they also reported four patterns of comorbidity clusters (cardiometabolic, respiratory, visceral-arthritic, and mental-sensory).[29] Work in the Irish Longitudinal Study on Ageing also reported graded relationships of increased number of comorbidities with pain, polypharmacy, and difficulties with activities of daily living; these factors explained the largest proportion of the multimorbidity–fall relationship.[30]

Beyond risk of disease, multimorbidity may also contribute to the treatment gap of osteoporosis. Bliuc and colleagues found that in an Australian cohort, a higher Charlson comorbidity index was associated with a lower likelihood of being investigated and treated following a fragility fracture.[31] Other researchers have reported links between Charlson comorbidity index and fracture risk, independent of falls, highlighting the need for appropriate management in individuals with multimorbidity.[13] Furthermore, there is evidence that multimorbidity may influence mortality risk following a fracture. For example, in a Danish study comprising 307 870 adults, post-fracture mortality risk differed depending on the fracture location and the comorbidity cluster at the time of fracture (low-multimorbidity, cardiovascular, diabetic, malignant, and mixed hepatic and/or inflammatory).[32] Multimorbidity and proximal or lower leg fractures were associated with increased post-fracture mortality risk, with the highest risk among patients in the malignant cluster with a hip fracture. Considering the population of community-dwelling older people, identifying strategies to reduce the treatment gap in this group is timely and important.

The link between OA and multimorbidity is well established, and a previous systematic review and meta-analysis suggested that multimorbidity is more common among participants with OA than among those without, such that individuals with OA are 1.2 times more likely to have any comorbidity than non-OA controls and 2.5 times more likely to have ≥3 comorbidities.[20] Hence our results accord with this. The authors of the systematic review thoughtfully considered the limitations in their analysis, including heterogeneity in study design, and some concerns about coding of comorbidity and OA. Hence, although we used a single sample, we hope that the level of detail captured in our own study participants reinforces their observations.

In conclusion, our study provides compelling evidence that multimorbidity in the form of systems involved is closely linked to

Table 3 Hazard ratios (95% confidence interval, CI) for health events during follow-up per additional system medicated at baseline

Health event	Men		Women	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Any fracture	1.10 (0.95, 1.27)	0.186	1.20 (1.12, 1.29)	<0.001
Fall	1.36 (1.22, 1.52)	<0.001	1.21 (1.12, 1.30)	<0.001
Lower limb joint replacement	1.20 (1.08, 1.34)	0.001	1.14 (1.05, 1.24)	0.002

Lower limb joint replacements included hip or knee replacements.

Hazard ratios were estimated using Cox regression models.

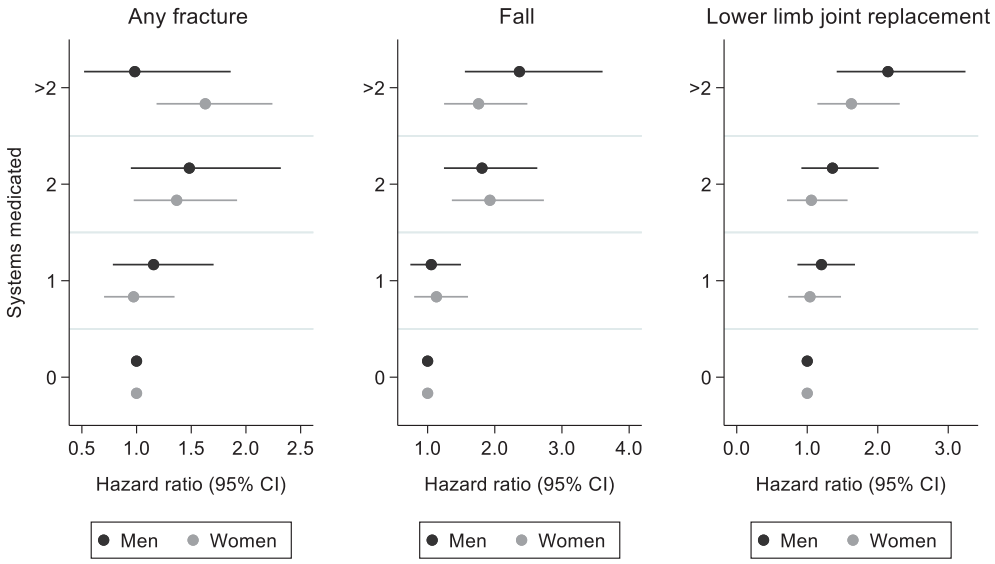

Figure 1 Hazard ratios (95% confidence interval) for adverse health events according to number of systems medicated at baseline (reference category of no systems medicated). Hazard ratios were estimated using Cox regression models.

an elevated risk of falls and lower limb joint replacements, with no 'safe' level of comorbidity observed, but rather a threshold effect observed at two systems medicated for falls and more than two systems medicated for lower limb joint replacements. Our findings regarding publicly funded joint arthroplasty are interesting, as previous authors have suggested that individuals with comorbid health conditions may be less likely to undergo surgery, despite evidence of good outcomes.[33,34] These findings emphasize the importance of addressing multimorbidity in healthcare practice and policy, particularly among older adults, to consider the associated risk of adverse musculoskeletal outcomes. If prevention of comorbid burden is not possible, careful consideration of attendant musculoskeletal risk, for example by addressing falls risk, is critical to reduce the personal and societal costs of musculoskeletal conditions of aging.

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Disclosure statement

EMD declares consultancy and speaker fees from Pfizer, UCB Pharma, and Lilly. The remaining authors declare no conflicts of interest.

Author contributions

LDW: methodology, formal analysis, writing—original draft; CP: methodology, formal analysis; RR: writing—review and editing; KAW: conceptualization, investigation, writing—review & editing; CC: conceptualization, writing—review and editing; EMD: conceptualization, writing—original draft, writing—review and editing, supervision, project administration. All authors made substantial contributions to the manuscript and approved the final version.

Data availability statement

Data relating to this study cannot be shared due to consent restrictions.

Ethics statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval for the HCS was obtained from the Hertfordshire and Bedfordshire Local Research Ethics Committee. Permission to obtain a HES extract for HCS participants was granted by the Ethics and Confidentiality Committee of the National Information Governance Board and NHS Digital.

Informed consent

All study participants provided written informed consent for the investigations they underwent and for researchers to access their medical records in the future.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1. Subhazard ratios (95% CI) for health events during follow-up per additional system medicated at baseline, with death as a competing event.

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