






RESEARCH ARTICLE OPEN ACCESS

Musculoskeletal Multimorbidity Burden and Trajectory in Relation to Later-Life Holistic Well-Being Among Middle-Aged and Elderly Individuals: A Prospective Study

Yuanpeng Zhu^{1,2,3}  | Haoran Zhang^{1,2,3}  | Qing Li^{1,2,3}  | Terry Jianguo Zhang^{1,2,3}  | Nan Wu^{1,2,3} 

¹State Key Laboratory of Complex Severe and Rare Diseases, Department of Orthopedic Surgery, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China | ²Beijing Key Laboratory for Genetic Research of Skeletal Deformity, Beijing, China | ³Key Laboratory of Big Data for Spinal Deformities, Chinese Academy of Medical Sciences, Beijing, China

Correspondence: Terry Jianguo Zhang (zhangjianguo@pumch.cn) | Nan Wu (dr.wunan@pumch.cn)

Received: 29 June 2024 | **Revised:** 12 September 2024 | **Accepted:** 18 September 2024

Funding: This study was supported by National Key Research and Development Program of China (Grant 2023YFC2507700); National High Level Hospital Clinical Research Funding (Grants 2022-PUMCH-C-033, 2022-PUMCH-D-002, 2022-PUMCH-D-004); National Natural Science Foundation of China (Grants 81930068, 82072391, 82172382, 82172525); CAMS Innovation Fund for Medical Sciences (Grants 2021-I2M-1-051, 2021-I2M-1-052, 2022-I2M-2-001, 2023-I2M-C&T-A-003).

Keywords: burden | multimorbidity | musculoskeletal | trajectory | well-being

ABSTRACT

Objectives: Understanding the patterns and implications of coexisting musculoskeletal conditions is crucial for developing effective management strategies and improving care for older adults. This study aimed to examine the associations between musculoskeletal multimorbidity burden and trajectory and holistic well-being among middle-aged and older adults.

Methods: This prospective study employed data from nine consecutive waves of the English Longitudinal Study of Aging (ELSA), spanning 2002–2018. We used latent class trajectory models (LCTM) to identify groups based on changes in musculoskeletal multimorbidity status. Subsequently, we employed linear mixed models to investigate the associations between musculoskeletal disease burden, trajectory groups, and seven dimensions of holistic well-being: Activities of Daily Living (ADLs), Instrumental Activities of Daily Living (IADLs), depression, memory, loneliness, social interactions, and life satisfaction.

Results: In total, 5272 participants (mean age: 71.9 years; SD: 8.9) were included in the final analysis. Four distinct trajectories were identified: a low-burden group (48.37%), an emerging group (14.76%), a moderate-burden group (26.00%), and a persistent burden group (10.87%). After adjustment, the findings demonstrate that the musculoskeletal disorder burden significantly impacts ADLs, depression, memory, social interactions, and life satisfaction in middle-aged and older adults, with minor effects on IADLs and loneliness. Moreover, with the escalation of the burden, its impact significantly intensifies (p for trend is < 0.001). Compared with the low-burden group, participants in both the moderate and persistent burden groups exhibited significantly lower capabilities in ADLs, poorer memory, increased social interactions, and lower life satisfaction. The emerging group displayed a similar trend, though without statistically significant results.

Conclusions: Our study suggests that the extent and persistence of musculoskeletal disease burden can significantly affect holistic well-being among middle-aged and older individuals.

The first two authors equally contributed to this article.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2024 The Author(s). *Orthopaedic Surgery* published by Tianjin Hospital and John Wiley & Sons Australia, Ltd.

1 | Introduction

Age-associated multiple chronic diseases (multimorbidity) are a growing issue and pose a major challenge to healthcare systems around the world [1]. Musculoskeletal diseases, the most common cause of severe long-term pain and physical disability, are prevalent and their impact is pervasive [2]. Musculoskeletal multimorbidity, defined as the coexistence of two or more musculoskeletal diseases, is increasingly common with population aging [3]. Understanding the patterns and implications of these coexisting conditions is crucial for developing effective management strategies and improving older care.

Well-being, a positive state experienced by individuals and societies, encompasses quality of life and the ability of people and societies to contribute to the world with a sense of meaning and purpose [4]. Focusing on well-being aids in monitoring the equitable distribution of resources, overall thriving, and sustainability [5]. Previous research indicates that certain musculoskeletal disorders, such as arthritis and lower back pain, significantly impact the quality of life, mental health, and psychological well-being of older individuals [6, 7]. Currently, most studies focus solely on the impact of a single musculoskeletal disorder at baseline on specific aspects of middle-aged and older individuals' lives, whereas the influence of the dynamic progression of chronic musculoskeletal disease accumulation on holistic well-being has received relatively minor attention. Recently, the Investigating Musculoskeletal Health and Wellbeing (IMH&W) study is developed to measure and characterize the development and progression of pain, frailty, and disability, and to identify discrete subgroups and their associations [8, 9]. Prior evidence linking the rapid accumulation of chronic conditions to poorer physical resilience and higher risk of disability suggests that the developmental trajectory of multimorbidity reflects the aging process and individuals' health deterioration [10]. Consequently, efforts to ascertain the developmental trajectory of musculoskeletal chronic conditions and explore their long-term association with holistic well-being are warranted [11].

To fill these research gaps, we conducted a longitudinal cohort study with a representative sample of middle-aged and elderly adults across Europe. The objectives of the study were to (i) identify associations between the burden of musculoskeletal multimorbidity at baseline and holistic well-being in later life, and (ii) explore the relationship between the trajectory patterns of musculoskeletal multimorbidity and holistic well-being in later life.

2 | Methods

2.1 | Study Population

The English Longitudinal Study of Aging (ELSA) is a longitudinal panel study that examines the dynamics of aging within a nationally representative sample of the English population residing in private households [12]. Participants were subsequently revisited biennially to collect data on their sociodemographic, lifestyle, and clinical information, among other aspects. Ethical

approval for each wave of ELSA was obtained from the National Research Ethics Service (London Multicenter Research Ethics Committee), and the IRB number assigned to the first wave was MREC/01/2/91. All participants provided written informed consent before participation.

This study utilized all available data over a 17-year period, from wave 1 (2002–2003) to wave 9 (2018–2019) [13]. Information on self- or proxy-reported chronic musculoskeletal conditions was collected between wave 1 and wave 5, spanning over 10 years, for subsequent analysis of musculoskeletal multimorbidity. Subsequently, wave 5 was established as the baseline for analyzing changes in holistic well-being across various aspects from wave 5 to wave 9. The initial sample of 12,099 individuals from wave 1 underwent screening based on the following exclusion criteria: (i) participants younger than 45 years were excluded, (ii) those lost to follow-up or who had died between wave 1 and wave 5 were excluded, and (iii) individuals with missing data on musculoskeletal diseases were excluded. This process resulted in the exclusion of 184, 6354, and 289 individuals, respectively, culminating in a final analytical sample of 5272 adults aged over 45 years (Figure 1). We conformed to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [14].

2.2 | Musculoskeletal Diseases, Burden, and Multimorbidity

We selected arthritis, lower back pain, and osteoporosis as representative musculoskeletal diseases because of their significant prevalence and impact among the middle-aged and older populations [15–17]. These conditions respectively epitomize degenerative changes in the joints, spine, and muscles, as well as bone health. The status of these chronic musculoskeletal diseases, self- or proxy-reported between 2002 and 2010, was classified as either present or absent. We calculated the cumulative number of the aforementioned three musculoskeletal diseases for each participant in every wave to quantify the burden of disease. Multimorbidity was defined as the presence of two or more chronic conditions [18].

2.3 | Holistic Well-Being

To comprehensively evaluate the facets of holistic well-being in middle-aged and older individuals, we selected seven dimensions: Activities of Daily Living (ADLs), Instrumental Activities of Daily Living (IADLs), depression, memory, loneliness, social interactions, and overall life satisfaction. ADLs, IADLs, depression, social interactions, and life satisfaction were quantified using corresponding scales completed by participants. Memory was assessed through the quantification of words recalled immediately and after a delay. Detailed information regarding the questionnaire items and their significance is available in Table S1. In this assessment, higher scores for ADLs and IADLs indicate enhanced functional abilities; elevated scores in depression and loneliness reflect more severe symptoms; increased scores in social interactions signify more frequent engagement with family and friends; improved memory is denoted by higher

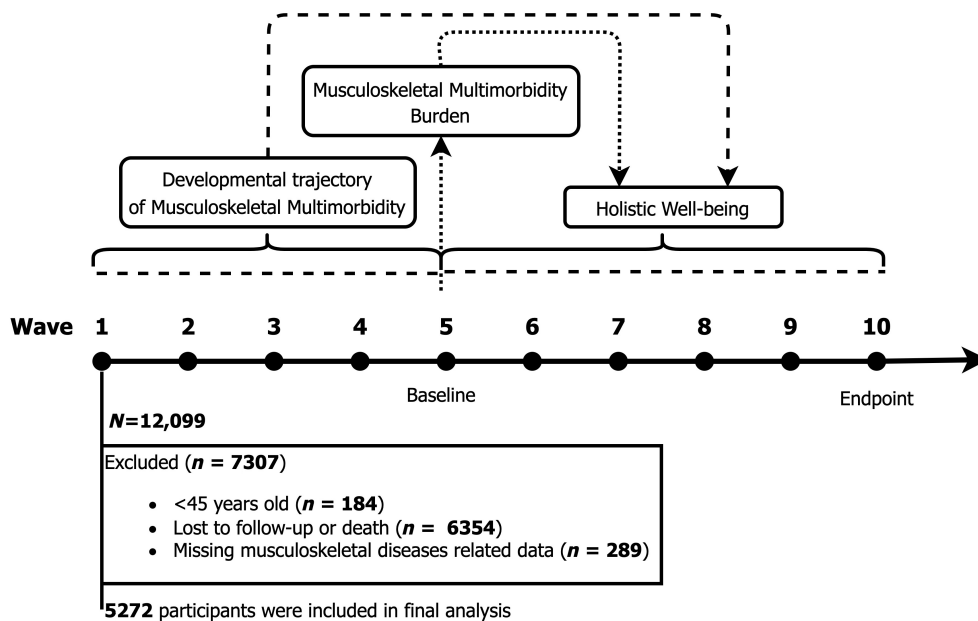


FIGURE 1 | Study design diagram.

scores in memory tests; and greater life satisfaction is reflected by higher scores.

2.4 | Covariates

At baseline (wave 5), we evaluated covariates, including a range of participant characteristics designed to minimize the impact of confounding factors. These encompassed personal variables such as age, sex, race/ethnicity (White, Black, Asian, and Other), marital status (never married, married, divorced, or widowed), education level (GCE A Level equivalent, lower, or higher), private health insurance (presence or absence), and income level (low, moderate, or high); lifestyle factors such as smoking status (never, former, or current smoker), alcohol consumption (never/low, moderate, or high frequency), body mass index (BMI) categories (< 25, 25–30, > 30 kg/m²), and activity level (sedentary, low, moderate, or high); and chronic health conditions including hypertension, diabetes, heart disease (0, 1, 2, or more), cancer, lung disease, and psychiatric problems (each classified as no or yes). We assumed that the missing covariate data were missing completely at random and employed multiple imputation to address the missing values [19]. The proportions of missing data were as follows: insurance (1.27%), income (1.46%), alcohol consumption (7.95%), BMI (7.02%), and activity level (0.97%).

2.5 | Statistical Analyses

We employed latent class trajectory models (LCTM), a specialized form of latent class growth analysis devoid of random effects, to categorize participants based on their unique temporal patterns of longitudinal musculoskeletal multimorbidity status change from wave 1 to wave 5. As a finite mixture model, LCTM can identify latent classes of individuals exhibiting similar progressions of a determinant over time or as they age [20]. Our models, utilizing second-order polynomials, calculated the posterior

probabilities for each trajectory, incorporating age-level considerations. Each participant was assigned to the trajectory with the highest probability. LCTM models with varying numbers of latent classes, ranging from one to six, were examined. The optimal number of trajectories was determined based on the minimum Bayesian Information Criterion (BIC), ensuring posterior probabilities by class exceeded 0.70 and class sizes comprised at least 2% of the population [21]. Baseline characteristics of the study participants were described using mean (standard deviation) for continuous variables and frequency (percentage) for categorical variables. The Kruskal–Wallis and chi-square tests were utilized to compare variable differences across identified trajectories.

To examine the associations between the burden of musculoskeletal diseases at baseline and seven dimensions of holistic well-being, we utilized linear mixed models with years since baseline as the timescale. These models featured a random intercept and slope at the individual level, providing estimates of beta coefficients and 95% confidence intervals (CIs). To assess varying potential confounding effects on this association, we sequentially integrated four groups of covariates into four distinct models. Model 1 incorporated basic personal variables, including sex and age, while Model 2 further included additional personal variables such as marital status, education level, race/ethnicity, insurance status, and income. Model 3 additionally incorporated lifestyle characteristics, including BMI, alcohol consumption status, smoking status, and activity level. Finally, Model 4 further included chronic health conditions, namely hypertension, diabetes, heart disease, cancer, lung disease, and psychiatric problems. The association between trajectory groups and holistic well-being was assessed using the same covariate adjustment technique in linear mixed models.

We conducted three sensitivity and exploratory analyses to assess the robustness of our primary findings: (1) by repeating the

TABLE 1 | Baseline characteristics of participants by trajectory groups of musculoskeletal disease burden among middle-aged and older individuals.

Characteristic	Overall		Trajectories of musculoskeletal multimorbidity			Statistic value	p ^b
	Overall, N= 5272 (100%) ^a	Low-burden group, N= 2550 (48%) ^a	Emerging group, N= 778 (15%) ^a	Moderate-burden group, N= 1371 (26%) ^a	Persistent-burden group, N= 573 (11%) ^a		
Age (years)	71.9 (8.9)	70.1 (8.5)	71.9 (8.8)	74.0 (8.9)	74.3 (9.0)	231	< 0.001
Gender						232	< 0.001
Female	3018 (57.2%)	1211 (47.5%)	484 (62.2%)	877 (64.0%)	446 (77.8%)		
Male	2254 (42.8%)	1339 (52.5%)	294 (37.8%)	494 (36.0%)	127 (22.2%)		
Race						0.952	0.124
White	5109 (96.9%)	2481 (97.3%)	750 (96.4%)	1329 (96.9%)	549 (95.8%)		
Black	25 (0.5%)	9 (0.4%)	7 (0.9%)	5 (0.4%)	4 (0.7%)		
Asian	42 (0.8%)	23 (0.9%)	4 (0.5%)	6 (0.4%)	9 (1.6%)		
Other	96 (1.8%)	37 (1.5%)	17 (2.2%)	31 (2.3%)	11 (1.9%)		
Marital State						116	< 0.001
Never married	262 (5.0%)	132 (5.2%)	36 (4.6%)	62 (4.5%)	32 (5.6%)		
Married	3408 (64.6%)	1800 (70.6%)	509 (65.4%)	799 (58.3%)	300 (52.4%)		
Divorced or widowed	1602 (30.4%)	618 (24.2%)	233 (29.9%)	510 (37.2%)	241 (42.1%)		
Education level						147	< 0.001
Lower	3074 (58.3%)	1290 (50.6%)	466 (59.9%)	899 (65.6%)	419 (73.1%)		
GCE A Level equivalent	427 (8.1%)	239 (9.4%)	66 (8.5%)	86 (6.3%)	36 (6.3%)		
Higher	1771 (33.6%)	1021 (40.0%)	246 (31.6%)	386 (28.2%)	118 (20.6%)		
Insurance	1772 (33.6%)	847 (33.2%)	271 (34.8%)	456 (33.3%)	198 (34.6%)	0.709	0.813
Earning						94.8	< 0.001
Low income	1740 (33.0%)	748 (29.3%)	254 (32.6%)	509 (37.1%)	229 (40.0%)		
Moderate income	1792 (34.0%)	816 (32.0%)	272 (35.0%)	486 (35.4%)	218 (38.0%)		
High income	1740 (33.0%)	986 (38.7%)	252 (32.4%)	376 (27.4%)	126 (22.0%)		
BMI (kg/m ²)						86.2	< 0.001
< 25	1341 (25%)	702 (28%)	214 (28%)	309 (23%)	116 (20%)		
25–30	2297 (44%)	1194 (47%)	311 (40%)	583 (43%)	209 (36%)		
> 30	1634 (31%)	654 (26%)	253 (33%)	479 (35%)	248 (43%)		
Smoking						21.8	0.001
Never	1920 (36.4%)	966 (37.9%)	305 (39.2%)	470 (34.3%)	179 (31.2%)		
Former smoker	2785 (52.8%)	1314 (51.5%)	407 (52.3%)	752 (54.9%)	312 (54.5%)		
Current smoker	567 (10.8%)	270 (10.6%)	66 (8.5%)	149 (10.9%)	82 (14.3%)		
Drinking						166	< 0.001
Low frequency	1223 (23.2%)	436 (17.1%)	179 (23.0%)	387 (28.2%)	221 (38.6%)		

(Continues)

TABLE 1 | (Continued)

Characteristic	Overall		Trajectories of musculoskeletal multimorbidity				Statistic value	p ^b
	Overall, N= 5272 (100%) ^a	Low-burden group, N= 2550 (48%) ^a	Emerging group, N= 778 (15%) ^a	Moderate-burden group, N= 1371 (26%) ^a	Persistent-burden group, N= 573 (11%) ^a			
Moderate frequency	2249 (42.7%)	1115 (43.7%)	340 (43.7%)	558 (40.7%)	236 (41.2%)			
High frequency	1800 (34.1%)	999 (39.2%)	259 (33.3%)	426 (31.1%)	116 (20.2%)			
Activity level						388	< 0.001	
Sedentary	377 (7.2%)	116 (4.5%)	48 (6.2%)	113 (8.2%)	100 (17.5%)			
Low	1378 (26.1%)	490 (19.2%)	185 (23.8%)	464 (33.8%)	239 (41.7%)			
Moderate	2589 (49.1%)	1367 (53.6%)	398 (51.2%)	624 (45.5%)	200 (34.9%)			
High	928 (17.6%)	577 (22.6%)	147 (18.9%)	170 (12.4%)	34 (5.9%)			
Hypertension	2756 (52.3%)	1180 (46.3%)	400 (51.4%)	800 (58.4%)	376 (65.6%)	98.2	< 0.001	
Diabetes	680 (12.9%)	277 (10.9%)	95 (12.2%)	218 (15.9%)	90 (15.7%)	24.8	< 0.001	
Heart disease (kinds)						125	< 0.001	
0	4236 (80.3%)	2169 (85.1%)	643 (82.6%)	1042 (76.0%)	382 (66.7%)			
1	776 (14.7%)	287 (11.3%)	104 (13.4%)	248 (18.1%)	137 (23.9%)			
2 or more	260 (4.9%)	94 (3.7%)	31 (4.0%)	81 (5.9%)	54 (9.4%)			
Cancer	629 (11.9%)	281 (11.0%)	118 (15.2%)	158 (11.5%)	72 (12.6%)	10.2	0.017	
Lung disease	463 (8.8%)	159 (6.2%)	66 (8.5%)	142 (10.4%)	96 (16.8%)	70.4	< 0.001	
Psychiatric problems	678 (12.9%)	266 (10.4%)	111 (14.3%)	178 (13.0%)	123 (21.5%)	52.7	< 0.001	

Note: Bold indicates $p < 0.05$, signifying statistically significant results.

^aMean (SD); n (%).

^bKruskal–Wallis rank sum test; Pearson’s Chi-squared test.

analyses after excluding individuals with missing values; (2) by limiting our analyses to cognitively unimpaired participants and those without psychiatric problems in wave 5; (3) by conducting further subgroup analyses based on gender (male and female) and age (middle-aged, 45–65, and older, > 65). Multiple imputation was performed using the “mice” package [19], LCTM were applied with the “lcm” package [21], and linear mixed models were analyzed using the “lme4” package [22] in R. In the data analysis, a 2-tailed p value of < 0.05 was considered statistically significant.

3 | Results

The study included 5272 participants (Table 1), with a mean baseline age of 71.9 years (SD = 8.9), of whom 57.2% were female and 96.9% were White. At wave 1, 3184 individuals had no musculoskeletal chronic conditions, 1367 had one condition, 651 had two, and 71 had three coexisting musculoskeletal conditions. With successive waves, the percentage of participants without any musculoskeletal diseases decreased, whereas the percentages of those with one, two, or three such conditions demonstrated an increasing trend (Figure 2A). Owing to the

relatively small percentage of participants with three musculoskeletal diseases, individuals with two or three such conditions were grouped into a category denoted as having two or more conditions.

3.1 | Trajectory Group Identification

Upon comparison, it was determined that the LCTM model exhibits the lowest BIC value with four latent categories, fulfilling other established criteria (Table S1). Figure 2B illustrates four distinct trajectories of musculoskeletal disease burden, characterized by patterns of consistently low, moderate, high, and initially low but increasing levels. To enhance interpretability, labels were assigned to the trajectories: low-burden group (48.37%), emerging group (14.76%), moderate-burden group (26.00%), and persistent burden group (10.87%). Compared with the low-burden group, participants in other trajectories were more likely to be older, female, divorced or widowed, possess lower educational levels, have lower incomes, be obese, have histories of smoking, consume alcohol infrequently or not at all, engage in less physical activity, and suffer from more chronic conditions ($p < 0.001$ for all) (Table 1).

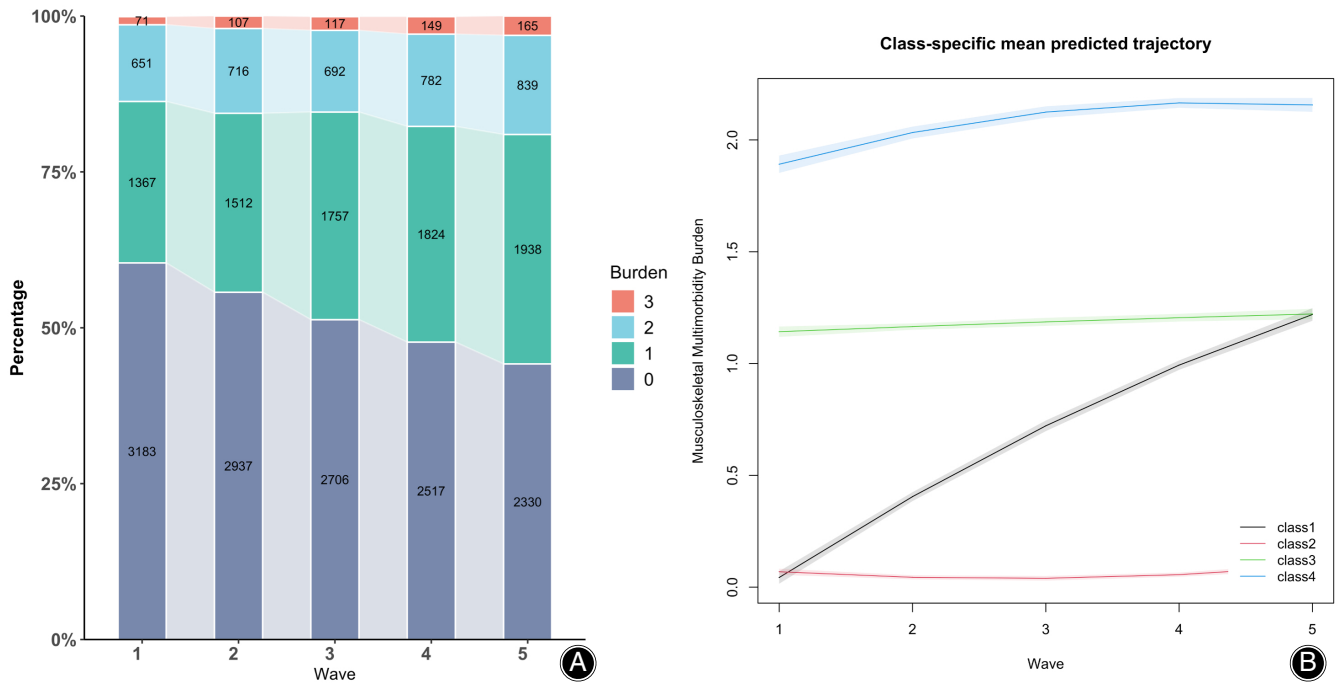


FIGURE 2 | Musculoskeletal disease burden and its trajectory. (A) Showing the changes in the percentage of musculoskeletal disease burden with the change of wave (wave 1 to wave 5); (B) Latent class trajectory models (LCTM) were used to analyze the trajectory of musculoskeletal disease burden, and four distinct trajectories were identified: Low-burden group (class 2), emerging group (class 1), moderate-burden group (class 3), and persistent-burden group (class 4).

3.2 | Musculoskeletal Burden, Multimorbidity, and Holistic Well-Being

After fully adjusted, the findings demonstrate a significant inverse relationship between the burden of musculoskeletal disorders and ADL capabilities (1: $\beta = -0.4$, 95% CIs = $[-0.59$ to $-0.22]$; 2 or more: -1.1 $[-1.4$ to $-0.91]$); with an increase in the number of disorders, the ADL score significantly decreases (p for trend < 0.001). For IADLs, a similar trend is observed, albeit with smaller effects and inconsistent significance across all models. Regarding depression, the data reveal a significant direct association between the burden of musculoskeletal disorders and the severity of depression (1: 0.39 $[0.14-0.65]$; 2 or more: 0.64 $[0.31-0.96]$), with each additional disorder leading to a notable increase in depression scores (p for trend < 0.001). Concerning memory, an inverse relationship is noted: as burdens escalate, memory scores significantly decline (1: -0.97 $[-1.6$ to $-0.37]$; 2 or more: -1.8 $[-2.5$ to $-1.0]$) (p for trend < 0.001), although the magnitude of this effect varies across assessments. Regarding loneliness, the burden of musculoskeletal disorders does not significantly affect the risk of loneliness. In terms of social interactions, within the fully adjusted model, compared with individuals without musculoskeletal disorders, those with one disorder exhibited a significant increase in communication frequency with relatives and friends (0.95 $[0.27-1.6]$). However, those with two or more disorders displayed a similar trend without significant results (0.85 $[-0.03$ to $1.7]$). Finally, regarding overall life satisfaction, the presence of one or more musculoskeletal disorders significantly diminishes life satisfaction, which deteriorates further with an increasing burden (1: -1.0 $[-1.7$ to $-0.34]$; 2 or more: -1.8 $[-2.7$ to $-0.85]$) (Table 2).

3.3 | Trajectory of Musculoskeletal Burden and Holistic Well-Being

The results of regression models, illustrating the association between distinct trajectories of musculoskeletal burden and pre-defined dimensions of well-being, are detailed in Figure 3 and Table S3. Compared with the low-burden group, the moderate and persistent burden groups were significantly associated with reduced ADL capabilities, impaired memory, more frequent social interactions, and diminished life satisfaction, with the persistent burden group experiencing the most pronounced effects. However, in the emerging group, despite a similar trend in the impact on these well-being dimensions, the effects were not statistically significant. Regarding depression, compared with the low-burden group, all other trajectory groups experienced more severe depression, though the increase was not statistically significant in the moderate-burden group. For ADL capabilities and loneliness, the impact across all other trajectory groups, when compared with the low-burden group, was not statistically significant.

3.4 | Sensitivity Analyses

After the exclusion of participants with missing values ($n = 4400$) or baseline cognitive impairments ($n = 5203$), the analysis results remained essentially consistent with the initial findings (Tables S4–S7; Figures S1 and S2). Subgroup analysis by gender indicated that musculoskeletal disorder burden increases communication frequency between women and their relatives and friends, yet the impact is not significant among men (Tables S8–S12). Furthermore, age-based subgroup analysis demonstrated

TABLE 2 | The relationship between musculoskeletal disease burden and the seven dimensions of holistic well-being among middle-aged and older individuals.

Burden	Model 1 ^a			Model 2 ^b			Model 3 ^c			Model 4 ^d		
	Beta	95% CI	p	Beta	95% CI	p	Beta	95% CI	p	Beta	95% CI	p
ADLs												
0	0.00	—		0.00	—		0.00	—		0.00	—	
1	-0.47	-0.65, -0.28	<0.001	-0.46	-0.65, -0.27	<0.001	-0.42	-0.61, -0.23	<0.001	-0.40	-0.59, -0.22	<0.001
2 or more	-1.4	-1.6, -1.1	<0.001	-1.4	-1.6, -1.1	<0.001	-1.2	-1.4, -0.94	<0.001	-1.1	-1.4, -0.91	<0.001
p for trend		<0.001		<0.001			<0.001			<0.001		
IADLs												
0	0.00	—		0.00	—		0.00	—		0.00	—	
1	-0.03	-0.19, 0.14	0.7	-0.02	-0.18, 0.15	0.8	0.03	-0.14, 0.19	0.8	0.05	-0.11, 0.21	0.6
2 or more	-0.34	-0.55, -0.13	0.001	-0.31	-0.52, -0.11	0.003	-0.14	-0.34, 0.07	0.2	-0.08	-0.29, 0.12	0.4
p for trend		0.004		0.009			0.3			0.6		
Depression												
0	0.00	—		0.00	—		0.00	—		0.00	—	
1	0.51	0.25, 0.77	<0.001	0.48	0.22, 0.73	<0.001	0.42	0.17, 0.68	0.001	0.39	0.14, 0.65	0.002
2 or more	0.91	0.58, 1.2	<0.001	0.86	0.54, 1.2	<0.001	0.68	0.36, 1.0	<0.001	0.64	0.31, 0.96	<0.001
p for trend		<0.001		<0.001			<0.001			<0.001		
Memory												
0	0.00	—		0.00	—		0.00	—		0.00	—	
1	-1.2	-1.8, -0.58	<0.001	-1.1	-1.7, -0.46	<0.001	-0.99	-1.6, -0.39	0.001	-0.97	-1.6, -0.37	0.001
2 or more	-2.3	-3.1, -1.5	<0.001	-2.1	-2.9, -1.4	<0.001	-1.8	-2.5, -1.1	<0.001	-1.8	-2.5, -1.0	<0.001
p for trend		<0.001		<0.001			<0.001			<0.001		
Loneliness												
0	0.00	—		0.00	—		0.00	—		0.00	—	
1	0.16	-0.10, 0.42	0.2	0.12	-0.14, 0.38	0.4	0.09	-0.17, 0.35	0.5	0.05	-0.21, 0.31	0.7
2 or more	0.27	-0.07, 0.60	0.12	0.20	-0.13, 0.52	0.2	0.08	-0.25, 0.41	0.6	-0.02	-0.35, 0.31	>0.9
p for trend		0.089		0.2			0.5			>0.9		
Social interactions												
0	0.00	—		0.00	—		0.00	—		0.00	—	

(Continues)

TABLE 2 | (Continued)

Burden	Model 1 ^a			Model 2 ^b			Model 3 ^c			Model 4 ^d		
	Beta	95% CI	p	Beta	95% CI	p	Beta	95% CI	p	Beta	95% CI	p
1	0.72	0.05, 1.4	0.037	0.87	0.19, 1.5	0.012	0.93	0.25, 1.6	0.007	0.95	0.27, 1.6	0.006
2 or more	0.41	-0.47, 1.3	0.4	0.59	-0.29, 1.5	0.2	0.82	-0.06, 1.7	0.068	0.85	-0.03, 1.7	0.058
p for trend		0.14			0.053			0.015			0.012	
Life satisfaction												
0	0.00	—	—	0.00	—	—	0.00	—	—	0.00	—	—
1	-1.5	-2.2, -0.74	<0.001	-1.4	-2.1, -0.65	<0.001	-1.2	-1.9, -0.50	<0.001	-1.0	-1.7, -0.34	0.004
2 or more	-2.9	-3.8, -2.0	<0.001	-2.7	-3.6, -1.8	<0.001	-2.1	-3.0, -1.2	<0.001	-1.8	-2.7, -0.85	<0.001
p for trend		<0.001			<0.001			<0.001			<0.001	

Note: Bold indicates $p < 0.05$, signifying statistically significant results.

Abbreviations: ADLs, activities of daily living; BMI, body mass index; CI, confidence interval; IADLs, instrumental activities of daily living.

^aModel 1 was adjusted for sex and age.

^bModel 2 further included additional personal variables such as marital status, education level, race/ethnicity, insurance status, and income.

^cModel 3 additionally incorporated lifestyle characteristics, including BMI, alcohol consumption status, smoking status, and activity level.

^dModel 4 further included chronic health conditions, including hypertension, diabetes, heart disease, cancer, lung disease, and psychiatric problems.

that musculoskeletal disorders do not significantly influence social interaction frequency among middle-aged individuals nor significantly affect memory decline among the older (Tables S13–S16).

4 | Discussion

This 17-year longitudinal study, utilizing a large English cohort, investigated the association between musculoskeletal disease burden and four distinct trajectories in later life, along with seven dimensions of holistic well-being: ADLs, IADLs, depression, memory, loneliness, social interactions, and life satisfaction. The results indicate that musculoskeletal disorders significantly affect ADLs, depression, memory, social interactions, and life satisfaction in middle-aged and older adults, though with lesser effects on IADLs and loneliness. Moreover, as the burden increases, its effects become more pronounced. Distinct trajectory patterns of musculoskeletal multimorbidity emerged, revealing that participants in the moderate and persistent burden groups exhibited significantly lower ADL capabilities, poorer memory, increased social interactions, and reduced life satisfaction, with the persistent burden group experiencing more pronounced effects.

4.1 | Musculoskeletal Burden, Multimorbidity, and Holistic Well-Being

As musculoskeletal disorders directly affect joint and muscle movements, impacting ADLs [23], numerous studies have shown that individuals with these conditions experience ADL difficulties more often than those without [24, 25], aligning with our findings. The results suggest that musculoskeletal disorders are not significantly associated with IADLs, likely because IADLs rely more on cognitive and decision-making skills, whereas musculoskeletal disorders have a more direct impact on ADLs [26]. Prior research suggests a bidirectional relationship between musculoskeletal disorders like arthritis and back pain and depression [27–30], mediated by factors such as pain [31], inflammation, [32] and restricted activity [33]. Conclusions about the impact of musculoskeletal disorders on memory remain inconsistent. A meta-analysis of 16 studies found only five significant associations between rheumatoid arthritis and cognitive impairments [34]. Another study proposed that arthritis might increase cognitive impairment risk in older Chinese adults, potentially because of symptoms of depression and anxiety [35]. Our findings suggest that middle-aged and older individuals with musculoskeletal disorders lean on friends and family for support, easing loneliness because of restricted activity, thus bolstering resilience and well-being in the older [36]. The effect of musculoskeletal diseases on life satisfaction in middle-aged and older adults may be intricate, potentially shaping their overall well-being [37].

4.2 | Trajectory of Musculoskeletal Burden and Holistic Well-Being

Compared with the low-burden group, participants in other trajectories were more likely to be older adults, female, divorced or

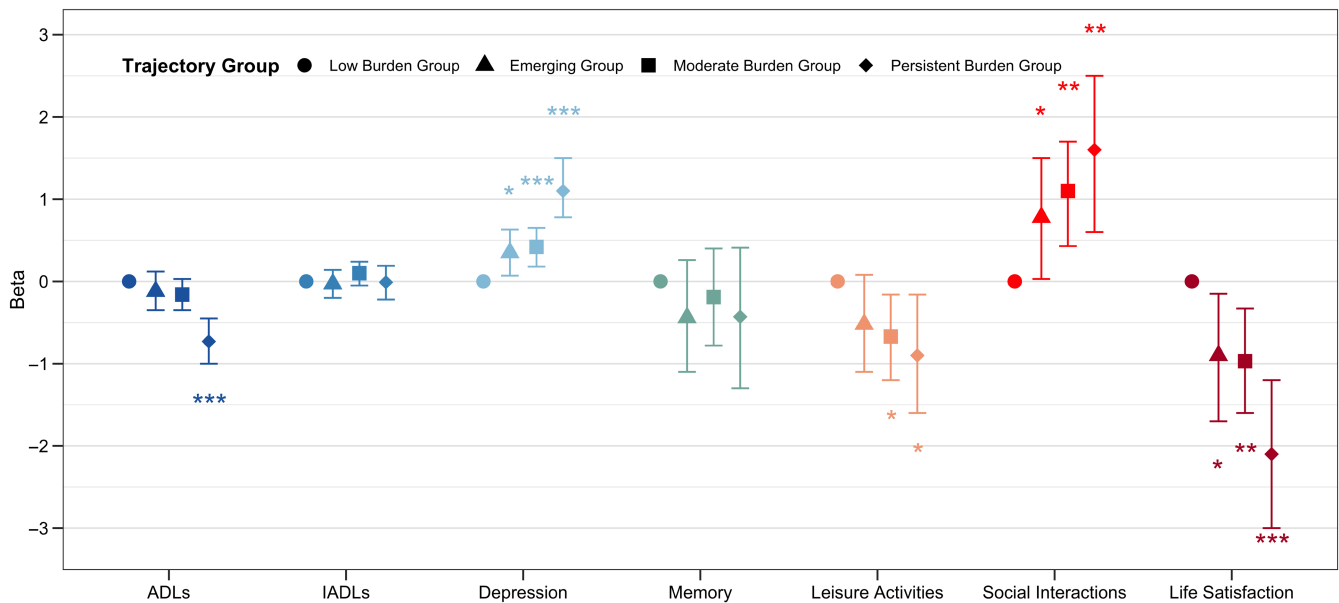


FIGURE 3 | The relationship between different musculoskeletal disease burden trajectory groups and the seven dimensions of holistic well-being among middle-aged and older individuals. The results were adjusted for sex, age, marital status, education level, race/ethnicity, insurance status, income, BMI, alcohol consumption status, smoking status, activity level, and chronic health conditions.

widowed, have a lower education level, have a low income, be obese, be ever smokers, be never or low-frequency drinkers, engage in less physical activity, and have more chronic conditions. The observed demographic and lifestyle characteristics among participants in the higher burden trajectories suggest that these factors may interact to exacerbate the impacts of musculoskeletal disorders [38–40]. This interaction could stem from a combination of reduced social support, lifestyle factors, and limited access to healthcare resources, which tend to be more pronounced in older, economically disadvantaged populations [41, 42]. Furthermore, the association between lower physical activity and the prevalence of other chronic conditions indicates a complex interplay between musculoskeletal disorders and overall health status [43–46]. These findings underscore the importance of a comprehensive approach to managing musculoskeletal disorders, which should encompass addressing social, economic, and lifestyle factors, as well as medical treatment.

Our findings indicate that the trajectory patterns of burden are directly correlated with the severity of impact on several aspects of life. Interestingly, the emerging group, although it demonstrated a trend akin to the moderate and persistent groups regarding the impact on ADLs, memory, social interactions, and life satisfaction, did not exhibit significant changes. This may imply that the duration or consistency of the burden plays a crucial role in the significance of its effects on these areas [47, 48]. For depression, all groups experienced a higher burden of musculoskeletal disorders and demonstrated increased severity compared with the low-burden group, yet this increase was not deemed significant in the moderate-burden group. This finding highlights a general trend toward worsening mental health with increased burden, underscoring the need for mental health support in managing musculoskeletal disorders [49, 50]. These findings reveal the importance of a holistic approach to treatment and support, one that addresses

not only the physical aspects of these conditions but also their psychological and social implications [51, 52].

4.3 | Sensitivity Analyses

Our subgroup analysis emphasized the differential impact of musculoskeletal disorders based on gender and age. Notably, the burden of these disorders was observed to increase the frequency of communication with relatives and friends among women, whereas no such trend was observed in men. This implies that women might seek more social support or engagement as a coping mechanism for their condition, whereas men may not exhibit or pursue similar behaviors [53, 54]. Conversely, when analyzing effects based on age, musculoskeletal disorders were not found to significantly affect the social interaction frequency among middle-aged individuals nor contribute to memory decline in the older. This demonstrates that the impact of these disorders varies not only by gender but also across different age groups [55, 56]. It highlights the need for targeted strategies in managing musculoskeletal disorders, taking into account the unique ways in which different demographics experience and respond to these conditions.

4.4 | Clinical Application Prospect

Clinicians should prioritize not only the management of the physical symptoms of musculoskeletal disorders but also the mental health and social well-being challenges that often accompany these conditions. Particular attention should be directed toward vulnerable populations, such as older adults, women, and individuals from socioeconomically disadvantaged backgrounds, who are at higher risk of more severe outcomes. Implementing early interventions, multidisciplinary care, and integrating mental health support with physical therapy could

significantly improve long-term quality of life and alleviate the overall burden of these chronic conditions.

4.5 | Strengths and Limitations

This study emphasizes its significant sample size and advanced statistical analysis as primary strengths, complemented by an extensive follow-up period and meticulous outcome documentation, with a focus on the broad impacts of musculoskeletal disorders on older well-being. However, the study encounters several limitations: First, the study's dependence on self-reported data could potentially introduce recall bias, which may affect accuracy. Future research should explore the incorporation of objective measures. Second, it assesses covariates such as physical activity at a single time point, without considering their potential variation over time. Third, the study does not include measurements of significant social factors, suggesting directions for future research. Fourth, although the study centers on three principal musculoskeletal diseases, it overlooks other conditions that impact the health of middle-aged and older individuals. Fifth, the predominately White cohort implies that the findings might not be entirely generalizable across racial groups. Sixth, this study treats arthritis as a broad category of disease, encompassing osteoarthritis and rheumatoid arthritis, among others. The incidence, sites of prevalence, and populations affected differ among these types, potentially introducing bias into our results. Future research should undertake more comprehensive analyses to validate our findings. Seventh, this study did not investigate the potential mechanisms between musculoskeletal disorders and holistic well-being, necessitating further research. Finally, although the study addresses crucial aspects of well-being, it potentially overlooks other dimensions of holistic well-being, underscoring the necessity for comprehensive, demographic-specific management approaches.

5 | Conclusion

In summary, our 17-year study demonstrates that musculoskeletal disease burden significantly impacts the holistic well-being of middle-aged and older adults, notably affecting ADLs, depression, memory, social interactions, and life satisfaction. Moreover, with increasing burden, the severity of its impact correspondingly intensifies. The study underscores gender and age differences in response to this burden and advocates for a comprehensive, personalized approach in managing these disorders. Furthermore, the duration and consistency of the burden are posited to play a crucial role in the extent of its effects on these areas.

Author Contributions

Yuanpeng Zhu: conceptualization, software, data curation, writing – original draft preparation, visualization. **Haoran Zhang:** methodology, software, visualization, investigation, writing – reviewing and editing. **Nan Wu:** supervision, funding acquisition. **Terry Jianguo Zhang:** supervision, funding acquisition. **Qing Li:** writing – reviewing and editing. All authors approved the final version to be published.

Acknowledgments

We would like to acknowledge the English Longitudinal Study of Aging (ELSA) for providing the publicly available data used in this research. The data collection was supported by the National Institute on Aging and a consortium of UK government departments.

Disclosure

During the preparation of this work the authors used Chatgpt to language polishing. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Ethics Statement

ELSA has already obtained local ethical approval, specific details of which can be found on the official website.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data used to generate the results in this study were obtained from the English Longitudinal Study of Aging (ELSA) which is publicly available.

References

1. X. Xu, G. D. Mishra, and M. Jones, "Evidence on Multimorbidity From Definition to Intervention: An Overview of Systematic Reviews," *Ageing Research Reviews* 37 (2017): 53–68.
2. A. D. Woolf and B. Pfleger, "Burden of Major Musculoskeletal Conditions," *Bulletin of the World Health Organization* 81, no. 9 (2003): 646–656.
3. S. J. Duffield, B. M. Ellis, N. Goodson, et al., "The Contribution of Musculoskeletal Disorders in Multimorbidity: Implications for Practice and Policy," *Best Practice & Research. Clinical Rheumatology* 31, no. 2 (2017): 129–144.
4. World Health Organization, "Health Promotion Glossary of Terms 2021," <https://www.who.int/publications/i/item/9789240038349>.
5. World Health Organization, "Promoting Well-Being 2024," <https://www.who.int/activities/promoting-well-being>.
6. Y. Chen, H. Guo, Z. Li, L. Huang, T. Hong, and H. Wang, "Association of Self-Reported Arthritis With Depression, Anxiety, and Comorbid Depression/Anxiety Among the Older Chinese Adults: A Cross-Sectional Study," *Journal of Affective Disorders* 354 (2024): 323–330.
7. D. Ceulemans, M. Moens, M. Reneman, et al., "Biopsychosocial Rehabilitation in the Working Population With Chronic Low Back Pain: A Concept Analysis," *Journal of Rehabilitation Medicine* 56 (2024): jrm13454.
8. B. Millar, D. F. McWilliams, A. Abhishek, et al., "Investigating Musculoskeletal Health and Wellbeing; a Cohort Study Protocol," *BMC Musculoskeletal Disorders* 21, no. 1 (2020): 182.
9. Pain Centre Versus Arthritis, "Investigating Musculoskeletal Health and Wellbeing (IMH&W) Cohort 2024," <https://www.nottingham.ac.uk/paincentre/resources/investigating-musculoskeletal-health-and-wellbeing-imhw-cohort.aspx>.

10. A. Calderón-Larrañaga, G. Santoni, H. X. Wang, et al., “Rapidly Developing Multimorbidity and Disability in Older Adults: Does Social Background Matter?,” *Journal of Internal Medicine* 283, no. 5 (2018): 489–499.
11. V. Y. Strauss, P. W. Jones, U. T. Kadam, and K. P. Jordan, “Distinct Trajectories of Multimorbidity in Primary Care Were Identified Using Latent Class Growth Analysis,” *Journal of Clinical Epidemiology* 67, no. 10 (2014): 1163–1171.
12. ELSA, “English Longitudinal Study of Aging 2024,” <https://www.elsa-project.ac.uk/>.
13. J. Banks, G. D. Batty, J. Breedvelt, et al., *English Longitudinal Study of Ageing: Waves 0-10, 1998–2023* (London, UK: UK Data Service, 2024).
14. J. P. Vandenbroucke, E. von Elm, D. G. Altman, et al., “Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration,” *PLoS Medicine* 4, no. 10 (2007): e297.
15. K. A. Theis, L. B. Murphy, D. Guglielmo, et al., “Prevalence of Arthritis and Arthritis-Attributable Activity Limitation – United States, 2016–2018,” *MMWR. Morbidity and Mortality Weekly Report* 70, no. 40 (2021): 1401–1407.
16. I. M. B. de Souza, T. F. Sakaguchi, S. L. K. Yuan, et al., “Prevalence of Low Back Pain in the Elderly Population: A Systematic Review,” *Clinics (São Paulo, Brazil)* 74 (2019): e789.
17. N. R. Fuggle, C. Beaudart, O. Bruyère, et al., “Evidence-Based Guideline for the Management of Osteoporosis in Men,” *Nature Reviews Rheumatology* 20 (2024): 241–251.
18. M. Jobe, I. Mactaggart, S. Bell, et al., “Prevalence of Hypertension, Diabetes, Obesity, Multimorbidity, and Related Risk Factors Among Adult Gambians: A Cross-Sectional Nationwide Study,” *Lancet Global Health* 12, no. 1 (2024): e55–e65.
19. I. R. White, P. Royston, and A. M. Wood, “Multiple Imputation Using Chained Equations: Issues and Guidance for Practice,” *Statistics in Medicine* 30, no. 4 (2011): 377–399.
20. H. Lennon, S. Kelly, M. Sperrin, et al., “Framework to Construct and Interpret Latent Class Trajectory Modelling,” *BMJ Open* 8, no. 7 (2018): e020683.
21. C. Proust-Lima, V. Philipps, and B. Lique, “Estimation of Extended Mixed Models Using Latent Classes and Latent Processes: The R Package lcmm,” *Journal of Statistical Software* 78 (2017): 1–56.
22. M. M. Douglas Bates, B. Bolker, and S. Walker, “Fitting Linear Mixed-Effects Models Using lme4,” *Journal of Statistical Software* 67 (2015): 1–48.
23. F. D. Wolinsky, S. E. Bentler, J. Hockenberry, et al., “Long-Term Declines in ADLs, IADLs, and Mobility Among Older Medicare Beneficiaries,” *BMC Geriatrics* 11 (2011): 43.
24. T. A. Stamm, K. Pieber, R. Crevenna, and T. E. Dorner, “Impairment in the Activities of Daily Living in Older Adults With and Without Osteoporosis, Osteoarthritis and Chronic Back Pain: A Secondary Analysis of Population-Based Health Survey Data,” *BMC Musculoskeletal Disorders* 17 (2016): 139.
25. M. A. Zalah, H. I. Alsabayel, F. S. Algarni, et al., “The Severity of Pain and Comorbidities Significantly Impact the Dependency on Activities of Daily Living Among Musculoskeletal Patients in Jizan, Saudi Arabia,” *Healthcare (Basel)* 11, no. 16 (2023): 2313.
26. D. X. M. Wang, J. Yao, Y. Zirek, E. M. Reijnierse, and A. B. Maier, “Muscle Mass, Strength, and Physical Performance Predicting Activities of Daily Living: A Meta-Analysis,” *Journal of Cachexia, Sarcopenia and Muscle* 11, no. 1 (2020): 3–25.
27. K. H. Jeon, K. Han, J. Jung, et al., “Rheumatoid Arthritis and Risk of Depression in South Korea,” *JAMA Network Open* 7, no. 3 (2024): e241139.
28. P. Wu, W. Li, R. Lv, et al., “Hyperactive Lateral Habenula Mediates the Comorbidity Between Rheumatoid Arthritis and Depression-Like Behaviors,” *Brain, Behavior, and Immunity* 117 (2024): 412–427.
29. M. Latas, B. Stefanovski, A. Mihaljević-Peleš, et al., “Diagnostic Psychiatric and Somatic Comorbidity in Patients With Depression in the Western Balkan Countries,” *PLoS One* 19, no. 1 (2024): e0295754.
30. D. C. Steffens, “Treatment-Resistant Depression in Older Adults,” *New England Journal of Medicine* 390, no. 7 (2024): 630–639.
31. J. Goesling, D. J. Clauw, and A. L. Hassett, “Pain and Depression: An Integrative Review of Neurobiological and Psychological Factors,” *Current Psychiatry Reports* 15, no. 12 (2013): 421.
32. K. Stefanov, S. Al-Wasity, J. T. Parkinson, G. D. Waiter, J. Cavanagh, and N. Basu, “Brain Mapping Inflammatory-Arthritis-Related Fatigue in the Pursuit of Novel Therapeutics,” *Lancet Rheumatology* 5, no. 2 (2023): e99–e109.
33. S. Jang and E. Yang, “Sleep, Physical Activity, and Sedentary Behaviors as Factors Related to Depression and Health-Related Quality of Life Among Older Women Living Alone: A Population-Based Study,” *European Review of Aging and Physical Activity* 20, no. 1 (2023): 6.
34. S. R. Sharma and Y. Chen, “Rheumatoid Arthritis and Cognitive Impairment or Dementia: An Updated Review of Epidemiological Data,” *Journal of Alzheimer’s Disease* 95, no. 3 (2023): 769–783.
35. Y. Y. He, K. R. Ding, W. Y. Tan, et al., “The Role of Depression and Anxiety in the Relationship Between Arthritis and Cognitive Impairment in Chinese Older Adults,” *American Journal of Geriatric Psychiatry* 32 (2024): 856–866.
36. S. Park, T. H. Kim, and T. R. Eom, “Impact of Social Network Size and Contact Frequency on Resilience in Community-Dwelling Healthy Older Adults Living Alone in the Republic of Korea,” *International Journal of Environmental Research and Public Health* 18, no. 11 (2021): 6061.
37. J. Heikkinen, R. J. Honkanen, S. E. Quirk, L. J. Williams, and H. Koivumaa-Honkanen, “Long-Term Life Satisfaction in Ageing Women With Work Disability due to Mental and Musculoskeletal Disorders,” *Maturitas* 178 (2023): 107849.
38. S. Safiri, A. A. Kolahi, M. Cross, et al., “Prevalence, Deaths, and Disability-Adjusted Life Years due to Musculoskeletal Disorders for 195 Countries and Territories 1990–2017,” *Arthritis & Rheumatology* 73, no. 4 (2021): 702–714.
39. S. Safiri, A. A. Kolahi, M. Cross, et al., “Prevalence, Incidence, and Years Lived With Disability due to Gout and Its Attributable Risk Factors for 195 Countries and Territories 1990–2017: A Systematic Analysis of the Global Burden of Disease Study 2017,” *Arthritis & Rheumatology* 72, no. 11 (2020): 1916–1927.
40. S. Safiri, A. A. Kolahi, E. Smith, et al., “Global, Regional and National Burden of Osteoarthritis 1990–2017: A Systematic Analysis of the Global Burden of Disease Study 2017,” *Annals of the Rheumatic Diseases* 79, no. 6 (2020): 819–828.
41. D. van Schaardenburg, K. J. van den Brande, G. J. Ligthart, F. C. Breedveld, and J. M. Hazes, “Musculoskeletal Disorders and Disability in Persons Aged 85 and Over: A Community Survey,” *Annals of the Rheumatic Diseases* 53, no. 12 (1994): 807–811.
42. E. Smith, D. G. Hoy, M. Cross, et al., “The Global Burden of Other Musculoskeletal Disorders: Estimates From the Global Burden of Disease 2010 Study,” *Annals of the Rheumatic Diseases* 73, no. 8 (2014): 1462–1469.
43. M. Grabara, “The Association Between Physical Activity and Musculoskeletal Disorders—A Cross-Sectional Study of Teachers,” *PeerJ* 11 (2023): e14872.
44. X. Zhao, Y. Yang, R. Yue, and C. Su, “Potential Causal Association Between Leisure Sedentary Behaviors, Physical Activity and

- Musculoskeletal Health: A Mendelian Randomization Study,” *PLoS One* 18, no. 3 (2023): e0283014.
45. J. H. Choi, H. R. Kim, and K. H. Song, “Musculoskeletal Complications in Patients With Diabetes Mellitus,” *Korean Journal of Internal Medicine* 37, no. 6 (2022): 1099–1110.
46. J. Qin, K. A. Theis, K. E. Barbour, C. G. Helmick, N. A. Baker, and T. J. Brady, “Impact of Arthritis and Multiple Chronic Conditions on Selected Life Domains – United States, 2013,” *MMWR. Morbidity and Mortality Weekly Report* 64, no. 21 (2015): 578–582.
47. E. L. Whitlock, L. G. Diaz-Ramirez, M. M. Glymour, W. J. Boscardin, K. E. Covinsky, and A. K. Smith, “Association Between Persistent Pain and Memory Decline and Dementia in a Longitudinal Cohort of Elders,” *JAMA Internal Medicine* 177, no. 8 (2017): 1146–1153.
48. A. F. Domenichiello and C. E. Ramsden, “The Silent Epidemic of Chronic Pain in Older Adults,” *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 93 (2019): 284–290.
49. M. Doumen, S. Pazmino, P. Verschueren, and R. Westhovens, “Viewpoint: Supporting Mental Health in the Current Management of Rheumatoid Arthritis: Time to Act!,” *Rheumatology (Oxford, England)* 62, no. 3 (2023): SI274–SI281.
50. T. P. Welsh, A. E. Yang, and U. E. Makris, “Musculoskeletal Pain in Older Adults: A Clinical Review,” *Medical Clinics of North America* 104, no. 5 (2020): 855–872.
51. N. M. Karttunen, J. Turunen, R. Ahonen, and S. Hartikainen, “More Attention to Pain Management in Community-Dwelling Older Persons With Chronic Musculoskeletal Pain,” *Age and Ageing* 43, no. 6 (2014): 845–850.
52. S. D. Anton, A. J. Woods, T. Ashizawa, et al., “Successful Aging: Advancing the Science of Physical Independence in Older Adults,” *Ageing Research Reviews* 24 (2015): 304–327.
53. L. A. Kort-Butler, “Coping Styles and Sex Differences in Depressive Symptoms and Delinquent Behavior,” *Journal of Youth and Adolescence* 38, no. 1 (2009): 122–136.
54. I. Sagar-Ouriaghli, E. Godfrey, L. Bridge, L. Meade, and J. S. L. Brown, “Improving Mental Health Service Utilization Among Men: A Systematic Review and Synthesis of Behavior Change Techniques Within Interventions Targeting Help-Seeking,” *American Journal of Men’s Health* 13, no. 3 (2019): 1557988319857009.
55. J. Di, J. Bai, J. Zhang, et al., “Regional Disparities, Age-Related Changes and Sex-Related Differences in Knee Osteoarthritis,” *BMC Musculoskeletal Disorders* 25, no. 1 (2024): 66.
56. R. Lewis, C. B. Gómez Álvarez, M. Rayman, S. Lanham-New, A. Woolf, and A. Mobasheri, “Strategies for Optimising Musculoskeletal Health in the 21(st) Century,” *BMC Musculoskeletal Disorders* 20, no. 1 (2019): 164.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.