Received: 30 June 2024 | Accepted: 25 September 2024

DOI: 10.1002/agm2.12365

Aging Medicine Open Access WILEY

ORIGINAL ARTICLE

Association of handgrip strength weakness and asymmetry with later life pain risk in middle-aged and older individuals: Results from four prospective cohorts

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Funding information
National Key Research and Development Program of China, Grant/Award Number: 2023YFC2507700; National Natural Science Foundation of China, Grant/Award Number: 81930068, 82072391, 82172382 and 82172525; National High Level Hospital Clinical Research Funding, Grant/Award Number: 2022-PUMCH-C-033, 2022-PUMCH-D-002 and 2022-PUMCH-D-004; CAMS Innovation Fund for Medical Sciences, Grant/Award Number: 2021-I2M-1-051, 2021-I2M-1-052, 2022-I2M-2-001 and 2023-I2M-C&T-A-003

Abstract

Objectives: The burden of pain in middle-aged and older adults is considerable and significantly increases healthcare expenditures. We aimed to investigate the roles of handgrip strength (HGS) weakness and asymmetry in predicting pain across four nationally representative cohorts.

Methods: This longitudinal study utilized data from four major surveys: the Health and Retirement Study (HRS); the English Longitudinal Study of Ageing (ELSA); the Survey of Health, Ageing and Retirement in Europe (SHARE); and the China Health and Retirement Longitudinal Study (CHARLS). Multivariable cubic regression splines were employed to visually explore the nonlinear associations between HGS and pain in each cohort. The Cox proportional hazard model was applied to analyze the independent and combined relationship between HGS weakness and asymmetry and pain risk.

Results: We included 41,171 participants in the final analysis, with a mean follow-up period of 4.68 ± 2.61 years (50.7% female, mean age 64.3 ± 9.3 years). No nonlinear relationship was found between HGS and pain incidence (nonlinear $p < 0.05$ in ELSA and SHARE; >0.05 in CHARLS and HRS). After adjustment, the highest quartile groups had a significantly reduced risk of pain compared to the lowest quartile groups across all cohorts, with hazard ratios of 0.81 (0.74, 0.89) in CHARLS, 0.86 (0.77, 0.97) in HRS, 0.88 (0.77, 0.98) in ELSA, and 0.78 (0.73, 0.84) in SHARE. Participants with normal HGS had approximately 20% lower risk of pain compared to those with weak HGS. Each 5 kg increase in HGS was associated with decreased hazard ratios for pain: 0.95 (0.93, 0.97) in CHARLS, 0.97 (0.94, 0.99) in HRS, 0.96 (0.94, 0.99) in ELSA, and 0.94 (0.92, 0.95) in SHARE. The association between HGS asymmetry and pain risk was significant only in a few cohorts (HRS at 10%, 1.10 (1.03, 1.18); SHARE at 30%, 1.12 (1.05, 1.21)). No interaction effect between HGS weakness and asymmetry on pain risk was observed (all p-values for interaction >0.05).

Yuanpeng Zhu and Haoran Zhang equally contributed to this work.

Conclusions: Our findings suggest that HGS can be used as an independent predictor of pain in middle-aged and older European, American, and Chinese populations. However, our results do not support the use of HGS asymmetry as an independent predictor of pain risk. It is necessary to establish appropriate criteria for HGS asymmetry across different populations. The use of both weak HGS and asymmetry as predictors of health outcomes requires further validation in more diverse populations.

KEYWORDS
handgrip strength, pain, weakness

1 | INTRODUCTION

Pain in the context of aging is not merely a symptom but is rather a complex experience that intersects with mobility, independence, and emotional well-being, profoundly influencing the lives of the middle-aged and older populations.[1] The economic burden of pain in this demographic is substantial, significantly escalating healthcare expenditures, including direct medical costs and the indirect costs of lost productivity and ongoing care.[2] This common yet intricate challenge necessitates a comprehensive understanding and targeted interventions to maintain the quality of life of these individuals.[3]

Handgrip strength (HGS) is a crucial indicator of muscle function and overall health, widely used in clinical and research settings as a measure of physical condition.[4] This simple, noninvasive measurement not only provides insights into muscle strength but also predicts risks associated with sarcopenia and frailty.[5] Moreover, HGS is associated with broader health outcomes such as cardiovascular health and longevity.[6,7] However, measuring only the maximal HGS of one hand may not provide an accurate reflection of total muscle functionality. Recent research on HGS asymmetry, or significant differences in strength between hands, has emphasized its importance in assessing muscle function impairment and its potential implications for future health challenges.[8,9]

However, research into the independent and combined impact of HGS weakness, asymmetry, and pain among middle-aged and older adults remains limited. It has not yet been established whether HGS can serve as a significant predictor of pain occurrence in later life among middle-aged and older individuals. To address these research gaps, we conducted a cross-cultural, longitudinal analysis based on four large, comparative cohort studies, representing middle-aged and older adults across 22 countries from three continents: North America, Europe, and Asia. This approach has the potential to assist in the early prevention and management of pain in middle-aged and older individuals, thereby mitigating its social burden.

2 | METHODS

2.1 | Study design and participants

Data were obtained from four international cohorts of aging: the Health and Retirement Study (HRS);[10] the English Longitudinal Study of Ageing (ELSA)[11]; the Survey of Health, Ageing and Retirement in Europe (SHARE);[12] and the China Health and Retirement Longitudinal Study (CHARLS).[13] These cohorts were designed with similar survey protocols to enable cross-regional comparisons. Detailed information about these cohorts is available on their respective official websites. To ensure comparability in HGS measurement and consistency in time ranges, this study utilized data spanning from 2008 to 2018 for the HRS and ELSA, from 2013 to 2018 for SHARE, and from 2011 to 2018 for CHARLS.

In this study, 120,716 (8326 from ELSA, 62,790 from SHARE, 35,925 from HRS, and 13,675 from CHARLS) participants aged 45 to 85 years from four cohorts were included in the baseline surveys. Participants were excluded if they lacked the required HGS data, had pain or did not clearly report pain at baseline, were lost to follow-up, or were missing necessary covariate data, resulting in 41,171 (4238 from ELSA, 22,799 from SHARE, 7457 from HRS, and 6677 from CHARLS) participants being included in the final analysis. All studies received ethical approval from the relevant local research ethics committees, and participants were recruited after providing written informed consent. Details of the selection process are depicted in Figure 1. We conformed to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[14]

2.2 | Handgrip strength weakness and asymmetry

HGS was measured using a handheld dynamometer (Smedley, S Dynamometer, TTM, Tokyo, 100 kg[15] or WCS-100, Nantong, China[16]) in the four cohorts at baseline. Before the measurement, participants were asked if they were in a safe state to proceed. The test was conducted with participants either standing or sitting, with their elbows bent at 90° angles. Weakness was defined using the Foundation for the National Institutes of Health Sarcopenia Project criteria: maximal HGS <26 kg for males and <16 kg for females.[17] The HGS ratio was calculated by dividing the maximal HGS of the nondominant hand by the dominant hand's maximal HGS. Following prior research, the 10% rule was employed to define HGS asymmetry, which indicates that the dominant hand's HGS is generally 10% greater than the nondominant hand's.[18] As a result, asymmetry was defined as an HGS ratio of <0.90 or

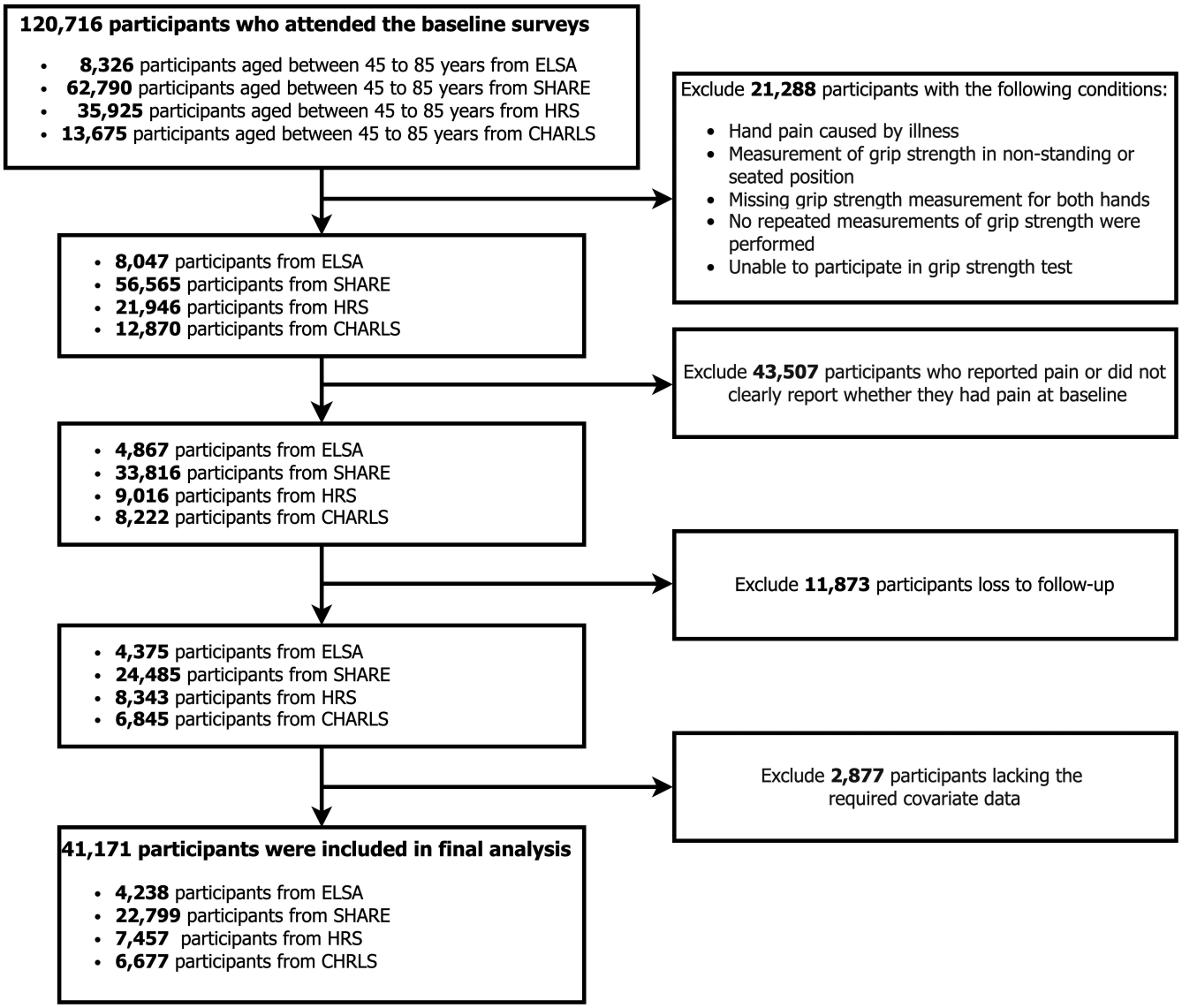

FIGURE 1 Flowchart of the selection of the study population.

>1.10. To further investigate the relationship between varying HGS ratios and pain, the 20% and 30% rules were also applied to define HGS asymmetry.

2.3 | Outcome ascertainment and follow-up

The primary outcome of this study was the incidence of pain, assessed using the question "Are you often troubled with pain?" in HRS, ELSA, and SHARE, and "Are you often troubled with any body pains?" in CHARLS. Participants who explicitly answered "yes" were considered to be suffering from pain. The follow-up endpoint was the first occurrence of pain, death, or the censoring date, whichever came first. The censoring date was defined as the date each participant attended their last survey. Death data were available up to the last survey in CHARLS, HRS, and SHARE, but in ELSA, they were available only until wave 6 (2012–2013).

2.4 | Covariates

Based on prior research, potential confounders were controlled for by evaluating participant characteristics at baseline, including sociodemographic, lifestyle, and health aspects such as age, sex (male, female), marital status (never married, married, divorced or widowed), insurance coverage (with or without), body mass index (BMI) (underweight, normal weight, overweight, and obesity), smoking status (never smoked or smoking), drinking status (non-drinker or drinking), activity level (low, moderate, high), and history of hypertension, diabetes, heart disease, and cancer (yes, no).[19,20]

All covariates were measured at baseline at the same time with HGS measurement.

2.5 | Statistical analysis

Baseline characteristics of the study participants are described using means (standard deviations(*SD*)) for continuous variables and frequencies percentagesfor categorical variables. The Kruskal–Wallis and Chi–Square tests were employed to compare differences in variables across the four cohorts.

Multivariable cubic regression splines were used to visually explore nonlinear associations between HGS and pain in each cohort. As shown in Figure 2, nonlinear relationship was not observed between HGS and the incidence of pain in all cohorts (Nonlinear $p < 0.05$ in ELSA and SHARE, while >0.05 in CHARLS and HRS). Additionally, we investigated the associations of HGS with the incidence of pain over the follow-up period using Cox proportional hazard models. Results were reported as hazard ratios with accompanying 95% confidence intervals. To more comprehensively analyze the characteristics of HGS, HGS was analyzed as both categorical (gender-specific quartiles, Q1-Q4; and gender-specific categories: weakness or normal strength) and continuous variables (per 5 kg increment). Moreover, participants in Q1 and those categorized as weak served as the reference group, with quartile ranges of HGS among male and female participants in four cohorts presented in **eTable 1**. For all Cox proportional hazard analyses, models incorporating all covariates were executed across the four cohorts.

To investigate the independent association between HGS asymmetry and pain, we established HGS asymmetry criteria at 10%, 20%, and 30%. Additionally, we utilized a Cox regression model with the HGS symmetric group as the reference to calculate the pain risk for the asymmetric group. To explore the combined effects of HGS weakness, asymmetry, and pain, participants were categorized into four groups based on the presence of weakness and asymmetry, designating the group with both "weakness and asymmetry" as the reference. Finally, we introduced the interaction term for HGS weakness and asymmetry in the Cox proportional hazards model to calculate their interaction effect. Cox proportional hazard analyses were conducted, comprehensively adjusting for covariates in all four cohorts.

Several sensitivity analyses were conducted: (1) For patients with incomplete covariate data, multiple imputation was employed to address the missing values, and subsequent analyses were conducted.[21] (2) Given that psychological factors[22] and cognitive function might affect patients' perception of pain, additional adjustments were made for mental and cognitive disorders, followed by a reiteration of all analyses. (3) Acknowledging that mortality could be a competing risk for pain, analyses were reconducted using the Fine-Gray model.[23] (4) HGS weakness was defined according to the Asian Work Group for Sarcopenia 2019 consensus (maximal HGS <28 kg for males and <18 kg for females),[24] and the data were reanalyzed.[5] To assess the risk of HGS weakness, subgroup analyses were conducted based on participant characteristics. Schoenfeld residuals were tested to verify the proportional risk assumption. Statistical analysis was performed using R 4.3.0. In the data analysis, a two-tailed *p*-value of less than 0.05 was deemed statistically significant.

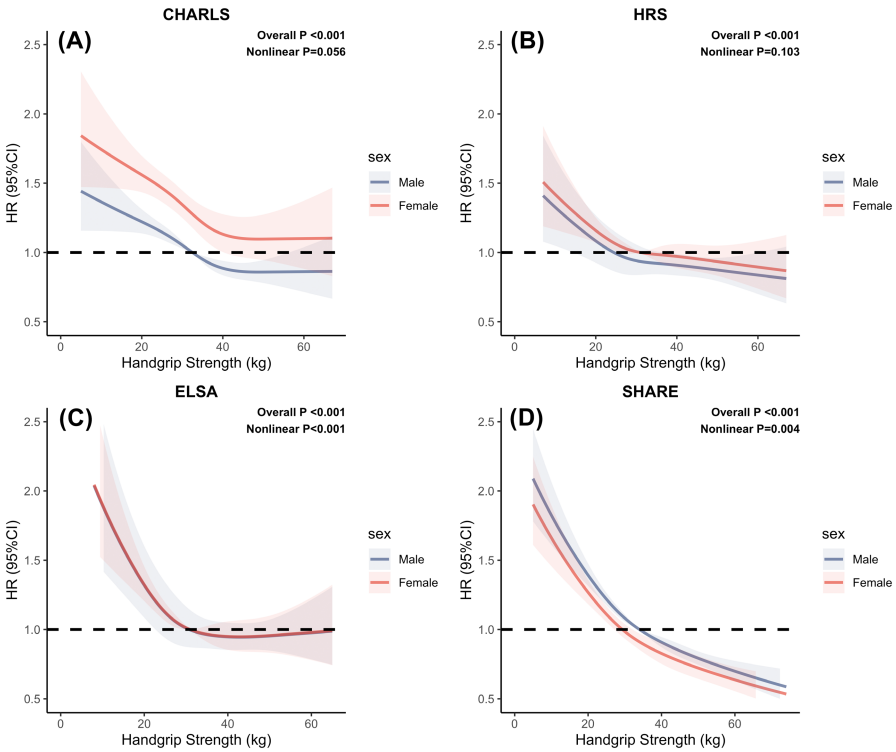

FIGURE 2 Restricted cubic spline analyses for association of handgrip strength with risk of pain in four cohorts. A, B, C, and D represent the association between them in CHARLS, HRS, ELSA, and SHARE cohorts, respectively.

3 | RESULTS

3.1 | Baseline characteristics of the study population

The characteristics of observations across the four cohort studies are presented in Table 1. According to inclusion and exclusion criteria, the final analysis included 7457 participants from HRS (female: 54.6%, mean age: 66.6 years), 4238 from ELSA (female: 51.3%, mean age: 64.3 years), 22,799 from SHARE (female: 50.0%, mean age: 65.0 years), and 6677 from CHARLS (female: 48.3%, mean age: 58.9 years). The mean HGS varied across cohorts, ranging from 33 to 36 kg, with males exhibiting higher values than females in all cohorts (eFigure 1a—Data S1). The mean HGS ratio ranged from 1.07 in CHARLS to 1.11 in HRS (Table 1), and eFigure 1b—Data S1 illustrates the percentages of individuals with varying HGS ratios across the four cohorts. The mean follow-up period across all cohorts was 4.68 years ($SD = 2.61$), with specific durations of 4.99 years ($SD = 2.26$) in CHARLS, 5.95 years ($SD = 3.33$) in ELSA, 6.06 years ($SD = 2.82$) in HRS, and 3.89 years ($SD = 2.14$) in SHARE.

3.2 | Association between HGS weakness and pain

Table 2 illustrates the independent associations between HGS weakness and the risk of pain across four cohorts. After

TABLE 1 Baseline characteristics of participants included in final analysis.

Characteristic	Overall	Cohort				
	Overall, $n = 41,171$ (100%)[a]	CHARLS, $n = 6677$ (16%)[a]	ELSA, $n = 4238$ (10%)[a]	HRS, $n = 7457$ (18%)[a]	SHARE, $n = 22,799$ (55%)[a]	p-value[b]
Age (years)	64.3 (9.3)	58.9 (9.3)	64.3 (8.5)	66.6 (9.6)	65.0 (8.7)	**<0.001**
Sex						
Female	20,859 (50.7%)	3227 (48.3%)	2173 (51.3%)	4070 (54.6%)	11,389 (50.0%)	**<0.001**
Male	20,312 (49.3%)	3450 (51.7%)	2065 (48.7%)	3387 (45.4%)	11,410 (50.0%)	
Marital status						
Never married	1796 (4.4%)	46 (0.7%)	258 (6.1%)	339 (4.5%)	1153 (5.1%)	**<0.001**
Married	30,978 (75.2%)	5934 (88.9%)	2994 (70.6%)	4894 (65.6%)	17,156 (75.2%)	
Divorced or widowed	8397 (20.4%)	697 (10.4%)	986 (23.3%)	2224 (29.8%)	4490 (19.7%)	
Insurance coverage	15,670 (38.1%)	3292 (49.2%)	1767 (41.7%)	4230 (56.7%)	6381 (28.0%)	**<0.001**
BMI						
Underweight	744 (1.8%)	384 (5.8%)	36 (0.8%)	62 (0.8%)	262 (1.1%)	**<0.001**
Normal weight	16,154 (39%)	4185 (63%)	1210 (29%)	1734 (23%)	9025 (40%)	
Overweight	15,917 (39%)	1748 (26%)	1891 (45%)	2739 (37%)	9539 (42%)	
Obesity	8356 (20%)	360 (5.4%)	1101 (26%)	2922 (39%)	3973 (17%)	
Smoking	9812.0 (23.8%)	2749 (41.2%)	583 (13.8%)	1344 (18.0%)	5136 (22.5%)	**<0.001**
Drinking	15,365.0 (37.3%)	4851 (72.7%)	3623 (85.5%)	3307 (44.3%)	3584 (15.7%)	**<0.001**
Activity level						
Low	7053 (17.1%)	4183 (62.6%)	780 (18.4%)	982 (13.2%)	1108 (4.9%)	**<0.001**
Moderate	9959 (24.2%)	1481 (22.2%)	2328 (54.9%)	2129 (28.6%)	4021 (17.6%)	
High	24,159 (58.7%)	1013 (15.2%)	1130 (26.7%)	4346 (58.3%)	17,670 (77.5%)	
Hypertension	14,883 (36.1%)	1472 (22.0%)	1544 (36.4%)	4003 (53.7%)	7864 (34.5%)	**<0.001**
Diabetes	4226 (10.3%)	322 (4.8%)	334 (7.9%)	1358 (18.2%)	2212 (9.7%)	**<0.001**
Heart disease	4742 (11.5%)	601 (9.0%)	475 (11.2%)	1433 (19.2%)	2233 (9.8%)	**<0.001**
Cancer	2302 (5.6%)	37 (0.6%)	297 (7.0%)	964 (12.9%)	1004 (4.4%)	**<0.001**
Handgrip strength	34 (11)	33 (10)	33 (11)	33 (11)	36 (11)	**<0.001**
Handgrip strength ratio	1.10 (0.24)	1.07 (0.30)	1.09 (0.18)	1.11 (0.19)	1.10 (0.24)	**<0.001**

Note: The significant values have been bolded.

Abbreviation: BMI, body mass index.

[a]Mean (*SD*); *n* (%).

[b]Kruskal-Wallis rank sum test; Pearson's Chi-squared test.

TABLE 2 The association of handgrip strength weakness and risk of pain in four cohorts.

	CHARLS			HRS			ELSA			SHARE		
Handgrip strength	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Quartiles												
Q1 (Ref)	1.00	–	–	1.00	–	–	1.00	–	–	1.00	–	–
Q2	0.88	0.81, 0.96	**0.003**	0.86	0.78, 0.95	**0.002**	0.85	0.76, 0.96	**0.011**	0.89	0.84, 0.94	**<0.001**
Q3	0.90	0.82, 0.97	**0.024**	0.88	0.79, 0.97	**0.013**	0.87	0.77, 0.99	**0.035**	0.83	0.78, 0.88	**<0.001**
Q4	0.81	0.74, 0.89	**<0.001**	0.86	0.77, 0.97	**0.011**	0.88	0.78, 0.98	**0.026**	0.78	0.73, 0.84	**<0.001**
p for trend	**<0.001**			**0.022**			0.131			**<0.001**		
Weakness versus normal strength[a]												
Weakness (Ref)	1.00	–	–	1.00	–	–	1.00	–	–	1.00	–	–
Normal strength	0.79	0.70, 0.90	**<0.001**	0.84	0.71, 0.99	**0.036**	0.78	0.64, 0.94	**0.008**	0.79	0.70, 0.88	**<0.001**
Per 5 kg increment	0.95	0.93, 0.97	**<0.001**	0.97	0.94, 0.99	**0.016**	0.96	0.94, 0.99	**0.047**	0.94	0.92, 0.95	**<0.001**

Note: All the models were adjusted for age, sex, marital status, insurance coverage, BMI, smoking status, drinking status, activity level, and history of hypertension, diabetes, heart disease, and cancer. The significant values have been bolded.

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Weakness was defined according to the Foundation for the National Institutes of Health Sarcopenia Project criteria (maximal HGS <26 kg for males and <16 kg for females).

comprehensive adjustments, the Q4 groups, representing the least weakness, were significantly associated with a reduced risk of pain compared to the Q1 groups (indicative of most weakness) across all cohorts. The hazard ratios (*HRs*) were 0.81 with a 95% confidence interval (*CI*) of (0.74, 0.89) in CHARLS, 0.86 (0.77, 0.97) in HRS, 0.88 (0.77, 0.98) in ELSA, and 0.78 (0.73, 0.84) in SHARE. In all cohorts, except for HRS, a decreasing trend in pain risk was observed across the quartile groups. Furthermore, compared to the weakness groups, the risk of pain decreased by approximately 20% in participants with normal HGS across the cohorts, with *HRs* of 0.79 (0.70, 0.90) in CHARLS, 0.84 (0.71, 0.99) in HRS, 0.78 (0.64, 0.94) in ELSA, and 0.79 (0.70, 0.88) in SHARE. Additionally, for each 5 kg increase in HGS, the hazard ratios decreased across all cohorts, with values being 0.95 (0.93, 0.97) in CHARLS, 0.97 (0.94, 0.99) in HRS, 0.96 (0.94, 0.99) in ELSA, and 0.94 (0.92, 0.95) in SHARE, respectively.

3.3 | Association between HGS asymmetry and pain

The independent associations between HGS asymmetry and pain are displayed in eTable 2—Data S1. When the HGS asymmetry ratio is set at 10%, there are no significant differences between asymmetric and symmetric HGS, except in the HRS cohort where the ratio is 1.10 (1.03, 1.18). At asymmetry ratios of 20% or 30%, asymmetric HGS is associated with a higher risk of pain compared to symmetric HGS; however, this effect is not statistically significant in the majority of groups. Notably, only when the HGS asymmetry ratio reaches 30% in the SHARE cohort, does the risk of pain increase significantly by 12% (1.12 (1.05, 1.21)).

3.4 | Association between weakness and asymmetry of HGS and pain

When the HGS asymmetry ratio is set at 10%, participants with only asymmetry exhibit a lower risk of pain compared to those with both weak and asymmetric HGS, although these results are not significant in most groups. Additionally, no clear relationship is evident in participants with only weak HGS and symmetric HGS. In contrast, individuals with normal and symmetric HGS consistently exhibit a lower risk of pain across all cohorts, with hazard ratios of 0.76 (0.67, 0.88) in CHARLS, 0.82 (0.71, 0.95) in HRS, 0.80 (0.65, 0.98) in ELSA, and 0.86 (0.75, 0.98) in SHARE. Similar results are observed when the asymmetry ratio is increased to 20% or 30%. Across all cohorts, no significant interaction is observed between weak HGS and asymmetry, with P for interaction exceeding 0.05. The detailed results are displayed in Table 3.

3.5 | Sensitivity analyses

We employed multiple imputation to address the missing data, and the associations remained consistent with the original results across all cohort studies (eTables and 4—Data S1). After additional adjustment for mental and cognitive disorders, the association between HGS weakness and pain was attenuated but remained significant (eTable 5—Data S1). We applied the Fine-Gray model to replicate the analyses, and the associations persisted (eTable 6—Data S1). Employing different weakness criteria, the results remained stable (eTable 7—Data S1). The results of the subgroup analysis pertaining to weak HGS and pain risk demonstrated consistent findings across all cohorts (eFigure 2—Data S1).

TABLE 3 The combined association of HGS weakness and asymmetry with risk of pain in four cohorts.

	CHARLS			HRS			ELSA			SHARE		
Characteristic	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
HGS asymmetry ratio at 10%												
Weakness and asymmetry	1.00	—		1.00	—		1.00	—		1.00	—	
Normal and asymmetry	0.97	0.86, 1.08	0.615	0.93	0.77, 1.13	0.522	0.90	0.75, 1.07	0.254	0.85	0.77, 0.94	**0.001**
Weakness and symmetry	0.93	0.82, 1.05	0.325	1.05	0.89, 1.25	0.558	1.02	0.85, 1.23	0.856	1.10	0.98, 1.23	0.125
Normal and symmetry	0.76	0.67, 0.88	**<0.001**	0.82	0.71, 0.95	**0.009**	0.80	0.65, 0.98	**0.028**	0.86	0.75, 0.98	**0.026**
p for interaction	0.321			0.523			0.812			0.125		
HGS asymmetry ratio at 20%												
Weakness and asymmetry	1.00	—		1.00	—		1.00	—		1.00	—	
Normal and asymmetry	0.93	0.80, 1.07	0.362	0.91	0.77, 1.07	0.278	0.95	0.76, 1.19	0.743	0.85	0.76, 0.96	**0.006**
Weakness and symmetry	0.95	0.83, 1.09	0.556	1.14	0.97, 1.35	0.112	0.93	0.77, 1.14	0.514	1.05	0.94, 1.17	0.455
Normal and symmetry	0.82	0.72, 0.93	**0.002**	0.78	0.66, 0.93	**0.005**	0.79	0.66, 0.95	**0.011**	0.82	0.74, 0.91	**<0.001**
p for interaction	0.532			0.112			0.512			0.423		
HGS asymmetry ratio at 30%												
Weakness and asymmetry	1.00	—		1.00	—		1.00	—		1.00	—	
Normal and asymmetry	0.99	0.81, 1.20	0.912	0.87	0.69, 1.09	0.214	0.91	0.65, 1.26	0.640	0.79	0.68, 0.92	**0.002**
Weakness and symmetry	0.87	0.74, 1.03	0.112	1.07	0.87, 1.31	0.513	0.92	0.71, 1.21	0.621	1.04	0.91, 1.18	0.664
Normal and symmetry	0.86	0.74, 0.99	**0.039**	0.84	0.72, 1.0	**0.043**	0.85	0.69, 1.04	0.115	0.85	0.76, 0.95	**0.003**
p for interaction	0.111			0.523			0.623			0.634		

Note: All the models were adjusted for age, sex, marital status, insurance coverage, BMI, smoking status, drinking status, activity level, and history of hypertension, diabetes, heart disease, and cancer. The significant values have been bolded.

Abbreviations: CI, confidence interval; HR, hazard ratio.

4 | DISCUSSION

This study is the first to conduct a cross-cultural and longitudinal investigation into the association between HGS weakness, asymmetry, and the risk of incident pain in later life among middle-aged and older individuals. Our findings indicate that a weak HGS significantly increases the risk of pain across all cohorts; however, the relationship between HGS asymmetry and pain risk is not clearly established. Additionally, we observed no interaction effect between HGS weakness and asymmetry in terms of pain risk across all cohorts.

Although previous studies have characterized HGS as a straightforward yet potent predictor of future disability, morbidity, and mortality, comparatively little evidence exists regarding its impact on pain among middle-aged and older individuals.[25,26] Moreover, Sayer et al. highlighted the need for further investigation to determine whether the relationship between HGS and health outcomes is consistent across countries with diverse socioeconomic conditions.[27] Our research clearly indicates that significant differences in HGS exist among middle-aged and older populations across various countries. However, the early detection and amelioration of weak HGS can potentially help mitigate the risk of subsequent pain in middle-aged and older adults, a factor that is significant across various socio-economic backgrounds. Nonetheless, it is important to note that the inverse correlation between HGS and pain risk (i.e., the stronger the HGS, the lower the risk of pain) diminishes above a certain threshold of HGS. By employing two criteria, we have demonstrated that categorizing HGS as "weak" or "normal" remains a robust indicator of pain risk across four cohorts.

Weak HGS can potentially increase the risk of pain through several pathways. First, weak HGS reflects a decrease in muscle mass and quality, potentially leading to increased physical stress on other body parts and heightened pain risk.[28] Second, weak HGS is frequently correlated with metabolic issues, such as insulin resistance, which involves fat accumulation in muscles, impairing muscle function and thereby increasing pain sensitivity.[29] Additionally, HGS weakness is associated with functional limitations that can result in injuries and an overreliance on other muscle groups, leading to overuse injuries.[30] Lastly, it may indicate a chronic inflammatory state that can damage muscle tissues and further reduce muscle functionality, thus contributing to enhanced pain perception.[31,32]

Regarding the relationship between HGS asymmetry and pain risk, current research has not established a direct correlation. Our research did not reveal a significant relationship between HGS asymmetry and pain risk, and these findings were significant only in a small subset of the group, aligning with previous research. Chen et al. demonstrated that low HGS, rather than asymmetry, is associated with functional mobility.[33] Several studies have reported that older individuals with HGS asymmetry face a higher risk of neurodegenerative diseases.[34,35] Previous research has shown that HGS asymmetry may suggest different activation of the cerebral hemispheres and an imbalance in neural function.[36] However, the relationship between HGS asymmetry and pain is complex, and the underlying mechanisms require further investigation. Simultaneously, HGS asymmetry may be more difficult to observe accurately because it likely occurs prior to weakness, which may explain the observed inconsistencies with pain. Our findings suggest that using HGS asymmetry as a predictive indicator of pain risk necessitates establishing different standards of HGS asymmetry for diverse populations.

Moreover, the combined analysis of weak and asymmetrical HGS indicates that weakness in HGS may serve as an effective indicator for screening pain risk in middle-aged and older adults, while HGS asymmetry might not be suitable. However, this finding contrasts with previous studies, which suggest that the combination of HGS asymmetry and weakness could be a more effective method of assessing health risks.[36,37] We propose that the reasons for these differences are as follows: (1) HGS asymmetry is more closely related to physical and brain cognitive functions, with a less direct relationship to pain. (2) The "10% rule" used as a threshold for HGS asymmetry might not be appropriate for all populations with diverse backgrounds. Compared to HGS weakness, fewer studies have explored the relationship between HGS asymmetry and health outcomes; therefore, validating its effectiveness in larger samples and more diverse populations is essential.

This study exhibits several strengths: (1) It included four prospective cohorts from diverse ethnicities with rigorous study designs and large sample sizes. (2) Results were consistent across the four cohorts, demonstrating the generalizability of our findings. (3) Asymmetry was investigated not only at a HGS ratio of 10%, as defined by previous studies, but also at 20% and 30%. (4) Diverse sensitivity analyses further confirmed the robustness of our results. However, the study has several limitations: (1) Reliance on self-reported data may introduce recall bias. (2) Assessment of covariates such as physical activity at a single time point does not consider potential variation over time. (3) Significant social factors were not measured, highlighting directions for future research. (4) In the ELSA, death data were available only up to wave 6, whereas outcome data were followed up to wave 9. (5) In various cohorts, factors such as the frequency of HGS measurements, the tools used, and the measurer's posture may influence the measurement of HGS.(6) Only overall pain was analyzed, without further analysis on pain in specific body parts or the causes of pain, necessitating additional research for further refinement. (7) Since this study uses multiple datasets, the lack of data harmonization may result in inconsistencies in the measurements, making it challenging to compare results across different datasets.

5 | CONCLUSION

In four prospective cohorts, it was found that middle-aged and older adults with HGS weakness are at a higher risk of future pain. HGS, recognized as a safe and expedient method for assessing muscle function, may be considered an effective approach for early screening of individuals at higher risk of pain and for interventions targeted at improving muscle strength. However, HGS asymmetry has not shown a clear relationship

with pain, highlighting the need for further research to supplement and verify these findings.

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 and Terry Jianguo Zhan: Supervision, funding acquisition. All authors approved the final version to be published.

ACKNOWLEDGMENTS

We appreciate the publicly available database resources provided by the CHARLS, HRS, ELSA, and SHARE cohorts.

FUNDING INFORMATION

This research was funded in part by the National Key Research and Development Program of China (2023YFC2507700 to J.Z. and N.W.), National Natural Science Foundation of China (82,072,391 to N.W., 81,930,068 to Z.W., 82,172,525 to G.Q., 82,172,382 to J.Z.), National High Level Hospital Clinical Research Funding (2022-PUMCH-D-004 to J.Z. and N.W., 2022-PUMCH-C-033 to N.W., 2022-PUMCH-D-002 to Z.W.), and CAMS Innovation Fund for Medical Sciences (CIFMS, 2021-I2M-1-051 to J.Z. and N.W., 2021-I2M-1-052 and 2022-I2M-2-001 to Z.W., 2023-I2M-C&T-A-003 to J.Z.).

CONFLICT OF INTEREST STATEMENT

The authors declare no financial support or other benefits from commercial sources for the work reported on in the manuscript, or any other financial interests that any of the authors may have, which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work.

DATA AVAILABILITY STATEMENT

The data used to generate the results in this study were obtained from the Health and Retirement Study (HRS); the English Longitudinal Study of Ageing (ELSA); the Survey of Health, Ageing and Retirement in Europe (SHARE); and the China Health and Retirement Longitudinal Study (CHARLS) which are publicly available.

ETHICS STATEMENT

All cohorts had already obtained local ethical approvals, specific details of which can be found on their official websites.

PATIENT CONSENT

Not applicable.

SUBMISSION STATEMENT

The work described has not been published previously.

ROLE OF THE FUNDER/SPONSOR

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

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

CLINICAL TRIAL REGISTRATION

Not applicable.

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REFERENCES

1. Reid MC, Eccleston C, Pillemer K. Management of chronic pain in older adults. *BMJ*. 2015;350:h532. doi:10.1136/bmj.h532
2. Qiu Y, Li H, Yang Z, et al. The prevalence and economic burden of pain on middle-aged and elderly Chinese people: results from the China health and retirement longitudinal study. *BMC Health Serv Res*. 2020;20(1):600. doi:10.1186/s12913-020-05461-6
3. Goyal AK, Mohanty SK. Association of pain and quality of life among middle-aged and older adults of India. *BMC Geriatr*. 2022;22(1):939. doi:10.1186/s12877-022-03480-y
4. Bohannon RW. Grip Strength: An Indispensable Biomarker For Older Adults. *Clin Interv Aging*. 2019;14:1681-1691. doi:10.2147/cia.S194543
5. Norman K, Stobäus N, Gonzalez MC, Schulzke JD, Pirlich M. Hand grip strength: outcome predictor and marker of nutritional status. *Clin Nutr*. 2011;30(2):135-142. doi:10.1016/j.clnu.2010.09.010
6. Celis-Morales CA, Welsh P, Lyall DM, et al. Associations of grip strength with cardiovascular, respiratory, and cancer outcomes and all cause mortality: prospective cohort study of half a million UK biobank participants. *BMJ*. 2018;361:k1651. doi:10.1136/bmj.k1651
7. Celis-Morales CA, Petermann F, Hui L, et al. Associations between diabetes and both cardiovascular disease and all-cause mortality are modified by grip strength: evidence from UK biobank, a prospective population-based cohort study. *Diabetes Care*. 2017;40(12):1710-1718. doi:10.2337/dc17-0921
8. Mahoney SJ, Hackney KJ, Jurivich DA, Dahl LJ, Johnson C, McGrath R. Handgrip strength asymmetry is associated with limitations in individual basic self-care tasks. *J Appl Gerontol*. 2022;41(2):450-454. doi:10.1177/0733464820982409
9. Go YJ, Lee DC, Lee HJ. Association between handgrip strength asymmetry and falls in elderly Koreans: A nationwide population-based cross-sectional study. *Arch Gerontol Geriatr*. 2021;96:104470. doi:10.1016/j.archger.2021.104470
10. Sonnega A, Faul JD, Ofstedal MB, Langa KM, Phillips JW, Weir DR. Cohort profile: the health and retirement study (HRS). *Int J Epidemiol*. 2014;43(2):576-585. doi:10.1093/ije/dyu067
11. Banks J, Batty GD, Breedvelt J, et al. English longitudinal study of ageing: waves 0-10, 1998-2023. *UK Data Service*. 2024;12:113-125. 10.5255/UKDA-SN-5050-27
12. Börsch-Supan A, Brandt M, Hunkler C, et al. Data resource profile: the survey of health, ageing and retirement in Europe (SHARE). *Int J Epidemiol*. 2013;42(4):992-1001. doi:10.1093/ije/dyt088

13. Zhao Y, Hu Y, Smith JP, Strauss J, Yang G. Cohort profile: the China health and retirement longitudinal study (CHARLS). *Int J Epidemiol*. 2014;43(1):61-68. doi:10.1093/ije/dys203
14. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. *PLoS Med*. 2007;4(10):e297. doi:10.1371/journal.pmed.0040297
15. Germain CM, Vasquez E, Batsis JA, McQuoid DR. Sex, race and age differences in muscle strength and limitations in community dwelling older adults: data from the health and retirement survey (HRS). *Arch Gerontol Geriatr*. 2016;65:98-103. doi:10.1016/j.archger.2016.03.007
16. Li G, Lu Y, Shao L, et al. Handgrip strength is associated with risks of new-onset stroke and heart disease: results from 3 prospective cohorts. *BMC Geriatr*. 2023;23(1):268. doi:10.1186/s12877-023-03953-8
17. 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(5):576-583. doi:10.1093/gerona/glu012
18. McGrath R, Tomkinson GR, LaRoche DP, Vincent BM, Bond CW, Hackney KJ. Handgrip strength asymmetry and weakness may accelerate time to mortality in aging Americans. *J Am Med Dir Assoc*. 2020;21(12):2003-2007. doi:10.1016/j.jamda.2020.04.030
19. Parker K, Rhee Y, Tomkinson GR, Vincent BM, O'Connor ML, McGrath R. Handgrip weakness and asymmetry independently predict the development of new activity limitations: results from analyses of longitudinal data from the US health and retirement study. *J Am Med Dir Assoc*. 2021;22(4):821-826. doi:10.1016/j.jamda.2020.11.006
20. de Lima TR, Silva DAS, de Castro JAC, Christofaro DGD. Handgrip strength and associated sociodemographic and lifestyle factors: A systematic review of the adult population. *J Bodyw Mov Ther*. 2017;21(2):401-413. doi:10.1016/j.jbmt.2016.08.017
21. Beesley LJ, Bondarenko I, Elliot MR, Kurian AW, Katz SJ, Taylor JM. Multiple imputation with missing data indicators. *Stat Methods Med Res*. 2021;30(12):2685-2700. doi:10.1177/09622802211047346
22. Nahman-Averbuch H, Nir RR, Sprecher E, Yarnitsky D. Psychological factors and conditioned pain modulation: A meta-analysis. *Clin J Pain*. 2016;32(6):541-554. doi:10.1097/ajp.0000000000000296
23. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. *Stat Med*. 2017;36(27):4391-4400. doi:10.1002/sim.7501
24. Chen LK, Woo J, Assantachai P, et al. Asian working Group for Sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. *J Am Med Dir Assoc*. 2020;21(3):300-307. doi:10.1016/j.jamda.2019.12.012
25. Liu CJ, Marie D, Fredrick A, Bertram J, Utley K, Fess EE. Predicting hand function in older adults: evaluations of grip strength, arm curl strength, and manual dexterity. *Aging Clin Exp Res*. 2017;29(4):753-760. doi:10.1007/s40520-016-0628-0
26. Leong DP, Teo KK, Rangarajan S, et al. Prognostic value of grip strength: findings from the prospective Urban rural epidemiology (PURE) study. *Lancet*. 2015;386(9990):266-273. doi:10.1016/s0140-6736(14)62000-6
27. Sayer AA, Kirkwood TB. Grip strength and mortality: a biomarker of ageing? *Lancet*. 2015;386(9990):226-227. doi:10.1016/s0140-6736(14)62349-7
28. Xu HQ, Shi JP, Shen C, Liu Y, Liu JM, Zheng XY. Sarcopenia-related features and factors associated with low muscle mass, weak muscle strength, and reduced function in Chinese rural residents: a cross-sectional study. *Arch Osteoporos*. 2018;14(1):2. doi:10.1007/s11657-018-0545-2
29. Park SH, Kim DJ, Plank LD. Association of grip strength with non-alcoholic fatty liver disease: investigation of the roles of insulin resistance and inflammation as mediators. *Eur J Clin Nutr*. 2020;74(10):1401-1409. doi:10.1038/s41430-020-0591-x
30. Zeng P, Han Y, Pang J, et al. Sarcopenia-related features and factors associated with lower muscle strength and physical performance in older Chinese: a cross sectional study. *BMC Geriatr*. 2016;16:45. doi:10.1186/s12877-016-0220-7
31. Kidd BL, Urban LA. Mechanisms of inflammatory pain. *Br J Anaesth*. 2001;87(1):3-11. doi:10.1093/bja/87.1.3
32. Breitinger U, Breitinger H-G. Excitatory and inhibitory neuronal signaling in inflammatory and diabetic neuropathic pain. *Mol Med*. 2023;29(1):53. doi:10.1186/s10020-023-00647-0
33. Chen KK, Lee SY, Pang BWJ, et al. Associations of low handgrip strength and hand laterality with cognitive function and functional mobility—the Yishun study. *BMC Geriatr*. 2022;22(1):677. doi:10.1186/s12877-022-03363-2
34. Chen Z, Ho M, Chau PH. Handgrip strength asymmetry is associated with the risk of neurodegenerative disorders among Chinese older adults. *J Cachexia Sarcopenia Muscle*. 2022;13(2):1013-1023. doi:10.1002/jcsm.12933
35. McGrath R, Cawthon PM, Cesari M, Al Snih S, Clark BC. Handgrip strength asymmetry and weakness are associated with lower cognitive function: A panel study. *J Am Geriatr Soc*. 2020;68(9):2051-2058. doi:10.1111/jgs.16556
36. Cui M, Zhang S, Liu Y, Gang X, Wang G. Grip strength and the risk of cognitive decline and dementia: A systematic review and meta-analysis of longitudinal cohort studies. *Front Aging Neurosci*. 2021;13:625551. doi:10.3389/fnagi.2021.625551
37. Jia S, Zhao W, Ge M, et al. Association of Handgrip Strength Weakness and Asymmetry with Incidence of motoric cognitive risk syndrome in the China health and retirement longitudinal study. *Neurology*. 2023;100(23):e2342-e2349. doi:10.1212/wnl.0000000000207308

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Zhu Y, Zhang H, Zhang TJ, Wu N. Association of handgrip strength weakness and asymmetry with later life pain risk in middle-aged and older individuals: Results from four prospective cohorts. *Aging Med*. 2024;7:596-605. doi:10.1002/agm2.12365