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Handgrip strength asymmetry is associated with the risk of neurodegenerative disorders among Chinese older adults

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Abstract

Background Neurodegenerative disorders, as the irreversible condition, have a long, silent preclinical period. Recognition of early physical signs of neurodegenerative disorders had important practical implications for identifying at-risk population. The aim of this study was to investigate whether handgrip strength (HGS) asymmetry was associated with the incidence of neurodegenerative disorders among Chinese older adults.

Methods This study used the data of participants aged 60 years and over from three waves (2011–2015) of China Health and Retirement Longitudinal Study. HGS asymmetry was measured with HGS ratio (maximal non-dominant HGS/maximal dominant HGS), with the value less than 0.9 or more than 1.1 considered as HGS asymmetry. Physician-diagnosed neurodegenerative disorders were identified by self-reported or proxy-reported information. Competing risk analysis was conducted to examine the association between HGS asymmetry and incident neurodegenerative disorders, with mortality treated as the competing event.

Results A total of 4925 participants were included in the analysis [mean (SD) age: 68.1(6.68); female: 49.7%]. Eight hundred and eighty-eight (18.0%) participants had low HGS and 2227 (45.2%) had HGS asymmetry. During the 4 years of follow-up, there were 156 cases of neurodegenerative disorders and 422 cases of mortality. The incidence of neurodegenerative disorders was 8.7 per 1000 person-years [95% confidence interval (CI): 7.4–10.2], and the incidence of mortality was 23.5 per 1000 person-years (95% CI: 21.4–25.9). Both the cause-specific model and the Fine–Gray subdistribution hazard model showed that participants with HGS asymmetry had increased hazard of neurodegenerative disorders [hazard ratio (HR) = 1.66, $P = 0.002$, 95% CI: 1.202–2.297; subdistribution hazard ratio (SHR) = 1.65, $P = 0.002$, 95% CI: 1.202–2.285]. Low HGS, but not HGS asymmetry, was related to the higher hazard of mortality (HR = 1.61, $P < 0.001$, 95% CI: 1.297–1.995; SHR = 1.58, $P < 0.001$, 95% CI: 1.286–1.951).

Conclusions Handgrip strength asymmetry was associated with the future risk of neurodegenerative disorders among Chinese older adults. Public healthcare providers could consider examining HGS asymmetry along with the maximal HGS as a way to identify those at elevated risk of neurodegenerative disorders.

Keywords Functional laterality; Muscle strength; Neurodegenerative disorders

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Introduction

Age-related neurodegenerative disorders, such as Parkinson's diseases (PD), Alzheimer's disease and other dementias, are posing increasing burdens to families and healthcare systems.[1,2] According to a systematic analysis for the Global Burden of Disease study 2016, neurodegenerative disorders ranked as the leading cause of disability-adjusted life-years (DALYs), contributing to nearly 11.6% of DALYs worldwide.[3] A recent national investigation reported the overall prevalence of dementia among Chinese adults aged 60 years and over was 6.0%, representing nearly 15 million people.[4] Based on an updated meta-analysis, the prevalence of PD in China was nearly 1.1% among older adults.[5] Individuals with neurodegenerative disorders usually experience a long asymptomatic period prior to diagnosis. However, by the point at which the diagnosis is confirmed, severe and irreversible damage to the nervous system has already occurred.[6,7] At present, neurodegenerative disorders are incurable and irreversible. Therefore, early identification of vulnerable groups and interventions targeting modifiable risk factors, preferably at the asymptomatic stage, are urgently needed. This urgency is promoted by the importance not only of preventing or delaying the occurrence of neurogenerative disorders but also of postponing the progression of the disease, and thus avoiding a series of potential complications.[8]

Many studies have investigated the modifiable risk factors of neurodegenerative disorders, such as lifestyle-related behaviours and health conditions.[8,9] More recently, growing evidence has indicated an association between low handgrip strength (HGS) and accelerated decline in neurocognitive function among middle-aged and older adults.[10,11] In terms of mechanism, the grip force generated during HGS assessments is partly regulated by the neural system that mediates the control of coordinated movements.[12] Therefore, the maximal HGS is postulated to partly reflect the functioning of the neural system or brain health.[12] Besides that, the difference in HGS between hands, as characterized by an asymmetrical deficit in HGS, has recently been proposed as a potential indicator of decreased cognitive function and functional disability.[13,14] It is generally known that the human body exhibits laterality, with the dominant and non-dominant side. The difference in strength between the dominant and non-dominant hand or leg exists even in healthy individuals.[15] Humans tend to use their dominant hands more frequently for daily activities, and the dominant side often demonstrates better motor performance than the non-dominant side.[16] However, a large motor asymmetry in functional performance between hands may indicate the deficit in neural system functioning or imbalance in brain hemisphere activation.[13,16,17] For example, McGrath *et al*. found that HGS asymmetry was independently associated with future impairment of instrumental activities of daily living (IADLs) and decreased cognitive function.[13,14] These findings support a possible link between HGS asymmetry and declines in neurocognitive function.

Unlike maximal HGS, HGS asymmetry may reflect another aspect of strength capacity, namely strength imbalance.[18] According to McGrath *et al*., HGS asymmetry is defined based on the HGS ratio, the ratio between the maximal non-dominant HGS and maximal dominant HGS.[13] Current protocols of HGS testing already recommend collecting information on hand dominance and multiple measures of HGS for both hands.[19] Therefore, HGS asymmetry can be easily evaluated by using the data obtained during standard HGS assessments. Recently, research on HGS asymmetry and its possible association with future health-related outcomes, such as functional disability and cognitive decline, has been increasing.[13,14,18] However, little is known about whether HGS asymmetry was associated with the incidence of neurodegenerative disorders. Therefore, the purpose of this study was to examine whether HGS asymmetry was associated with the incidence of physician-diagnosed neurodegenerative disorders among Chinese adults aged 60 years and over.

Methods

Data source

This study used data from the China Health and Retirement Longitudinal Study (CHARLS), an ongoing longitudinal survey of a nationally representative sample of Chinese adults aged 45 years and over. Details of the CHARLS have been documented elsewhere.[20] Briefly, the baseline survey (Wave 1) of the CHARLS was conducted in 2011, involving 17 708 respondents (response rate: 80.5%) from 28 Chinese provinces. Subsequent follow-up with these participants has occurred every 2 years, with the first follow-up survey (Wave 2) in 2013 and the second (Wave 3) in 2015. The original CHARLS researchers obtained ethical approval for the data collection from the Biomedical Ethics Review Committee of Peking University (IRB00001052–11015).

Participants

In this study, we included data from participants aged 60 years and over at Wave 1 (baseline). We excluded participants with a history of physician-diagnosed psychiatric problems or neurodegenerative disorders at baseline. We also excluded those who had missing data on the main independent variable (HGS asymmetry) or the main outcome variable of interest (neurodegenerative disorders) at baseline. Furthermore, to reduce the uncertainty in identifying the onset time of events, we excluded participants who did not experience the competing event (mortality) but had missing infor-

mation to determine whether the main outcome (neurodegenerative disorders) occurred at Wave 2.

Measures

Maximum handgrip strength

In the CHARLS, HGS is measured with the mechanical dynamometer (YuejianTM WL-1000, Nantong, China). According to the manufacturer, the precision of this type of dynamometer was ±3% (http://www.ntyuejian.com/3e/4.htm). In the present study, this dynamometer showed satisfactory test–retest reliability for both hands (interclass correlation: 0.94 for the left hand; 0.95 for the right hand). Those who have experienced the surgery, inflammation, severe pain, or injury on one or both hands in the preceding 6 months are not asked to complete the HGS testing. After reporting their hand dominance, participants are instructed to bend the elbow at 90° angle and squeeze the dynamometer as hard as they can for a couple of seconds. Those unable to stand unassisted can complete the test while seated. The test is conducted twice on each hand, and the maximum reading from all four tests is used to reflect HGS. The HGS is coded as missing if the participants cannot complete the test for either hand (i.e., the maximal HGS on the one hand is zero). According to the Asian Work Group for Sarcopenia 2019 consensus, low HGS is defined as the maximum HGS less than 28 kg in men and less than 18 kg in women.[21]

Handgrip strength asymmetry

The percent difference in HGS between hands is calculated as the ratio of the maximal non-dominant HGS and maximal dominant HGS (non-dominant HGS/dominant HGS).[22] Following previous literature, the '10% rule', the general 10% difference in HGS between dominant and non-dominant hand, was applied to define the HGS asymmetry.[13,15] That is, participants with the ratio less than 0.9 or more than 1.1 were classified as having HGS asymmetry.

Physician-diagnosed neurodegenerative disorders

In CHARLS, physician-diagnosed neurodegenerative disorders are determined through a self-reported question asking participants whether they have been diagnosed with any neurodegenerative disorders (e.g. dementia, brain atrophy or Parkinson's disease) by a doctor. The onset time was estimated as the midpoint of the time interval between the last wave when the participant was free of neurodegenerative disorders and the next wave in which the new diagnosis was recorded.

Mortality

Due to increasing age and comorbidities among older populations, mortality is an important source of censoring in geriatric cohort studies.[23] Mortality occurring before the occurrence of the main outcome can be considered a competing event that precludes the onset of the main outcome. Therefore, to obtain more accurate estimates, the competing event of mortality was considered in our examination of the association between HGS asymmetry and the incidence of neurodegenerative disorders. Participants enrolled at baseline were followed up in two subsequent waves. At Wave 2, death information, including death status and death time, was collected. However, at Wave 3, only the death status was recorded. To be consistent with our method of estimating the onset time of neurodegenerative disorders, the time of mortality was calculated as the midpoint of the time interval between the previous wave and the one in which the mortality was recorded.

Demographic characteristics

Demographic characteristics from the baseline of the CHARLS were extracted. Age was divided into three subgroups: 60 to 69, 70 to 79, and 80 and above. We categorized participants' highest education level into three groups: primary school and below, secondary school, and high school and above. Marital status was dichotomized into either (1) married or (2) single, divorced, or widowed. Rural or urban residence was determined based on the administrative divisions established by the National Bureau of Statistics China.[24]

Lifestyle-related behaviours

Baseline data on lifestyle-related behaviours, including smoking and drinking status, physical activity, social participation, and sleep duration, were considered. Smoking and drinking status were grouped into three categories (never, ever but quit and current usage). Participants were considered as having moderate to vigorous physical activity (MVPA) if they reported engaging in such activity for at least 10 min in a usual week.[13] Social participation was determined based on whether participants reported having taken part in any of the following activities in the past month: interacting with friends; playing mah-jongg, chess, or cards; going to the sport, social, or other kind of club; participating in a community-related organization; caring for sick or disabled adults; doing voluntary or charity work; attending the educational or training courses; investing in stocks; using the Internet and other social activities. Sleep duration was categorized into three groups: short ($<$7 h), normal (7–9 h) and long time ($\geq$9 h).[25]

Health conditions

Body mass index (BMI) was calculated as weight in kilogrammes divided by the square of height in metres. BMI status was categorized into four groups: obese (BMI $\geq$ 25), overweight (23 $\leq$ BMI $<$ 25), normal (18.5 $\leq$ BMI $<$ 23) and underweight (BMI $<$ 18.5).[26] Chronic conditions, such as cardiovascular diseases (viz. heart disease and stroke), hypertension and metabolic disorders (viz. dyslipidaemia and diabetes), which have been reported as risk factors of neurodegenerative disorders, were considered in our study.[8]

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Cognitive status was assessed using 10 mental status items from the Telephone Interview of Cognitive Status (TICS-10), which includes tasks about identifying today's date (month, day and year), the day of the week, and the season of the year, along with the serial 7 subtraction task that involves subtracting from 100 up to five times. The total score is the sum of correct answers (ranging from 0 to 10).[27] Depression was measured with the validated 10-item Center for Epidemiologic Studies Depression Scale short form.[28] Participants were asked to rate the frequency with which each mood or symptom occurred in the preceding week. Each item score could range from 0 to 3. The total score was calculated by summing all item scores after reversing two items that were positively formulated (items 5 and 8). A total score greater than or equal to 12 indicated depression.[28] Furthermore, participants were asked to rate their general health status using a single item. Following the previous study, self-rated health was dichotomized into two categories: (1) good and above or (2) poor/fair.[29]

Statistical analysis

Descriptive analysis was used to present the baseline characteristics of the analytical sample. Baseline characteristics were compared between subjects with and without HGS asymmetry. The main outcome of interest in this study was the time to onset of physician-diagnosed neurodegenerative disorders among older adults. However, in this study, some participants might die before receiving a diagnosis of a neurodegenerative disorders, thereby preventing the main event of interest from happening. These deaths would decrease the actual number of neurodegenerative disorders, which accordingly influenced the probability of the events of neurodegenerative disorders.[30] Hence, in this study, death before the diagnosis of a neurodegenerative disorder was regarded as the competing event. In survival analysis, ignoring competing risks may overestimate the incidence of the event of interest especially when the competing risk is high.[30] Accordingly, we employed competing risk analysis to examine the adjusted association between baseline HGS asymmetry and the risk of neurodegenerative disorders, taking account of the competing risk of mortality. In the context of competing event, the time of event was calculated as the midpoint of the time interval between the wave of no diagnosed neurodegenerative disorders and death until the wave of first event occurred, either the diagnosis of a neurodegenerative disorder or death without a neurodegenerative disorder diagnosis.

The cause-specific hazard model and Fine–Gray model are commonly used approaches to analyse competing risk endpoints. The cause-specific hazard model estimates the hazard of an event of interest by excluding individuals from the risk set from the moment of the onset of a competing event; that is, competing events are treated as censored observations.[31] The Fine–Gray model, also known as the subdistribution hazard model, estimates the effect of covariates on the cumulative incidence function for the event of interest while taking competing events into account.[30] Those who experienced a competing event would remain in the risk set, but with no chance of experiencing the event of interest.[30] This apparently unnatural setting is necessary to establish the direct association between covariates and the cumulative incidence function.[30] As suggested by Latouche *et al*.,[31] in order to gain a complete understanding of the relationship between covariates and competing endpoints, both the cause-specific hazard model and the Fine–Gray subdistribution hazard model should be fitted for both the outcome of interest and the competing event. Hence, in this study, both models were fitted for the incidence of neurodegenerative disorders and mortality separately, adjusted for socio-demographic characteristics, lifestyle-related behaviours, health conditions and maximal HGS. The cause-specific hazard ratio (HR, for the cause-specific model) and the subdistribution hazard ratio (SHR, for the Fine–Gray model) with 95% confidence intervals (CIs) were presented.

The proportional hazard assumption for these models was checked by testing the significance of the time-by-covariate interaction, with significant interactions indicating violations of the proportional hazard assumption for the covariate being interacted with time.[31] If there was evidence of non-proportionality, the interaction term between time and the covariates violating the proportional assumption would be included in the model.[30]

Missing data were present in some baseline covariates. Among the final analytical sample, missing data were present in the following covariates: education level (0.1%), smoking status (0.7%), drinking status (0.1%), MVPA participation (58.6%), social participation (1.4%), sleep duration (2.5%), BMI (1.8%), cardiovascular diseases (0.5%), hypertension (0.3%), metabolic disorders (1.7%), TICS-10 score (1.9%) and depression (7.5%). The large proportion of missing data with regard to MVPA participation arose because data on physical activity were collected only from a random subgroup of almost two-fifths of all CHARLS participants. Therefore, it was safe to assume that the data were missing at random (MAR). Previous evidence has suggested that when compared with complete data analysis, valid multiple imputation reduced bias even when the proportion of missingness was large (60% and above) for MAR data.[32] Accordingly, in this study, multiple imputation with 10 times using chained equation model was performed to impute those covariates with missing values.[33] We performed all above models using the imputed dataset as the main results of the study.

Two sensitivity analyses were conducted to test the robustness of the results. First, all above models were repeated using the complete dataset with no missing values in all baseline covariates. Second, due to the large proportion of missing data in MVPA participation, all above models, but

with MVPA participation excluded, were repeated with the complete dataset. All analyses were performed using ming Significance was set at the 0.05 level, using two-tailed tests.

Results

Sample characteristics

At baseline, there were 7669 participants aged 60 years and over. Among those, 124 had psychiatric problems, 308 had physician-diagnosed neurodegenerative disorders or had missing information with regard to neurodegenerative disorders. After excluding those with missing data on HGS (n = 1553) and HGS asymmetry (n = 328, including 266 ambidextrous respondents and 62 persons with no hand dominance information), there remained 5356 participants at baseline. We further excluded those with missing information on neurodegenerative disorders but who did not experience the competing event (mortality) at Wave 2 (n = 431). Therefore, a total of 4925 participants were included in our analysis.

Baseline characteristics for the analytical sample were presented in Table 1. The mean age was 68.1 ± 6.68 years. Of the 4925 participants, 18.0% had low HGS, and 45.2% had HGS asymmetry. Participants with HGS asymmetry at baseline were more female (P = 0.001), generally older ($P < 0.001$), had a lower TICS-10 score ($P < 0.001$), and had the higher proportion of low HGS ($P < 0.001$), no MVPA participation (P = 0.019), cardiovascular diseases (P = 0.005), metabolic disorders (P = 0.049), depression (P = 0.009), and poor or fair self-rated health ($P < 0.001$) (Table 2).

At the end of the follow-up, there were 156 cases of neurodegenerative disorders and 422 cases of mortality. The incidence rate of neurodegenerative disorders was 8.7 (95% CI: 7.4–10.2) per 1000 person-years. The incidence rate of mortality was 23.5 (95% CI: 21.4–25.9) per 1000 person-years.

Cause-specific hazard model

As shown in Table 3, HGS asymmetry was independently associated with a 66% increase in the hazard of neurodegenerative disorders (HR = 1.66, 95% CI: 1.202–2.297). Though participants with low HGS showed increased risk of neurodegenerative disorders (HR = 1.29, 95% CI: 0.886 – 1.886), the statistical significance was not reached.

For the competing event of mortality, among participants who were alive and free of neurodegenerative disorders, HGS asymmetry was not significantly associated with the

Table 1 Characteristics of study sample at baseline (n = 4925)

Characteristics	Freq	(%)
HGS		
Normal	4037	82.0
Low	888	18.0
HGS asymmetry		
No	2698	54.8
Yes	2227	45.2
Gender		
Female	2446	49.7
Male	2479	50.3
Age		
60–70	3152	64.0
70–80	1428	29.0
80 and over	345	7.0
Education		
Primary school and below	4100	83.3
Secondary school	552	11.2
High school and above	269	5.5
Marriage		
Married	3875	78.7
Single, divorced or widowed	1050	21.3
Residence		
Urban	1688	34.3
Rural	3237	65.7
Smoking status		
Never	2791	57.0
Ever but quit	571	11.7
Current smoke	1530	31.3
Drinking status		
Never	2858	58.1
Ever but quit	551	11.2
Current drink	1513	30.7
MVPA participation		
No	836	41.0
Yes	1203	59.0
Social participation		
No	2531	52.1
Yes	2323	47.9
Sleep duration		
Short	2608	54.3
Normal	1788	37.3
Long	404	8.4
BMI		
Underweight	509	10.5
Normal	2181	45.1
Overweight	908	18.8
Obesity	1242	25.6
Cardiovascular diseases		
No	4072	83.1
Yes	830	16.9
Hypertension		
No	3396	69.2
Yes	1513	30.8
Metabolic disorders		
No	4166	86.1
Yes	675	13.9
TICS-10 (mean ± SD)	—	6.7 ± 3.26
Depression		
No	3135	68.8
Yes	1421	31.2
Self-rated heath		
Good and above	2097	42.6
Poor/fair	2828	57.4

BMI, body mass index; HGS, handgrip strength; MVPA, moderate to vigorous physical activity; TICS-10, Telephone Interview of Cognitive Status (10 items).

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Table 2 Characteristics among participants with and without HGS asymmetry at baseline (n = 4925)

Characteristics	HGS asymmetry (%) (n = 2227)	No HGS asymmetry (%) (n = 2698)	P value
HGS			<0.001
Normal	78.0	85.2	
Low	22.0	14.8	
Gender			0.001
Female	52.2	47.5	
Male	47.8	52.5	
Age			<0.001
60–70	61.0	66.4	
70–80	30.9	27.5	
80 and over	8.1	6.1	
Education			0.673
Primary school and below	83.6	83.0	
Secondary school	10.8	11.6	
High school and above	5.6	5.4	
Marriage			0.020
Married	77.2	79.9	
Single, divorced or widowed	22.8	20.1	
Residence			0.796
Urban	34.1	34.4	
Rural	65.9	65.6	
Smoking status			0.017
Never	59.3	55.2	
Ever but quit	11.1	12.1	
Current smoke	29.6	32.7	
Drinking status			0.003
Never	60.3	56.2	
Ever but quit	11.4	11.0	
Current drink	28.3	32.8	
MVPA participation			0.019
No	43.8	38.7	
Yes	56.2	61.3	
Social participation			0.819
No	52.0	52.3	
Yes	48.0	47.7	
Sleep duration			0.942
Short	54.5	54.2	
Normal	37.0	37.5	
Long	8.5	8.3	
BMI			0.066
Underweight	11.7	9.5	
Normal	44.8	45.3	
Overweight	18.0	19.4	
Obesity	25.5	25.8	
Cardiovascular diseases			0.005
No	81.4	84.4	
Yes	18.6	15.6	
Hypertension			0.071
No	67.9	70.3	
Yes	32.1	29.7	
Metabolic disorders			0.049
No	85.0	87.0	
Yes	15.0	13.0	
TICS-10 (mean ± SD)	6.5 ± 0.07	6.9 ± 0.06	<0.001
Depression			0.009
No	66.8	70.4	
Yes	33.2	29.6	
Self-rated heath			<0.001
Good and above	39.4	45.2	
Poor/fair	60.6	54.8	

BMI, body mass index; HGS, handgrip strength; MVPA, moderate to vigorous physical activity; TICS-10, Telephone Interview of Cognitive Status (10 items).

hazard of mortality (HR = 1.04, 95% CI: 0.861–1.268), whereas low HGS was associated with a 61% increase in the hazard of mortality (HR = 1.61, 95% CI: 1.297–1.995) (Table 4).

Fine–Gray subdistribution hazard model

For the Fine–Gray subdistribution hazard model of neurodegenerative disorders, with mortality as the competing risk,

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Table 3 Competing risk analysis of incident neurodegenerative diseases, with mortality as the competing event (n = 4925)

	Cause-specific hazard model[a]			Subdistribution hazard model[b]		
Neurodegenerative disorders	HR	95% CI	*P* value	SHR	95% CI	*P* value
HGS asymmetry	**1.66**	1.202–2.297	0.002	**1.65**	1.202–2.285	0.002
Low HGS	1.29	0.886–1.886	0.183	1.28	0.884–1.842	0.192
Male	1.20	0.751–1.920	0.444	1.19	0.719–1.973	0.498
Age (ref: 60–70)			0.283			0.280
70–80	1.34	0.929–1.920		1.33	0.927–1.907	
80 and over	1.10	0.579–2.104		1.07	0.566–2.032	
Education (ref: primary and below)			0.007			0.010
Secondary school	**2.09**	1.300–3.352		**2.07**	1.281–3.351	
High school and above	1.69	0.813–3.528		1.69	0.791–3.606	
Single, divorced or widowed	0.98	0.653–1.472	0.925	0.97	0.645–1.467	0.894
Rural residence	1.41	0.912–2.184	0.122	1.42	0.913–2.195	0.120
Smoking status (ref: never)			0.285			0.281
Ever but quit	1.46	0.875–2.447		1.44	0.867–2.391	
Current smoke	1.05	0.667–1.646		1.04	0.646–1.670	
Drinking status (ref: never)			0.115			0.153
Ever but quit	1.41	0.862–2.320		1.40	0.843–2.337	
Current drink	1.52	1.009–2.276		1.53	0.982–2.372	
MVPA participation	0.88	0.577–1.327	0.527	0.88	0.582–1.336	0.550
Social participation	0.76	0.545–1.061	0.107	0.76	0.544–1.059	0.105
Sleep duration (ref: normal)			0.185			0.173
Short	0.79	0.550–1.123		0.79	0.555–1.112	
Long	0.59	0.297–1.179		0.59	0.294–1.171	
BMI (ref: underweight)			0.775			0.774
Normal	0.93	0.544–1.578		0.93	0.557–1.564	
Overweight	0.99	0.531–1.854		1.00	0.548–1.840	
Obesity	1.16	0.639–2.098		1.17	0.653–2.085	
Cardiovascular diseases	1.40	0.953–2.044	0.087	1.39	0.952–2.022	0.089
Hypertension	**1.42**	1.007–2.014	0.046	**1.41**	1.008–1.981	0.045
Metabolic disorders	1.01	0.639–1.594	0.968	1.01	0.623–1.641	0.965
TICS-10	**0.90**	0.848–0.950	0.001	**0.90**	0.847–0.955	<0.001
Depression	1.09	0.758–1.564	0.645	1.08	0.760–1.548	0.654
Poor/fair self-rated heath	**1.47**	1.017–2.132	0.040	**1.47**	1.025–2.104	0.036
Time-by-covariate interaction						
Rural residence	**0.44**	0.222–0.871	0.019	**0.44**	0.222–0.857	0.016

BMI, body mass index; CI, confidence interval; HGS, handgrip strength; HR, hazard ratio; MVPA, moderate to vigorous physical activity; SHR, subdistribution hazard ratio; TICS-10, Telephone Interview of Cognitive Status (10 items).
[a]Rural residence did not meet proportional hazard assumption (P = 0.019 for the interaction). Therefore, time by residence interaction term was added in the cause-specific model.
[b]Rural residence did not meet proportional hazard assumption (P = 0.016 for the interaction). Therefore, time by residence interaction term was added in the subdistribution hazard model.

the results were similar to those of the cause-specific model. HGS asymmetry was associated with a 65% increase in the subdistribution hazard of neurodegenerative disorders (SHR = 1.65, 95% CI: 1.202–2.285), and low HGS was not significantly associated with increased risk of neurodegenerative disorders (SHR = 1.28, 95% CI: 0.884–1.842) (Table 3).

For the subdistribution hazard of mortality, with neurodegenerative disorders as the competing risk, the results showed that HGS asymmetry was not significantly associated with the incidence of mortality (SHR = 1.04, 95% CI: 0.860–1.246). However, low HGS was associated with a 58% increase in the subdistribution hazard of mortality (SHR = 1.58, 95% CI: 1.286–1.951) (Table 4).

Sensitivity analysis

Both two sensitivity analyses, (1) using the complete dataset without missing data in all covariates (n = 1841) and (2) using the complete dataset but excluding MVPA participation from the models (n = 4363), showed consistent results with our main findings that HGS asymmetry was independently associated with increased hazard of neurodegenerative disorders (Tables S1 and S3), and low HGS, but not HGS asymmetry, was related to the higher risk of mortality (Tables S2 and S4). Although the first sensitivity analysis (Table S1) showed insignificant association between HGS asymmetry and the incidence of neurodegenerative disorders (HR = 1.45, 95% CI: 0.863–2.438; SHR = 1.44, 95% CI: 0.863–2.410), the estimates

Table 4 Competing risk analysis of incident mortality, with neurodegenerative disorders as the competing event (n = 4925)

	Cause-specific hazard model			Subdistribution hazard model		
Mortality	HR	95% CI	*P* value	SHR	95% CI	*P* value
HGS asymmetry	1.04	0.861–1.268	0.658	1.04	0.860–1.246	0.716
Low HGS	**1.61**	1.297–1.995	<0.001	**1.58**	1.286–1.951	<0.001
Male	**1.41**	1.062–1.880	0.018	**1.41**	1.067–1.856	0.016
Age (ref: 60–70)			<0.001			<0.001
70–80	**1.93**	1.519–2.445		**1.92**	1.525–2.424	
80 and over	**3.62**	2.655–4.938		**3.66**	2.729–4.911	
Education (ref: primary and below)			1.101			0.079
Secondary school	0.87	0.592–1.269		0.85	0.584–1.235	
High school and above	**0.50**	0.262–0.961		**0.49**	0.258–0.934	
Single, divorced or widowed	**1.38**	1.106–1.728	0.004	**1.39**	1.121–1.719	0.003
Rural residence	0.94	0.751–1.171	0.570	0.93	0.749–1.159	0.525
Smoking status (ref: never)			<0.001			<0.001
Ever but quit	**2.12**	1.557–2.876		**2.09**	1.560–2.795	
Current smoke	**1.48**	1.126–1.957		**1.49**	1.146–1.936	
Drinking status (ref: never)			0.290			0.208
Ever but quit	1.15	0.859–1.541		1.15	0.875–1.517	
Current drink	0.90	0.703–1.164		0.89	0.705–1.133	
MVPA participation	**0.69**	0.498–0.958	0.028	**0.70**	0.506–0.957	0.027
No social participation	0.84	0.686–1.023	0.082	0.84	0.692–1.018	0.075
Sleep duration (ref: normal)			0.338			0.269
Short	1.15	0.922–1.424		1.15	0.933–1.411	
Long	1.20	0.869–1.671		1.22	0.895–1.675	
BMI (ref: underweight)			0.026			0.013
Normal	**0.71**	0.543–0.932		**0.71**	0.554–0.914	
Overweight	**0.59**	0.410–0.851		**0.59**	0.416–0.833	
Obesity	**0.67**	0.471–0.946		**0.66**	0.477–0.924	
Cardiovascular diseases	1.18	0.924–1.511	0.185	1.17	0.927–1.483	0.184
Hypertension	**1.44**	1.163–1.785	0.001	**1.43**	1.165–1.751	0.001
Metabolic disorders	0.93	0.682–1.260	0.628	0.93	0.694–1.255	0.650
TICS-10	0.97	0.939–1.006	0.110	0.98	0.944–1.008	0.142
Depression	1.09	0.869–1.373	0.447	1.10	0.888–1.366	0.379
Poor/fair self-rated heath	1.23	0.991–1.529	0.061	**1.22**	1.000–1.499	0.050

BMI, body mass index; CI, confidence interval; HGS, handgrip strength; HR, hazard ratio; MVPA, moderate to vigorous physical activity; SHR, subdistribution hazard ratio; TICS-10, Telephone Interview of Cognitive Status (10 items).

(HR and SHR) were similar with our main results. The insignificance might manifest the insufficient statistical power due to the complete case analysis. Nevertheless, these two sensitivity analyses further supported the robustness of our results.

Discussion

In this study, we examined the association between HGS asymmetry and the incidence of neurodegenerative disorders among Chinese older adults using a 4-year population-based longitudinal study. Our results suggested that when compared with participants without HGS asymmetry, older adults with HGS asymmetry had an increased hazard of neurodegenerative disorders, after considering the competing event of mortality and controlling for socio-demographic characteristics, lifestyle-related behaviours, health conditions and maximal HGS. This was the first study to investigate the association between HGS asymmetry and the incidence of neurodegenerative disorders.

Our study showed that low HGS was not associated with an increased hazard of future neurodegenerative disorders among older population. The significant association between HGS and neurodegenerative disorders was reported by some,[10,11] but not all prospective studies.[34] Furthermore, most research focused on the dementia risk, while limited evidence was available for other types of neurodegenerative disorders. Decline in HGS has been considered primarily as an age-related change in the musculoskeletal system, whereas it has increasingly been viewed as associated with diminished neurological function and brain health.[12] The grip force and muscle coordination involved in the maximum HGS assessment are heavily controlled by the neural system.[12] Therefore, HGS might be a potential indicator of nervous system function and reflect brain health.[12] The absence of significance in our study might show HGS asymmetry as a stronger predictor than low HGS. Yet, future studies are needed to vigorously compare the predictive performance of them.

Our study found that HGS asymmetry was significantly associated with the future risk of neurodegenerative disorders in Chinese older population, after taking mortality into account and controlling for other covariates including HGS. Although no published research has investigated the longitudinal association between HGS asymmetry and the incidence

of neurodegenerative disorders, some studies have examined the association of HGS asymmetry with other outcomes that also involved neurocognitive function.[13,14] For example, a recent prospective cohort study found that older adults with HGS asymmetry had higher odds of future limitations in IADL, which might reflect impaired neurophysiological function.[14] Furthermore, a panel study showed HGS asymmetry was related to lower cognitive function among older adults.[13] Based on previous evidence, maximum grip force is a complex coordinated behaviour involving the engagement of numerous motor units which requires the activation across brain networks.[12] Disorders in the neural system or brain functioning might affect upper limb functions, which could manifest in decreased coordination when completing various tasks, such as the difficulty in holding an object, needing more time to accomplish a task, decreased strength capacity and asymmetrical performance between hands.[35] Given that strength asymmetry between limbs might indicate the imbalance in the brain hemisphere activation and neurological function, that might explain our findings that HGS asymmetry was associated with the higher risk of neurodegenerative disorders and underpin why previous research found that older adults with HGS asymmetry had higher odds of IADL limitations and lower cognitive function. However, the mechanism of and rationale for the association between HGS asymmetry and neurodegenerative disorders remain unclear and need further research. Moreover, our supplementary analysis showed only the participants with the HGS ratio < 0.9 showed the increased hazard of neurodegenerative disorders (HR = 1.71, 95% CI: 1.217–2.415; SHR = 1.71, 95% CI: 1.223–2.402), while estimates for the HGS ratio > 1.1 were not significant (HR = 1.51, 95% CI: 0.924–2.466; SHR = 1.49, 95% CI: 0.914–2.446) (Table S5). The difference in the risk of neurodegenerative disorders between the HGS ratio < 0.9 and >1.1 needed to be explored further.

Considering that common neurodegenerative disorders develop insidiously, with a long, silent preclinical period, recognition of early physical signs of neurodegenerative disorders had important practical implications for identifying at-risk population, especially when the measures (e.g. HGS and HGS asymmetry) could be easily assessed in primary care settings. Our findings suggested that HGS asymmetry might be a potential screening tool to detect the risk of neurodegenerative disorders. Older adults with HGS asymmetry might benefit from early cognitive or neuroprotective intervention programmes. Current evidence has shown that exercise intervention, especially the progressive strength training, could not only improve the overall physical functioning but could also slow the degeneration in brain areas that are particularly susceptible to dementia.[36] However, it is unclear whether the strength training programmes that target asymmetric deficits would have additional protective effect on brain function. Because our study is the first preliminary examination of the association between HGS asymmetry and the risk of neurodegenerative disorders, future studies could consider to verify this association in other populations.

In agreement with previous evidence, our study also found low HGS was associated with an increased risk of mortality.[37,38] Especially, Leong *et al*. generalized the association between HGS and future mortality across countries with diverse socio-economic circumstances.[37] Therefore, the low HGS might serve as a good marker of future risk of mortality. Although the underlying mechanism was uncertain, it was speculated that the loss of HGS might be a sensitive indicator of the ageing process.[39] Additionally, our findings suggested that HGS asymmetry was not associated with the risk of mortality. Although McGrath *et al*. found older adults with HGS asymmetry showed increased hazard of mortality based on a large sample of older Americans from the Health and Retirement Study (n = 19 325), the small effect size might not be clinically significant (HR = 1.10 95% CI: 1.03–1.17).[38] Future research could continue examining whether HGS asymmetry was associated with all-cause and/or cause-specific mortality among older population.

Among the main strengths of this study, we used a prospective design based on a nationwide representative sample of Chinese older population, and a sophisticated statistical model was applied to investigate the association between HGS asymmetry and the incidence of neurodegenerative disorders, taking into account the competing risk of mortality. However, our study was still subject to several limitations. Firstly, to define HGS asymmetry, we excluded participants who were ambidextrous or unable to complete the HGS test on either hand. Therefore, the observed association might not be generalized to the general older population. Secondly, due to data availability, physician-diagnosed neurodegenerative disorders were self-reported or proxy-reported, which did not provide the detailed information about diagnostic criteria and might underestimate the incidence. Nevertheless, this self-reported measure of neurodegenerative disorders was more feasible in large population-based surveys and was shown generally valid in previous research.[30,41] Although the case ascertainment based on medical records was a more objective method, reliance on this approach also resulted in the underdiagnosis due to the socio-economic status, disabling stigma, or reimbursement scheme and so forth.[41] Previous research suggested that the usage of any single information source (e.g. self-reports, medical claims, cognitive tests or prescribed medication) in the case determination might produce underestimates.[42,43] Future studies could consider using multiple sources of information to define the neurodegenerative disorders. Besides, due to the self-reported nature of the outcome, it was reasonable to expect that people with HGS asymmetry would be more likely to see a doctor as their condition progressed and became serious enough to influence their daily life. Therefore, differen-

tial misclassification of the outcome might exist. Thirdly, it was unknown about whether the neurodegenerative disorders existed at the time of death. Therefore, some cases of neurodegenerative disorders might be under-reported. Nevertheless, our results still found the significant association between the HGS asymmetry and neurodegenerative disorders. Moreover, it was possible that the impact of HGS asymmetry on the incidence might vary across different types of neurodegenerative disorders. However, due to data availability, we could not conduct the subgroup analyses to examine the association between HGS asymmetry and the risk of different types of neurodegenerative disorders separately (e.g. Alzheimer's disease and Parkinson's disease). Future study could further examine the risk of different neurodegenerative disorders among older adults with HGS asymmetry. Furthermore, we only observed the 4-year risk of neurodegenerative disorders. However, the follow-up time might not be long enough for the development of neurodegenerative disorders. Future studies could consider to verify the impact of HGS asymmetry on the longer term risk of neurodegenerative disorders. In addition, we had missing data in some baseline covariates. In particular, nearly 60% of the baseline MVPA participation data were missing due to the survey design. However, we conducted sensitivity analyses to support the robustness of the main results using the imputed dataset. Furthermore, some covariates (e.g. HGS, depression and BMI) might change during the follow-up. However, we only considered all covariates at the baseline level. Future studies could examine the impact of changes in these variables on the risk of neurodegenerative disorders. Besides, although we adjusted for numerous potential covariates, residual confounding from unmeasured covariates still existed, for example, family history of neurodegenerative disorders and history of traumatic brain injury. Future studies should consider including these potential covariates. Finally, although this study was prospective, only association rather than causal relationship could be claimed due to its observational nature.

Conclusions

This study indicated that HGS asymmetry was associated with the increased risk of neurodegenerative disorders among Chinese older adults. Public healthcare providers could consider examining HGS asymmetry along with the maximal HGS to help in early detection of vulnerable groups at risk of future neurodegenerative disorders. Because neurodegenerative disorders develop insidiously at the asymptomatic stage, regular assessment of neurocognitive function and early prevention strategies for at-risk populations are encouraged.

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Online supplementary material

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

Conflicts of interest

The authors declare that they have no competing interests.

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