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Prospective Association of Handgrip Strength with Risk of New-Onset Cognitive Dysfunction in Korean Adults: A 6-Year National Cohort Study

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Dementia is one of the priority public health problems in the older population, and the number of people with dementia is steadily increasing. The longitudinal association of muscle strength with risk of new-onset cognitive dysfunction in a general population including middle and older adults remains unknown. The purpose of this study was to investigate the effects of low muscle strength on risk for new-onset cognitive dysfunction over 6 years using a large nationwide sample of cognitively healthy adults. Study participants included 6,435 middle and older adults (33,554 person-years of follow-up), using data from the Korean Longitudinal Study of Ageing 2006-2012. Muscular strength was measured using the maximum handgrip strength of each participant as an index of muscle quality. Low muscle strength was defined as one standard deviation below the mean using the handgrip strength index based on the study population. Cognitive function was evaluated using the Mini-Mental Status Evaluation. The hazard ratio (HR) for cognitive dysfunction significantly and linearly increased according to muscle strength status independent of potential confounding factors (HR: 1.36, 95% confidence interval [CI]: 1.18-1.56 for low vs. normal-high group). Using stratified analyses, a significant association between muscle strength status and risk of cognitive impairment was observed in those with low physical activity, but not those with high physical activity. We show that handgrip strength is associated with increased risk of new-onset cognitive dysfunction over 6 years of follow-up in cognitively healthy middle aged and older adults at baseline.

Keywords: cognitive function; cognitive impairment; handgrip strength; muscle strength; sarcopenia
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Introduction

Dementia is one of the priority public health problems in the older population. The number of people with dementia is steadily increasing, faster even than its prevalence (Alzheimer's Disease International 2015). The World Alzheimer Report 2015 estimated that 46.8 million people worldwide were living with dementia at that time, and the number of people with dementia was estimated to double every 20 years, reaching 74.7 million by 2030 (Alzheimer's Disease International 2015). Moreover, the estimated annual cost of dementia was US$818 billion worldwide in 2015, which was 1.09% of the global GDP (Alzheimer's Disease International 2015). Cognitive dysfunction is characterized as a deterioration in cognitive function falling somewhere between normal aging and dementia. Previous studies suggest that 10%-15% of older people with cognitive dysfunction will develop dementia each year, compared with just 1%-2% of older people without cognitive dysfunction (Ferri et al. 2005). Additionally, cognitive dysfunction is associated with physical functional impairment and decreased quality of life, and is linked to early mortality (Murad et al. 2015; Nishiguchi et al. 2015). Therefore, it is a priority public health issue to identify risk factors that might help prevent individuals from developing cognitive dysfunction.

There is growing evidence for decline in muscle mass and/or strength to readily assess functional and clinical health outcome (Janssen et al. 2002; Bouchard et al. 2009; An and Kim 2016). Handgrip strength is widely used to evaluate muscle strength that is used as a measurement for whole-body muscle strength. This is advantageous because it is easily and safely assessed in older people (Roberts et al. 2011). Previous studies in older people have shown that decreased handgrip strength can predict adverse health-related events such as falls, disability, frailty, hospitalization costs, and mortality (Sallinen et al. 2010; Xue et al. 2011; Chen et al. 2012; Guerra et al. 2015), and it is commonly used as an objective measure of muscle strength in epidemiological studies.

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Previous studies with cross-sectional designs have reported that decline in muscle mass or strength was associated with cognitive function in the elderly (Anstey and Smith 1999; Nourhashemi et al. 2002; Chang et al. 2016). For example, Nourhashemi et al. (2002) showed that low muscle mass was associated with cognitive impairment in 7,105 older women. Another study reported that handgrip strength can explain differences in cognitive performances, using data from 180 community-dwelling women aged 60-90 years (Anstey and Smith 1999). Moreover, the meta-analysis of seven cross-sectional studies shows that sarcopenia is defined as low muscle mass and/or function (handgrip strength or gait speed) that is independently associated with cognitive impairment in elderly individuals (Chang et al. 2016). Although the association between muscle mass or strength and cognitive function has been well documented cross-sectionally in elderly individuals, longitudinal studies are still required to understand the causality of these associations. Moreover, a recent review of longitudinal studies that have investigated the association between sarcopenia (decline in muscle mass or strength) and cognitive function indicated a decline in elderly individuals (Fritz et al. 2017). However, the prospective association is still not certain in the general population, including in middle-aged adults (Alfaro-Acha et al. 2006; Mori et al. 2016). No studies on the causal relationship between lower muscle strength and new-onset cognitive dysfunction in cognitively healthy middle-aged and older adults are available.

We therefore assessed the longitudinal relationship between muscle strength using handgrip strength as a measure of muscle quality and the risk of new-onset cognitive dysfunction in a general population of Korean middle-aged and older adults using data collected from a national cohort study over six years.

Materials and Methods

Study Population

Data from the Korean Longitudinal Study of Ageing (KLoSA) were used in the study. The KLoSA is an ongoing nationwide cohort study of a nationally representative sample of Korean adults aged ≥ 45 years. Details of the study participants, design and methods used in KLoSA are reported in our previous study (Jang and Kim 2015). In brief, the KLoSA aims to obtain fundamental data that can be used to inform and establish social and economic policies in an ageing society (KEIS, Korea Employment Information Service 2015). In 2006, a total of 10,254 participants completed the baseline survey conducted using the Computer Assisted Personal Interviewing method, and were followed-up in a 2-year cycle until 2012. In the present study, to determine the risk of developing cognitive dysfunction, we excluded participants who had cognitive dysfunction (Mini-Mental Status Evaluation (MMSE) score < 24) or those who had dementia at baseline (n = 2,955) obtained from family interviews. We also excluded 299 participants who had missing data for handgrip strength, and 565 subjects were excluded due to missing data for other variables used as covariates. Therefore, a total of 6,435 participants (3,220 male and 3,215 female) were included. The KLoSA study was approved by the Institutional Review Board of the Korea Employment Information Service (IRB: No-33602) and all participants provided written informed consent. All methods were performed in accordance with relevant guidelines and regulations.

Cognitive function measure

We assessed cognitive function using the MMSE Korean version score for each participant at baseline and during the follow-up period at each 2-year cycle (Kim et al. 2003). The MMSE is a brief instrument developed to measure global cognitive performance, and it can screen for dementia. The MMSE comprises 11 questions covering five areas of cognitive function such as orientation in time and place, registration of three objects, attention and calculation, memory (recall of three words), and language (Folstein et al. 1975, Kim et al. 2003). We defined normal cognitive function as having an MMSE ≥ 24 and cognitive dysfunction as an MMSE < 24 (Jang and Kim 2015).

Muscular strength

Muscular strength was measured using the maximum handgrip strength of each participant. Handgrip strength was assessed at least twice using a dynamometer (kg), with the participant in a seated or standing position, their elbow by their side and flexed at right angles, and a neutral wrist position. We calculated the mean of the maximum handgrip strength from both hands. We used handgrip strength as an index of muscle quality (Hamer et al. 2015; Cuthbertson et al. 2016). To investigate the effect of muscle strength on cognitive dysfunction risk, we divided the participants into four groups based on sex-specific categories (Janssen et al. 2002; An and Kim 2016): low (< mean value minus one standard deviation [SD]), normal-low (mean value minus one SD to < mean value), normal-high (mean value to < mean value plus one SD), and high (≥ mean value plus one SD). The cut-off points were < 25.0 (low), 25.0- < 29.0 (normal-low), 29.0- < 32.5 (normal-high), and ≥ 32.5 kg (high) for male participants; < 14.5 (low), 14.5- < 17.5 (normal-low), 17.5- < 20.0 (normal-high), and ≥ 20.0 kg (high) for female, respectively.

Assessment of other variables

We considered for baseline characteristics as potential confounders. The information of demographics (age, sex, education level, household income, and living status), health-related behaviors (physical activity and smoking status), body mass index (BMI), and clinical health conditions were obtained from personal interview. Household income was classified in terms of quartiles of the overall population. Education level was classified as: ≤ Middle school, high school, or ≥ College. All participants self-reported the frequency of their physical activities (days/week) and duration (minutes). Total activity times were calculated considering the frequency and duration in minutes/week. Participants were also categorized into two groups based on the total physical activity level: < 150 or ≥ 150 min/week based on the current guidelines for Korean adults (The Ministry of Health and Welfare 2013). BMI was calculated from body weight and height (weight/height^2), and split into two groups defined as normal and obese (BMI < 25 and ≥ 25 kg/m^2) based on a reference for Asian (World Health Organization 2000). Self-reported smoking status was categorized as never, former smoker and current smoker. Clinical health conditions were diagnosed based on self-reported physician diagnosis. We also calculated the number of clinical chronic diseases, including: hypertension, diabetes, cardiovascular disease,

cerebrovascular diseases, and cancer. These were categorized into three groups as no diseases, one disease, or two or more diseases (An and Kim 2016). We also evaluated the index for depression measured using the Center for Epidemiologic Studies Depression Scale (CES-D10) that is a widely used tool to screen for depression (Bjorgvinsson et al. 2013).

Statistical analysis

All data were analyzed using R ver. 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria) (R Core Team 2017). We considered *P*-values of < 0.05 as statistically significant. Baseline characteristics were presented as mean ± SD or percentages. To compare baseline characteristics between participants with and without new onset cognitive dysfunction during follow-up, we used chi-squared tests for categorical variables and t-tests for continuous variables. We also tested statistical significance for participant characteristics according to muscle strength status using chi-squared tests. Cox proportional hazard models were used to predict the risk of new-onset cognitive dysfunction according to muscle strength status, and hazard ratio (HR) and 95% confidence interval (CI) were estimated. To assess the effects of covariates on the impact of muscle strength on the risk of new-onset cognitive dysfunction, we developed four different sequential models. Model 1 adjusted for age and sex. Model 2 also adjusted for education level, living status and household income. Model 3 further adjusted for smoking status and physical activity. Finally, in model 4, we also adjusted for obesity, clinical health conditions and CES-D10 score. We also considered linearity according to muscle strength status in all Cox proportional hazard models. In addition, we conducted sensitivity analyses stratified by age groups (< 60 years vs. ≥ 60 years), sex (male vs. female), obesity (obese vs. non-obese), smoking status (non-smoker vs. former/current smoker), physical activity (< 150 vs. ≥ 150 min/week), and clinical health conditions (none vs. one or more diseases).

Results

Table 1 shows the participants' general characteristics at baseline according to incidence of cognitive dysfunction over the 6-year follow-up period. In this study, the mean follow-up period was 5.21 years. A total of 2,092 participants had new-onset cognitive dysfunction during the 33,554 person-years of follow-up. The incidence of cognitive dysfunction was significantly higher in participants who were aged ≥ 60 years, female, less well-educated, had less income, living alone, lower physical activity, never smoker and those who had medical health condition. The mean handgrip strength was 28.7 ± 8.3 kg for participants without cognitive dysfunction and 25.8 ± 8.0 kg for participants who developed cognitive dysfunction ($P < 0.001$). In addition, the CES-D10 score was significantly higher in participants had cognitive dysfunction compared with normal group ($P < 0.001$).

Table 2 shows the characteristics of participants according to muscle strength status. We found that the frequency of age group, obesity, smoking status, physical activity, and medical health condition were significantly different across muscle strength status (Table 2, $P < 0.05$). We also found significant differences in the frequency of participants who had new-onset cognitive dysfunction during the follow-up period (high: 21.6%, normal-high: 25.3%, normal-low: 36.5%, and low: 49.6%, $P < 0.001$).

Table 3 shows the results of Cox proportional hazard models of muscle strength with the HR for cognitive dysfunction by muscle strength status. Muscle strength status was significantly and linearly associated with increased risk for new-onset cognitive dysfunction after adjusting for age and sex (model 1); in addition to education level, household income, and living status (model 2); and also adjusting for physical activity and smoking status (model 3). In the fully adjusted model, muscle strength status showed a significant increased HR for new-onset cognitive dysfunction (HR: 1.36, 95% CI: 1.18-1.56 for low group, HR: 1.17, 95% CI: 1.05-1.31 for normal-low vs. normal-high group) after additionally adjusting for obesity, medical health condition and CES-D10 score.

In a sensitivity analysis, the significant association between muscle strength status and risk of cognitive dysfunction was observed in the both middle aged and older adults. Moreover, the significant association between muscle strength status and risk of cognitive dysfunction was observed for those with low physical activity, but not those with high physical activity (Fig. 1). We also found a marginally significant interaction between muscle strength and physical activity on the risk of cognitive dysfunction onset (P-interaction = 0.055). Significant associations were observed between muscle strength status and increased risk of new-onset cognitive dysfunction in other stratified models, consistent with findings in the overall participants (Fig. 1).

In this study, the cognitive function score in participants who had new-onset cognitive dysfunction was significantly lower than in those without cognitive dysfunction (Table 1). These results suggest that the cognitive function at baseline can affect the association between handgrip strength and the incidence of cognitive dysfunction. Therefore, we also analyzed the association between muscle strength status and an increased risk of new-onset cognitive dysfunction after excluding participants with incidences of cognitive dysfunction within the two-year follow-up period ($n = 852$), and found the results were unchanged (Table 4).

Discussion

In this large longitudinal study, we investigated the effects of handgrip strength on the risk of new-onset cognitive dysfunction in middle-aged and elderly Korean adults. To our knowledge, this is the first population-based prospective study exploring the relationship between handgrip strength and risk of cognitive dysfunction. Our findings suggest that lower muscle strength (i.e., dynapenia/sarcopenia), evaluated by handgrip strength, is significantly associated with an increased risk of new-onset cognitive dysfunction in cognitively healthy middle-aged and older adults over a 6-year follow-up period, independent of chronic disease, physical activity, and other potential confounding factors. Thus, our findings suggest that the skeletal muscle

Table 1. Baseline characteristics of study participants according to new-onset cognitive dysfunction during follow-up.

Characteristics	Overall (n = 6,435)	Cognitive dysfunction status during follow-up		P-value
		Normal cognitive function (n = 4,343)	Cognitive dysfunction (n = 2,092)	
Age group (%)				
45-59 years	3,837 (59.6)	2,982 (68.7)	855 (40.9)	*< 0.001*
≥ 60 years	2,598 (40.4)	1,361 (31.3)	1,237 (59.1)	
Sex (%)				
Male	3,220 (50.0)	2,242 (51.6)	978 (46.7)	*< 0.001*
Female	3,215 (50.0)	2,101 (48.4)	1,114 (53.3)	
Education (%)				
≤ Middle school	3,278 (50.9)	1,902 (43.8)	1,376 (65.8)	*< 0.001*
High school	2,224 (34.6)	1,694 (39.0)	530 (25.3)	
≥ College	933 (14.5)	747 (17.2)	186 (8.9)	
Household income (%)				
Low	1,472 (22.9)	836 (19.2)	636 (30.4)	*< 0.001*
Lower-middle	1,712 (26.6)	1,078 (24.8)	634 (30.3)	
Upper-middle	1,247 (19.4)	895 (20.6)	352 (16.8)	
High	2,004 (31.1)	1,534 (35.3)	470 (22.5)	
Living status (%)				
Living together	6,068 (94.3)	4,151 (95.6)	1,917 (91.6)	*< 0.001*
Living alone	367 (5.7)	192 (4.4)	175 (8.4)	
Physical activity (%)				
< 150 min/week	4,391 (68.2)	2,915 (67.1)	1,476 (70.6)	*0.006*
≥ 150 min/week	2,044 (31.8)	1,428 (32.9)	616 (29.4)	
Smoking status (%)				
Never	4,356 (67.7)	2,886 (66.5)	1,470 (70.3)	*< 0.001*
Former smoker	668 (10.4)	448 (10.3)	220 (10.5)	
Current smoker	1,411 (21.9)	1,009 (23.2)	402 (19.2)	
Obesity				
No	4,943 (76.8)	3,362 (77.4)	1,581 (75.6)	*0.102*
Yes	1,492 (23.2)	981 (22.6)	511 (24.4)	
Medical health condition (%)				
None	4,405 (68.5)	3,137 (72.2)	1,268 (60.6)	*< 0.001*
One disease	1,524 (23.7)	943 (21.7)	581 (27.8)	
Two or more diseases	506 (7.9)	263 (6.1)	243 (11.6)	
Handgrip strength (kg, mean ± SD)	27.8 ± 8.3	28.7 ± 8.3	25.8 ± 8.0	*< 0.001*
CES-D10 (score, mean ± SD)	3.21 ± 2.74	2.77 ± 2.55	3.97 ± 2.89	*< 0.001*
MMSE (score, mean ± SD)	27.4 ± 1.6	27.6 ± 1.5	26.9 ± 1.7	*< 0.001*

Values are number (%) or mean ± SD. We used chi-squared test for categorical variables and t-tests for continuous variables. Medical health condition was defined as any clinical multi-morbidity of hypertension, diabetes, cardiovascular disease, stroke or cancer; CES-D10, Center for Epidemiological Studies Depression; MMSE, mini mental status evaluation.

strength is an independent risk factor of incidence of cognitive dysfunction in general population.

In the present study, the risk of cognitive dysfunction was approximately 1.4 times higher in the lower muscle strength group compared with those with normal-high muscular strength, after adjusting for potential confounding variables. Our findings support the previous cross-sectional studies that suggest a relationship between skeletal muscle mass or strength and decline in cognition (Anstey and Smith 1999; Nourhashemi et al. 2002; Rosano et al. 2005; Chang et al. 2016). However, most of these observational studies considered only cross-sectional associations of muscular strength and specific cognitive function score, therefore limiting conclusions with regard to long-term decline in muscle strength (Chang et al. 2016). Several studies have investigated the longitudinal association between muscle strength and cognitive function (Fritz et al. 2017). One community-based 3.5-year follow-up study, reported that handgrip strength was linked to the greater variability of memory decline in a small sample of 426 elderly individuals (Christensen et al. 1999), with an alternative study reporting that low handgrip strength was associated with an

Table 2. Characteristics of study participants according to muscle strength status at baseline.

	Muscle strength status at baseline				P-value
	High	Normal-high	Normal-low	Low	
Age groups (%)					
<60 years	799 (87.3)	1,597 (73.2)	1,195 (50.0)	246 (25.9)	*< 0.001*
≥60 years	116 (12.7)	586 (26.8)	1,194 (50.0)	702 (74.1)	
Sex (%)					
Male	475 (51.9)	1,099 (50.3)	1,164 (48.7)	482 (50.8)	*0.352*
Female	440 (48.1)	1,084 (49.7)	1,225 (51.3)	466 (49.2)	
Obesity					
No	608 (66.4)	1,683 (77.1)	1,898 (79.4)	754 (79.5)	*< 0.001*
Yes	307 (33.6)	500 (22.9)	491 (20.6)	194 (20.5)	
Smoking status (%)					
Never	614 (67.1)	1,494 (68.4)	1,626 (68.1)	622 (65.6)	*0.011*
Former smoker	93 (10.2)	189 (8.7)	263 (11.0)	123 (13.0)	
Current smoker	208 (22.7)	500 (22.9)	500 (20.9)	203 (21.4)	
Physical activity (%)					
< 150 min/week	597 (65.2)	1,465 (67.1)	1,637 (68.5)	692 (73.0)	*< 0.001*
≥ 150 min/week	318 (34.8)	718 (32.9)	752 (31.5)	256 (27.0)	
Medical health condition (%)					
None	708 (77.4)	1,633 (74.8)	1,559 (65.3)	505 (53.3)	*< 0.001*
One disease	171 (18.7)	444 (20.3)	621 (26.0)	288 (30.4)	
Two or more diseases	36 (3.9)	106 (4.9)	209 (8.7)	155 (16.4)	
Onset cognitive dysfunction during follow-up (%)					
No	717 (78.4)	1,630 (74.7)	1,518 (63.5)	478 (50.4)	*< 0.001*
Yes	198 (21.6)	553 (25.3)	871 (36.5)	470 (49.6)	

Values represent number of occurrences (%). Analyses used chi-squared tests for categorical variables. Medical health condition was defined as any clinical multi-morbidity of hypertension, diabetes, cardiovascular disease, stroke or cancer.

Table 3. Hazard ratio (95% CI) for the new-onset cognitive dysfunction by muscle strength.

Muscle strength status	Total person-years	No. of cognitive dysfunction/participants	Event rate (1000-person year)	HR (95% CI)			
				Model 1	Model 2	Model 3	Model 4
High	5,054	198/915	39.2	0.84 (0.71-0.99)*	0.94 (0.80-1.11)	0.94 (0.80-1.11)	0.95 (0.80-1.12)
Normal-high	11,804	553/2,183	46.9	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Normal-low	12,254	871/2,389	71.1	1.51 (1.36-1.68)*	1.21 (1.08-1.35)*	1.21 (1.08-1.35)*	1.17 (1.05-1.31)*
Low	4,442	470/948	105.8	2.23 (1.97-2.52)*	1.38 (1.21-1.58)*	1.38 (1.21-1.58)*	1.36 (1.18-1.56)*
P-trend				*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*

Values denote hazard ratio (95% CI). Model 1 was adjusted for age and sex. Model 2 also adjusted for education, household income, and living status. Model 3 further adjusted for physical activity and smoking status. Model 4 also adjusted for obesity, medical health condition, and CES-D10 score.

CI, confidence interval; CES-D10, Center for Epidemiological Studies Depression.

*P-value < 0.05 compared with reference group.

increased risk of Alzheimer's disease in cognitively healthy elderly individuals (Boyle et al. 2009). Furthermore, longitudinal studies, based on 20-year follow up data for a population (Sternang et al. 2016), identified that changes in handgrip strength are associated with changes in cognitive abilities. Moreover, a recent review of longitudinal studies investigated the association between sarcopenia (muscle mass and/or strength) and cognitive function, and indicated a decline of these conditions in elderly individuals (Fritz et al. 2017). However, evidence on the contributing relation-

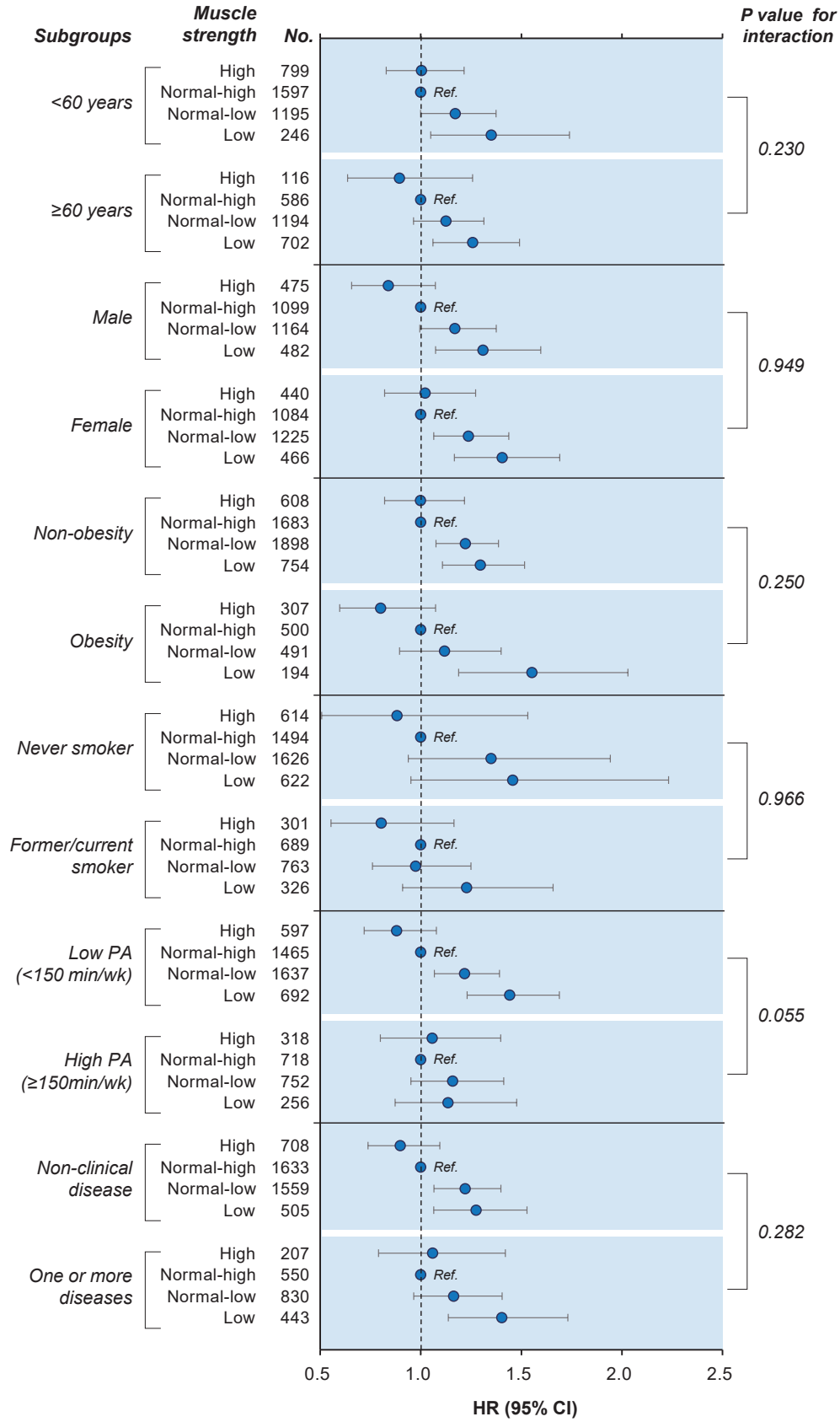

Fig. 1. The risk of cognitive dysfunction according to handgrip strength by subgroups.
All models were adjusted for age, sex, education level, household income, living status, physical activity, smoking status, obesity, clinical health conditions and CES-D10 score.

Table 4. Hazard ratio (95% CI) for the new-onset cognitive dysfunction by muscle strength after excluding participants had an incidence of cognitive dysfunction within two years.

Muscle strength status	No. of cognitive dysfunction/participants	HR (95% CI)
High	133/850	0.95 (0.78-1.01)
Normal-high	346/1,976	1.00 (Reference)
Normal-low	516/2,034	1.24 (1.08-1.43)*
Low	245/723	1.39 (1.17-1.67)*
P-trend		*< 0.001*

Values denote hazard ratio (95% CI). Adjusted for age, sex, education, household income, living status, physical activity, smoking status, obesity, medical health condition, and CES-D10 score.
CI, confidence interval; CES-D10, Center for Epidemiological Studies Depression.
*P-value < 0.05 compared with reference group.

ship between lower muscle strength and new-onset cognitive dysfunction in the cognitively healthy and the general population are rare, as the majority of previous studies have investigated the older population only. Our findings suggest that muscle strength directly contributes to the future development of cognitive dysfunction, implying that this is an important public health issue that would benefit from improvement with middle-aged adults also being included.

Several biological factors could explain our findings on the longitudinal association between muscle strength and risk of new-onset cognitive dysfunction. One possible explanation for the association between muscle strength and cognitive dysfunction risk pertains to oxidative stress and inflammation (Chi et al. 2017). Oxidative stress and inflammation are well known to be directly linked to a decline in cognitive function (Glade 2010), and may play a role in the onset of cognitive dysfunction (Pedersen and Febbraio 2012). It is understood that skeletal muscle is the target of numerous hormones, and recent evidence has shown that skeletal muscle has a role as a secretory organ of cytokines and other peptides, as well as denominated myokines such as brain-derived neurotrophic factor (BDNF), interleukin-6 (IL-6), IL-8, IL-15, and leukaemia inhibitory factor, which have autocrine, paracrine, or endocrine actions and are involved in inflammatory processes (Pedersen and Febbraio 2012). Decline in muscle mass and strength also may reduce expression of BDNF, insulin-like growth factor-1, both of which are thought to play a role in learning and neural plasticity (Pedersen and Febbraio 2012).

Lower muscle strength that occurs in concert with biological aging may also predict chronic diseases and decline in physical and cognitive function (Bohannon 2008). Higher levels of skeletal muscle mass and strength are associated with a lower risk of frailty, cardiovascular disease, and cardiovascular and all-cause mortality (Janssen et al. 2002; Bouchard et al. 2009; Guadalupe-Grau et al. 2015). Additionally, many studies have shown that physical functional decline and chronic disease are linked with cognitive health decline (Rosano et al. 2005; Auyeung et al. 2008; Nishiguchi et al. 2015). Critically, decline of handgrip strength may represent an age-related change in physical function and progression to frailty, whilst contributing to cognitive decline and increasing the risk of cognitive dysfunction. Taken together, these results provide a possible interpretation of our finding of an association between muscle strength and cognitive dysfunction risk. Additionally, declining central nervous system function with age may be an important mechanism in the association between decline in muscle function and cognitive dysfunction (Baltes and Lindenberger 1997). For example, Salthouse (1996) reported that slow reaction times are associated with cognitive function in the elderly. Moreover, muscle strength may be a general predictor of central nervous system integrity (Salthouse et al. 1998). Thus, muscle strength could be an early marker of a decrease in nervous system function associated with aging, which is reflected in cognitive function (Raji et al. 2005).

Physically inactivity is one of the major factors known to accelerate both muscle loss and strength with aging (Mijnarends et al. 2016). However, functional decline caused by decline in muscle strength also contributes to lack of physical activity. Many previous studies have shown that physical inactivity contributes to cognitive function decline. Furthermore, physically active lifestyles have a benefit in maintaining skeletal muscle mass and strength that may itself contribute to cognitive decline and increasing the risk of cognitive dysfunction. Indeed, we found that the association between muscle strength and the risk of cognitive dysfunction was modified by physical activity status, although the associations were not different across sex, age groups, and other demographic variables. In the present study, the HR for cognitive dysfunction was 1.44-fold higher in participants with low muscle strength than in those with normal-high muscle strength in a low physical activity group, but we did not observe the same association in those with higher levels of physical activity (HR: 1.13 in low group vs. normal-high group, Fig. 1). Several observational and intervention studies have also reported that physically active lifestyles have a benefit in maintaining of cognitive function (Espeland et al. 2017; Jeong and Jang 2017; Zhu et al. 2017). Our findings and

those of previous studies suggest that participation in physical activity might offset the negative impacts of low muscle strength on risk of cognitive dysfunction.

The major strengths of our study are that it used a prospective design with a 6-year follow-up period in a large, representative sample of adults in the general population. We also controlled for important potential confounding factors including demographics, health-related behaviors, and other clinical health conditions, and index for depression. Nevertheless, some limitations of the present study should be considered. First, we assessed muscle strength by using handgrip strength as a measurement of quality of muscular strength, but did not evaluate muscle mass or other muscle functional parameters that have been shown to predict cognitive decline previously (Auyeung et al. 2008). However, handgrip strength as a measurement of muscle strength and quality is easily and safely investigated, particularly in elderly populations. It is also used as a representative measure of whole-body muscular strength, and it may be an effective index to predict development of cognitive dysfunction. Furthermore, a recent study has shown clearer associations between sarcopenia assessed by muscular strength with health outcomes, then by sarcopenia assessed by muscle mass (Menant et al. 2017). We evaluated cognitive function using only the MMSE scores. The MMSE is an adequate tool for screening dementia in elderly individuals with minimum literacy skills (Scazufca et al. 2009). However, misclassification is also highly unacceptable for elderly individuals who are illiterate (Scazufca et al. 2009).

In conclusion, during a 6-year follow-up period, we found that handgrip strength was strongly associated with an increased risk of new-onset cognitive dysfunction in cognitively healthy middle-aged and older adults at baseline. Furthermore, physical activity may offset the negative impacts of lower muscle strength on the risk of cognitive dysfunction.

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Conflict of Interest

The authors declare no conflict of interest.

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