

PREVALENCE OF COGNITIVE FRAILTY PHENOTYPES AND ASSOCIATED FACTORS IN A COMMUNITY-DWELLING ELDERLY POPULATION

Q. RUAN¹, F. XIAO², K. GONG³, W. ZHANG¹, M. ZHANG², J. RUAN⁴, X. ZHANG³, Q. CHEN³, Z. YU¹

1. Shanghai Institute of Geriatrics and Gerontology, Shanghai Key Laboratory of Clinical Geriatrics, Department of Geriatrics, Huadong Hospital, and Research Center of Aging and Medicine, Shanghai Medical College, Fudan University, 221 West Yan An Road, Shanghai 200040, China; 2. Zhoujiaqiao Primary Health Service Centre, 1700 chongning road, Shanghai 200040, China; 3. Department of social work, Huadong Hospital, Shanghai Medical College, Fudan University, 221 West Yan An Road, Shanghai 200040, China; 4. Molecular and Cellular Biology Core Facility, institute of neuroscience, Chinese academy of science, 320, Yueyang Road, Shanghai 200031, China. Corresponding author: Dr Zhuowei Yu, Shanghai Institute of Geriatrics and Gerontology, Shanghai Key Laboratory of Clinical Geriatrics, Department of Geriatrics, Huadong Hospital, and Research Center of Aging and Medicine, Shanghai Medical College, Fudan University, 221 West Yan An Road, Shanghai 200040, P.R. China, Tel: 86-21-62483180 Fax: 86-21-62484981 Email: hdyuzhuowei@163.com

Abstract: *Objectives:* Cognitive frailty was notable target for the prevention of adverse health outcomes in future. The goal of this study was to use a population-based survey to investigate cognitive frailty phenotypes and potentially sociodemographic factors in elderly Chinese individuals. *Design:* Cross-sectional study. *Setting:* General community. *Participants:* A total of 5328 elderly adults (aged 60 years or older, mean age 71.36 years) enrolled in the Shanghai study of health promotion for elderly individuals with frailty. *Measurements:* The 5-item FRAIL scale and the 3-item Rapid Cognitive Screen tools were used to assess physical frailty and cognitive impairment, including dementia or mild cognitive impairment (MCI). Physical frailty was diagnosed by limitations in 3 or more of the FRAIL scale domains and pre-physical frailty by 1–2 limitations. Subjective cognitive decline (SCD) and pre-MCI SCD, was diagnosed with two self-report measures based on memory and other cognitive domains in elderly adults. *Results:* Of the participating individuals, 97.17% (n= 5177, female 53.4%) were eligible. Notably, 9.67%, 41.61% and 35.20% of participants were MCI, SCD and pre-MCI SCD; 35.86% and 4.41% exhibited physical pre-frailty and frailty; and 19.86% and 6.30% exhibited reversible and potential reversible cognitive frailty. Logistic regression analyses indicated that physical frailty phenotypes were significantly associated with MCI with SCD, and pre-MCI with SCD. Older single females with a high education level were more likely to exhibit the reversible cognitive frailty; and younger elderly individuals with a middle education level were at lower risk for potentially reversible cognitive frailty. *Conclusions:* The prevalence of pre-physical and reversible cognitive frailty was high in elderly individuals and age was the most significant risk factor for all types of frailty phenotypes. To promote the rapid screening protocol of cognitive frailty in community-dwelling elderly is important to find high-risk population, implement effective intervention, and decrease adverse prognosis.

Key words: Physical pre-frailty, physical frailty, pre-MCI subjective cognitive decline, potentially reversible cognitive frailty, reversible cognitive frailty.

Introduction

Physical (1), cognitive (2), social(3, 4), psychological (5) or psychosocial (6) and mental frailty phenotypes (7) have been reported. Physical frailty in combination with dysfunction in cognitive, psychosocial domains increases the risk of dependency, disabilities, dementia, and mortality (3, 4, 6, 8, 9, 10). Cognitive frailty, referred to as the simultaneous presence of physical frailty and cognitive impairment without dementia (2), includes reversible and potentially reversible 2 subtypes (11), which could predict adverse health outcomes (12, 13). Cognitive frailty, especially reversible cognitive frailty is an ideal target to prevent asymptomatic cognitive impairment and dependency (14).

Cognitive frailty has had different operational models (15, 16). Some models included physical pre-frailty and physical frailty (10, 17, 18), and more models contained only physical frailty (15, 16). Until now, reversible cognitive frailty, which comprises physical frailty and pre-mild cognitive impairment subjective cognitive decline (pre-MCI SCD), was explored in 1 clinical study (13).

Many well-validated physical frailty models, such as the cardiovascular health study (CHS) model (1), deficit model (19), FRAIL model (20, 21), and multidimensional Tilburg Frailty Index (TFI) model (22) and Groningen Frailty Indicator model (23) have been used to assess physical frailty in cognitive frailty epidemiological investigations. The CHS Frailty Screening Measure is the most commonly used to screen for physical frailty phenotype (1, 15, 16). The validated simple FRAIL questionnaire screening tool (21) is a good alternative physical frailty screening instrument without objective measures, can rapidly identify individuals with physical frailty or physical pre-frailty in large clinical cohort studies.

Many measurement tools for Pre-MCI SCD and MCI screening have been used in cognitive frailty epidemiological studies (15, 16). Pre-MCI SCD was diagnosed with research criteria (24) and a self-report measure based on cognitive domains for SCD. The Cognitive Difficulties Scale (25), the subjective cognitive Decline Questionnaire (22, 26), Subjective memory decline scale (27) or simple memory questionnaire (28) were the common tools to screen SCD. Memory domain assessment can only measure preclinical Alzheimer disease

(26, 27). Time-consuming neuropsychological measures, global cognitive evaluation by using the Mini Mental State Examination, Montreal Cognitive Assessment cut-off scores, or clinical dementia rating=0.5 have often been used to assess MCI (15, 16). However, these time-consuming tools are not available for a large clinical cohort study. A brief validated screening tool (<3 min), the Rapid Cognitive Screen (RCS) (29) could be used to assess dementia, MCI, and pre-MCI SCD in combination with SCD questionnaire after excluding dementia and MCI.

Different instruments for physical and cognitive status significantly influence the prevalence of cognitive frailty. The prevalence of potentially reversible cognitive frailty in cross-sectional studies has been reported 1.2% (>3 CHS criteria) (30), 4.4% (>1 CHS criterion) (18), and 1.8% (>3 FRAIL criteria) in older adults (31). Several longitudinal population-based studies have indicated the prevalence of potentially reversible cognitive frailty was 1~1.8% (CHS or modified CHS) (12, 32, 33). Only a retrospective study reported that the prevalence of reversible cognitive frailty was 2.5% when physical frailty was assessed based on CHS criteria (>3 criteria) (13). According to a review of the literature, a systemic study on the prevalence of cognitive frailty phenotypes has almost been absent. In this study, FRAIL and RCS scales in combination with modified SCD questionnaire were used to systemically assess the prevalence of physical and cognitive frailty phenotypes and their association with the sociodemographic characteristics in a community-dwelling elderly cohort.

Methods

Participants

This population-based study assessed 5328 residents aged 60 years and older enrolled in the Shanghai study of health promotion for the frail elderly individuals. Participants were recruited from 20 communities in the Zhoujiaqiao Primary Health Service Area in Changning district, Shanghai, at the time of examination (2018 or 2019). We excluded 128 participants with dementia, whose RCS score were 0~5 points, 5 participants with missing age, and 18 participants with severe disabilities. We assessed the prevalence of SCD in 4964 participants, MCI in 5172 participants, physical frailty phenotype in 5175 participants, and cognitive frailty phenotype in 5076 participants (Figure 1) and the associated sociodemographic characteristics. The Ethics Committee of Huadong hospital approved the research protocol and informed consent was obtained from each study participant.

Measurements

The evaluations were performed by well-trained staff who had general practice, rehabilitation medicine, geriatrics, nursing, or similar qualifications. The measurement protocol contained sociodemographic information, and physical and cognitive tests or questionnaires. The battery of tests was

administered on an individual basis.

Operationalization of physical pre-frailty and physical frailty phenotype

The 5-item FRAIL scale (Fatigue, Resistance, Ambulation, Illness, and Loss of Weight) (21) was used to assess physical frailty phenotypes in the sample because it has been extensively validated in numerous populations across various populations and clinical studies, including in Chinese (21) and multiethnic Asian populations (31). Similar to the CHS scale, the range of scores for the FRAIL scale is from 0 to 5: scores 3 to 5 and 1 to 2 represented frail and, prefrail, respectively.

Operationalization of dementia and MCI

Cognitive dysfunction was assessed by using RCS (29), which comprises 3-items: recall of 5 words (5 points), a clock drawing test (4 points; 2 points for hour markers, 2 points for time), and the ability to remember a story and convert the fact that Chicago is in Illinois (1 point). We replaced “Chicago is in Illinois” with “Nanjing in Jiangsu.” The range of the RCS scores was 0=worst to 10=best (Scores of 8 to 10 represented normal cognition, 6 to 7 MCI, and 0 to 5 dementia).

Operationalization of SCD

According to the SCD criteria proposed by the SCD-I Working Group (24), individuals have self-experienced persistent decline in cognitive capacity compared with a previously normal status and unrelated to an acute event, including psychiatric illness (severe depression and anxiety), neurologic diseases, medical disorders, medication, or substance use. We excluded dementia based on RCS scores less than 5 points. Here, SCD was assessed with the simplified SCD questionnaire (22, 26) and 2 questions involved memory and other domains. SCD was diagnosed if a positive response was given to 1 of 2 questions—“In the last 2 years, has your memory declined?” or “Has your other cognition declined, such as having difficulty remembering family members’ or close friends’ names, finding your way around your neighborhood, or handling money?”—and MCI with SCD was diagnosed if a positive response was given for 1 of the aforementioned questions in combination with an RCS score between 6 and 7 points. Pre-MCI SCD included these SCD individuals without MCI (24).

Operationalization of reversible and potentially reversible cognitive Frailty Phenotype

Reversible cognitive frailty was assessed with the simultaneous presence of physical pre-frailty or physical frailty and pre-MCI SCD. Potentially reversible cognitive frailty was assessed with the combined presence of physical pre-frailty or physical frailty and MCI.

Statistical analysis

All data statistical computations were conducted with Statistical Package for Social Sciences (SPSS), VERSION 22.0

PREVALENCE OF COGNITIVE FRAILTY IN ELDERLY CHINESE

Table 1
 Number of participants and prevalence of all types of frailty phenotypes

		With physical pre-frailty	Prevalence (%)	With physical frailty	Prevalence (%)
All participants	5175	1856	35.86	228	4.41
Age, y			P<0.001		P<0.001
60-69	2372	584	24.62	38	1.60
70-79	1936	804	41.53	51	2.63
≥80	867	468	53.98	139	16.03
Sex			P<0.001		P=0.215
Females	2766	1034	37.38	128	4.63
Males	2409	822	34.12	100	4.15
Educational level, y			P<0.001		P=0.037
≤6	489	230	47.03	63	12.88
6-12	3459	1146	33.13	113	3.27
≥15	822	389	47.32	39	4.74
Marital status			P=0.825		P=0.067
Single	75	30	40	5	6.67
Married	4719	1639	34.73	201	4.26
Widowed	262	126	48.09	19	7.25
		With reversible cognitive frailty	Prevalence (%)	With potentially reversible cognitive frailty	Prevalence (%)
All participants	5076	1008	19.86	320	6.30
Age, y			P<0.001		P<0.001
60-69	2327	363	15.60	47	2.02
70-79	1900	386	20.32	97	5.11
≥80	849	259	30.51	176	20.73
Sex			P<0.001		P=0.858
Females	2717	584	21.49	160	5.88
Males	2359	424	17.97	160	6.78
Educational level, y			P<0.001		P=0.001
≤6	466	117	25.11	82	17.60
6-12	3417	618	18.09	161	4.71
≥15	814	204	25.06	67	8.23
Marital status			P=0.033		P=0.02
Single	75	25	33.33	5	6.67
Married	4648	893	19.21	254	5.46
Widowed	258	54	20.93	52	20.16

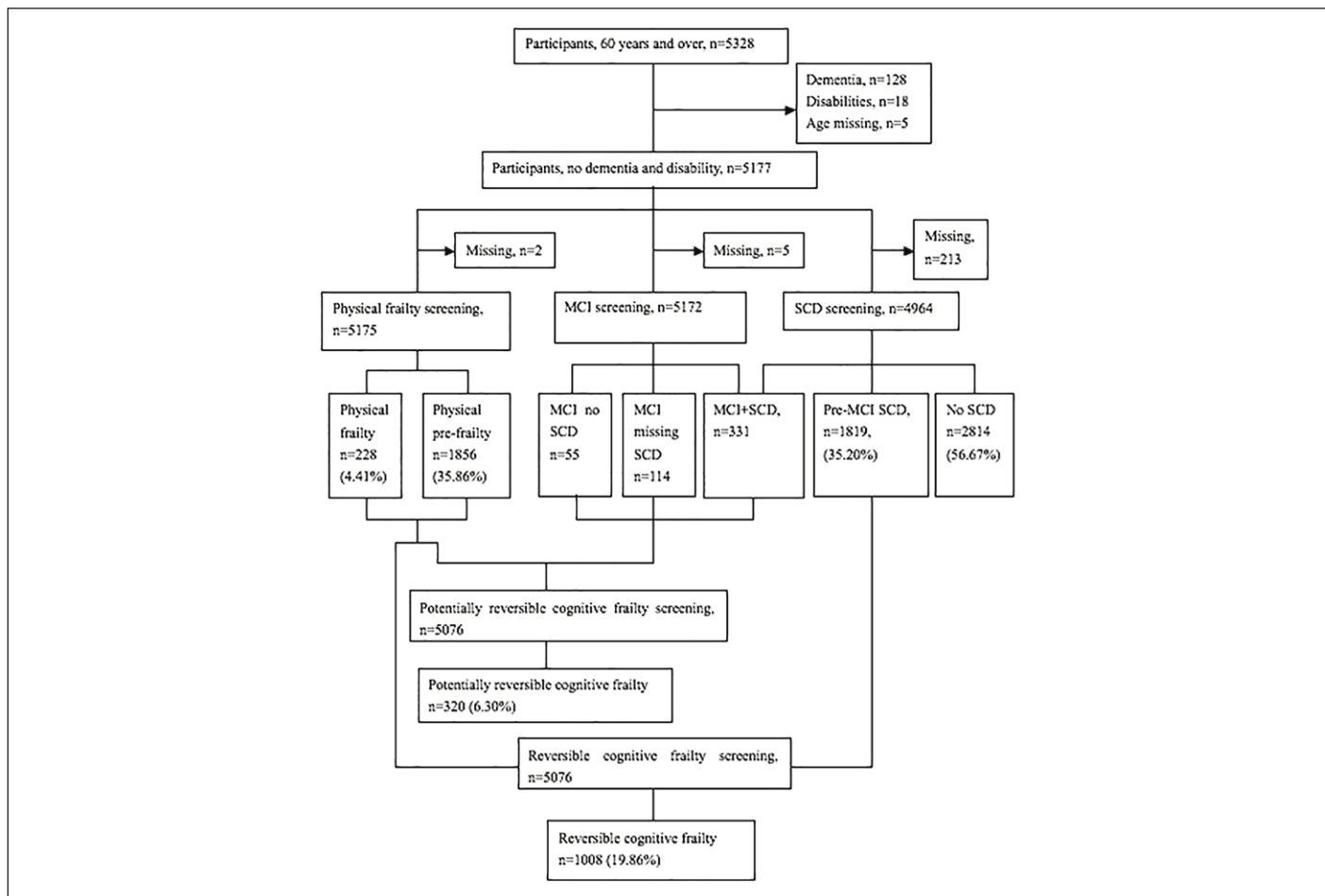
(SPSS Inc., Chicago, IL, USA). Mean and standard deviations were calculated for continuous variables, and frequencies and percentages were calculated for categorical variables. A multivariate logistic regression model was used to determine the odds ratios of physical and cognitive frailty phenotypes of sociodemographic variables including age, sex, marital status, and education level category; and the odds ratios of MCI, MCI with SCD, pre-MCI SCD with the physical frailty states (prefrail and frail) after adjusting for sociodemographic variables. Statistical significance was determined by using the

cut-off P value of .05.

Results

We identified 228 (4.41%) elderly participants with physical frailty, 1856 (35.86%) with physical pre-frailty (Figure 1 and Supplementary Figure 1, Table 1), 500 (9.67%) with MCI, 2152 (41.61%) with SCD, 1819 (35.20%) with pre-MCI SCD (Figure 1 and Supplementary Figure 1, Table 2). Figure 1 and Table 1 also indicate our findings on the prevalence of reversible

Figure 1
Participants' flow to screen frail phenotypes of cognitive impairment in older adults



cognitive frailty (n=1008, 19.86%) and potentially reversible cognitive frailty (n=320, 6.30%).

We observed that the prevalence of physical frailty phenotypes significantly increased with advancing age (Table 1). The prevalence was 24.6% in physical pre-frailty, 1.60% in physical frailty in the age range 60–69, and significantly increased to 53.98% and 16.03%, respectively, at age 80 years and older. The prevalence of both physical frailty phenotypes were higher in females than in males but significant difference was observed in only physical pre-frailty (Table 1). A lower level of education (≤ 6 years) and a higher level of education (≥ 15 years) significantly increased the prevalence of physical pre-frailty ($p < 0.001$). There was no significant effect of marital states on physical frailty phenotypes.

Age was the most significant influence factor of cognition. The rate of MCI, SCD, and pre-MCI SCD increased approximately 6-, 2-, and 2-fold when the age of individuals aged 60–69 years increases to 80 years and older (Table 2). The prevalence of MCI was lower in women than in men ($p = 0.041$), but the rate of SCD and pre-MCI SCD was significantly higher in females than in males ($p < 0.001$). Participants with ≤ 6 years

of education had a 20.86% rate of MCI, 58.49% rate of SCD, and 47.24% rate of pre-MCI SCD, and the rates were reduced to 8.42%, 37.04%, and 31.26% in participants who reported 6–12 years of education. However, the rates increased to 11.07%, 37.04%, and 42.09% in participants who reported 15 or more years of education (Table 2). Marital status significantly affected the rate of MCI ($p < 0.001$), SCD ($p = 0.034$), and Pre-MCI SCD ($p < 0.001$). Participants with a single status had the highest rate of SCD and pre-MCI SCD, and participants with a widowed status had the highest rate of MCI (Table 2).

Our multivariate analysis indicated that participants with physical frailty showed a high risk of MCI with SCD (odds ratio [OR] = 2.21, 95% confidence interval [95%CI] 1.50–3.27) and low risk of pre-MCI SCD risk ([OR] = 0.55, [95%CI] 0.40–0.77) but was not associated with MCI without SCD ($p = 0.519$) (Table 3). Participants with physical pre-frailty showed high cognitive impairment risk. Physical pre-frailty was marginally associated with MCI without SCD ([OR] = 1.71, [95%CI] 0.95–3.05) and significantly associated with MCI with SCD ([OR] = 1.51, [95%CI] 1.16–1.97) and pre-MCI SCD ([OR] = 2.45, [95%CI] 2.14–2.81).

PREVALENCE OF COGNITIVE FRAILTY IN ELDERLY CHINESE

Table 2
 Number of participants and prevalence of MCI, MCI+SCD, and Pre-MCI SCD

		MCI			Prevalence (%)	Pre-MCI SCD	Prevalence (%)	SCD	Prevalence (%)
		With MCI and no SCD	With MCI and missing SCD	With MCI+SCD					
All participants	5172	55	114	331	9.67	1821	35.20	2152	41.61
Age, y					P<0.001		P<0.001		P<0.001
60-69	2372	21	21	63	4.43	631	26.60	694	29.26
70-79	1934	27	37	117	9.36	764	39.50	881	45.55
≥80	866	7	56	151	24.71	426	49.19	577	66.63
Sex					P=0.041		P<0.001		P<0.001
Females	2764	29	49	172	9.04	1038	37.55	1210	43.78
Males	2408	26	65	159	10.38	783	32.52	942	39.12
Educational level, y					P=0.147		P<0.001		P<0.001
≤6	489	11	36	55	20.86	231	47.24	286	58.49
6-12	3458	34	57	200	8.42	1081	31.26	1281	37.04
≥15	822	8	18	65	11.07	346	42.09	411	50
Marital status					P<0.001		P=0.001		P=0.034
Single	75	0	0	7	9.33	45	60	52	69.33
Married	4717	52	86	272	8.69	1648	34.94	1920	40.70
Widowed	262	3	26	42	27.1	90	34.35	132	50.38

Table 3
 Results from logistic regression analyses that evaluated the association among MCI, MCI+SCD, and pre-MCI SCD with physical pre-frailty or physical frailty after adjusting by sex, age, education level, and marital status

	%	MCI without SCD	p	MCI with SCD	p	Pre-MCI SCD	p
		OR(95%CI)		OR(95%CI)		OR(95%CI)	
Physical frailty	4.41	1.50(0.44-5.17)	0.519	2.21 (1.50-3.27)	<0.001	0.55 (0.40-0.77)	<0.01
Physical pre-frailty	35.86	1.71(0.95-3.05)	0.072	1.51 (1.16-1.97)	0.002	2.45 (2.14-2.81)	<0.001

Odds Ratio (95% Confidence Interval) Adjusted for age, sex, educational level and marital status

Age was also a key influence factor of cognitive frailty phenotypes. The rate of reversible and potentially reversible cognitive frailty was 15.60% and 2.02% in the age range of 60–69 years and significantly increased to 30.51% and 20.73% at 80 years and older (Tables 1 and 4). The rate of cognitive frailty phenotypes was higher in females than in males but not significant in potentially reversible cognitive frailty. Participants with ≤6 years of education had a 25.11% rate of reversible cognitive frailty and 17.60% rate of potentially reversible cognitive frailty, whereas the rates were reduced to 18.09% and 4.71% in participants who reported 6–12 years of education. However, the rates increased to 25.06% and 8.23% in participants who reported 15 or more years of education (Tables 1 and 4). Participants with a single status had a significantly high rate of reversible cognitive frailty (33.33%), and these participants with a widowed status had higher rate of potentially reversible cognitive frailty (20.16%), but that was not significant compared with individuals with other marital

status (Table 4).

Multivariate logistic regression analysis indicated that age was the most significant influence factor of frailty phenotypes (Table 4). Compared with participants aged 60–69 years, the OR values and 95%CI significantly increased to 5.58 (4.55-6.83) in physical pre-frailty, 13.20 (8.64-20.15) in physical frailty, 4.45 (3.65-5.44) in reversible cognitive frailty, and 19.71 (13.49-28.79) in potentially reversible cognitive frailty at 80 years and older. Males had significantly low prevalence of physical pre-frailty and reversible cognitive frailty. Participants with a middle education level (6–12 years) had a significantly low rate of physical frailty ([OR] = 0.618, [95%CI] 0.428-0.893) and potentially reversible cognitive frailty ([OR] = 0.58, [95%CI] 0.40-0.84) compared with participants with a low education level (≤6 years). However, participants with a high education level (≥15 years) had a significantly high rate of physical pre-frailty ([OR] = 1.43, [95%CI] 1.10-1.86) and reversible cognitive frailty ([OR] = 1.48, [95%CI] 1.12-1.94)

Table 4

ORs and 95% confidence intervals for prevalence of the physical and cognitive frailty phenotypes by sex, age, education, and marital status

	Physical pre-frailty		Physical frailty		Reversible cognitive frailty		Potentially reversible cognitive frailty	
	OR (95% Confidence Interval)	P	OR (95% Confidence Interval)	P	OR (95% Confidence Interval)	P	OR (95% Confidence Interval)	P
Age, y		0.000		0.000		0.000		0.000
60-69	1		1		1		1	
70-79	2.142 (1.867-2.458)	0.000	1.859 (1.176-2.94)	0.008	1384(1.179-1.625)	0.000	2.928(2.03-4.222)	0.000
≥80	5.576(4.549-6.834)	0.000	13.195(8.642-20.145)	0.000	4.454(3.65-5.436)	0.000	19.708(13.492-28.788)	0.000
Sex		0.000		0.215		0.000		0.858
Females	1		1		1		1	
Males	0.764(0.671-0.869)		0.827(0.612-1.117)		0.744(0.644-0.859)		0.975(0.741-1.284)	
Educational level, y		0.000		0.037		0.000		0.001
≤6	1		1		1		1	
6-12	0.845 (0.672-1.062)	0.148	0.618(0.428-0.893)	0.01	0.954(0.751-1.21)	0.696	0.583(0.404-0.84)	0.004
≥15	1.434(1.104-1.862)	0.007	0.73(0.459-1.161)	0.184	1.476(1.124-1.938)	0.005	1.004(0.647-1.558)	0.986
Marital status		0.825		0.067		0.033		0.02
Single	1		1		1		1	
Married	0.879(0.489-1.581)	0.667	2.093 (0.627-6.983)	0.229	0.479(0.273-0.841)	0.01	0.995(0.327-3.025)	0.993
Widowed	0.826(0.435-1.568)	0.558	1.194 (0.328-4.345)	0.788	0.452(0.241-0.847)	0.013	1.802(0.564-5.757)	0.32

(Table 4). Participants with a married ([OR] = 0.50, [95%CI] 0.27-0.84) or widowed status ([OR] = 0.45, [95%CI] 0.24-0.85) had significantly low rate of reversible cognitive frailty compared with those with a single status (Table 4).

Discussion

Our study indicated that the rate of reversible cognitive frailty was 19.86%. According to our review of the literature, our study was the first to investigate the prevalence of reversible cognitive frailty in a large cross-sectional population setting. Only 1 retrospective analysis demonstrated that the combined prevalence of physical frailty and pre-MCI SCD was 2.5% (13). The evident difference in our report resulted from the different diagnostic criteria. The rate of physical pre-frailty, physical frailty, and physical frailty combined pre-MCI SCD in our study was 35.86%, 4.41%, and 2.5%, respectively. The same rate of reversible cognitive frailty would be obtained if physical pre-frailty was excluded in our model even if we used different assessment tool for physical frailty (Supplementary figure 1). In a sample of 1051 community-dwelling older adults aged 65 years or older in Singapore, physical frailty and physical pre-frailty was 6.2% and 37%, respectively, which were similar with our rates when same assessment tool FRAIL was used (31). The similar rate of frailty and pre-frailty was approximately 3% and 33% and had been reported in 2375 community-living Chinese aged 55 years and older without dementia (12) and 2% and 32% in 1575 community-living

Chinese older adults when CHS or modified CHS criteria was applied (32). The rate of physical frailty in this study was also comparable to the reported results in large cohort of community-dwelling elderly aged 65 years and over of other different countries' studies (1, 7, 8, 30, 34-39).

The other component of the construct of reversible cognitive frailty was pre-MCI SCD, after excluding MCI with SCD in nondementia individuals. Different questionnaires (13, 22, 26, 40) or simple questions about memory domain (41) have been used to assess SCD. In this study, according to the criteria proposed by the SCD-I Working Group (24), we excluded dementia and MCI by using RCS score criteria. Next, we assessed pre-MCI SCD in participants with an RCS score 8-10 and MCI with SCD in participants with RCS scores 6-7 by using the simplified SCD questionnaire (22, 26). The prevalence of pre-MCI SCD was 35.20% in our study. In a Greek population of 1454 elderly adults aged 65 years or older who had no dementia, MCI, and severe anxiety or depression, the rate of pre-MCI SCD was 58.3% (with one of SCD complains) or 21.5% (with two of SCD complains) (22). The rate of pre-MCI SCD were between 58.3% and 21.5%.

Additionally, 6.3% of participants had potentially reversible cognitive frailty in our study, which was lower than the rate (10.7%) in a sample of 2375 Chinese Singaporeans aged ≥55 years without dementia (12). But the prevalence of coexisting physical frailty and MCI and physical pre-frailty with MCI was 1.8% and 8.9%, which was similar to the 2% and 8.5% reported in our results (Supplementary figure 1), despite the different

PREVALENCE OF COGNITIVE FRAILITY IN ELDERLY CHINESE

screening tools used. In another same cognitive frailty model including physical pre-frailty in an Italian older population, the rate (4.4%) of potentially cognitive frailty was similar to our report (18). Only 1 reported rate of potentially cognitive frailty in a retrospective study of older population (≥ 65 years) was higher than in our study, in which physical frailty was screened with a frailty index (>0.25) (42).

In most studies of older populations in other countries (8, 30, 31, 32, 33), physical pre-frailty was excluded in the cognitive frailty construct. In a sample of 8864 older adults aged ≥ 65 years in Japan, the rate of MCI and potentially reversible cognitive frailty was 5.2% and 1.2%, which were lower than our results (9.67% and 6.2%) even if a higher rate of physical frailty (7.2%) was observed in the aforementioned cohort (30). The different screening tool for physical frailty and MCI, and cognitive frailty model might result in the different results. In addition, in all types of clinical studies, the significantly high prevalence of potentially cognitive frailty was reported (9, 17, 43-45).

The relationship between sociodemographics and physical and potentially reversible cognitive frailty had been reported (7, 16, 22, 31, 36, 39, 46). However, the relationship with reversible cognitive frailty was absent. Our multivariate logistic analysis indicated that the participants with the highest risk of developing physical and cognitive frailty phenotypes were aged 80 years and older (Table 4). Females with high education had significantly increased risk of physical pre-frailty and reversible cognitive frailty (Table 4). Participants with a single status had significantly high risk of reversible cognitive frailty. Individuals with a middle level of education had a lower risk of all frailty phenotypes and a significantly low risk for physical and potentially reversible cognitive frailty. A similar trend of education's effect had also been observed in cognitive impairments (Table 2). The more working stress with high education level which lead to chronic systemic information, which might be the potential mechanism.

The association of physical frailty and cognitive impairment, including MCI (39, 47) and SCD (22, 42), had been reported. But physical pre-frailty was not included in physical frailty construct. Our logistic model indicated that physical frailty phenotypes were significantly associated with SCD, including MCI with SCD and pre-MCI SCD. Same as the combination of cognitive impairment and physical frailty, the combination of physical pre-frailty also could predict risks of adverse health outcomes (10). Therefore, physical pre-frailty was suggested to add to cognitive frailty construct. Our results indicated pre-MCI SCD had a positive association with physical pre-frailty and was negatively related to physical frailty (Table 3). Nevertheless, these associations could not explain the causal relationship of the 2 disorders. The emergence order of physical frailty and cognitive impairment might evolve into different etiologies (48), which might result in different diseases. Thus, a follow-up of the progress of these participants with only a physical frailty phenotype or cognitive impairment would

be a worthwhile topic for further research to improve the understanding of the potential mechanisms of cognitive frailty.

According to our review of the literature, this representative epidemiological study is the first with a large number of participants that systemically explores the rate of cognitive impairment, physical, and cognitive frailty phenotypes for a Chinese population of elderly adults. Additionally, the risk-related sociodemographics of these disorders and the relationship between physical frailty phenotypes and cognitive impairment were also investigated in depth. Moreover, broadly validated screening tools or an accepted questionnaire that assured the feasibility, and considered correctness were used. A limitation of our study is as follows: because frailty phenotype consensus is absent, we did not screen other frailty phenotypes.

We developed a rapid screening tool of cognitive frailty phenotypes based on validated questionnaires of physical frailty and cognitive function. The prevalence of reversible and potentially reversible cognitive frailty was 19.86% and 6.3%. Older single females with a high education level had a high risk of reversible cognitive frailty, and younger individuals with a middle education level had a low risk of potentially reversible cognitive frailty. Physical pre-frailty was associated with SCD and should include in cognitive frailty construct. Increasing elderly (aged 60 years and over) population in the municipality of Shanghai represents more than 33% of its total permanent population. Screening high-risk individuals and implementing adequate intervention would significantly improve their functional status and the quality of life.

Acknowledgements: We would like to thank the healthcare staff members who were involved in this study.

Statement of author's contributions to manuscript: RQ, YZ: Study design. RQ, YZ: Writing the manuscript. RQ, XF, GK, ZW, RJ: Analysis and interpretation of data. All authors contributed to experimental investigation and gave final approval of this version.

Ethics approval: Informed consent was obtained from all individual participants included in the study. And the study protocol was approved by Hudong Hospital Research Ethics Committee, Fudan University.

Sources of Financial Support: The Shanghai study of health promotion for elderly individuals with frailty was supported by the Medical Science and Technology Support Project of Shanghai Science and Technology Commission (grant no.18411962200), the Shanghai Hospital Development Center (grant no. SHDC12014221) and the Shanghai key Clinical Geriatric Medicine Center Construction (grant no. 2017ZZ02010).

Conflicts of interest: There are no conflicts of interest.

References

1. Fried, L.P., Tangen, C.M., Walston, J., Newman, A.B., Hirsch, C., Gottdiener, J., Seeman, T., Tracy, R., Kop, W.J., Burke, G., McBurnie, M.A. Frailty in older adults: evidence for a phenotype. *The journals of gerontology. Series A, Biological sciences and medical sciences* 2001;56 (3):M146-156. doi:10.1093/gerona/56.3.m146
2. Kelaiditi, E., Cesari, M., Canevelli, M., van Kan, G.A., Ousset, P.J., Gillette-Guyonnet, S., Ritz, P., Duveau, F., Soto, M.E., Provencher, V., Nourhashemi, F., Salva, A., Robert, P., Andrieu, S., Rolland, Y., Touchon, J., Fitten, J.L., Vellas, B. Cognitive frailty: rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. *The journal of nutrition, health & aging* 2013;17 (9):726-734. doi:10.1007/s12603-013-0367-2
3. Ma, L., Sun, F., Tang, Z. Social Frailty Is Associated with Physical Functioning, Cognition, and Depression, and Predicts Mortality. *The journal of nutrition, health & aging* 2018;22 (8):989-995. doi:10.1007/s12603-018-1054-0
4. Yamada, M., Arai, H. Social Frailty Predicts Incident Disability and Mortality Among

- Community-Dwelling Japanese Older Adults. *Journal of the American Medical Directors Association* 2018;19 (12):1099-1103. doi:10.1016/j.jamda.2018.09.013
5. Rietman, M.L., Spijkerman, A.M.W., Wong, A., Steeg, H.V., Bürkle, A., Moreno-Villanueva, M., Sindlinger, T., Franceschi, C., Grubeck-Loebenstien, B., Bernhardt, J. Antioxidants linked with physical, cognitive and psychological frailty: Analysis of candidate biomarkers and markers derived from the MARK-AGE Study. *Mechanisms of Ageing & Development* 2018;1043659618772347
 6. Solfrizzi V, Scafato E, Lozupone M, et al. Biopsychosocial frailty and the risk of incident dementia: The Italian longitudinal study on aging. *Alzheimers Dement*. 2019;pii: S1552-5260(1519)30120-30127.
 7. Josep, G.O., Laia, C.P., Secundino, L.P., Manuel, D.G.B., Joan, V.F. Prevalence of frailty phenotypes and risk of mortality in a community-dwelling elderly cohort. *Age & Ageing* 2013;42 (1):46-51
 8. Hiroyuki, S., Takehiko, D., Sangyoon, L., Hyuma, M., Liang-Kung, C., Hidenori, A. Cognitive Frailty Predicts Incident Dementia among Community-Dwelling Older People. *Journal of Clinical Medicine* 2016;20:729-735
 9. Jha, S.R., Hannu, M.K., Gore, K., Chang, S., Newton, P., Wilhelm, K., Hayward, C.S., Jabbour, A., Kotlyar, E., Keogh, A. Cognitive impairment improves the predictive validity of physical frailty for mortality in patients with advanced heart failure referred for heart transplantation. *Journal of Heart & Lung Transplantation the Official Publication of the International Society for Heart Transplantation* 2016;35 (9):1092-1100
 10. Yu, R., Morley, J.E., Kwok, T., Leung, J., Cheung, O., Woo, J. The Effects of Combinations of Cognitive Impairment and Pre-frailty on Adverse Outcomes from a Prospective Community-Based Cohort Study of Older Chinese People. *Frontiers in Medicine* 2018;5:50
 11. Ruan, Q., Yu, Z., Chen, M., Bao, Z., Li, J., He, W. Cognitive frailty, a novel target for the prevention of elderly dependency. *Ageing Research Reviews* 2015;20:1-10
 12. Feng, L., Ma, S.Z.N., Gao, Q., Feng, L., Yap, K.B., Ng, T.P. Cognitive Frailty and Adverse Health Outcomes: Findings From the Singapore Longitudinal Ageing Studies (SLAS). *Journal of the American Medical Directors Association* 2017;18 (3):252-258
 13. Solfrizzi, V., Scafato, E., Seripa, D., Lozupone, M., Imbimbo, B.P., D'Amato, A., Tortelli, R., Schilardi, A., Galluzzo, L., Gandin, C. Reversible Cognitive Frailty, Dementia, and All-Cause Mortality. *The Italian Longitudinal Study on Aging. Journal of the American Medical Directors Association* 2017;18 (1):89.e81-89.e88
 14. Panza, F., Lozupone, M., Solfrizzi, V., Stallone, R., Bellomo, A., Greco, A., Daniele, A., Seripa, D., Logroscino, G. Cognitive Frailty: A Potential Target for Secondary Prevention of Dementia. *Expert Opinion on Drug Metabolism & Toxicology* 2017;13 (10):17425255.17422017.11372424
 15. Panza, F., Lozupone, M., Solfrizzi, V., Sardone, R., Dibello, V., Lena, L.D., D'Urso, F., Stallone, R., Petrucci, M., Giannelli, G. Different Cognitive Frailty Models and Health- and Cognitive-related Outcomes in Older Age: From Epidemiology to Prevention. *Journal of Alzheimers Disease* 2018;62 (3):993-1012
 16. Sugimoto, T., Sakurai, T., Ono, R., Ai, K., Saji, N., Niida, S., Toba, K., Chen, L.K., Arai, H. Epidemiological and clinical significance of cognitive frailty: A mini review. *Ageing Research Reviews* 2018;44:1
 17. Delrieu, J., Andrieu, S., Pahor, M., Cantet, C., Cesari, M., Ousset, P.J., Voisin, T., Fougère, B., Gillette, S., Carrie, I. Neuropsychological profile of "cognitive frailty" subjects in MAPT study. *Journal of Prevention of Alzheimers Disease* 2016;3 (3):151
 18. Roppolo, M., Mulasso, A., Rabaglietti, E. Cognitive frailty in Italian community-dwelling older adults: Prevalence rate and its association with disability. *Journal of Nutrition Health & Aging* 2017;6(6):631-636
 19. Rockwood, K., Mitnitski, A. Frailty in relation to the accumulation of deficits. *The journals of gerontology. Series A, Biological sciences and medical sciences* 2007;62 (7):722-727. doi:10.1093/gerona/62.7.722
 20. Morley, J.E., Malmstrom, T.K., Miller, D.K. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *Journal of Nutrition Health & Aging* 2012;16 (7):601-608
 21. Woo, J., Leung, J., Morley, J.E. Comparison of frailty indicators based on clinical phenotype and the multiple deficit approach in predicting mortality and physical limitation. *Journal of the American Geriatrics Society* 2012;60 (8):1478-1486
 22. Margioli, E., Kosmidis, M.H., Yannakoulia, M., Dardiotis, E., Hadjigeorgiou, G., Sakka, P., Ntanasi, E., Vlachos, G.S., Scarmeas, N. Exploring the association between subjective cognitive decline and frailty: the Hellenic Longitudinal Investigation of Aging and Diet Study (HELIAD). *Ageing & Mental Health* 2019:1-11
 23. Peters, L.L., Han, B., Buskens, E., Slaets, J.P.J. Measurement Properties of the Groningen Frailty Indicator in Home-Dwelling and Institutionalized Elderly People. *Journal of the American Medical Directors Association* 2012;13 (6):546-551
 24. Jessen, F., Amariglio, R.E., Bostel, M.V., Breteler, M., Ceccaldi, M., Chételat, G., Dubois, B., Dufouil, C., Ellis, K.A., Flier, W.M.V.D. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimers & Dementia the Journal of the Alzheimers Association* 2014;10 (6):844-852
 25. Perrotin, A., La, J.R., De, L.S.V., Barré, L., Mézenge, F., Mutlu, J., Guilleateau, D., Egret, S., Eustache, F., Chételat, G. Subjective cognitive decline in cognitively normal elders from the community or from a memory clinic: Differential affective and imaging correlates. *Alzheimers & Dementia the Journal of the Alzheimers Association* 2017;13 (5):550-560
 26. Lorena, R., Mollica, M.A., Carmen, G.S., Judith, S.A., Belen, S., Isabel, S., Cinta, V.P., Magda, C., Jaume, O., Molinuevo, J.L. The Subjective Cognitive Decline Questionnaire (SCD-Q): a validation study. *Journal of Alzheimers Disease* 2014;41 (2):453
 27. Steffen, W., Frank, J., Alexander, K., Luca, K., Klaus, S., Lutz, F.L., Alexander, K., Stefanie, S., Harald, H., Isabella, H. Subjective cognitive decline is related to CSF biomarkers of AD in patients with MCI. *Neurology* 2015;84 (12):1261-1268
 28. Roeher, S., Luck, T., Pabst, A., Bickel, H., König, H.H., Lüthmann, D., Fuchs, A., Wolfsgruber, S., Wiese, B., Weyerer, S. Subjective cognitive decline is longitudinally associated with lower health-related quality of life. *International Psychogeriatrics* 2017;29 (12):1-12
 29. Malmstrom, T.K., Voss, V.B., Cruz-Oliver, D.M., Cummings-Vaughn, L.A., Tomosa, N., Grossberg, G.T., Morley, J.E. The Rapid Cognitive Screen (RCS): A point-of-care screening for dementia and mild cognitive impairment. *Journal of Nutrition Health & Aging* 2015;19 (7):741-744
 30. Shimada, H., Makizako, H., Lee, S., Doi, T., Lee, S., Tsutsumimoto, K., Harada, K., Hotta, R., Bae, S., Nakakubo, S. Impact of cognitive frailty on daily activities in older persons. *Journal of Nutrition Health & Aging* 2016;20 (7):729-735
 31. Merchant, R.A., Chen, M.Z., Tan, L., Lim, M.Y., Ho, H.K., van Dam, R.M. Singapore Healthy Older People Everyday (HOPE) Study: Prevalence of Frailty and Associated Factors in Older Adults. *Journal of the American Medical Directors Association* 2017;18 (8):S1525861017302438
 32. Feng, L., Nyunt, M.S., Gao, Q., Feng, L., Lee, T.S., Tsoi, T., Chong, M.S., Lim, W.S., Collinson, S., Yap, P. Physical Frailty, Cognitive Impairment, and the Risk of Neurocognitive Disorder in the Singapore Longitudinal Ageing Studies. *The journals of gerontology. Series A, Biological sciences and medical sciences* 2016;72 (3):369-375
 33. Solfrizzi, V., Scafato, E., Lozupone, M., Seripa, D., Giannini, M., Sardone, R., Bonfiglio, C., Abbrescia, D.I., Galluzzo, L., Gandin, C. Additive Role of a Potentially Reversible Cognitive Frailty Model and Inflammatory State on the Risk of Disability: The Italian Longitudinal Study on Aging. *Am J Geriatr Psychiatry* 2017;20 (6):704
 34. Matteo, C., Christiaan, L., Fulvio, L., Graziano, O., Stefania, B., Cinzia, M., Guralnik, J.M., Marco, P., Luigi, F. Frailty syndrome and skeletal muscle: results from the Invecchiare in Chianti study. *American Journal of Clinical Nutrition* 2006;83 (5):1142-1148
 35. Avila-Funes, J.A., Helmer, C., Amieva, H., Barberger-Gateau, P., Le, G.M., Ritchie, K., Portet, F., Carrière, I., Tavernier, B., Gutia@Rez-Robledo, L.M. Frailty among community-dwelling elderly people in France: the three-city study. *The journals of gerontology. Series A, Biological sciences and medical sciences* 2008;63 (10):1089-1096
 36. Holly, S., Roberts, H.C., Maria, E., Cyrus, C., Howard, B., Avan, A.S. Prevalence and correlates of frailty among community-dwelling older men and women: findings from the Hertfordshire Cohort Study. *Age & Ageing* 2010;39 (2):197-203
 37. Garcia-Garcia, F.J., Avila, G.G., Alfaro-Acha, A., Andres, M.S.A., Lanza, M.D.L.A.d.I.T., Aparicio, M.V.E., Aparicio, S.H., Zugasti, J.L.L., Reus, G.S., Rodriguez-Artalejo, F. The prevalence of frailty syndrome in an older population from Spain. The Toledo study for healthy aging. *Journal of Nutrition Health & Aging* 2011;15 (10):852-856
 38. Castell, M.V., Sánchez, M., Julián, R., Queipo, R., Martín, S., Otero, Á. Frailty prevalence and slow walk-ing speed in persons age 65 and older: implications for primary care. *BMC Family Practice* 2013;14 (1):86-86
 39. Shimada, H., Makizako, H., Doi, T., Yoshida, D., Tsutsumimoto, K., Anan, Y., Uemura, K., Ito, T., Lee, S., Park, H. Combined Prevalence of Frailty and Mild Cognitive Impairment in a Population of Elderly Japanese People. *Journal of the American Medical Directors Association* 2013;14 (7):518-524
 40. Rabin, L.A., Smart, C.M., Crane, P.K., Amariglio, R.E., Berman, L.M., Mercé, B., Buckley, R.F., Gal, C., Bruno, D., Ellis, K.A. Subjective Cognitive Decline in Older Adults: An Overview of Self-Report Measures Used Across 19 International Research Studies. *Journal of Alzheimers Disease* 2015;48 Suppl 1 (s1):S63
 41. Hsieh, T.J., Chang, H.Y., Wu, I., Chen, C.C., Tsai, H.J., Chiu, Y.F., Chuang, S.C., Chao, A.H., Hsu, C.C. Independent association between subjective cognitive decline and frailty in the elderly. *Plos One* 2018;13 (8):e0201351
 42. St John, P.D., Tyas, S.L., Griffith, L.E., Menec, V. The cumulative effect of frailty and cognition on mortality - results of a prospective cohort study. *International Psychogeriatrics* 2017;29 (4):535-543
 43. Monterodasso, M.M., Barnes, B., Speechley, M., Muir Hunter, S.W., Doherty, T.J., Duque, G., Gopaul, K., Sposato, L.A., Casasherrero, A., Borrie, M.J. Disentangling cog-nitive-frailty: results from the gait and brain study. *Journals of Gerontology* 2016;glw044

PREVALENCE OF COGNITIVE FRAILTY IN ELDERLY CHINESE

44. Fougere, B., Dumas, M., Lilamand, M., Sourdet, S., Delrieu, J., Vellas, B., Abellan van Kan, G. Association Between Frailty and Cognitive Impairment: Cross-Sectional Data From Toulouse Frailty Day Hospital. *J Am Med Dir Assoc* 2017;18 (11):990-991. doi:10.1016/j.jamda.2017.06.024
45. Wanasatna, K., Muangpaisan, W., Kuptniratsaikul, V., Chalerm Sri, C., Nuttamonwarakul, A. Prevalence and Factors Associated with Frailty and Cognitive Frailty Among Community-Dwelling Elderly with Knee Osteoarthritis. *Journal of Community Health* 2019;44(3):587-595
46. Brigola, A.G., Alexandre, T.D.S., Inouye, K., Yassuda, M.S., Pavarini, S.C.I., Mioshi, E. Limited formal education is strongly associated with lower cognitive status, functional disability and frailty status in older adults. *Dement Neuropsychol* 2019;13(2):216-224. doi:10.1590/1980-57642018dn13-020011
47. Brigola, A.G., Rossetti, E.S., Santos, B.R.D., Neri, A.L., Zazzetta, M.S., Inouye, K., Pavarini, S.C.I. Relationship between cognition and frailty in elderly: A systematic review. *Dementia & Neuropsychologia* 2015;9 (2):110-119
48. Chu, N.M., Bandeen-Roche, K., Tian, J., Kasper, J.D., Gross, A.L., Carlson, M.C., Xue, Q.L. Hierarchical Development of Frailty and Cognitive Impairment: Clues into Etiological Pathways. *J Gerontol A Biol Sci Med Sci*. 2019;pii: glz134.