

Loneliness as a risk factor for frailty transition among older Chinese people

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Abstract

Background: Previous literature has reported that loneliness is a strong predictor of frailty risk. However, less is known about the role of loneliness in frailty transition types. This study aimed to examine whether and how loneliness are related to frailty transition among older Chinese people.

Methods: Our study used participants (aged ≥ 60 years) from 2008/2009, 2011/2012 and 2014 waves of the Chinese Longitudinal Healthy Longevity Survey (CLHLS). Loneliness was assessed by a single question asking how often the respondent feels lonely. The FRAIL Scale was created to measure physical frailty for our study, and frailty was also assessed by a broader definition of the frailty index. Frailty transition as an outcome variable has been designed as two types according to the measurement of frailty.

Results: Greater loneliness at baseline reduced the possibility of remaining in a robust or prefrail physical frailty state after 3 years (OR=0.78, 95%CI: 0.68–0.91, $p<0.01$). Greater loneliness was associated with an increased risk of worsening physical frailty over time: compared with those who had never felt lonely, the odds ratios for people who often felt lonely were 1.19 (95%CI: 1.01–1.41, $p<0.05$) after 3 years and 1.34 (95%CI: 1.08–1.66, $p<0.01$) after 6 years. The association between loneliness and change in the frailty index differed in the survey periods: loneliness at baseline was found to increase the possibility of participants remaining in frailty (seldom loneliness: OR= 1.78, 95%CI: 1.25–2.55, $p<0.01$; often loneliness: OR= 1.74, 95%CI: 1.21–2.50, $p<0.01$) after 6 years, but no significance was shown in the 3-year follow up. Additionally, loneliness at baselines was significantly associated with frailty transition at follow up among the male participants. However, a similar association was not observed among the female participants.

Conclusion: Older people with a high level of loneliness tend to be frail in the future, and greater loneliness is related to an increased risk of worsening frailty and remaining frail. Male elderly with a high level of loneliness were more likely to have a worse frailty transition than female elderly in China.

Background

Populations around the world are rapidly aging and this is a particularly severe challenge in China, a country where population is aging at a significantly faster rate than other low and middle-income countries [1]. According to data published by the National Bureau of Statistics of China, 17.3% of total population were aged 60 years and over in 2017. On the other hand, due to the implementation of the one-child policy in the earlier decades and recent increasing population mobility, the family size in China has been declining substantially, leading to over 50% of the urban and 60% of rural elderly living in empty-nest households, and the proportion of older people living alone in China was 12.5% in 2010, an increase by 30% in prior two decades [2, 3]. These all have important implications for the health and social care for the elderly.

Frailty is the most outstanding expression of population aging [4]. It is a syndrome that predicts vulnerability to adverse outcomes and is recognized as a dynamic state with the potential for reversibility [4-7]. There are currently two major models of frailty: firstly, the frailty phenotype model which views frailty from the physiological systems defined frailty as several biological syndromes [8]; secondly, the frailty deficit model measures frailty as problems resulting from a multidimensional system, including biological, physiological and psychological [9]. Despite a sizeable literature on the adverse outcomes of frailty, such as falls [10], disability [11, 12], hospitalization [13], institutional care [14, 15], and mortality [16-18], relatively little is known about the transition of frailty in old people. Although frailty is inevitable with increasing age [19], it is not irreversible, as well as agreeable to be a dynamic process involving improvement and natural procession [4].

Loneliness is a common and dissatisfaction feeling of one's social relationship which is nowadays becoming a serious public health issue for old people [20, 21]. Loneliness has been observed to be associated with subsequent adverse outcomes, such as mortality [22, 23], comorbidity [24, 25], poor functional ability [26, 27], depression [28], and cognitive decline [29]. At the biological level, a large number of studies had found that the feeling of loneliness is associated with increased blood pressure [30, 31], increased risk of cardio-cerebrovascular and inflammatory diseases [32-34], impaired immune function[35], and increased likelihood of sarcopenia[36].

Frailty, defined by phenotype model or frailty index, is associated with loneliness [37-39]. A cross-sectional study of Mexican community-dwelling elderly found that loneliness was independently associated with frailty [37]. The cohort study discovered that

the relationship between frailty and loneliness may be bidirectional: loneliness was related to the change in frailty status, and vice versa [38, 40]. However, studies on the association between loneliness and frailty were focused on loneliness and frailty risk, and none have specified the association between loneliness and frailty transition types, including remaining frail, worsening or improvement in frailty status, etc. Furthermore, the existing research was based mostly on the Western society, and much less is known for old people in others.

A study of Chinese older adults had reported that 51.2% and 7.0% of older adults aged 60 years and above were prefrail and frail [41]. However, there is little research on frailty transitions in China. It had reported that about 30.4% of participants had transitioned between different frailty status in 2002-2005 [42]. Meanwhile, one study had shown that loneliness was related to culture and social policies [43]. People from collectivist cultures are more likely to feel lonely [44]. It was reported that about 30% of Chinese older adults reported feeling of loneliness [45]. We speculated that loneliness could have more influence on frailty transition in China. Gender difference in frailty and loneliness is well-known [46, 47]. Females tend to have a higher incidence of frailty than males [48, 49] and it was suggested that this may be attributable to both biological and socioeconomic factors [50]. Studies had shown that loneliness was strongly associated with adverse health conditions in males than in females [51, 52]. Thus, it can be assumed that association between loneliness and frailty transitions is gender-related.

Our study aims to examine the association between loneliness and frailty transition among older adults over 60 years in China. We have made two hypotheses: 1) loneliness is related to frailty transition; and 2) the relationship in loneliness and frailty is different by gender. We believe that our study would help to close the gap in the existing literature by using a nationally representative longitudinal sample in China and the results would also be useful in informing policy making in health and social care.

Method

Data

The data comes from the Chinese Longitudinal Healthy Longevity Survey (CLHLS) which was the first and largest nationwide longitudinal survey in China. It is designed to investigate the determinants of health and longevity of older adults in China. So far, it had collected information in half of the randomly selected cities/counties in 23 out of 31 provinces in China, with a total number of 113,000 households being interviewed. The CLHLS was initiated in 1998, and follow-up interviews were conducted in 2000–2002–2005–2008/2009–2011/2012–2014 and 2017-2018 respectively [53]. The questionnaire contained demographic information, lifestyle, diet, self-reported health, psychological health, activities of daily living (ADL) and instrumental activities of daily living (IADL), etc. The rationales, more details of the survey design, and data quality were published elsewhere [54].

Our study utilized the participants of CLHLS in 2008/2009, 2011/2012 and 2014 to conduct two cohorts. Briefly, among the 16840 participants (aged ≥ 60 years) in 2008/2009, 2782 (17%) were lost to follow-up and 5633 (33%) died before the 2011/2012 survey. We excluded those lost to follow-up due to their unknown information and removed those who died before the follow-up to eliminate the effect of mortality. That leaves a valid sample size of 8425 participants to be analyzed for the 3-year follow-up period (2008-2011). Among the 16840 participants (aged ≥ 60) in 2008/2009, 8415 (50%) died or lost to follow-up in 2008-2011 waves, 591 (4%) were lost to follow-up in the 2014 survey and 2589 (15%) died before 2014 survey. There were 5245 (31%) participants alive for analysis for the 6-year follow-up period (2008-2014). The Flowchart of the study is shown in Figure 1.

Measures

Loneliness

Loneliness was measured with one single question asking how often the respondent feels lonely. The 5-point response scale ranged from “never” to “always”. Single-item questions are sometimes known as self-rating measures of loneliness as they can ask directly for the individual’s assessment of how lonely they feel. The single-question of loneliness has been used widely [55-57] and proved to be valid and highly correlated with multi-item loneliness scales [58, 59]. Because the question on loneliness in CLHLS is highly skewed with fewer respondents in

the “always” and “often” categories, we classified “sometimes” “often” and “always” into one category and “seldom” and “never” into another category to show the level of loneliness.

Frailty status

FRAIL Scale [60] was created to measure physical frailty for our study. It consists of 5 simple questions to assess the presence of fatigue, muscle resistance, aerobic capacity, disease burden, and weight loss [61]. Those who met three or more components were defined as frail, those 1 or 2 components as prefrail and those without any were defined as robust [60, 62]. Based on the CLHLS questionnaire design, we made some adjustments to the FRAIL Scale indicators. Each item in the FRAIL Scale was dichotomized and mapped to the interval 0-1. Fatigue was measured using the question of “Do you feel the older you get, the more useless you are?” The analysis codes “never”, “seldom”, and “sometimes” as 0 and 1 if otherwise. Resistance was measured with “Can you continuously crouch and stand up three times?” and Ambulation with “Can you walk continuously for 1 kilometer at a time by yourself?”. For the two variables, the analysis recodes 0 for “without assistance” and 1 for otherwise. Illness was measured by self-reporting of more than 5 kinds of illness was coded as 1. Loss of weight was measured by BMI (weight (in kilograms)/height (in meters) ²) with the same cutoff points of underweight (<18.5).

Our study also used another model of the frailty index to measure the dimensions of frailty. It has been suggested that at least 30 deficits are needed in the frailty index [63]. We used 37 indicators of various dimensions of frailty status, which was coded as 1 when deficits happened and assigned a score of 2 if the respondents had a serious illness that caused him/her to be hospitalized or bedridden two or more times [18, 64, 65]. A high value in frailty index indicated poorer frailty. We also classified the continuous frailty index into nonfrail (FI≤0.21) and frail (FI>0.21) based on previous studies [42, 66]. Full description of the frailty index can be found in Table 1.

Table 1 list of items included in a frailty index

NO.	Items
1	ADLs: needs assistant in bathing
2	ADLs: needs assistant in dressing
3	ADLs: needs assistant in toileting
4	ADLs: needs assistant in indoor transferring
5	ADLs: needs assistant in continence
6	ADLs: needs assistant in eating
7	IADLs: unable to visit neighbors by himself/herself
8	IADLs: unable to go shopping by himself/herself
9	IADLs: unable to cook a meal by himself/herself
10	IADLs: unable to wash clothing by himself/herself
11	IADLs: unable to walk continuously for 1 kilometer at a time by himself/herself
12	IADLs: unable to lift a weight of 5kg
13	IADLs: unable to continuously crouch and stand up three times
14	IADLs: unable to take public transportation by himself/herself
15	Cognitive impairment(based on Mini Mental State Examination)
16	Poor self-reported health
17	Health state compared to past year
18	Poor interviewer-rated health
19	Vision loss
20	Psychological distress(based on usefulness, fearfulness)
21	Number of serious illnesses in the past two years*
22	Suffering from hypertension
23	Suffering from diabetes
24	Suffering from heart disease
25	Suffering from stroke or cerebrovascular disease
26	Suffering from bronchitis, emphysema, pneumonia, asthma
27	Suffering from tuberculosis
28	Suffering from cataract
29	Suffering from cancer
30	Suffering from Parkinson's disease
31	Suffering from arthritis
32	Suffering from dementia
33	Functional limitations: unable to put hand behind neck
34	Functional limitations: unable to put hand behind lower neck
35	Functional limitations: unable to raise arm upright
36	Functional limitations: unable to stand up from sitting in a chair
37	Functional limitations: unable to pick up a book from floor

* Two or more serious illnesses in the past two years are assigned a value of 2.

Frailty transitions

The change in frailty status between the 2008 and follow-up in 2011 and 2014 was used as the outcome. Frailty transitions had been created into two types in our study since we used two kinds of frailty models.

Four transitions between physical frailty states were designed in our study according to the Frail Scale: remaining robust or prefrail, which means that the elderly have remained healthy to some extent; improvement, which means improvement or a change from prefrail to robust or from frail to robust or prefrail; worsening, which is a transition to greater frailty; and remaining frail, meaning that the elderly has remained unhealthy.

Change types in the frailty index was classified into four categories: remaining nonfrail, which means that the frailty index of the elderly was under 0.21 during the period; worsening, which means that the frailty index of the elderly had changed from nonfrail to frail; improvement, which means that the frailty scores declined to nonfrail in the follow-up year; remaining frail, which means that the frailty index remained in frail in follow-up.

Covariates

Covariates were measured at baseline and included age, gender, living arrangement, residential area, education, relative economic status, smoking, drinking alcohol and the baseline physical frailty state.

Living arrangement was coded as 0 if participants were living independently, otherwise as 1. The residential area was commonly used in studies about China because urban and rural areas differ greatly in socioeconomic development[67]. Participants were asked about their years of education, which is used as a continuous variable in our study. Relative economic status was measured with the question: "How do you rate your economic status compared with others in your local area?". The response was classified into three categories and we reverse-coded them so that higher categories indicated higher economic status (1=poor; 2=so so; 3=rich). Frailty transition between frailty states was highly dependent on the preceding frailty state[5] and baseline frailty states were viewed as the number of components of frail scale present in baseline.

Analytical sample

In the 3-year period, 8425 participants included in the 2008-2011 waves. Analysis of loneliness with frailty transition is based on 5746 (68%) re-interviewed participants with completed data. Analysis of frailty index change is based on 5618 (67%) re-interviewed participants with completed data.

In the 6-year period, 5245 participants included in the 2008-2014 waves. Analysis of loneliness with frailty transition is based on 3548 (68%) participants with completed data by re-interviewed participants. Analysis of frailty index change is based on 3288 (63%) participants with completed data among re-interviewed participants.

Method of analysis

Descriptive statistics at baseline were summarized using the mean (\pm standard deviation) or counts (percentages). Logistic regression was used to derive the odds ratio of loneliness for physical frailty transition types and frailty index change types. Logistic regression was also conducted for females and males separately to explore gender differences in the relationships between frailty transition and loneliness. Estimates are shown, adjusted for age and the number of components of baseline physical frailty and more others. All analysis was performed using statistical package STATA version 15.0. A p-value<0.05 was calculated as statistically significant.

Results

Descriptive characteristics

Table 2 summarized the characteristic of participants at baseline by survey period. In the 2008-2011 waves, the prevalence of often loneliness at baseline was 28.2%, which slightly decreased to 25.8% in the 2008-2014 waves. Compared with the 6-year follow-up, participants in the 3-year period were older, more female, had less education, were more likely to live independently, smoked and drank less, and were more frail both in the physical frailty scale and frailty index at baseline.

Table 2 characteristic of the participants at baseline in two survey periods

	3-year period (2008-2011) (N = 8425)	6-year period(2008-2014) (N = 5245)
Age, mean(SD)	82.6 (11.0)	79.1 (10.1)
Gender:female, n(%)	4607(54.7)	2800(53.4)
Education year, mean(SD)	2.4 (3.6)	2.6 (3.6)
Residenc:Rural, n(%)	5207 (61.8)	3319 (63.3)
Living arrangement: independently, n(%)	1368 (16.2)	843 (16.1)
Relative economic status, n(%)		
rich	1467 (17.4)	873 (16.7)
so so	5778 (68.7)	3622 (69.2)
poor	1162 (13.8)	740 (14.1)
Current somker, n(%)	1710 (20.3)	1178 (22.5)
Current drinker, n(%)	1670 (19.8)	1114 (21.2)
Loneliness, n(%)		
never	3262 (41.9)	2208 (43.8)
seldom	2330 (29.9)	1532 (30.4)
often	2195 (28.2)	1301 (25.8)
No. of components of frail scale at baseline, mean(SD)	1.20 (1.2)	0.98 (1.1)
Frailty index score at baseline, mean(SD)	0.13 (0.1)	0.11 (0.1)

Frailty transitions

Table 3 shows the transition in frailty status between baseline and follow-up. In 2008 and 2011 waves, nearly half (49.3%) of the participants transitioned between different frailty states (robust, prefrail and frail), 2605(45.3%) remained robust or prefrail state, and 5.3% remained frail states at follow-up. Of the total participants in 2008 and 2014 waves, more than half (51.0%) of participants changed, 1617(45.6%) had maintained robust or prefrail state, and 3.5% remained frail states in follow-up visit. Overall, the frailty transition was similar in the two periods.

There was a clear difference between the distribution of frailty transition among female and male participants. In the two periods, nearly half of male participants remained in the robust or prefrail states, whereas about 40% of female participants remained in the same level. More female participants worsened in physical frailty state than male participants, and male participants had a lower prevalence of remaining frail than females. However, females presented more probability of recovering from greater frailty than males. More than a fifth of the females had improved from greater frailty state in both periods, while 17.3% and 19.5% of males had improved in the two periods respectively.

Table 3 physical frailty transitions between baseline and follow-up, n (%)

	3 -year period (2008-2011)			6-year period (2008-2014)		
	Total	female	male	Total	female	male
Remaining robust and prefrail	2605(45.3)	1160(40.0)	1445(50.8)	1617(45.6)	731(40.9)	886(50.3)
Worsening	1649(28.7)	870(30.0)	779(27.4)	1132(31.9)	586(32.8)	546(31.0)
Improvement	1185(20.6)	630(21.7)	555(19.5)	676(19.1)	371(20.8)	305(17.3)
Remaining frail	307(5.3)	241(8.3)	66(2.3)	123(3.5)	98(5.5)	25(1.4)
Total	5746	2901	2845	3548	1786	1762

[chi-squared test](#) for physical frailty transitions by gender in 3-year period: $p < 0.0001$

[chi-squared test](#) for physical frailty transitions by gender in 6-year period: $p < 0.0001$

Physical frailty transition as outcome

The associations between physical frailty transition and loneliness are shown in Table 4. In the remaining robust or prefrail group, after adjusting for age, gender, components number in the frail scale and others at baseline, significant trends in remaining frail state was associated with a high level of loneliness observed in the 3-year

period: compared to never loneliness participants, those who often felt lonely were unlikely to remain robust or prefrail states (OR=0.78, 95%CI: 0.68 - 0.91, p<0.01). In the worsening group, loneliness was a significant risk factor in that a high level of loneliness was associated with worsened frailty states after years (3-year period: OR=1.19, 95%CI: 1.01 - 1.41, p<0.05;6-year period: OR=1.34, 95%CI: 1.08 - 1.66, p<0.01). In the improvement group, loneliness showed no significant influence on frailty transition. Loneliness at baseline was positively associated with remaining frail in the 6-year period (seldom loneliness: OR=2.47, 95%CI: 1.25 - 4.85, p<0.01) but no significant association had shown in the 3-year period.

We also investigated whether the association between loneliness and physical frailty transition differed by gender. Male participants who felt lonely often were negatively related to remaining robust and prefrail (3-year period: OR=0.73, 95%CI: 0.59 - 0.89, p<0.01;6-year period: OR=0.75, 95%CI: 0.57 - 0.99, p<0.05), and positively related to worsening frail (3-year period: OR=1.37, 95%CI: 1.07 - 1.75;6-year period: OR=1.54, 95%CI: 1.13 - 2.11) in the two survey periods. Loneliness of male participants was also found to be related to remaining frail after 6 years (seldom loneliness: OR=12.68, 95%CI: 1.66 - 96.71, p<0.05).

Table 4 odds ratios (95% CI) for physical frailty transitions and loneliness

	3 - year period (2008-2011)			6-year period (2008-2014)				
	Remaining robust and prefrail	Worsening	Improvement	Remaining frail	Remaining robust and prefrail	Worsening	Improvement	Remaining frail
Total								
never	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
seldom	0.99 (0.87 - 1.13)	1.05 (0.90 - 1.21)	1.03 (0.86 - 1.23)	1.15 (0.76 - 1.73)	0.98 (0.83 - 1.15)	1.02 (0.85 - 1.22)	0.99 (0.77 - 1.26)	2.47** (1.25 - 4.85)
often	0.78** (0.68 - 0.91)	1.19* (1.01 - 1.41)	1.14 (0.94 - 1.39)	1.00 (0.67 - 1.51)	0.84 (0.70 - 1.01)	1.34** (1.08 - 1.66)	0.85 (0.65 - 1.12)	1.88 (0.93 - 3.79)
Female								
never	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
seldom	1.00 (0.83 - 1.21)	1.01 (0.82 - 1.25)	1.02 (0.79 - 1.32)	1.17 (0.73 - 1.87)	1.01 (0.80 - 1.28)	1.12 (0.86 - 1.46)	0.77 (0.55 - 1.08)	1.77 (0.83 - 3.77)
often	0.85 (0.69 - 1.05)	1.04 (0.82 - 1.32)	1.07 (0.82 - 1.40)	0.96 (0.60 - 1.53)	0.94 (0.73 - 1.21)	1.20 (0.89 - 1.60)	0.78 (0.55 - 1.10)	1.40 (0.65 - 3.02)
Male								
never	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
seldom	0.99 (0.83 - 1.18)	1.08 (0.88 - 1.33)	1.03 (0.80 - 1.34)	1.35 (0.55 - 3.32)	0.96 (0.77 - 1.20)	0.92 (0.71 - 1.18)	1.28 (0.90 - 1.82)	12.68* (1.66 - 96.71)
often	0.73** (0.59 - 0.89)	1.37* (1.07 - 1.75)	1.25 (0.93 - 1.68)	1.37 (0.58 - 3.24)	0.75* (0.57 - 0.99)	1.54** (1.13 - 2.11)	0.94 (0.61 - 1.44)	8.89 (0.75 - 105.30)

***P<0.001, **P<0.01, *P<0.05;

Sample size: 2008-2011 waves: total participants: 5689; for female participants:2866; for male participants:2823;

2011-2014 waves: total participants: 3529; for female participants:1776; for male participants:1753.

Notes: Model had been adjusted for age, components number in the frail scale at baseline, residence, education year, living arrangement, relative economic status, smoking and drinking alcohol at baseline. In total participants, adjustment for gender was also performed.

Frailty Index as outcome

Table 5 presents odds ratios (95%CI) for change in the frailty index and loneliness. Loneliness at baseline was observed to be a protective factor for the improvement of frailty index only in 3-year period (seldom loneliness: OR= 1.42, 95%CI: 1.04 - 1.95, p<0.05; often loneliness: OR= 1.50, 95%CI: 1.08 - 2.08, p<0.05). In terms of 6-year period, loneliness at baseline was found to increase the possibility of participants to remain frail (seldom loneliness: OR= 1.78, 95%CI: 1.25 - 2.55, p<0.01; often loneliness: OR= 1.74, 95%CI: 1.21 - 2.50, p<0.01) after 6 years.

There were also gender differences in the transition type of frailty index and loneliness. Loneliness in male participants tends to be related to remaining in frail in 6-year period (seldom loneliness: OR= 3.58, 95%CI: 1.73 - 7.41, p<0.001; often loneliness: OR=2.70, 95%CI: 1.27 - 5.76, p<0.01), but no significant relationship was found in female participants. A high level loneliness in female participants was associated with improvement of frailty in 3-year period (OR= 1.54, 95%CI: 1.02 - 2.31, p<0.05). The association between loneliness and frailty index in male participants was the same with that found in all participants, except that no relationship with improvement of frailty index in the 3-year period was observed in male participants with seldom loneliness.

Table 5 odds ratios (95% CI) for transition type in frailty index and loneliness

	3 -year period (2008-2011)				6-year period (2008-2014)			
	Remaining nonfrail	Worsening	Improvement	Remaining frail	Remaining nonfrail	Worsening	Improvement	Remaining frail
Total								
never	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
seldom	1.03 (0.87 - 1.20)	0.94 (0.79 - 1.11)	1.42* (1.04 - 1.95)	1.03 (0.82 - 1.30)	0.99 (0.82 - 1.20)	0.93 (0.77 - 1.13)	0.76 (0.47 - 1.22)	1.78** (1.25 - 2.55)
often	0.89 (0.75 - 1.05)	0.96 (0.80 - 1.16)	1.50* (1.08 - 2.08)	1.07 (0.84 - 1.36)	0.83 (0.67 - 1.02)	1.00 (0.80 - 1.24)	0.88 (0.54 - 1.42)	1.74** (1.21 - 2.50)
Female								
never	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
seldom	1.20 (0.96 - 1.49)	0.89 (0.71 - 1.11)	1.12 (0.73 - 1.72)	0.93 (0.70 - 1.23)	1.02 (0.78 - 1.33)	0.98 (0.76 - 1.28)	0.65 (0.35 - 1.22)	1.39 (0.92 - 2.10)
often	0.96 (0.77 - 1.21)	0.87 (0.68 - 1.10)	1.54* (1.02 - 2.31)	0.98 (0.73 - 1.31)	0.77 (0.58 - 1.01)	1.04 (0.79 - 1.38)	0.93 (0.51 - 1.67)	1.50 (0.99 - 2.27)
Male								
never	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
seldom	0.87 (0.69 - 1.10)	0.97 (0.76 - 1.25)	2.00** (1.23 - 3.24)	1.30 (0.86 - 1.96)	0.96 (0.73 - 1.27)	0.88 (0.66 - 1.16)	0.95 (0.46 - 1.98)	3.58*** (1.73 - 7.41)
often	0.84 (0.64 - 1.09)	1.05 (0.79 - 1.39)	1.41 (0.81 - 2.44)	1.35 (0.88 - 2.05)	0.94 (0.68 - 1.30)	0.95 (0.68 - 1.33)	0.77 (0.34 - 1.77)	2.70** (1.27 - 5.76)

***P<0.001, **P<0.01, *P<0.05.

Sample size: 2008-2011 waves: total participants: 5548; female participants:2833; male participants:2715;

2011-2014 waves: total participants: 3381; for female participants:1737; for male participants:1644.

Notes: Model had been adjusted for age, components number of frail scale at baseline, residence, education year, living arrangement, relative economic status, smoking and drinking alcohol at baseline. In total participants, adjustment for gender was also performed.

Discussion

The present study investigated the association between loneliness and frailty transitions. We used the 2008/2009, 2011/2012 and 2014 surveys of CLHLS for the analysis, with a attention to the difference in the relationships between males and females.

Nearly half of the participants remained in the robust or prefrail status in follow-up years, irrespective of gender. The percentage was higher than the previous study in China which reported that 39.6% participants remained in robust or prefrail in 2002-2005 [42], while it is close to a pooled frailty transition rates among 16 cohorts from 2010-2018 [68]. This difference may be due to the baseline time, variations in follow-up year and the measurement of frailty. Obviously, they may indicate that there may be a window during which early interventions may be taken for the elderly to maintain their health status as far as possible. Furthermore, we found that changes from worsening to greater physical frailty tended to be more common than recovering from greater physical frailty, and this pattern of transition was consistent with the previous study [42, 68]. Evidence on gender difference in frailty transition is rare. One study of old people in Hongkong between 2001 and 2003 found that females were less likely to decline in frailty status than males [69] whereas a longitudinal study in San Antonio did not find men to be at higher risk of declining frailty status [70]. Another cohort study in Italian older adults found that females were more likely to progress into worsened physical frailty than males with a mean follow-up of 4.4 years [71]. Our study showed that, compared with males, females were more likely to change frailty status, either for improving or worsening, which was in line with a recent systematic review [68]. This will have to be further confirmed by more studies, but it implies that frailty interventions might have different efficacy for men and women.

Our study designed four kinds of physical frailty transition types: remaining robust or prefrail, improvement, worsening and remaining frail to ascertain the specific relationship between loneliness and frailty transition. Previous studies identified loneliness to be related to frailty [37, 38]. In our study, we found that greater loneliness reduced the possibility of remaining robust or prefrail physical frailty after 3 years, and this finding is consistent with a study in England, which found that greater loneliness was associated with increased risk of physical frailty around 4 years later [40]. Also, our study used two follow-up periods to validate the relationship. We found that loneliness increased the risk of old people worsening frail as well as remaining in frail after 6 years, but no significant sign was showed in 3-year period. These findings may indicate that loneliness does not only increase the possibility of frail in older adults but also increase the likelihood of older adults becoming frailer and chronically frail.

Our study also used another model of frailty, the frailty index, to further verify results on the relationship between loneliness and frailty transition. We found a clear difference in the association between levels of loneliness and frailty index between two survey periods. In the 3-year follow-up, we found that loneliness at baselines was related to recovering frailty status in the frailty index. This may be explained by the frailty status at baseline, as severe baseline frailty status is more likely to be improved during the follow-up period. Corresponding to that, the relationship between frailty improvement and loneliness was no longer significant in the 6-year follow-up, which suggests that shorter follow-up periods seem to provide more time for old people to change their frailty status. During the 6-year follow-up, loneliness was found to be positively related to remaining in frail status, but no significant relationship was found in the 3-year follow-up. This finding was supported by a previous study that showed that a longer follow-up period was associated with lower rates of remaining in the same frailty status [68]. Besides, the relationship between frailty index transition and loneliness was different from that between loneliness and physical frailty. For example, loneliness was found not to be associated with worsening in frailty index, but with worsening physical frailty after years. It is possible that the broader definition of frailty index does not have the same risk factors as physical frailty [40]. Our findings confirmed this point and more studies are needed to consolidate the possibility.

Our study had also shown that loneliness varied by gender [52]. Low resilience was associated significantly with loneliness, which was more pronounced in males [51]. While high resilience can be a protective factor in facilitating old people to maintain their health status [72, 73]. Previous research also indicated the stressful impact of loneliness on men as manifested by increased inflammatory responses [74]. Inflammatory response was a specific physiological basis to the geriatric syndrome of frailty [75], which may be a mechanism underlying gender difference in the relationship between loneliness and physical frailty. Moreover, females tended to have more informal networks which may lead to more social support, whereas males have their social relationships more from the public sphere which may not always be socially supportive [59, 76]. Our study indicated that males were more sensitive to the relationship between loneliness and frailty transitions, defined by either physical frailty or the frailty index. Most of the significant relationships observed in the male participants were identical to the findings for all participants. This calls for more attention to loneliness in males.

Given that frailty in older adults may be modifiable, our findings have potential implications for both health and social care policy and practice. Firstly, our study gives a picture of frailty transition among old people in China, which highlights the importance of early interventions for old people to maintain or improve their health status, particularly for those robust or prefrail elderly.

Secondly, our study used two models of frailty which demonstrated that accumulated disadvantages can endanger the elderly in long term. Frailty management is more than treating specific clinical syndromes and physiological risk factors. Thirdly, previous studies had identified health behavior and management can be useful for delaying or reversing frailty, such as physical activity, nutrition and rehabilitation [77], etc. The relationship between loneliness and frailty transition indicated that psychological treatment is also worthwhile for frailty intervention in older adults. Effective loneliness interventions can delay the progressing of frailty. Finally, findings in gender differences in our study suggested that attention should be given to elderly men with loneliness and its adverse outcomes.

The study has several limitations. First, among the total participants, 68% has completed data on the frail scale and 63%-67% on the frail index in two survey periods. Those who did not complete the questionnaire tend to be frailer and lonelier. Our finding may underestimate the relationship between frailty transition and loneliness. Second, as we mentioned earlier, there is only one single question of loneliness in CLHLS and it may underrate the prevalence of loneliness. However, one single question of loneliness was widely used in the studies and it is more feasible for older adults to understand the investigation of loneliness [78, 79]. Finally, mental health variables, such as depression is not included in the CLHLS.

Conclusions

Our study examined the association between loneliness and frailty transition among old people of China, and attempted to explore gender differences in the relationships. The results revealed that loneliness at baseline may lead to decline the possibility of remaining robust or prefrail frailty states and that greater loneliness is associated with increased risk of worsening frailty and remaining in frail. The association between loneliness and frailty transition differs obviously between men and women. These findings should be considered when designing and implementing health and social care policies for old people.

Abbreviations

CLHLS: Chinese Longitudinal Healthy Longevity Survey;

ADL: Activities of daily living;

IADL: Instrument activities of daily living;

Declarations

Ethics approval and consent to participate

Not applicable since the dataset used in the study is publicly available.

Consent for publication

Not applicable.

Availability of data and materials

The datasets that support this article are publicly available from the project of the Chinese Longitudinal Healthy Longevity Survey (CLHLS). Questionnaires are free download at website (<http://centerforaging.duke.edu/datadownloads>) and the datasets can be obtained after sending a data user agreement to the CLHLS team.

Competing interests

None.

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None.

Authors' contributions

SHASHA designed, drafted, and revised the text. SHASHA also performed the analyses. Xu yuebin drafted and revised the text. Chenlin revised and interpreted the results. All authors read and approved the final version of the manuscript.

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References

1. WHO: **China country assessment report on ageing and health**. Switzerland: WHO Press; 2015.
2. Hu Z, Peng X: **Household changes in contemporary China: an analysis based on the four recent censuses**. *The Journal of Chinese Sociology* 2015, **2**(1):9.
3. Gu D, Feng Q, Yeung W-JJ: **Reciprocal Dynamics of Solo-Living and Health Among Older Adults in Contemporary China**. *Journals of Gerontology Series B-Psychological Sciences and Social Sciences* 2019, **74**(8):1441-1452.
4. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K: **Frailty in elderly people**. *Lancet* 2013, **381**(9868):752-762.
5. Gill TM, Gahbauer EA, Allore HG, Han L: **Transitions between frailty states among community-living older persons**. *Archives of Internal Medicine* 2006, **166**(4):418-423.
6. Slaets JPJ: **Vulnerability in the elderly: Frailty**. *Medical Clinics of North America* 2006, **90**(4):593+.
7. Rockwood K, Fox RA, Stolee P, Robertson D, Beattie BL: **Frailty in elderly people: an evolving concept**. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 1994, **150**(4):489-495.
8. Theou O, Brothers TD, Mitnitski A, Rockwood K: **Operationalization of Frailty Using Eight Commonly Used Scales and Comparison of Their Ability to Predict All-Cause Mortality**. *Journal of the American Geriatrics Society* 2013, **61**(9):1537-1551.
9. Rockwood K, Mitnitski A: **Frailty defined by deficit accumulation and geriatric medicine defined by frailty**. *Clin Geriatr Med* 2011, **27**(1):17-26.
10. Ensrud KE, Ewing SK, Taylor BC, Fink HA, Stone KL, Cauley JA, Tracy JK, Hochberg MC, Rodondi N, Cawthon PM: **Frailty and risk of falls, fracture, and mortality in older women: the study of osteoporotic fractures**. *J Gerontol A Biol Sci Med Sci* 2007, **62**(7):744-751.
11. Kojima G: **Frailty as a predictor of disabilities among community-dwelling older people: a systematic review and meta-analysis**. *Disability and Rehabilitation* 2017, **39**(19):1897-1908.
12. Hoogendijk EO, Romero L, Sanchez-Jurado PM, Flores Ruano T, Vina J, Rodriguez-Manas L, Abizanda P: **A New Functional Classification Based on Frailty and Disability Stratifies the Risk for Mortality Among Older Adults: The FRADEA Study**. *J Am Med Dir Assoc* 2019.
13. Kojima G: **Frailty as a predictor of hospitalisation among community-dwelling older people: a systematic review and meta-analysis**. *Journal of Epidemiology and Community Health* 2016, **70**(7):722-729.

14. Lambotte D, De Donder L, Van Regenmortel S, Fret B, Dury S, Smetcoren AS, Dierckx E, De Witte N, Verte D, Kardol MJM *et al*: **Frailty differences in older adults' use of informal and formal care.** *Arch Gerontol Geriatr* 2018, **79**:69-77.
15. Rose M, Pan H, Levinson MR, Staples M: **Can frailty predict complicated care needs and length of stay?** *Intern Med J* 2014, **44**(8):800-805.
16. Grabovac I, Haider S, Mogg C, Majewska B, Drgac D, Oberndorfer M, Dorner TE: **Frailty Status Predicts All-Cause and Cause-Specific Mortality in Community Dwelling Older Adults.** *Journal of the American Medical Directors Association* 2019, **20**(10):1230+.
17. Kojima G: **Frailty Defined by FRAIL Scale as a Predictor of Mortality: A Systematic Review and Meta-analysis.** *J Am Med Dir Assoc* 2018, **19**(6):480-483.
18. Yang F, Gu D: **Predictability of frailty index and its components on mortality in older adults in China.** *Bmc Geriatrics* 2016, **16**.
19. Collard RM, Boter H, Schoevers RA, Voshaar RCO: **Prevalence of Frailty in Community-Dwelling Older Persons: A Systematic Review.** *Journal of the American Geriatrics Society* 2012, **60**(8):1487-1492.
20. Cacioppo JT: **The growing problem of loneliness.** *Lancet* 2018, **391**(10119):426-426.
21. Hawkey LC, Cacioppo JT: **Loneliness matters: a theoretical and empirical review of consequences and mechanisms.** *Ann Behav Med* 2010, **40**(2):218-227.
22. Luo Y, Waite LJ: **Loneliness and mortality among older adults in China.** *J Gerontol B Psychol Sci Soc Sci* 2014, **69**(4):633-645.
23. Luo Y, Hawkey LC, Waite LJ, Cacioppo JT: **Loneliness, health, and mortality in old age: A national longitudinal study.** *Social Science & Medicine* 2012, **74**(6):907-914.
24. Hakulinen C, Pulkki-Raback L, Virtanen M, Jokela M, Kivimaki M, Elovainio M: **Social isolation and loneliness as risk factors for myocardial infarction, stroke and mortality: UK Biobank cohort study of 479 054 men and women.** *Heart* 2018, **104**(18):1536-1542.
25. Hawkey LC, Thisted RA, Masi CM, Cacioppo JT: **Loneliness Predicts Increased Blood Pressure: 5-Year Cross-Lagged Analyses in Middle-Aged and Older Adults.** *Psychology and Aging* 2010, **25**(1):132-141.
26. Perissinotto CM, Cenzer IS, Covinsky KE: **Loneliness in Older Persons A Predictor of Functional Decline and Death.** *Archives of Internal Medicine* 2012, **172**(14):1078-1083.
27. Shankar A, McMunn A, Demakakos P, Hamer M, Steptoe A: **Social Isolation and Loneliness: Prospective Associations With Functional Status in Older Adults.** *Health Psychology* 2017, **36**(2):179-187.
28. Cacioppo JT, Hawkey LC, Thisted RA: **Perceived Social Isolation Makes Me Sad: 5-Year Cross-Lagged Analyses of Loneliness and Depressive Symptomatology in the Chicago Health, Aging, and Social Relations Study.** *Psychology and Aging* 2010, **25**(2):453-463.
29. Zhong BL, Chen SL, Tu X, Conwell Y: **Loneliness and Cognitive Function in Older Adults: Findings From the Chinese Longitudinal Healthy Longevity Survey.** *J Gerontol B Psychol Sci Soc Sci* 2017, **72**(1):120-128.
30. Cacioppo JT, Hawkey LC, Crawford LE, Ernst JM, Bureson MH, Kowalewski RB, Malarkey WB, Van Cauter E, Bertson GG: **Loneliness and health: Potential mechanisms.** *Psychosom Med* 2002, **64**(3):407-417.
31. Hawkey LC, Masi CM, Berry JD, Cacioppo JT: **Loneliness is a unique predictor of age-related differences in systolic blood pressure.** *Psychology and Aging* 2006, **21**(1):152-164.
32. Hawkey LC, Bureson MH, Bertson GG, Cacioppo JT: **Loneliness in everyday life: Cardiovascular activity, psychosocial context, and health behaviors.** *Journal of Personality and Social Psychology* 2003, **85**(1):105-120.
33. Cole SW, Hawkey LC, Arevalo JM, Sung CY, Rose RM, Cacioppo JT: **Social regulation of gene expression in human leukocytes.** *Genome Biology* 2007, **8**(9).
34. Cole SW, Hawkey LC, Arevalo JMG, Cacioppo JT: **Transcript origin analysis identifies antigen-presenting cells as primary targets of socially regulated gene expression in leukocytes.** *Proceedings of the National Academy of Sciences of the United States of America* 2011, **108**(7):3080-3085.
35. Pressman SD, Cohen S, Miller GE, Barkin A, Rabin BS, Treanor JJ: **Loneliness, social network size, and immune response to influenza vaccination in college freshmen.** *Health Psychology* 2005, **24**(3):297-306.

36. Cooper C, Fielding R, Visser M, van Loon LJ, Rolland Y, Orwoll E, Reid K, Boonen S, Dere W, Epstein S *et al*: **Tools in the Assessment of Sarcopenia**. *Calcified Tissue International* 2013, **93**(3):201-210.
37. Herrera-Badilla A, Patricia Navarrete-Reyes A, Amieva H, Alberto Avila-Funes J: **LONELINESS IS ASSOCIATED WITH FRAILTY IN COMMUNITY-DWELLING ELDERLY ADULTS**. *Journal of the American Geriatrics Society* 2015, **63**(3):607-609.
38. Hoogendijk EO, Suanet B, Dent E, Deeg DJH, Aartsen MJ: **Adverse effects of frailty on social functioning in older adults: Results from the Longitudinal Aging Study Amsterdam**. *Maturitas* 2016, **83**:45-50.
39. Rockwood K, Howlett SE, MacKnight C, Beattie BL, Bergman H, Hébert R, Hogan DB, Wolfson C, McDowell I: **Prevalence, attributes, and outcomes of fitness and frailty in community-dwelling older adults: report from the Canadian study of health and aging**. *J Gerontol A Biol Sci Med Sci* 2004, **59**(12):1310-1317.
40. Gale CR, Westbury L, Cooper C: **Social isolation and loneliness as risk factors for the progression of frailty: the English Longitudinal Study of Ageing**. *Age Ageing* 2018, **47**(3):392-397.
41. Wu C, Smit E, Xue QL, Odden MC: **Prevalence and Correlates of Frailty Among Community-Dwelling Chinese Older Adults: The China Health and Retirement Longitudinal Study**. *J Gerontol A Biol Sci Med Sci* 2017, **73**(1):102-108.
42. Liu ZY, Wei YZ, Wei LQ, Jiang XY, Wang XF, Shi Y, Hai H: **Frailty transitions and types of death in Chinese older adults: a population-based cohort study**. *Clin Interv Aging* 2018, **13**:947-956.
43. Gierveld JdJ, Tesch-Roemer C: **Loneliness in old age in Eastern and Western European societies: theoretical perspectives**. *Eur J Ageing* 2012, **9**(4):285-295.
44. de Jong-Gierveld J, van Tilburg TG, Dykstra PA: **Loneliness and social isolation**. Cambridge: Cambridge University Press; 2006.
45. Yang K, Victor CR: **The prevalence of and risk factors for loneliness among older people in China**. *Ageing Soc* 2008, **28**:305-327.
46. Hubbard RE: **Sex Differences in Frailty**. *Interdisciplinary topics in gerontology and geriatrics* 2015, **41**:41-53.
47. Aartsen M, Jylha M: **Onset of loneliness in older adults: results of a 28 year prospective study**. *Eur J Ageing* 2011, **8**(1):31-38.
48. Kojima G, Iliffe S, Taniguchi Y, Shimada H, Rakugi H, Walters K: **Prevalence of frailty in Japan: A systematic review and meta-analysis**. *Journal of Epidemiology* 2017, **27**(8):347-353.
49. Gordon EH, Peel NM, Samanta M, Theou O, Howlett SE, Hubbard RE: **Sex differences in frailty: A systematic review and meta-analysis**. *Experimental Gerontology* 2017, **89**:30-40.
50. Ofori-Asenso R, Chin KL, Mazidi M, Zomer E, Ilomaki J, Zullo AR, Gasevic D, Ademi Z, Korhonen MJ, LoGiudice D *et al*: **Global Incidence of Frailty and Prefrailty Among Community-Dwelling Older Adults A Systematic Review and Meta-analysis**. *Jama Network Open* 2019, **2**(8).
51. Zebhauser A, Hofmann-Xu L, Baumert J, Hafner S, Lacruz ME, Emeny RT, Doring A, Grill E, Huber D, Peters A *et al*: **How much does it hurt to be lonely? Mental and physical differences between older men and women in the KORA-Age Study**. *International Journal of Geriatric Psychiatry* 2014, **29**(3):245-252.
52. Zhou Z, Wang P, Fang Y: **Loneliness and the risk of dementia among older Chinese adults: gender differences**. *Aging & Mental Health* 2018, **22**(4):519-525.
53. Zeng Y, Poston DL Jr, Vlosky DA, Gu D: **Healthy longevity in China: demographic, socioeconomic, and psychological dimensions**; 2008.
54. Zeng Y: **Towards Deeper Research and Better Policy for Healthy Aging –Using the Unique Data of Chinese Longitudinal Healthy Longevity Survey**. *China economic journal* 2012, **5**(2-3):131-149.
55. Patterson AC, Veenstra G: **Loneliness and risk of mortality: A longitudinal investigation in Alameda County, California**. *Social Science & Medicine* 2010, **71**(1):181-186.
56. Savikko N, Routasalo P, Tilvis RS, Strandberg TE, Pitkala KH: **Predictors and subjective causes of loneliness in an aged population**. *Archives of Gerontology and Geriatrics* 2005, **41**(3):223-233.
57. Theeke LA: **Predictors of Loneliness in US Adults Over Age Sixty-Five**. *Archives of Psychiatric Nursing* 2009, **23**(5):387-396.
58. Tilvis RS, Pitkala KH, Jolkkonen J, Strandberg TE: **Social networks and dementia**. *Lancet* 2000, **356**(9223):77-78.
59. Pinquart M, Sorensen S: **Influences on loneliness in older adults: A meta-analysis**. *Basic and Applied Social Psychology* 2001, **23**(4):245-266.
60. Abellan van Kan G, Rolland YM, Morley JE, Vellas B: **Frailty: toward a clinical definition**. *J Am Med Dir Assoc* 2008, **9**(2):71-72.

61. Aprahamian I, Cezar NOC, Izbicki R, Lin SM, Paulo DLV, Fattori A, Biella MM, Jacob Filho W, Yassuda MS: **Screening for Frailty With the FRAIL Scale: A Comparison With the Phenotype Criteria.** *J Am Med Dir Assoc* 2017, **18**(7):592-596.
62. Morley JE, Malmstrom TK, Miller DK: **A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans.** *Journal of Nutrition Health & Aging* 2012, **16**(7):601-608.
63. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K: **A standard procedure for creating a frailty index.** *BMC Geriatrics* 2008, **8**:24.
64. Gu D, Dupre ME, Sautter J, Zhu H, Liu Y, Yi Z: **Frailty and mortality among Chinese at advanced ages.** *J Gerontol B Psychol Sci Soc Sci* 2009, **64**(2):279-289.
65. Goggins WB, Woo J, Sham A, Ho SC: **Frailty index as a measure of biological age in a Chinese population.** *J Gerontol A Biol Sci Med Sci* 2005, **60**(8):1046-1051.
66. Zhu A, Yan L, Wu C, Ji JS: **Residential Greenness and Frailty Among Older Adults: A Longitudinal Cohort in China.** *J Am Med Dir Assoc* 2020, **21**(6):759-765.e752.
67. Gu D, Yang F, Sautter J: **Socioeconomic status as a moderator between frailty and mortality at old ages.** *BMC Geriatr* 2016, **16**:151.
68. Kojima G, Taniguchi Y, Iliffe S, Jivraj S, Walters K: **Transitions between frailty states among community-dwelling older people: A systematic review and meta-analysis.** *Ageing Res Rev* 2019, **50**:81-88.
69. Lee JS, Auyeung TW, Leung J, Kwok T, Woo J: **Transitions in frailty states among community-living older adults and their associated factors.** *J Am Med Dir Assoc* 2014, **15**(4):281-286.
70. Espinoza SE, Jung I, Hazuda H: **Frailty Transitions in the San Antonio Longitudinal Study of Aging.** *Journal of the American Geriatrics Society* 2012, **60**(4):652-660.
71. Trevisan C, Veronese N, Maggi S, Baggio G, Toffanello ED, Zambon S, Sartori L, Musacchio E, Perissinotto E, Crepaldi G *et al*: **Factors Influencing Transitions Between Frailty States in Elderly Adults: The Progetto Veneto Anziani Longitudinal Study.** *Journal of the American Geriatrics Society* 2017, **65**(1):179-184.
72. Ferrucci L, Giallauria F, Schlessinger D: **Mapping the road to resilience: Novel math for the study of frailty.** *Mechanisms of Ageing and Development* 2008, **129**(11):677-679.
73. Cesari M, Prince M, Thiyagarajan JA, De Carvalho IA, Bernabei R, Chan P, Gutierrez-Robledo LM, Michel JP, Morley JE, Ong P *et al*: **Frailty: An Emerging Public Health Priority.** *J Am Med Dir Assoc* 2016, **17**(3):188-192.
74. Hermes GL, Rosenthal L, Montag A, McClintock MK: **Social isolation and the inflammatory response: sex differences in the enduring effects of a prior stressor.** *American Journal of Physiology-Regulatory Integrative and Comparative Physiology* 2006, **290**(2):R273-R282.
75. Walston J, McBurnie MA, Newman A, Tracy RP, Kop WJ, Hirsch CH, Gottdiener J, Fried LP, Cardiovascular Hlth Study I: **Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities - Results from the Cardiovascular Health Study.** *Archives of Internal Medicine* 2002, **162**(20):2333-2341.
76. Stevens N: **Gender and adaptation to widowhood in later life.** *Ageing and Society* 1995, **15**:37-58.
77. Puts MTE, Toubasi S, Andrew MK, Ashe MC, Ploeg J, Atkinson E, Ayala AP, Roy A, Monforte MR, Bergman H *et al*: **Interventions to prevent or reduce the level of frailty in community-dwelling older adults: a scoping review of the literature and international policies.** *Age and Ageing* 2017, **46**(3):383-392.
78. Victor C, Grenade L, Boldy D: **Measuring loneliness in later life: A comparison of differing measures.** *Reviews in Clinical Gerontology* 2006, **15**(01):63.
79. Jylha M: **Old age and loneliness: Cross-sectional and longitudinal analyses in the tampere longitudinal study on aging.** *Canadian Journal on Aging-Revue Canadienne Du Vieillessement* 2004, **23**(2):157-168.

Figures

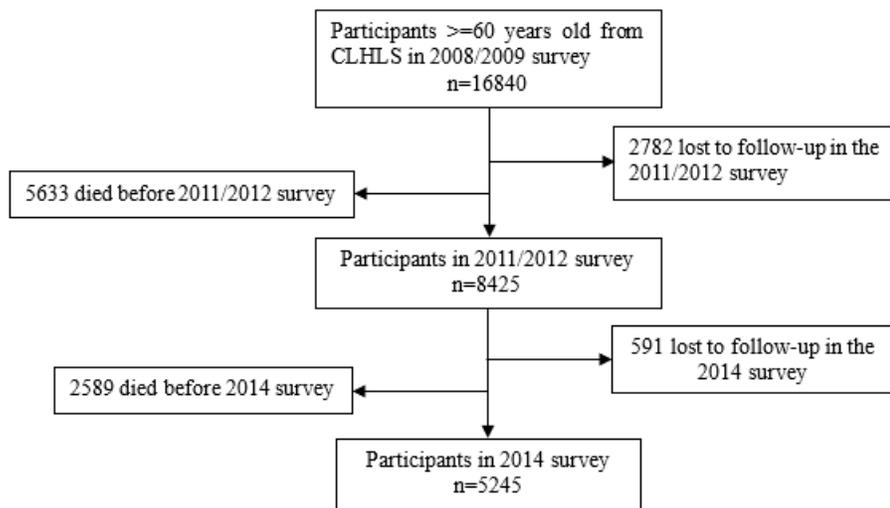


Figure 1

flow diagram of participants