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PREVALENCE AND RISK FACTORS FOR FRAILTY AMONG COMMUNITY-DWELLING OLDER PEOPLE IN CHINA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract: *Objective:* To systematically assess the prevalence of frailty, including prefrailty, stratified prevalence according to frailty criteria, gender, age, and region, and the risk factors for frailty in China. *Design:* We conducted a systematic literature review and meta-analysis using articles available in 8 databases including PubMed, Cochrane Library, Web of Science, CINAHL Plus, China Knowledge Resource Integrated Database (CNKI), Wanfang Database, Chinese Biomedical Database (CBM), and Weipu Database (VIP). *Setting:* Cross-sectional and cohort data from Chinese community. *Participants:* Community-dwelling adults aged 65 and older. *Measurements:* Two authors independently extracted data based upon predefined criteria. Where data were available we conducted a meta-analysis of frailty parameters using a random-effects model. *Results:* We screened 915 different articles, and 14 studies (81258 participants) were ultimately included in this analysis. The prevalence of frailty and prefrailty in individual studies varied from 5.9% to 17.4% and from 26.8% to 62.8%, respectively. The pooled prevalence of frailty and prefrailty were 10% (95% CI: 8% to 12%, I^2 = 97.4%, P = 0.000) and 43% (95% CI: 37% to 50%, I^2 = 98.0%, P = 0.000), respectively. The pooled frailty prevalence was 8% for the Fried frailty phenotype, 12% for the frail index, and 15% for the FRAIL scale. Age-stratified meta-analyses showed the pooled prevalence of frailty to be 6%, 15%, and 25% for those aged 65-74, 75-84, and ≥85 years old, respectively. The pooled prevalence of frailty was 8% for males and 11% for females. The pooled prevalence of frailty in Mainland China, Taiwan, and Hong Kong was 12%, 8%, and 14%, respectively. The pooled frailty prevalence was 10% in urban areas and 7% in rural areas. After controlling for confounding variables, increasing age (OR = 1.28, 95% CI: 1.2 to 1.36, I^2 = 98.0%, P = 0.000), being female (OR = 1.29, 95% CI: 1.16 to 1.43, I^2 =92.7%, P=0.000), activities of daily living (ADL) disability (OR = 1.72, 95% CI: 1.57 to 1.90, I^2 = 99.7%, P = 0.000), and having three or more chronic diseases (OR = 1.97, 95% CI: 1.78 to 2.18, I^2 = 97.5%, P = 0.000) were associated with frailty. *Conclusions:* These findings of this review indicate an overall pooled prevalence of frailty among Chinese community-dwelling older people of 10%. Increasing age, being female, ADL disability, and having three or more chronic diseases were all risk factors for frailty. Further research will be needed to identify additional frailty risk factors in order to better treat and prevent frailty in the community.

Key words: Chinese, community-dwelling older people, frailty, prevalence.

Introduction

Aging is an important public health issue throughout the world. In China, 11.4% of the population in 2017 were age 65 or older (1). Given this ever-expanding older population, frailty is increasingly becoming a major public health priority (2). As frailty is associated with negative health outcomes including falls, hospitalization, institutionalization, fracture, disability, dementia, lower quality of life, and mortality, frailty is a major concern for affected individuals and their families (3-10). These healthy problems are thought to more frequently affect individuals due to a decline in their reserve capacity for multiple physiological systems. Frailty appears when this reserve capacity has decreased to a critically low point, at which point even small disturbances can lead to a series of complications. More broadly speaking, frailty can also lead to increased rates of disabilities and health care costs, adversely affecting society as a whole. Therefore, researching the basic epidemiology of frailty in older adults is essential for policymakers, public health authorities, clinicians, and the general population.

Prefrailty is an intermediate state between frailty and robustness, with a high risk of progressing to frailty (11). Among published studies on frailty, no consensus exists regarding the prevalence of frailty owing to heterogeneity of study designs, populations, settings, and different frailty criteria used in individual studies. Although the concept of frailty has long been a facet of geriatric medicine, there is still no gold standard definition of frailty. The most frequently used frailty assessment methods in the literature are the Fried phenotype of frailty, comprising five phenotypic criteria (unintentional weight loss, self-reported exhaustion, weakness, slowness, and low physical activity), and the frailty index (comprising a list of specific deficits) (3, 12, 13). Many studies to date have focused on the prevalence of frailty in Western countries, where the prevalence of frailty in community-dwelling older persons ranges from 4% to 10% , 6.5% in Italy, 7.0% in France,7.4% in Canada, 8.1% in the United Kingdom, and 9.4% in Australia

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based on the Fried phenotype of frailty criteria (14). To date however, only a limited number of studies have focused on frailty in Chinese community-dwelling older adults, and the prevalence and risk factors identified differ substantially among these published studies. Little effort has been made to conduct a systematic review of both frailty prevalence and associated risk factors in the Chinese population. To the best of our knowledge, the present study is the first to conduct a comprehensive systematic review and meta-analysis of this research area, making it of great significance for disease prevention.

The objectives of this systematic review were two-fold: to conduct a meta-analysis synthesizing the pooled prevalence and risk factors of frailty among Chinese community-dwelling older adults, and to provide an evidence-based basis on which the government can base relevant public health strategy decisions.

Methods

Protocol

This review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.

Search strategy

We performed a comprehensive search of the literature using eight electronic databases. PubMed, Cochrane Library, Web of Science, CINAHL Plus, China Knowledge Resource Integrated Database (CNKI), Wanfang Database, Chinese Biomedical Database (CBM), and Weipu Database (VIP) were searched from their dates of inception through 15 September 2018. The search strategy is shown in Appendix. No language restrictions were imposed.

Reference lists of included articles were also manually searched in order to identify additional relevant articles. Ethical approval was not required for this study, as it was based entirely on published studies.

Inclusion and exclusion criteria

The inclusion criteria were as follows: observational studies (cross-sectional, cohort), participants were over 65 years of age; participants were community-dwelling participants residing in China (including Mainland China, Hong Kong, Macao, and Taiwan); exact frailty diagnostic criteria were available; prevalence of frailty reported.

The exclusion criteria were as follows: participants with severe diseases; solitary older participants; studies with incomplete data the sample size is less than 50» to the exclusion criteria.

Study selection methods

After duplicate studies were removed, two investigators (MYX & HB) independently assessed the eligible studies according to the inclusion and exclusion standards via screening titles and abstracts. Full-text articles were obtained unless both reviewers decided that an abstract was ineligible for inclusion. Each full-text report was assessed independently for final study inclusion. Disagreements were resolved through discussion.

Quality appraisal

The quality of the included studies was assessed independently by two investigators (MYX & HB) through disease prevalence quality tool created by Loney et al. (15). They used a methodological scoring system (16) designed to rate the quality of included studies (Table 1). And quality disagreements were resolved by a third author (MB).

Data extraction

Data were extracted from the included studies by two independent investigators (MYX, HB), and included the following items: first author name, publication year, study location, sample size, diagnostic criteria, prevalence of prefrailty and frailty, and risk factors mentioned. All extracted data were stored in the Microsoft Excel file format.

Data analysis

The literature data were input into Stata 12.0 (Stata Corp LP, College Station, TX) for analysis. Heterogeneity among studies was tested using Cochrane's Q statistic. The degree of heterogeneity was assessed using the I^2 statistic, with I^2 values of 25%, 50%, and 75% being considered to indicate low, moderate, and high heterogeneity, respectively (17). Pooled prevalence and 95% CIs for frailty and prefrailty were calculated using a random-effects model if the Cochrane's Q statistic detected significant heterogeneity; otherwise a fixed-effects model was used. $P < 0.05$ was the threshold for statistical signficance. Findings are illustrated in the form of forest plots. The proportions of participants having frailty and prefailty were extracted from all included studies in order to calculate the pooled prevalence of these conditions. To assess the risk factors for frailty among Chinese community-dwelling older adults, the odds ratios (ORs) and associated 95% CIs from included studies were extracted, and all eligible available data was summarized.

In stratified meta-analyses, the literature data were divided into subgroups according to frailty criteria, gender, age, and region, and pooled estimates of frailty prevalence with 95% CIs were calculated.

Results

Study process

Our initial search retrieved 1151 articles, of which 236 were duplicates. After screening titles and abstracts, 51 articles remained, all of which were evaluated in detail. Of these, we excluded 16 studies because they did not contain frailty criteria, 8 studies because their sample sizes were less than 50, and 13 studies because they failed to provide data on the target cohort. In total, 14 studies ultimately met the inclusion criteria and were included in this meta-analysis (Figure 1).

Table 1
Critical appraisal of studies

Study	Score of Item (point)								Total score	Limitations
	Random sample or whole population	Unbiased sampling frame (i.e. census data)	Adequate sample size (>300 subjects)	Measures were the standard	Outcomes measured by unbiased assessors	Adequate response rate, refusers described	Confidence intervals, subgroup analysis	Study subjects described		
Chen et al. (20)	1	1	1	1	0	0	0	1	5	No CI Refusers not described Unbiased assessors not described
Wu et al. (21)	1	1	1	1	0	0	1	1	6	Refusers not described Unbiased assessors not described
Chang et al. (22)	1	1	1	1	0	0	1	1	6	Response rate and refusers not described Unbiased assessors not described
Zheng et al. (23)	1	0	1	1	1	0	1	1	6	Refusers not described Census data not used
Ma et al. (24)	1	0	1	1	0	0	0	1	4	No CI Refusers not described Unbiased assessors not described Census data not used
Woo et al. (25)	1	0	1	1	1	0	0	1	5	No CI Response rate and refusers not described Census data not used
Rodriguez et al. (26)	1	0	1	1	0	0	1	1	5	Response rate and refusers not described Unbiased assessors not described Census data not used
Chen et al. (27)	1	1	1	1	0	0	0	1	5	No CI Response rate and refusers not described Unbiased assessors not described
Woo et al. (28)	1	0	1	1	1	1	0	1	6 .	No CI Census data not used»

Table 1 (continued)
Critical appraisal of studies

Study	Score of Item (point)								Total score	Limitations
	Random sample or whole population	Unbiased sampling frame (i.e. census data)	Adequate sample size (>300 subjects)	Measures were the standard	Outcomes measured by unbiased assessors	Adequate response rate, refusers described	Confidence intervals, subgroup analysis	Study subjects described		
Chang et al. (29)	1	0	1	1	0	1	0	1	5	No CI Unbiased assessors not described Census data not used
Dong et al. (30)	1	0	1	1	1	0	0	1	5	No CI Response rate and refusers not described Census data not used
Chen et al. (31)	1	0	1	1	0	0	0	1	4	No CI Unbiased assessors not described Response rate and refusers not described
Tao et al. (18)	1	0	0	1	0	0	0	1	3	Census data not used Response rate and refusers not described Unbiased assessors not described Sample size <300 Census data not used
Xi and Guo (19)	0	0	1	1	0	0	0	1	3	No CI Refusers not described Unbiased assessors not described Census data not used Not random sample or whole population

Score = Methodological strength of study (maximum 8)

Table 2
Characteristics of included studies

Authors	Publication Years	Study area	Sample size	Diagnostic criteria	Prevalence (%)		Risk factors Assessed
					prefrail	frail	
Chen et al. (20)	2014	Taiwan	781	FFI	45.9	8.3	Age; Depression syndrome; No. of activities; male
Wu et al. (21)	2017	28 provinces in China	17708	FFI	51.2	7.0	Lung disease; Having ≥2 diseases; Falls in previous year; Depression; ADL disability; IADL disability; Lower extremity functional limitation; Upper extremity functional limitation
Chang et al. (22)	2011	Taiwan	6828	FFI&EFS	—	11.3 (FFI) 14.9 (EFS)	Age; Depression; Comorbidity; MMSE score; Depression; Incontinence
Zheng et al. (23)	2016	Beijing	10039	FI scale	—	9.1	Female
Ma et al. (24)	2018	7 cities in China	6867	FI scale	—	12.0	Education; Monthly income; Marital status; Daily exercise; ADL/IADL ability; Depression; Weekly meat intake; Female Number of chronic diseases
Woo et al. (25)	2015	Beijing and Hong Kong	14039	FI scale	52.0	15.4	Female; Age; Education; Living alone; Daily exercise <0.5 h; No. of activities ≥3; Daily drugs≥4
Rodriguez et al. (26)	2018	urban and rural catchment areas in China	17031	FFI	—	8.3	Physical Impairments; Stroke; Disability; Dependence
Chen et al. (27)	2010	Taiwan	2238	FFI	33.6	8.2	Specific drugs; Female
Woo et al. (28)	2015	Hong Kong	816	Frail scale	52.4	12.5	SARC-F; ADL disability; AMIC score
Chang et al. (29)	2012	Taiwan	900	FFI	62.8	5.9	Health-related quality of life
Dong et al. (30)	2018	Jinan City, Shandong Province, Eastern China	1235	Frail scale	26.8	17.4	—
Chen et al. (31)	2016	Taiwan	1839	FFI	40.4	6.8	—
Tao et al. (18)	2015	Langfang city, Hebei Province, Northern China	254	FFI	40.2	7.5	Chronic diseases; fail; Male
Xi and Guo (19)	2014	Beijing	683	FFI	45.7	11.1	increasing age; poorer self-report health; depression; cognitive impairment; poor sleep quality; Female

Note: ADL=activity of daily living; IADL=instrumental activity of daily living; MMSE=Mini-Mental State Examination; SARC-F=strength, assistance with walking, rise from a chair, climb stairs, and fall; AMIC=Abbreviated Memory Inventory for the Chinese.

Characteristics of the included studies

The characteristics of the 14 studies are summarized in Table 2. Two articles were written in Chinese (18, 19), while the remainder were in English (18-31). Five studies were conducted in Taiwan (20, 22, 27, 29, 31), two in Hong Kong (25, 28), and the remainder on the Chinese mainland (18, 19, 21, 23, 24, 26, 30). Sample sizes ranged from 254 (18) to 17708 (21). 12 studies reported the risk factors of frailty (18-29).

Prevalence of frailty and prefrailty

Data from 14 studies were available for a meta-analysis of the prevalence of frailty status. The prevalence of frailty and prefrailty in included studies ranged from 5.9% (29) to 17.4% (30), and from 26.8% (30) to 62.8% (29), respectively. From a random-effects model-based meta-analysis conducted on all data points, we estimated an overall frailty prevalence of 10% (95% CI: 8% to 12%, I^2 = 97.4%, P = 0.000) among Chinese

community-dwelling older persons, with an estimated pooled prevalence of prefrailty of 43% (95% CI: 37% to 50%, I^2 = 98.0%, P = 0.000) (Figure 2 and Figure 3).

Figure 1
Preferred Reporting Items for Systematic Reviews and MetaAnalyses (PRISMA) flow diagram for the study selection process

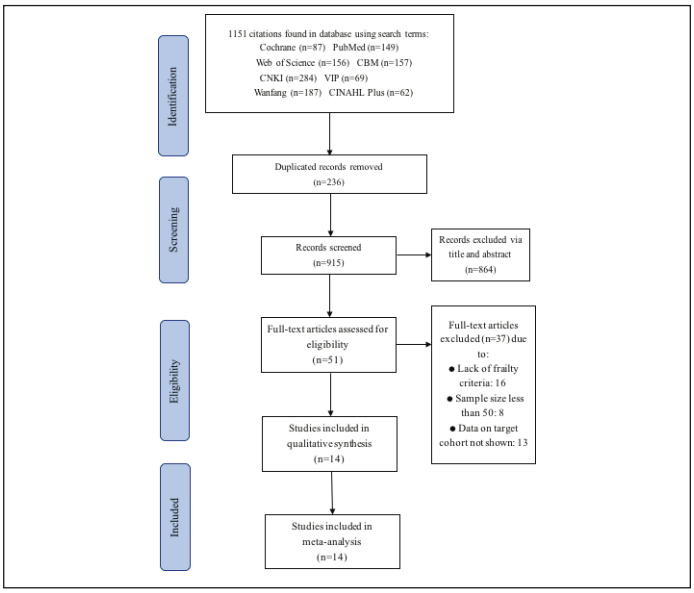
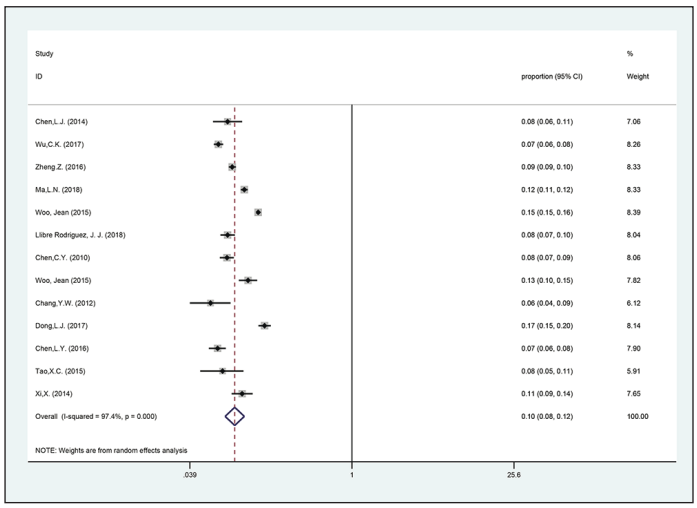


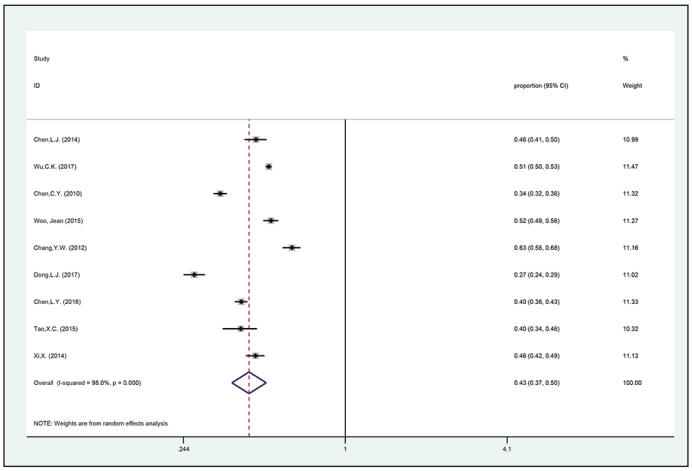
Figure 2
Forest plot of prevalence of frailty



Stratified prevalence of frailty according to frailty criteria, gender, age, and region

The pooled estimates of frailty prevalence based on the FFI, FI, and Frail Scales were 8%, 12%, and 15%, respectively. The pooled estimates of frailty prevalence for individuals aged 65-74, 75-84, and ≥85 were 6%, 15%, and 25%, respectively. The estimated pooled prevalence of frailty was 8% in males and 11% in females. The pooled prevalence of frailty in Mainland China, Taiwan, and Hong Kong were 12%, 8%, and 14%, respectively. The pooled prevalence of frailty in the urban settings was higher than that in the rural settings. Results of subgroup analyses are shown in Table 3.

Figure 3
Forest plot of prevalence of prefrailty



Risk factors

For the pooled analysis, we were able to identify 4 potential risk factors (increasing age, being female, suffering from ADL disability, and having three or more chronic diseases), which were associated with frailty. Results of a risk factors analysis are shown in Table 4.

Discussion

Based on 14 studies involving a total of 81258 participants living in the community, the estimated prevalence rates of frailty and prefrailty in China are 10%, and 43%, respectively. When assessing potential risk factors associated with frailty in China, four factors - increasing age, being female, having ADL disability, and having three or more chronic diseases - were associated with frailty.

The pooled prevalence of frailty documented in the current meta-analysis (10%; 95% CI: 8% to 12%) appeared to be slightly lower than the global estimate (10.7%; 95% CI: 10.5% to 10.9%) (14). However, this rate was higher than that of neighboring Japan (7.4%; 95% CI: 6.1% to 9.1%) (32). Differences in frailty prevalence estimates between China and the global average may be due to the characteristics of studies included in this meta-analysis, dietary habits, or forms of exercise. Dietary quality is known to be linked with frailty, and the Chinese diet has been found to be similar to the Mediterranean diet as both are characterized by high vegetable and fruit consumption and low meat consumption (33). A higher adherence to a Mediterranean diet is associated with a lower risk of frailty in old age, which may be associated with the reduced frailty rate in China in this analysis (34). With

Table 3
Subgroup analyses by frailty criteria, age, gender, and region

Subgroups	Prefrailty				Frailty			
	Prevalence	95%CI	I^2	P value	Prevalence	95%CI	I^2	P value
Frailty criteria								
FFI	—	—	—	—	8	7-9%	73.7	0.000
FI	—	—	—	—	12	9-16%	98.8	0.000
Frail Scale	—	—	—	—	15	11-21%	88.4	0.003
age								
65-74	34%	26-44%	97.6%	0.000	6%	5-9%	95.3%	0.000
75-84	44%	35-54%	96.3%	0.000	15%	12-18%	92.4%	0.000
≥85	20%	12-22%	95.8%	0.000	25%	22-28%	46.1%	0.000
gender								
Male	44%	37-51%	95.5%	0.000	8%	7-10%	88.3%	0.000
female	42%	36-49%	96.3%	0.000	11%	9-13%	96.6%	0.000
region								
Mainland	37%	26-53%	97.3%	0.000	12%	9-15%	97.1%	0.000
Taiwan	44%	34-57%	98.2%	0.000	8%	7-10%	67.4%	0.027
Hong Kong	—	—	—	—	14%	12-17%	71.3%	0.062
Urban	—	—	—	—	10%	7-14%	98.6%	0.000
rural	—	—	—	—	7%	4-11%	97.8%	0.000

respect to forms of exercise, Tai Chi, a type of Chinese exercise derived from martial arts, has gained popularity among Chinese older adults, and this has the potential to improve the health status of older adults who are at risk of frailty, preventing or delaying its onset (35). The observed higher rate of frailty than that detected in Japan may be related to the sample included in the Japanese study. Because the review of Japan (32) excluded participants with ADL disability, this may have led to a lower pooled frailty prevalence than that detected by our review. Another possible explanation is that Japan is a hyper-aged country, and has better mechanisms and policies in place for dealing with aging and frailty than does China. Although most reports to date have focused on the prevalence of frailty, screening for prefrail conditions is also of great importance. The pooled prevalence of prefrailty in this meta-analysis was found to be 43% (95% CI: 37% to 50%). This is lower than that in Japan (48.1%; 95% CI: 41.6% to 54.8%) (32) but higher than the worldwide estimate (41.6%; 95%CI: 41.2 to 42.0%) (14) – an outcome which is the opposite of that observed for frailty prevalence. The reasons for this result are unclear due to the limitations of frailty-associated knowledge at present. Further studies are warranted to further explore this phenomenon.

Our analysis found that pooled prevalence of frailty varied based on the assessment method employed. Most of included studies relied upon the Fried frailty phenotype, frail index, and Frail Scale to assess frailty incidence. In this meta-analysis, we detected the lowest prevalence of frailty when we restricted the assessment method only to the Fried frailty phenotype. Differences among frailty prevalence based on these three assessment methods may be due to the differences in sensitivity and specificity of these scales. Therefore, further work should be conducted to identify a uniform scale that can be used by clinicians and policy-makers to accurately identify frailty among populations.

Table 4
Pooled risk factors of frailty

No.	Risk factors	OR	95% CI	I^2	P- value
1	Increasing age	1.28	1.2-1.36	98.0%	0.000
2	Female	1.29	1.16-1.43	92.7%	0.000
3	ADL disability	1.72	1.57-1.90	99.7%	0.000
4	Having three or more chronic diseases	1.97	1.78-2.18	97.5%	0.000

The result of our gender-stratified analysis revealed that females were more likely to be frail than males, which was consistent with previous reports (14, 32, 36). This finding is not unexpected, given that most elderly women are postmenopausal, and postmenopausal women have a high prevalence of vitamin D deficiency (37) which has a negative impact on muscle strength, neuromuscular function, and postural stability (38). The relationship between frailty

and sarcopenia has been confirmed in previous studies (39). Additionally, one study has found that males have a higher likelihood of dying suddenly than females, whereas females present with a more-steady, progressive decline (40). This decline has the potential to lead to frailty, providing females with a greater apparent degree of frailty. Another possible explanation is that females have a longer life expectancy, resulting in the lower quality of life and poorer health status in their later years (41). The current meta-analysis also identified a significant relationship between being female and frailty risk based on pooled OR (1.29; 95% CI: 1.16 to 1.43), further emphasizing that being female is a significant risk factor for frailty.

Also as expected, an age-stratified analysis indicated that a steadily increasing prevalence of frailty with increasing age, consistent with previous reports (14, 32). Interestingly, our study found that the frailty prevalence rose almost in multiples substantially as age increased. The frailty prevalence in the 75-84-year age group (15%) was more than twice that of the rate in those aged 65-74 years (6%), while the prevalence in individuals ≥85 years of age (25%) was more than four times that of those aged 65-74-years. That is likely due to the fact that with increasing age, organs gradually undergo degenerative changes, and an individual's reserve capacity similarly decreases. Consistent with these results, we found that increasing age served as a risk factor for frailty based on its pooled OR (1.28; 95% CI:1.20 to 1.36). Further research regarding the prevalence of frailty in particular age groups will allow for targeted frailty interventions and prevention efforts.

Based on a sub-regional analysis, we observed that the prevalence of frailty was higher among city dwellers than that among those in rural areas (10% vs. 7%), which may be related to an imbalance in samples included in our study. The current meta-analysis included more urban individuals (67.9%) than rural ones, and so the overall prevalence of frailty among urban dwellers may be overestimated. Additionally, people lived in urban areas pay more attention to health care and have a higher rate of hospital visitation than do rural populations, leading to a higher probability of being screened for frailty among city dwellers. We further found that people living in Mainland China and Hong Kong was more likely to be frail than were those living in Taiwan. This may due to the fact that the awareness on frailty among older adults living in Taiwan is higher than that among individuals living on the mainland. Studies of frailty in Taiwan are more common at 4.3% of worldwide studies, while those on the mainland represent just 3.9% of total global studies (42), emphasizing the importance of nationwide research in order to prevent and treat frailty.

We further found that having ADL disability (OR:1.72; 95% CI:1.57-1.90) and having three or more chronic disease (OR:1.97; 95% CI:1.78-2.18) were both risk factors for frailty in Chinese community-dwelling older persons, which has not been mentioned in previously synthesized results. It is noteworthy that the OR values for these risk factors presented in our present meta-analysis are less than 2, indicating that the correlation strength between frailty and these risk factors is not high. Moreover, the risk factors incorporated in the included studies varied greatly, making it difficult to accurately conduct pooled OR-based assessments of all potential risk factors. Therefore, future studies aimed at more objectively exploring frailty-associated risk factors are needed.

A principal strength of this study is its robust methodology: the literature was comprehensively searched in both Chinese and English in a total of 8 electronic databases by two reviewers, increasing our ability to accurately catalog all of frailty epidemiology in China and to stratify studies based on frailty criteria, gender, age, and region. To the best of our knowledge, the current study is the first to provide both the pooled prevalence and an assessment of associated risk factors among Chinese community-dwelling older people, and the findings of this study will be of value to researchers, clinicians, policymakers, and the general population. However, potential limitations of the current study should be noted. For one, there was a high degree of variability among frailty risk factors in the included studies, making it difficult to conduct meta-analysis of these same risk factors and leading to limitation in our statistical power when doing so. Bearing those limitations in mind, further studies will be needed to better interrogate frailty risk factors within the Chinese population.

In conclusion, this systematic review found that the pooled prevalence of frailty among Chinese community-dwelling older persons was 10%. Being female, increasing age, ADL disability, and having three or more chronic diseases were all risk factors for frailty in individuals in China. These findings provide evidence-based data that can help promote further frailty research and prevention efforts throughout the nation. The current prevalence of frailty among Chinese community-dwelling older persons is roughly on par with the average global rate. Most of the study populations assessed to date are from northern China, Taiwan, and Hong Kong, while other parts of China have not received significant attention, and as such frailty prevalence in these regions warrants further research. With regard to risk factors for frailty, some significant risk factors, such as social and psychological factors, were not assessed in the present meta-analysis. Therefore, further study of these areas will be needed to lay the foundations for future meta-analyses.

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Ethical Standards: This study did not include any animal or human experiments.

Conflict of Interest: The authors declare that no competing interest.

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