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Frailty in the Elderly is Associated with an Increased Risk of Depression: A Systematic Review and Meta-Analysis

ABSTRACT

Objective: The aim was to systematically review the association between depression and frailty in the elderly.

Methods: Databases such as PubMed, Web of Science, Embase, and Scopus were searched for articles on the link between the risk of depression and frailty since the creation of the databases to September 1, 2023. A pair of investigators collaboratively conducted the screening, collected data, and evaluated the potential for bias in the included studies. R software was utilized for meta-synthesis.

Results: Eight cohort studies comprising 13 043 participants and 14 854 senior individuals with depression were included. The meta-analysis showed that there was a significant connection regarding frailty and the incidence of depression among the elderly (Risk Ratio [RR] = 3.26, 95% Confidence Interval [CI]: 1.68-6.32). Subgroup evaluations showed that there was no association between frailty and depression in the community-dwelling elderly (RR = 2.28, 95% CI: 0.644-8.102) and in the elderly patients with depression assessed by Center for Epidemiological Studies Depression Scale (CES-D) (RR = 5.82, 95% CI: 0.481-70.526).

Conclusion: Frailty is correlated with the risk of depression in the elderly. Frailty is a contributing factor to depression in the elderly.

Keywords: Frailty syndrome, geriatric depression, association, contributory factor, systematic review

Introduction

Frailty syndrome refers to the degeneration of the body and the decline of physiological function in the elderly, which makes it difficult for the body to maintain its normal physiological balance in response to external shocks and stresses. This can lead to small external stimuli that can cause adverse events.[1-3] It is estimated that 25%-50% of people aged over 85 years are frail.[4] The clinical manifestations of frailty include extreme fatigue, inexplicable weight reduction, slow movement, low grip strength, and low mobility. It can result to falls, fractures, disability, and even death in the elderly,[5-7] accompanied by a range of adverse symptoms like depression, sleep disturbance, and pain. This brings a huge economic and medical burden to the family and society.[8,9] Prevalence of frailty characteristics is high in communities, with estimates showing that 7% of community-dwelling older individuals over 65 years of age exhibit one or two characteristics of frailty, and this prevalence increases significantly among those over 80 years of age.[10] The 3-year follow-up data revealed that the mortality risk among frail elderly individuals was 3 times higher compared to their nonfrail counterparts. Furthermore, the risk of death in frail elderly persons was found to be up to 6 times greater than in the general population of older adults.[1] As a result, a significant proportion of community-dwelling older adults are at the "tipping point" toward a dire outcome.

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Depression is very common in the elderly, which is manifested by low mood, physical decline, hopelessness, and sleep disorders. The incidence of depression ranges from 8% to 12% in community homes, 5% to 10% in outpatient and inpatient settings, and 10% to 12% in inpatient settings, respectively, with the peak prevalence in nursing homes at 14%-67%.[11-14] Depression in later life is a widespread psychological disorder that affects the outcome of many medical diseases, including functional disability. Depression and cognitive impairment often co-occur. Detecting variable indicators of depressive symptoms can help reduce and prevent physical and mental health problems in older individuals.

There is a remarkable overlap between late-life melancholia and weakness, with each melancholia and weakness sharing common symptoms (weight loss, reduced physical activity, and low energy) and frailty (fatigue, decreased leisure activity, and weight loss). Cardiovascular health studies have reported that the incidence of depressive symptoms is proportional to the count of weakness features present.[15] However, despite these associations, few studies have concentrated on the causal link between weakness and depression. Currently, numerous studies on the correlation between weakness syndrome and depression in seniors have been reported both domestically and internationally. This study systematically reviews the association between weakness and the peril of geriatric depression, in order to provide a basis for the clinical assessment of weakness as a risk element in the field of geriatric medicine.

Material and Methods

Search Strategy

PubMed, Web of Science, Scopus, and Embase were searched by computer from the establishment of each database to September 2023. The search terms included: (1) depression, depress, (2) frail*, frailty, frail syndrome, weakness, and (3) aged, elder*, old*. The 3 aspects of the search terms were connected by "OR", while the 3 aspects of the content were connected by "and". Each database was searched using a combination of subject terms and free words adjusted for the specific database. At the same time, the references and citations of the retrieved literature were traced using the snowball method, so as to expand the search scope and check the relevant literature. In the case of PubMed, the specific search strategy is shown in Supplementary Material. This study was guided by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.

Inclusion Criteria

- Study classification: observational study, including cross-sectional study, cohort study, and case–control study.
- Elderly population (over 60 years old): if the study group is not systematically selected from the general population, the study is eligible only if (1) it attracts a wide and varied population, such as the total number of hospitalized patients in a country; and (2) there is no bias in the study reporting, that is, the study included complete reporting of the enlistment and choice procedure.
- Exposure: presence of frailty, with clearly proposed frailty assessment methods, and divided into frailty group and control group (the control group included pre-frailty and non-frailty).
- Results: Clinically significant depression diagnosed as primary depressive disorder (PDD) adhering to recognized diagnostic criteria (e.g., DSM or ICD), or above a benchmark on the established psychopathology rating scales for depression, as assigned by the study authors. Diagnoses may be derived from assessment scoring scales, systematized interviews such as WHO-CIDI, or registries that include clinical data with proven dependability.

Disqualification Criteria

- Non-Chinese and English literatures.
- Literature that could not be directly extracted or calculated to obtain the required data.
- Unable to access the full text.
- Repeated publication.
- Literature with low methodological quality score.

Literature Review and Information Gathering

Two researchers independently scrutinized the literature, collected the data, and verified them. In case of disagreement, a third party was asked to aid in decision-making, and authors lacking comprehensive data were contacted to try to supplement. Inadequate screening was first performed by reading titles and abstracts, and after excluding obviously unrelated literature, further full text was read to determine final inclusion. The content of data extraction mainly included: (1) fundamental details of the included studies, including the research heading, primary author, date of publication, etc. (2) The initial characteristics of the subjects, including the number of participants in each group, age, sex, etc. (3) Key elements of bias risk evaluation. (4) Outcome measures and outcome variables of interest. The data extraction form was designed based on the Cochrane Handbook for Systematic Reviews of Interventions. Two researchers independently evaluated the risk of bias of the literature obtained after re-screening, and the decision was made after discussion with a third party in case of disagreement. The prospective cohort study used the Newcastle-Ottawa scale, which consisted of 3 dimensions and 9 items, with a total score of 0-9. The quality assessment checklist 17 of the Agency for Healthcare Research and Quality was used in this cross-sectional study, with a total score of 0-11 points.

MAIN POINTS

- *Frailty in the elderly is significantly associated with an increased risk of depression, with a relative risk (RR) of 3.26, indicating that frail individuals are over three times more likely to develop depression.*
- *Subgroup analysis reveals that the association between frailty and depression is not significant among community-dwelling elderly, suggesting that the impact of frailty on depression may vary by living situation.*
- *The Fried frailty phenotype is recommended as a screening tool for frailty in the elderly, as it seems to provide a better screening capability than the FRAIL scale.*
- *The Geriatric Depression Scale (GDS) and the Center for Epidemiological Studies Depression Scale (CES-D) are both utilized to assess depression, with GDS showing a higher prevalence of diagnosed depression.*
- *This systematic review emphasizes the necessity for early detection and intervention for frailty and depression in the elderly to improve their quality of life.*

Literature Quality Assessment

Two researchers conducted an independent evaluation of the bias risk of the literature obtained after re-screening, and the decision was made after debate with a third party in case of disagreement. The prospective cohort study used the Newcastle–Ottawa Scale, which consisted of 3 dimensions and 9 factors, with a total score of 0.9-1.5, indicating the caliber of the study. The Agency for Healthcare Research and Quality was used in this longitudinal study, with a total range of 0-11 points. The total score was considered as medium or high-quality literature.[16]

Statistical Analysis

All data was statistically analyzed using R software 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria). A mixed-effects model was used to summarize the studies evaluated. The impact of geriatric frailty syndrome on depression was expressed using RR and 95% Confidence Interval (CI). The Cochran *Q* test and I^2 index were used to evaluate the heterogeneity between studies. [17,18] The I^2 statistic was ≥50%, and $P < .05$ was the criterion for significant heterogeneity among studies.[17,18] Funnel plot and Egger's test were used to evaluate $P < .05$ indicating potential publication bias.[19] Subgroup analyses were performed according to study design, depression assessment method, and study cohort. Sensitivity evaluations were performed after excluding individual studies from the included studies that may affect the study conditions. A statistically significant difference was defined as $P < .05$.

Results

This study reviewed a total of 13 566 documents and filtered them according to the inclusion and exclusion criteria. Finally, 8 studies were selected for inclusion in this meta-analysis. The specific literature screening process is shown in Figure 1.

Basic Characteristics of Included Studies

Table 1 summarizes the basic characteristics of the included studies. There were 8 cohort studies in total, involving 13 043 participants. Most of the study subjects were over 65 years old. Two studies[20,21] had participants aged 60 years, while 2 studies[22,23] had participants over 70 years old. There were 2 studies in China, 1 study in Spain, 1 study in Singapore, 1 study in Brazil, 1 study in the United States, 1 study in South Korea, and 1 study in Italy. The number of men and women included in the studies was roughly equal. The NOS scale was used to evaluate the quality of the included literature, with a score ranging from 8 to 9 points.

Measurement of Physical Frailty

(1) Frailty profile: Governed by the 5 benchmarks established by Fried and associates (2001) in the Cardiovascular Health Study (CHS), encompassing low body mass, absence of exercise, exhaustion, frailness, and sluggishness.[25]
(2) Archetype vulnerability is bifurcated into 3 levels: non-frailty (inadequacy to satisfy the 5 domains), borderline frailty, and definite frailty (meets any one or more criteria). Seven studies used this measurement tool.
(3) Encompasses 5 elements: exhaustion, endurance, ambulation, sickness, and accidental weight reduction.[25]
(4) Frailty index scores vary from 0 to 5 (i.e., 1 score for each element; 0 optimal to 5 poorest). Frailty was categorized as 3-5 scores, borderline frailty was 1-2 scores, and robust status was 0 score. Only 1 study utilized this measurement instrument.

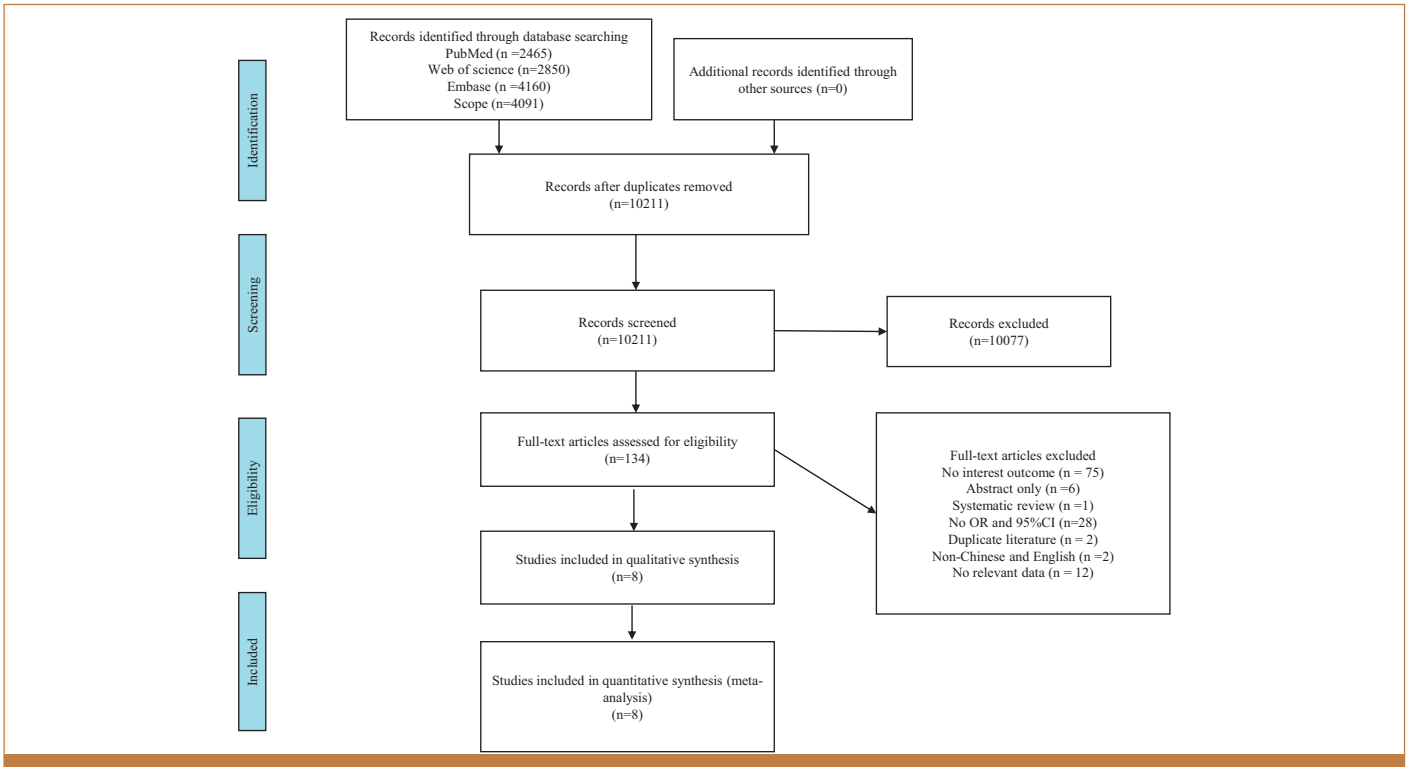

Figure 1. Literature screening flowchart.

Table 1. Basic Characteristics of the Included Studies

Author	Study Design	Country	Participant	Frailty Criteria	Depression Criteria	Sample Size	Gender	Age (Years)	Length of Follow-up	Quality Assessment	Use of Follow-up Data
Figueiredo et al 2021[20]	Cohort study	Brazil	Community-dwelling	Fried frailty phenotype	GDS-15≥5	735	F/M	>60	4	8	Yes
Veronese et al 2017[21]	Cohort study	Italy	Community-dwelling	Fried frailty phenotype	CES-D-20 ≥16	2.277	F/M	>60	2	8	Yes
Zhang et al 2020[22]	Cohort study	China	General	Fried frailty phenotype	GDS-15≥6	1.168	F/M	>70	3	8	Yes
Carolina et al 2020[23]	Cohort study	Spain	General	Fried frailty phenotype	GDS-15≥5	800	F/M	>70	10	8	Yes
Feng et al 2014[24]	Cohort study	Singapore	Community-dwelling	Fried frailty phenotype	GDS	1.827	F/M	>55	4	8	Yes
Jung et al 2016[25]	Cohort study	Korea	General	Fried frailty phenotype	CES-D-30 ≥21	380	F/M	>65	5	9	Yes
Wu et al 2020[26]	Cohort study	China	Geriatric Clinic	FRAIL Scale	GDS-15≥6	157	F/M	>65	1	8	No
Fried et al 2001[27]	Cohort study	United States	General	Fried frailty phenotype	CES-D-20 ≥10	5.317	F/M	>65	7	9	Yes

GDS, Geriatric Depression Scale; CES-D, Center for Epidemiological Studies Depression Scale; F/M, Female/Male.

Evaluation of Depression

In terms of depression assessment, 5 studies used the Senior Depression Scale (GDS) to characterize depression in the elderly. Three studies utilized the Center for Epidemiological studies depression (CES-D).

Synthesis of Study Findings

The aggregated meta-analysis ascertained that due to the high statistical heterogeneity between studies ($P < .001$, $I^2 = 96\%$), a mixed-effects model was employed. The correlation between frailty and the likelihood of depression in the elderly is statistically meaningful (Risk Ratio [RR] = 3.26, 95% CI: 1.68-6.32) (Figure 2).

Subgroup Analysis

Subgroup analyses of study population, depression diagnoses, and frailty diagnoses were performed on the included studies to reduce the possibility of the above potential influencing factors. The specific results are shown in Table 2. Table 2 shows the results of the subgroup analysis based on the study population, the diagnosis of frailty, and the diagnosis of depression. The results suggest that the association between frailty and depression was significant in the general population, the geriatric clinic population, the studies that used the Fried frailty phenotype, the studies that used the FRAIL scale, and the studies that used the GDS. However, the association was not significant in the community-dwelling population and the studies that used the CES-D.

Sensitivity Analysis

Sensitivity analysis was performed after eliminating individual studies one by one. The results showed that the results of the meta-analysis of this study were stable (Figure 3).

Publication Bias

To assess the potential publication bias in the meta-analysis, we constructed a funnel plot of the effect size against the standard error and performed Egger's test. The funnel plot is shown in Figure 4. Egger's test also confirmed the absence of significant publication bias ($P = .932$).

Discussion

Previous longitudinal findings indicate that factors akin to elements of frailty, such as mobility difficulties,[28,29] physical inactivity,[30] and fatigue,[31] seem to elevate the risk of depressive symptoms in older adults. The current longitudinal data suggest an important role for physical frailty as a forecaster of depressive indicators. To our awareness, only one meta-analysis of research using Clinical Biology Synthesis has been reported. Physical frailty defined by the condition (including weight loss, fatigue, inactivity, slowness, and frailty) is a harbinger of depressive symptoms in residents of elderly communities. A comprehensive examination by Soysal et al[32] found that frail older adults have an augmented probability of developing depression (Odds Ratio [OR] = 4.42, 95% CI: 2.66-7.35), and the risk quotient was reduced after adjusting for confounding bias (OR = 2.64, 95% CI: 1.59-4.37). A total of 8 research projects were encompassed in this study, and the outcomes indicated that frail elderly people have a elevated likelihood of depression than those without frailty, indicating a substantial positive link between frailty and depression.

A subgroup analysis was executed based on the study population and found that frailty was not related to depression among

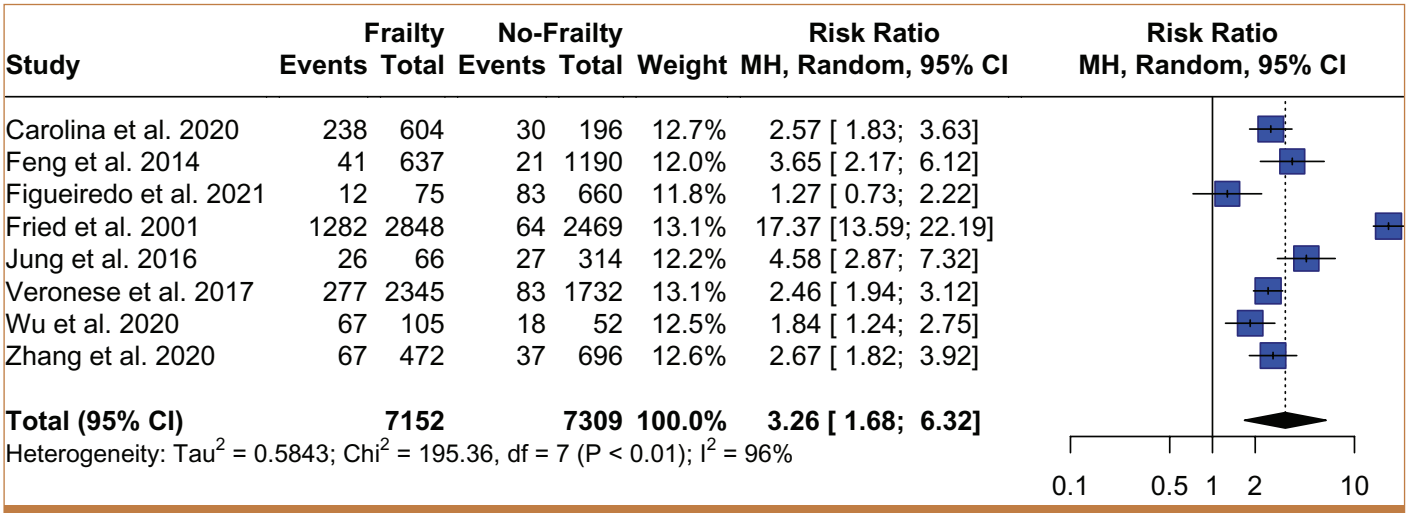

Figure 2. Meta-analysis results.

Table 2. Subgroup Analysis

	Subgroup	Numbers of Studies	RR (95% CI)	I^2	*P*
Population	General	4	4.8746 (1.1646; 20.4034)	97.30	.038
	Community-dwelling	3	2.2841 (0.6439; 8.1022)	73.60	.107
	Geriatric clinic	1	1.8434 (1.2352; 2.7510)	–	.002
Diagnosis of frailty	Fried frailty phenotype	7	3.5320 (1.6576; 7.5260)	96.60	.006
	FRAIL scale	1	1.8434 (1.2352; 2.7510)	–	.003
Diagnosis of depression	GDS	5	2.2890 (1.4355; 3.6499)	58.10	.008
	CES-D	3	5.8269 (0.4814; 70.5265)	98.40	.093

GDS, Geriatric Depression Scale; CES-D, Center for Epidemiological Studies Depression Scale; RR, Risk Ratio; CI, Confidence Interval.

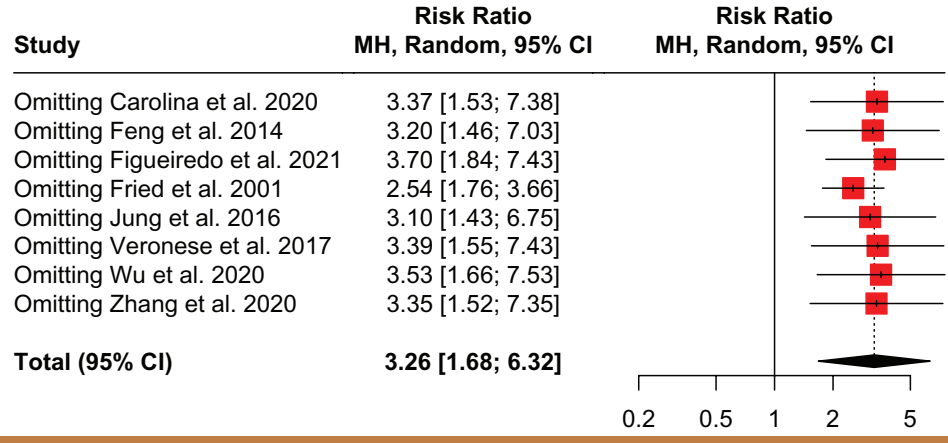

Figure 3. Sensitivity analysis.

community-dwelling elderly people. This may be due to the large disparity between the results of Figueiredo et al.'s study and other results and the high heterogeneity.[20] Likewise, variations in the depression scales used also affected the incidence of depression in frail older adults; contrasts between subgroups were statistically pivotal. However, most studies use the GDS or GDS-15, with fewer studies utilizing other scales. Compared with GDS-15, GDS has a higher prevalence of diagnosed depression, and the former is more significantly associated with frailty. Meta-analysis results showed that the combined accuracy and precision of GDS were 82% and 76%, respectively, and the diagnostic accuracy was higher (area beneath the curve = 0.85). The pooled accuracy and precision of GDS-15 were 86% and 79%, respectively, with higher diagnostic accuracy (area beneath the curve = 0.90). The diagnostic efficacy of GDS-15 is significantly superior to that of GDS,[3334] so GDS-15 is advocated as a screening tool for depression in the future. Among elderly patients using the CES-D to assess depression (RR = 5.82, 95% CI: 0.481-70.526).

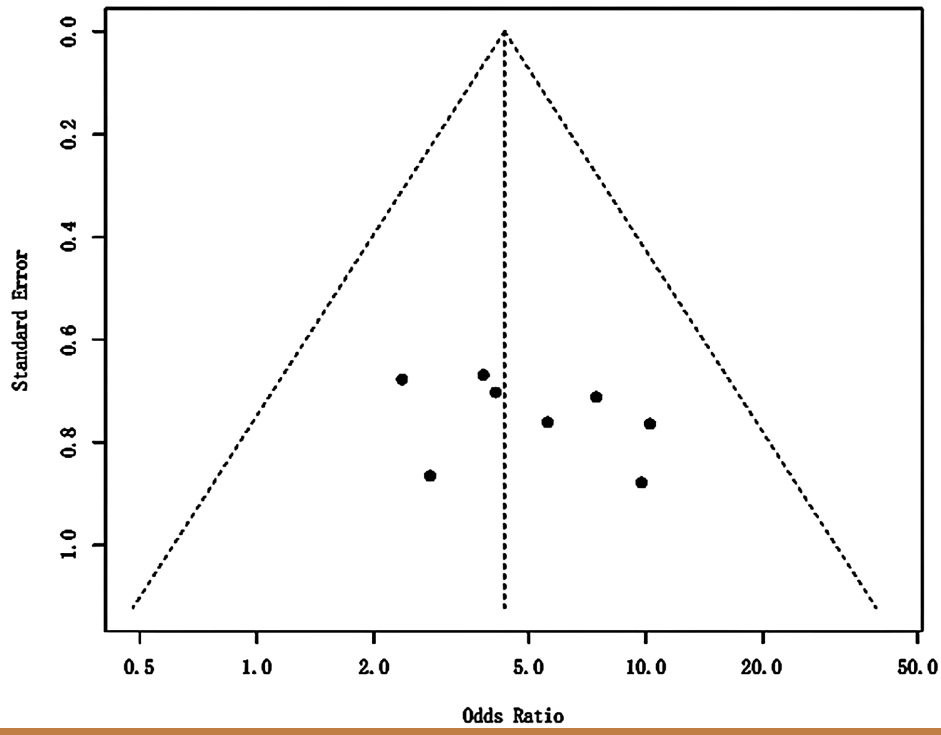

Figure 4. Funnel plot for the meta-analysis of the short-term safety (periprocedural mortality or stroke) of carotid endarterectomy compared with carotid artery stenting.

There is no correlation between frailty and depression. Perhaps owing to the limited quantity of included studies, the results of Fried et al.[25] were considerably different from those of other studies, which is related to excessive heterogeneity. Group comparison assessment based on frailty classifications found that most studies used frailty phenotypes to assess patients' frailty condition. However, there were also marked disparities in the results of subgroups assessing frailty. The RR value using frailty categorization was significantly higher than that of FRAIL scale and is also slightly higher than the overall meta-analysis results, indicating that the frailty phenotype can better screen patients for frailty status. The frailty phenotype is therefore recommended as a screening tool for future feasibility.

Although group comparison assessment and sensitivity analyses were executed, the heterogeneity of the meta-analysis was still large, which may be due to the following rationales: firstly, although all included studies diagnosed frailty based on frailty classification and FRAIL scale, some studies did not grade pre-frailty, so the intensity of frailty may not be uniform among different studies. Secondly, most of the research included used the GDS or GDS-15 to ascertain depressive conditions. GDS is an efficacious metric to assess depressive symptoms and has reliable psychometric characteristics, which can be widely used to assess depression in the elderly in various settings. However, it is only a depression assessment instrument, not a diagnostic instrument, and depressive conditions linked with GDS may be associated with physical illness. In addition, the degree of depression in the included subjects was also different. Depression was diagnosed using questionnaires (e.g., GDS, CED-S), so self-report biases and recall biases are inevitable. This may have influenced the relationships between frailty and depressive symptoms to varying degrees. Thirdly, lack of consideration for demographic information (including age, sex, Body Mass Index [BMI], education) and many confounding factors (e.g., disability, frailty, physical activity, and sex hormones) may have influenced the association between frailty and depression. All confounding factors could not be unified in this study. Fourthly, all the subjects included in the study were the elderly. Most patients have multiple coexisting conditions, each affecting the other patients. The more the comorbidity count, the more likely the incidence of depression. The included studies also differed in terms of comorbidities. Lastly, differences in race, region, and quality control of the study process between studies may lead to greater heterogeneity.

Although the exact mechanism of the correlation between depression and frailty is not yet clear, it may be that frailty and depression share similar symptoms, and they may have the same pathophysiological mechanisms, such as changes in hormone levels secreted by the hypothalamic pituitary–adrenocortical axis, cardiovascular and cerebrovascular diseases. Abnormal levels of inflammatory factors caused by diseases and chronic inflammatory reactions, etc.[35] In addition, depression may affect mitochondrial function and energy production, resulting in decreased physical function, slower walking speed, and reduced exercise in the elderly.[36,37] From a physical health perspective, older adults are more likely to face physical health challenges such as chronic disease, pain, and reduced physical function. These health problems may cause physical discomfort, pain, fatigue, and reduced physical fitness, thereby affecting their quality of life.[38] These physical ailments can trigger feelings of depression. Furthermore, as they age, many older adults are at risk of social isolation, especially after losing a spouse, friend, or family member. Social isolation can lead to feelings of loneliness and depression[39] Additionally, older adults may experience a shift in their self-identity

and feel a loss of their role in society and their sense of self-worth, which may also trigger feelings of depression. In addition to the above, there may be side effects of medications, sleep disturbances, or cognitive decline, which may be causes of depression in frail older adults.[40-42]

This study is the first to conduct a systematic literature review and meta-analysis using pooled RR values to analyze the association between frailty and depression in subgroups of older adults using different study designs, study populations, depression diagnoses, and frailty screening. This study has the following limitations. Firstly, the heterogeneity of this study is high. Although subgroup analysis was conducted, the source of heterogeneity in the included studies was not identified. This may be related to the different study populations in the included literature. Secondly, most studies lack multifactor adjusted OR values, so this study used RR values for merging, which cannot exclude the influence of confounding factors such as age and gender. Furthermore, there are differences in the follow-up time among the analyzed studies. The follow-up period of some studies is 2-4 years, or the follow-up time is not reported. These lead to differences in follow-up time. Due to the large difference in follow-up time among various documents, it cannot be carried out. Subgroup analysis further analyzed the impact of follow-up time on outcomes. However, although these limitations may have affected the conclusions and correlation inferences of the meta-analysis, the study results may still provide a favorable reference for meta-analysis.

Frailty and depression are common among the elderly, and the levels of frailty and depression are at high levels. Current evidence suggests a clear correlation between frailty and depression risk in older adults. This result provides theoretical support for building a more complete elderly care system. It is recommended that disease screening projects, such as frailty or depression in community health services, be included into basic physical examination projects for the elderly in the future, so as to detect and solve problems as early as possible and improve the quality of life of the elderly. For the elderly in the early stages of frailty, medical staff should take measures and pay attention to them to prevent further changes in the disease.

Availability of Data and Materials: *The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Interested researchers may contact the author for access to the data underpinning the findings of this study.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept – J.Z., H.C., C.L.; Design – J.Z., H.C., C.L.; Supervision – C.L.; Resources – J.Z.; Materials – J.Z.; Data Collection and/or Processing – J.Z.; Analysis and/or Interpretation – J.Z.; Literature Search – H.C.; Writing – H.C., J.Z.; Critical Review – C.L., J.Z., H.C.*

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#1 ((depression[Title/Abstract]) OR (depress[Title/Abstract])) OR ("Depression"[Mesh])

#2 ("Frailty"[Mesh]) OR ((((frail*[Title/Abstract]) OR (frailty[Title/Abstract])) OR (frail syndrome[Title/Abstract])) OR (weakness[Title/Abstract]))

#3 ("Aged"[Mesh]) OR (((aged[Title/Abstract]) OR (elder*[Title/Abstract])) OR (old*[Title/Abstract])) OR (late-life[Title/Abstract]) OR (elderly[Title/Abstract])

#4 #1 AND #2 AND #3

Supplementary Material. Search strategy.