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REVIEW ARTICLE

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The association between frailty and anxiety: A systematic review

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Abstract

Objectives: Previous systematic reviews show a clear relationship between frailty and depression, however the association with anxiety is much less frequently explored. Previous single studies indicate evidence is mixed. We completed a systematic review and meta-analysis to identify the relationship between frailty and anxiety.

Methods: We searched five electronic databases for observational studies in older people in community, care home and outpatient settings with any/no health conditions that measured the association between anxiety and frailty using validated measures. Studies were screened by one reviewer with 10% checked by a second reviewer. The Mixed Methods Appraisal Tool was used to assess study quality. We used meta-analysis to aggregate study findings, with subgroup analyses to explore heterogeneity.

Results: Out of 1272 references, a total of 20 cross-sectional and 1 longitudinal studies were eligible. Older adults with frailty were substantially more likely to display anxiety symptoms than robust populations, across both dichotomous and continuous data sets ($n = 10$, OR = 3.48, 95% CI: 2.08, 5.81, $p < 0.0001$, $I^2 = 94\%$; $N = 5$, SMD = 3.13, 95% CI: 1.06, 5.21, $I^2 = 98\%$). Similarly, pre-frail older adults were more likely to have anxiety symptoms than robust older adults but to a lesser extent ($N = 6$, OR = 1.95, 95% CI: 1.41, 2.71, $I^2 = 63\%$; $N = 3$, SMD = 1.70, 95% CI: 0.01, 3.38, $I^2 = 98\%$).

Conclusions: There is a clear association between pre-frailty/frailty and anxiety in older adults. However, data are heterogeneous and primarily from cross-sectional studies so causality cannot be determined. Future research should evaluate the effectiveness of anxiety screening and treatments in frail older adults.

KEYWORDS
anxiety, frailty, meta-analysis, older people, systematic review

Key points

- Frailty is associated with increased risk of anxiety and higher anxiety scale scores
- Pre-frailty is also associated with increased risk of anxiety, but to a lesser extent
- Further research needs to determine the direction of effect and the effectiveness of proactive anxiety screening and treatment of anxiety in frail older adults

1 | INTRODUCTION

Frailty is a common geriatric syndrome. It refers to an accelerated reduction in physiological reserve whereby there is increased vulnerability to poor functioning of homeostatic mechanisms following a stressor event.[1] In the UK, routine screening for frailty in primary care settings was introduced in 2017.[2] It is a significant public health and social issue given the association with increased risk of adverse outcomes such as falls, dementia, hospitalisation, and mortality, even in the absence of comorbidities.[3] Similarly, studies have illustrated a distinct pattern of increased healthcare use and costs linked with frailty syndrome.[3]

In the global context of rising average life expectancy, the levels of frailty may be exacerbated by a rapidly expanding ageing population.[1] The current global prevalence of frailty and pre-frailty using physical frailty measures is estimated at 12% and 46% respectively, with an overall higher prevalence among females.[4] Given that the global proportion of people aged 60 years or older is projected to double by the year 2050, there may be a concomitant rise in the prevalence of frailty and associated adverse outcomes, including a rise in mental health conditions.[1]

Frailty-associated mental health conditions are underreported and poorly-understood,[5] although previous systematic reviews have demonstrated a clear link between frailty and depression.[3,6] Depression and anxiety have similar adverse outcomes to that of frailty. This includes increased healthcare utilisation and reductions in functioning.[7,8] Where depression occurs in combination with frailty, there is an associated rise in mortality, accelerated cognitive decline,[5] and increased use of healthcare services.[9] Other indicators of frailty, such as exhaustion and reduced mobility, can similarly have a substantial influence on mood.[5]

In contrast, symptoms and clinical diagnoses of anxiety in frail older adults are less well documented.[10] Anxiety is often neglected in comparison to depression despite having strong impacts on daily life[10] and being associated with increased risk of cognitive decline.[11] Studies exploring the association between anxiety and frailty suggest that there may be an association, but the evidence is mixed.[12,13] To our knowledge, there has been no systematic or narrative review of the evidence regarding the association between frailty and anxiety.

We therefore aimed to: (1) to investigate the association between frailty and anxiety; and (2) to discuss the clinical relevance of the relationship between anxiety and frailty.

2 | MATERIALS AND METHODS

We performed a systematic review and meta-analysis in accordance with PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines.[14] The review followed a published protocol registered on PROSPERO (ID CRD42020167955).

2.1 | Search strategy

We searched MEDLINE, EMBASE, PsycINFO, CINAHL, and Web of Science from inception to October 2021. The search strategy consisted of MeSH/Emtree and free terms pertinent to three concepts: older age, anxiety and frailty (Supplementary File 1). We screened reference lists of identified studies and past systematic reviews on similar topics. Due to funding restrictions, only studies published in English were eligible for inclusion. There was no restriction on year of publication.

2.2 | Selection criteria

We included (a) observational studies that reported a statistic for an association between pre/frailty and anxiety or reported sufficient data within the paper for us to calculate this (e.g. numbers of anxious/non-anxious by frailty level) (b) in community-dwelling older adults (including residential care), (c) where frailty was assessed with recognised criteria, and (d) anxiety measured according to clinician diagnosis or symptoms with validated anxiety screening measures, (e) and full text published in English. We defined older adults as a population with a median/mean age above 60 years, and included studies if they were carried out in older people with specific conditions. Studies were excluded if they were: (a) randomised controlled trials or reviews, (b) frailty assessment validity studies, (c) qualitative studies, (d) conference abstracts, (e) studies where both anxiety and frailty are measured but with no calculation or data reported regarding the association between these, (f) studies where anxiety was grouped collectively under the umbrella of mental health and no separate data were provided, and (g) acute inpatients.

2.3 | Screening and data extraction

We entered the studies identified from the searches into EndNote Library and deduplicated these. One reviewer (MT) screened the

remaining titles, abstracts, and full texts against the agreed inclusion and exclusion criteria using Rayyan.[15] A second reviewer (RF) checked 10% titles, abstracts, and full texts. If the disagreement between the two reviewers was >5%, an agreed additional 10% of titles and abstracts was to be checked. Percentage agreement between the two reviewers was 96% at title and abstract review (Cohen's $\kappa = 0.88$) and 95.8% at full text stage ($\kappa = 0.89$). One author (MT) independently extracted data from selected studies in a standardised Microsoft Excel™ extraction sheet to catalogue information including: study aim; study characteristics; scales used; participant characteristics study results for primary/secondary outcomes; adjusted covariates; and author conclusions. A second reviewer (RF) independently checked all data used in meta-analysis against the primary papers. If we required additional data to either confirm or enable study inclusion, we contacted the primary authors ($n = 2$ contacted, no response).

2.4 | Study quality assessment

Two authors (MT, RF) assessed study quality of the eligible studies using the Mixed Methods Appraisal tool (MMAT) for quantitative non-randomised studies,[16] which assesses five key domains regarding representativeness, measures used, missing data, confounders and whether the exposure occurred as intended. Study quality was used to inform the synthesis through the level of evidence available for comparisons and was not used to exclude studies.

2.5 | Outcome measures

Primary outcomes were 1) odds ratio/relative risk (OR/RR) of anxiety symptoms or diagnosis in older adults with frailty compared to those who are non-frail/robust; or 2) OR/RR of frailty in older adults with anxiety symptoms or diagnosis compared to those without anxiety. Where possible, we carried out analyses exploring these associations in those who are pre-frail. Terms such as 'low frailty' were considered to indicate pre-frailty. Secondary outcomes were:

1. Incidence and prevalence of frailty in older adults with anxiety symptoms or a diagnosis of anxiety, and vice versa.
2. Difference in frailty level in older adults with anxiety symptoms or a diagnosis of anxiety, measured on a continuous validated scale, and vice versa
3. Correlations between two continuous validated measures of anxiety and frailty

Please note that continuous measures of association were added to our protocol prior to starting this review but we were unable to update the Prospero record, as this was registered in 2019 by a previous MSc student we were unable to contact.

2.6 | Statistical analysis

We used RevMan™ 5.4 to calculate and pool mean differences (MD) or standardised mean differences (SMDs) and 95% confidence intervals using inverse-variance random-effects model for continuous anxiety data.[17] For dichotomous data, we calculated ORs and 95% confidence intervals using Mantel-Haenszel random-effects model. Where adjusted ORs were reported, we log transformed these and combined them separately. Where we used adjusted data, we selected data from the model with the greatest number of variables adjusted for. We evaluated frail versus robust as our primary analysis and carried out secondary analyses comparing pre-frail and frail, and pre-frail and robust. We evaluated the heterogeneity across individual studies by using I^2 statistics, with proportions greater than 25%, 50%, and 75% considered to have low, moderate, and high heterogeneity, respectively.[18] Where there was high heterogeneity we carried out exploratory post hoc subgroup analyses by health condition, as health conditions may be independently associated with anxiety (e.g. cardiovascular disease).[19] We also carried out exploratory post hoc analyses for different measures of our outcomes, with a particular focus on physical measures of frailty versus those which were multidimensional and included a psychological element (such as the Kihon checklist), as for the latter associations between anxiety and frailty may be artificially inflated. Studies with data which could not be included in meta-analysis were summarised narratively.

3 | RESULTS

Out of 1144 deduplicated abstracts, 241 full text articles were reviewed, and 220 articles were excluded (reasons summarised in Figure 1). We included 21 articles, 17 of which had data that could be included in meta-analysis. No new relevant study was found in review articles or from reference list screening.

3.1 | Study and participants' characteristics

There were 15 cross-sectional studies, 5 cross-sectional analyses of cohort studies and 1 secondary analysis of cohort data (Table 1). Across the 21 studies, there were 444,315 participants with mean age of 73.2 years (range 60–98 years), and 61.8% were female. Study sample sizes ranged from 36 to 430,862. Overall, there were 203,726 (46.3%) frail, 4921 (1.1%) prefrail, and 231,589 (52.6%) robust participants, although two studies[20,21] grouped prefrail and robust populations together due to a small sample size of robust participants. In meta-analysis, these have been conservatively considered to be the robust group.

The majority of the studies were conducted among community-dwellers ($n = 19$,[12,13,20–36]). One study was conducted in residential care[37] and one study did not record population setting.[38] The study locations included Europe ($n = 10$,[12,21,24,26,27,29,30,32,35,38]), North America ($n = 8$,[13,20,22,23,25,31,33,39]), Asia ($n = 2$,[28,34]) and Australia

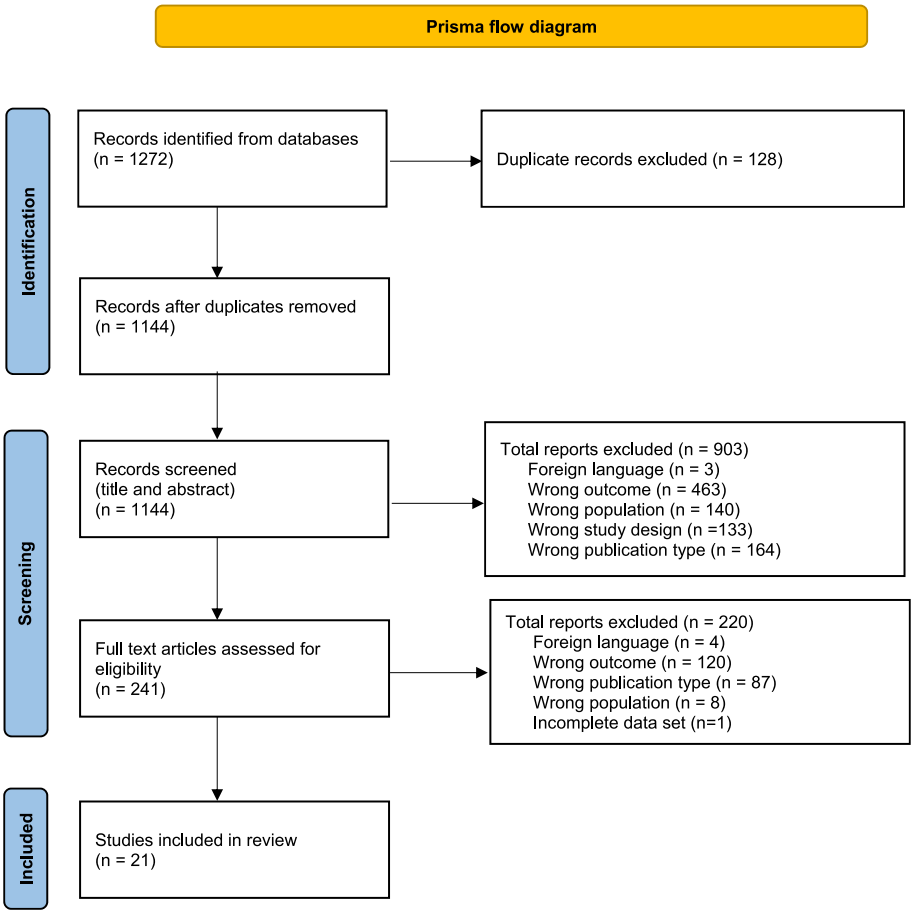


FIGURE 1 Prisma flow diagram illustrating the screening process.

(n = 1,[37]). When stratified by condition, the majority of studies examined the general older adult population (n = 9,[12,24,25,27,29,31,32,34,37]). Other populations categorised by condition included patients with health problems of the cardiovascular system (n = 6,[13,20,22,23,28,38]), respiratory system (n = 3,[21,30,35]), cancer (n = 2),[33,39] and rheumatology (n = 1,[26]).

3.2 | Study quality

Overall study quality was variable (Table 2), with only two studies meeting all quality criteria. Seven studies had fulfiled the criteria for representativeness. Those which did not were often carried out at a single site with a small sample size. All but one study used appropriate measures for anxiety and frailty; one was classed as 'Can't tell' as it used the frailty index but did not specify the cut-off point used for frailty. Twelve studies had complete outcome data, with others having higher attrition rates than 20%. Only eight papers adjusted for one or more confounders; the majority of studies reported unadjusted comparisons. For the vast majority of studies, measurement of frailty and anxiety occurred at the same timepoint for cross-sectional analyses (exposure occurred as intended), but for eight studies the timing of measurements was not clearly reported.

3.3 | Measurement of frailty

Twelve studies evaluated frailty using the Fried frailty phenotype, with various modifications.[12,13,20–24,27,29,30,34,35] Other measures included Edmonton Frail Scale,[25] Frailty Index Score ([37], FRAIL scale questionnaire,[31] Groningen Frailty Indicator,[26] Deficit Accumulation Index,[39] Kihon checklist,[28] Canadian Study of Health and Ageing (CSHA) Clinical Frailty Scale,[32] Carolina Frailty Index,[33] and Tilburg Frailty Indicator scale.[38]

3.4 | Measurement of anxiety

Anxiety was mainly measured the Hospital Anxiety and Depression Scale (HADS, n = 9,[12,13,21,26,29–31,35,38]). The other measures of anxiety included General Anxiety Disorder questionnaire (n = 4,[22,23,34,39]), State-Trait Anxiety Inventory (n = 3,[25,27,28]), PROMIS (n = 2,[20,33]), Geriatric Anxiety Scale (n = 1,[24]), Geriatric Anxiety Inventory (n = 1,[32]) and clinician diagnosis (n = 1,[37]). Anxiety was often classified as a binary variable using a cut off score rather than as a continuous measure of symptoms. The cut-off mark differed according to anxiety measure and within the same anxiety measure in some studies.

TABLE 1 Presents the study and population characteristics of 21 studies included in the systematic review and meta-analysis.

Study ID study location study design	Population setting method of recruitment	Frailty criteria	Anxiety criteria	Inclusion and exclusion criteria	Sample size (*n*)	Mean age (SD) Sex %	Ethnicity (%)
Amare 2020 Australia Retrospective cross-sectional	(a) Permanent residential aged care (b) National historical cohort of the registry of senior Australians	Frailty index score	Clinician diagnosis	Inc: Aged ≥65 years who entered permanent residential aged care between 1 Jul 2008 and 30 Jun 2016	430,862	82.4 (7.0) 38.1%m 61.9%f	NR
Bekic 2019 Croatia Retrospective cross-sectional	(a) Academic general medicine practice (b) NR	Fried phenotype	Geriatric anxiety scale	Inc: Community-dwelling patients aged >60 years Exc: Acute medical conditions, acute exacerbation of chronic diseases, patients who were actively treated with chemotherapy or biological treatments, and patients with a diagnosis of psychosis or dementia.	184	71.26 (6.13) 69.0%m 31.0%f	NR
Bernal-lopez 2012 Mexico Cross-sectional	(a) Community (b) NR	Fried phenotype	HADS-A	Inc: Aged ≥70, living in Mexico city and participating in the mexican study of nutritional and psychosocial markers of frailty (The coyoacan cohort)	927	78.2 (6.2) 45.1%m 54.9%f	NR
Bourgault-fagnou 2009 Canada Cohort	(a) Community (b) A list of clients was generated from the case coordinators' current case- loads and every fourth person on the list was contacted by telephone	Edmonton frail scale	State-trait anxiety inventory	Inc: Adults aged 65 years and older who were receiving home care services in a mid-size metropolitan area Exc: Younger adults excluded from the study if they reported any health conditions	112	82.3 25.9%m 74.1%f	NR
Cleutjens 2021 Netherlands Cross-sectional	(a) Outpatients clinic (b) Consecutive patients visiting the outpatient rheumatology clinic; exact method and selection of participants for 2nd survey NR	Groningen frailty indicator	HADS	Inc: Adults ≥55 years, able to understand the study information, returned study consent forms and questionnaires Exc: Patients with RA living in nursing homes or severely disabled patients who are not visiting outpatient clinic	32	70.5 (6.3) 37.5%m 62.5%f	NR

(Continues)

TABLE 1 (Continued)

Study ID study location study design	Population setting method of recruitment	Frailty criteria	Anxiety criteria	Inclusion and exclusion criteria	Sample size (*n*)	Mean age (SD) Sex %	Ethnicity (%)
Damluji 2020 USA Cohort	(a) Community (b) CHD identified based on medicare data 12 months prior to the 2011 NHATS baseline visit using ICD-9 codes	Fried phenotype	GAD2	Inc: Adults ≥65 years of age enroled during the 2011 NHATS baseline visit, for whom linked medicare data were available for analysis prior to their baseline visit	1213	79.8 49.5%m 50.5%f	Non-hispanic white 74.2 Non-hispanic black 17.9 hispanic 5.3 others 2.6
Damluji 2021USA Cohort	(a) Community (b) a sample of medicare beneficiaries from 2011 NHATS baseline cohort	Fried phenotype	GAD2	Inc: Adults >65 years of age enroled during the 2011 NHATS baseline visit who also had linked medicare data available for analysis prior to their baseline visit Exc: History of CHD or stroke	3259	77.6 39.3%m 60.7%f	Non-hispanic white 72.0 Non-hispanic black 21.2 hispanic 4.2 others 2.6
Denfeld 2021 USA Cross-sectional	(a) Outpatients clinic (b) Convenience sampling from HF and general cardiology clinics at a single centre in the pacific northwest	Modified fried phenotype	PROMIS	Inc: Age 21 years or older, ability to read and comprehend fifth grade English, and New York heart association functional classification I–IV Exc: Documented major cognitive impairment (eg, Alzheimer disease) or active psychosis that would preclude study participation, prior heart transplantation or durable mechanical circulatory support, major and uncorrected hearing dysfunction, or were otherwise unable to complete the requirements of the study (eg, life-threatening illness)	115	63.6 (15.7) 51%m 49%f	Non-hispanic white 84
Dziubek 2020 Poland Cohort	(a) Outpatients PT department (b) NR	Fried phenotype	State-trait anxiety inventory	Inc: ≥3 out 5 frailty symptoms or 1–2 symptoms for pre-frailty confirmed by a doctor, no contraindications to the tests and trials, no participation in another rehabilitation programme, absence of dementia (MMSE >24), and consent to participate in tests and trainings.	36	63–89 years, 72.1 years (6.4) NR	NR

TABLE 1 (Continued)

Study ID study location study design	Population setting method of recruitment	Frailty criteria	Anxiety criteria	Inclusion and exclusion criteria	Sample size (*n*)	Mean age (SD) Sex %	Ethnicity (%)
				Exc: Contraindications to exercise tests and physical training, dysfunctions that make it impossible to perform tests and participate in trainings, less than 70% of training attendance.			
Geophone 2021 France Cross-sectional	(a) Community (b) Referred to the home-based PR by their pulmonologist	Fried phenotype	HADS	Inc: Aged 40 years+, diagnosis of COPD, chronic respiratory failure, defined as the requirement for either LTOT and/or NIV. Exc: Poorly controlled psychiatric illness, neurological sequelae, or any bone and joint diseases preventing physical activity.	44	66 (8) 68%m 32%f	NR
Gilmore 2021 USA Cross-sectional	(a) Community (b) Secondary analysis of baseline cross-sectional data from national cluster RCT	Deficit accumulation index	GAD-7	Inc: Aged ≥70, a diagnosis of stage III/IV solid tumour or lymphoma that was considered by their treating oncologists to be incurable, were considering or receiving any type of cancer treatment (of any line), and had an impairment in at least 1 GA domain (excluding polypharmacy)	541	70–96 years, 77 5 1.1%m 48.9%f	White 89.3, nonwhite 10.7
Honzawa 2020 Japan Retrospective cross-sectional	(a) Community (b) Early phase II CR programme patients from Nov 2015-dec 2016 at juntendo university hospital	Kihon checklist (KCL)	STAI	Inc: Elderly patients (aged ≥65 years) who participated in CR	255	74.9 (5.8) 67%m 33%f	NR
McHugh 2016 Ireland Prospective cohort	(a) Community (b) Convenience sampling (67% self-referrals, 33% referred by health professionals)	Modified fried phenotype	HADS	Inc: Community dwelling, able to walk independently, and able to provide written informed consent	447	72.75 (7.21) 31.4%m 68.6%f	NR

(Continues)

TABLE 1 (Continued)

Study ID study location study design	Population setting method of recruitment	Frailty criteria	Anxiety criteria	Inclusion and exclusion criteria	Sample size (*n*)	Mean age (SD) Sex %	Ethnicity (%)
Medina-Mirapeix 2018 Spain Cross-sectional	(a) Outpatients clinic (b) Prospectively and consecutively recruited from an outpatient pulmonary service over 1 year	Fried phenotype	HADS-A	Inc: Patients with COPD, aged 40–80 years, post-bronchodilator ratio of FEV1/FVC <0.70. Exc: Patients with an unstable cardiac condition within 4 months of the start of the study, as well as those with cognitive deterioration or unable to walk	137	66.9 (8.3) 87.6%m 12.4%f	NR
Mhaolain 2012 Ireland Cross-sectional	(a) Outpatients clinic (b) Convenience sample	Fried phenotype	HADS	Inc: People aged ≥60 years recruited from the technology research for independent living (TRIL) clinic. Exc: Parkinson's disease, dementia or previous stroke	567	73 (7.4) 29.3%m 70.7%f	NR
Naval 2021 Spain Cross-sectional	(a) Outpatients clinic (b) NR	Fried phenotype	HADS	Inc: Aged ≥40 years, diagnosed with COPD Exc: Experienced a COPD exacerbation within 4 weeks before the initial visit, presented with any other clinically relevant respiratory disease and/or a concomitant oncological disease, life expectancy <6 months.	127	66.5 (7.9) 85%m 15%f	NR
Uchmanowicz 2015 Poland Cross-sectional	(a) NR (b) NR	Tilburg frailty indicator scale	HADS	Inc: Age >60 years, diagnosis of HF, written informed consent. Exc: Communication barriers (e.g., deafness or blindness) or problems related to manual dexterity, patients who had stroke, obstructive pulmonary disease previously.	100	67.28 53%m 47%f	NR
Wang 2021 USA Secondary analysis of prospective cohort	(a) Outpatients clinic (b) NR	FRAIL scale questionnaire	HADS	Inc: Patients who were ≥65 years and underwent major noncardiac elective surgery at the mount sinai medical centre Exc: History of psychiatric (major depressive disorder, bipolar disorder, and schizophrenia) or neurologic disorder (Parkinson's disease and stroke)	167	67–74 age range, 70 44.9%m 55.1%f	Black 17.5, white hispanic 7.2, white non-hispanic 74.7, asian 0.6

TABLE 1 (Continued)

Study ID study location study design	Population setting method of recruitment	Frailty criteria	Anxiety criteria	Inclusion and exclusion criteria	Sample size (*n*)	Mean age (SD) Sex %	Ethnicity (%)
Welzel 2019 Germany Cross-sectional	(a) Community (b) Longitudinal German study on ageing, cognition and dementia in primary care patients (AgeCoDe) and its follow-up study - all randomly selected from participating GPs	Canadian study of health and ageing (CSHA) clinical frailty scale	Geriatric anxiety inventory	Inc: Aged 75+ years, absence of dementia, ≥1 GP contact within the last 12 months Exc: GP consultations were home visits only, patients lived in a nursing home, GPs diagnosed a severe illness that would deem fatal within 3 months, patients were deaf or blind, lacked sufficient proficiency in the German language, or lacked an ability to provide informed consent.	897	82–98 age range, 86.8 (3.02) 34.3%m 65.7%f	NR
Williams 2019 USA Cross-sectional	(a) Community (b) Eligible participants from carolina seniors registry (CSR)	Carolina frailty index	PROMIS	Inc: Older women (≥65 years) with breast cancer as those who had completed the GA either before or during treatment through Aug 2015.	190	65–86 age range, 70 NR	Non-hispanic white 91, Black/other 9
Zhao 2020 China Cross-sectional	(a) Community (b) Multi-stage random cluster sampling	Fried phenotype	GAD-7	Inc: Aged 60+ years, residing for more than 36 months in the same area Exc: Severe diseases or a life expectancy <6 months, those who were unable to complete all the interview and examination independently, refused to sign the informed consent	4103	60–95 age range, 67.8 (5.9) 41.7% mm 58.3%f	Han 29.0, wiang 31.8, Tibetan 14.1, yi 8.7, uighur 7, other 9.3

Abbreviations: CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CR, cardiac rehabilitation; GA, geriatric assessment; GAD, generalised anxiety disorder; GP, general practice; HADS, hospital anxiety and depression scale; HF, heart failure; ICD, international classification of diseases; LTOT, long term oxygen therapy; NHATS, national health and aging trends study; NIV, non-invasive ventilation; NR, none recorded; PR, pulmonary rehabilitation; PROMIS, patient-reported outcomes measurement information system; RA, rheumatoid arthritis PR; RCT, randomised control trial; STAI, state trait anxiety inventory.

TABLE 2 Presents the ratings of each study in order to assess study quality and risk of bias using MMAT.

Report ID (author and year)	Are the participants representative of the target population?	Are measurements appropriate regarding both the outcome and exposure?	Are there complete outcome data?[a]	Are the confounders accounted for in the design and analysis?[b]	During the study period, is the exposure occurred as intended?[c]
Mhaolain 2012[51]	No	Yes	Yes	Yes	Can't tell
Amare 2020[37]	Yes	Can't tell	Yes	No	Can't tell
Damluji 2021[23]	Yes	Yes	Yes	No	Yes
Bekic 2019[24]	No	Yes	Yes	No	Yes
Cleutjens 2021[26]	No	Yes	No	No	Yes
Damluji 2020[22]	Yes	Yes	Can't tell	No	Yes
Denfeld 2021[20]	No	Yes	No	No	Can't tell
Dziubek 2020[27]	No	Yes	No	No	Can't tell
Gephine 2021[21]	No	Yes	No	No	Yes
Gilmore et al. 2021	Yes	Yes	Yes	Yes	Yes
Honzawa 2020[28]	No	Yes	No	No	Yes
Medina-Mirapeix 2018[30]	No	Yes	Yes	No	Can't tell
Uchmanowicz 2015[38]	No	Yes	Yes	Yes	Can't tell
Wang 2021[31]	No	Yes	Yes	No	Can't tell
Welzel 2019[32]	Yes	Yes	No	Yes	Yes
Williams 2019[33]	No	Yes	No	Yes	Yes
Zhao 2020[34]	Yes	Yes	Yes	Yes	Can't tell
Bernal-lopez 2012[13]	Yes	Yes	Yes	Yes	Yes
Naval 2021[35]	No	Yes	Yes	No	Yes
Bourgault-fagnou 2009[25]	Can't tell	Yes	Yes	No	Yes
McHugh 2016[29]	No	Yes	No	Yes	Yes

[a]Defined as <20% missing data in this review.

[b]Defined as one or more confounders adjusted for (variables were not pre-specified).

[c]Defined as measurements of frailty and anxiety clearly carried out at the same timepoint in cross-sectional studies, or for longitudinal studies that the exposure clearly occurred prior to the outcome.

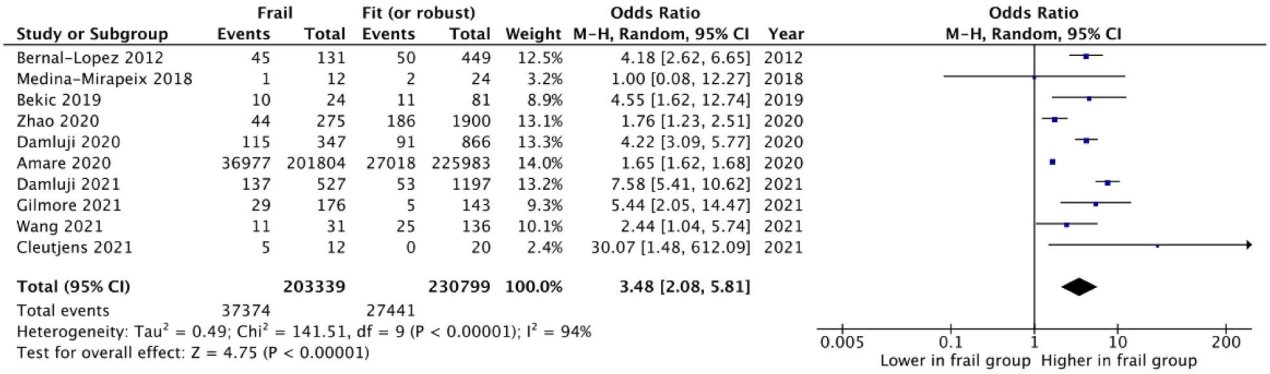
3.5 | Observational studies and meta-analysis findings

3.5.1 | Odds of anxiety in older adults with frailty versus robust

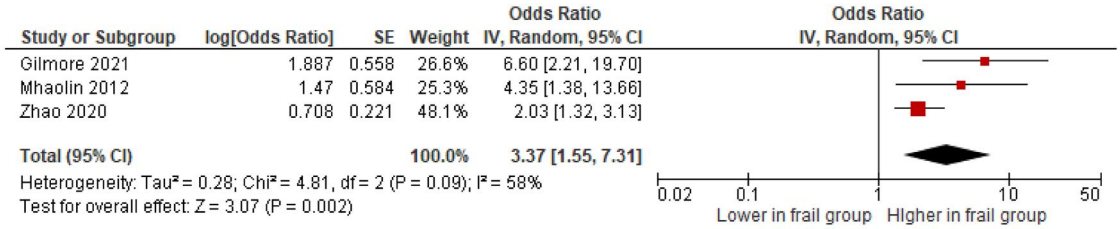
Among the 21 studies, 10 studies measured the odds of anxiety according to frailty status.[13,22–24,26,30,31,34,37,39] Frail participants had significantly higher levels of anxiety versus robust participants (OR = 3.48, 95% CI: 2.08, 5.81, Figure 2A). Positive associations were consistent across studies but high heterogeneity was found (I^2 = 94%). Three studies[12,34,39] applied a multivariable logistic regression model to adjust for covariates, including sociodemographic, behavioural and health characteristics. We analysed these separately and found similar a similar value to the meta-analysis of unadjusted ORs (OR 3.37, 95% CI 1.55–7.31, $N = 3$, I^2 58%, Figure 2B).

As the levels of anxiety between frailty and robustness were characterised by high heterogeneity (I^2 = 94%), we conducted a subgroup analysis stratified by frailty criteria. When restricting to studies that utilised the Fried frailty phenotype,[13,22–24,30,34] the effect estimates (OR = 3.79, 95% CI: 2.21, 6.49, I^2 = 86%, Supplementary file 2A) did not significantly change compared to the primary analysis and heterogeneity lowered slightly but was still substantial.

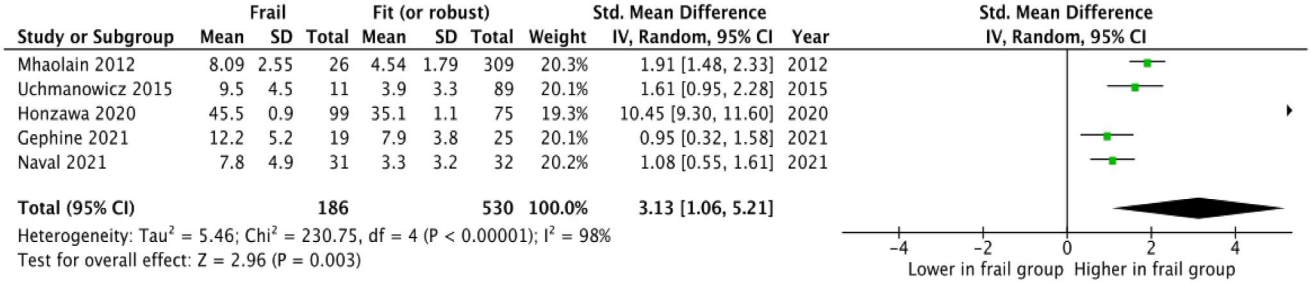
We also carried out subgroup analyses by single clinical conditions (Supplementary file 2B). There were significant associations in cardiovascular conditions, cancer, other and in general older adult populations and none in respiratory (but it should be noted that this is one very small study). Heterogeneity ranged from 0% in the general population to 72%–73% in clinical populations, suggesting that estimates may be more homogenous in general populations. This may arise from the small, single site nature of some



A Summary effect on the increased risk of anxiety in frail vs robust groups derived from dichotomous data



B Summary effect on anxiety risk in frail vs robust groups derived from adjusted odds ratios



C Summary effect on anxiety symptoms in frail vs robust groups derived from continuous data and random effect model

FIGURE 2 Forrest plots of studies assessing frail versus robust populations.

of the studies in single clinical populations, which may affect generalisability, or may be a chance finding from the small number of studies available as general populations can also include older people with a range of health conditions. Visual inspection of the funnel plot revealed no evidence of publication bias (Supplementary file 3).

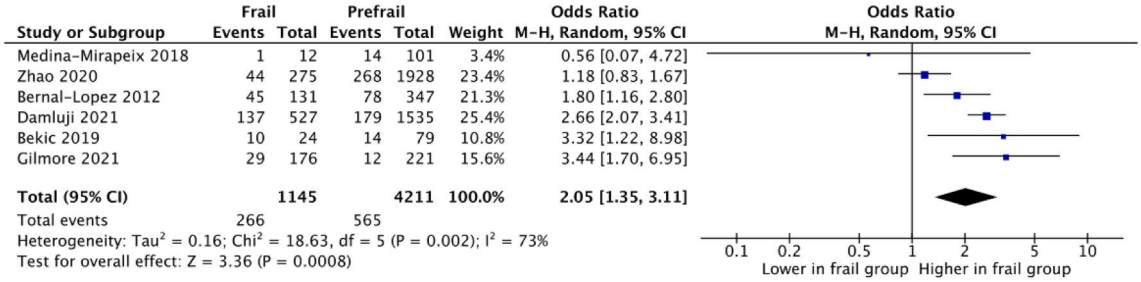
3.5.2 | Odds of anxiety in older adults with pre-frailty

We conducted further analyses to explore the odds of anxiety between frail versus prefrail participants (Figure 3). Across six studies,[13,23,24,30,34,39] frail participants had higher odds of having anxiety than those who were prefrail (OR = 2.05, 95% CI: 1.35, 3.11, I^2 = 73%, Figure 3A), but to a lesser extent than frail versus robust comparisons.

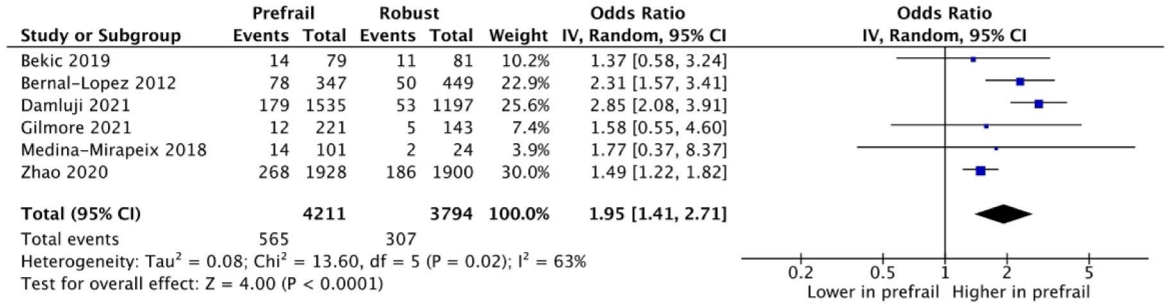
Across the same six studies, older adults with prefrailty had higher odds of having anxiety than robust participants (OR = 1.95, 95% CI: 1.41, 2.71, I^2 = 63%, Figure 3B), again to a lesser extent than frail versus robust comparisons. Pre-frailty analyses also had substantial levels of heterogeneity. This association was also present but to a lesser extent when adjusted ORs were combined (N = 3, 1.46, 95% CI 1.19–1.79, I^2 = 0%, Figure 3C), confirming these findings.

3.5.3 | Odds of frailty in older people with anxiety

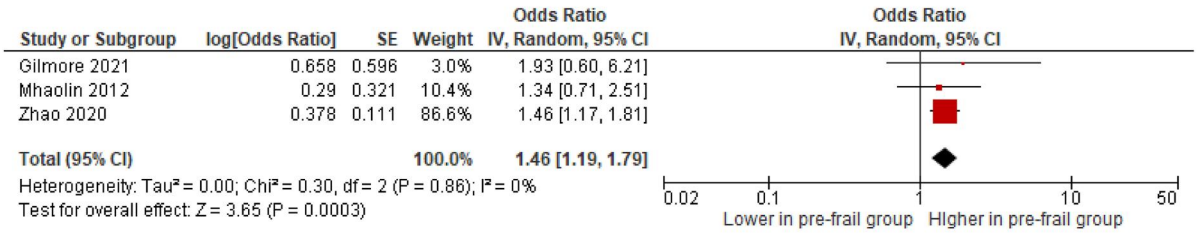
Only one study was found which assessed the odds of frailty in older people with anxiety. Welzel[32] recorded higher frailty scores in the group with anxiety when compared to participants with no anxiety, however a binary logistic regression model showed no significant association between frailty and anxiety. One longitudinal study,



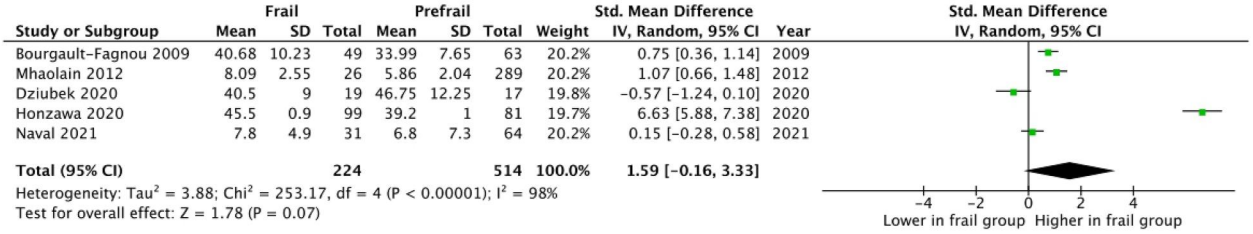
a Summary effect on the increased risk for anxiety in frail vs prefrail groups derived from dichotomous data and random effect model.



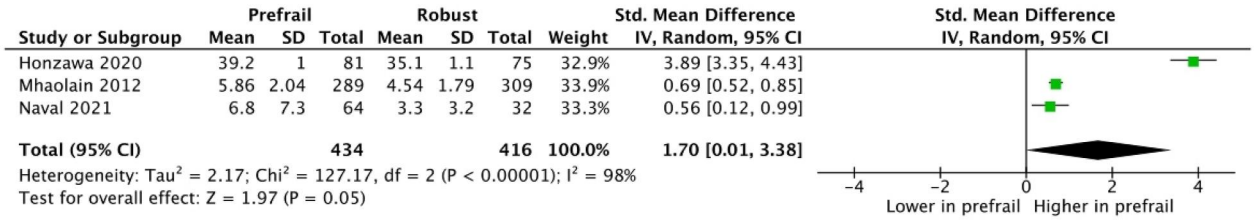
B Summary effect on the increased risk for anxiety in prefrail vs robust groups derived from dichotomous data and random effect model.



C Summary effect on the increased risk for anxiety in prefrail vs robust groups derived from adjusted ORs



D Summary effect on the increased risk for anxiety in frail vs prefrail groups derived from continuous data and random effect model.



E Summary effect on the increased risk for anxiety in prefrail vs robust groups derived from continuous data and random effect model.

FIGURE 3 Forrest plots of studies assessing prefrail versus robust and frail populations.

McHugh,[29] reported that anxiety as an antecedent was not associated with an increased likelihood of frailty transitions after 2 years. No studies explored the odds of pre-frailty in older people with anxiety.

3.5.4 | Incidence and prevalence

As most of the studies included were cross-sectional, we could not assess incidence. The overall prevalence of anxiety in 203,339

people with frailty across the 10 studies was averaged at 18.4%.[13,22–24,26,30,31,34,37,39]

3.5.5 | Anxiety symptoms and frailty

Five studies[12,21,28,35,38] reported that frail participants had significantly higher symptoms of anxiety than robust participants (SMD = 3.13, 95% CI: 1.06, 5.21, I^2 = 98%, Figure 2C). To explore heterogeneity, we carried out a sensitivity analysis excluding Honzawa 2020s high value (the only study to measure anxiety using the STAI rather than HADS), which reduced heterogeneity to 66% and the effect size to SMD 1.41 (95% CI: 0.93, 1.89). MD could now also be calculated, reflecting an increase of almost four scale points in frail older adults (MD 3.95, 95% CI: 3.13, 4.76). As Kihon and Tilburg frailty criteria contain psychological elements, we conducted a subgroup analysis on the three studies utilising Fried frailty phenotype.[12,21,35] The combined effect size and level of heterogeneity were lower (SMD 1.34, 95% CI: 0.71, 1.97, I^2 = 77%, Supplementary file 2C).

Frail participants had mildly higher levels of anxiety than prefrail older adults (SMD = 1.59, 95% CI: −0.16, 3.33, I^2 = 98%, Figure 3D) although this was not statistically significant. Removing Honzawa's data reduced the effect size and heterogeneity but did not change non-significance (SMD 0.39 95% CI: −0.22, 1.00, I^2 = 86%, Supplementary file 2D). When examining anxiety in prefrail versus robust older adults, prefrail participants had mildly higher levels of anxiety (SMD = 1.70, 95% CI: 0.01, 3.38, I^2 = 98%, Figure 3E).

Two studies could not be included in meta-analysis due to reporting T-scores[20,33] and had mixed evidence. Williams[19] reported a non-significant difference in anxiety between frail/prefrail and robust participants, whereas Denfeld[20] found higher anxiety scores in the frail group when compared to the robust one. No studies reported correlations between frailty and anxiety.

4 | DISCUSSION

This systematic review and meta-analysis explored the relationship between frailty and anxiety from mainly cross-sectional studies. Our comparative meta-analyses support a clear relationship between frailty and anxiety. Frail older adults are more than three times as likely to experience anxiety symptoms than robust adults; studies that adjusted for covariates found similar estimates. Frail older adults had substantially higher anxiety scores than robust individuals, with a likely effect size of >1 SMD. Our review also showed trends by frailty level: frail older adults were more likely to experience anxiety than prefrail populations and prefrail participants are more likely to experience anxiety or higher levels of anxiety symptoms than robust participants. The association between frailty and anxiety is clear. However, evidence was of variable quality, there was little evidence exploring the levels of frailty in anxious older populations versus non-anxious and only one longitudinal analysis, which limits our ability to draw conclusions as to the direction of effect.

Previous studies have shown a clear bidirectional relationship between frailty and depression in older adults.[5,6,40] Our review confirms a similar relationship for frailty and anxiety, although direction of effect could not be determined. The relationship between mood disorders and frailty is complex. Both anxiety and depression share overlapping symptomology like functional impairment and sleep disturbance leading to increased risk of disability,[41] which may also be a consequence of increasing frailty.[34,42] As frailty is multifactorial in nature, the drivers of frailty (including obesity or malnutrition, low physical activity, smoking) may lead to disability through reduced functioning and subsequently cause depression or anxiety. Likewise, depression may exacerbate the elements that precipitate frailty.[40] Although the co-occurrence of depression and anxiety is relatively common, four studies in this review still reported higher levels of anxiety in frail older adult populations after adjusting for depression.[12,13,32,38] Anxiety alone also has clear associations with cognitive decline, functional dependence and increased medical morbidity,[11,43] all closely linked to frailty. In addition, age is closely associated with frailty. In papers which adjusted for confounders, all but one adjusted for age. As the meta-analyses based on adjusted data reported similar values to those based on unadjusted data, it seems that age is unlikely to affect the relationship between frailty and anxiety, but this warrants further exploration.

In contrast to more familiar depressive symptoms, older people may struggle to differentiate between realistic worries about daily situations (e.g. falls) and ongoing problematic anxiety.[10] Mental health conditions are often normalised as part of multiple comorbidities, age-related issues, and functional difficulties.[44] This highlights the importance of a proactive approach to ensure that anxiety assessment is part of comprehensive and holistic frailty assessments. Since 2017, frailty has been routinely identified by UK general practices using the electronic Frailty index (eFI) score, although this does not currently include anxiety as one of the deficits. Older adults with moderate to severe frailty are offered a review, which could provide a window of opportunity for asking about anxiety symptoms.[45] By shifting to patient-centred and shared-knowledge consultation models, education of older adults in recognising anxiety is important. Campaigns to highlight the issue of anxiety in later life, and particularly in frailty, may help to reduce any stigma associated with mental health and encourage older adults to present with symptoms. Further research is warranted to understand whether proactive anxiety screening and treatment in frail older adults will lead to a reduction in anxiety symptoms and improvements in other outcomes. Community and primary care professionals play a vital role in identifying anxiety in prefrail and frail populations. As observed with depression,[46] successful prevention and treatment of anxiety may have beneficial effects on frailty by increasing physical and social activity, improving the physical indicators of frailty.

There is evidence for pharmacological and non-pharmacological treatments for generalised anxiety disorder in older people.[47,48] However, the majority of these trials focus on those aged 65–75,

with little evidence for non-pharmacological treatments for anxiety in frail older people.[49] Given the clear associations identified in our review, future research could evaluate the benefits and risks of anxiety treatments in frailer populations. There is evidence that some drugs such as selective serotonin reuptake inhibitors can lead to a higher risk of postural hypotension and falls.[50]

Strengths of our review include broad inclusion criteria in order to ensure the results were as generalisable as possible, while exploring subgroups to further understand the data. The majority of screening was undertaken by only one reviewer, however we involved a second reviewer at critical stages of the screening and agreement on inclusion decisions was high. The review was limited by the studies included, which varied in size and quality. The majority of studies utilised cross-sectional methods, and therefore the directionality of the relationship between frailty and anxiety is uncertain. Further research should explore longitudinal associations and examine which factors moderate this relationship. This may help determine optimal timing of interventions for frail and/or anxious older adults. Although we observed high statistical and clinical heterogeneity, our findings were largely consistent across studies in finding positive relationships. Our subgroup analyses were post hoc rather than based on pre-specified hypotheses and are limited in how well they can explore heterogeneity. They therefore should be understood as exploratory rather than definitive. These analyses suggest that the different criteria and cut-off values used for defining frailty did not explain the high heterogeneity, but the choice of anxiety instrument may be more important and that different underlying health conditions may play a role. These hypotheses warrant further exploration in future studies, in addition to exploring other sources of heterogeneity using more rigorous techniques such as meta-regression when further data are available.

5 | CONCLUSION

This is the first systematic review to synthesise the associations between frailty and anxiety, and to present definitive evidence of an association. It is therefore recommended that future research evaluates the effectiveness of proactive anxiety screening and anxiety treatments for frail older adults. Further research is also needed to understand the direction of effect in this population.

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CONFLICT OF INTEREST STATEMENT

No conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the original published papers included within the systematic review.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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