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The impact of frailty on clinical outcomes among individuals with COPD: a systematic review and meta-analysis

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Abstract

Background Frailty is a prevalent and robust predictor of poor outcomes for older adults and those with chronic disease. We performed a systematic review and meta-analysis of the literature to understand the association between frailty and clinical outcomes for people with COPD.

Methods We searched MEDLINE, EMBASE, Cochrane Central, CINAHL, and Web of Science from inception to February 2022, for observational studies evaluating the association between frailty and clinical outcomes among individuals with COPD. Included studies defined COPD by spirometry, used a validated frailty assessment tool, and compared dyspnea, symptom burden, health related quality of life, exacerbations, hospitalization, or mortality between frail and non-frail individuals. Risk of bias was assessed using the Newcastle Ottawa Scale. Mean differences or hazard ratios were calculated using inverse variance (IV) methods, odds ratios were calculated using Mantel–Haenszel methods, and homogeneity was assessed using I^2 statistics. Results were pooled using a random effects model.

Results Of 1385 identified studies, 16 studies were included with 7 studies included in the meta-analyses, representing 5903 individuals. The Fried Frailty Phenotype instrument was used in 50% of included studies. When comparing frail vs. non-frail people with COPD, pooled estimates revealed frail people with COPD had higher dyspnea scores [modified Medical Research Council (mMRC) score standardized mean difference (95% CI): 1.67 (1.40–1.92), $I^2 = 24\%$]; higher symptom burden [COPD Assessment Test (CAT) score mean difference (95% CI): 10.24 (8.30–12.17), $I^2 = 31\%$]; more COPD exacerbations in the prior year [mean difference (95% CI): 1.09 (0.62–1.56), $I^2 = 0\%$), and increased odds of being hospitalized in the previous year [OR (95% CI): 2.94 (1.57–5.50); $I^2 = 0\%$]. The largest study with longest follow up period showed increased mortality risk among frail vs. non-frail individuals with COPD, [HR (95% CI): 1.83 (1.24–2.68)].

Conclusions People with COPD and frailty experience increased dyspnea, symptom burden, exacerbation history, and hospitalizations compared to non-frail patients with COPD. Frailty is a robust predictor of outcomes among people with COPD and should be considered a treatable trait. Additional work is needed to standardize screening

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methods for frailty, and to understand the optimal timing of non-pharmacologic interventions to treat frailty among people with COPD.

Prospero Registry ID CRD42022329893

Keywords Frailty, Pre-frailty, COPD, Treatable trait

Introduction

Frailty is a multi-dimensional syndrome characterized by accumulating physiologic deficits that result in a loss of physical, cognitive, and functional reserves [1]. The presence and progression of frailty increases a person's vulnerability to health stressors such as falls, hospitalizations, and acute exacerbations of chronic illness [1]. Frailty is a robust predictor of death and need for long term care among older adults, but can be mitigated by comprehensive exercise, nutritional, social, and cognitive interventions [1–4].

While the putative mechanisms behind frailty are complex, they include features that overlap with hallmarks of COPD, such as chronic systemic inflammation, reduced muscle mass and function, and endocrine dysregulation [2]. A previous systematic review found more than 56% of patients with COPD are pre-frail, while 19% are frail [5]. Pre-frailty can be conceptualized as the loss of physiological reserves that predisposes an individual to frailty [6]. Individuals with COPD are more likely to be frail than individuals without COPD [5]. COPD is also associated with a progression from non-frail to pre-frail to frail status [7].

Individual studies have yielded variable associations between frailty and respiratory symptoms, acute exacerbations of COPD, hospitalizations, and mortality [8–10]. In part, a variety of frailty assessment tools, clinical, geographic, and cultural settings may account for these differences. The diversity of measurement tools and clinical impacts makes it challenging for clinicians and decision makers to understand how frailty should be used as an important phenotype to guide treatment interventions and prognosis for individuals with COPD. This is of particular importance since a cornerstone of COPD management is pulmonary rehabilitation, which is a complex multisystem intervention that is more effective in frail patients with COPD and can potentially improve the degree of frailty in the short term [11].

We conducted a systematic review and meta-analysis to identify the most common frailty measurement tools used in clinical studies and to summarize the association between frailty and patient-reported symptoms, quality of life, exacerbations, hospitalizations, and mortality among individuals with COPD.

Methods

We included quantitative observational studies (case–control, cross sectional, cohort) assessing the association between frailty and clinical outcomes among patients with COPD, using non-frail people with COPD as a comparator. This review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations [12]. The protocol was registered with Prospero Registry number: CRD42022329893.

Search strategy and selection criteria

We searched MEDLINE, EMBASE, Cochrane Central, CINAHL, and Web of Science databases for relevant articles from inception to February 15th, 2022. Medical Subject Headings (MeSH) and key words identified by the authors and prior relevant systematic reviews were chosen, including: "Chronic Obstructive Lung Disease", "COPD", "Chronic Obstructive Airway Disease", "Chronic Bronchitis", "Emphysema", or "frail elderly", and "frailty".

We included studies that were published or in-press, cohort, case–control, and cross-sectional in study design, published in English or French, and with recruited participants with spirometry-defined COPD: FEV1/FVC ratio < 0.70 or an FEV1/FVC ratio below the lower limit of normal range.

Studies must have compared frail versus non-frail participants, and reported data on any of dyspnea, health-related quality of life, COPD exacerbations, hospitalizations, or mortality. We defined frailty based on measurement with a validated assessment tool as reported in the list of frailty instruments cited by Buta et al. [13].

Excluded studies included editorials, letters, review articles, and studies that did not use a validated instrument to measure frailty, did not define frail, pre-frail, and non-frail states, did not define COPD using spirometry measurement, included participants with respiratory disease other than COPD, or measured frailty with objective data from the *acute* hospitalization (reflecting the state of the patient while hospitalized).

Study selection and data extraction

All titles and abstracts were screened for relevance to the study question and duplications by two independent

reviewers (MC and PM). Disagreements were assessed and resolved by a third reviewer (SM). Full text articles were obtained for studies meeting initial inclusion criteria and were evaluated based on the detailed inclusion and exclusion criteria above.

Data was extracted using a pre-defined standardized tool. The tool was pilot tested on 5 studies, refined, and implemented to collect pre-specified data from included studies. Collected data included bibliographic information, methods, characteristics of study participants, frailty assessment and measurement instruments used, clinical outcomes of interest, and covariates used in adjusted multivariate models.

Assessment of risk of bias

The Newcastle Ottawa Scale (NOS) was used to assess the quality of included studies in this review [14]. The NOS was devloped to assess the quality of non-randomized studies and provides perspectives in three domains including the selection of study groups, the comparability of groups, and the ascertainment of exposure or outcome [14]. The content validity and inter-rater reliability have been established [14]. Two reviewers independently evaluated each study. Any discrepancies were resolved by consensus discussion among three reviewers (MC, PM, SM). Studies with scores > 7 were considered low risk of bias; 5–7 were considered a moderate risk of bias, < 5 were considered a high risk of bias. Funnel plots to examine publication bias were constructed for studies included in meta-analyses and examined for asymmetry.

Analysis

Meta-analyses were performed on studies with homogeneity of both clinical setting, outcome measure, and analysis in the same time period (i.e. retrospective, longitudinal). Meta-analyses were organized a-priori into comparisons between frail and non-frail (this comparison did not include pre-frail participants), and pre-frail and non-frail participants.

Data from the following outcomes were pooled: standardized mean difference in the modified Medical Research Council (mMRC) Dyspnea Scale; mean difference in the COPD Assessment Test (CAT) score; mean difference in the number of COPD exacerbations in the prior year; odds of having been hospitalized for COPD in prior year; risk of mortality over 2 years.

Due to variable study designs and methodology in observational studies, pooled estimates were obtained using random effects models. Mean differences and hazard ratios (95% confidence intervals) were calculated using inverse variance (IV) methods. Odds ratios (95% confidence intervals) were calculated using Mantel–Haenszel methods. Homogeneity within pooled studies was estimated using the I^2 statistic. All analyses were performed with Review Manager (RevMan), Version 5.4. The Cochrane Collaboration, 2020.

Results

Description of included studies

Figure 1 describes the screening and selection of studies recommended by the PRISMA guidelines [12]. We identified 1385 unique studies and abstracts, with 1298 records excluded and 87 records selected for full text review. After review, 16 studies were included in the systematic review with 7 included in the meta-analyses.

Table 1 describes characteristics of the 16 included studies. Nine studies presented longitudinal data ranging from 2 months to 12 years of follow up time [8–11, 15–19], while 7 studies presented cross-sectional data alone [20–26]. Thirteen studies recruited patients from outpatient clinical settings [8–11, 15, 17, 20–26], two studies recruited from the general population [16, 18] and one study recruited from an acute medical ward [19].

Eight studies (50%, 8/16) measured frailty using the Fried Frailty Phenotype [9–11, 16, 17, 22, 23, 27], 3 studies used the Kihon Checklist [21, 24, 25], 1 study each used the Reported Edmonton Frail Scale [19], Fatigue Resistance Ambulation Illness Loss of Weight (FRAIL) Scale [20], Frailty Staging System (FSS) [18], and Tillburg Frailty Test [26]. One study used four measures of Frailty: Fried Frailty Phenotype, Clinical Frailty Scale, Frailty Index of Accumulative Deficits, and Short Physical Performance Battery [15].

Four studies compared frail participants with non-frail participants [10, 15, 17, 26], ten studies had three comparison groups (frail, pre-frail, and non-frail) [8, 9, 11, 16, 20–25], and 2 studies compared non frail, mildly frail, moderately frail, and severely frail groups (Table 1) [18, 19].

Risk of bias

The quality of included studies was variable (Table 2), with median NOS score of 7 (IQR 5.75—8). Five studies were assessed to be low risk of bias [10, 16, 18, 19, 23], nine studies were moderate risk of bias [8, 9, 11, 15, 21, 22, 24–26], and two studies were high risk of bias [17, 20].

Of the seven studies included in meta-analyses, one study was assessed to be low risk of bias [23], five were at moderate risk of bias [8, 9, 11, 21, 22], and one was at high risk of bias [20]. Median NOS score of meta-analyzed studies was 7 (IQR 6.5–7). Funnel plots for each outcome were inspected visually; however, small numbers of studies included in the meta-analyses limited ability to meaningfully assess publication bias.

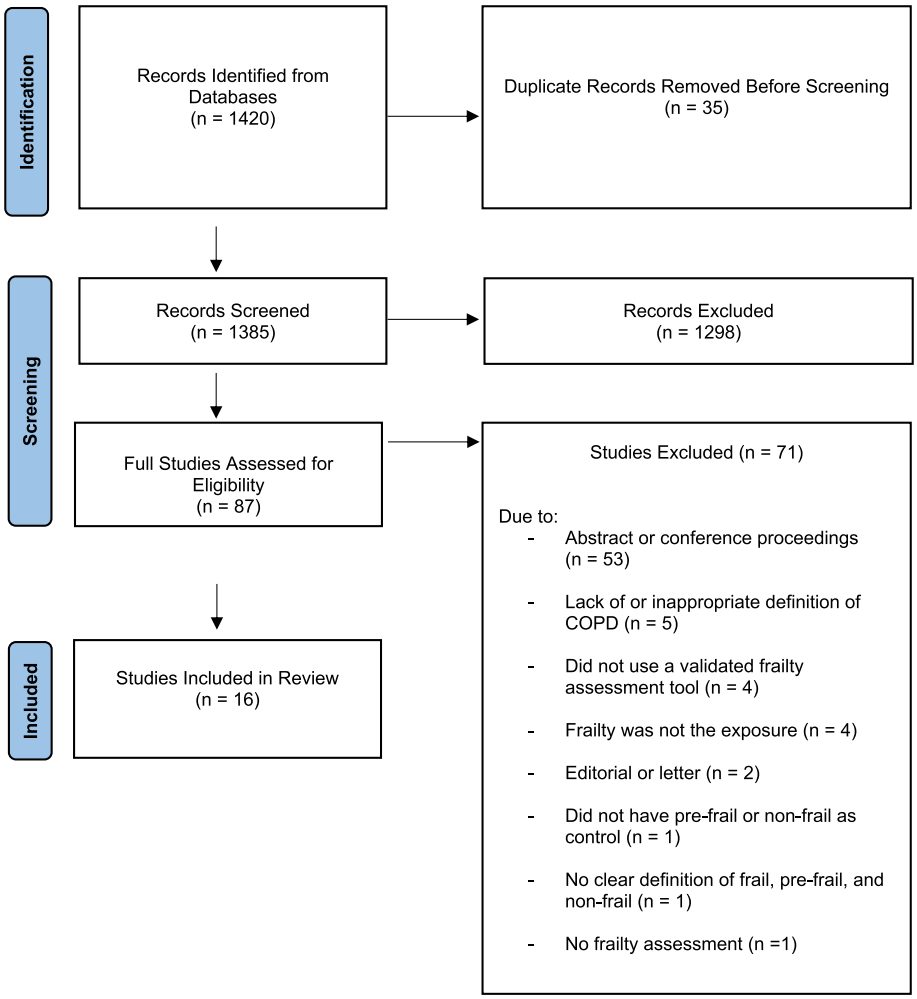

Fig. 1 Flowchart of study selection and inclusion in the systematic review based on PRISMA recommendations [12]

Association between frailty and clinical outcomes:

Modified medical research council (mMRC) dyspnea scale

Nine included studies assessed mMRC scores between frail and non-frail participants. All nine assessed the outcome cross-sectionally [8, 10, 11, 15, 17, 19, 20, 23, 26].

Four studies reported mean mMRC scores and standard deviations [11, 17, 23, 27]. Three of those four studies excluded pre-frail participants from the non-frail group and were pooled in meta-analysis representing 304 frail individuals and 154 non-frail individuals [11, 23, 27]. Pooled analyses identified a standardized mean difference of 1.69 [95% CI 1.47–1.92, $I^2 = 24\%$] points, suggesting higher dyspnea scores (more shortness of breath) in the frail group (Fig. 2A).

COPD assessment test (CAT) score

Seven studies compared CAT scores between frail and non-frail participants [11, 15, 20–23, 28]. All seven studies examined CAT scores cross-sectionally. Four studies reported mean CAT score with standard deviations and all four excluded pre-frail participants from the non-frail group [11, 21–23]. Pooled analysis of CAT scores from these four studies representing 269 frail and 176 non-frail individuals showed a mean difference of 10.24 [95% CI 8.30—12.17, $I^2 = 31\%$, $p < 0.00001$] points suggesting higher symptom burden in frail individuals (Fig. 2B).

St. George's respiratory questionnaire (SGRQ) score

Two studies compared SGRQ scores between frail and non-frail participants indicating higher scores in frail participants (worsened health status) [9, 21]. Kennedy et al. report a median SGRQ score of 48.7 (IQR 35.7—60.2) and 60.3 (IQR 52.8—69.1) among non-frail and frail participants, respectively. Kennedy et al. excluded pre-frail participants from the non-frail group in this analysis. Kusunose et al. reported a mean (SD) SGRQ score of 13.8 (10.1) vs 45.9 (19.0) among non-frail vs frail participants, respectively.

Table 1 Characteristics of studies included in the systematic review

Study (Author, Year)	Country	Population type	Participants (n)	Age, mean, (SD)	Female, (n, %)	FEV1% predicted, mean, (SD)	BMI, mean, (SD)	Comorbidities	Active smokers, (n, %)	Frailty tool used	Study groups (n, %)
Bernabeu-Mora, 2017 [19]	Spain	Diagnosis of COPD (GOLD), admission (> 24 h) with AECOPD	103	71.0 (9.1)	7 (6.8)	52.2 (15.2)	28.6 (5.6)	Mean number (SD) 1.7 (1.3)	35 (34)	Edmonton Frail Scale	Severe Frailty ($n=19$, 18.4%), Moderate Frailty ($n=18$, 17.5%), Mild frailty ($n=20$, 19.4%), Not Frail ($n=46$, 44.7%)
Kennedy, 2019 [9]	United States	NETT Trial participants 12 months after randomization: Non-smokers (abstinent > 6 mon) with moderate to severe COPD	902	Median (IQR) 67 (63–70)	365 (40.5)	Median (IQR): 26 (20, 33)			0 (0)	Fried frailty phenotype	Frail ($n=57$, 6.3%), Pre-frail/Normal ($n=845$, 93.7%)
Dias, 2020 [20]	Brazil	Age > = 40, diagnosis of COPD (GOLD)	153	Median (IQR): Non-frail: 69.5 (60.5–80.5) Pre-frail: 70.0 (65.0–73.0) Frail: 67.0 (61.0–71.5)	Non-frail: 10 (45.5) Pre-frail: 32 (38.9) Frail: 38 (49.4)	Median (IQR): Non-frail: 61.5 (48.1, 70.1) Pre-frail: 52.2 (39.8, 61.4) Frail: 44.0 (33.4, 61.0)	Median (IQR): Non-frail: 24.7 (22.1, 26.9) Pre-frail: 25.0 (22.0, 27.3) Frail: 23.7 (22.0, 28.8)	CCI, median (IQR): Non-frail: 3.5 (2.8, 4.3) Pre-frail: 4.0 (3.0, 4.0) Frail: 3.0 (3.0, 4.5)	Non-frail: 2 (9.1) Pre-frail: 6 (11.3) Frail: 10 (13.0)	FRAIL Scale	Frail ($n=77$, 50.3%), Pre-frail ($n=54$, 35.3%), Non-frail ($n=22$, 14.4%)
Galizia, 2011 [18]	Italy	Population based sampling of random subjects from a polling station list of those > 65y, stratified by sex and age	489 with COPD 799 without COPD	COPD: 74.9 (6.3) No COPD: 73.7 (6.3)	COPD: 221 (45.2) No COPD: 513 (64.2)		26.5 (4.9)	CCI, mean (SD): 1.6 ± 1.6	COPD: 109 (22.3) No COPD: 109 (13.6)	Frailty Staging System	Severe Frailty ($n=43$, 8.8%), Moderate Frailty ($n=89$, 18.2%), Mild Frailty ($n=107$, 21.8), Not Frail ($n=250$, 51.1%)
Gephine 2021 [17]	France	Age > 40 years, COPD (GOLD), Chronic Respiratory Failure defined by LTOT and or NIV, who referred for pulmonary rehab	44	66 (8)	14 (32)	33 (13)	26 (7)	CCI, mean (SD): 2.7 ± 1.9	8 (18)	Fried frailty phenotype	Frail ($n=19$, 43.2%), Non-frail ($n=25$, 56.8%)

Table 1 (continued)

Study (Author, Year)	Country	Population type	Participants (n)	Age, mean, (SD)	Female, (n, %)	FEV1% predicted, mean, (SD)	BMI, mean, (SD)	Comorbidities	Active smokers, (n, %)	Frailty tool used	Study groups (n, %)
Kusunose, 2017 [21]	Japan	Age > 50, Smoking history > 10 pack years, FEV1/FVC < 0.7, no x-ray abnormalities, absence of other lung disease, absence of uncontrolled comorbidity, no change in treatment over prior 4 weeks	79	74.8 (6.3)		69.3 (20.4)	22.4 (3.1)			Kihon Checklist	Robust (*n* = 38, 48.1%), Pre-frail (*n* = 24, 30.4%), Frail (*n* = 17, 21.5%)
Lee, 2021 [16]	Singapore	Age > 55y, living in Southeast and Southwest Singapore	1162 with COPD 3465 without COPD	COPD: 68.3 (7.9) No COPD: 65.7 (7.5)	COPD: 730 (62.8) No COPD: 2186 (63.1)	COPD: 94.5 (27.8) No COPD: 111.9 (22.4)	23.8 (3.8)	Mean number (SD): 1.7 (1.4)	COPD: 158 (13.6) No COPD: 234 (6.8)	Fried frailty phenotype	Frail (*n* = 191, 4.1%), Pre-frail (*n* = 2092, 45.2%), Non-frail (*n* = 2344, 50.7%)
Luo, 2021 [10]	China	Age > = 65y, diagnosis of COPD (GOLD), good mental and cognitive status able to complete frailty assessment	309	Median (IQR): 86 (80,90)	68 (22)	Median (IQR): 74.2 (60.4, 85.3)	24.1 (3.8)	CCI, median (IQR): 4 (3, 5)	67 (21.7)	Fried frailty phenotype	Frail (*n* = 154, 49.8%), Non-frail (*n* = 155, 50.2%)
Maddocks, 2016 [11]	United Kingdom	Age > = 35 years, physician diagnosis of COPD (GOLD), appropriate for pulmonary rehab referral	816	69.8 (9.7)	332 (40.7)	48.9 (21.0)	27.8 (6.7)	Age-adjusted CCI, mean (SD): 4.3 (1.6)	146 (17.9)	Fried frailty phenotype	Frail (*n* = 209, 25.6%), Pre-frail (*n* = 525, 64.3%), Not frail (*n* = 82, 10.0%)
Medina-Mirapeix, 2018 [22]	Spain	Age 40-80y, diagnosis of COPD (GOLD)	137	66.9 (8.3)	17 (12.4)	50.2 (16.4)	28.9 (5.0)	Comorbidities ≥ 4, n (%): 50 (36.5)		Fried frailty phenotype	Frail (*n* = 12, 8.8%), Pre-frail (*n* = 101, 73.7%), Non-frail (*n* = 24, 17.5%)

Table 1 (continued)

Study (Author, Year)	Country	Population type	Participants (n)	Age, mean, (SD)	Female, (n, %)	FEV1% predicted, mean, (SD)	BMI, mean, (SD)	Comorbidities	Active smokers, (n, %)	Frailty tool used	Study groups (n, %)
Naval, 2021 [23]	Spain	Age > = 40y, diagnosis of COPD (GOLD)	127	66.5 (7.9)	19 (15.0)	Post-bronchodilator FEV1: Non-frail: 50 (12.7) Pre-frail: 48.7 (13) Frail: 44.5 (15.1)	27.6 (5.4)	CCI, mean (SD): 4.5 (1.8)	29 (22.8)	Fried frailty phenotype	Frail ($n=31$, 24.4%), Pre-frail ($n=64$, 50.4%), Fit ($n=32$, 25.2%)
Nishimura, 2021 [24]	Japan	Stable COPD from outpatient clinic at 1 center	89	Median (IQR): 78.0 (74, 82)	6 (6.7)		Median (IQR): 22.6 (20.9, 24.4)		13 (14.6)	Kihon Checklist	Non- frail ($n=37$, 41.6%), Pre-frail ($n=23$, 25.8%), Frail ($n=29$, 32.6%)
Takahashi, 2021 [25]	Japan	Stable COPD with no AECOPD in preceding 3 months	40	70.63 (8.21)	1 (2.5)	73.96 (18.07)	23.26 (3.29)		12 (30)	Kihon Checklist	Non-frail ($n=9$, 22.5%), Pre-frail ($n=11$, 27.5%), Frail ($n=20$, 50%)
Talay Mustafaoglu, 2020 [26]	Turkey	Stable COPD patients at one center	61	Not frail, Ages 65-74yrs: 16 (72.7%), 75-84yrs: 6 (27.3%); Frail, Age 65-74yrs: (27, 69.2%), 75-84yrs: 12 (30.8%)	Not frail: 0 (0); Frail: 2 (5.1)		Non-frail: < =21: 0 (0%) > 21: 22 (100%) Frail: < =21: 7 (17.9%) > 21: 32 (82.1%)	n (%), Non-frail, ≥ 2: 8 (36.4) < 2: 14 (63.6) Frail, ≥ 2: 28 (71.8) < 2: 11 (28.2)		Tillburg Frailty Test	Not frail: ($n=22$, 36.1%); Frail: ($n=39$, 63.9%)
Yee, 2020 [27]	United States	Analysis of participants in the CASCADE study	280	Not frail: 69.4 (8.0); Pre-Frail: 66.9 (8.4); Frail 68.6 (9.2)	Not frail: 10 (25); Pre frail: 34 (19.3); Frail: 12 (18.2)	Not frail: 49.5 (15.1) Pre-frail: 46.9 (15.4) Frail: 36.9 (14.5)	Non-frail: 28.5 (3.9) Pre-frail: 28.0 (5.9) Frail: 28.0 (7.9)	CCI ≥ 1, n (%): Non-frail: 18 (45.0) Pre-frail: 85 (48.3) Frail: 35 (53.0)	Not frail: 8 (20), Pre frail: 47 (26.7), Frail 21 (31.8)	Fried Frailty Phenotype	Not frail ($n=40$, 14.2%), Pre-frail ($n=176$, 62.8), Frail (64, 22.8)
Zhang, 2022 [15]	China	Patients aged ≥ 65 years with stable COPD recruited in outpatient settings	302	Median (IQR): 86 (80, 90)	66 (22.2)	Median (IQR): 73.5 (60.3, 85.3)	24.2 (3.7)	CCI, median (IQR): 4 (3, 5)	63 (20.9)	Fried Frailty Phenotype, Short Physical Performance Battery, Clinical Frailty Score, Frailty Index of Accumulated Deficits	Frail ($n=154$, 51%), Non-frail ($n=148$, 49%)

Table 2 Assessment of Risk of Bias of include studies, using the Newcastle Ottawa Scale (NOS)

Author, Year	NOS Consensus Score	Study included in meta-analyses	Risk of bias
Bernabeu-Mora, 2017 [19]	9		Low
Kennedy, 2019 [9]	7	x	Moderate
Dias, 2020 [20]	5	x	High
Galizia, 2011 [18]	8		Low
Gephine 2021 [17]	4		High
Kusunose 2017 [21]	7	x	Moderate
Lee, 2021 [16]	8		Low
Luo, 2021 [28]	8		Low
Maddocks, 2016 [33]	6	x	Moderate
Medina-Mirapeix, 2018 [22]	7	x	Moderate
Naval, 2021 [23]	8	x	Low
Nishimura, 2021 [24, 24]	6		Moderate
Takahashi, 2021 [25]	5		Moderate
Talay Mustafaoglu, 2020 [26]	5		Moderate
Yee, 2020 [27]	7	x	Moderate
Zhang, 2022 [15]	7		Moderate

Acute exacerbations of COPD (AECOPD)

Ten retrospective studies compared AECOPD between frail and non-frail participants [8, 11, 15, 17, 19, 20, 22, 23, 26, 28]. Two of these studies of the studies also presented longitudinal prospective analyses [8, 28].

Four studies reported the proportions in frail and non-frail groups with 2 or more AECOPD in the preceding two years, and there were no reported statistical differences between groups [17, 20, 22, 26]. Studies by Luo et al. and Zhang et al., using data from the same cohort, reported that frail patients were more like to have had 1 or more moderate-severe AECOPD in the past 1 year [15, 28]. Yee et al. revealed no significant difference of moderate-severe AECOPD in frail patients compared to non-frail patients in adjusted analysis [8].

Two studies [11, 23] reported mean number of AECOPDs for non-frail and frail participants in the prior 1 year, and both studies excluded pre-frail participants from the non-frail group. These two studies were pooled with a mean difference of 1.09 (95% CI 0.62—1.56, $I^2 = 0\%$) more exacerbations in the frail group in the prior year (Fig. 3A).

Hospitalizations

Eight studies compared hospitalizations between frail and non-frail participants [8–10, 15, 19, 20, 23, 26]. Five studies presented retrospective data on AECOPD specific hospitalizations [19, 20, 23, 26, 27]. Four studies presented longitudinal prospective data on all-cause hospitalizations [8, 9, 15, 28].

Among studies with longitudinal data on all-cause hospitalization in frail vs non-frail people, Yee et al. reported a non-significant adjusted Incident Rate Ratio of 1.96 (95% CI: 0.92—4.19) hospitalizations in frail vs non-frail people, however, a larger study by Kennedy

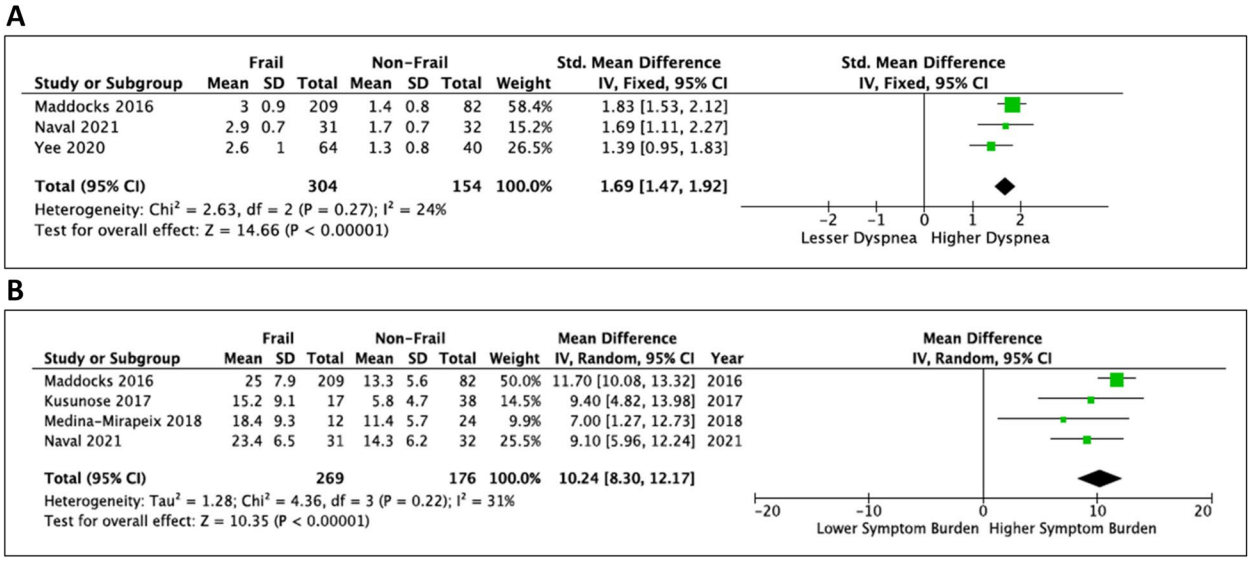

Fig. 2 **A** and **B:** Association between frailty and dyspnea (mMRC) and CAT scores in Frail vs Non-Frail participants with COPD. **A:** Dyspnea as measured by the mMRC dyspnea scale; **B:** Symptom burden as measured by the CAT score. **A:** Mean difference in dyspnea scores measured by mMRC scale. **B:** Mean difference in symptom burden measured by COPD Assessment Test

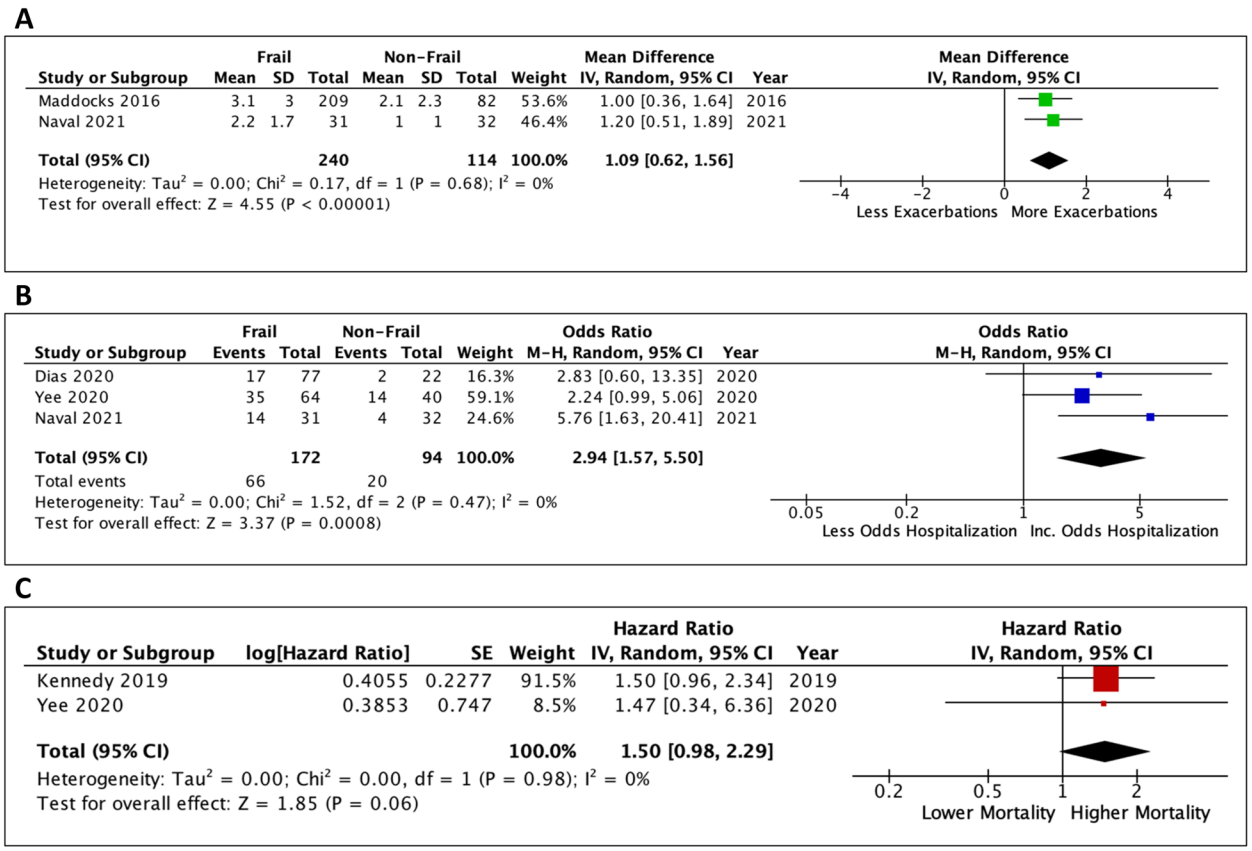

Fig. 3 Association between frailty and exacerbations, COPD-related hospitalization, and mortality among frail vs non-frail individuals with COPD. **A:** Mean difference in exacerbations in prior 1 year; **B:** Odds Ratio of ≥ 1 COPD related hospitalization in past 1 year; **C:** Mortality at two-years

et al. identified a statistically significant increase in all cause hospitalizations in frail vs non frail participants in adjusted analyses [HR (95% CI):1.8 (1.1—2.9)] [8, 9].

Three retrospective studies reported the proportion of participants who were hospitalized the prior year and did not include pre-frail participants in the non-frail group [8, 20, 23]. When these studies were pooled, frail individuals a 3-fold increase in odds of having a prior hospitalization among vs non-frail patients [OR (95% CI): 2.94 (1.57—5.50); $I^2 = 0\%$] (Fig. 3B).

Mortality

Six studies compared all-cause mortality between frail and non-frail participants [8, 9, 15, 16, 18, 28].

Three studies compared non frail participants with frail and pre-frail participants combined [15, 16, 28]. Another large study analyzed the Singapore Longitudinal Ageing Study (SLAS) cohort with mean follow up of 9.5 years for SLAS 1 and 6.5 years for SLAS 2 cohorts (1162 patients with COPD). This study reported an increased risk of mortality [Adjusted HR (95% CI): 1.83 (1.24–2.68)] among frail vs non-frail participants [16].

Another study compared non-frail participants, to mild, moderate, and severely frail participants and followed patients for 12 years. It reported an increased risk of mortality for every increase in the Frailty Staging System score [Adjusted HR (95% CI): 1.80 (1.28–2.53)] [18]. Two studies excluded pre-frail participants from the non-frail group and followed patients for 2 years [9, 27]. Pooled analysis these two studies identified a non-significant increased risk of 2-year mortality in adjusted models [adjusted HR (95% CI): 1.50 (0.98—2.29); $I^2 = 0\%$] (Fig. 3C).

Association between pre-frailty and outcomes

Meta-analyses comparing pre-frail participants with non-frail participants revealed a statistically significant standardized mean difference in mMRC score [0.65 (95% CI: 0.42–0.89); $I^2 = 35\%$] and mean difference in CAT score [5.00 (95% CI: 3.95–6.05); $I^2 = 83\%$] favoring higher scores in the pre-frail group (supplementary appendices).

However, meta-analysis did not reveal a significant mean difference in number of reported exacerbations in the preceding year [0.27 (95% CI: −0.51–1.05); $I^2 = 78\%$]; in odds of being hospitalized in the prior year [OR (95%

CI): 1.57 (0.88–2.79); $I^2=0$]; nor in mortality [HR (95% CI): 1.06 (0.78–1.45); $I^2=0$]. Results describing associations between pre-frailty and outcomes is available in the supplementary appendix.

Discussion

This systematic review and meta-analysis describes the types of frailty instruments used in published studies among people with COPD and assessed the association between frailty and COPD-related outcomes. We found that half of published studies used the Fried Frailty Phenotype measurement. The meta-analyses identified that frail people with COPD have worsened dyspnea, higher symptom burden, with both outcomes above the established minimally important clinical threshold compared to non-frail people [29, 30]. We found frailty is also associated with statistically more exacerbations and hospitalizations, while the largest study (>1000 people) to evaluate mortality over the longest follow up period (9.5 years) revealed a statistically significant increase in mortality among frail vs non-frail patients with COPD.

The evaluation of frailty among individuals with COPD is even more important considering the nascent paradigm of treatable traits in managing COPD. This approach involves a multidisciplinary assessment of individuals with COPD to identify a set of treatable problems, which can be addressed through an individualized treatment plan that targets each identified problem [31]. While some traits are well recognized and widely treated, such as dyspnea and recurrent exacerbations, other traits, particularly extrapulmonary and behavioral traits are less recognized, defined, measured, and treated. The identification of new treatable traits in COPD is an important research priority. Candidate treatable traits are required to be clinically relevant, measurable, and treatable.

Our meta-analyses suggest that frailty is a clinically relevant trait in COPD. However, the method to screen for and measure frailty in this population remains less clear. The Fried Frailty Phenotype was the most common instrument to assess frailty in studies included in this systemic review, used in 8 of 16 included studies. It defines frailty as the presence of three or more of the following: unintentional weight loss, weakness, exhaustion, slowness, and reduced physical activity [32]. This measure was shown to be predictive of mortality in people with COPD as well as responsive to change after pulmonary rehabilitation [15, 33]. However, operationalizing the Fried Frailty phenotype is challenging in clinical settings; it is time consuming and requires equipment, at times, unavailable in pulmonary outpatient clinics. Also, as with most metrics of frailty, it remains unclear if respiratory illness affects the prognostic abilities of this tool. Furthermore, differing clinical scenarios require targeting the frailty tool used to the purpose of measurement. This is particularly important given the variability of data captured by the numerous validated measures of frailty [34]. For example, a highly sensitive test (i.e. timed up and go) would be appropriate as a tool to screen for frailty among older community dwellers [35], while a highly specific test (i.e. fried frailty phenotype) would be more appropriate as a tool to predict 3 year mortality, and a responsive tool would be more appropriate to capture change in frailty status after pulmonary rehabilitation. Consequently, more research is needed to elucidate clinically relevant and feasible metrics of frailty specific to respiratory disorders.

Burgeoning evidence demonstrates that frailty is reversible at the least in the short term [11, 36]. A previous study suggests that that pre-frail individuals are more likely to revert to a non-frail state than frail individuals [36]. This highlights that timely identification of pre-frail individuals with COPD may represent a unique opportunity to intervene with a multicomponent exercise and education program, such as pulmonary rehabilitation. While frail individuals have been shown to have a larger improvement between baseline and after pulmonary rehabilitation, the benefits gained are shorter lived among frail individuals with COPD compared to non-frail individuals [36].

Despite high prevalence, prediction of poor outcomes, and the availability of an effective intervention to treat frailty (e.g. pulmonary rehabilitation) [11], several systemic barriers exist to systematically identify, measure, and quantify frailty in the real-world clinical setting, and no consensus exists on which instrument is most appropriate to use [13]. It is likely that current frameworks of healthcare delivery are too narrowly disease-specific to identify a complex issue such as frailty which lies at the intersection of multimorbidity, polypharmacy, and worsening functional capacity, and which is associated with worse outcomes across multiple diseases, including several cardiovascular diseases [37]. Approaches may require population level interventions, such the frailty screening protocols used by the National Health Service in England [38]. The electronic Frailty Index (eFI) recently implemented by the National Health Service in England uses routinely collected health data to calculate a score to identify people likely to be living with frailty and likely to benefit from targeted interventions such as fall risk assessment, drug reviews, and cognitive assessment, among others [38].

There are limitations to our work. As our study focused on real-world evidence, there is substantial variability in study designs, participants, and instruments. For example, 6 different instruments to measure frailty were used to define study groups in the included 16 studies, and

some studies included pre-frail participants within the non-frail group, while others did not. We addressed this issue by only pooling data from studies that had similar study group definitions, in particular studies that did not include pre-frail participants in the non-frail group. Furthermore, similar outcomes were reported differently, even if measured using the same tool. For example, some studies reported mMRC in mean (SD), while others reported median (IQR) or n (%) greater than mMRC 2. We were only able to pool similarly reported data, thereby limiting the number of studies we could include in pooled analyses. The studies included in this review were of variable quality, with five out of seven studies in the meta-analysis rated as moderate risk of bias. We attempted to rigorously evaluate each study for risk of bias and have presented results of this assessment above. We did not use criteria to exclude studies from the meta-analysis based on data quality, and one study of high risk of bias was included in the meta-analysis. Lastly, observational study designs are limited by confounding, selection, and information biases, and pooled observational data will thus have the same limitations [39].

In conclusion, we found that people with COPD who are frail were likely to be more dyspneic, have larger symptom burden, more exacerbations, more hospitalizations, and increased mortality, in comparison to COPD patients who were not frail. This adds to the growing evidence that frailty is an important treatable trait in patients with COPD and should be measured in standard practice. However, questions remain regarding the best way to measure and identify frailty, and which targeted interventions are most effective in frail and pre-frail patients with COPD. Answering these questions with rigorous study designs and use of standard frailty instruments and outcomes will be important to advance personalized care for patients with COPD who are frail or prone to frailty.

Supplementary Information

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Supplementary Material 1

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Authors' contributions
MC, SM, JS conceived the question, RS created the search strategy and performed the search of multiple databases. MC, PM, SM screened studies and extracted data. MC, PM, and SM performed the analyses. MC and SM drafted the initial manuscript, while all authors provided critical revision of the manuscript for content and clarity.

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Declarations

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Competing interests
The authors declare no competing interests.

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