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Abstract:

Background

Frailty is a risk factor for adverse health outcomes. There is a paucity of literature on frailty progression defined by a cumulative deficit model among community dwelling older people. The objective of this review was to synthesise evidence on these changes in health and mortality among community-dwelling older people.

Methods

Six databases (Medline, Embase, CINAHL, Cochrane, PsycInfo, Web of Science) and a clinical trials registry were searched in July 2021. The inclusion criteria were studies using a frailty index and providing information on transition between frailty states or to death in community-dwelling older people aged ≥ 50 . Exclusion criteria were studies examining specific health conditions, conference abstracts and non-English studies. To standardise the follow-up period and facilitate comparison, we converted the transition probabilities to annual transition rates.

Results

Two reviewers independently screened 5078 studies and 61 studies were included for analysis. Of these, only three used the same frailty state cut-points to facilitate cross-cohort comparison. This review found that frailty tends to increase with time, people who are frail at baseline have greater likelihood to progress in frailty and die, and the main factor that accelerates frailty progression is age. Other risk factors for progression are having chronic disease, smoking, obesity, low-income or/and low-education levels. A frailty index is an accurate predictor of adverse outcomes and death.

Discussion

This systematic review demonstrated that worsening in frailty was a common frailty transition, and older people who are frail at baseline are more likely to die. A frailty index has significant power to predict adverse health outcomes. It is a useful tool for within-cohort comparison but there are challenges comparing different cohorts due to dependence of frailty progression on age and differences in how frailty index is defined and measured.

Key words: frailty, progression, cumulative deficit model, community-dwelling older people, systematic literature review

1. Introduction

Ageing is associated with increased probability of ill health (Clegg et al., 2013), poor quality of life (Nikolova et al., 2020), hospitalisation (Kojima, 2016) and death (Shamliyan et al., 2013, Chang and Lin, 2015, Kojima et al., 2018). Individuals of the same age can differ greatly in terms of their underlying health (Mitnitski and Rockwood, 2015) and associated vulnerability to adverse outcomes. This variability in vulnerability is often referred to as frailty (Clegg et al., 2013). There are two established models of frailty: the phenotype model and cumulative deficit model. The phenotype model of frailty is based on the five physical characteristics as reported in the original Cardiovascular Health Study (slow walking speed, weight loss, exhaustion, weak grip strength, low energy expenditure). These physical components enable categorisation into three states: non-frail, pre-frail or frail (Fried et al., 2001). Evidence on transitions between states of the phenotype model and death has been recently summarised

(Kojima et al., 2019). The cumulative deficit model counts the number of health deficits, including cognition, mood and social support (Mitnitski et al., 2001). Owing to this more comprehensive information on health, the cumulative deficit model is considered more sensitive to modifications in underlying health than the phenotype frailty (Cesari et al., 2014), and a more accurate predictor of mortality (Kojima et al., 2018). Thus, the cumulative frailty model may be a more useful tool to explore changes in health (Mitnitski and Rockwood, 2015) in response to interventions to improve frailty-related outcomes (Cesari et al., 2014).

A frailty index (FI) is calculated by dividing the number of present health deficits by the total number of deficits measured. The FI can take value from 0.0-1.0, where a higher score is associated, on average, with higher frailty. This continuous variable is useful when frailty is assessed at the individual level. To operationalise the frailty index for clinical use, it is usually categorised into a small number of ordered states based on established cut-points (Hoover et al., 2013). A set of standard criteria which include counting only deficits associated with health status, have increasing prevalence with age and cover a range of physiological systems is available to guide operationalisation of the frailty index (Searle et al., 2008). This suggests that frailty indices implemented in different samples can be based on different deficits when exploring changes in health. There is however a paucity of literature on progression in frailty defined by FI among community-dwelling older people.

The aim of this review is to synthesise the evidence on changes in health and mortality when changes are operationalised as transitions between states of a cumulative frailty model. We sought to explore whether changes could be summarised, to what extent these changes depend on baseline health and age and how often improvement occurred relative to deterioration.

2. Method

2.1. Protocol

A review protocol was developed in accordance with the Preferred Reporting Items for Systematic review (PRISMA) statement (Moher et al., 2015) (PROSPERO registration number CRD42020218187).

2.2. Search Strategy

In June 2020 we conducted searches to determine the rate of progression of frailty for groups defined by risk factors using the search strategy and search terms published in the review by Kojima et al. (Kojima et al., 2019). The search terms included database subject headings (eg MeSH) and textwords: Frail elderly (MesH), Frailty(MeSH), frailty, transition, progression, prognosis or course. These searches were rerun in full on 13th July 2021 using the same strategies and date limits in Medline, Embase, PsycInfo, CINAHL, Cochrane CENTRAL, and Web of Science and We also searched. We also searched ClinicalTrials.gov (U.S. NIH) to identify any ongoing trials. Since the frailty index was introduced in 2001 (Mitnitski et al., 2001) we limited our search to articles published from 2000. The search strategies were peer reviewed by an information specialist using the PRESS checklist (McGowan et al., 2016). Please see Supplementary 1 for full search strategies.

The results of the database searches were stored and de-duplicated in an EndNote X9 library. Further relevant studies were sought by citation searching (backwards) of the included studies.

2.3. Study selection

As opposed to Kojima et al. (2019) review where they synthesised evidence of transitions between frailty states with phenotypic frailty defined by Fried et al. (2001) we limited our search to articles where frailty is defined by a frailty index defined by Mitnitski et al. (2001).

Screening was conducted in two stages using the Rayyan web tool (Ouzzani et al., 2016). Two authors (DK, HJ) independently screened titles and abstracts for eligibility followed by reading of the full texts. Disagreements were resolved with a third reviewer (SN). We included studies which: 1) used a frailty index defined by Mitnitski et al. (2001); or used both approaches; 2) studied people aged 50 and over living in the community, as nationally representative cohorts of respondents in different countries focus on individuals aged 50 and over (Mansor et al., 2019, Perianayagam et al., 2019, Shin, 2019, Ichimura et al., 2009, Zaninotto and Steptoe, 2019, Börsch-Supan et al., 2013, Rosero-Bixby et al., 2019, Wong et al., 2015, Kearney et al., 2011, Sonnega et al., 2014, Zhao et al., 2012); 3) provided information on transition between frailty states or to death; 4) published since 2000; and 5) prospective design. We excluded studies which: 1) used only phenotypic frailty defined by Fried et al. (2001);

2) analysed only a selected sample (e.g., people with specific health conditions); 3) conference abstracts and reviews; 4) non-English studies.

2.4. Quality assessment

The quality of the included studies was assessed using a modified Newcastle-Ottawa scale (NOS) (Wells et al., 2000). We modified NOS to include an additional criterion – the frailty index must include at least 30 deficits as suggested by Searle et al. (2008).

2.5. Data extraction

Data were independently extracted by two reviewers using an Excel spreadsheet. Data extracted directly from the studies included: first author's name, publication year, cohort name, sample size, mean age at baseline, proportion of female participants, cohort characteristics, duration of follow up, follow up rate, cut-points for FI score, number of deficits used to construct FI, number and percentage of participants in each frailty category (non-frail, pre-frail, frail) at baseline and follow up as well as number and percentage of deaths at follow up.

2.6. Data synthesis

Due to the heterogeneous nature of many frailty studies, we synthesised evidence from studies which used the same cut-points. Data on changes of frailty status from baseline to follow up were converted to annual transition probabilities by calculating the N th root of a transition probability matrix using eigen-decomposition approach introduced in Chhatwal et al. (2016). Unlike the traditional method the eigen-decomposition method matches exactly the observed probabilities for lower frequencies. The findings from the rest of the studies were narratively synthesised to investigate associations between socio-demographic factors and progression in frailty.

3. Results

3.1. Selection processes, study characteristics and assessment of study quality

The final search identified a total of 10697 records. After deduplication 5619 articles were screened. Of these, 4977 studies were excluded through title and abstract screening. The full texts for one hundred and one studies were reviewed of

which fifty-seven were excluded because they used a selected sample ($n = 7$), used a frailty definition which did not meet the cumulative frailty model criteria or did not contain information on changes between frailty categories and/or death ($n = 26$). We also excluded systematic reviews ($n = 1$), non- English publications ($n = 1$), and conference abstracts ($n = 21$). The full text for one study was not found. Sixty one studies were identified for inclusion in the current systematic reviews. The PRISMA flow diagram is presented in Figure 1. Citation searches identified sixteen records. The detailed study characteristics of included studies are presented in Table 1.

The majority of included studies reported data extracted from longitudinal population-based cohort studies and local administrative data spanning more than eighteen countries: United States ($n=8$), Canada ($n=9$), England ($n=8$), China ($n=7$), the Netherlands ($n=4$), Australia ($n=2$), France ($n=2$), Germany ($n=2$), Korea ($n=2$), Wales ($n=1$), Great Britain ($n=1$), Sweden ($n=1$), Spain ($n=1$), Turkey ($n=1$), Japan ($n=1$), Taiwan ($n=1$), Brazil ($n=1$), Mexico ($n=1$). Most measured FI in accordance with the Searle et al. (Searle et al., 2008) guidance, and one study (Jung et al., 2014) proposed a novel approach to create FI, which applies weighting factors with respect to clinical significance.

Only three of the sixty-one included studies (Figure 1) used more than 30 deficits to calculate FI score and discretise it into three categories: non-frail, pre-frail and frail. The cohorts were from Australia ($n = 1$), and China ($n = 2$), their participants' mean age at baseline varied between 70 and 80 years, all consisted of more women than men. These three studies were related to be of good quality (the NOS score is 9, Supplementary Table 3). The remaining fifty-eight studies used different number of deficits used as well as cut-points. Information reported in the remaining fifty-eight studies was used for a narrative summary.

Figure 1 PRISMA flow diagram

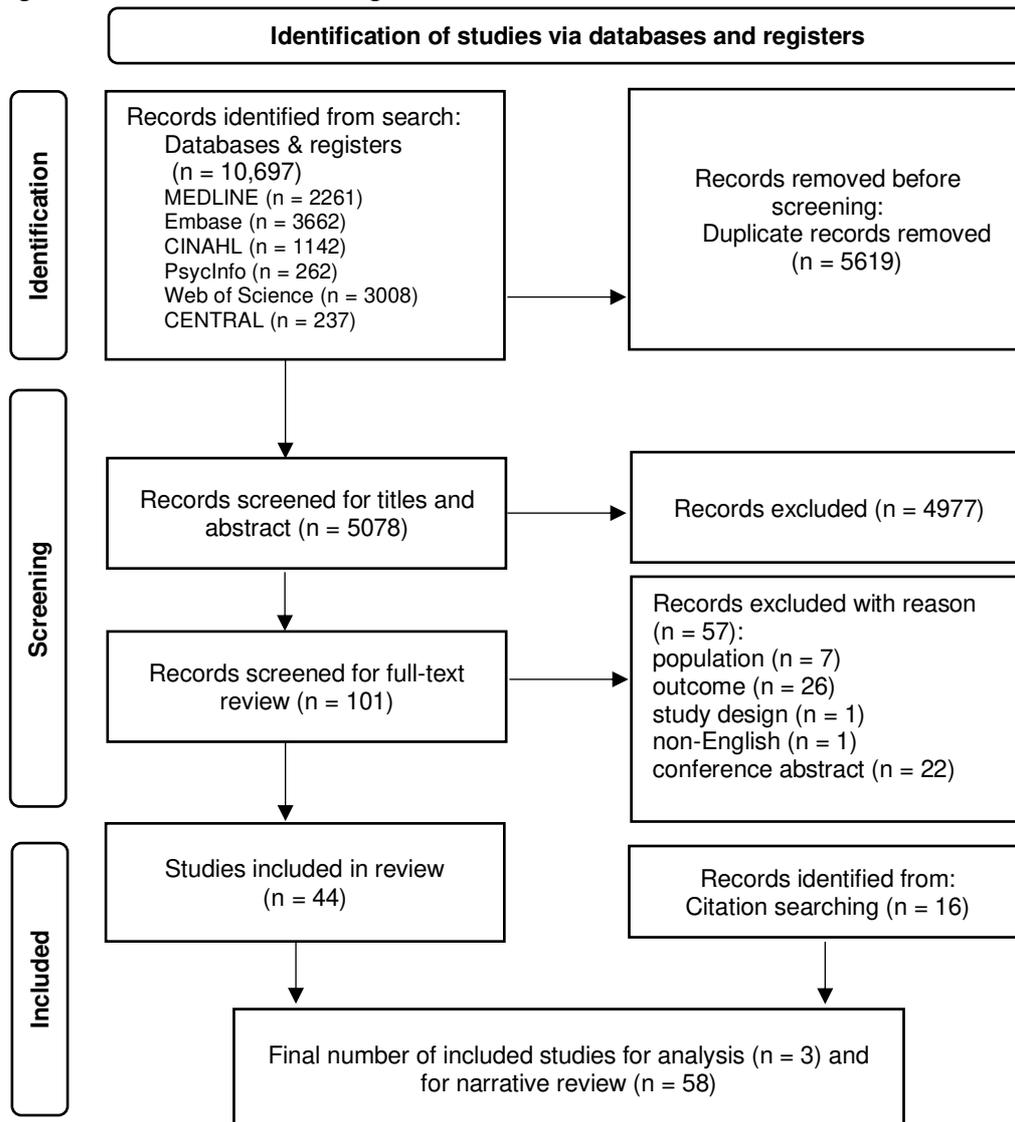


Table 1 Characteristics of studies included for a) cross-cohort comparison; and b) studies included for narrative discussion

Study ID	a) Study First Author, year	Setting: cohort name (if reported)	Number of participants	Mean age at baseline (range)	Women (%)	Baseline period, year(s)	Follow-up period	Number of deficits	Frailty cut- points
1	Thompson et al., 2018	The North West Adelaide Health Study, South Australia	696	73.4 (≥ 65)	53.1%	2004-2006	4.5 years	34	Non-frail ($FI \leq 0.10$); Prefrail ($0.10 < FI \leq 0.21$); Frail ($FI > 0.21$)
2	Ye et al., 2020	China, Shanghai	3988	69.38 (≥ 60)	56.5%	2015	2 years	36	Non-frail ($FI \leq 0.10$); Prefrail ($0.10 < FI \leq 0.21$); Frail ($FI > 0.21$)
3	Liu et al., 2018	Chinese Longitudinal Healthy Longevity Survey, China	11,165	82.6 (80; 100]	52.0%	2002	3 years	44	Non-frail ($FI \leq 0.10$); Prefrail ($0.10 < FI \leq 0.21$); Frail ($FI > 0.21$)

Study ID	b) Study First Author, year	Setting: cohort name (if reported)	Number of participants	Mean age at baseline (range)	Women (%)	Baseline period, year(s)	Follow-up period	Number of deficits	Frailty cut- points
4	Armstrong et al. (2015a)	USA (Oahu, Hawaii): Honolulu-Asia Aging Study	3845	77.9 (≥ 71)	Men only	1991	Approximately every 3 years	48	NR
5	Armstrong et al. (2015b)	USA (Oahu, Hawaii): Honolulu-Asia Aging Study	3845	NR (72 - 93)	Men only	1991	Every 2-3 years over 20 years	NR	NR
6	Bartley et al. (2016)	USA (Olmsted County, Minnesota): Mayo Clinic Study of Aging	2356	78.8 (70 - 89)	49.8	2008	Every 15 months	36	Fit ($FI \leq 0.10$); At Risk ($0.10 < FI \leq 0.20$); Frail ($0.21 \leq FI < 0.30$); Frailtest ($FI > 0.30$)
7	Blodgett et al. (2017)	USA: National Health and Nutrition Examination Survey	8888	49.4 (≥ 20) ¹	51.7	2003-2006	NR	68	Frailty scores are categorised incrementally
8	Chamberlain et al. (2016)	USA (Olmsted County, Minnesota)	12270	70.5 (60 - 89)	55	2005	8 years	32	NR
9	Fallah et al. (2011)	USA (New Haven, Connecticut): Yale Precipitating Events Project	754	78.0 (≥ 70)	64	NR	Every 1.5 years	36	NR
10	Shi et al. (2020)	USA: The National Health and Aging Trends Study	7033	NR (≥ 65)	55.8	2011-2016	NR	41	Percentile distribution
11	Brown et al. (2020)	USA: Lifestyle Interventions and Independence for Elders Study	1635	79.0 (≥ 70)	67.2	NR	3 years	75	Percentile distribution
12	Mitnitski et al. (2007)	Canada: Canadian National Population Health Survey	4330	67.1 (≥ 55)	58.8	1994-1995	Every 2 years	22	NR
13	Mitnitski et al. (2012)	Canada: Canadian National Population and Health Survey	4333	68.4 (≥ 55)	58.8	1994	12 years (every 2 years)	31	NR
14	Rockwood et al. (2007)	Canada: Canadian Study of Health and Aging	2305	73.4 (69 - 109)	53.1	1990-1991	NR	70	Non-frail ($FI < 0.25$); Frail ($FI \geq 0.25$)

¹ Analysis is stratified by age categories

15	Song et al. (2010)	Canada: National Population and Health Survey	2740	74.0 (>65)	60.8	1994-1995	10 years	36	Non-frail (FI≤0.08); Pre-frail (0.08<FI<0.25); Frail (FI ≥ 0.25)
16	Zimmer et al. (2021)	Canada: Health and Retirement Study	17115	NR (>=55)	NR	NR	NR	59	Frailty free (FI≤0.19); Mild frailty (0.19<FI≤0.39); Severe frailty (FI>0.39)
17	Bohn et al. (2021)	Canada: Victoria Longitudinal Study	649	70.6 (53 - 95)	66.0	NR	NR	54	NR
18	Mitnitski et al., (2006)	Canada: Canadian Study of Health and Aging	5586	NR (>=65)	NR	1990-1991	every 5 years	31	NR
19	Hubbard et al., (2009)	Canada: The Canadian Study of Health and Aging	9008	NR (>=65)	59.5	1991	10 years	40	NR
20	Hill et al. (2021)	Canada	368798	74.2 (>=55)	46.7%	2002-2015	every year	11 clusters of conditions	NR
21	Gale et al. (2017)	England: The English Longitudinal Study of Aging	5314	70.0 (50 - 75)	54.4	2010-2011	2 years	44	NR
22	Gale et al. (2018)	England: The English Longitudinal Study of Aging	2817	69.3 (>=60)	56.9	2004-2012	Every two years	52	NR
23	Niederstrasser et al. (2019)	England: The English Longitudinal Study of Aging	8780	66.9 (>=50)	55.02	2004-2005	every 2 years	NR	Frail (FI≥0.25)
24	Rogers and Fancourt (2020)	England: The English Longitudinal Study of Aging	4575	64.7 (>=50)	52.7	2004-2015	10 years	56	NR
25	Rogers et al. (2017a)	England: The English Longitudinal Study of Aging	8649	64.0 (>=50)	53.2	2002-2003	10 years	56	Non-frail (FI<0.25); Frail (FI ≥ 0.25)
26	Rogers et al. (2017b)	England: The English Longitudinal Study of Aging	8722	64.4 (>=50)	54.9	2002-2003	10 years	47	non-frail (FI≤0.08); pre-frail (0.08 < FI ≤0.25); frail (FI >0.25)
27	Stow et al. (2018)	England	26298	85.4 (>=75)	55.6	2015	1 year	36	NR
28	Hubbard et al. (2010)	England: The English Longitudinal Study of Ageing	3055	NR (>=65)	55.5	2004	NC	58	NR
29	Ma et al. (2018)	China: Beijing Longitudinal Study of Aging	1810	74.5 (>=60)	51.9	2004	8 years	68	Frail (FI≥0.25)

30	Zheng et al. (2016)	China: Beijing Longitudinal Study of Aging	10039	70.5 (≥ 55)	61.0	2009	1 year	34	Frail (FI ≥ 0.25)
31	Gu et al. (2009)	China: Chinese Longitudinal Healthy Longevity Survey	13861	NR (65 - 109)	57.2	2002	3 years	39	quartile
32	Shi et al. (2011)	China: Beijing Longitudinal Study of Aging	3257	NR (≥ 55)		1992	every 2-3 years	35	0.10, 0.20, 0.30, 0.40, 0.5.
33	Woo et al. (2015)	China: Beijing Longitudinal Study of Aging II; Hong Kong cohort	11298	NR (≥ 55 Beijing cohort, ≥ 65 Hong Kong cohort)	57.0	2009 (Beijing cohort); 2001 (Hong Kong cohort)	every 2-3 years	30 (Beijing cohort), 33 (Hong Kong cohort)	Non-frail (FI < 0.25); Frail (FI ≥ 0.25)
34	Hao et al. (2018)	China: The Project of Longevity and Aging in Dujiangyan	705	93.6 (90 - 108)	67.4	2005	4 years	34	Non-frail (FI < 0.21); Frail (FI ≥ 0.21)
35	Fang et al. (2012)	China: The Beijing Longitudinal Study of Aging	3257	NR (≥ 55)		1992	8 years	33	0.03, 0.1, 0.20, 0.50
36	Gobbens and van der Ploeg (2021)	The Netherlands (Roosendaal)	1154	80.3 (≥ 75)	56.8	2008	1,2,3,4,5,6 and 7 years	15	Frail (FI ≥ 5)
37	Drubbel et al. (2013)	The Netherlands	1679	median 73 (≥ 60)	58.8	2008	2 years	36	tertile
38	Hoogendijk et al. (2017)	The Netherlands: The Longitudinal Aging Study Amsterdam	2218	NR (55 - 85)	NR	1995-1996	19 years	32	0.10, 0.20, 0.30, 0.40
39	Hoogendijk et al. (2018)	The Netherlands: The Longitudinal Aging Study Amsterdam	1,659	75.7 (≥ 65)	52.9	1995 -1996	17 years	32	Non-frail (FI < 0.25); Frail (FI ≥ 0.25)
40	Blodgett et al. (2016)	Eight European countries: European Male Aging Study	3369	60.2 (40 - 79) ¹	Men only	2003	4 years	39	Frailty scores are categorised incrementally
41	Jazbar et al. (2021)	Europe: Survey of Health, Ageing and Retirement Survey	25225	73.8 (≥ 65)	55.5	2013	2 years	30	Frail (FI ≥ 0.25)
42	Romero-Ortuno and Kenny (2012)	Europe: The Survey of Health, Ageing and Retirement in Europe	29905	NR (≥ 50)	54.2	2004	1 year	40	quartile
43	Romero-Ortuno (2014)	Europe: The Survey of Health, Ageing and Retirement in Europe	29905	NR (≥ 50)	54.2	2004	1 year	40	quartile

44	Hyde et al. (2016)	Australia: Kimberly region	363	60.7 (≥ 45)	54.5	2004 -2006	7 years	20	Non-frail (FI<0.2); Frail (FI \geq 0.2)
45	Siejka et al. (2020)	Australia (Tasmania): The Tasmanian Study of Cognition and Gait	388	72.0 (65 - 80)	44.0	2005-2008	every 2 years	41	NR
46	de Souto Barreto et al. (2018)	France: Multidomain Alzheimer's Preventive Trial	Control group : 842; Multidomain group : 837	Control: 75.3 (≥ 70); Multidomain group: 75.3 (≥ 70)	Control group: 65.0; Multidomain group: 64.3	NR	6 months; 1, 2 and 3 years	32	Frail (FI \geq 0.25)
47	Herr et al. (2015)	France: SIPAF ²	2350	83.3 (≥ 70)	59.4	2008-2010	Median 2.8 years	43	0.11; 0.17; 0.29
48	Gao et al. (2017)	Germany (Saarland): ESTHER ³	Discovery set: 978; Validation set: 531	Discovery set: 62.1 (50 - 75); Validation set: 62.0 (50 - 75)	Discovery set: 49.4%; Validation set: 61%	2000-2002	NR	34	Non-frail (FI \leq 0.20); Pre-frail (0.20<FI<0.45); Frail (FI \geq 0.45)
49	Saum et al. (2014)	Germany (Saarland): ESTHER ³	9,886	62.0 (50 - 75)	50.0	200-2002	10 years	34	0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45
50	Jung et al. (2014)	Korea: Korean Longitudinal Study on Health and Aging	693	75.9 (≥ 65)	50.8	2005-2006	5 years	NR	Pre-frail (0.2 \leq FI<0.35); Frail (FI \geq 0.35)
51	Nari et al. (2021)	Korea: Korean Longitudinal Study of Aging	2375	NR	NR	2008	2 years	NR	robust (FI \leq 1); pre-frail (1<=FI<=2); frail (FI \geq 2)
52	Hollingshurst et al. (2019)	Wales	496000	75.0 (≥ 65)	55.0	2000-2009	1, 3 and 5 years	36	Fit (efi \leq 0.12); Mild (0.12<efi \leq 0.24); Moderate (0.24 <efi \leq 0.36); Severely frail (efi>0.36)

² SystèmeHERR, M., ROBINE, J.-M., AEGERTER, P., ARVIEU, J.-J. & ANKRI, J. 2015. Contribution of socioeconomic position over life to frailty differences in old age: comparison of life-course models in a French sample of 2350 old people. *Annals of Epidemiology*, 25, 674-680.e1. d'Information sur la Perte d'Autonomie Fonctionnelle de la personne âgée

³ Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung.

53	Kamaruzzaman et al. (2010)	Great Britain: The British Women's Heart and Health Study	NR	NR (60 -79)	100.0	1999-2001	median 8.2 years	35	NR
54	Bartosch et al. (2018)	Sweden: Osteoporosis Risk Assessment study	1044	75.2 (≥ 75)	100.0	1995-1999	5 years and 10 years	13	Varies for each year category
55	Amblas-Novellas et al. (2021)	Spain: Patients admitted to the Acute Geriatric Unit	590	86.4 (≥ 85)	57.5	2015	2 years	25	No frailty ($FI \leq 0.2$); Mild frailty ($0.2 < FI \leq 0.35$); Moderate frailty ($0.35 < FI \leq 0.5$); Advanced frailty ($FI > 0.5$)
56	Ozmen et al. (2020)	Turkey	99	74.0 (≥ 70)	64.7	2018	10 months	NR	NR
57	Ohashi et al. (2021)	Japan (Agano city): The Kihon Checklist survey	551	67.3 (65 - 70)	51.9	2011	2016	25	Robust (0; 3); Prefrail (4; 7); Frail (≥ 8)
58	Chen et al. (2021)	Taiwan's National Health Insurance Reimbursement Database	100000	73 median (≥ 65)	51.6	2006	mean 7.58 years	NR	NC
59	Borges et al. (2021)	Brazil: The Multimorbidity and Mental health Cohort Study in Frailty and Aging	315	NC (≥ 60)	NC	NC	NC	36	NC
60	García-González et al. (2009)	Mexico: The Mexican Health and Aging Study	4082	73 (65 - 105)	52.5	2001	2 years	34	0.07, 0.14, 0.21, 0.35, 0.65
61	Li et al. (2016)	Ten countries: Global Longitudinal Study of Osteoporosis in Women 3-Year Hamilton cohort	3985	69.4 (≥ 55)	100.0	2008-2009	1,2 and 3 years	34	Frailty scores are categorised incrementally

NR – not reported, NC - not clear.

3.2. Annual transitions between frailty states and to death

Table 2 presents annual transition probabilities extracted from the three included studies (ID:1,2,3). As cycle length was respectively 4.5, 2, and 3 years we converted to annual transition probabilities using an eigen-decomposition technique (Chhatwal et al., 2016). Findings suggest participants were likely to remain in their current frailty category (non-frail state 86%, 84%, 62%; pre-frail state 79%, 57%, 70%; and frail state 89%, 68%, 65%). Most transition in either direction are gradual. Results from the three cohorts highlight the decline in health with annual transitions from pre-frail to frail status being 13%, 15%, 15%. Frail participants at baseline were more likely to die in all three studies.

Health tends to decline with age. In support of this observation, we have found that age tends to accelerate transition from being non-frail to frail (34% vs 13%) and from being frail to death (28% vs 12%) when comparing youngest (mean age 69.4 (ID:2)) to oldest (mean age 82.6 (ID:3)) cohort. At the same time the youngest cohort had almost 30% chances of health improvement by going from pre-frail to non-frail state.

Table 2 Annual transition probabilities

Thompson et al. (2018) (ID:1)		Annual transition			
Frailty status at baseline		Non-frail	Pre-frail	Frail	Death
	Non-frail	0.86	0.12	0.01	0.01
	Pre-frail	0.06	0.79	0.13	0.01
	Frail	0.00	0.03	0.89	0.08

Ye et al. (2020)(ID:2)		Annual transition			
Frailty status at baseline		Non-frail	Pre-frail	Frail	Death
	Non-frail	0.84	0.13	0.02	0.01
	Pre-frail	0.27	0.57	0.15	0.01
	Frail	0.03	0.17	0.68	0.12

Liu et al. (2018)(ID:3)		Annual transition			
Frailty status at baseline		Non-frail	Pre-Frail	Frail	Death
	Non-frail	0.62	0.34	0.00	0.04
	Pre-frail	0.09	0.70	0.15	0.07
	Frail	0.00	0.07	0.65	0.28

3.3. Narrative synthesis

Fifty-eight studies did not report sufficient data for analysis but provided additional information to describe the complex nature of these changes. Many of them reported that frailty tends to increase over time (ID: 5,8,9,12-14,27,36,38,39,49,52,54), and greater frailty at baseline increased the likelihood of increasing frailty at follow ups (ID:12,17,21,22,44). One study which measured frailty transition times using the electronic FI (Clegg et al., 2016) reported that the frailty transition times shorten as a frailty state deteriorates (ID:52). Other studies reported that improvement in frailty is also possible (ID:9,12,13,36,57,46).

Association between FI, age and gender

Whilst the included studies consistently reported that the frailty increases with age (ID:1,2,5-9,15-17,19-21,23,28-33,35-41,44-47,49,50,52,53,60), results with respect to gender are inconsistent. Seventeen studies reported that females are more likely to develop frailty (ID:2,15,16,20,21,23,27,30,31,33,35,36,41,47,49,50,60), whereas one study found frailty worsening in men (ID:1) and another reported that FI score is higher in males than in females (ID:6). Two studies found that frailty, as measured by a FI, is associated with greater risk of death in older women (ID:6,61), whilst other studies reported the opposite – older women tolerated deficits better than men as older men tend to have higher death rates (ID:15,31,32,49,60).

Association between FI and psychosocial and behavioural factors

Several risk factors associated with progression to higher frailty states are reported in the included studies. These factors include urbanicity (ID:30,31,33,35), smoking (ID:8,19,21,23,48) and/or alcohol consumption (ID:8), obesity (ID:1,23,28), low intensity of physical activity (ID:2,21,23,29,33), low income status (ID:16,21,36,43,47), low level of education (ID:2,6,8,16,23,33,36,43), not married (ID:2,8,33,36), lonely (ID:22,23,39) or living alone (ID:1,2,33), and not having shower facilities at home (ID:2). One study reported that stratification by gender revealed that non-frail women living alone are less likely to transit to a higher frailty state, whereas such association for non-frail men was not confirmed (ID:1). Two studies reported that social isolation did not predict change in frailty index (ID:22,23). The rate of increase in frailty was lower with more frequent engagement in cultural activities (ID:24) and religious

activities (ID:31). Among older people smoking and alcohol consumption become less influential factors in frailty progression (ID:8, 33, 47).

Association between progression of frailty, physical and mental health

The likelihood of developing frailty increases with the number of chronic conditions (ID:1,30,45,61), multimorbidity (ID:1,33) and/or comorbidity (ID:20), late-life depression (ID:59) and/or taking medication (ID:1,30,33,41).

People with better baseline mobility are more likely to experience improvement in frailty or remain stable, while those with poor baseline mobility are more likely to die (ID:9). One study showed that multidomain interventions that included cognitive training, counselling to effect nutrition and advice on physical activity seem to decrease risk of progression in frailty (ID:46), and another reported that a physical activity intervention is effective among frailest older people (ID:11). Moreover, moderate physical activity reduces progression in frailty among people aged 65 and above, and vigorous physical activity reduces progression in frailty among older people (ID:25).

FI as a predictor of adverse health outcomes, mortality, and hospital outcomes

The included studies report that a FI is a significant predictor of cognitive decline (ID:4,17,51) or dementia (ID:26), adverse outcomes such as decline in activities of daily living disability or functional decline (ID:10,30,50), falls (ID:10,30,35,61), and death (ID:14,26,30,42,49). Studies that explored association between FI and mortality risk reported that:

- a) the frailest people are more likely to die (ID:5,6,12,14,15,20,27,44,54,56,58,60);
- b) an increase in the number of frailty deficits of the FI increases the risk of death (ID:5-7,12,14,18,32,35,38,40,44,49,55,60), and institutionalisation (ID:40,44,53);
- c) age is a significant predictor of death among the most people (ID:5,12,15,31,40); and FI score is a predictor of time to death (ID:5);
- d) worsening in frailty or remaining in the same frailty state increases the risk of a painful death (ID:3);
- e) people aged 90 and over with frailty and cognitive impairment have higher risk of death (ID:34).

The included studies report that a FI is also a significant predictor of hospitalisation (ID:10,30,50,52,53). Frailer people have higher chances to be

hospitalised or readmitted to a hospital (ID:20), die in the year following unplanned hospitalisation (ID:20,52,58) or stay longer in hospital (ID:20,52). Healthcare costs after a hospital admission tend to be higher among frailer people (ID:20).

Predictive ability of FI compared with other tools

Compared to the Schonberg (Schonberg et al., 2009) and Lee (Lee et al., 2006) indices, FI better predicts decline in activities of daily living and falls, but its predictive ability of mortality is comparable to these two prognostic indices (ID:10). When FI is compared to the phenotype measure of frailty, FI predicts adverse outcomes as accurately as phenotype frailty (ID:14), but better predicts mortality, functional decline and hospitalisation when using a weighting factor approach (ID:50). At the same time these two methods (FP and FI) do not share the same risk factors - loneliness is a risk factor for progression in frailty when it is measured with FP, but not a predictor for change in FI (ID:22).

4. Discussion

The results of this systematic review showed that combining evidence from existing literature on frailty operationalised using a research standard frailty model is a challenging task due to dependence of frailty progression on age and inconsistency in how the frailty index is defined and measured across studies. We addressed the latter challenge of synthesising the evidence from those studies that have the same cut points between frailty states. We converted transitions probabilities to annual transition rates to standardise follow-up period and facilitate comparison.

In line with a recently published systematic review that used a phenotypic defined frailty [9], this review showed that worsening in frailty was a common frailty transition. Improvement and stability in frailty status were also possible.

Consistent with the previous literature, where frailty was measured using the frailty phenotype (Kojima et al., 2019, Thompson et al., 2018, Espinoza et al., 2012, Gill et al., 2006, Lee et al., 2014) this review found that frailty tends to increase with time, people who are frail at baseline have greater likelihood to progress in frailty and die, and that age is the main factor that accelerates progression in frailty. Other risk

factors for progression in frailty were: having chronic disease, smoking, obesity, low-income or/and low-education level.

The controversial results with respect to association between transition in frailty, survival rates, social status and gender might be due to cohort limitation in the included studies and the male-female health-survival paradox, when compared to men women tend to have a greater chance of survival despite having more health-related issues (Alberts et al., 2014).

This review shows that the FI approach has several advantages and disadvantages stemming from differences in the way the cumulative frailty model has been operationalised in different data sets. First, the FI approach does not require a specific set of health deficits to construct a frailty index. Second, the approach enables usage of routinely collected data extracted from large healthcare databases across the world instead of conducting interviews. Using these large datasets allows for a comprehensive within cohort analysis. Third, a frailty index has better predictive power of adverse health outcomes, hospitalisation, and mortality, and finally FI has more opportunity to observe frailty trajectory. On the other hand, the flexible nature of this approach limits cross-cohort comparison. The inconsistency in cut points used to define frailty indices states prevents comprehensive between cohort analysis.

We could not conduct a comprehensive meta-analysis due to the high level of heterogeneity in the evidence on frailty transitions. We were also unable to conduct subgroup analysis by gender due to limited data reported in the included studies. Heterogeneity in age across cohorts presented a challenge when synthesising evidence across cohorts.

This review is the first to provide synthesised evidence on frailty transition between the stages of frailty and to death among community-dwelling older people, as well as to demonstrate the associations between frailty indices and social and behavioural factors, and the capacity of FI to act as an accurate predictor of adverse outcomes and death. Another strength of the review is the comprehensive methodology including extensive and reproducible search strategy using seven electronic databases. The identified studies were screened with standardised processes and assessed for methodological quality independently by two reviewers.

The review findings contribute to understanding frailty progression in older people living in the community and underscore the role of geriatric medicine in smoothing natural progression of human life to death. The frailty index is proved to be

a flexible tool to measure frailty transitions. Moreover, it allows measurement of frailty in many cohorts, for which FI estimates seemed to be similar - older people with frailty are more likely to experience deterioration and, like in the review on phenotypic frailty (Kojima et al., 2019), the reverse is also possible. Hence, FI is a useful tool for a within cohort comparison. The between cohorts' comparison yet is a challenging task. Multidomain lifestyle interventions may help to reduce the risk of becoming frail (de Souto Barreto et al., 2018). Therefore, it is important to identify signs of frailty at an earlier stage to help older people with some level of frailty to slow down the progression in frailty and/or delay the incidence (de Souto Barreto et al., 2018).

To summarise, measuring frailty using cumulative deficits offers a practical approach with the potential to achieve greater sensitivity to interventions, provided a sufficient range of deficits is included. The definition of frailty states, essentially a categorisation of the frailty index, might be considered with the support of a mapping to a phenotype frailty measure to provide greater consistency between studies.

Supplementary 1

Search Strategies

Date: 13 July 2021

CINAHL (EBSCO)

Tuesday, July 13, 2021 12:06:34 PM

Search date: 13 July 2021

```
S11 S8 OR S9 Limiters - Published Date: 20000101-20201231 1,142
S10 S8 OR S9 1,265
S9 TI ("incident frailty" or "incidence of frailty" ) OR AB ( "incident frailty" or
"incidence of frailty" ) OR SU ( "incident frailty" or "incidence of frailty" ) 145
S8 S4 AND S7 1,133
S7 S5 OR S6 284,782
S6 TI (Progression* or outcome* or prognosis or course*) 224,800
S5 TI transition* OR AB transition* OR SU transition* 62,525
S4 S1 OR S2 OR S3 14,501
S3 TI frailty OR AB frailty OR SU frailty 9,324
S2 (MH "Frail Elderly") 7,973
S1 (MH "Frailty Syndrome") 2,816
```

Cochrane Library (Wiley)

Search date: 13 July 2021

Cochrane Central Register of Controlled Trials: Issue 7 of 12, July 2021 (=237)

Search Name: Frailty Transition Kojima update

Date Run: 13/07/2021 14:26:51

Comment: 25-6-20

```
ID Search Hits
#1 MeSH descriptor: [Frail Elderly] explode all trees 739
#2 MeSH descriptor: [Frailty] explode all trees 185
#3 frailty:ti,ab,kw 2129
#4 #1 or #2 or #3 2639
#5 (Progression* or outcome* or prognosis or course*):ti 68144
#6 transition*:ti,ab,kw 10643
#7 #5 or #6 78173
#8 #4 AND #7 213
#9 ("incident frailty" or "incidence of frailty"):ti,ab,kw 24
#10 #8 or #9 237
```

Embase (Ovid)<1996 to 2021 Week 27>

Search date: 13 July 2021

```
1 frailty/ (15602)
2 frail elderly/ (10407)
3 frailty.tw,kw. (26909)
4 or/1-3 [frailty terms Kojima 2019] (35044)
```

5 transition*.tw,kw. (433044)
 6 (Progression* or outcome* or prognosis or course*).ti. (773925)
 7 5 or 6 [transition terms Kojima 2019] (1194353)
 8 4 and 7 (3384)
 9 (incident frailty or "incidence of frailty").tw,kw. [supplementary transition terms
 searched by Kojima 2019] (319)
 10 8 or 9 (3678)
 11 limit 10 to yr="2000 -Current" (3662)

Ovid MEDLINE(R) ALL <1946 to July 12, 2021>

Search date: 13 July 2021

1 Frail Elderly/ 12710
 2 Frailty/4489
 3 frailty.tw,kw. 17513
 4 or/1-3 [frailty terms Kojima 2019] 24978
 5 transition*.tw,kw. 444532
 6 (Progression* or outcome* or prognosis or course*).ti. 595894
 7 5 or 6 [transition terms Kojima 2019]1031399
 8 4 and 72113
 9 (incident frailty or "incidence of frailty").tw,kw. [supplementary transition terms
 searched by Kojima 2019] 227
 10 8 or 9 2322
 11 limit 10 to yr="2000 -Current" 2261

APA PsycInfo (Ovid)<1806 to July Week 1 2021>

Search date: 13 July 2021

1 frailty.tw,hw,id. 2470
 2 frailty.mh. 107
 3 "Frail Elderly".mh. 1755
 4 or/1-3 [frailty terms Kojima 2019] 3719
 5 transition*.tw,hw,id. 81454
 6 (Progression* or outcome* or prognosis or course*).ti. 93436
 7 5 or 6 [transition terms Kojima 2019]172521
 8 4 and 7251
 9 (incident frailty or "incidence of frailty").tw,hw,id. [supplementary transition terms
 searched by Kojima 2019] 26
 10 8 or 9 273
 11 limit 10 to yr="2000 -Current" 262

Web of Science Core Collection

Search date: 13 July 2021

Web of Science Core Collection: Citation Indexes simultaneous search of the following

- Science Citation Index Expanded (SCI-EXPANDED) --1900-present
- Social Sciences Citation Index (SSCI) --1900-present
- Arts & Humanities Citation Index (A&HCI) --1975-present

- Conference Proceedings Citation Index- Science (CPCI-S) --1990-present
- Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH) --1990-present
- Emerging Sources Citation Index (ESCI) --2015-present

Data last updated: 2021-07-12

# 8	3,008	#6 OR #5	Timespan=2000-2021
# 7	3,043	#6 OR #5	
# 6	264	TOPIC: ("incident frailty" or "incidence of frailty")	
# 5	2,803	#4 AND #1	
# 4	2,688,304	#3 OR #2	
# 3	889,608	TITLE: ((Progression* or outcome* or prognosis or course*))	
# 2	1,813,123	TOPIC: (transition*)	
# 1	28,249	TOPIC: ("frail elderly" OR frailty)	

[Clinical trials.gov](https://clinicaltrials.gov)

Search date: 13 July 2021

Condition or disease: frailty AND *Other terms* transition OR transitions OR incidence OR incident OR progression OR prognosis = 125

[outcome or course were not used as these were too nonspecific to use here]

Supplementary 2

Table 3 Risk of bias assessment (modified Newcastle-Ottawa Quality Assessment Scale)

Study	Selection			Comparability		Outcome			NOS Quality score	
	Representativeness of Exposed Cohort	Selection of the Non-Exposed Cohort from Same Source as Exposed Cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts	Assessment of outcome	Follow-up long enough for outcomes to occur (Duration of outcome >= 1 year)	Adequacy of follow up		Number of deficits >=30 (y/n)
Thompson et al. (ID:1)	Community-dwelling older adults (>=65) living in the North West of Adelaide, South Australia. Participants were truly representative of the community (data were weighted to the area population). *	Yes *	Participants were interviewed *	Yes *	Controlled for the most important factors: age, gender, education level, marital status, income level; Controlled for additional factors: smoking status, alcohol consumption, waist circumference, multimorbidity, polypharmacy, living arrangements * *	Self-report and record linkage *	Yes *	83% participated at 4.5-year follow up *	Yes *	Good

Ye et al. (ID:2)	Community-dwelling older adults (>=60) living in the Shanghai community. Two out of 11 streets were selected from each street four communities selected. *	Yes *	Participants completed questionnaires *	Yes *	Controlled for the most important factors: age, gender, education level, marital status; Controlled for additional factors: living alone, having shower facility at home, smoking status, alcohol consumption, reading, playing cards or mahjong, physical exercise, meeting with children and neighbour interaction, social participation * *	Self-report and record linkage *	Yes *	99% participated at 2-year follow up *	Yes *	Good
Liu et al. (ID:3)	Community-dwelling oldest old (>=80, but <100) from half of the counties and cities selected in 22 provinces (out of 23) in China. *	Yes *	Participants were interviewed *	Yes *	Controlled for the most important factors: age, gender, education level, marital status, ethnicity, residence; Controlled for additional factors: primary lifetime occupation, smoking status, regular exercise, economic independence, adequate medication * *	Self-report and record linkage *	Yes *	87% participated at 3-year follow up *	Yes *	Good

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor)

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

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