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A systematic review and meta-analysis**

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Association of polypharmacy and hyperpolypharmacy with frailty states: a systematic review and meta-analysis

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Abstract

Purpose To investigate: (1) the cross-sectional association between polypharmacy, hyperpolypharmacy and presence of prefrailty or frailty; (2) the risk of incident prefrailty or frailty in persons with polypharmacy, and vice versa.

Methods A systematic review and meta-analysis was performed according to PRISMA guidelines. We searched PubMed, Web of Science, and Embase from 01/01/1998 to 5/2/2018. Pooled estimates were obtained through random effect models and Mantel–Haenszel weighting. Homogeneity was assessed with the I^2 statistic and publication bias with Egger's and Begg's tests.

Results Thirty-seven studies were included. The pooled proportion of polypharmacy in persons with prefrailty and frailty was 47% (95% CI 33–61) and 59% (95% CI 42–76), respectively. Increased odds ratio of polypharmacy were seen for prefrail (pooled OR = 1.52; 95% CI 1.32–1.79) and frail persons (pooled OR = 2.62, 95% CI 1.81–3.79). Hyperpolypharmacy was also increased in prefrail (OR = 1.95; 95% CI 1.41–2.70) and frail (OR = 6.57; 95% CI 9.57–10.48) persons compared to robust persons. Only seven longitudinal studies reported data on the risk of either incident prefrailty or frailty in persons with baseline polypharmacy. A significant higher odds of developing prefrailty was found in robust persons with polypharmacy (pooled OR = 1.30; 95% CI 1.12–1.51). We found no papers investigating polypharmacy incidence in persons with prefrailty/frailty.

Conclusions Polypharmacy is common in prefrail and frail persons, and these individuals are also more likely to be on extreme drug regimens, i.e. hyperpolypharmacy, than robust older persons. More research is needed to investigate the causal relationship between polypharmacy and frailty syndromes, thereby identifying ways to jointly reduce drug burden and prefrailty/frailty in these individuals.

Prospero registration number CRD42018104756.

Keywords Frail · Prefrail · Polypharmacy · Drugs · Ageing · Medications · Hyperpolypharmacy

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Introduction

Frailty is a geriatric syndrome characterized by decreased reserve and function across multiple physiologic systems, leading to a compromised ability to respond to common acute stressors [1]. Various definitions and diagnostic criteria for frailty are currently in use [2], some focus on specific physical symptoms and signs such as exhaustion, weakness, weight loss, low physical activity or slow gait [3]. More complex definitions include multidimensional aspects such

as physical, social, cognitive, medical, and psychological features [4]. Frailty is a dynamic process, passing through different states, including a prefrail phase (sometimes referred to as “intermediate frailty”) which lies on the pathway between being robust and the full frailty syndrome. In community-dwelling older adults, the prevalence of frailty is estimated to be between 8 and 16% [5, 6] and is associated with higher risks of adverse health-related outcomes, including hospitalization, longer hospital stays, nursing home admissions, disability and death [1, 3, 7].

There are several factors that are significantly associated with the frailty syndrome, including chronic non-communicable diseases such as kidney disease [8], chronic obstructive pulmonary disease [9], anaemia [10], atrial fibrillation [11], and multimorbidity (i.e. the presence of two or more chronic medical conditions in an individual) [12]. Several papers have also suggested that polypharmacy is associated with frailty. Polypharmacy is defined as the concurrent use of multiple prescription drugs in an individual. A recent systematic review [13] identified up to 138 different definitions of polypharmacy in the literature, but they concluded that the most common definition is the use of five or more medications daily, which is the criterion used by almost half of the studies in the literature. In addition, several authors also describe hyperpolypharmacy, an extreme form of excessive polypharmacy, usually defined as the use of ten or more medications. Polypharmacy and hyperpolypharmacy are prevalent in older persons, especially those in long-term care facilities [14]. They have been associated with numerous negative health outcomes including, but not limited to, adverse drug reactions, drug–drug interactions, drug–disease interactions, cognitive impairment, malnutrition, decline in physical functioning, and increased risk of falls and delirium [1, 14–20].

Frailty is a complex condition, and may be associated with medication use via numerous pathways, such as chronic diseases, hormonal deficits, and sarcopenia [21]. Also, the use of a high number of drugs may cause clinical or subclinical adverse drug reactions or side effects that increase the risk of frailty. Drug–drug interactions can also reduce the effect of some medications, thus compromising their efficacy and potentially promoting ill health and frailty. A previous review [22] identified a link between frailty and polypharmacy. In the current review, we provide the first meta-analysis of available evidence, and add an update, focusing on the various ways in which different levels of frailty status (including both frailty and prefrailty) are associated separately to both polypharmacy and hyperpolypharmacy. The aims of this systematic review and meta-analysis are to investigate: (1) The cross-sectional association between polypharmacy, hyperpolypharmacy and presence of prefrailty or frailty; (2) the risk of incident prefrailty or frailty in persons with polypharmacy, and vice versa.

Methods

The review was conducted by the European Geriatric Medicine Society (EuGMS) Pharmacology special interest group, which aims to create a European network of clinicians and researchers devoted to promote appropriate drug prescription in older people, and develop pharmacogenetic research in older patients. The protocol of the present study was registered in the international prospective register of systematic reviews PROSPERO (registration number CRD42018104756). The review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [23].

Search terms

We searched three databases for relevant articles published in the last 20 years from 01/01/1998 to 5/2/2018: (1) PubMed electronic database of the National Library of Medicine, (2) Web of Science and; (3) Embase. MeSH terms and free words referring to prefrailty, frailty and polypharmacy were used as keywords. Keywords were chosen by a group of 5 of the authors through discussion and consensus, and by examining keywords from other reviews and articles on similar topics.

The PubMed search term was as follows: (“Frailty”[Mesh] OR “Frail Elderly”[Mesh] OR frail*[Title/Abstract] OR frailty[Title/Abstract] OR prefrailty[Title/Abstract] OR prefrail[Title/Abstract]) AND (“Polypharmacy”[Mesh] OR Polypharmacy[Title/Abstract] OR polytherapy[Title/Abstract] OR “medication appropriateness”[Title/Abstract] OR overprescribing[Title/Abstract] OR multidrug[Title/Abstract] OR “medication*”[Title/Abstract] OR “multiple medications”[Title/Abstract] OR “multiple drug*”[Title/Abstract] OR “beers criteria”[Title/Abstract] OR “STOPP AND START”[Title/Abstract] OR “Potentially Inappropriate Medication List”[Mesh] OR “Potentially Inappropriate Medication”[Title/Abstract] OR “Inappropriate Prescribing”[Mesh] OR “Inappropriate Prescribing”[Title/Abstract] OR “Drug Therapy, Combination”[Mesh] OR “Pharmaceutical Preparations”[Mesh]). References from the selected papers and from other relevant articles were also screened to identify additional papers.

Study selection and data extraction

The abstracts were divided between five teams, with two researchers in each group who independently screened the abstracts (ET, AG, Tvdc, GZ, RvM, MP, MW, FP, RC, ERV). We considered studies with cross-sectional and

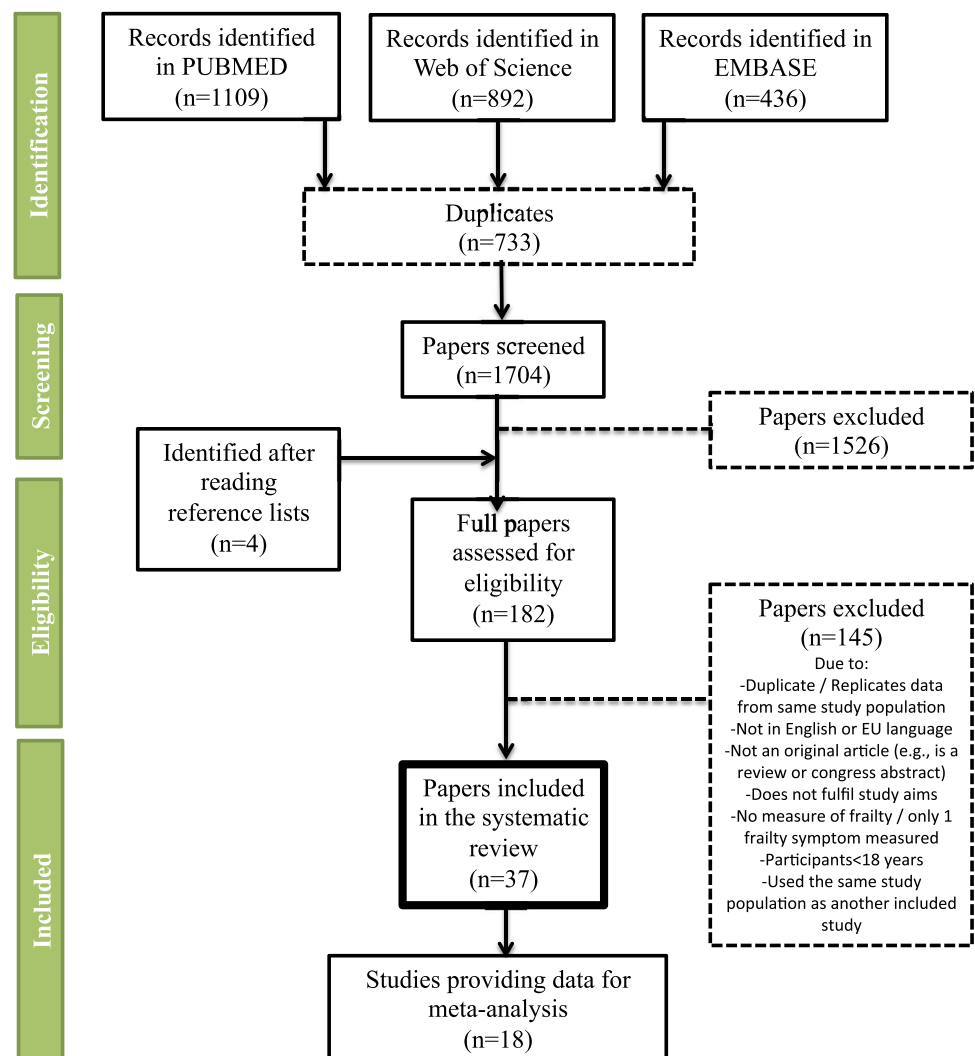
longitudinal measures of association between polypharmacy and/or hyperpolypharmacy with prefrailty and/or frailty and as well as case–control studies. Exclusion criteria were: (1) data relevant to the review aims not included; (2) included adults (< 18 years); (3) not an original research article (e.g. editorial, review, or congress abstract); (4) the definition of frailty not explicitly described and; (5) frailty assessed only with a single symptom or measure (e.g. only weight loss or grip strength); (6) not written in English or any other European language. The full text of the articles selected by one or both of the assessors were retrieved for full evaluation. Five teams of two reviewers (KP, GO, GZ, ACJ, AC, WK, ERV, DOM, DM, DC, TvdC) read the full texts and independently extracted the information from the studies. A third person (KP or ERV) reviewed the data extraction, and disagreements were resolved through consensus.

The numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, are presented in Fig. 1.

Statistical analysis

We performed a meta-analysis with three or more studies using the same definition of frailty. Due to the observational design of the studies, and the methodological differences that may have contributed to a significant share of the variance within the measures of interest, the pooled estimates were obtained through random effect models and Mantel–Haenszel weighting. Homogeneity within the pooled studies was assessed through the I^2 statistics (significant if $\geq 50\%$ or p value < 0.05). Publication bias was assessed with the Egger's and the Begg's tests. For longitudinal studies, we only included studies that used measures of incident frailty or polypharmacy (e.g. that clearly exclude persons with frailty or polypharmacy prevalent at baseline, respectively). For the meta-analyses, when exact data were not provided in the relevant articles, we approached authors for additional data. All statistical analyses were performed with STATA version

Fig. 1 PRISMA flow chart of search strategy and abstract screening



14 (StataCorp, TX, USA), with p value < 0.05 considered statistically significant.

Results

Study characteristics

After removing duplicates, we screened 1704 abstracts (Fig. 1), and 182 papers were chosen to be read in full for potential data extraction. After excluding papers that did not fulfill our inclusion criteria, 37 papers were included in the review; 30 provided only cross-sectional data, 5 provided only longitudinal data, and 2 studies provided both cross-sectional and longitudinal data [24, 25].

As this was a systematic review of already published papers, we did not collect any patient data and, therefore, ethical permission was not required. The characteristics of the studies providing cross-sectional and longitudinal data are shown in Tables 1 and 2, respectively. Twenty-four studies (66.7%) analysed community-dwelling populations, 25% hospitalized patients, and 8.3% nursing home residents. The majority of studies were from Europe (43.2%), 24.4% from Asia, 16.2% from Australia, 8.1% from USA or Canada, and 8.1% from South America. Most studies (59.4%) used Cardiovascular Health Study (CHS) criteria (also known as Fried's criteria), three (8.1%) used the Reported Edmonton Frail Scale, and the rest of the studies used different criteria including the Tilburg Frailty Indicator or Groningen Frailty Indicator, with none of these remaining studies using the same assessments. Prefrailty was most frequently defined as scoring 1–2 out of 5 criteria from the CHS definition. Some studies examined and compared multiple frailty definitions [26, 27]. Polypharmacy was most frequently defined as the use of 5 or more medications, although 17 studies had a slightly lower or higher threshold. Eleven studies also included a measure of hyperpolypharmacy, which was always defined as the use of 10 or more medications. It is noteworthy that in some of the studies addressing hyperpolypharmacy, the polypharmacy definition differs from those in other studies, because it excludes persons with hyperpolypharmacy; for example, persons would be classified with polypharmacy only if they use 5–9 drugs (e.g. excluding those taking ten or more medications). In contrast, studies that did not have a separate category of hyperpolypharmacy included people with hyperpolypharmacy in their definition of polypharmacy (e.g. ≥ 5 medications, with no limit).

Many (40.5%) of the studies provided both frailty and prefrailty categories, 45.9% of the studies considered a single frailty category (often including prefrail patients among the robust/non-frail ones) and the remaining papers (13.6%) used a continuous frailty variable, such as the number of frailty items impaired, or a frailty index score.

Meta-analysis

A meta-analysis was performed only with studies using the CHS criteria, as there were a sufficient number of papers (≥ 3) using this definition. Eighteen studies provided data that could be used in one or more of the meta-analyses. Most used the same definition of polypharmacy (≥ 5 medications) except four studies, which used slightly different cut-offs; Eyigor et al. [28] (≥ 4 medications), Moulis et al. [29] (≥ 6 medications), Diaz et al. [30] (≥ 6 medications), Chang et al. [31] (≥ 8 medications). Four of the studies that investigated both polypharmacy and hyperpolypharmacy restricted the polypharmacy category to 5–9 medications only (e.g. excluded hyperpolypharmacy from the polypharmacy category) [25, 32–34]. Despite these small variations in definitions, we ran the meta-analyses including all these studies, as the differences were not deemed sufficient to exclude them.

Assessment of bias

No strong evidence of publication bias was detected in our meta-analyses (Egger's test $p = 0.789$; Begg's test $p = 0.102$).

Association between polypharmacy and prefrailty

The lowest reported proportion of people with polypharmacy who also had prefrailty was 37% and the highest was 58% (Fig. 2a) and the pooled proportion of people on polypharmacy with prefrailty was 48% (95% CI 43–54; $I^2 = 91.1\%$).

As shown in Fig. 2b, the proportion of prefrail persons with polypharmacy ranged from 5 to 69% with a pooled proportion of 47% (95% CI 33–61; $I^2 = 99.0\%$). In persons with prefrailty, the odds of polypharmacy was increased by 52%, with a pooled OR = 1.52 (95% CI 1.32–1.79; $I^2 = 50.2\%$, Fig. 3a).

Association between polypharmacy and frailty

Seventeen studies reported a statistically significant difference in the proportion of frailty in persons with polypharmacy, with the exception of one [35], which used the Reported Edmonton Frail scale and excluded hyperpolypharmacy from the polypharmacy category.

Ten studies provided data on the proportion of frailty among persons with polypharmacy, using the same criteria (CHS), and thus were included in the meta-analysis. As shown in Fig. 3b, the lowest reported proportion of people with polypharmacy who also had frailty was 5% and the highest was 52%. The pooled proportion of people with polypharmacy who also had frailty was 27% (95% CI 17–38, $I^2 = 98.6\%$).

Eleven studies provided data on the proportion of polypharmacy among persons with frailty.

Table 1 Summary of 32 cross-sectional studies on the occurrence of polypharmacy and hyperpolypharmacy in relation to prefrailty and frailty

First author (year)	Study name	Type of population	Country	N	% Women	Age Mean (SD)	Frailty criteria	Polypharmacy	Hyper-poly-pharmacy definition	Results	Odds ratios for prefrailty or frailty according to polypharmacy status	Adjustment variables
Ballew et al. (2017) [58]	Atherosclerosis Risk in Communities Study	Community-dwelling	USA	4987	55.8	≥ 66	Fried	5+	10+	Hyperpolypharmacy was seen in 54.0% of frail versus 38.4% of non frail, $p \leq 0.001$ Mean number of medications in robust = 8.8 (4.6) vs frail = 10.5 (5.0), $p \leq 0.001$		
Bonaga et al. (2018) [59]	Frailty and Dependence in Albacete (FRADEA) Study	Community-dwelling	Spain	773	59.1	78.5 (5.8)	Fried	5+		% With polypharmacy = 39.2 Robust = 39.2 Prefrail = 63.5 Frail = 81.9		
Buttery et al. (2015) [60]	German Health Interview and Examination Survey for Adults (DEGS1)	Community-dwelling	Germany	1843	50.1	65–79	Fried	5+		% With polypharmacy = 41.5 Robust = 41.5 Prefrail = 51.7 Frail = 86.7	Prefrail and polypharmacy OR = 1.5 (1.2–1.9) Frail and polypharmacy OR = 7.8 (2.9–20.7)	Age, sex, SES
Cakmur et al. (2015) [61]		Community-dwelling	Turkey	168	53.6	72.7 (7.7)	Fried	1+ ^a		Association between frailty and polypharmacy $\chi^2 = 15.766 < 0.001$		
Castell et al. (2013) [62]		Community-dwelling	Spain	1325	53.4	75.4 (7.4)	Fried	5+		% with polypharmacy Robust = 55.4 Frail = 77.0 $p < 0.001$	Frail and polypharmacy OR = 1.2 (1.1–1.3)	Age, sex, self-rated health, comorbidity, number of drugs, cognitive decline, physical disability

Table 1 (continued)

First author (year)	Study name	Type of population	Country	N	% Women	Age Mean (SD)	Frailty criteria	Polypharmacy	Hyperpolypharmacy definition	Results	Odds ratios for frailty or frailty according to polypharmacy status	Adjustment variables
Chang et al. (2011) [31]		Community-dwelling	Taiwan	275	53.8	65–79	Fried	8+		% with polypharmacy Robust = 3.7 Prefrail = 5.0 Frail = 16.1 $p = 0.034$		
Cheung et al. (2017) [63]		Patients discharged from surgical wards	Australia	100	58	78.0 (7.0)	Reported Edmonton Frail Scale	5+		% With polypharmacy Robust = 50.7 Frail = 90.9 $p = 0.001$		
Closs et al. (2016) [64]	Multidimensional Study of the Elderly in the Family Health Strategy (EMI-SUS)	Community-dwelling	Brazil	521	64.3	68.5 (6.8)	Fried	5+		% With polypharmacy Robust = 28.0 Prefrail = 41.4 Frail = 57.1	Prefrail and polypharmacy OR = 1.2 (0.9–3.1) Frail and polypharmacy OR = 2.9 (1.1–7.8)	Sex, age, depression, self-perception of health, MNA, history of falls, vision and hearing.
Diaz-Toro et al. (2017) [30]		Inpatients	Chile	79	48.1	71 (8)	Fried	6+		% With polypharmacy Robust = 7.7 Frail = 100.0 $p < 0.001$		
Eyigor et al. (2015) [28]		Community-dwelling persons attending rehab clinics	Turkey	1126	65.7	65 to > 85	Fried	4+		% With polypharmacy Robust = 29.4 Prefrail = 42.6 Frail = 66.2 $p < 0.001$	Frail and polypharmacy OR = 2.0 (1.3–3.2)	CES-D, Ambulation Scale, fatigue, sex, sedentary behaviour, recreational walking, hearing problems, acute care admission, malnutrition

Table 1 (continued)

First author (year)	Study name	Type of population	Country	N	% Women	Age Mean (SD)	Frailty criteria	Polypharmacy	Hyper-polypharmacy definition	Results	Odds ratios for frailty or frailty according to polypharmacy status	Adjustment variables
Gnjidic et al. (2012) [24]	Concord Health and Ageing in Men Project (CHAMP)	Community-dwelling	Australia	1662	0	> 70	Fried	5+	10+	% With polypharmacy Robust = 27.2 Prefrail = 44.4 Frail = 64.7 $p < 0.0001$	Prefrail and polypharmacy OR = 1.5 (1.2–1.9) Frail and polypharmacy OR = 2.6 (1.7–3.8) Prefrail and hyperpolypharmacy OR = 1.9 (1.04–3.6) Frail and hyperpolypharmacy OR = 5.8 (2.9–11.6)	Age, education, marital status, and comorbidity

Table 1 (continued)

First author (year)	Study name	Type of population	Country	N	% Women	Age Mean (SD)	Frailty criteria	Polypharmacy	Hyper-polypharmacy definition	Results	Odds ratios for frailty or frailty according to polypharmacy status	Adjustment variables
Gutiérrez-Valencia et al. (2018) [27]		Nursing home	Spain	110	71.8	86.3 (SD 7.3)	Four criteria used	5+			Fried criteria: Frail and polypharmacy OR = 1.1 (0.1–11.3) Imputed Fried score: Frail and polypharmacy OR = 0.7 (0.2–2.4) Frail in nursing homes scale: Frail and polypharmacy OR = 1.3 (0.4–3.7) Rockwood et al. criteria: Frail and polypharmacy OR = 4.3 (1.0–18.33)	Age, sex, multi-morbidity and cognitive impairment

Table 1 (continued)

First author (year)	Study name	Type of population	Country	N	% Women	Age Mean (SD)	Frailty criteria	Polypharmacy	Hyperpolypharmacy definition	Results	Odds ratios for frailty or frailty according to polypharmacy status	Adjustment variables
Hasan et al. (2017b) [65]		Nursing home	Malaysia	202	59.8	76.8 (7.8)	Groningen Frailty Indicator (GFI)	5+		Average GFI score was higher in those with polypharmacy (7.2 (3.4)) than without (5.7 (3.6)). Correlation coefficient between number of drugs and GFI was $r = 0.21$, $p = 0.002$		
Herr et al. (2015) [34]	SIPAF study “Système d’Information sur la Perte d’Autonomie Fonctionnelle de la personne âgée”	Community-dwelling	France	2350	59.4%	83.3 (7.5)	Fried modified	5–9	10+	% w With polypharmacy Robust = 44.6 Prefrail = 69.4 Frail = 75.8 $p < 0.001$	Prefrail and polypharmacy OR = 1.8 (1.4–2.4) Frail and polypharmacy OR = 1.8 (1.2–2.6) Prefrail and hyperpolypharmacy OR = 2.5 (1.5–4.2) Frail and hyperpolypharmacy OR = 4.5 (2.4–8.4)	Age, gender, other health variables

Table 1 (continued)

First author (year)	Study name	Type of population	Country	N	% Women	Age Mean (SD)	Frailty criteria	Polypharmacy	Hyper-polypharmacy definition	Results	Odds ratios for prefrailty or frailty according to polypharmacy status	Adjustment variables
Herr et al. (2017) [66]	ESPS “Enquête sur la santé et la protection sociale”	Community-dwelling	France	1890	53.1	74.7 (7.4)	Fried modified	5–9	10+		Adjusted Poisson regression: Polyparmacy 1.163 per frailty item Hyperpolypharmacy 1.451 per frailty item”	Age, gender, ADL, self perceived health, BMI, comorbidity
Jankowska-Polanska et al. (2016) [67]		Inpatients with hypertension	Poland	296	55.7	68.8 (8.0)	Polish version of the Tilburg Frailty Indicator (TFI)	N/R		% With polypharmacy Robust = 21.4 Frail = 37.9 $p = 0.047$		
Jung et al. (2016) [26]	Aging Study of Pyeongchang Rural Area	Community-dwelling	Korea	382	56.3	74.4 (6.5)	Fried and K-FRAIL scale	5+		% With polypharmacy Robust = 2.2 Frail = 4.5		

Table 1 (continued)

First author (year)	Study name	Type of population	Country	N	% Women	Age Mean (SD)	Frailty criteria	Polypharmacy	Hyper-polypharmacy definition	Results	Odds ratios for frailty or frailty according to polypharmacy status	Adjustment variables
MacLagan et al. (2017) [68]		Nursing home	Canada	41,351	64.7	≥ 65	72-item frailty index based on the measure developed by Hogan et al.	N/R		% With polypharmacy Robust = 74.2 Prefrail = 79.6 Frail = 83.5 $p = 0.001$ 43.3% of robust, 54.3% of prefrail and 61.2% of frail persons had hyperpolypharmacy. Extremely high medication use (≥ 20 drugs was seen in 6.7% of robust, 9.2% of prefrail and 11.7% of frail		
Merchant et al. (2017) [69]	Singapore Healthy Older People Everyday (HOPE) Study	Community-dwelling	Singapore	1051	57.2	71.2	5-item FRAIL scale	5+		% With polypharmacy Robust = 18.1 Prefrail = 29.8 Frail = 41.5 $p < 0.001$		
Moulis, et al. (2015) [29]		Inpatients	France	437	62.7	83.1 (6.2)	Fried	6+			Frail and polypharmacy OR = 1.9 (1.2–2.8)	Age, MMSE, exposure to atropinic drug

Table 1 (continued)

First author (year)	Study name	Type of population	Country	N	% Women	Age Mean (SD)	Frailty criteria	Polypharmacy	Hyperpolypharmacy definition	Results	Odds ratios for prefrailty or frailty according to polypharmacy status	Adjustment variables
Pegorari et al. (2014) [70]	Community-dwelling	Brazil	958	64.4	73.7	Fried	5+			% With polypharmacy Robust = 20.1 Prefrail = 36.8 Frail = 52.0	Prefrail and polypharmacy OR = 2.4 (1.4–4.1) Frail and polypharmacy OR = 6.1 (1.7–22.2)	Age, sex, marital status, housing, schooling, income, hospitalized, disability, depression, health perception, comorbidities
Poudel et al. (2016) [71]		Australia	1418	55	81	InterRAI	5+	10+		Frailty index score was lower in persons without polypharmacy (mean = 0.30, SD = 0.17) than those with polypharmacy (mean = 0.32; SD = 0.15) or hyperpolypharmacy (mean = 0.34; SD = 0.13)		
Rosted et al. (2016) [53]	Acute care inpatients	Denmark	189	≥ 65	ISAR	5+				% With polypharmacy Robust = 29.0 Frail = 77.2		

Table 1 (continued)

First author (year)	Study name	Type of population	Country	N	% Women	Age Mean (SD)	Frailty criteria	Polypharmacy	Hyperpolypharmacy definition	Results	Odds ratios for frailty or frailty according to polypharmacy status	Adjustment variables
Saum et al. (2017) [25]		Community-dwelling	Germany	3058	52.4	57–84	Fried	5–9	10+	% With polypharmacy Robust = 37.4 Prefrail = 49.5 Frail = 78.2 $p < 0.001$	Prefrail and polypharmacy OR = 1.2 (1.0–1.4) Frail and polypharmacy OR = 2.3 (1.6–3.3) Prefrail and hyperpolypharmacy OR = 1.5 (1.03–2.1) Frail and hyperpolypharmacy OR = 4.9 (2.9–8.3)	Sex, age, BMI, education, smoking, morbidity
Serra-Prat et al. (2016) [33]		Primary care centres	Spain	324	47.5	≥ 75	Fried	6–10	11+	% With polypharmacy Robust = 33.7 Prefrail = 46.6 Frail = 84.8 $p < 0.001$	Frail and polypharmacy OR = 6.1 (2.6–14.4) Frail and hyperpolypharmacy OR = 24.9 (7.4–84.1)	
Serra-Prat et al. (2016) [32]		Community-dwelling: Prefrail sample	Spain	171	55.6	78.4 (4.9)	Fried	4+	9+	In this prefrail sample 55.1% had polypharmacy and 12.7% had hyperpolypharmacy		

Table 1 (continued)

First author (year)	Study name	Type of population	Country	N	% Women	Age Mean (SD)	Frailty criteria	Polypharmacy	Hyperpolypharmacy definition	Results	Odds ratios for prefrailty or frailty according to polypharmacy status	Adjustment variables
Sutorius et al. (2016) [72]	Identification of frail elderly study in the Netherlands	Community-dwelling	Netherlands	102	56.9	78.6 (7.1)	Fried (note multiple methods were used but Fried was gold standard)	7+		Polypharmacy (≥ 7 medications) was used as a predictor for frailty (defined as ≥ 3 Fried categories) AUC was 0.76 indicating good predictive performance		
Tan et al. (2017) [73]	A study of medical outpatient clinics in Singapore	Singapore		115	52.2	76.6 (6.5)	Reported Edmonton Frail Scale	5+		% With polypharmacy Robust = 39.0 Frail = 87.1 $p < 0.001$		
Thai et al. (2015) [35]	Inpatients	Australia		180	47.2	≥ 65	Reported Edmonton Frail Scale	5–9	10+	% With polypharmacy Robust = 64.1 Frail = 54.0 $p = 0.095$ Hyperpolypharmacy was seen in 28.2% of robust and 42.9% of frail persons		

Table 1 (continued)

First author (year)	Study name	Type of population	Country	N	% Women	Age Mean (SD)	Frailty criteria	Polypharmacy	Hyperpolypharmacy definition	Results	Odds ratios for frailty or frailty according to polypharmacy status	Adjustment variables
Turner et al. (2014) [74]		Older adults attending a medical oncology clinic	Australia	385	41	76.7 (4.8)	Fried	5+	10+		Prefrail and polypharmacy OR = 1.6 (1.3–2.0) Frail and polypharmacy OR = 4.5 (1.9–10.5) Prefrail and hyperpolypharmacy OR = 3.3 (1.3–8.8) Frailty and hyperpolypharmacy OR = 10.3 (3.3–31.8)	Age, sex, comorbidity
Woo et al. (2015) [75]		Community-dwelling	Hong Kong	255	89.8	65+	5-item FRAIL scale	N/R	N/R		Frail and polypharmacy OR = 1.3 (1.1–1.5) Frail and hyperpolypharmacy OR = 10.3 (3.3–31.8)	Age and sex

Table 1 (continued)

First author (year)	Study name	Type of population	Country	N	% Women	Age Mean (SD)	Frailty criteria	Polypharmacy	Hyperpolypharmacy definition	Results	Odds ratios for prefrailty or frailty according to polypharmacy status	Adjustment variables
Woo et al. (2015) [76]	Beijing Longitudinal study of aging II	Community-dwelling	China	10,980	57.1	65+	Frailty Index	4+			Frail and polypharmacy in urban area OR = 3.4 (2.9–4.0) Frail and polypharmacy in rural area OR = 5.9 (3.1–11.6)	Multiple logistic regression with backward variable selection method

BMI body mass index, N/R not reported, SD standard deviation

^aUsing a drug for more than 1 indication at the same time

There was a wide variation in the proportion of frail persons who also had polypharmacy, ranging from 5 to 87%, with a pooled proportion of 59% (95% CI 42–76; $I^2 = 98.5\%$, Fig. 4a). Note that some studies used different thresholds to define polypharmacy, for example in Chang et al.'s [31] study 16% of frail persons had polypharmacy, but it was defined at the higher threshold of ≥ 8 medications. Persons with frailty had a significantly increased odds of polypharmacy, with a pooled OR = 2.62 (95% CI 1.81–3.79; $I^2 = 84.8\%$, Fig. 4b). Most studies provided ORs that had been adjusted for multiple confounders, though the variables slightly differed, but three studies [26, 30, 33] made no adjustment, therefore, the crude ORs were used in the meta-analyses.

It is noteworthy that Gutiérrez-Valencia et al. [27] used four different frailty criteria within the same population. They found a significant association between frailty and polypharmacy when Rockwood's criteria were used (OR = 1.1, 95% CI 1.0–18.33) but not when using CHS criteria (OR = 1.1; 95% CI 0.1–11.3), although in their sample CHS criteria could only be assessed completely in 44 of 110 participants, and thus the confidence intervals are wide.

Association between prefrailty and hyperpolypharmacy

Four studies provided data on the adjusted odds ratios of hyperpolypharmacy in persons with prefrailty (according to CHS criteria), and all reported a significant association. Persons with prefrailty had an almost double higher odds of hyperpolypharmacy than robust persons (pooled OR = 1.95 (95% CI 1.41–2.70; $I^2 = 27.8\%$, Fig. 5a).

Association between frailty and hyperpolypharmacy

Five studies provided multivariate odds ratios of hyperpolypharmacy in persons with frailty, and all found a significant association. In all studies, ORs were adjusted for other variables including health status and comorbidities. In persons with frailty odds of hyperpolypharmacy was increased six-fold compared to robust persons (pooled OR = 6.57; 95% CI 9.57–10.48; $I^2 = 46.5\%$, Fig. 5b).

Longitudinal risk of incidence frailty in persons with baseline polypharmacy

Seven studies reported longitudinal incidence data [24, 25, 36–38]. There was also an additional paper by Gnjjidic et al. [39] that included data from the same populations, therefore, here we report data from only one of their articles [24]. The study by Trevisan et al. [37] did not provide the exact data for non-significant results in their multivariate models and, therefore, we contacted the authors for additional information. They provided us with specific data to use in the

Table 2 Summary of longitudinal studies on the risk of incidence prefrailty and frailty according to baseline polypharmacy status in community-based samples

First author (year)	Follow-up years	Study name	Country	N	Age mean (SD)	% female	Polypharmacy definition/number of medications	Results: risk of incident frailty and prefrailty according to baseline hyper/polypharmacy status	Adjustment variables
Gnjidic et al. (2012) [24]	2	Concord Health and Ageing in Men Project (CHAMP)	Australia	1242	76.9 (5.4)	0	Polypharm: ≥ 5 Hyperpoly: ≥ 10	Polypharmacy and prefrailty OR = 1.6 (1.2–2.1) Polypharmacy and frailty OR = 2.5 (1.4–4.2) Hyperpolypharmacy and prefrailty OR = 2.5 (1.1–5.8) Hyperpolypharmacy and frailty OR = 2.5 (0.8–8.3)	Age, education, marital status, and comorbidity
Jansen et al. (2016) [36]	5	The Concord Health and Ageing in Men Project Cohort Study	Australia	1705	Median 76 (IQR = 8)	0	Number of medications	Number of medications and transition in frailty status (HR) Robust to prefrail HR = 1.0 (1.00–1.09) Prefrail to robust HR = 0.99 (0.93–1.05) Prefrail to frail HR = 1.06 (0.99–1.13) Frail to prefrail HR = 0.95 (0.85–1.06)	Age, cognitive impairment, comorbidity, education, living status
Saum et al. (2017) [25]	3	ESTHER cohort study	Germany	3058	69.6 (6.3)	52.4	Polypharm: ≥ 5 Hyperpoly: ≥ 10	Polypharmacy and prefrailty OR = 1.3 (1.1–1.7) Polypharmacy and frailty OR = 1.9 (1.2–2.8) Hyperpolypharmacy and prefrailty OR = 1.9 (1.1–3.1) Hyperpolypharmacy and frailty OR = 3.1 (1.6–6.1)	Sex, Age, BMI, education, smoking, comorbidity

Table 2 (continued)

First author (year)	Follow-up years	Study name	Country	N	Age mean (SD)	% female	Polypharmacy definition/number of medications	Results: risk of incident frailty and prefrailty according to baseline hyper/polypharmacy status	Adjustment variables
Trevisan (2016) [37]	4.4	The Progetto Veneto Anziani cohort study	Italy	2925	74.4 (7.3)	59.7	Polypharm: ≥ 3 Polypharm: ≥ 5	Polypharmacy and prefrailty OR = 1.1 (1.0–1.2) ^c Polypharmacy and frailty OR = 1.0 (0.9–1.1) Polypharmacy and prefrailty OR = 1.2 (1.1–1.4) Polypharmacy and frailty OR = 1.0 (0.9–1.4)	Age, sex, BMI, education, comorbidities, ADL, income
Veronese et al. (2017) [41] ^a	8	Osteoarthritis Initiative Study	USA	4402	60.0 (9.1)	54.3	Polypharm: 4–6 Hyperpoly: ≥ 7	Polypharmacy and frailty HR = 1.6 (1.2–2.0) Hyperpolypharmacy and frailty HR = 2.5 (1.8–3.4)	Age, sex, race, BMI, education, smoking, diet, income, physical activity, energy intake, comorbidity
Wang (2015) [38]	5	Longitudinal study of elderly Chinese veterans	China	1562	85.2	0	Number of medications	Number of medications and frailty OR = 1.1 (1.02–1.1)	Age, type of medications and co-morbidities
Zheng et al. (2016) [42] ^b		Beijing Longitudinal Study Ageing II	China	803	70.5 (7.8)	61.3	Polypharm: ≥ 4	Hyperpolypharmacy and frailty OR = 1.4, $p < 0.05$	Sex, residence, age, education, comorbidity

Unless specified, frailty was defined according to Fried's criteria

^aUsed study of osteoporotic fracture index as frailty measure

^bUsed Rockwood's cumulative deficits index as frailty measure

^cThe authors were contacted to provide additional data that was not reported in the original manuscript

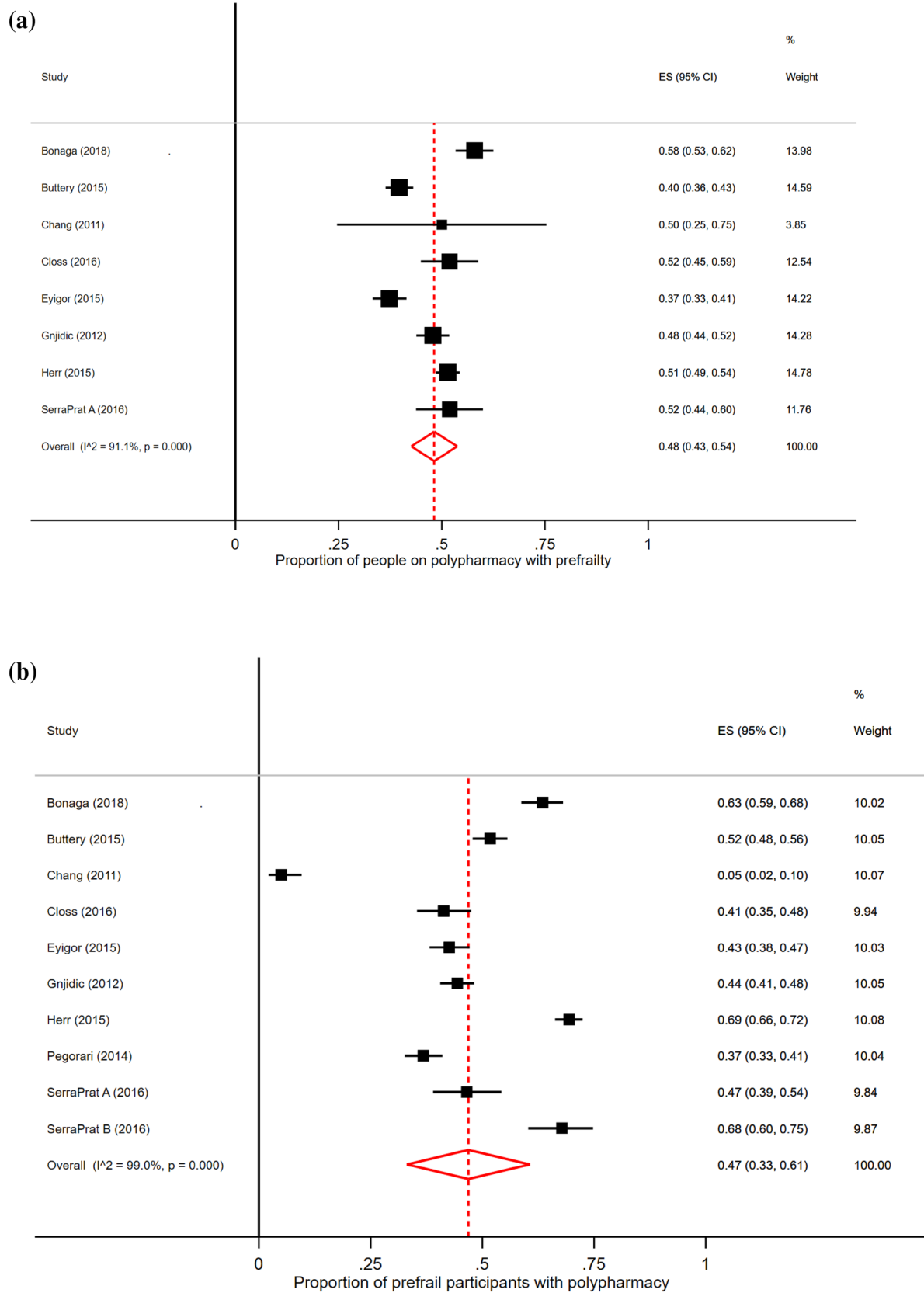


Fig. 2 **a** Proportion of people on polypharmacy who have prefrailty. **b** Proportion of prefrail persons with polypharmacy

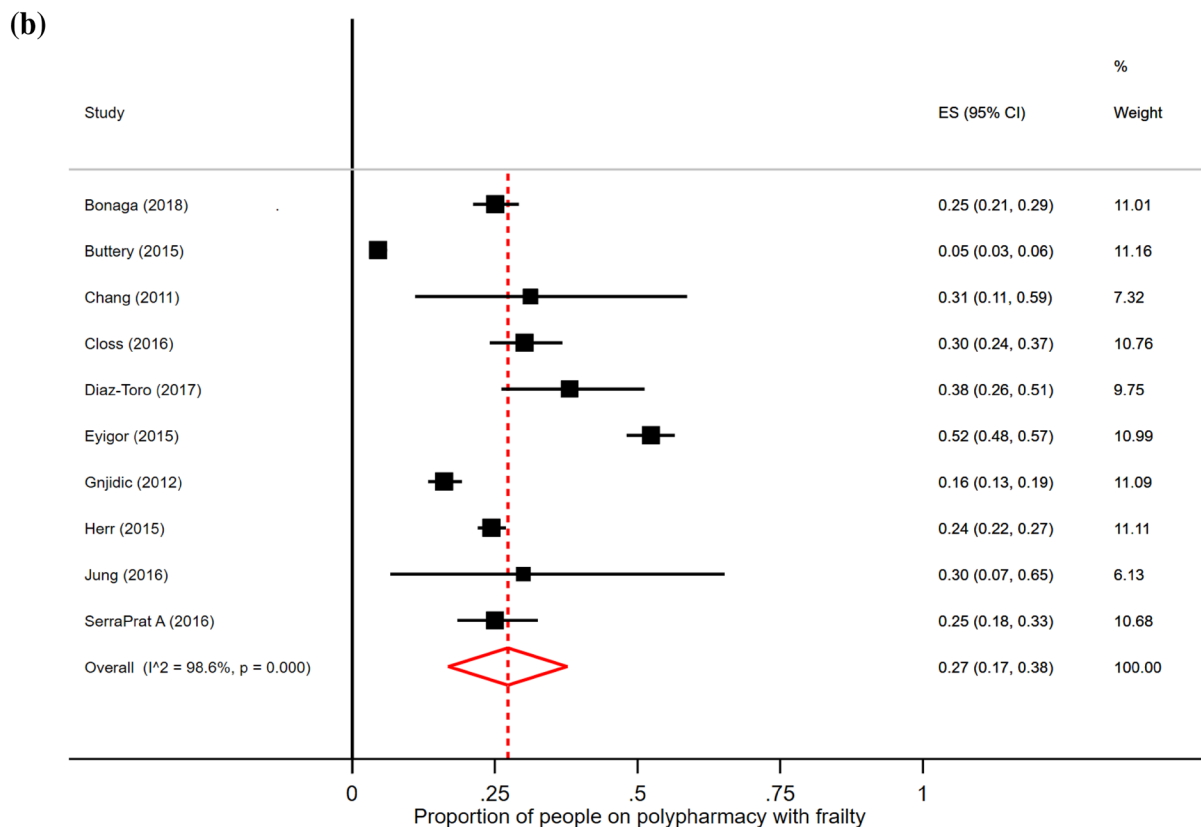
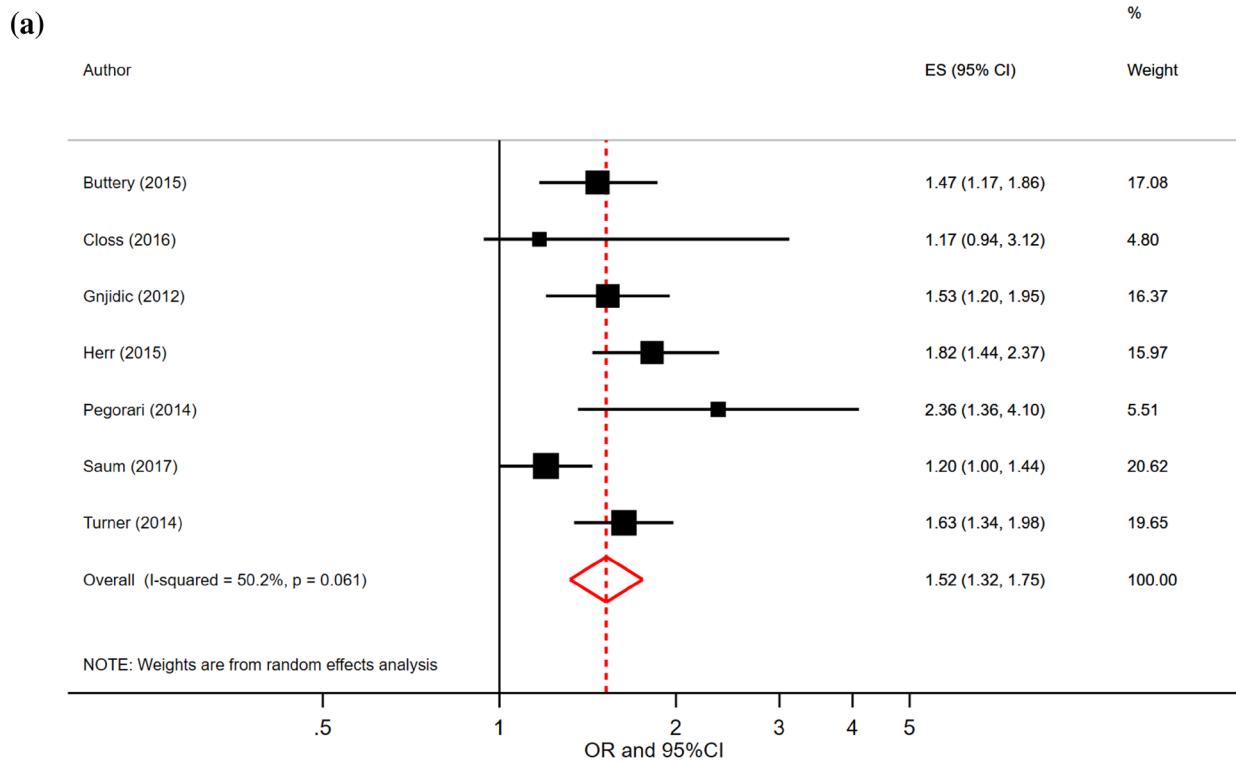


Fig. 3 **a** Pooled odds ratios (OR) of the association between prefrailty and polypharmacy. **b** Proportion of people on polypharmacy who have frailty

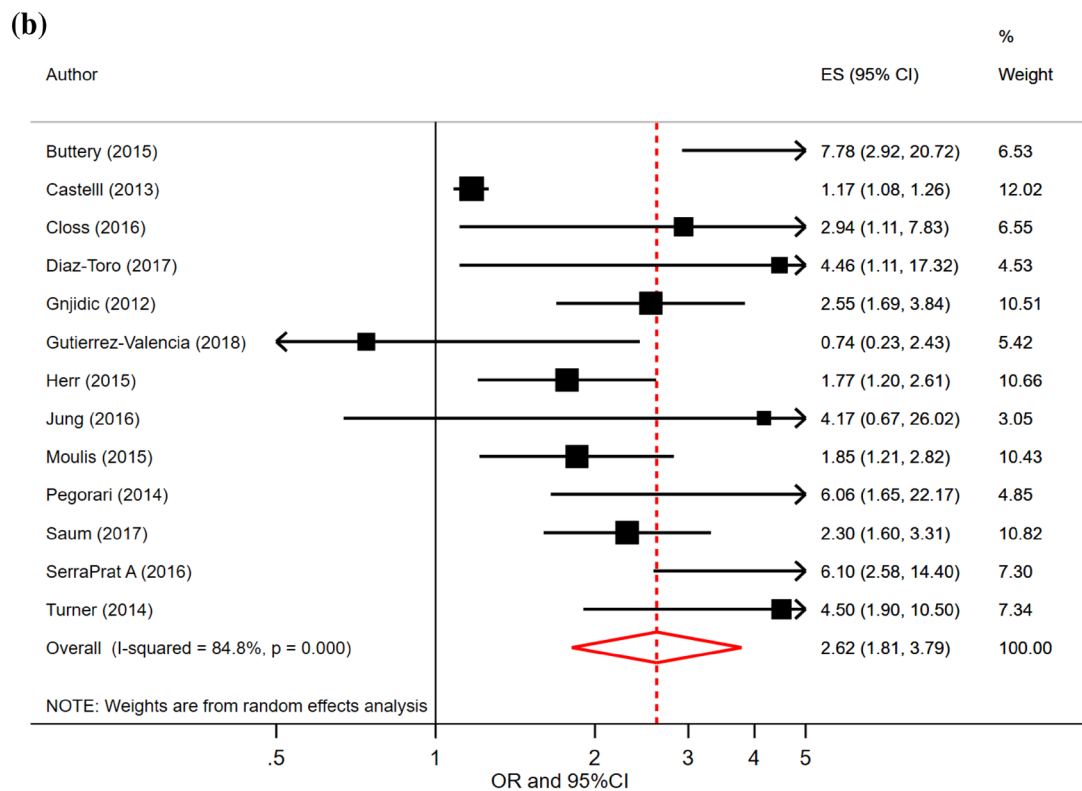
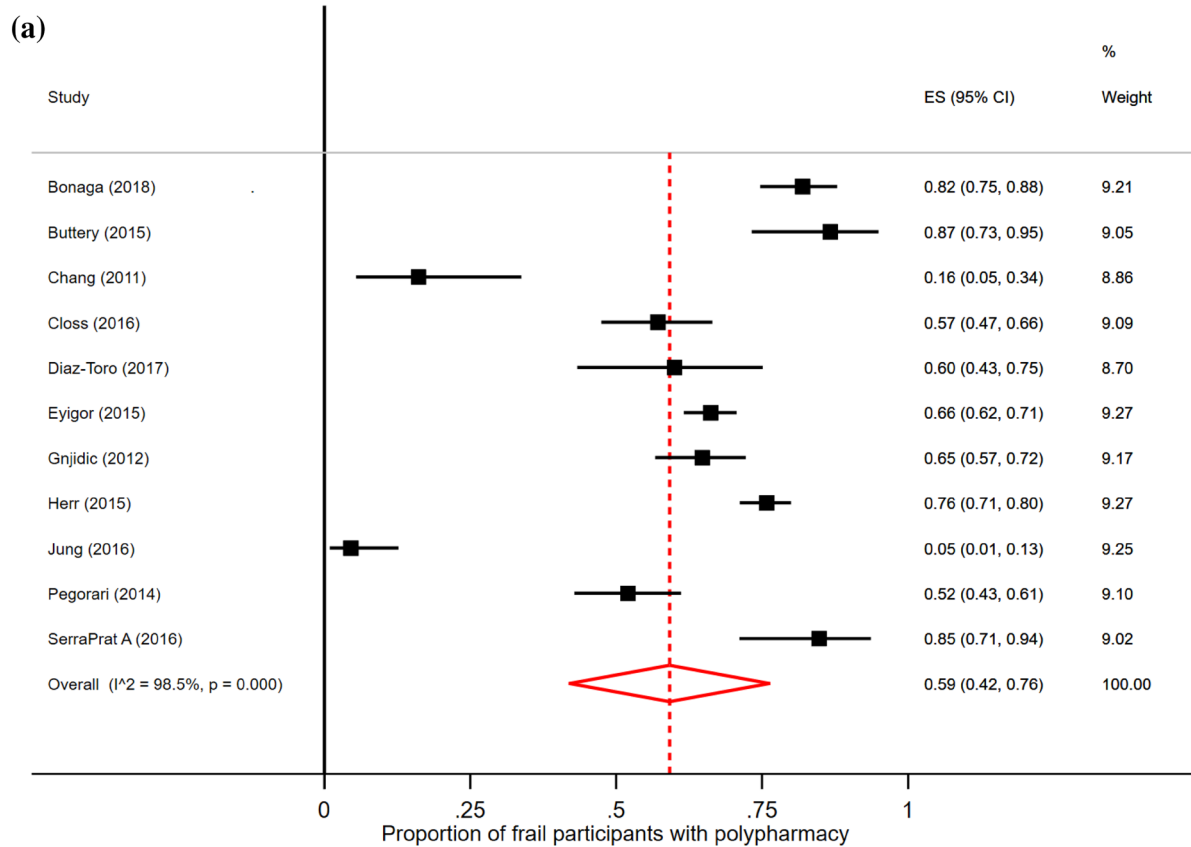


Fig. 4 **a** Proportion of frail persons with polypharmacy. **b** Pooled odds ratios (OR) of the association between frailty and polypharmacy

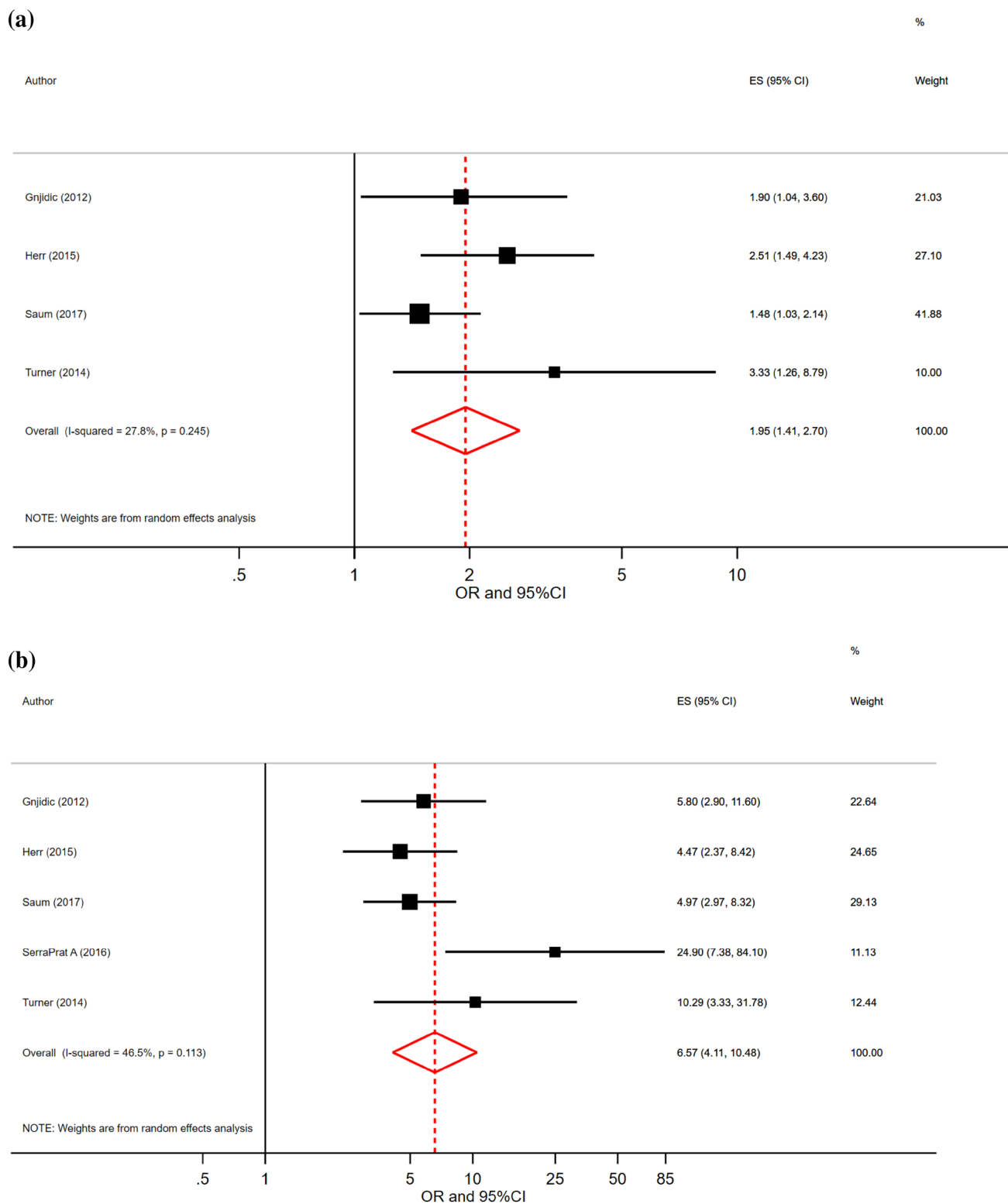


Fig. 5 **a** Pooled odds ratios (OR) of the association between prefrailty and hyperpolypharmacy. **b** Pooled odds ratios (OR) of the association between frailty and hyperpolypharmacy

meta-analysis, including a reanalysis of the data using the threshold of ≥ 5 drugs as the definition of polypharmacy, to provide comparable results to the other studies.

Several studies also reported data on baseline polypharmacy status and frailty at follow-up but not using incidence data (e.g. they included both frail and robust persons in the baseline cohort), for example, Blodget et al. [40]. These are not included here to focus on the risk of incident prefrailty and frailty only.

All studies except two [41, 42] used the CHS criteria for frailty. It is important to note that all studies adjusted their analyses for comorbidities and other factors, as shown in Table 1.

Trevisan et al [37] did not find an association between polypharmacy (defined as ≥ 5 drugs) and incident frailty in persons who were robust or prefrail at baseline (adjusted OR = 1.0; 95% CI 0.9–1.4) but they did find a significant result when removing the prefrail persons from the baseline population; robust to frail (OR = 1.5; 95% CI 1.1–2.0). Four studies reported a significant risk of future frailty as well as prefrailty in persons with baseline polypharmacy after adjustment for confounders, with increased relative risks for prefrailty ranging from 1.3 to 1.6 and frailty ranging from 1.6 to 2.5.

Saum et al [25] reported that persons with hyperpolypharmacy had an increased risk of developing both prefrailty and frailty (hazard ratios = 1.9 and 3.1, respectively) while Gnjjidic et al. [24], found a significantly increased risk for prefrailty (OR = 2.5) but not for frailty. Veronese et al. [41], found that taking 7 or more medications was associated with a 2.5 increased risk of developing frailty over 8 years.

Three studies were included in the meta-analyses [24, 25, 37] using the same frailty criteria (CHS) and the same threshold for measuring polypharmacy (≥ 5 drugs). Note that Trevisan et al. [37] provided data to us directly, which was not reported in their paper, to calculate the pooled ORs. Robust and prefrail persons at baseline did not have a significantly increased odds of incident frailty at follow-up (pooled OR = 1.59; 95% CI 0.9–2.82; $I^2 = 42.9\%$, Fig. 6b), but there was a significantly higher odds of prefrailty in robust persons with baseline polypharmacy (pooled OR = 1.30; 95% CI 1.12–1.51; $I^2 = 42.9\%$, Fig. 6a).

Longitudinal risk of incident polypharmacy in persons with baseline frailty

Although some studies, such as those by Blodget et al. [43], Woo et al. [43], and Nguyen et al. [44] reported data on baseline polypharmacy status and frailty at follow-up, they did not provide incidence data (since they included both frail and robust persons in the baseline cohort). These are not included in this review, which focuses on risk of incident prefrailty and frailty only.

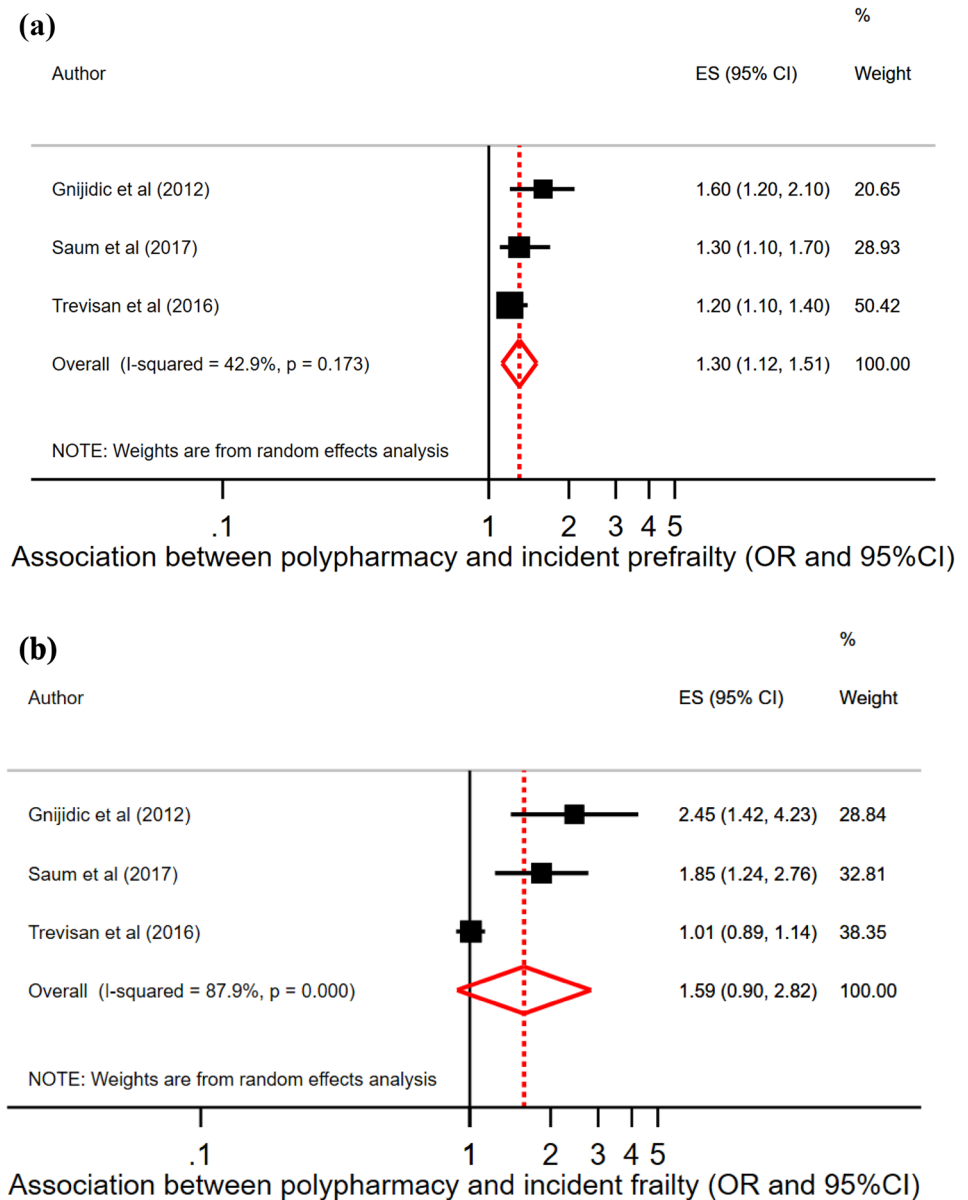
Discussion

This systematic review and meta-analysis identified a large number of studies on the topic of polypharmacy and frailty. We found a strong association between both polypharmacy and hyperpolypharmacy and frailty syndromes. Almost half of the persons with prefrailty and six out of ten of frail persons undergo polypharmacy. Further, our results indicate that three-quarters of people with polypharmacy are either prefrail or frail. There is an increased odds of polypharmacy in both prefrail and frail persons even after adjustment for multiple confounders, including comorbidities. Persons with frailty also have a sixfold higher odds of hyperpolypharmacy compared to robust ones, after taking into account comorbid medical conditions. Longitudinally, robust persons with polypharmacy have an increased odds of developing incident prefrailty than persons without polypharmacy, although longitudinal data is sparse.

The finding that 47% of prefrail persons and 59% of frail persons have polypharmacy is likely due to the high co-occurrence of chronic diseases, which trigger complex drug regimens, with frail conditions. Indeed, recent reviews have reported an increase of frailty in persons with chronic obstructive pulmonary disease [9], anaemia [10], atrial fibrillation [11], and, importantly, multimorbidity [12]. In their meta-analysis of 25 studies, Vetrano et al. [12], reported that 72% of frail persons have multimorbidity, defined as the occurrence of multiple conditions in a single individual. Not surprisingly, persons with multimorbidity are often prescribed multiple medications [45]. However, an important finding from our review is that even after adjustment is made for comorbid conditions, there is still a significant association between both prefrailty and frailty with polypharmacy, and even hyperpolypharmacy. Thus, after taking into account the potential confounding effect of chronic illness and multimorbidity, there is still a higher odds of being frail in persons with polypharmacy.

The finding that 75% of people with polypharmacy are either prefrail or frail in crude analyses support this and, thus, another possible interpretation to consider is that the use of drugs, potential side-effects, inappropriate prescribing or other mechanisms might play a role in the development of frailty, rather than (or in addition to) the underlying disease itself. Factors associated with polypharmacy are well known, including risk of falls, delirium, changes in nutritional status and malnutrition, decline in physical functioning, inappropriate prescribing and increased risk of adverse drug reactions [20, 46–48], all of which can be linked with the specific symptoms of frailty such as weight loss and/or weakness. Further, polypharmacy is often associated with a higher anticholinergic burden and

Fig. 6 **a** Pooled odds ratios (OR) of the longitudinal association between polypharmacy and incident prefrailty. **b** Pooled odds ratios (OR) of the longitudinal association between polypharmacy and incident frailty



higher inappropriate prescribing, which eventually affect physical and cognitive function, and consequently frailty [49, 50].

As there were very few longitudinal studies on the relationship between polypharmacy and frailty, it is difficult to establish any potential causal relationships. Results from the meta-analysis, which included only three studies, showed an increased odds of incident prefrailty in robust persons with polypharmacy compared to those without polypharmacy. Further, four of five longitudinal studies demonstrated an increased incidence of frailty in persons with baseline polypharmacy. However, it is plausible that there may be a relationship in the other direction; that frailty can increase the risk of polypharmacy. We did not find any true incidence studies that excluded prevalent cases of polypharmacy at

baseline, and thus could not investigate this topic. Results of the studies in this review, though small, show that such populations are available; not all persons with prefrailty or frailty had polypharmacy. Therefore, future research should focus on these persons to see if their long-term risk of polypharmacy is increased compared to robust persons.

There were several limitations to our study. First, as previously mentioned, there was an insufficient number of longitudinal studies to determine the causal direction of the associations. The meta-analysis of incident data was based on only three studies. Second, although some of the studies primarily aimed to investigate the association between frailty and medication used, most of them investigated multiple different risk factors in relation to frailty, and often the measures of polypharmacy were less thorough in those cases

(for example using self-reported questionnaires assessing multiple different risks). Studies used different measures of polypharmacy, both in terms of the definition (number of drugs) and in terms of whether it was self-reported or if medical records were examined. Polypharmacy is associated with non-compliance [51] and therefore, we cannot be certain that the measures of polypharmacy in all studies reflect actual drug consumption. Third, it was difficult to compare study results due to the wide variation of frailty indices, although almost 60% used Fried's criteria. It is known that there is a large variation in frailty definitions and diagnostic criteria [2], thus future research should focus on establishing whether the associations differ when using complex, multidimensional features (e.g. physical, social, cognitive, and psychological aspects [4]). Cumulative, deficit-oriented indices that use mainly data on certain diseases could largely differ from physical frailty indices as many diseases might be more clearly associated with medication than functional parameters. It is also worth noting that some frailty instrument uses drug use and polypharmacy as part of their criteria, including, for example, the Edmonton frailty scale, the Frailty Index, and the Groningen index. However, all the studies included in the meta-analysis used Fried's definition of frailty, which does not include drug use in the criteria. Another limitation is that some studies did not include a separate prefrailty category, with those persons consequently often falling into the "robust" category. This might have led to an underestimation of the association between polypharmacy and frailty. There were also some differences in the categorization of polypharmacy in the eleven studies that also investigated hyperpolypharmacy. Usually, the polypharmacy definition differed from those in other studies, because it excluded persons with hyperpolypharmacy; for example, persons would be classified with polypharmacy if they used 5–9 drugs (e.g. excluding those taking ten or more medications). Again, this likely might have led to an underestimation of the association between frailty and polypharmacy. Finally, we could not find any studies that identified persons free from polypharmacy at baseline to assess the risk of incident polypharmacy associated with baseline frailty status. This may be due to the fact that samples of frail persons without polypharmacy might be low, as our cross-sectional data suggest.

Despite these limitations, there are several strengths of our study. PRISMA recommendations were followed and we performed an extensive literature search with three medical databases. As the EuGMS includes members from throughout Europe, we did not include only papers written in English, but were also able to extract data from papers in other European languages. All abstract screening and data extraction was conducted independently by teams of two researchers. Although different frailty scales were used, most studies used a thorough evaluation of frailty according to standard

criteria. A major strength of our review is that we included only studies with a specific measurement of frailty according to standardized criteria, although there are numerous articles on frailty that have frail populations without using a standardized frailty definition (such as nursing home patients). Finally, our review addresses the topic from a wide angle, including both prefrailty and frailty, and including hyperpolypharmacy in addition to polypharmacy.

Our review highlights several important avenues for future research. Longitudinal incidence data are needed, particularly on how frailty may increase the risk of incident polypharmacy, although it might be difficult to find large samples of patients with frailty who are not already taking multiple medications at baseline. Further, due to the potential association of comorbidity on the association, it would be interesting to stratify populations according to the presence of comorbidities at baseline to see whether the risk of frailty in persons with polypharmacy differs in persons with or without multimorbidity. It would also be interesting to see how results change when directly comparing different frailty definitions within the same population such as the study by Gutiérrez-Valencia et al. [27]. During our abstract search we also identified a number of studies investigating inappropriate drug prescribing in persons with frailty. However, the tools used to measure inappropriate drug use differed considerably, and papers focused on different drug types. Consequently, there were not enough studies to warrant a meta-analysis. However, one of the most important topics for future research is to establish the risk of potentially inappropriate or clinically irrelevant drug prescribing in persons with frailty and the associated consequences such as adverse drug reactions, drug–drug-interactions, and prescribing cascades. The results of our review highlighted a sixfold higher odds of hyperpolypharmacy in persons with frailty even after adjustment for comorbidities, and this warrants further investigation to establish the causes and long-term effects of such high medication use.

Our results provide relevant insights for clinicians, and those working in geriatric research. Clinically, there are many negative consequences of polypharmacy, especially inappropriate medication use, and the strong link between frailty and polypharmacy suggests that any clinical evaluation of geriatric patients should include screening for frailty, as well a structured medication review that comprehensively evaluates prescribing and its appropriateness and clinical relevance. It is possible that the pharmacological burden might be reduced in persons with frailty and, therefore, drug treatment should consider different factors [52]. Frailty needs to be taken into account when treating chronic diseases [52] in older individuals; patients with both polypharmacy and frailty have longer hospital stays, and higher risk of hospital readmission [53]. Further, certain drugs or other non-pharmacological treatments may have different efficacy in

frail compared to non-frail patients [54] [55]. In this context, the impact of a structured medication review including an explicit screening tool aimed at medication optimization such as START/STOPP or FORTA [56, 57] on prefrailty and frailty should be clinically tested. Physicians need to rely on evidence to help them decide treatment strategies that avoid the risk of negative outcomes, which is difficult as current clinical trials often exclude frail, older individuals, or when included they are often more likely to drop out, leading to an urgent need for well-conducted randomized control trials that study more realistic outcomes of drug treatments for chronic diseases, including frailty-related factors [21].

In conclusion, our systematic review and meta-analysis highlights that polypharmacy is common in prefrail and frail persons, and that these individuals are also more likely to be on extreme drug regimens, i.e. hyperpolypharmacy, than robust older persons. More research is needed to investigate the causal relationship between polypharmacy and frailty syndromes, thereby identifying ways to jointly reduce drug burden and frailty in these individuals.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this kind of study formal consent is not required.

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