The relationship between Frailty and Polypharmacy in older people: a Systematic Review

Frailty and Polypharmacy: a Systematic review

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Declaration of interest

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ABSTRACT

Aim: Frailty is a complex geriatric syndrome resulting in decreased physiological reserves. Frailty and polypharmacy are common in older adults and the focus of extensive studies, although little is known about the impact they may have on each other. This is the first systematic review analyzing the available evidence on the relationship between frailty and polypharmacy in older adults.

Methods: Systematic review of quantitative studies. A comprehensive literature search for publications in English or Spanish was performed on MEDLINE, CINAHL, the Cochrane Database and PsycINFO in September 2017 without applying restrictions on the date of publication. Studies reporting any relationship between frailty and polypharmacy in older adults were considered.

Results: A total of 25 publications were included, all of them observational studies. Evaluation of Fried´s frailty criteria was the most common approach, followed by the Edmonton Frail Scale and FRAIL scale. 16 of 18 cross-sectional analyses and 5 of 7 longitudinal analyses demonstrated a significant association between an increased number of medications and frailty. The causal relation is unclear and appears to be bidirectional. Our analysis of published data suggests that polypharmacy could be a major contributor to the development of frailty.

Conclusions: A reduction of polypharmacy could be a cautious strategy to prevent and manage frailty. Further research is needed to confirm the possible benefits of reducing polypharmacy in the development, reversion or delay of frailty.

KEYWORDS

frailty, older adults, polypharmacy, systematic review

1. INTRODUCTION

Frailty is a complex geriatric syndrome resulting in decreased physiological reserves. Over the last few years, it has attracted increasing interest due to its direct relationship with adverse health effects such as physical and functional decline and increased mortality[1, 2]. There are different approaches to define and measure frailty, but all of them aim to identify or quantify vulnerability in older adults. There are two main established methods for the evaluation of frailty. i) Fried's criteria[1], which define a clinical syndrome or phenotype, including weight loss, exhaustion, weak grip strength, slow walking speed and low physical activity; ii) The Frailty Index, first developed by Rockwood et al.[3], counts accumulated deficits of measures such as symptoms, signs, diseases and disabilities with the hypothesis that the more deficits a person has, the more likely that person is to be frail. This method considers frailty as a multidimensional risk state, and measures it by the quantity rather than by the nature of health problems. Sometimes a prefrail category is considered as a third intermediate clinical stage between robust and frail individuals[1].

Similarly, polypharmacy or the use of multiple medications has also been categorized as a geriatric syndrome and it is frequently present in older adults[4]. Polypharmacy is a major issue of concern for its association with adverse health outcomes, including falls, functional impairment, adverse drug reactions, increased length of hospital stay, readmissions and mortality[5-7]. Multiple factors positively associated with polypharmacy like drug-drug interactions, drug-disease interactions or potentially inappropriate prescriptions may be involved in these adverse outcomes[8]. Thus, polypharmacy is considered an important and increasing challenge in clinical practice.

Frailty and polypharmacy are common and widely studied entities in geriatric patients, although little is known about the impact they may have on each other[9]. It is possible to imagine a network of connections through which drugs and frailty might interact, including

physiological changes, multiple pathologies and chronic diseases, life expectancy, or functional or cognitive status. Frailty may influence a number of factors, including drugs pharmacokinetics and pharmacodynamics, toxicity, and their therapeutic efficacy. In turn, these factors may be involved in the development of frailty or in ways to prevent it. In the past few years, an increasing number of studies have tried to resolve and measure the relationship between frailty and polypharmacy and its underlying mechanisms.

Here, we aim to analyze the available research evidence on the relationship between frailty and polypharmacy in older adults.

2. MATERIALS AND METHODS

2.1 Search strategy

The study was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[10] (see supplementary material) and the method used was based on the minimum criteria established by the Cochrane Back Review Group (CBRG)[11].

A scientific literature search was conducted in September 2017 to identify all relevant studies published in English or Spanish without applying date restrictions. Queries of the literature were performed using the electronic databases PubMed (MEDLINE), CINAHL (Cumulative Index to Nursing and Allied Health Literature), the Cochrane Library (DARE, HTA, EED, CDSR, CENTRAL), and PsycINFO.

The literature search was designed with Medical Subject Headings (MeSH) terms for MEDLINE and adapted to the other databases according to their descriptors or by using keywords. A combination of the following search terms was used: ("frail elderly" or frail*) AND ("drug prescriptions" OR "drug therapy" OR "polypharmacy" OR "prescription drugs"). Also, the reference lists were examined to detect studies potentially eligible for inclusion.

2.2 Selection criteria

Original quantitative studies, regardless of their design, examining any relation between frailty and polypharmacy in older adults were included. Frailty had to be defined with a validated measurement tool, or a non-validated but available and well described one. Case reports, case series, single-case studies, conference proceedings, letters to the editor, dissertations, review articles or systematic reviews and meta-analyses were excluded. Authors were contacted to provide missing data when necessary.

The exclusion criteria were as follows:

- Studies with participants with mean age below 65 years.

- Studies focused exclusively on cancer, due to the unique features of the patients and the treatments used.

2.3 Data extraction

Two of our coauthors (MGV & NMV) independently screened the titles and abstracts of potentially eligible studies identified by the search strategy. If necessary, a third researcher (ACH) was consulted. Next, they examined the potentially eligible articles after a first evaluation of the whole text and selected those that met the inclusion standards for this review. The reviewers extracted relevant data from the selected articles, including study design, setting, number and characteristics of study participants, analyzed measurements, and outcomes. Outcome measures extracted from included studies are detailed in Table 1.

2.4 Quality of the studies

Two researchers assessed the quality of the studies and any differences were resolved by consensus. For longitudinal observational studies, the Newcastle-Ottawa Scale (NOS)[12] was used, and for cross-sectional studies a modified NOS (see Supplementary data) was used, as described in previous studies[13, 14]. The NOS assigns up to a maximum of nine points and the adapted NOS up to a maximum of 10, based on three quality parameters: selection, comparability, and outcome.

2.5 Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [15], and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 [16].

RESULTS

3.1 Search results

The search identified 1236 non-duplicated references, with 87 classified as potentially relevant after checking the titles and abstracts. After the screening of the full texts, 62 articles were excluded because they did not meet the inclusion criteria. Therefore, 25 publications were ultimately selected and included in the review[17-41] (Figure 1).

3.2 Quality (risk of bias)

All 25 publications included in the study were considered of acceptable quality. Studies assessed through NOS had a median score of 7.5 out of 9 (range: 6-8). Studies assessed through adapted NOS for cross-sectional studies had a median score of 8 out of 10 (range: 6-9).The quality assessment of the included studies is shown in Figure 2.

3.3 Characteristics of studies and participants

All studies were published from 2009 until 2017 and only five were published more than five years ago. All the studies were observational; 11 were cross-sectional studies and 14 were prospective cohort studies. However, in some of them, outcomes of interest for this review were obtained from cross-sectional analyses of baseline data [18, 19, 22, 28, 33, 34]. Different measurements or definitions of frailty were used: Fried´s criteria with various adjustments were the most used tool (in 14 studies), followed by the Edmonton Frail Scale (in four studies), the FRAIL scale (in three studies), the Frailty Index (in two studies) (FI, the Frailty index, based on Rockwood's cumulative deficits), and the Portuguese version of the Tilburg Frailty Indicator and the Groningen Frailty Indicator (in one study). Frailty cut-off scores varied depending on the method used for measurement. In some of the studies two groups of patients were defined (frail and robust/non-frail) and other studies included a third group, consisting of pre-frail subjects. Definitions of polypharmacy varied between studies, from more than three to more than six medications, but the most repeated definition is the use of five or more drugs. Some studies also defined a third category among polypharmacy

groups, when ten or more drugs were consumed: hyperpolypharmacy[24, 34-36] or excessive polypharmacy[26, 27, 38].

Sample size ranged between 31 participants in Hilmer et al.[28] and 10,039 in Zheng et al.[41]. Most studies (n: 13) included patients aged 65 years or older and the cut-off age ranged from 50[35] to 80 years[38]. Based on previous data, the mean age varied noticeably between 69.6 years in Saum et al.[35] and 85.2 in Wang et al.[38]. The prevalence of frailty ranged between 6.2%[31] and 76%[25]. Regarding study setting, 13 studies included community-dwelling individuals, five studies included hospitalized patients in acute units and the rest included outpatients, care home residents or mixed populations. Participants had to meet specified inclusion criteria in some of the studies, like the use of statins [36] or disability[22]; or exclusion criteria, including shorter life expectancy[38, 39], severe cognitive[21, 33] or functional[36] impairment, or the presence of cancer or other advanced diseases[33].

3.4 Objectives and measurements analyzed

The objectives and variables of the studies included in this review were heterogeneous. Most of the studies provide outcomes of interest in a circumstantial way when describing their participant characteristics, and only some studies were aimed at analysing the possible association or interaction between frailty and polypharmacy or the number of medications used[21, 23, 24, 26, 27, 29, 35, 37-39, 41]. The included studies present a wide range of outcome measures of interest. The most important ones are shown in Table 1.

3.4.1 Frailty and polypharmacy/number of drugs

Eighteen cross-sectional analyses assessed the link between polypharmacy and frailty status in various populations, and sixteen of them demonstrated a significant association. From seven longitudinal analyses, five demonstrated significant associations. Table 2 summarizes the most relevant characteristics and outcomes extracted from included studies. Most of the

results come from cross-sectional studies. Several studies show that the mean drug consumption by frail patients is higher than that of robust ones[17, 18, 26, 28, 30, 36, 40], although in Perera et al.[33] the difference was not statistically significant for a group of hospitalized patients aged ≥ 70 years with atrial fibrillation. Gnjidic et al. (2012a) established that the optimal discriminating number of concomitant medications associated with the presence of frailty was 6.5[23]. Other studies revealed that the prevalence of frailty was higher among patients with polypharmacy or hyperpolypharmacy (≥10 drugs)[20, 24, 35]. This was not the case in the study by Wang et al.[38] in which an inverse relation was determined with a sample of 1592 men aged ≥ 80 years. Another study by Gnjidic et al. (2012b) also showed a greater prevalence of prefrailty in increasing polypharmacy groups[24].

Furthermore, several studies show the likelihood of being frail increasing with every medication added to the treatment (OR between 1.13 and 1.20)[20, 23, 26], with polypharmacy (OR between 1.77 and 2.55)[24, 26, 32, 35], and with hyperpolypharmacy (OR between 4.47 and 5.8)[24, 26, 35]. Some of these studies report the same results when the status of prefrailty was examined[26, 35], although the relationship was not always linear when the three groups (robust, prefrail, frail) were considered[26]. In another study by Coelho et al.[21], the association was found only with the physical frailty domain, and no with psychological and social domains. Additionally, the relation between frailty and the use of a larger number of drugs was not significant in analyses with more complex multivariate regression models including the type of medication used. Herr et al. show that polypharmacy was associated with the number of frailty criteria in models adjusted for socio-demographic and health characteristics in a French representative study with people aged 65 years or older[27]. Poudel et al. and Hasan et al. [25, 34] identified an increase in the mean frailty index and Groningen Frailty Indicator associated to polypharmacy category:

(hyperpolypharmacy>) polypharmacy>no polypharmacy. Similarly, Crentsil et al. [22] reported a higher probability of consuming more medications in association with frailty (OR 1.10). Bonaga et al. and Merchant et al. [19, 31] showed that the prevalence of polypharmacy was higher in frail patients. Furthermore, Thai et al. [36] show the same trend with polypharmacy and hyperpolypharmacy, but without statistically significant differences.

Regarding longitudinal studies, Woo et al. (2014) [39] did not find statistically significant differences in the incidence of polypharmacy (≥ 4) after four years according to baseline frailty. Other studies with a prospective design showed a higher incidence of frailty or probability of becoming frail when a larger number of drugs was taken[38] or with the presence of polypharmacy/hyperpolypharmacy[24, 35, 41]. However, Jamsen et al. [29] did not find a relationship between the use of a larger number of drugs and transitions to prefrailty or frailty state after a five-year follow-up period. Trevisan et al. [37], found an association between transitions to prefrailty or frailty and the use of > 3 drugs with a univariate analysis, but not with a multivariate analysis after a four-year follow-up.

4. DISCUSSION

Here, we aim to summarize the evidence available to date on the relationship between frailty and polypharmacy in older adults. To the best of our knowledge, this is the first systematic review evaluating this relevant health issue. Frailty is a recent concept that is increasingly attracting interest, as evidenced by the contemporaneity of most of the publications evaluated.

Many different outcome measures regarding the interaction between frailty and polypharmacy have been examined, yielding a large amount of information. However, the observational design of the studies did not allow for the analysis of high-quality evidence. Nevertheless, the association between frailty and polypharmacy in older people seems clear, despite the various study designs, measurements, or patient groups evaluated.

The first difficulty encountered when analyzing the ensemble of selected studies was the lack of homogeneity in the definition and quantification of frailty. The different scales used and their underlying concepts lead to a wide variability in the calculation of prevalence and incidence of frailty, prefrailty and of all outcomes associated with these syndromes[42]. Additionally, different study settings, age ranges and pathologies of the participants, or differences in inclusion or exclusion criteria may influence the results and conclusions of every study.

The association between frailty and polypharmacy seems so evident that even some scales or tools to measure frailty, including the Edmonton Frail Scale, the Groningen Frailty Indicator or some versions of Frailty Index include the consumption of drugs. To properly examine the relationship between polypharmacy and frailty, the number of medications used should have been excluded for assessing frailty status, as done in the study by Poudel et al.[34].

Although polypharmacy is a widespread concept, there is not a single and clear definition for it[43]. Different definitions of polypharmacy of included studies (from > 3 to ≥ 6)[32, 37] may lead to confusion and difficulty when comparing results and drawing general conclusions. A low threshold for defining polypharmacy could explain the difficulty to demonstrate a significant association between polypharmacy and frailty. For example Trevisan et al. [37] did not find an association between transitions to prefrailty or frailty and the use of > 3 drugs with a multivariate analysis. This could be a consequence of selecting the low threshold of 3 drugs. In a sample of community-dwelling men aged ≥ 70 years in Australia, Gnjidic et al. [23] defined a cut-off score of 6.5 drugs as the best discriminatory number for frailty. Moulis et al. [44] presented a similar analysis with men and women aged ≥ 65 years in France, reporting a cut-off score of ≥ 6 drugs. It may be interesting to assume this threshold to standardize the definition of polypharmacy in future studies about the relationship of polypharmacy and frailty, or to use the mean number of drugs instead of a cut-off.

Another possible limitation of our analysis of published data is the fact that most of the studies were not designed to determine the association between frailty and polypharmacy (it was not the primary outcome). Thus, the sample size of some of the studies may not provide enough power to find significant associations. From the four publications that did not find any association between frailty and polypharmacy[29, 33, 36, 39], two of them did not describe it among their objectives, and had small sample sizes (180 and 220)[33, 36]. Jamsen et al. and Woo et al. [29, 39] had the association between frailty and polypharmacy as a primary outcome, and have large sample sizes (1705 and 4000 participants). It should be noted that results from Jamsen et al., Gnjidic et al 2012(a) and Gnjidic et al 2012(b) come from the same pool of participants, and that Bennett et al., Hilmer et al., Perera et al. and Thai

et al. all use small inpatient cohorts from the same hospital. Repeated analyses within the same or similar populations do not provide additional evidence.

Despite the obvious association, it is difficult to establish causality and determine what occurs first: frailty or polypharmacy. Longitudinal studies measuring the impact of polypharmacy in the incidence of frailty could be important in this regard. Several studies reported a higher probability of becoming frail over time in patients with polypharmacy[24, 35, 41], although in another study this association was not maintained following a multivariate analysis[37]. A recent study by Veronese et al. [45], that has not been selected for this review because it included younger individuals, showed after a 8-year follow-up of 4402 participants at baseline, that use of 4-6 medications had a higher risk of developing frailty. Those using more than seven drugs were at even higher risk. Wang et al. [38] concluded that the risk of developing frailty increases with the number of medications taken, although Jamsen et al. did not achieve conclusive results in a similar analysis after a five-year follow-up period [29] . Of note, all these studies used adjusted models including comorbidity as a covariate (comorbidity indexes or presence or number of different chronic diseases). Thus, comorbidities may not be the only cause of increased risk of frailty associated to polypharmacy. Conversely, Woo et al. assessed the incidence of polypharmacy over time according to frailty status but no clear association was identified [39]. The relationship between frailty and polypharmacy has also been addressed in animal models. Huizer-Pajkos et al. [46] performed an interventional mouse study of short-term polypharmacy that showed a non-significant trend towards increased frailty index after 2-4 weeks of administering polypharmacy in the diet.

The association of frailty and polypharmacy may be complex and bidirectional. On the one hand, frailty is linked to certain chronic diseases and multimorbidity[47], which can consequently lead to polypharmacy. On the other hand, there are plausible mechanisms by

which drugs may affect the development of frailty. As indicated by Gnjidic and Hilmer[48], several elements that may be considered clinical components or characteristics of frailty have been directly linked with the number of drugs taken, including weight loss, balance disorders, poor nutritional status, or functional deterioration[49, 50]. The available evidence so far does not allow to confirm which of these elements are involved in the pathogenesis of frailty associated with polypharmacy. However, polypharmacy may be recognized as a major contributor to the development of frailty. Thus, reducing polypharmacy in older adults has been suggested as a recommended measure for both prevention and management of frailty[51]. Further studies should be carried out in the future to confirm the possible benefits of reducing polypharmacy in the development, reversion or delay of frailty.

Furthermore, the consumption of a greater number of drugs is associated with an increase in other negative medication-related variables like drug-drug interactions, potentially inappropriate prescribing, anticholinergic burden of treatments or adverse drug reactions[52-54]. This may explain why some studies have found a higher proportion of these factors in frail older people, and suggest other possible mechanisms by which polypharmacy interferes with frailty[18, 24, 29, 32, 36, 55, 56].

In addition to the reciprocal impact that frailty and polypharmacy may have on each other, some studies suggest that they can act as modulators for their negative effect in health outcomes, so their interaction could determine the frequency of some health related adverse events. Bonaga et al. [19] showed that polypharmacy was associated with an increased risk of adverse events (disability, hospitalization, emergency department visits and mortality) in prefrail and frail older adults, but not in non-frail individuals. Herr et al. showed that excessive polypharmacy and frailty are independent risk factors for mortality, but the combination of both multiplied by 6.30 the risk of dying during a 2.6 year-follow-up period[26].

It is also worth noting that the relationship between frailty and medications is a very complex issue. There seems to be a stronger association between frailty and changes in pharmacokinetic responses, specially metabolism and excretion, than with chronological age[17, 28]. This could also contribute to a higher risk of adverse drug reactions and toxicity in frail older people. Older people seem to have an increased sensitivity to certain drugs, but the evidence of the possible influence of frailty on pharmacodynamics and efficacy is scarce[18, 57, 58], although plausible due to physiological changes[59]. Moreover, as a predictor of clinical outcomes and limited life expectancy, frailty may modify the goals of health care and its priorities, and influence decision-making regarding the use of medicines[21, 56]. These issues have been addressed more in depth in other publications[59, 60].

Finally, our study has some potential limitations. Despite the comprehensive search strategy, the heterogeneity of terms and definitions of frailty and polypharmacy may have affected the sensitivity of the search because some plausible data of interest could not be the primary outcome of the studies. Different studies comparing frail and non-frail participants including polypharmacy in the baseline characteristics may have been missed. However, the selection bias should not affect most relevant studies evaluating the relationship between frailty and polypharmacy as a primary outcome.

5. CONCLUSIONS

Results from this review suggest that polypharmacy is associated with frailty in older people, although the causal relation is unclear and, in fact, appears to be bidirectional. The lack of standardized definitions for frailty and polypharmacy hinders research in this area and leads to a wide range of outcomes. There is still scarce evidence of the mechanisms involved, and it is difficult to form conclusions on clinical practice based on the observational studies

available at the moment. However, polypharmacy may be recognized as a major contributor to the development of frailty. It seems clear that frailty is an important issue that must be taken into account for decision-making in drug prescribing to older patients, and that polypharmacy should be assessed with special caution in frail older adults. Therefore, it has been suggested that a reduction of polypharmacy could be a strategy to prevent and manage frailty. Further research is needed to confirm the possible benefits of reducing polypharmacy in the development, reversion or delay of frailty.

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Table 1. List of outcome measures extracted from included studies

Outcomes of interest	Measures/Units	Studies
Correlation between number of medications/polypharmacy groups and level of frailty	Regression coefficient (b) Semi-partial correlation coefficient (r) OR IRR	Coelho et al., Crentsil et al., Hasan et al., Herr et al. 2017
Average number of medications according to frailty status	Number of medications	Ballew et al., Bennett et al., Herr et al. 2015, Hilmer et al., Jung et al., Perera et al., Thai et al., Woo et al. 2015
Average frailty score according to polypharmacy group	frailty score	Hasan et al., Poudel et al.
Prevalence of polypharmacy according frailty status	% participants OR	Bonaga et al., Merchant et al., Thai et al.
Prevalence of frailty according to polypharmacy group/number of drugs	% participants OR	Castell et al., Gnjidic et al.(a), Gnjidic et al.(b), Herr et al. 2015, Moulis et al., Saum et al., Wang et al.
Incidence of polypharmacy according to frailty status	% participants OR	Woo et al. 2014
Incidence of frailty according to polypharmacy group/ number of drugs	% participants OR	Gnjidic et al.(a), Saum et al., Wang et al., Zheng et al.
Transitions between frailty states according to polypharmacy group/ number of drugs	HR OR	Jamsen et al., Trevisan et al.

HR: hazard ratio; IRR: incidence rate ratio; OR: odds ratio

Table 2. Characteristics and main outcomes of included studies

Authors, year	Design of the study	Country/ setting	Characteristics of the participants	Definition of frailty	Measurements	Outcomes
Ballew et al., 2017	Cross-sectional study	USA. Community-dwelling	4987 >65 years NF 75.4 ± 5.1 F 78.0 ± 5.6	Fried ≥ 3: frail	Average number of drugs according to frailty status	Non-frail 8.8 ± 4.6 vs frail 10.5 ± 5.0
Bennett et al., 2014	Cohort study, cross-sectional analysis of baseline data for outcomes of interest	Australia. Hospitalized	204 ≥ 60 years. 80.5 ± 8.3 years 65% female	Reported Edmonton Frail Scale ≥ 8: frail	Average number of drugs according to frailty status	At admission (non-frail 4.4 ± 3.3 vs frail 9.8 ± 4.3) At discharge (NF 4.9 ± 3.3 vs F 10.3 ± 4.2) ($p < 0.0001$)
Bonaga et al., 2017	Cohort study, cross-sectional analysis of baseline data for outcomes of interest	Spain. Population based	773≥ 70 years 78.5±5.8 years 59.1% female	Fried 0: non-frail 1-2: prefrail ≥ 3: frail	Prevalence of polypharmacy (≥ 5 drugs) according to frailty status	Non-frail 40.2% vs prefrail 63.5% vs frail 81.9%
Castell et al., 2013	Cross-sectional study	Spain. Urban population in primary care	1 327 ≥ 65 years 75.4 ± 7.4 years 53.4% female	Fried ≥ 3: frail	-Prevalence of frailty according polypharmacy groups (≥ 5 drugs) -OR for frailty according to increasing number of drugs (higher for each additional drug)	With polypharmacy: 14.9%; without polypharmacy: 4.9%; $p < 0.001$ OR:1.17 (95% CI 1.08-1.26)
Coelho et al., 2015	Cross-sectional study	Portugal. Community-dwelling	252 ≥ 65 years 79.2 ±7.3 years 75.8% female	Tilburg Frailty Indicator (TFI) Portuguese version. (0-15)	Association between number of drugs and frailty by a hierarchical multiple regression analysis	Regression coefficient: 0.20 (p<0.001) (95% CI 0.08-0.3) Semi-partial correlation coefficient: 0.16 Higher number of drugs is associated to greater levels of frailty (not maintained when drug type is introduced in the regression model)
Crentsil et al., 2010	Cohort study, cross-sectional analysis of baseline data	USA. Community-dwelling	1 002 disabled women ≥ 65 years 78.3 ±8.1 years	Fried ≥ 3: frail <3: non-frail	OR for the use of a larger number of drugs according to the presence of frailty	OR:1.10 (95% CI 1.01-1.20)
Gnjidic et al.,	Cohort study	Australia.	1 705 men ≥ 70 years	Fried	-Cut-off drug score for presence	Cut-off score: 6.5 drugs

2012a		Community-dwelling	76.9 ±5.5 years	0: non-frail 1-2: prefrail ≥ 3: frail	of frailty: -OR for frailty according increasing number of drugs (higher for each additional drug)	OR 1.13 (95% CI 1.06-1.21) (p = 0.0002)
Gnjidic et al., 2012b	Cohort study	Australia. Community-dwelling	1 662 men ≥ 70 years 76.9 ±5.4 years	Fried 0: non-frail 1-2: prefrail ≥ 3: frail	-Prevalence of prefrailty and frailty according to polypharmacy group -OR for frailty according to polypharmacy group -Incidence of frailty at two years: OR for frailty according to polypharmacy group	Robust/prefrail/frail (%) (p < 0.0001) Polypharmacy (≥ 5) 27.2/44.4/64.7 Hyperpolypharmacy (≥ 10) 1.9/5.3/17.3 Polypharmacy OR 2.55 (95% CI 1.69-3.84) Hyperpolypharmacy OR 5.80 (95% CI 2.90-11.61) Polypharmacy OR 2.45 (95% CI 1.42-4.23) Hyperpolypharmacy OR 2.5 (95% CI 0.76-8.26)
Hasan et al., 2017	Cross-sectional study	Malaysia. Care home residents	202 ≥ 65 years 76.8±7.8 years 62% female	Groningen Frailty Indicator (GFI) ≥ 4: frail	-Average GFI score according to polypharmacy group -Relationship between GFI and number of medications used per participant	With polypharmacy: 7.2±3.4 / Without polypharmacy: 5.7±3.6 (p=0.002) Significantly and positively correlated (r=0.21, p=.002)
Herr et al., 2015	Cross-sectional study	France Community-dwelling	2 350 ≥ 70 years 83.3 ±7.5 years 59.4% female	Fried 1-2: prefrail ≥ 3: frail	- Average number of drugs according to frailty status - For each additional drug: OR for pre-frailty OR for frailty - According to the presence of polypharmacy (5-9) OR for pre-frailty OR for frailty - According to the presence of excessive polypharmacy (≥ 10) OR for pre-frailty OR for frailty	Non-frail/prefrail/frail: 4.6/6.1/7.1 (p < 0.001) OR 1.12 (95% CI 1.07-1.17) OR 1.20 (95% CI 1.12-1.28) OR 1.82 (95% CI 1.44-2.37) OR 1.77 (95% CI 1.20-2.61) OR 2.51 (95% CI 1.49-4.23) OR 4.47 (95% CI 2.37-8.42)
Herr et al., 2017	Cross-sectional study	France Community-dwelling	1890≥ 65 years 74.7±7.4 years 60.5% female	Fried ≥ 3: frail	IRR number of frailty criteria-polypharmacy 5–9 vs 0–4 drugs 10+ vs 0–4 drugs	 1.587 (p<0.001). With confounders 1.163 (p<0.05) 2.710 (p<0.001). With confounders 1.451 (p<0.001)
Hilmer et al.,	Cohort	Australia	31≥ 65 years	Reported	Average number of drugs	Frail 4.6±2.0 vs non-frail 2.1±1.8 (p=0.001)

2011	study, cross-sectional analysis of baseline data for outcomes of interest	Hospitalized	77.0±7.1 years 19.4% female	Edmonton Frail Scale ≥8: frail <8: not frail	according to frailty status	
Jamsen et al., 2016	Cohort study	Australia. Community-dwelling	1 705 men ≥ 70 years 76.9 ±5.5 years	Fried 0: robust 1-2: prefrail ≥ 3: frail	HR for transition to a state of - prefrailty - frailty by increasing number of drugs	 HR 1.04 (95% CI 1.00-1.09) HR 1.06 (95% CI 0.99-1.13)
Jung et al., 2016	Cross-sectional study	Korea. Outpatient and impatient	103≥ 65 years 76.8 ± 6.1 years 46.6% female	FRAIL scale (Korean version) 0: robust 1-2: prefrail ≥ 3: frail	Average number of drugs according to frailty status	Robust 5.4 ± 3.7 vs prefrail 6.4±4.4 vs frail 9.0±4.3 (p=0.014)
Merchant et al., 2017	Cross-sectional study	Singapore. Community-dwelling	1051 71.2 years 57.2% female	FRAIL scale 1-2: prefrail ≥ 3: frail	Prevalence of polypharmacy (≥ 5) according to frailty status	Robust 18.1%, prefrail 29.8%, frail 41.5% (p<0.001)
Moulis et al., 2015	Cross-sectional study	France. Outpatient	437 ≥ 65 years 83.05 ± 6.5 years 62.7% female	Fried 1-2: prefrail ≥ 3: frail	OR for frailty according to the presence of polypharmacy (≥ 6)	OR 1.85 (95% CI 1.21-2.82. $p < 0.02$)
Perera et al., 2009	Cohort study, cross-sectional analysis of baseline data for outcomes of interest	Australia. Hospitalized	220 ≥ 70 years 82.7 ± 6.3 years 54% female	Edmonton Frail Scale	Average number of drugs according to frailty status	Frail 8.2±3.2 vs non-frail 7.8±3.6 (p NS)
Poudel et al., 2016	Cohort study, cross-sectional analysis of baseline data for outcomes of interest	Australia. Hospitalized	1 418 ≥ 70 years 81.0 ± 6.8 years 55% female	Frailty index Low: 0-0.25 Mean: 0.26-0.39 High: ≥ 0.4	Average FI according to polypharmacy group	0-4 drugs FI 0.30±0.17 5-9 FI 0.32±0.15 ≥ 10 FI 0.34±0.13 (p = 0.003)
Saum et al., 2016	Cohort study	Germany. Community-	3 058 patients (50-75 years)	Fried 0: non-frail	- Prevalence of frailty according to polypharmacy group	Hyperpolypharmacy (≥ 10): 24.9% Polypharmacy (5-9) 12.1%. No polypharmacy

		dwelling	69.6±6.3 years 52.4% female	1-2: prefrail ≥ 3: frail	- OR for pre-frailty according to the presence of polypharmacy hyperpolypharmacy - OR for frailty according to the presence of polypharmacy hyperpolypharmacy - Incidence of frailty by polypharmacy group - OR for incident prefrailty according to the presence of polypharmacy hyperpolypharmacy - OR for incident frailty according to the presence of polypharmacy hyperpolypharmacy	(0-4) 3.7% ($p < 0.01$) OR 1.20 (95% CI 1.00-1.44) OR 1.48 (95% CI 1.03-2.14) OR 2.30 (95% CI 1.60-3.31) OR 4.97 (95% CI 2.97-8.32) No polypharmacy: 5.8%; polypharmacy: 13.0%, hyperpolypharmacy 19.3% OR 1.33 (95% CI 1.05-1.67) OR 1.86 (95% CI 1.11-3.10) OR 1.85 (95% CI 1.24-2.76) OR 3.08 (95% CI 1.55-6.12)
Thai et al., 2015	Cross-sectional study	Australia. Hospitalized (acute)	180 patients ≥ 65 years, Median 78 years (IQR=14) 47.2% female	Reported Edmonton Frail Scale 0-7: robust ≥ 8: frail	- Average number of drugs according to frailty status - Prevalence of polypharmacy (≥ 5 drugs) according to frailty status - Prevalence of 5-9 drugs according to frailty status - Prevalence of hyperpolypharmacy (≥ 10 drugs) according to frailty status	Robust 8 (IQR 4) vs frail 9 (IQR 5) R 92.3% vs F 96.9% R 64.1% vs F 54.0% R 28.2% vs F 42.9%. p = 0.095
Trevisan et al., 2016	Cohort study	Italy. Outpatient	2 925 patients ≥ 65 years 74.4 ±7.3 years 59.7% female	Fried 1-2: prefrail ≥ 3: frail	OR for transitions to prefrailty or frailty status according to use of > 3 drugs	Univariate analysis: OR from non-frail: 1.24 (1.13-1.37) (p<0.0001) OR from prefrail: 1.55 (1.39-1.73) (p<0.0001) Multivariate analysis: OR from non-frail: 1.05 (0.94-1.17) OR from prefrail: 1.04 (0.92-1.18)
Wang et al., 2015	Cohort study	China. Outpatient	1 592 men ≥ 80 years 85.2 (80-104) years	Fried ≥ 3: frail	-Prevalence of frailty according to baseline polypharmacy group -Prevalence of frailty according to polypharmacy group at five	No polypharmacy (0-5): 30.5%, polypharmacy (6-9): 29.3%, excessive polypharmacy (≥ 10): 29.6% ($p = 0.261$). No polypharmacy: 42.7%, polypharmacy: 34.2%, excessive polypharmacy: 33.7% ($p <$

					years - OR for incident frailty according to increasing number of drugs	0.05). OR 1.06 (95% CI 1.02-1.11)
Woo et al., 2014	Cohort study	Hong Kong. Community-dwelling	4 000 patients ≥ 65 years	Fried 1-2: prefrail ≥ 3: frail	-Prevalence of polypharmacy (≥ 4) after a follow-up period according to baseline frailty status -OR for polypharmacy after a follow-up according to baseline frailty status	Robust: 13.7%; prefrail: 18.9%; frail 21.5% (p = 0.7036). OR according to two models: 1.36 (95% CI 0.72-2.56). 1.30 (95% CI 0.68-2.48)
Woo et al., 2015	Cross-sectional study	Hong Kong. Community-dwelling	816 ≥ 65 years 58.9% ≥ 75 years 85.4% female	FRAIL Scale 0: robust 1-2: prefrail ≥ 3: frail	Average number of drugs according to frailty status	Frail 4.3 ± 2.9; non-frail 2.9 ± 2.2 (p = 0.001)
Zheng et al., 2016	Secondary analysis of a cohort study	China Community-dwelling	10 039 ≥ 55 years 70.5 ± 7.8 years 61.3% female	FI 34 items Frailty FI ≥ 0.25	OR for incident frailty according to the presence of polypharmacy (≥ 4 drugs)	Adjusted OR =1.37 (p < 0.05).

CI: confidence interval; F: frail; FI: frailty index; HR: hazard ratio; IQR: interquartile range; IRR: incidence rate ratio; NF: non-frail; NS: non-significant; OR: odds ratio; R: robust

* Results from Gnjidic et al 2012(a), Gnjidic et al 2012(b) and Jamsen et al. 2016 come from the same pool of participants (Concord Health and Aging in Men Project, CHAMP)

Figure 1.

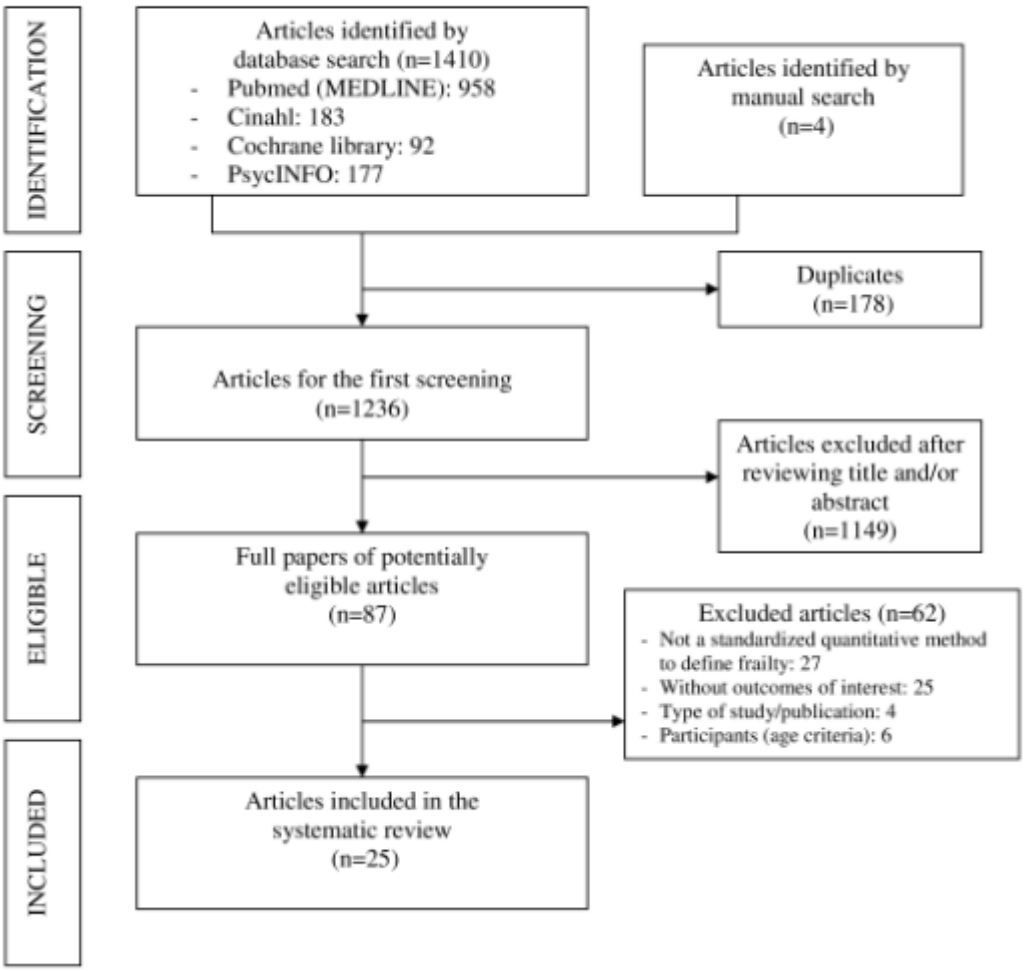

Figure 1. Flowchart of the selection process of study publications

Figure 2a.

	Selection				Comparability	Outcomes			Score
	1	2	3	4	1	1[a]	2	3	Total
Bennet et al.	*	*	*		**		*	*	7/9
Gnjidic et al.	*	*	*		**	*	*		7/9
Hilmer et al.	*	*	*			*	*	*	6/9
Jamsen et al.	*	*	*		**	*	*	*	8/9
Perera et al.	*	*	*	*	**		*	*	8/9
Saum et al.	*	*	*	*	**	*	*		8/9
Trevisan et al.	*	*	*		**	*	*	*	8/9
Wang et al.	*	*	*		**	*	*		7/9
Woo et al.	*	*	*		**	*	*	*	8/9
Zheng et al.	*	*	*		**	*			6/9

Criteria items:
Selection:
1. Truly or somewhat representative of the average=*
2. Selection of the non exposed cohort: drawn from the same community as the exposed=*
3. Ascertainment of exposure: secure record or structured interview=*
4. Outcome of interest was not present at start of study=*
Comparability
1. Study controls for most important factor=*. For any additional factor=*
Outcome
1. Assessment of outcome: independent blind assessment=*. record linkage=*
2. Follow-up long enough for outcomes to occur=*
3. Complete follow up or subjects lost to follow up unlikely to introduce bias=*

Figure 2b.

	Selection				Comparability	Outcomes		Score
	1	2	3	4	1	1	2	Total
Ballew et al.	*	*		**		**	*	7/10
Bonaga et al.	*	*		**		**		6/10
Castell et al.	*	*		**	**	**	*	8/10
Coelho et al.	*			**	**	**	*	8/10
Crentsil et al.	*	*	*	**	**	*	*	9/10
Gnjidic et al.	*	*		**	**	**	*	9/10
Hasan et al.	*	*		**		**	*	7/10
Herr et al. 2015	*	*		**	**	**	*	9/10
Herr et al. 2017	*	*		**	**	**	*	9/10
Jung et al.	*			**		**	*	6/10
Merchant et al.	*	*		**		**	*	7/10
Moulis et al.	*	*		**	**	**	*	9/10
Poudel et al.	*	*		**		**	*	7/10
Thai et al.	*	*		**		**	*	7/10
Woo et al.	*			**	**	**	*	8/10

Criteria items:
Selection:
1. Truly or somewhat representative of the average=*
2. Sample size justified and satisfactory=*
3. Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory=*
4. Assessment of the exposure: validated measurement tool=**. Non-validated, but available or described=*
Comparability
1. Study controls for most important factor=*. For any additional factor=*
Outcome
1. Assessment of outcome: validated measurement tool=**. Non-validated, but available or described=*
2. The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented=*

Figure 2a. Newcastle-Ottawa Quality Assessment Scale for exposure and outcome of interest in cohort-studies

Figure 2b. Modified Newcastle-Ottawa Quality Assessment Scale for exposure and outcome of interest in cross-sectional studies

Hyperlinks

http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=639#Inhibitors