

A Systematic Review of the Evidence for Deprescribing Interventions Among Older People Living With Frailty

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Abstract

Background: Older people living with frailty are often exposed to polypharmacy and potential harm from medications. Targeted deprescribing in this population represents an important component of optimizing medication. This systematic review aims to summarise the current evidence for deprescribing among older people living with frailty.

Methods: The literature was searched using Medline, Embase, CINAHL, PsycInfo, Web of Science, and the Cochrane library up to May 2020. Studies with any design or setting were included if they reported deprescribing interventions among people aged 65+ who live with frailty identified using reliable measures. The primary outcome was safety of deprescribing; whereas secondary outcomes included clinical outcomes, medication-related outcomes, feasibility, acceptability and cost-related outcomes. Narrative synthesis was used to summarise findings and study quality was assessed using Joanna Briggs Institute checklists.

Results: 2322 articles were identified and six (two randomised controlled trials) were included with 53 participants in total (mean age range 79–87 years). Studies were heterogenous in their designs, settings and outcomes. Deprescribing interventions were pharmacist-led ($n=3$) or multidisciplinary team-led ($n=3$). Frailty was identified using several measures and deprescribing was implemented using either explicit or implicit tools or both. Three studies reported safety outcomes and showed no significant changes in adverse events, hospitalisation or mortality rates. Three studies reported positive impact on clinical outcomes including depression, mental health status, function and frailty; with mixed findings on falls and cognition; and no significant impact on quality of life. All studies described medication-related outcomes and reported a reduction in potentially inappropriate medications and total number of medications per-patient. Feasibility of deprescribing was reported in four studies which showed that 72–91% of recommendations made were implemented. Two studies evaluated and reported the acceptability of their interventions and further two described cost saving.

Conclusion: There is a paucity of research about the impact of deprescribing in older people living with frailty. However, included studies suggest that deprescribing could be safe, feasible, well tolerated and can lead to important benefits. Research should now focus on understanding the impact of deprescribing on frailty status in high risk populations.

Trial registration: the review was registered on the international prospective register of systematic reviews (PROSPERO) ID number: CRD42019153367.

Background

One-third of people aged over 65 years live with multimorbidity and take five or more regular medicines (polypharmacy), increasing to 50% in over 85 year olds [1, 2]. Polypharmacy in older people is associated with increased risk of serious adverse events, falls, cognitive impairment, functional decline, hospitalisation, length of stay and death, [3-5]. Such harms are amplified in older people living with frailty,

a complex geriatric syndrome resulting in decreased physiological reserve [6]. In frail older people the harm might outweigh benefits for some medications e.g. intensive blood glucose control in type 2 diabetes, or the known time to benefit exceeds projected life expectancy e.g. statins [7, 8]. Additionally, the goals of drug treatment in older people living with frailty may change compared with older people in general shifting the focus from reducing the risk of disease and prolonging life to reducing the burden of treatment and maintaining quality of life [9]. The bi-directional relationship between polypharmacy and frailty has been reported. Drugs and frailty might interact through network of connections, including physiological changes, multiple pathologies and chronic diseases, life expectancy, or functional or cognitive status [10-14]. Frailty may influence factors such as drugs pharmacokinetics and pharmacodynamics, toxicity, and their therapeutic efficacy. In turn, these factors may be involved in the development of frailty [15].

The cure for polypharmacy appears simple and involves deprescribing - the process of tapering /dose reduction, stopping, or switching drugs, with the goal of managing polypharmacy and improving outcomes [16]. There has been considerable research conducted on deprescribing since the term was first used in 2003 [17], and more recently there has been a focus on deprescribing for those living with frailty. Several tools have been developed to assist physicians with deprescribing decisions such as STOPPFrail [18, 19]. However, investigation of the impact of deprescribing on those living with frailty has been limited to date.

Several systematic reviews have synthesised the evidence on outcomes of deprescribing interventions among older people in general [20, 21], or defined by setting including care homes [22, 23], primary care and community [24, 25] and hospitals [26]. These reviews reported that deprescribing is feasible, well tolerated, safe, and generally effective in reducing the number of inappropriate prescriptions. However, these reviews either did not include frail older people or frailty was poorly defined in their included studies, for example based on age or setting such as being in a care home with definition subject to international variability [27]. There is an increasing awareness that identifying frail older people or those at risk of frailty using reliable tools should be part of routine clinical practice to guide appropriate interventions to improve clinical outcomes [28]. The dynamic nature of frailty highlights a potential for preventive and restorative interventions to maintain the capacity for self-care and to prevent disabilities, falls, functional decline, institutionalization, hospitalization and death [29]. For example, it could be crucial to identify older people living with frailty and polypharmacy to be target for a medication review and deprescribing intervention that could potentially reduce harm from medications and improve patients' outcomes.

Therefore, the aim of this systematic review was to explore the safety and impact of deprescribing among older people living with frailty identified by reliable measures.

Methods

2.1. Data Sources and Searches

The search strategy was developed with a senior librarian and used the following databases: Medline, Embase, CINAHL, PsycInfo, Web of science, and the Cochrane library from database conception until January 2020. Keywords such as deprescribing, deprescribe*, polypharmacy, inappropriate prescribing were used (the full search strategy is available from the authors on request). Reference lists of retrieved articles were searched for additional relevant studies. The search was re-run in May 2020 but no further eligible papers were retrieved. The review was carried out using the methods recommended by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [30] and was registered on the international prospective register of systematic reviews (PROSPERO) ID number: CRD42019153367.

2.2. Study inclusion

Type of studies

We anticipated a small number of studies to explore deprescribing in frail older people therefore studies with any design, setting or language were included (Table 1).

Type of participants

We included interventions that targeted an older population with a median age of 65 years and over, who are identified to be frail using reliable measures including but not limited to Freid Frailty Phenotype, FRAIL scale, PRISMA-7, electronic-Frailty Index, Edmonton Frail Scale Gérontopôle Frailty Screening Tool and Clinical Frailty Scale. To be included, studies had to have at least 50% of their study population identified as frail.

Type of interventions

Studies involving deprescribing as the only intervention or as part of medication review intervention where deprescribing accounts for at least 50% of the recommendations were included. Studies where deprescribing formed part of a multi-dimensional intervention (such as in combination with nutritional and physical activity components) were excluded as it is difficult to ascertain which component of the intervention was responsible for the reported outcomes.

Type of outcomes

The primary outcome we chose was safety of deprescribing. We defined safety in terms of reported adverse events, hospital admission and/or all-cause mortality.

Secondary outcomes included clinical outcomes (such as frailty status, function, falls, cognition, depression, quality of life), medication-related outcomes (such as changes in number of medications and Potentially Inappropriate Medications PIMs), feasibility of deprescribing (defined by the number of

patients/proportion who successfully stopped medications), its acceptability by patients or healthcare practitioners, and cost-related outcomes.

2.3. Study selection

Two authors (KI & NC) independently screened the title and abstracts of identified articles using the Rayyan electronic platform to identify studies that met the inclusion criteria [31]. Following each stage, any disagreement was resolved by discussion.

2.4. Quality assessment

Study quality was assessed separately by two authors (SL & SF) using the standardized Joanna Briggs Institute checklists for each study type, with total scores of 13 for randomized controlled trials (RCTs) and 9 for non-randomised experimental studies. Final scoring was agreed by discussion. A score $\geq 7/13$ for RCTs and 5/9 for non-randomised experimental trials were considered to represent good quality.

2.5. Data Abstraction and Synthesis

Due to heterogeneity of study designs and outcome measures, quantitative synthesis (meta-analysis) was not possible and narrative synthesis of the findings was conducted following the Synthesis Without Meta-analysis (SWiM) guideline [32]. Data from included studies were extracted independently by two authors (KI & JS) into a pre-defined template for conceptualization and construction of the literature review (Table 2). Data abstracted included: year of publication, country, setting, number and age of participants, description of the deprescribing intervention and any comparator, type of medications deprescribed, frailty measures used, deprescribing tools and outcomes of deprescribing. Studies were grouped according to intervention type (pharmacist-led or multidisciplinary team-led) due to the heterogeneity of study designs and outcomes. Outcome data were summarised for each study and compared.

Results

2322 articles were identified, and 57 articles were selected for full text assessment from which six journal articles were included in this review (Figure 1). Six conference abstracts were excluded due to limited information available and poor quality of reporting. No articles in any language other than English were identified. The quality of the full text articles included was good: $\geq 6/9$ for the four non-randomised experimental studies and 10/13 for the two randomised-controlled trials RCTs.

3.1. Participants characteristics

The total number of participants in all included studies was 553, while individual sample sizes ranging from 46 to 177 and mean participant age range from 79–85 years. The Canadian Clinical Frailty Score (CFS) was the most commonly used frailty measure (n=2)[33, 34], with others including: the Edmonton Frailty Scale [35], Identification of Seniors At Risk (ISAR) [36], the Electronic Frailty Index (e-FI) [37], and Fried Frailty Phenotype [38].

3.2. Study characteristics and deprescribing interventions

This review includes two RCTs, two pre- and post- comparison studies and two prospective interventional cohort studies (Table 2). Studies were conducted in Ireland, Belgium, New Zealand, Canada, and Israel. Study settings included: hospital (3), care home (1), primary care (1), community (1). All included articles were published between 2014-2019.

Several tools and algorithms were used to guide deprescribing. Two studies used explicit criteria (lists of drug names targeted); one used only the STOPP criteria [36], one used the STOPPFrail tool [34]. Two studies utilised implicit criteria (lists of evaluative questions or a process) developed by the research teams themselves including the Garfinkel algorithm for concurrent deprescribing of multiple medications [38], and guidelines for targeted deprescribing of anticholinergic and sedative medicines [35]. The remaining two studies used a combination of both explicit criteria and implicit criteria; one used STOPP and Beer's alongside pharmacist's judgment [37], and the second used an algorithm based on STOPP guidelines, Beers criteria, Choose Wisely and Choose Wisely Canada [33]. The medications most frequently deprescribed across the studies regardless of the setting were: benzodiazepines, antidepressants, neuroleptics, opiates, lipid-lowering agents (statins), vitamin and nutritional supplements, proton pump inhibitors, and cardiovascular drugs (aspirin, antiplatelets, b-blockers, digoxin).

Due to heterogeneity of the outcome measures and study designs, studies were grouped according to interventions: pharmacist-led deprescribing interventions (n=3) and multidisciplinary team-led intervention (n=3).

3.2.1. Pharmacist-led deprescribing

Three of the six studies described pharmacist-led deprescribing interventions: one in a care home [35], one in primary care [37] and one in hospital [33]. The three studies were non-randomised experimental studies with a good quality scoring >6/9. Follow up periods were three months (after discharge from hospital), six months (in primary care) and twelve months (in care home).

The care home and primary care studies used a person-centred collaborative pharmacist-led deprescribing medication review with the General Practitioner (GP) [35, 37]. Both interventions involved a detailed medication review process that engaged patients and their relatives in decisions about

medication discontinuation; both drafted and shared a medication plan and followed patients for close monitoring. While the hospital study was a prospective interventional cohort study that employed medication reviews by a Medication Rationalization (MERA) team led by pharmacists and involved physicians among frail inpatients ($CFS \geq 4$) and compared them with 51 patients in the control arm who did not receive the MERA review [33]. In one study, the pharmacist used implicit guidelines of sedatives and anticholinergic medicines developed by the research team among 46 residents identified to be frail using Edmonton Frailty Scale in three residential care facilities [35]. Whereas the two studies in primary and secondary care, the pharmacists used the STOPP and Beers criteria to identify prescribing problems among 54 community dwelling older people with some degree of frailty using the electronic frailty index (e-FI) across six practices [37] and 53 frail inpatients ($CFS \geq 4$ [33]).

3.2.2. Multidisciplinary team (MDT)-led deprescribing

Three studies implemented multidisciplinary team-led deprescribing focused medication review: two were RCTs in hospital settings (high quality score of 10/13) and one was a longitudinal prospective interventional study in community (good quality, 6/9). Follow up periods were three and twelve months in hospital studies and three years in the community study.

One RCT of 146 patients (74 in the intervention group vs 71 in the control group) living with frailty (ISAR $\geq 2/6$) implemented medication review using STOPP criteria on admission by an inpatient geriatric team consisting of nurses, geriatricians, a dietitian, an occupational therapist, a physiotherapist, a speech therapist, and a psychologist [36]. Another RCT of 130 inpatients (65 in the intervention group vs 65 in the control group) living with frailty ($CFS \text{ score } \geq 7$) used a STOPPFrail-guided deprescribing intervention by a research physician pre-discharge to care home [34]. A longitudinal prospective nonrandomized study among 177 community dwelling older people living with frailty (median Fried Frailty Phenotype=3) employed concurrent deprescribing of multiple medications based on the Garfinkel algorithm by a geriatric consultant in collaboration with GPs [38]. The intervention group included patients who had 3 or more medications deprescribed (Poly-De-Prescribing PDP group n=122), while the control group included participants who agreed to stop only 2 medication or less (n=55).

3.3. Outcomes of deprescribing

The outcomes reported in the included studies are presented in Table 2; safety of deprescribing in three studies; clinical outcomes (n=3); medication-related outcomes (n=6); feasibility of deprescribing (n=4); acceptability (n=2) and cost-related outcomes (n=2).

3.3.1. Primary outcome

Safety of deprescribing

Three studies reported the safety of deprescribing and its impact on adverse events [34, 35, 38]. Potential adverse drug reactions using the UKU-SERS score in a pharmacist-led deprescribing intervention among 46 care home residents decreased by a mean difference of 2.8 (95% CI; $p < 0.05$) after three months and 4.2 (95% CI; $p < 0.05$) after six months of deprescribing of sedative and antipsychotic medications [35]. In addition, adverse effects of psychotropic medications decreased significantly by a mean difference of 1.8 (95%, CI; $p < 0.05$) three months after deprescribing, and by a mean difference of 2.24 (95%, CI; $p < 0.05$) after six months of deprescribing. One RCT in hospital reported that 88% of deprescribing recommendations based on STOPPFrail were accepted and implemented and no adverse events were reported of MDT-led deprescribing during three months follow-up [34].

Two MDT-led deprescribing studies in hospital and community showed no significant differences in unplanned hospitalisation and mortality [34, 38]. The RCT in hospital showed no statistically significant differences between the intervention and control groups for three months unscheduled hospital presentations [0.14 intervention vs 0.08 control, 95% CI, $P=0.27$] and mortality [0.18 vs 0.28, 95% CI; $P=0.22$] [34] . Similarly a longitudinal cohort study in community reported that the incidence of hospitalizations per patient per year (0.39 intervention vs 1.02 comparator, $p= 0.1006$) and survival (77% intervention vs 67% comparator group, $p=0.026$) was comparable between the groups after three years [38]. This study also reported that the incidence of significant complications per patient/year was significantly reduced with deprescribing [0.22 intervention vs 1.72 comparator group, $p= 0.0047$] [38].

3.3.2. Secondary outcomes

Clinical outcomes

Frailty and function: Two studies reported the outcomes of deprescribing on frailty and function [35, 38]. Pharmacist-led deprescribing sedatives and anticholinergic medicines among 46 care home residents showed a significant decrease in frailty scoring (mean difference of 1.35, 95% CI, $P<0.05$) using the Edmonton Frailty scale after six months of deprescribing. Another pharmacist-led deprescribing study did not report whether deprescribing has led to changes in frailty status but reported a positive and statistically significant correlation between number of PIMs (STOPP and Beers criteria) and frailty using e-FI ($r = 0.280$, $P = .040$) [37]. The impact of deprescribing on functional status defined using a 5 point scale (1= independent, 2=frail, 3= mild disability, 4=disability, 5=severe disability) was examined in another MDT-led deprescribing study [38]. Patients in the poly-deprescribing group had less functional deterioration compared to the comparator group [38(69.1%) vs 42(34.4%), $P<0.001$].

Falls: The impact on falls was mixed and reported in two studies [34, 35]. Significant decreases in falls rate, defined as the number of falls in the past 90 days, was reported after pharmacist-led deprescribing psychotropic medicines among care home residents [35]. But on the other hand, falls risk (determined using an inhouse falls risk assessment tool utilised by most residential care facilities in New Zealand) remained the same six months after deprescribing. Another MDT-led deprescribing RCT study using

STOPPFrail at hospital discharge reported no significant difference in incidence of falls [0.27 vs 0.30, 95% CI, P=0.75] and non-vertebral fractures [0.02 vs 0.09, 95% , P=0.18] among patients who moved to nursing home after three months of deprescribing [34].

Cognition, depression and mental status: two studies reported outcomes on cognition, depression and mental status [35, 38]. No change in cognition using the interRAI cognitive performance scale was observed after three and six months of pharmacist-led deprescribing antipsychotic medications among care home residents (mean difference of 0, p=0.26), however significant improvement of depression scores using the geriatric depression scale (GDS) (mean difference of -2, p<0.05) were seen after six months [35]. Another MDT-led deprescribing study reported that patients in the poly-deprescribing (PDP) group had improvement in mental status using the Mini Mental State Examination (MMSE) test (3 comparator vs 63 intervention, p<0.0001) and cognitive status (0 comparator vs 7 intervention, P=0.0004) [38]. These improvements occurred within three months after deprescribing in 83% and persisted for ≥ 2 years in 68%.

Quality of life (QoL): Two studies assessed QoL of participants and showed no significant differences after implementing deprescribing interventions [34, 35]. QoL among care home residents was assessed using EQ-5D-3L and showed no significant different pre and six months after deprescribing [35]. QoL in one RCT in hospital using QUALIDEM or ICECAP-O scores showed deterioration in both the intervention and the control group from baseline to three months follow-up, but no statistically significant differences were found in the mean change between groups from baseline to follow-up [34].

Medication-related outcomes

All six studies reported medication-related outcomes [33-38]. Four studies reported a significant reduction in the number of medications taken by patients living with frailty after implementing deprescribing, ranging from a mean of 2-3 medicines stopped per patient [33-35] across the different settings to unsurprisingly 7 medications per patient when poly-deprescribing of three or more drugs was implemented in people's home [38]. Two studies also reported significant decreases of potentially inappropriate medications associated with deprescribing interventions [36, 37]; for example the deprescribing interventions in two hospital studies reported a mean decrease in PIMs number of 2.2 (p<0.01) in a pharmacist-led study and a reduction in PIMs was twice as high for the intervention group compared to the control group in a MDT-led deprescribing intervention. One care home study reported a significant decrease in the drug burden index (by 0.34) six months after deprescribing in care home residents with pharmacist-led deprescribing intervention [35].

Feasibility of deprescribing

Four studies reported the feasibility of deprescribing among older people with frailty [33-35, 38]. They displayed that 72-91% of the suggestions to deprescribe medications made by either pharmacists or the

MDT were accepted and implemented across the different settings [33-35, 38]. For example, in care homes, forty-five PIMs were identified and suggested to be stopped by pharmacists, of which 82% were agreed upon by the residents' GP and 96% were agreed upon by the resident or their relatives/family resulting in implementing 72% of the recommendations [35]. Similarly in two hospital studies, 72% and 81% of the recommendations made were accepted and implemented by the admitting physician and then patients [33, 34]. And in one community study, 91% of the recommendations made by a geriatrician were accepted by GPs [38].

Deprescribing was also reported to be well tolerated as most medications stopped were not restarted. For example, in care homes, medicines were re-prescribed by the GP in only five instances (15%); stopping medication was not completed in 13 residents (28%) due to mood changes, increased pain levels or overall health deterioration [35]. Similarly in hospital, of the 162 medications that were stopped only 40 (25%) were restarted during hospital admission or at time of discharge and 81% of medications stopped during hospitalisation remained discontinued after three months [33]. Another RCT study among hospitalised older patients discharged to care homes showed that only three medications stopped at discharge by the MDT were restarted [34].

Acceptability of deprescribing

Two studies evaluated the acceptability of their MDT-led deprescribing interventions and showed that patients and healthcare professionals were happy to stop unnecessary medication [33, 38]. For example, following a pharmacist-led intervention 87% participants felt comfortable stopping medications as recommended by the team and only a very small number found the experience stressful or confusing (5% and 11% respectively) [33]. In the poly-deprescribing intervention in community, the overall satisfaction of patient/family from the changes was defined as high/very high in 89 % ($n = 109$) [38].

Cost-related outcomes

Two studies reported the cost implications of deprescribing [33, 34]. A pharmacist-led intervention reported a total saving of \$1508.47 or \$94.28 per 100 patient-days when STOPP criteria were implemented in hospital [33]. Using STOPPFrail by MDT at discharge from hospital also led to a mean change in monthly medication cost of -\$74.97 compared to -\$13.22 in the control group (mean difference \$61.74; 95% CI; P = .02) [34].

Discussion

This review expands on prior literature reviews by synthesising studies on medication deprescribing that specifically addressed older people living with frailty as they are more vulnerable to the adverse effects of medicines compared to older people in general. Only six studies (two were RCTs) with overall good quality that reported the outcomes of deprescribing interventions among older people with reliably

identified frailty were found. The outcomes of deprescribing in older people living with frailty were similar to those reported in older people in general in terms of feasibility, acceptability and safety as mortality and hospitalisation rates did not increase after stopping medications. Deprescribing interventions led to a significant reduction in number of medications and PIMs with potential cost saving. Included studies also suggest some evidence of potential improvement in function, frailty status, mental health and depression scores. Outcomes did not differ whether the intervention was led by a pharmacist or MDT including mainly medical practitioners and whether explicit or implicit criteria were used. But the heterogeneous study designs limit our ability to make firm conclusions regarding this matter.

Deprescribing medications has raised some ethical dilemmas and fear of negative outcomes has been reported by prescribers as a barrier to deprescribing [39]. Among older people with identified frailty, there is some evidence from the included studies in this review that deprescribing is safe as it did not adversely change hospitalisation and mortality rates. A number of systematic reviews investigated the impact of deprescribing on mortality among general population of older people; one reported that deprescribing reduced mortality in non-randomized studies but no changes were observed in RCTs [40]; other reviews suggested a reduction in all-cause mortality with deprescribing interventions in nursing home residents [22, 23]. We reported some evidence that deprescribing is feasible and well tolerated by older people living with frailty and is acceptable by healthcare professionals and patients, which is in agreement with existing studies in older people in general [41, 42]. In our review we identified that 72-91% of recommendations made were implemented and very few patients (25%) restarted their medications. A recent review of 26 papers reported the proportion of patients who successfully stopped their medication varied from 20% to 100% and in 19 studies the proportion was >50% [24]. The feasibility and safety of deprescribing should encourage clinicians to regularly discuss the decision to continue or deprescribe chronic medications with their patients living with frailty following a patient-centred, structured deprescribing process with planning, tapering and close monitoring during, and after medication withdrawal.

Few studies in the review reported clinical outcomes such as frailty, falls, cognition and depression; with more focus placed on the success of the interventions in reducing number of medications and especially inappropriate ones. This focus on process and lack of clinical outcome data with inconsistency in outcome measurement have also been highlighted as limitations in deprescribing studies to date. A 2017 review of deprescribing interventional studies among older people in general reported the outcome measures most commonly used were number of medications or PIMs stopped, healthcare use, and adverse events [43]. Patient-reported outcomes, geriatric syndromes (e.g. falls, fractures, gait speed, depression and delirium) or costs evaluation were infrequently reported, and frailty was not used as either inclusion criteria or an outcome measure. There is no consensus among researchers and clinicians on appropriate outcomes of deprescribing and more research is needed in this area. Frailty should be considered as an outcome in deprescribing interventions in older people and the focus should be placed on understanding the impact of deprescribing on frailty trajectory.

The strong relationship between polypharmacy and frailty and the potential to reverse frailty status [44], makes it important to understand the impact of deprescribing on frailty. Only one study included in our review examined the impact of deprescribing on frailty status which was 46 among care home residents using the Edmonton frailty tool and reported positive results [35]. The Edmonton frailty tool consists of 9 domains including number of medications [45]. It is unclear from the study which domains were influenced by the deprescribing intervention or to what extent the improvement could simply reflect a decrease in number of medications used. Another included study reported that frailty and PIMs were significantly correlated but did not report the impact of deprescribing on frailty status. There is a lack of research on the impact of stopping medications on frailty status but some current registered clinical trials propose to measure the impact of medication review and deprescribing on frailty [46, 47]. It is also important to understand the mechanism by which deprescribing might influence frailty via functional or cognitive changes or through other possible mechanisms.

No effect of deprescribing on the quality of life among older people with frailty was reported in only two studies included in our review. These findings are consistent with literature published in older people in general [20, 21, 48, 49]. We found a positive impact of deprescribing sedative and psychotic medications using a specific algorithm on rate of falls among older care home residents living with frailty, but no similar impact was obtained when the STOPPFrail tool was used among hospitalised patients discharged to care homes. This might be explained by the fact that the deprescribing algorithm focused on sedative and psychotic medications resulting in a higher proportion of anticholinergic medications being stopped compared to a tool with a broader remit like STOPPFrail. The inconsistency in reported findings regarding the relationship between falls and deprescribing is clear in the literature. For example, a recent review published in 2017 reported that fall-risk increasing drugs withdrawal strategy did not significantly change the rate of falls, number of people who fall or rate of fall-related injuries over a 6 to 12 months follow-up period in five included papers [50]. However, another review suggested that deprescribing interventions could significantly reduce the number of people who fall in care homes by 24% [51]. They related that to the significant reduction in number of residents on PIMs by 60% such as anticholinergics which have been consistently associated with cognitive impairment and falling in older people. As we mentioned above the impact of deprescribing on falls could be mediated by the deprescribing tools used and further research should explore this relationship.

The intervention process, who lead deprescribing or the deprescribing tools used appeared to have no differing effects in reducing unnecessary medications in our review. But the heterogeneity in study designs and the small number of included studies limit our ability to conclude whether one approach is more or less effective than another. Other reviews suggested that pharmacists-led deprescribing intervention in older people in general were more effective in reducing unnecessary medications compared to interdisciplinary team interventions [52, 53]. The concurrent use of both explicit lists of potentially inappropriate medications and systematic appraisal of every medication taken was suggested to help improve complex regimes [54]. Deprescribing techniques may be guided by the clinical situation. Stopping medicines one at a time might be most appropriate for managing people whose health status is stable in out-patient settings, whereas concurrent deprescribing' of multiple medications may be more

appropriate for inpatients where it is easier to monitor for withdrawal effects [54]. It is also recommended to use deprescribing as a 'drug holiday trial' as sometimes drugs will need to be restarted when symptoms recur or withdrawal effects are experienced, which necessitates monitoring and follow up [54].

This review is the first to summarise the evidence and impact of deprescribing among older people identified as living with frailty. Most published reviews focused on the general population of older people or on those at specific setting. With the increasing awareness of the importance of identifying frailty using reliable measures to allow implementation of effective interventions, this review expands our knowledge of the evidence of deprescribing among this population who are more **vulnerable** to harm from medications. However, there were several limitations in our review. The inclusion criteria required a reliable and valid measure of frailty so we may have excluded articles with less specific methods of assessing frailty or those that assumed frailty depending on age or setting such as studies in care homes. Multicomponent interventions including deprescribing or medication review where deprescribing accounted for less than half of the recommendations were excluded as our aim was to understand the evidence and impact of deprescribing among those living with frailty. We did not search the grey literature and may have missed some additional resources. Although we followed SWiM criteria, our synthesis of the studies should be treated with caution because of the limited number of included studies and their heterogeneity. We were also unable to perform a meta-analysis because of the heterogeneity of outcomes within the included studies.

Conclusion

This review highlights the paucity of published literature on deprescribing among older people living with frailty. The included studies were heterogeneous in their settings, designs and outcomes reported which mean it is difficult to make definite conclusions. However, we suggest that deprescribing could be safe, feasible, well tolerated and can lead to important benefits on geriatric conditions such as depression, function and frailty. Deprescribing interventions in this review appear to be effective whether led by pharmacists or multidisciplinary teams using explicit or implicit tools. This has implications for clinical practice as deprescribing could be effectively led by pharmacists in liaison with GPs in community settings, whereas multidisciplinary teams (with or without access to pharmacists) could play a key role in deprescribing in acute settings. However, more research is needed in the area of deprescribing and frailty and future studies should include those living with frailty in their samples. Moreover, in order to address the gap in our understanding of the effectiveness of deprescribing interventions on reducing and reversing frailty or stopping its progression, adequately powered randomised controlled trials that include reliable measures of frailty should be conducted.

List Of Abbreviations

PRISMA= the Preferred Reporting Items for Systematic reviews and Meta-Analyses; PROSPERO = the international prospective register of systematic reviews; PIMs = Potentially Inappropriate Medications; RCTs = randomized controlled trials; SWiM= the Synthesis Without Meta-analysis; CFS= The Canadian

Clinical Frailty Score; ISAR = Identification of Seniors At Risk; e-FI = the Electronic Frailty Index; GP = General Practitioner; MERA = Medication Rationalization; MDT = Multidisciplinary team; PDP = Poly-De-Prescribing; GDS = the geriatric depression scale; MMSE = Mini Mental State Examination; QoL = quality of life

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Author Contributions

KI, NC, JMS, SL, SF and HCR contributed to the conception and design of the review. KI & NC completed literature search and screening, KI & JMS extracted data from included studies and SL & SF assessed the quality of studies. KI drafted the manuscript and HCR contributed editing. All authors read and approved the final manuscript.

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References

1. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. *BMC Geriatrics*. 2017;17:230.
2. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call to action. *J Am Med Dir Assoc*. 2013;14(6):392-7.
3. Gnjidic D, Hilmer SN. Use of potentially inappropriate medications in the care of frail older people. *Aging Health*. 2010;6(6):705-16.
4. Christensen M, Lundh A. Medication review in hospitalised patients to reduce morbidity and mortality. *Cochrane Database Syst Rev*. 2013;2.
5. Chang C-B, Chen J-H, Wen C-J, Kuo H-K, Lu IS, Chiu L-S, et al. Potentially inappropriate medications in geriatric outpatients with polypharmacy: application of six sets of published explicit criteria. *British Journal of Clinical Pharmacology*. 2011;72(3):482-9.
6. Frailty, polypharmacy and deprescribing. *Drug and Therapeutics Bulletin*. 2016;54(6):69-72.
7. Hilmer SN, McLachlan AJ, Le Couteur DG. Clinical pharmacology in the geriatric patient. *Fundamental & clinical pharmacology*. 2007;21(3):217-30.
8. Kutner JS, Blatchford PJ, Taylor DH, Ritchie CS, Bull JH, Fairclough DL, et al. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: a randomized clinical trial. *JAMA internal medicine*. 2015;175(5):691-700.
9. Hilmer SN, Mager DE, Simonsick EM, Ling SM, Windham BG, Harris TB, et al. Drug burden index score and functional decline in older people. *Am J Med*. 2009;122(12):1142-9.e1-2.
10. Jyrkkä J, Enlund H, Lavikainen P, Sulkava R, Hartikainen S. Association of polypharmacy with nutritional status, functional ability and cognitive capacity over a three-year period in an elderly population. *Pharmacoepidemiology and drug safety*. 2011;20(5):514-22.
11. Rawle MJ, Cooper R, Kuh D, Richards M. Associations between polypharmacy and cognitive and physical capability: a British birth cohort study. *Journal of the American Geriatrics Society*. 2018;66(5):916-23.
12. Hubbard RE, O'Mahony MS, Woodhouse KW. Medication prescribing in frail older people. *European journal of clinical pharmacology*. 2013;69(3):319-26.
13. Gutiérrez-Valencia M, Izquierdo M, Cesari M, Casas-Herrero Á, Inzitari M, Martínez-Velilla N. The relationship between frailty and polypharmacy in older people: A systematic review. *British journal of clinical pharmacology*. 2018;84(7):1432-44.
14. Stevenson JM, Davies JG, Martin FC. Medication-related harm: a geriatric syndrome. *Age and Ageing*. 2019;49(1):7-11.

15. Veronese N, Stubbs B, Noale M, Solmi M, Pilotto A, Vaona A, et al. Polypharmacy is associated with higher frailty risk in older people: an 8-year longitudinal cohort study. *Journal of the American Medical Directors Association*. 2017;18(7):624-8.
16. Thompson W, Farrell B. Deprescribing: what is it and what does the evidence tell us? *The Canadian journal of hospital pharmacy*. 2013;66(3):201-2.
17. Woodward MC. Deprescribing: achieving better health outcomes for older people through reducing medications. *Journal of Pharmacy Practice and Research*. 2003;33(4):323-8.
18. Curtin D, Gallagher P, O'Mahony D. Deprescribing in older people approaching end-of-life: development and validation of STOPPFrail version 2. *Age and Ageing*. 2020.
19. Thompson W, Lundby C, Graabæk T, Nielsen DS, Ryg J, Søndergaard J, et al. Tools for Deprescribing in Frail Older Persons and Those with Limited Life Expectancy: A Systematic Review. *Journal of the American Geriatrics Society*. 2019;67(1):172-80.
20. Rankin A, Cadogan CA, Patterson SM, Kerse N, Cardwell CR, Bradley MC, et al. Interventions to improve the appropriate use of polypharmacy for older people. *Cochrane Database Syst Rev*. 2018;9:Cd008165.
21. Iyer S, Naganathan V, McLachlan AJ, Le Couteur DG. Medication withdrawal trials in people aged 65 years and older: a systematic review. *Drugs Aging*. 2008;25(12):1021-31.
22. Kua CH, Mak VSL, Huey Lee SW. Health Outcomes of Deprescribing Interventions Among Older Residents in Nursing Homes: A Systematic Review and Meta-analysis. *J Am Med Dir Assoc*. 2019;20(3):362-72.e11.
23. Almutairi H, Stafford A, Etherton-Bee C, Flicker L. Optimisation of medications used in residential aged care facilities: a systematic review and meta-analysis of randomised controlled trials. *BMC Geriatrics*. 2020;20(1):236.
24. Thio SL, Nam J, van Driel ML, Dirven T, Blom JW. Effects of discontinuation of chronic medication in primary care: a systematic review of deprescribing trials. *Br J Gen Pract*. 2018;68(675):e663-e72.
25. Ulley J, Harrop D, Ali A, Alton S, Fowler Davis S. Deprescribing interventions and their impact on medication adherence in community-dwelling older adults with polypharmacy: a systematic review. *BMC Geriatrics*. 2019;19(1):15.
26. Thillainadesan J, Gnjidic D, Green S, Hilmer SN. Impact of Deprescribing Interventions in Older Hospitalised Patients on Prescribing and Clinical Outcomes: A Systematic Review of Randomised Trials. *Drugs & Aging*. 2018;35(4):303-19.
27. Sanford AM, Orrell M, Tolson D, Abbatecola AM, Arai H, Bauer JM, et al. An international definition for "nursing home". *Journal of the American Medical Directors Association*. 2015;16(3):181-4.
28. Faller JW, Pereira DdN, de Souza S, Nampo FK, Orlandi FdS, Matumoto S. Instruments for the detection of frailty syndrome in older adults: A systematic review. *PloS one*. 2019;14(4):e0216166-e.
29. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet (London, England)*. 2013;381(9868):752-62.

30. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
31. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev*. 2016;5(1):210.
32. R; R. Cochrane Consumers and Communication Review Group: data synthesis and analysis'. <http://ccrcg.cochrane.org>, (accessed 26.11.2019). 2013.
33. Whitty R, Porter S, ra, Battu K, Bhatt P, Koo E, et al. A pilot study of a Medication Rationalization (MERA) intervention. *CMAJ open*. 2018;6(1):E87-E94.
34. Curtin D, Jennings E, Daunt R, Curtin S, Randles M, Gallagher P, et al. Deprescribing in Older People Approaching End of Life: A Randomized Controlled Trial Using STOPPFrail Criteria. *Journal of the American Geriatrics Society*.n/a(n/a).
35. Ailabouni N, Mangin D, Nishtala PS. DEFEAT-polypharmacy: deprescribing anticholinergic and sedative medicines feasibility trial in residential aged care facilities. *International journal of clinical pharmacy*. 2019;41(1):167-78.
36. Dalleur O, Boland B, Losseau C, Henrard S, Wouters D, Speybroeck N, et al. Reduction of Potentially Inappropriate Medications Using the STOPP Criteria in Frail Older Inpatients: A Randomised Controlled Study. *Drugs & Aging*. 2014;31(4):291-8.
37. Khera S, Abbasi M, Dabrvolskaj J, Sadowski CA, Yua H, Chevalier B. Appropriateness of Medications in Older Adults Living With Frailty: Impact of a Pharmacist-Led Structured Medication Review Process in Primary Care. *J Prim Care Community Health*. 2019;10:2150132719890227.
38. Garfinkel D. Poly-de-prescribing to treat polypharmacy: efficacy and safety. *Therapeutic advances in drug safety*. 2018;9(1):25-43.
39. Reeve E, Denig P, Hilmer SN, Ter Meulen R. The ethics of deprescribing in older adults. *Journal of bioethical inquiry*. 2016;13(4):581-90.
40. T. PA, M. CR, Kathleen P, Darren S, D. EBC. The feasibility and effect of deprescribing in older adults on mortality and health: a systematic review and meta-analysis. *British Journal of Clinical Pharmacology*. 2017:583-623.
41. Garfinkel D, Mangin D. Feasibility Study of a Systematic Approach for Discontinuation of Multiple Medications in Older Adults: Addressing PolypharmacyDiscontinuation of Multiple Dugs in Older Adults. *JAMA Internal Medicine*. 2010;170(18):1648-54.
42. Garfinkel D, Zur-Gil S, Ben-Israel H. The war against polypharmacy: a new cost-effective geriatric-palliative approach for improving drug therapy in disabled elderly people. *IMAJ-RAMAT GAN-*. 2007;9(6):430.
43. Beuscart JB, Pont LG, Thevelin S, Boland B, Dalleur O, Rutjes AWS, et al. A systematic review of the outcomes reported in trials of medication review in older patients: the need for a core outcome set. *British journal of clinical pharmacology*. 2017;83(5):942-52.
44. Ng TP, Feng L, Nyunt MS, Feng L, Niti M, Tan BY, et al. Nutritional, Physical, Cognitive, and Combination Interventions and Frailty Reversal Among Older Adults: A Randomized Controlled Trial.

Am J Med. 2015;128(11):1225-36.e1.

45. Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton Frail Scale. Age and ageing. 2006;35(5):526-9.
46. Nct. The Impact of Statin Holiday in Dialysis Patients Over 70 Years Old on Mental Function, Physical Function and Frailty. [Https://clinicaltrials.gov/show/nct03663049](https://clinicaltrials.gov/show/nct03663049). 2018.
47. Actrn. Opti-Med: a randomised controlled trial of deprescribing to optimise health outcomes for frail older people. [Http://wwwwhoint/trialsearch/trial2aspx?Trialid=actrn12613001204730](http://wwwwhoint/trialsearch/trial2aspx?Trialid=actrn12613001204730). 2013.
48. Eckert KA, Shi Z, Taylor AW, Wittert G, Price K, Goldney RD. Learning from an epidemiological, population-based study on prescribed medicine use in adults. Pharmacoepidemiol Drug Saf. 2013;22(3):271-7.
49. Pruskowski JA, Springer S, Thorpe CT, Klein-Fedyshin M, Handler SM. Does Deprescribing Improve Quality of Life? A Systematic Review of the Literature. Drugs & Aging. 2019.
50. Lee J, Negm A, Wong E, Holbrook A. DOES DEPRESCRIBING FALL-ASSOCIATED DRUGS REDUCE FALLS AND ITS COMPLICATIONS?: A SYSTEMATIC REVIEW. Innovation in Aging. 2017;1(suppl_1):268-.
51. Kua C-H, Mak VSL, Huey Lee SW. Health Outcomes of Deprescribing Interventions Among Older Residents in Nursing Homes: A Systematic Review and Meta-analysis. Journal of the American Medical Directors Association. 2019;20(3):362-72.e11.
52. Verhue CL, Petrovic M, Mehuys E, Remon JP, Vander Stichele R. Pharmacists' interventions for optimization of medication use in nursing homes. Drugs & aging. 2009;26(1):37-49.
53. Tjia J, Velten SJ, Parsons C, Valluri S, Briesacher BA. Studies to reduce unnecessary medication use in frail older adults: a systematic review. Drugs Aging. 2013;30(5):285-307.
54. Woodford HJ, Fisher J. New horizons in deprescribing for older people. Age and Ageing. 2019;48(6):768-75.

Tables

Table 1: PICO statement for study inclusion

Population	Older people (mean age 65+) who live with frailty measured objectively by any reliable tool.
Intervention	Studies at any setting and any language that included deprescribing medication review (including tapering/dose reduction, stopping or switching drugs). Deprescribing as the only intervention or part of medication review where deprescribing accounts for at least 50% of changes.
Comparator	Any, or no, comparator considered
Outcomes	Primary outcome: safety of deprescribing Secondary outcomes: clinical outcomes, medication-related outcomes, feasibility of deprescribing, acceptability and cost-related outcomes.

Due to technical limitations, table 2 is only available as a download in the Supplemental Files section.

Figures

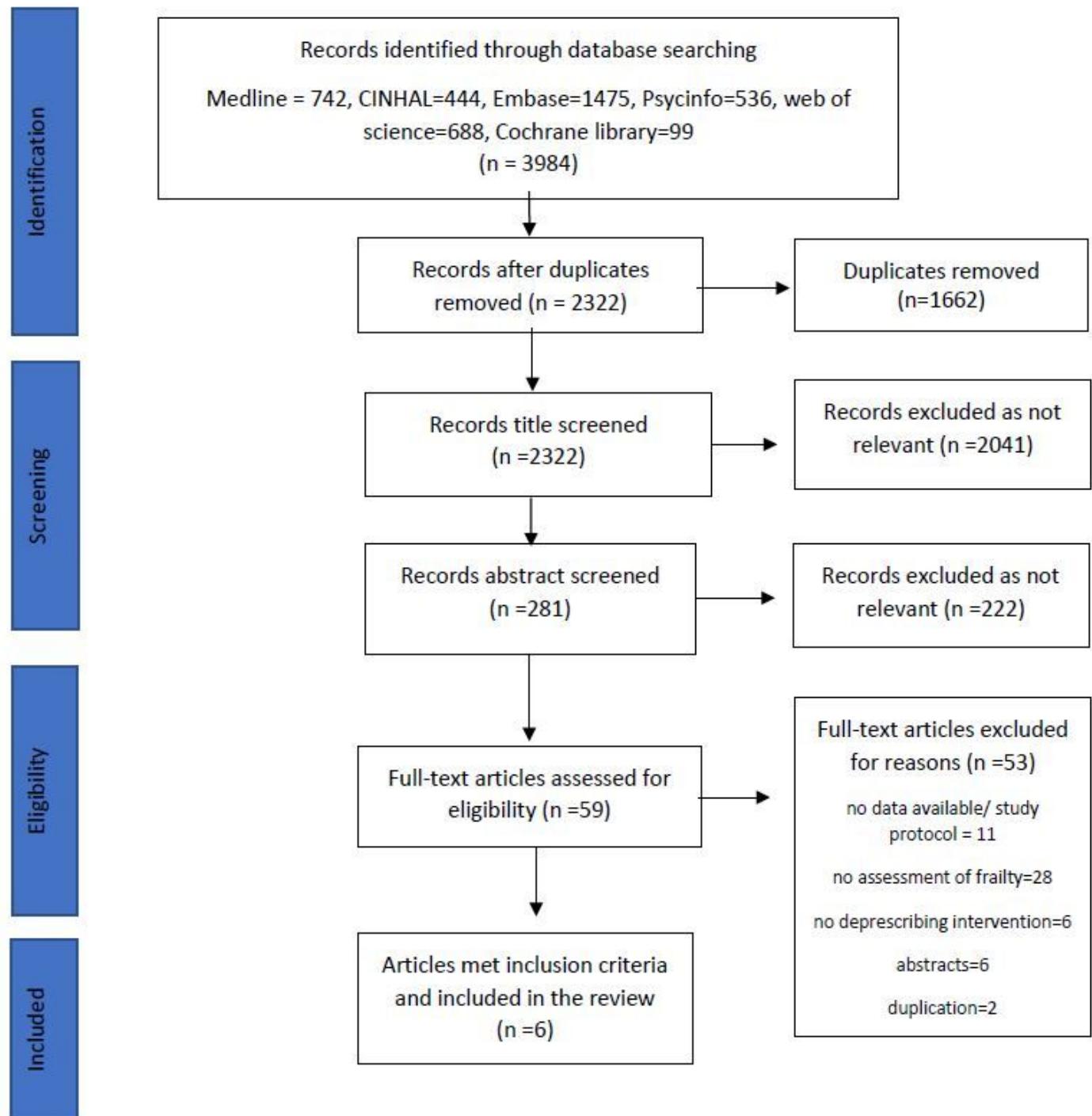


Figure 1

PRISMA Flow Diagram of identification of articles

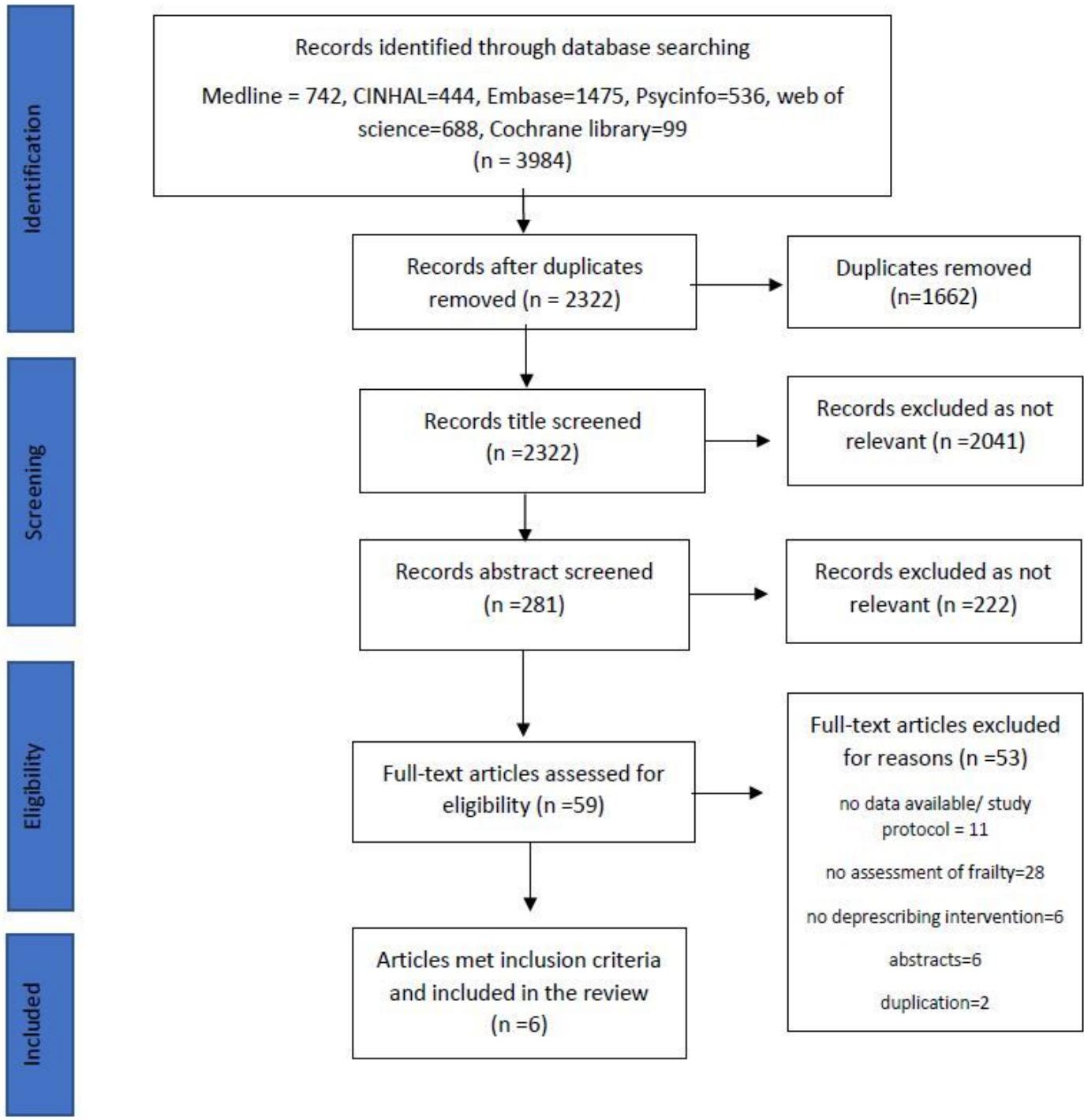


Figure 1

PRISMA Flow Diagram of identification of articles

Supplementary Files

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