**Full title: Multi-faceted Interventions Inclusive of Medication Optimization for Frailty in Aged Care: A Systematic Review**

**Authors and affiliations**

Chidiamara M Njoku, MPharm[a]; Fiona Barnett, PhD[a]; Maria A. Fiatarone Singh AM, MD[b,c,d] Trinidad Valenzuela, MS, PhD[a,b] and Michael Inskip, PhD[a,b]

[a] College of Healthcare Sciences, Sport and Exercise Science, James Cook University, Townsville, QLD, Australia

[b] Sydney School of Health Sciences, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia

[c] The Hinda and Arthur Marcus Institute for Aging Research, Hebrew SeniorLife, Boston, MA, USA

[d] Sydney Medical School, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia

**Corresponding author:** Chidiamara M Njoku, College of Healthcare Sciences, Sport and Exercise Science, James Cook University, Townsville, QLD, Australia. Email: chidi.njoku@my.jcu.edu.au

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**Brief Summary:**

We conducted the first systematic review exploring the use of multi-faceted intervention inclusive of medication optimisation in long-term care and found a concerning scarcity of literature.

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We would like to acknowledge the contribution of Mr. Stephen Anderson, the head research & learning librarian from James Cook University for his support in refining the search strategy used for this review.

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## Abstract

**Objectives:** Implementation of best practice frailty guidelines in residential aged care is currently unclear, and there is a particular paucity of evidence regarding multi-faceted frailty treatments inclusive of medication optimization in these settings, despite the bi-directional relationship between polypharmacy and frailty. This review aimed to retrieve all relevant literature and evaluate the effect of medication optimization delivered in conjunction with exercise and/or nutritional interventions in the best-practice management of frailty in residential aged care.

**Design:** Systematic review with a qualitative synthesis

**Settings and Participants:** Older adults residing within residential aged care (otherwise referred to as nursing homes or long-term care)

**Methods:** The protocol was prospectively registered on PROSPERO (Reg. No.: CRD42022372036) using the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. Five electronic databases were searched from inception to 23 November 2023 with alerts monitored until 28 March 2024. Quality of studies was assessed using the ROB 2 and ROBIN-1 tools.

**Results**: A total of 10,955 articles were retrieved; 62 full articles were reviewed with three studies included (2 randomized controlled trials and 1 non-randomized controlled trial) involving 1,030 participants. Included studies did not use specific frailty scores but reported individual components of frailty such as weight loss or number of medications prescribed. No trial combining medication review, exercise and nutrition was identified. Medication review reduced the number of medications prescribed, while the use of nutritional support reduced gastrointestinal medication and maintained weight.

**Conclusion and Implications:** There is no published research investigating best-practice guidelines for medication optimization used in combination with both exercise and nutrition in aged care to address frailty. This review confirms the need for studies implementing Consensus Guidelines for frailty treatment in this vulnerable cohort.

**List of Abbreviation:** ADL, activities of daily living; CGIC, clinical global impressions of change; CT, control parallel trial; EQ-VAS, European QoL-visual analogue scale; QoL, quality of life; NPI-NH, Neuropsychiatric Inventory- Nursing Home Version; QUALIDEM, QoL dementia scale; QUALID, QoL late-stage dementia scale; RCT, Randomized control trial; RACF, Residential Aged Care Facilities

## Introduction

The global population is aging rapidly, and life expectancy is increasing. In 2020, there were 727 million people aged 65 years or more and this number is projected by the United Nations to increase to 1.5 billion by 2050, due to a change in the proportion of older adults from 9.3% to 16.0% over this period[1]. In Australia, 16% of the total population are currently aged over 65 years[2], with the proportion projected to increase to 21-23% over the next four decades[2]. An aging population represents a significant healthcare and economic challenge, with AUD $23.6 billion spent on the 1.5 million Australians who accessed aged care in 2020-2021[3]. Furthermore, a proactive strategy is required to mitigate and treat the projected increase in the prevalence of age-related chronic conditions and geriatric syndromes. One particular condition prevalent in older age is frailty, which has broad implications for the prognosis of many chronic conditions, overall morbidity, institutionalization, and premature mortality in older adults[4].

Frailty is reduced physiological reserve and resilience that increases an individual's susceptibility to dependency, vulnerability to stressors, and death[1]. Contributors to frailty include physiological changes and/or diseases associated with aging such as inflammation, sarcopenia, malnutrition, polypharmacy, cognitive dysfunction, social isolation, and poverty, among others[2]. The prevalence of frailty and pre-frailty amongst *community-dwelling* adults 60 years or older is 10.7% and 41.6%, respectively[5]. Frail older adults are at increased risk of falls, fractures, delirium, hospitalization, transition to residential care and premature mortality[6,7]. It is therefore unsurprising that people living in residential aged care facilities (RACFs), are at an even greater risk of frailty and its effects due to advanced age, comorbidities, and functional impairment. The prevalence of frailty in aged care settings (residents aged ≥60 years) is estimated to be up to 61% in Australia, with virtually *all* aged care residents being either *frail* or *pre-frail*[1]. In aged care, the presence of frailty is associated with poorer quality of life,

93 greater risk of hospitalization, excess morbidity and pre-mature death[8]. Importantly, however, decades
94 of research have confirmed that frailty is not inevitable, but amenable to evidence-based interventions
95 that are accessible in clinical practice[9].

96

97 These interventions involve the combination of medication optimization, resistance exercise, and
98 nutritional support as minimum components of management, as documented within several guidelines
99 such as the Asia-Pacific Clinical Practice Consensus Clinical Practice Guidelines for the Management
100 of Frailty[2]. There is strong evidence that interventions of this nature result in clinically significant
101 improvements in frailty when applied in community settings[10]. However, despite the strength of this
102 evidence in community settings, it is still unclear whether these guidelines have been implemented in
103 RACF settings.

104

105 Furthermore, management strategies are often delivered in isolation, leading to decreased adherence,
106 efficacy, and sustainability over time, as the interventions fail to capture the complexity of treatment
107 requirements for frailty. For example, recent literature suggests that medication optimization strategies
108 involving deprescribing delivered alone are generally effective for a short period of active monitoring
109 before the medications are re-prescribed due to poor implementation of non-pharmacological
110 alternatives[11]. Additionally, there is a paucity of evidence on the use of medication optimization in
111 isolation or in combination specifically for the management of frailty in residential aged care despite
112 the strong, bi-directional relationship between polypharmacy and frailty[12]. Importantly, the use of
113 resistance exercise and nutritional support, which are currently used in combination to successfully
114 treat a variety of chronic conditions including frailty in community-dwelling older adults[13], could be
115 the missing link in providing suitable non-pharmacological alternatives to support medication
116 withdrawal in aged care settings.

Therefore, our objective was to systematically search and review existing literature to identify and evaluate the effect of medication optimization delivered in conjunction with exercise and/or nutritional support interventions on frailty and other clinically relevant outcomes to identify any gaps and guide future research and clinical practice.

## Methods

This study was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[14]. The protocol was registered on PROSPERO (Reg. No.: CRD42022372036).

### Eligibility criteria

#### Inclusion criteria:

- **Study design**: Experimental studies including randomized controlled trials (RCTs), non-randomized controlled trials, cluster-randomized trials, and uncontrolled trials. Grey literature such as thesis and preprints were included if they met the criteria.
- **Population**: Older adults (65 years or older) residing in institutionalized care facilities. Institutionalized care facilities include nursing homes and residential homes (UK); residential aged care facilities providing low-level and high-level care (Australia); skilled-nursing facilities and assisted-living facilities (US) or the equivalent terms in various countries (e.g., hostel). The population did not have to be classified as frail to be eligible for review.
- **Intervention**: Studies evaluating intervention or exposure involving medication optimization delivered in combination with exercise or physical activity and/or nutritional support/education interventions.

- **Comparator(s)/control**: There were no comparator restrictions for inclusion in this review however it was anticipated that interventions would be compared to usual care or passive interventions.
- **Outcome:**

  *Primary outcome*

  Frailty: The study must have reported frailty, or a component of frailty, as defined by any phenotypical [(e.g., Fried Frailty Phenotype[15]) or index model (i.e., Frailty Index)[16] or validated questionnaire (e.g., FRAIL-NH Scale[17])] as a primary or secondary outcome of the intervention. Additionally, if a measure of frailty or its components could be derived from other reported outcomes such as any of the components of these models (i.e., weight loss, weakness, slowness, shrinkage of lean mass, exhaustion, low physical activity, number of medications, functional independence, etc.), the study would be included.

  *Secondary outcomes* are defined in **Supplement 1**.

**Exclusionary criteria:**

- Older adults receiving home care, hospital care, outpatient services, day hospital care, inpatient/outpatient rehabilitation services, respite care, short stay post-acute care services, hospital in-the-home services
- Studies of medication optimization in isolation (without concurrent nutritional and/or exercise intervention) or nutritional or exercise interventions without concurrent medication optimization intervention.

## Study definitions

*Medication optimization* must have optimized prescribing for residents [i.e., educational interventions aimed at prescribers; medication review services (uni- or multi-professional, including comprehensive geriatric assessment); case conferencing; or information and communications technology (ICT) interventions such as clinical decision support systems] compared with usual care as defined by the study.

*Exercise* was defined as planned, structured, and repetitive movement to improve or maintain one or more components of physical fitness. This may have included, but was not limited to, resistance/strength training, aerobic activities, balance training, tai chi, flexibility interventions, dancing/movement therapy, and physical therapy intervention involving a significant activity component (not passive interventions such as transcutaneous electrical nerve stimulation or massage).

*Physical activity* was defined as any bodily movement produced by skeletal muscles that requires energy expenditure, referring to all movements included during leisure time that are unstructured and typically of lower intensity compared to exercise (i.e., leisurely walking, diversional therapy interventions that require significant movement components such as gardening, cleaning).

*Nutritional interventions* may have involved, but were not limited to, changes to food intake, caloric or vitamin supplementation, meal programs designed to improve delivery and/or eating environment, and/or education of residents or caregivers.

## Information Source, Search Strategy, Study Selection, Data Extraction and Risk-of-Bias Assessment

The comprehensive search strategy, risk-of-bias assessment and data extraction process utilized for this review are detailed in **Supplement 1**.

## Data synthesis

Meta-analysis (i.e., quantitative pooling of data) was intended at the time of the PROSPERO registration if two or more studies were identified with sufficient homogeneity in study design, interventions and outcomes[18]. However, due to the lack of homogenous data, only a qualitative synthesis was undertaken to explain the depth and breadth of the literature.

## Results

### Search results

The search identified 10,955 papers, of which 3,902 were duplicates and excluded. Following the initial screening of 7,053 titles and abstracts, 62 full-text articles were assessed for eligibility and three papers met the inclusion criteria (see **Figure 1**).

### Study characteristics

The three included studies (**Table 1**) consisted of one 4-month RCT[19] in 33 nursing homes (n=723), one 9-month clustered RCT[20] in 16 nursing homes (n=277) and one 3-month non-RCT[21] in 1 nursing home (n=30) .

### Risk of bias

The two RCT studies by Husebo et. al.[19] and Ballard et. al.[20] were evaluated using ROB-2 tool[22] had an overall *low risk* of bias. The non-RCT study by Sturtzel et al.[21] was assessed using ROBINS-I tool[23] and had overall *serious risk* of bias due to lack of clarity regarding confounding impact on measurement of outcome and lack of information on missing data (**Figure 2**).

## Baseline cohort characteristics

Sturtzel et. al.[21] included 30 participants from 57-98 years of age. No further demographic information nor outcome measures such as body mass index and fibre intake were reported.

Husebo et. al.[19] included 723 participants from 67 units in 33 nursing homes (control group: 31 units, n=329; intervention group: 36 units, n=394). The baseline characteristics of the control and intervention groups were similar in mean age [87.0 (7.2) vs. 86.5 (7.7), respectively], proportion female [186 (75%) vs. 216 (73%)], comorbidities [5.5 (3.7) vs 4.8 (3.6)], number of regular medications [7.6 (3.7) vs. 7.6 (3.8)], and proportion of urban nursing homes [16 (52%) vs. 19 (53%)].

Ballard et. al[20] included 277 participants from 16 nursing homes (8 intervention homes, n=146 ; 8 control homes, n=131). The baseline characteristics of the control and intervention groups were similar in mean age [85.2 (7.0) vs. 85.3 (7.0), respectively], proportion of female participants [95 (72.5%) vs. 100 (75.3%)], proportion taking antipsychotic medication [23 (17.6%) vs. 26 (17.8%) and proportion Caucasian [115 (87.8%) vs. 132 (90.4%)].

## Intervention characteristics

Husebo et al.[19] implemented a multifaceted intervention comprised of a 2-day education seminar, systematic pain management, medication review and initiation of a minimum of 90 minutes of personalized weekly activities which may have included physical activity monitored by accelerometry, however these activities were not defined.

Ballard et. al.[20] evaluated the impact of antipsychotic medication review (AMR) in combination with non-pharmacological interventions [i.e., social interaction (SI), person-centered care (PCC) and exercise] on antipsychotic use in people with dementia using a 2x2x2 factorial design. All 16 homes received PCC. The intervention groups received AMR either in isolation or with a combination of SI and/or exercise.(i.e., PCC and AMR, n=2; PCC, AMR and exercise, n=2; PCC, AMR and SI, n=2;

PCC, AMR, SI and exercise, n=2) The active control groups did not receive AMR but received PCC with a combination of social interaction and/or exercise, or neither (PCC only, n=2; PCC and SI, n=2; PCC and exercise, n=2 and PCC, SI and exercise, n=2).

The Sturtzel et al.[21] study evaluated the addition of oat bran (containing 8.3g of non-digestible, nonfermentable fibre per 100g) to the oral diet of the intervention group (n=15) with the view of reducing laxative medication usage compared to usual care controls (see Table 1).

## Outcomes

### Frailty components:

None of the three studies reported the level of frailty by any model, however all reported individual components of frailty.

#### *Medications*

All three studies reported the number of prescribed medications (i.e., a component of the FRAIL scale[17]).

Husebo et al[19] reported the number of regular medications decreased significantly from baseline to month 4 (active intervention period) in the intervention group compared to the control group [-0.8 (-1.2, -0.4), $p<0.001$]. The number of psychotropic drugs also was reduced significantly in the intervention group when compared to the control group at month 4 [-0.4 (95% CI -0.6, -0.10), $p<0.05$].

Ballard et al.[20] reported a significant reduction in antipsychotic use in the AMR group compared to the non-AMR group from baseline to month 9 [0.17 (95% CI 0.05-0.60), p=0.006].(see Table 2), with no interaction with, or independent benefit from, the other treatments (exercise, SI). Importantly, SI and AMR in combination ameliorated negative neuropsychiatric withdrawal symptoms, and those receiving exercise had less symptoms than those not receiving exercise (detailed in **Supplement 1**).

Sturtzel et al.[21] reported that nutritional support (i.e., increase in oat fibre consumption) was associated with a reduction in the use of medications for constipation (i.e., laxatives) and maintained body weight. The prescribing of laxatives was significantly reduced by 59% ($p<0.001$) compared to the control group who had 8% increase in laxative usage ($p=0.22$).

*Nutritional status*

Sturtzel et. al.[21] reported weight loss which is one of the phenotypical aspects of Fried frailty criteria[15]. Body mass was significantly reduced in the control group ($p<0.005$) only, constituting a mean loss of 3% body mass (2kg) during a three-month period. If this is extrapolated out to 12 months, it exceeds the *clinically significant* frailty threshold of 4.5 kg or 10% of body mass loss annually[15] (see Table 2).

*Functional independence*

Husebo et al.[19] reported dependency in a daily living via activities of daily living (ADL) measure, which is related to the phenotypical Clinical Frailty Scale (CFS)[16] and a component of the Frailty Index. Dependency, as measured by the ADL scale, did not change significantly between the control and intervention group in the first four months (-0.8 (95% CI -1.6, 0.0) but was significantly improved in the intervention group compared to control group at month nine [-1.4 (95% CI -2.7, -0.1), $p<0.05$].

**Other measured outcomes**

*Other outcomes* are reported in **Supplement 1,** including quality of life, clinical global impressions of change, neuropsychiatric symptoms, and mortality.

## Discussion

The aim of this review was to identify and evaluate the effects of best practice frailty interventions involving medication optimization delivered in combination with exercise and/or nutrition support for the management of frailty. This review found a very small literature base evaluating some components of best practice frailty interventions in aged care, highlighting the need for more multi-dimensional interventions in aged care.

### Quantity of literature available

Despite an exhaustive search, only two RCTs and one non-RCT study informed this review, and no study employed all three recommended basic components of frailty treatment nor included resistance exercise. A total of 62 full articles were reviewed and 95% subsequently deemed ineligible due to the exclusion of studies that focused on single interventions, were not experimental in design, or not conducted in residential aged care. This paucity of literature may represent a broad pessimism and low expectation of a good prognosis following rehabilitation in the industry[24], which may flow onto poor design and motivation to implement suitable translation interventions.

The reason for such a small literature may also be related to differing views on frailty and its amenability to change. For example, some phenotypical definitions of frailty such as Fried[15] are more likely to be viewed as amenable to intervention as they are predicated on treating the effects of catabolism (i.e., weakness, shrinkage, sedentariness) rather than overall accrued/immutable disease processes (i.e., the Frailty Index[16]), Additionally, there is also the complexity of health conditions for those living within aged care (e.g., high levels of multimorbidity and polypharmacy) and limitations that come with government funding models which may further make it difficult to implement translational research or develop new clinical models in aged care settings. An example within the Australian context is the recent change in November 2022 in funding models from the outdated disablement model of the *Aged Care Funding Instrument* (ACFI)[25] to the modern *Australian National*

*Aged Care Classification* (ANACC)[26] which is intended to give greater flexibility to providers over the choice and delivery of evidence-based treatments in aged care such as those described within this review. While the current literature on medication optimization implemented *concurrently* with exercise and nutritional support for the management of frailty in aged care is non-existent according to our review, these changes to funding in aged care may lead to vital future research in this space.

### Quality of literature retrieved

We acknowledge the high quality and low risk of bias of the two RCTs. However, the non-RCT study had limited reporting of intervention details and fidelity to the intervention. Frailty itself was not an outcome reported by any of the studies, hence no definitive conclusion can be made from the two RCTs as they did not include robust resistance exercise interventions, nor did they target frailty specifically as an outcome. Sturtzel et al.[21] did not report with sufficient clarity participant allocation, baseline demographic, outcome measures, adherence to the intervention, or data analysis[21]. Clear, concise, and detailed reporting of these trial elements for replication is important as residents in aged care have complex conditions and interactions between medications and diet, which may not be captured by insufficient reporting. While Husebo et al.[19] was of a higher overall trial quality, it did not indicate what proportion, if any, of the mandated minimum of 90 minutes of activity for every participant during the study period was *exercise*. Adherence to these tasks was not reported, which may have produced heterogenous results as well. For example, the variable inclusion or exclusion of exercise from the mandated 90 minutes could have impacted the physical function and quality of life of residents, thus confounding the results. As little as three months of high-intensity exercise in aged care settings is sufficient to improve physical function, strength, muscle mass and measures of quality of life by clinically relevant amounts[27,28], suggesting that exercise exposure and modality needs to be more rigorously documented in future trials. Ballard et al.[20] was also a high quality study, however it only

focused on antipsychotic medication without consideration of other medications the residents were taking. Considering that polypharmacy is present in up to 91% of aged care residents[29], comprehensive medication optimization strategies such as that used in Husebo et al.[5] appear warranted. Thus, more targeted, and holistic research within aged care to better capture the risk factors and complex nature of frailty is needed.

**Benefits of interventions reported**

Despite the limitations noted above, the interventions reported led to positive outcomes for a variety of clinical measures. The use of nutritional support (i.e., oat fibre) in Strutzel et al.[21] led to a significant reduction (59%) in the use of laxatives in older adults living in nursing home. There was no indication of the clinical characteristics of participants (i.e. comorbidities, diagnoses, type of laxatives, or other medications they were taking), however these results are promising even if only targeting one class of medication. Frailty development has been linked to polypharmacy[12] and *deprescribing of inappropriate medications* for older adults with frailty is the *only* pharmacological strategy supported by current guidelines[30,31]. However, the lack of clarity in the demographic and clinical characteristics of the participants reported in Sturtzel et al.[21] limit the ability to generalize these findings. Husebo et al.[19] indicated their intervention had positive effects on preservation of functional independence and reduction in the number of regular medications, on-demand medications and psychotropic medications used during the intervention period (0-4 months). Most benefits were either unchanged during the follow-up period or attenuated. This may be due in part to the lack of integration of suitable non-pharmacological treatments to sustain the effects of deprescribing. For example, several large deprescribing-only trials conducted in community settings have reported no benefit for adverse events, hospitalizations, and deterioration of function in deprescribing intervention groups compared to usual care over even longer follow-up periods[32]. However, there is promising evidence to suggest that in

community settings, appropriate physical activity, and nutrition, combined with comprehensive geriatric evaluation involving medication review may reduce frailty and sustain deprescribing benefits over longer periods[33]. Thus, pharmacological interventions offered in aged care to reduce polypharmacy and target frailty should ideally be integrated with non-pharmacological interventions such as exercise and nutritional support to sustain clinical improvements.

## Strengths & limitations of this review

This is the first review of medication optimization interventions delivered in conjunction with exercise and/or nutritional support as best-practice treatment for older adults living with frailty in aged care. Strengths of this review include the large scope and search strategy across several reputable databases with no search limits and the inclusion of grey literature; the incorporation of all operational definitions of frailty and its components, robust analysis using two reviewers during the full-text and risk of bias stage, and the prospective registration of this review with PROSPERO[34] conforming to PRISMA guidelines in all the process[14].

Limitations of the review include that due to time restraints, authors of the included articles were not contacted to request further data or clarification for purpose of quality assessment or extraction of outcomes if it was unclear within the reporting of the article and any associated protocol papers. Furthermore, while not an inherent weakness of the review process itself, the small body of retrieved articles limits the generalizability of statements made within this review regarding the effects of interventions on the treatment of frailty components, however, reaffirms the conclusion that more robust research is needed in this setting.

## Conclusion

This review identified and evaluated for the first time the effects of multifaceted interventions involving medication optimization in combination with exercise and/or nutrition support for the management of frailty in aged care. The review found only 3 trials, none of which targeted frailty as a primary outcome of the trial and as a result did not employ the full scope of best practice interventions recommended for frailty (i.e., optimization of medications, nutrition, and resistance exercise) in this setting. Future studies should be designed to explore the impact of multifaceted interventions specifically in the management of frailty in older adults in residential aged care facilities with clear and concise measurement of frailty outcomes, cohort and intervention descriptions, and measurements of intervention fidelity.

**Conflict of Interest:** The authors declare no conflicts of interest.

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**Figure Titles & Captions**

**Figure 1. PRISMA Study flowchart of included studies**

**Figure 2. Risk of Bias for Included Studies**
The traffic light plot showing risk of bias using ROB-2 assessment for RCTs and ROBIN-1 assessment for non-RCTs. Studies are stratified by overall risk of bias with green color representing low risk of bias, blue no/missing information, and red high risk of bias