Title: Association of drug therapy with the risk of incident frailty: a systematic review

Running title: Drug therapy and frailty

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Association between drug therapy and risk of incident frailty: a systematic review

Abstract

Medication is a potential factor influencing frailty. However, the relationship between pharmaceutical treatments and frailty remains unclear. Therefore, we conducted the present systematic review to summarize the association between drug therapy and the risk of incident frailty in older adults. We systematically searched the MEDLINE electronic database for articles indexed between January 1, 2000, and December 31, 2021, for randomized controlled trials (RCTs) and cohort studies reporting frailty changes associated with drug therapy. A total of 6 RCTs and 13 cohort studies involving 211,948 participants were identified, and their treatments were categorized into six medication classes: analgesics, cardiometabolic medication, chemotherapy, central nervous system (CNS)-active medication, hormonal therapy, and nutritional supplements. While the analysis revealed that only CNS-active medications were associated with an elevated risk of frailty, other medication classes also affected frailty; however, this is not conclusively attributable to a class-wide effect.

Keywords: drug, therapy, medication, frailty
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Introduction

Frailty is a state of increased susceptibility to stress that results in adverse health outcomes.\(^1\)

Currently, no gold standard exists for diagnosing frailty; however, one of the most widely applied tools is the Fried frailty phenotype, which assesses physical frailty using five criteria: unintentional weight loss, exhaustion, weakness, slow walking speed, and low physical activity.\(^2\) A previous systematic review among community-dwelling adults reported prevalence rates of frailty and pre-frailty of 12% (11–13%) and 46% (45–48%), respectively, when assessed based on physical frailty, while the rates based on the frailty index (FI) were 24% (22–26%) and 49% (46–52%), respectively.\(^3\) Moreover, the prevalence of frailty increases with age.\(^4\) In a cohort study in England, the prevalence rates of frailty in the 50–64, 65–74, 75–84, and >85 years age groups were 9.9%, 29.3%, 53.5%, and 68.8%, respectively.\(^5\)

Genetic and environmental factors, along with epigenetic mechanisms, are believed to be associated with frailty development.\(^1\) Some studies have also demonstrated that certain factors are associated with an increased risk of frailty.\(^6-8\) While an older age and female sex are unmodifiable, other factors, including a higher body mass index (BMI), living alone, low levels of exercise, polypharmacy, smoking, drinking, malnutrition, and low vitamin D levels, can be improved.\(^6\) Additionally, controlling certain comorbidities such as diabetes, hearing dysfunction, cognitive impairment, poor sleep, fall history, pain, depression, and respiratory diseases may decrease the risk of frailty.\(^6\)

Therefore, identifying the modifiable risk factors for frailty is imperative to prevent its development and progression. This could mitigate adverse health outcomes and improve the quality of life in older adults. One potentially modifiable risk factor is medication. As individuals age, they tend to have an increased burden of medication. A meta-analysis revealed a prevalence of polypharmacy of 45% among individuals aged >65 years compared with 25% among younger age groups.\(^9\) Furthermore, meta-analyses have suggested that polypharmacy increases the risk of frailty.\(^6, 8, 10, 11\) Several cross-sectional studies
have shown inconsistent results regarding the association of anticholinergic or sedative drugs with frailty. Angiotensin-converting enzyme inhibitors (ACEI), testosterone, and vitamin D may improve muscle function, leading to decreased frailty. Thus, understanding the associations between individual drug therapies and frailty may be useful in preventing frailty development and progression.

However, comprehensive reviews investigating the link between specific drugs or medication classes and the risk of frailty are lacking. To address this gap, we conducted the present systematic review to summarize evidence of the association between drug therapies and incident frailty in older adults.

**Methods**

**Data Sources and Study Selection**

We conducted a systematic search of the MEDLINE electronic database for English-language articles indexed between January 1, 2000, and December 31, 2021, using the keywords “drug therapy” and “frailty” to identify publications from randomized controlled trials (RCTs) and observational studies that reported changes in frailty associated with drug therapies. We also manually searched for articles from recent publications to ensure completeness.

Studies were eligible if: 1) they were RCTs or cohort studies; 2) they used pharmacotherapy as a study intervention or exposure; and 3) they reported frailty as a study outcome. Studies were excluded if: 1) they were non-human studies, reviews, commentaries, case reports, or abstracts without full reports; 2) they did not use a pharmacotherapy intervention; or 3) they did not report the frailty status at baseline or as an outcome.
Two investigators (S.T. and T.C.) independently assessed the abstracts and full-text articles for eligibility. Disagreements were resolved by a third reviewer (D.K.). Our systematic search identified five RCTs and 13 cohort studies (Appendix Figure 1).

This systematic review was registered with the International prospective register of systematic reviews (PROSPERO) database (identification number: CRD42023463023).

Data Extraction

Two investigators (S.T. and T.C.) independently used a standardized form to extract study characteristics, including information on the first author, publication year, country, study type, sample size, mean age, sex, follow-up time, study population, type of medication therapy, and method of frailty measurement.

The outcome of interest was the incidence of frailty or change in frailty scores from the baseline to the end of the follow-up study after pharmacotherapy interventions.

Quality Assessment

Two investigators (S.T. and T.C.) independently evaluated each study using version 2 of the Cochrane Risk-of-Bias Tool for randomized trials (RoB 2)(26) and the Newcastle-Ottawa quality assessment scale to assess the RCTs (Appendix Table 1) and cohort studies, respectively.(27) We also assessed a new user design that reduced bias in observational studies (Appendix Table 2). Any disagreements were resolved by a consensus involving a third reviewer (D.K.). We determined the overall quality of evidence for each study as having a high, moderate, or low risk of bias (Appendix Figure 2).

Data Synthesis

Due to the heterogeneity of the included studies, we qualitatively summarized the evidence based on the type of pharmacological intervention without performing a meta-analysis.
Results

Characteristics of the Included Studies

We identified six RCTs (28-33) and thirteen cohort studies (34-46). The studies were published between 2011 and 2022 and included 211,948 participants, with sample sizes ranging from 23 to 41,378 participants. The mean age of the participants ranged from 55.6 to 81.7 years. The mean follow-up duration ranged from 2 weeks to 11 years. Seventeen studies were conducted in community settings (28-32, 34-37, 39-46), while two were conducted in nursing home settings (33, 38). Four studies included participants with no frailty at baseline (38, 40, 41, 43). We categorized pharmacological interventions into six classes: analgesics, cardiometabolic medication, chemotherapy, central nervous system (CNS)-active medication, hormonal therapy, and nutritional supplements (Table 1).

Quality of the Included Studies

The risk of bias was low, moderate, and high in six (28, 30, 32, 33, 37, 39), ten (31, 34-36, 38, 40, 41, 43, 45, 46), and three (29, 42, 44) studies, respectively. According to the study type, four RCTs had a low risk of bias (28, 30, 32, 33), one had a moderate risk (31), and one had a high risk (29). Among the cohort studies, two studies had a low risk of bias (37, 39), nine had a moderate risk (34-36, 38, 40, 41, 43, 45, 46), and two had a high risk (42, 44) (Appendix Figure 2).

Effect of Pharmacologic Interventions on Frailty

The associations between medication and frailty according to the type of medication used were summarized (Table 2). The studies used different criteria to identify frailty: seven studies used the frailty phenotype (28, 33, 38, 43-46), six used the frailty index (28, 30, 32, 34, 35, 41), three used the Study of Osteoporotic Fractures (SOF) index or modified SOF (34-36, 47), and two used the FRAIL scale or
modified FRAIL scale, (40, 42) Frailty-related disease, Geriatrics 8 (G8) score, Balducci score, Leuven Oncogeriatric score, and liver frailty index were also used.

In the analgesic group, one study that reported the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for >60 days per year was associated with an increased risk of frailty in a cohort study of male physicians free of cancer and cardiovascular diseases (CVDs) (odds ratio [OR], 1.26; 95% confidence interval [CI], 1.07–1.49). (34) However, studies on aspirin use yielded conflicting results. (28, 35) A cohort study by Orkaby et al. in male physicians free of cancer and CVDs (35) showed that aspirin use was associated with a decreased risk of frailty (OR, 0.85; 95% CI, 0.76–0.96), while an RCT by Espinoza et al. in participants free of CVDs, dementia, and major disability (28) showed no association with frailty (HR, 1.04; 95% CI, 0.96–1.13).

In cohort studies of cardiometabolic medications, ACEI was associated with a lower risk of frailty in patients with osteoarthritis (risk ratio [RR], 0.72; 95% CI, 0.53–0.99). (36) Metformin use was associated with decreased frailty-related diseases in patients with type II diabetes (absolute risk reduction [ARR] of 5% in the healthy group, 13.7% in the cancer high-risk group, 6.3% in the CVD risk group, and 23.8% in the frailty high-risk group). (37) Statin use was not associated with frailty in postmenopausal women (OR, 1.00; 95% CI, 0.85–1.16). (38)

Regarding chemotherapy, an RCT of pertuzumab, trastuzumab, and a metronomic regimen in patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (29) and a cohort study of docetaxel with a cyclophosphamide regimen in patients with breast cancer (39) were not associated with frailty.

All CNS-active medications in the cohort studies were associated with an increased risk of frailty. (40-43) Use of muscle relaxants in patients with diabetic kidney disease (OR, 2.75; 95% CI, 1.84–4.11) (40), and sleep and/or pain medication in the Health and Retirement Study (hazard ratio [HR], 1.36; 95% CI, 1.14–
1.62, HR, 1.51; 95% CI, 1.36–1.68, and HR, 1.82; 95% CI, 1.45–2.30) (41) were associated with increased risk of frailty. Selective serotonin reuptake inhibitors (SSRI) used in patients with depression (OR, 2.75; 95% CI, 1.84–4.11), and all antidepressants in patients with (OR, 3.64; 95% CI, 2.41–5.53) and without depression (OR, 1.79; 95% CI, 1.47–2.19) (43) were associated with an increased risk of frailty.

In cohort studies of hormonal therapy, oral, buccal, or transdermal testosterone in patients with hypogonadal hyperglycemia was associated with a lower risk of frailty. (44) Androgen deprivation therapy (ADT) in patients with prostate cancer was initially associated with an increased risk of frailty (mean adjusted difference of Fried phenotype score; ADT vs control, 0.72; 95% CI, 0.37–1.06) (45) but not after two years of follow-up (OR, 1.86; 95% CI, 0.2–21.0). (46)

In RCTs on nutritional supplementation, the administration of a protein supplement (14.7 g AXA1665) three times daily was associated with a decreased risk of frailty in patients with cirrhosis (ARR, -0.70 vs. -0.14 and a percentage change of 20.5% reduction vs. 5.0%), whereas 4.9 g of AXA1665 administered three times daily did not show the same benefit. (31) A study on L-carnitine use in participants without any CVD and cancer demonstrated its possible association with a lower risk of frailty. (32) In contrast, prebiotics (inulin and fructooligosaccharides) in mobile older adults free of dementia (33) and vitamin D3 or omega-3 fatty acid supplements in participants free of CVDs and cancer (30) were not associated with frailty.

Discussion

In this systematic review of six RCTs and thirteen cohort studies of six medication classes, we found that CNS-active medications were associated with an increased risk of frailty. The other medication classes yielded inconsistent results. The studies included in our review had diverse baseline characteristics, including participant age, participant comorbidities, follow-up time, setting, population, frailty status, and frailty measurement tools. These variables could potentially influence the reliability of the
outcomes, particularly when interpreted at the medication class level. Medications can influence frailty in both beneficial and detrimental ways. The potential mechanisms of medications (34, 40-43, 45) that tend to increase the risk of frailty can be explained through their effects on increasing cardiovascular risk (34, 48, 49), cognitive impairment (50, 51), fall and fracture risk (52-58), and fatigue and low energy (45). Conversely, some medications (31, 32, 35-37, 44) may decrease the risk of frailty by reducing inflammation and oxidative biomarkers, including interleukin-6, tumor necrosis factor (TNF)-alpha or TNF-receptor 2, and C-reactive protein (59-61). They may also improve cardiac and vascular function (62), enhance skeletal muscle function (63), improve energy expenditure (64, 65), reduce fatigue, and boost immune function (33, 66-69).

In the analgesic group, non-aspirin NSAIDs were associated with a risk of frailty (34), whereas aspirin showed conflicting results. NSAIDs inhibit cyclooxygenase-2-mediated prostaglandin-2, which may increase cardiovascular risk and, subsequently, frailty (34, 48, 49). However, aspirin increases the production of anti-inflammatory aspirin-triggered lipoxins, thereby reducing cardiovascular risk (35, 70). A long-term follow-up RCT (35) reported that 325 mg aspirin was associated with a lower risk of frailty. In contrast, another RCT (28) did not demonstrate an association between 100 mg aspirin and the development of frailty. This discrepancy may be because low-dose aspirin has little effect on the levels of inflammatory markers such as C-reactive protein (28, 71-73).

In the cardiometabolic group, ACEI (36), metformin (37), and statins (38) have been hypothesized to reduce the risk of frailty through anti-inflammatory mechanisms. However, only ACEI and metformin were associated with a lower risk of frailty. In addition to their anti-inflammatory effect, ACEI might reduce frailty by improving cardiac and vascular functions, increasing nitric oxide production, enhancing skeletal muscle function, and preventing age-related mitochondrial dysfunction (36, 47, 62, 63, 74, 75). Contrastingly, statins were not associated with frailty. This might be because most study participants were healthy at baseline and showed improvement in frailty (38).
We observed no significant correlation between chemotherapy and frailty in patients with breast cancer. Although acute and subacute toxicity of chemotherapy could decrease patients’ fitness and quality of life, the effect might be temporary, and the patient’s frailty returned to baseline after one year. Participants receiving CNS-active medications, muscle relaxants, sleep and pain medications, SSRIs, and antidepressants appear to have increased risks of frailty through the CNS effects of these drugs. The use of CNS-active medications is linked to higher risks of cognitive impairment, immobilization, fall-related injuries, and fractures, which could contribute to the development of frailty.

Testosterone replacement therapy can reduce the risk of frailty in patients with late-onset hypogonadism by improving glucose metabolism and obesity, reducing waist circumference and BMI, and increasing physical activity energy expenditure. In contrast, ADT increased the risk of frailty in patients with PCa. Although ADT may affect changes in body composition, resulting in decreased physical performance, one study reported that changes in body composition were not associated with frailty. ADT-associated fatigue, apathy, and low energy levels may also play a role. However, after two years, ADT was not associated with frailty despite incomplete recovery of body composition, increased insulin resistance, and reduced physical aspects of quality of life. The frailty measure used in this study may not have been sensitive enough to detect changes in frailty.

Vitamin D3 or omega-3 fatty acids, AXA1665, L-carnitine, and probiotics may reduce the risk of frailty by improving skeletal muscle and physical function. However, only AXA1665 and L-carnitine demonstrated decreased risks of frailty. One study showed that vitamin D3 or omega-3 fatty acid supplementation failed to improve frailty in healthy participants, although low levels of vitamin D or omega-3 fatty acid supplementation were associated with frailty and sarcopenia. Moreover, while probiotics do not affect frailty, they can improve exhaustion and handgrip strength,
which are assumed to improve immune function, leading to decreased cytokine production and reduced macrophage activation.\(^{(33, 66-69)}\)

The various frailty assessment methods used in the included studies make it challenging to compare outcomes across studies. Modifications to validated frailty assessments may lead to the misclassification of frailty status.\(^{(79)}\) Some studies have used existing databases that were not primarily designed to measure frailty. Studies by Orkaby \(^{(34, 35)}\) and Brouwers \(^{(39)}\) reported different results depending on the frailty definitions. This highlights the importance of specifying a frailty definition before conducting a trial and using validated frailty measurements.

This is the first systematic review to demonstrate the potential positive and negative influences of medication on frailty. However, only CNS-active medications showed a class effect, leading to an increased risk of frailty. Consequently, our findings suggest that physicians should take care when prescribing CNS-active medications to prevent frailty onset and mitigate the worsening of frailty in vulnerable groups. Furthermore, the necessity of CNS-active medications for patients already receiving them should be reviewed and reconsidered. This approach could potentially prevent frailty onset or improve the condition of patients with frailty.

Future research should focus on a broader range of medications that could potentially increase the risk of frailty as well as those that could decrease this risk as potential treatments for frailty. To enhance the reliability of this study, we recommend conducting additional RCTs or employing new user designs in observational studies. Additionally, a prolonged follow-up period should be considered in these studies because some medications may exert long-term effects on frailty.

**Limitations**

Our systematic review is limited by the risk of bias, inconsistent results, and significant heterogeneity in the study population, medication classes, and frailty measurements. As most of the included studies
examined medications intended to treat patients with specific conditions, the results may not apply to
the general population. Publication bias could be a concern because we only searched the MEDLINE
database and limited the search to English-language publications.

**Conclusion**

The results of this systematic review revealed moderate evidence of a possible association between
CNS-active medications and an increased risk of frailty, little evidence of associations between ACE and
metformin with a decreased risk of frailty, and associations between NSAIDs and an increased risk of
frailty. Further research is warranted to confirm the findings of these studies, elucidate the underlying
mechanisms, and explore the effects of other commonly used medications on frailty.
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Conflict of Interest Disclosures

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Authors’ contributions

Study design: ST, TC, and DK. Data acquisition, analysis, and interpretation: ST, TC, SMS, CP, SDS, and DK. Writing of the first draft: ST and DK. Revision of the first draft for important intellectual content: ST, TC, SMS, CP, SDS, and DK. All authors have read and approved the final version of the manuscript.