Association Between Chronic Proton Pump Inhibitor Use and Frailty in Geriatric Patients in Primary Care

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Abstract

Introduction: Proton pump inhibitors (PPIs) are among the most frequently prescribed medications for acid-related disorders and are widely used by the geriatric population. However, emerging evidence suggests that long-term use may be associated with the development of conditions related to geriatric frailty.
Methods: A systematic literature review was conducted in accordance with the PRISMA 2020 guidelines. The following databases were searched: PubMed/MEDLINE, Scopus, Web of Science, Embase, Cochrane Library, LILACS, and the Virtual Health Library (BVS), including studies published between 2021 and 2026. Evidence regarding the impacts of PPIs on frailty, micronutrient deficiency, bone health, cognitive decline, cardiovascular events, polypharmacy, and deprescribing strategies was selected.
Results: Studies demonstrated an association between long-term PPI use and deficiencies in vitamin B12, magnesium, calcium, and iron, as well as an increased risk of osteoporosis, fractures, cognitive decline, dementia, cardiovascular events, and polypharmacy. These alterations showed the potential to reduce functional capacity and increase clinical vulnerability in the geriatric population. Deprescribing strategies demonstrated benefits in reducing unnecessary medication exposure and promoting therapeutic safety.
Conclusion: Chronic PPI use may contribute to the development or exacerbation of geriatric frailty through multiple pathophysiological mechanisms. Periodic assessment of therapeutic necessity and the implementation of deprescribing strategies are essential measures for promoting healthy aging and enhancing the quality of care in primary health care settings.

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1. Introduction

Population aging represents one of the most significant challenges for contemporary health systems. The increase in life expectancy has been accompanied by a higher prevalence of chronic diseases, multimorbidity, and long-term medication use, particularly among older adults managed within Primary Health Care (PHC). In this context, frailty emerges as a multifactorial geriatric syndrome characterized by a decline in physiological reserve and an increased vulnerability to adverse outcomes, such as hospitalizations, falls, functional disability, and mortality

(JOHNSON *et al*., 2024; PRIDHAM; ROCKWOOD; RUTENBERG, 2024) [31, 52].

Frailty results from the interplay of biological, clinical, social, and environmental factors, and is currently considered a significant marker of vulnerability in older adults. Recent studies demonstrate that alterations in the cardiovascular, neuromuscular, immunological, and metabolic systems contribute to the development of this condition, reinforcing the need for early identification in clinical practice (ARRUÉ *et al*., 2024; SILAN; NICOLAIO; BOCCUZZO, 2025) [5, 62].

Parallel to this, proton pump inhibitors (PPIs) are among the most frequently prescribed medications worldwide. Drugs such as omeprazole, pantoprazole, esomeprazole, and lansoprazole are widely used for the treatment of gastroesophageal reflux disease, gastritis, and peptic ulcers, as well as for the prevention of gastric lesions induced by non-steroidal anti-inflammatory drugs (NSAIDs) (AHMED *et al*., 2023; KAMBOJ *et al*., 2024) [2, 33].

Although PPIs demonstrate high therapeutic efficacy and a favorable safety profile in short-term treatments, recent evidence has raised concerns regarding their long-term use, particularly in older populations. Several observational studies and systematic reviews suggest an association between the chronic use of these medications and an increased risk of clinically significant adverse events, including micronutrient deficiency, osteoporosis, fractures, respiratory infections, chronic kidney disease, cardiovascular alterations, and cognitive decline (ANDRAWES *et al*., 2025; LAKSHMISAI *et al*., 2025; CHAUDHRY *et al*., 2025) [3, 36, 14].

Among the pathophysiological mechanisms proposed for such complications, the reduction in intestinal absorption of vitamin B12, magnesium, calcium, and iron—essential nutrients for maintaining muscular, neurological, and bone function—is particularly noteworthy. The deficiency of these elements may directly contribute to loss of strength, sarcopenia, fatigue, and functional impairment, all of which are factors closely linked to the development of geriatric frailty (COSTA *et al*., 2021; SILVA *et al*., 2022; BARBOSA *et al*., 2025) [19, 64, 8].

Long-term PPI use has been associated with an increased risk of osteopenia, osteoporosis, and fragility fractures, especially in older adults with multiple comorbidities. These conditions may accelerate the loss of functional independence and promote the progression of frailty syndrome, thereby significantly increasing the demand for health care services (MARQUES *et al*., 2021; ROBERT *et al*., 2025; SILVA *et al*., 2024) [41, 53, 63].

Another relevant aspect refers to the association between PPIs and cognitive alterations. Recent studies have investigated potential links between the long-term use of these medications and a higher incidence of cognitive impairment and dementia. Although the underlying mechanisms have not yet been fully elucidated, it is hypothesized that metabolic, inflammatory, and vascular changes may contribute to this process, negatively impacting the functionality of older adults (CHAN *et al*., 2023; XIE *et al*., 2024; PENG *et al*., 2026) [13, 72, 49].

Cardiovascular repercussions have also garnered increasing attention. Research indicates an association between chronic PPI use and an increased risk of heart failure, cardiovascular events, and QT interval prolongation, particularly in older adults and patients with chronic conditions. Such alterations may contribute to a reduction in functional capacity and an increase in clinical vulnerability, both of which are central components of frailty (BELL *et al*., 2021; GENG *et al*., 2023; FAN *et al*., 2024) [11, 29, 25].

Polypharmacy, frequently observed in the geriatric population, constitutes another important factor in this discussion. The simultaneous use of multiple medications increases the risk of drug-drug interactions, adverse reactions, and potentially inappropriate prescribing. In this scenario, PPIs often remain prescribed for periods exceeding the necessary duration, even after the resolution of the initial indication, contributing to prolonged exposure and cumulative risks (LAWSON *et al*., 2022; OLIVEIRA *et al*., 2023; MOREIRA; RODRIGUES, 2025) [37, 48, 43].

Numerous studies have demonstrated a high prevalence of inappropriate PPI prescribing in outpatient settings, long-term care facilities, and primary health care services. This reality highlights the need for periodic medication reviews and the implementation of deprescribing strategies based on scientific evidence (ÇELIK *et al*., 2021; MUHEIM *et al*., 2021; WABE *et al*., 2025) [12, 44, 70].

In recent years, initiatives focused on PPI deprescribing have shown promising results in reducing adverse events and optimizing pharmacotherapy in older adults. International guidelines recommend continuous assessment of the need to maintain these medications, particularly in patients without a current clinical indication (TARGOWNIK; FISHER; SAINI, 2022; ROSSI *et al*., 2024; PEREIRA *et al*., 2024) [66, 55, 50].

Primary Health Care (PHC) holds a strategic position in the early identification of frailty and in the rationalization of medication use among older adults. As the primary point of entry into the health system, PHC facilitates longitudinal follow-up, monitoring of risk factors, and the implementation of preventive interventions capable of reducing complications associated with polypharmacy (ARAGONEZ, 2025; CORRÊA *et al*., 2022; SANTOS *et al*., 2025) [4, 17, 59].

Despite the growing number of studies on the safety of PPIs, important gaps remain regarding their specific influence on the development and progression of frailty in older adults. Understanding this association may contribute to improving clinical protocols, guiding deprescribing strategies, and strengthening safe practices in health care for the geriatric population (DEWI *et al*., 2024; WU *et al*., 2025; CONDUR *et al*., 2025) [22, 71, 15].

Given this scenario, it is essential to synthesize and critically analyze the available scientific evidence regarding the relationship between the chronic use of proton pump inhibitors and frailty in geriatric patients monitored within Primary Health Care, aiming to understand their mechanisms, associated factors, and potential implications for clinical practice.

2. Objectives

2.1. General Objective

To analyze, through a systematic literature review, the relationship between the chronic use of proton pump inhibitors (PPIs) and the development or exacerbation of frailty in geriatric patients monitored within Primary Health Care, by identifying the primary pathophysiological mechanisms, associated factors, and clinical impacts resulting from this association.

2.2. Specific Objectives

- To identify available scientific evidence regarding the association between long-term proton pump inhibitor use and frailty in older adults.
- To evaluate the primary adverse effects associated with chronic PPI use that may contribute to the development of frailty syndrome, including micronutrient deficiencies, sarcopenia, osteoporosis, fractures, cognitive impairment, and cardiovascular alterations.
- To investigate the pathophysiological mechanisms involved in the relationship between long-term PPI use and the reduction of functional capacity in geriatric patients.
- To analyze the influence of polypharmacy and potentially inappropriate prescribing on the long-term use of PPIs in the older adult population.
- To describe the prevalence and patterns of chronic PPI utilization among older adults managed within Primary Health Care services.
- To assess deprescribing strategies for PPIs described in the literature and their impacts on medication safety and the quality of life of older adults.
- To identify clinical, behavioral, and environmental factors associated with an increased risk of frailty in chronic PPI users.
- To analyze the role of Primary Health Care in the prevention, monitoring, and management of risks related to the long-term use of proton pump inhibitors.
- To synthesize evidence-based recommendations to optimize the prescription and monitoring of PPIs in geriatric patients, aiming to reduce adverse avvents and minimize the progression of frailty

3. Hypothesis

The chronic use of proton pump inhibitors is associated with increased frailty in geriatric patients monitored within Primary Health Care, due to a higher occurrence of micronutrient deficiency, musculoskeletal alterations, cognitive impairment, polypharmacy, and other adverse events that contribute to the reduction of the physiological reserve and functional capacity of these individuals. Thus, monitoring and rational deprescribing strategies for PPIs can reduce clinical risks and promote healthier and more functional aging.

4. Methods

4.1. Study Design

This is a systematic review conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. The objective of this study is to identify, select, critically appraise, and synthesize the available scientific evidence regarding the relationship between the chronic use of proton pump inhibitors (PPIs) and frailty in geriatric patients monitored within Primary Health Care (TARGOWNIK; FISHER; SAINI, 2022; ROSSI *et al*., 2024; CONDUR *et al*., 2025) [66, 55, 15].

4.2. Information Sources and Search Strategy

The bibliographic search was performed in the following databases: PubMed/MEDLINE, Scopus, Web of Science, Embase, Cochrane Library, LILACS, and the Virtual Health Library (VHL). These were selected as relevant sources for studies in the fields of geriatrics, clinical pharmacology, and primary health care.

We utilized controlled descriptors from the Medical Subject Headings (MeSH) and the Health Sciences Descriptors (DeCS) vocabularies, combined using the Boolean operators "AND" and "OR." The search strategy was structured using the following terms:

- "Proton Pump Inhibitors" OR "PPI" OR "Omeprazole";
- "Frailty" OR "Frailty Syndrome" OR "Frailty Index";
- "Older Adults" OR "Aged" OR "Elderly";
- "Primary Health Care" OR "Primary Care";
- "Polypharmacy";
- "Deprescribing".

An example of the search strategy applied in PubMed was as follows:

("Proton Pump Inhibitors"[MeSH] OR "PPI") AND ("Frailty"[MeSH] OR "Frailty Syndrome") AND ("Aged"[MeSH] OR "Older Adults").

4.3. Search Period

The search included studies published between January 2021 and June 2026. This period was selected to encompass the most recent scientific evidence regarding the potential impacts of long-term PPI use on the health of the older adult population.

4.4. Inclusion Criteria

Studies were considered eligible if they met the following criteria:

- **Study Design:** Original articles, systematic reviews, meta-analyses, observational studies, and clinical trials.
- **Timeframe:** Publications between January 2021 and June 2026.
- **Language:** Publications available in Portuguese, English, or Spanish.
- **Population:** Studies involving individuals aged 60 years or older.
- **Topic:** Research addressing the long-term use of proton pump inhibitors (PPIs) and its relationship with frailty, functional capacity, sarcopenia, polypharmacy, or adverse events related to aging.
- **Setting:** Studies conducted in outpatient settings, community-based settings, hospital settings, or Primary Health Care.

4.5. Exclusion Criteria

Studies were excluded if they met any of the following criteria:

- **Duplicates:** Duplicate records across the searched databases.

- **Non-original publications:** Letters to the editor, editorials, expert opinions, and conference abstracts lacking full-text availability.
- **Population:** Studies involving exclusively pediatric or young adult populations.
- **Scope:** Research that did not directly address the relationship between proton pump inhibitor (PPI) use and frailty or related clinical outcomes.
- **Methodological limitations:** Studies with poorly described methodologies or those for which the full text was not accessible.

4.6. Study Selection Process

The study selection process was conducted in three independent stages:

- **Stage 1:** Screening of titles and abstracts identified across the databases.
- **Stage 2:** Full-text reading of potentially eligible articles.
- **Stage 3:** Application of eligibility criteria to define the final sample.

The entire selection process was conducted by two independent reviewers. Any discrepancies were resolved through consensus or by consultation with a third reviewer. The process of identification, screening, eligibility, and inclusion of studies is detailed in the PRISMA 2020 flow diagram.

4.7. Data Extraction

Data from the included studies were extracted using a standardized form, ensuring consistency in the synthesis of results. The following information was collected:

- **Study identification:** Authors and year of publication.
- **Geographic context:** Country of the study.
- **Methodology:** Study design.
- **Population characteristics:** Number of participants and age range.
- **Exposure parameters:** Type and duration of PPI use.
- **Frailty assessment:** Instruments used to measure frailty.
- **Clinical outcomes:** Main endpoints evaluated.
- **Synthesis of findings:** Results regarding the association between PPI use and frailty.
- **Study quality:** Limitations identified by the authors.

4.8. Methodological Quality Assessment

The methodological quality of the included studies was assessed using specific instruments tailored to each study design:

- **Newcastle-Ottawa Scale (NOS):** Used for observational studies.
- **AMSTAR-2:** Used for systematic reviews.
- **RoB 2 (Risk of Bias Tool):** Used for randomized clinical trials.

The studies were classified as having a low, moderate, or high risk of bias, according to the criteria established by each respective tool.

4.9. Data Synthesis and Analysis

The results were synthesized through a narrative and descriptive approach, accounting for the methodological heterogeneity of the included studies. The analysis focused on identifying the primary mechanisms through which long-term PPI use may contribute to the development or exacerbation of geriatric frailty, including nutritional alterations, musculoskeletal impairment, cognitive decline, cardiovascular events, polypharmacy, and reduced functional capacity.

Whenever possible, results were grouped into thematic categories to facilitate the interpretation of findings and the comparison across studies.

4.10. Ethical Aspects

As this study is a systematic review based exclusively on secondary data available in the scientific literature, without direct involvement of human subjects or access to individualized information, submission to a Research Ethics Committee was not required, in accordance with the guidelines of Resolution No. 466/2012 of the Brazilian National Health Council.

4.11. PRISMA Flow Diagram

The study selection process is presented in the PRISMA 2020 flow diagram (Figure 1), covering the identification, screening, eligibility, and inclusion stages of the articles, thereby ensuring the transparency and reproducibility of the methodological process.

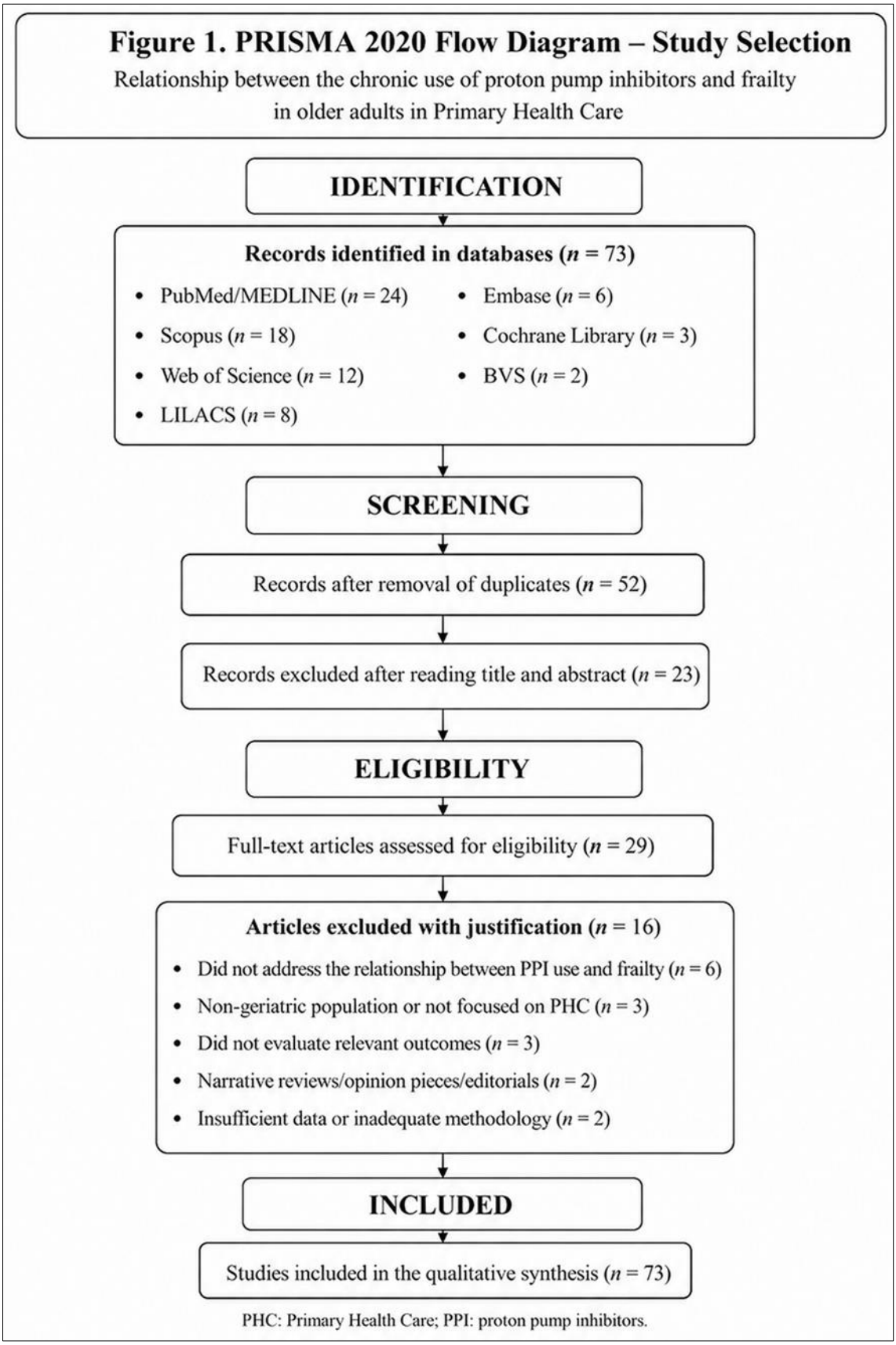


Fig 1: PRISMA 2020 flow diagram illustrating the identification, selection, eligibility, and inclusion process of studies on the relationship between long-term proton pump inhibitor use and frailty in geriatric patients within Primary Health Care.

5. Results

The search strategy adopted enabled the identification of relevant studies published between 2021 and 2026, which addressed the chronic use of proton pump inhibitors (PPIs) and their potential impacts on the health of the elderly population. Following the application of the eligibility criteria established in this systematic review, evidence was selected from observational studies, systematic reviews, meta-analyses, clinical guidelines, and research conducted across various care settings, including Primary Health Care, outpatient services, long-term care institutions, and hospitals. The analyzed studies primarily investigated the association between long-term PPI use and outcomes related to geriatric frailty, such as micronutrient deficiencies, musculoskeletal impairment, osteoporosis, fractures, cognitive decline, cardiovascular events, polypharmacy, and reduced functional capacity.

Overall, the results demonstrated that long-term PPI use is frequently associated with factors that may contribute to the development or exacerbation of frailty in the elderly. The most commonly reported mechanisms involved impaired absorption of essential nutrients, particularly vitamin B12, magnesium, calcium, and iron, as well as increased susceptibility to adverse clinical events that compromise the autonomy and functionality of this population. Furthermore, several studies highlighted a high prevalence of long-term prescriptions without periodic reassessment of therapeutic necessity, underscoring the importance of monitoring strategies and deprescribing within the context of Primary Health Care (SHAHID *et al*., 2025; MUHEIM *et al*., 2021; TARGOWNIK; FISHER; SAINI, 2022) [61, 44, 66].

Table 1 presents a synthesis of the main studies included in this systematic review, highlighting authors, methodological design, study population, key findings, and the observed relationship between long-term proton pump inhibitor use and geriatric frailty. The collective analysis of the evidence allowed for the identification of multiple pathophysiological mechanisms involved in this association, as well as clinical and pharmacological factors capable of increasing vulnerability in the elderly (WU *et al*., 2025; DEWI *et al*., 2024; CONDUR *et al*., 2025) [71, 22, 15].

The selected studies underscore the relevance of periodic pharmacotherapy assessment and the implementation of safe deprescribing strategies, especially in patients monitored within Primary Health Care who are exposed to polypharmacy (ROSSI *et al*., 2024; PEREIRA *et al*., 2024; CORRÊA *et al*., 2022) [55, 50, 17].

Table 1: Summary of main studies on long-term proton pump inhibitor use, frailty, and clinical outcomes in geriatric patients.

Authors/Year	Study Design	Population / Setting	Main Findings	Relationship with Frailty
Wu *et al*., 2025	Observational study and Mendelian randomization	Elderly PPI users	Identified an association between PPI use and higher frailty index.	Suggests a possible link between chronic PPI exposure and increased functional vulnerability.
Dewi *et al*., 2024	Observational clinical study	Elderly on long-term PPIs	Linked long-term PPI use to frailty syndrome.	Points to PPIs as a potential factor associated with the development or worsening of frailty.
Condur *et al*., 2025	Clinical review	Elderly with multiple chronic conditions	Discussed clinical risks of PPI use in multimorbid elderly patients.	Multimorbidity and long-term PPI use may intensify the risk of functional decline.
Lakshmisai *et al*., 2025	Systematic review	Patients on chronic PPI therapy	Reported adverse events, including renal, bone, and nutritional alterations.	These effects may contribute to loss of physiological reserve and increased frailty.
Chaudhry *et al*., 2025	Systematic review	Chronic PPI users	Associated PPIs with kidney disease, fractures, and cognitive decline.	These outcomes are directly related to functional deterioration in older adults.
Robert *et al*., 2025	Systematic review and meta-analysis	Elderly exposed to PPIs	Demonstrated an association between PPIs and increased fracture risk.	Fracture-related disability can accelerate dependency and frailty.
Shahid *et al*., 2025	Systematic review	Elderly in polypharmacy	Linked long-term PPI use to micronutrient depletion.	Vitamin B12, magnesium, calcium, and iron deficiency may contribute to sarcopenia, fatigue, and frailty.
Barbosa *et al*., 2025	National review/study	Chronic elderly PPI users	Described the impact of PPIs on micronutrient absorption.	Nutritional malabsorption represents an important mechanism contributing to frailty.
Costa *et al*., 2021	Integrative review	Elderly on long-term PPIs	Reported vitamin B12 deficiency and hypomagnesemia associated with prolonged PPI use.	Metabolic alterations may impair muscle strength, cognition, and functional capacity.
Silva *et al*., 2022	National study/review	Elderly PPI users	Associated hypovitaminosis B12 with long-term PPI therapy.	B12 deficiency may contribute to neuropathy, anemia, fatigue, and functional decline.
Marques *et al*., 2021	National review	Elderly PPI users	Linked long-term PPI use with osteoporosis and fractures.	Bone loss increases falls, disability, and frailty risk.
Silva *et al*., 2024	National study/review	Elderly PPI users	Evaluated effects of PPIs on bone health.	Reinforces association between chronic PPI use, bone fragility, and fracture risk.
Chan *et al*., 2023	Observational study	Older adults	Investigated association between PPIs, incident dementia, and cognitive decline.	Cognitive impairment may increase dependency and frailty.

Xie *et al*., 2024	Review of observational evidence	PPI users	Updated evidence regarding PPIs and dementia risk.	Cognitive decline contributes to geriatric vulnerability and reduced autonomy.
Peng *et al*., 2026	Updated review	Patients on PPIs	Discussed association between PPIs and dementia.	Potential impact on cognition and functional independence.
Bell *et al*., 2021	Observational study	PPI users	Linked PPI use with increased cardiovascular disease and heart failure risk.	Cardiovascular disease may reduce functional capacity and increase frailty.
Geng *et al*., 2023	Observational study	Patients with type 2 diabetes	Associated PPI use with increased cardiovascular risk.	Cardiovascular vulnerability may worsen frailty in elderly diabetic patients.
Fan *et al*., 2024	Clinical study	Elderly PPI users	Reported QT interval prolongation associated with PPI use.	Cardiovascular alterations may increase adverse events and functional limitations.
Maret-Ouda *et al*., 2023	Observational study	Elderly PPI users	Investigated pneumonia risk associated with PPI use.	Respiratory infections may precipitate functional decline and frailty.
Oliveira *et al*., 2023	National study	Elderly in Primary Health Care	Evaluated polypharmacy and potentially inappropriate prescribing.	Polypharmacy is associated with frailty and inappropriate long-term PPI use.
Moreira and Rodrigues, 2025	National study	Elderly in Primary Care	Discussed potentially inappropriate medications in older adults.	Highlights medication review as a strategy to reduce frailty risk.
Santos *et al*., 2025	National study	Community-dwelling elderly	Linked frailty, polypharmacy, and potentially inappropriate medications.	Demonstrates the importance of evaluating medication profiles in frailty assessment.
Çelik *et al*., 2021	Observational study	Outpatients	Demonstrated inappropriate PPI prescribing in outpatient settings.	Unnecessary prolonged PPI exposure may increase adverse events in elderly patients.
Muheim *et al*., 2021	Population study	General population	Identified potentially inappropriate PPI prescribing.	Supports screening and deprescribing among frail elderly individuals.
Dixon and Bolt, 2023	Outpatient study	Geriatric patients	Evaluated appropriateness of PPI therapy.	Highlights risks of unnecessary long-term PPI maintenance.
Wabe *et al*., 2025	Long-term care study	Institutionalized elderly	Identified inappropriate PPI use and underutilization.	Institutionalized elderly are at higher risk of frailty and polypharmacy.
Targownik, Fisher, and Saini, 2022	Clinical practice update	Patients on PPIs	Presented recommendations for PPI deprescribing.	Provides strategies to reduce medication-related risks associated with chronic PPI use.
Rossi *et al*., 2024	Systematic review	Studies on deprescribing	Evaluated clinical approaches for PPI deprescribing.	Deprescribing may reduce adverse events and improve medication safety.
Pereira *et al*., 2024	National review	Elderly PPI users	Discussed deprescribing strategies in geriatric populations.	Reinforces the role of Primary Health Care in safe PPI management.
Lai *et al*., 2021	Intervention study	Family medicine	Evaluated deprescribing of inappropriate PPIs in residency practice.	Demonstrated feasibility of reducing unnecessary PPI use in primary care.
Ayoub *et al*., 2021	Intervention study	Community health center	Evaluated opportunities for PPI de-escalation.	Shows potential for reducing chronic PPI exposure through primary care interventions.

Source: Prepared by the authors (2026), based on studies included in the systematic review.

The main studies analyzed indicate that the long-term use of proton pump inhibitors (PPIs) in geriatric patients may be associated with the development or exacerbation of frailty through multiple mechanisms, including micronutrient deficiency, bone alterations, increased risk of fractures, cognitive decline, cardiovascular events, infections, polypharmacy, and potentially inappropriate prescribing. In Primary Health Care, these findings underscore the importance of periodic pharmacotherapy review, early identification of frailty, and the implementation of safe deprescribing strategies, especially in elderly patients with multimorbidity and higher functional vulnerability (CONDUR *et al*., 2025; WU *et al*., 2025; ROSSI *et al*., 2024) [15, 71, 55].

Frailty represents a multifactorial clinical condition characterized by a decline in physiological reserve and a reduced capacity of the organism to respond adequately to stressors. This geriatric syndrome is associated with a higher risk of falls, hospitalizations, functional disability, institutionalization, and mortality, serving as a key marker of vulnerability in the elderly. In recent years, the growing aging population has expanded scientific interest in identifying potentially modifiable factors related to the development and progression of frailty (JOHNSON *et al*., 2024; PRIDHAM; ROCKWOOD; RUTENBERG, 2024; SILAN; NICOLAIO; BOCCUZZO, 2025) [31, 52, 62].

In this context, several studies have investigated the potential impact of chronic PPI use on the functional health of the elderly. Although these drugs are widely used and considered safe for short-term treatment, recent evidence suggests that prolonged use may be associated with metabolic, nutritional, and clinical alterations capable of promoting the onset or worsening of frailty. Among the most frequently described mechanisms are micronutrient deficiency, muscle mass loss, reduced bone mineral density, cognitive decline, and

increased multimorbidity burden (ANDRAWES *et al*., 2025; LAKSHMISAI *et al*., 2025; SHAHID *et al*., 2025) [3, 36, 61]. Given this scenario, the assessment of frailty using specific indices has been widely employed to quantify the degree of vulnerability in the elderly and to understand the factors associated with its progression. Table 2 presents the main studies identified in this systematic review that investigated the association between long-term PPI use and geriatric frailty indicators, highlighting their key findings and clinical implications (WU *et al*., 2025; DEWI *et al*., 2024; ARRUÉ *et al*., 2024) [71, 22, 5].

Table 2: Summary of main studies on frailty and frailty indices associated with long-term proton pump inhibitor use in geriatric patients.

Authors/Year	Study Design	Population	Frailty Assessment	Main Results
WU *et al*., 2025	Observational and Mendelian randomization	Elderly PPI users	Frailty Index (FI)	Identified a significant association between long-term PPI use and increased frailty scores.
DEWI *et al*., 2024	Observational study	Elderly in clinical follow-up	Frailty Criteria	Demonstrated a higher prevalence of frailty syndrome among chronic PPI users.
JOHNSON *et al*., 2024	Longitudinal study	Community-dwelling elderly	Frailty Index Subdimensions	Showed that multiple frailty dimensions are related to the accumulation of clinical deficits.
PRIDHAM; ROCKWOOD; RUTENBERG, 2024	Longitudinal study	Geriatric population	Frailty Index	Demonstrated that the progressive increase in the frailty index is associated with worse clinical outcomes.
SILAN; NICOLAIO; BOCCUZZO, 2025	Population study	Elderly in administrative databases	Frailty Index	Developed a simplified model for the early identification of frailty in the elderly.
ARRUÉ *et al*., 2024	Clinical study	Elderly with functional changes	Multidimensional assessment	Linked cardiovascular and motor alterations to increased frailty.
SANTOS *et al*., 2025	Observational study	Community-dwelling elderly	Standardized geriatric instruments	Demonstrated an association between frailty, polypharmacy, and potentially inappropriate medications.
CONDUR *et al*., 2025	Clinical review	Multimorbid elderly	Global functional assessment	Identified that chronic PPI users are at higher risk for frailty-related events.
LAWSON *et al*., 2022	Clinical review	Elderly on polypharmacy	Functional assessment	Showed that multiple medication use significantly increases the risk of frailty.
MOREIRA; RODRIGUES, 2025	Observational study	Elderly in Primary Care	Geriatric criteria	Linked potentially inappropriate medications to increased clinical vulnerability.
OLIVEIRA *et al*., 2023	Cross-sectional study	Primary Care users	Multidimensional assessment	Demonstrated an association between polypharmacy and functional impairment in the elderly.
WABE *et al*., 2025	Long-term care study	Institutionalized elderly	Vulnerability indices	Identified a high prevalence of frailty associated with inappropriate medication use.
ARAGONEZ, 2025	Review	Elderly in PHC	Beers-Fick criteria	Highlighted the role of potentially inappropriate medications in worsening frailty.
CORRÊA *et al*., 2022	Deprescribing study	Elderly in Primary Care	Comprehensive Geriatric Assessment	Demonstrated the benefits of therapeutic review in reducing risks associated with frailty.

Source: Prepared by the authors (2026), based on studies included in the systematic review.

The potential adverse effects associated with the long-term use of proton pump inhibitors (PPIs) have sparked growing interest in scientific literature, especially given their widespread use among elderly patients. Although these drugs are considered safe for short-term treatments, recent evidence suggests that their chronic use may interfere with the absorption of essential nutrients, compromising different organic systems and contributing to the development of conditions associated with geriatric frailty (ANDRAWES *et al*., 2025; KAMBOJ *et al*., 2024; LAKSHMISAI *et al*., 2025) [3, 33, 36].

Among the main pathophysiological mechanisms described, the reduced intestinal absorption of vitamin B12, magnesium, calcium, and iron stands out, as these are essential micronutrients for the maintenance of neurological, muscular, and bone function. Furthermore, studies have demonstrated an association between long-term PPI use and a higher risk of osteoporosis, fragility fractures, cognitive impairment, and the development of dementia. Such conditions can result in a progressive loss of functional autonomy, increased dependency, and greater clinical vulnerability in the elderly (COSTA *et al*., 2021; ROBERT *et al*., 2025; XIE *et al*., 2024) [19, 53, 72].

Table 3 presents the main studies identified in this systematic review that investigated the relationship between the long-term use of proton pump inhibitors and outcomes related to micronutrient deficiency, bone health, fracture risk, cognitive decline, and dementia, highlighting the mechanisms involved and their clinical repercussions in the geriatric population (SHAHID *et al*., 2025; CHAN *et al*., 2023; PENG *et al*., 2026) [61, 13, 49].

Table 3: Summary of main studies on micronutrient deficiency, bone health, fracture risk, cognitive decline, and dementia associated with long-term proton pump inhibitor use in geriatric patients.

Authors/Year	Outcome Evaluated	Main Findings	Potential Impact on Frailty
COSTA *et al*., 2021	Vitamin B12 deficiency and hypomagnesemia	Demonstrated an association between long-term PPI use and reduced serum levels of vitamin B12 and magnesium.	Favors fatigue, sarcopenia, neuropathies, and functional loss.
SILVA *et al*., 2022	Hypovitaminosis B12	Identified a higher frequency of vitamin B12 deficiency in chronic PPI users.	May contribute to neurological and cognitive impairment.
BARBOSA *et al*., 2025	Micronutrient absorption	Evidenced impairment in the absorption of calcium, iron, magnesium, and vitamin B12.	Increases metabolic and functional vulnerability.
SHAHID *et al*., 2025	Micronutrient depletion	Systematic review demonstrated a consistent association between PPIs and nutritional deficiency in the elderly.	Relates to increased risk of frailty and functional dependency.
SANTOS *et al*., 2025	Nutritional alterations	Reported impaired micronutrient absorption due to PPI-induced hypochlorhydria.	Favors muscle loss and worsening physical performance.
MARQUES *et al*., 2021	Osteoporosis and fractures	Demonstrated an association between long-term PPI use and increased risk of osteoporosis.	Increases the occurrence of falls and fragility fractures.
SILVA *et al*., 2024	Bone health	Evidenced the negative impact of PPIs on bone mineral density.	Contributes to functional disability and loss of independence.
ROBERT *et al*., 2025	Fractures	Meta-analysis identified a higher risk of fractures in chronic PPI users.	Fractures are associated with institutionalization and mortality.
CHAUDHRY *et al*., 2025	Fractures and kidney disease	Systematic review linked PPIs to osteoporotic fractures and renal alterations.	Potentiates the progression of geriatric frailty.
MAES *et al*.	Adverse effects in the elderly	Reported increased risk of bone impairment in long-term users.	Favors reduced mobility and functionality.
CHAN *et al*., 2023	Cognitive decline and dementia	Demonstrated an association between PPI use and higher incidence of cognitive decline.	May accelerate dependency and functional impairment.
XIE *et al*., 2024	Dementia	Observational review identified consistent evidence on the association between PPIs and dementia.	Aggravates the clinical and social vulnerability of the elderly.
PENG *et al*., 2026	Dementia	Updated evidence reinforced the possible relationship between long-term PPI use and cognitive impairment.	Contributes to a worse functional prognosis.
KOUNDINYA *et al*., 2025	Cognitive decline	Narrative review highlighted inflammatory and metabolic mechanisms associated with dementia.	Relates to increased cognitive frailty.
EMAD *et al*., 2025	Dementia	Umbrella review identified a moderate association between PPIs and risk of cognitive impairment.	Potentiates loss of autonomy and independence.
SERENO *et al*., 2024	Vitamin B12 and nervous system	Demonstrated the importance of vitamin B12 for the maintenance of neurological function.	PPI-induced deficiency may favor cognitive alterations.
LOUREDO *et al*., 2021	Metabolic changes in aging	Evidenced the relevance of metabolic balance for the maintenance of geriatric functionality.	Nutritional disorders may accelerate frailty.

Source: Prepared by the authors (2026), based on studies included in the systematic review.

Beyond the effects related to micronutrient deficiency, bone health, and cognitive impairment, recent evidence has demonstrated that long-term use of proton pump inhibitors may be associated with significant cardiovascular repercussions and increased therapeutic complexity in elderly patients. Considering that the geriatric population frequently presents with multiple chronic diseases and high medication consumption, it is essential to understand the impact of PPIs within the context of polypharmacy and the potential risks arising from the prolonged maintenance of these drugs (BELL *et al*., 2021; FORESTA *et al*., 2024; CONDUR *et al*., 2025) [11, 27, 15].

Observational studies and systematic reviews have reported an association between chronic PPI use and an increased risk of cardiovascular events, including heart failure, coronary artery disease, QT interval prolongation, and higher cardiovascular mortality. Although the underlying mechanisms are not yet fully elucidated, it is believed that endothelial, inflammatory, metabolic, and electrolyte alterations may contribute to these outcomes. Concurrently, several authors highlight that the unnecessary continuation of PPIs in geriatric therapeutic regimens represents one of the most frequent forms of potentially inappropriate prescribing observed in clinical practice (BELL *et al*., 2021; FAN *et al*., 2024; MUHEIM *et al*., 2021).

In this context, medication review and deprescribing strategies have been widely recommended by national and international guidelines as tools capable of reducing adverse events, optimizing pharmacotherapy, and minimizing factors associated with geriatric frailty. Table 4 presents the main studies related to cardiovascular events, polypharmacy, and PPI deprescribing strategies identified in this systematic review (TARGOWNIK; FISHER; SAINI, 2022; ROSSI *et al*., 2024; PEREIRA *et al*., 2024) [66, 55, 50].

Table 4: Summary of main studies on cardiovascular events, polypharmacy, and deprescribing strategies associated with long-term proton pump inhibitor use in geriatric patients.

Author/Year	Focus Area	Main Findings	Relevance to Geriatric Frailty
BELL *et al*., 2021	Cardiovascular disease	Identified an association between long-term PPI use and increased risk of cardiovascular disease and heart failure.	May reduce functional capacity and increase clinical vulnerability.
GENG *et al*., 2023	CV risk in T2DM	Demonstrated an association between PPIs and increased cardiovascular risk in diabetic patients.	Potentiates adverse outcomes in elderly patients with multimorbidity.
FAN *et al*., 2024	QT interval prolongation	Evidenced an association between PPI use and electrocardiographic alterations.	Increases the risk of cardiovascular events and clinical complications.
FORESTA *et al*., 2024	Cardiovascular complications	Reported a higher frequency of cardiovascular events in elderly PPI users.	Contributes to functional decline and progression of frailty.
SONG *et al*., 2023	Mortality	Meta-analysis demonstrated increased mortality in long-term elderly PPI users.	Reflects greater clinical vulnerability and risk of adverse outcomes.
LAWSON *et al*., 2022	Polypharmacy	Identified challenges related to the simultaneous use of multiple medications.	Polypharmacy is a recognized factor in the development of frailty.
OLIVEIRA *et al*., 2023	Inappropriate prescribing	Demonstrated a high prevalence of potentially inappropriate medications in PHC.	Increases the risk of adverse events and functional impairment.
MOREIRA; RODRIGUES, 2025	Inappropriate medications	Linked inappropriate prescriptions to increased geriatric vulnerability.	Favors functional decline and dependency.
SANTOS *et al*., 2025	Frailty and polypharmacy	Evidenced an association between polypharmacy and higher frailty indices.	Reinforces the need for periodic therapeutic review.
FURTADO *et al*., 2021	Physiological impact	Demonstrated the negative impact of excessive medication exposure in the elderly.	Relates to an increase in adverse events and frailty.
ROCHA *et al*., 2021	Medication interactions	Highlighted pharmacodynamic and pharmacokinetic risks in the elderly.	Contributes to clinical instability and reduced functionality.
ARAGONEZ, 2025	Beers-Fick criteria	Reinforced the importance of identifying potentially inappropriate medications.	Assists in preventing drug-related frailty.
TARGOWNIK; FISHER; SAINI, 2022	Deprescribing guidelines	Presented recommendations for the safe discontinuation of PPIs without current indication.	Reduces exposure to adverse events related to long-term use.
ROSSI *et al*., 2024	Deprescribing strategies	Systematic review demonstrated the efficacy of deprescribing programs.	Contributes to greater therapeutic safety in the elderly.
PEREIRA *et al*., 2024	Deprescribing in PHC	Evidenced clinical benefits of periodic re-evaluation of PPI use.	Favors the reduction of polypharmacy and frailty factors.
CORRÊA *et al*., 2022	Deprescribing screening	Demonstrated the feasibility of identifying patients eligible for deprescribing.	Reduces risks associated with unnecessary medication use.
LAI *et al*., 2021	Family medicine intervention	Demonstrated success in withdrawing inappropriately prescribed PPIs.	Improves the quality of geriatric pharmacotherapy.
AYOUB *et al*., 2021	Therapeutic de-escalation	Evidenced opportunities for the safe reduction of PPI use.	Minimizes cumulative risks associated with long-term exposure.
WABE *et al*., 2025	Uso inadequado em instituições geriátricas	Identificaram elevada prevalência de utilização inadequada de IBPs.	Reforça a necessidade de monitoramento contínuo da farmacoterapia.

Source: Prepared by the authors (2026), based on studies included in the systematic review.

The integrated analysis of the studies included in this systematic review allowed not only for the identification of the association between chronic proton pump inhibitor (PPI) use and geriatric frailty, but also for an understanding of the underlying pathophysiological mechanisms, the factors that potentiate this relationship, and the possible intervention strategies applicable to clinical practice. Understanding these elements is fundamental to supporting preventive and therapeutic actions aimed at promoting healthy aging and reducing the impacts arising from frailty in the elderly population (WU *et al*., 2025; CONDUR *et al*., 2025; ROSSI *et al*., 2024) [71, 15, 55].

The analyzed studies demonstrated that frailty associated with long-term PPI use does not result from a single isolated factor, but rather from the interaction between metabolic, nutritional, cardiovascular, musculoskeletal, and cognitive alterations that accumulate over time. Thus, identifying the primary mechanisms involved is essential to understanding how these medications can influence the reduction of physiological reserve and increase the clinical vulnerability of the elderly (SHAHID *et al*., 2025; KAMBOJ *et al*., 2024; DEWI *et al*., 2024) [61, 33, 22].

Beyond biological mechanisms, literature highlights the importance of clinical and sociodemographic factors capable of potentiating the risks related to long-term PPI use. Characteristics such as advanced age, multimorbidity, polypharmacy, institutionalization, and nutritional impairment were frequently associated with increased frailty, reinforcing the need for a multidimensional approach in the follow-up of geriatric patients (LAWSON *et al*., 2022; SANTOS *et al*., 2025; WABE *et al*., 2025) [37, 59, 70].

Finally, considering that Primary Health Care (PHC) constitutes the primary setting for the longitudinal follow-up of the elderly population, several studies emphasize the need to implement strategies aimed at periodic pharmacotherapy review, early frailty screening, and the promotion of the rational use of medications. In this context, the safe deprescribing of PPIs emerges as an important tool for

minimizing adverse events and optimizing the quality of care provided to the elderly (TARGOWNIK; FISHER; SAINI, 2022; PEREIRA *et al*., 2024; AYUB *et al*., 2021) [66, 50, 7].

Table 5 presents the main pathophysiological mechanisms described in the literature that relate chronic PPI use to the development and exacerbation of geriatric frailty. Table 6 synthesizes the main risk factors identified in the selected studies, highlighting the clinical and epidemiological elements associated with the greater vulnerability of elderly PPI users. Lastly, Table 7 brings together the main recommendations for Primary Health Care, emphasizing monitoring, prevention, and deprescribing strategies that may contribute to reducing the risks associated with long-term PPI use and to preserving the functionality and autonomy of the geriatric population.

Table 5: Main pathophysiological mechanisms linking long-term PPI use to the development and exacerbation of geriatric frailty.

Mechanism	Evidence Found	Potential Clinical Consequence
Vitamin B12 deficiency	Reduced gastric absorption	Neuropathy, cognitive deficit
Hypomagnesemia	Long-term PPI use	Muscle weakness, arrhythmias
Reduced calcium absorption	Chronic hypochlorhydria	Osteoporosis and fractures
Altered gut microbiota	Continuous PPI use	Systemic inflammation
Renal impairment	Interstitial nephritis and CKD	Accelerated frailty
Cardiovascular alterations	Endothelial dysfunction	Reduced functional capacity

Source: Prepared by the authors (2026), based on studies included in the systematic review.

Table 6: Main risk factors identified for frailty in long-term PPI users.

Risk Factor	Frequency in Literature	Impact
Age ≥ 80 years	Very frequent	High
Polypharmacy	Very frequent	High
Multimorbidity	Very frequent	High
PPI use > 1 year	Frequent	Moderate/High
Low nutritional status	Frequent	High
Physical inactivity	Frequent	Moderado

Source: Prepared by the authors (2026), based on studies included in the systematic review.

Table 7: Recommendations for Primary Health Care (PHC): Monitoring, prevention, and deprescribing strategies.

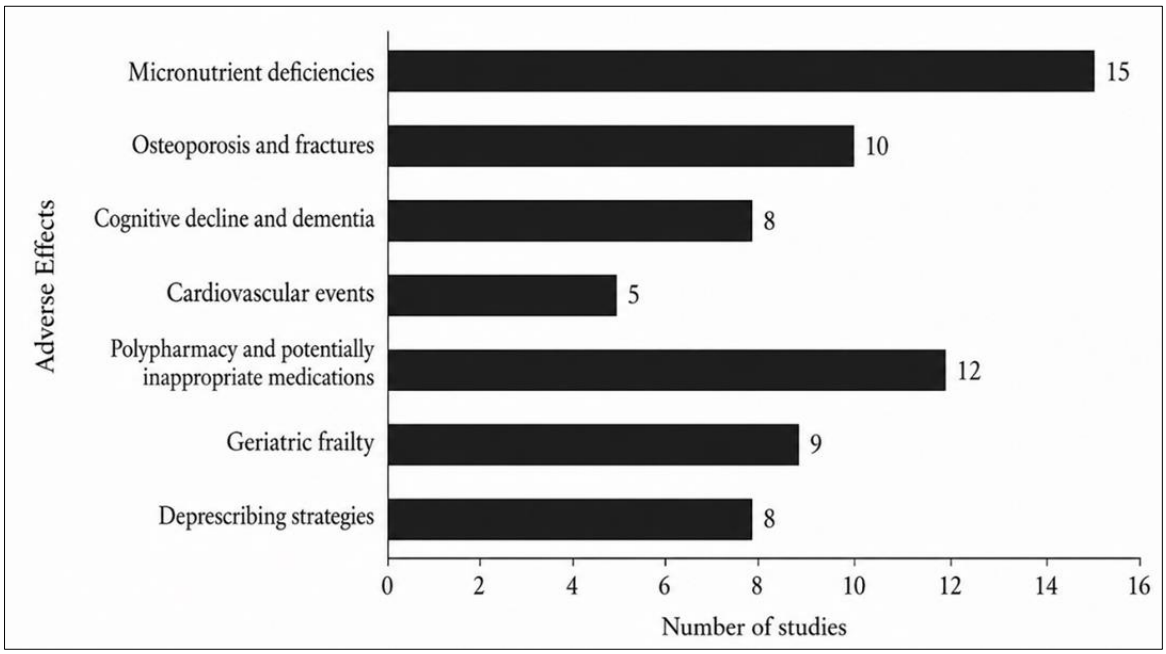
Strategy	Objective
Annual PPI review	Identify use without clinical indication
Application of the Frailty Index	Early screening
Nutritional assessment	Detect micronutrient deficiencies
Laboratory monitoring	Monitor B12, magnesium, calcium, and iron levels
Polypharmacy review	Reduce drug-drug interactions
Deprescribing protocols	Reduce adverse events
Health education	Improve therapeutic adherence

Source: Prepared by the authors (2026), based on studies included in the systematic review.

With the objective of complementing the analysis of the results obtained in this systematic review, visual representations were developed to synthesize the main findings identified in scientific literature regarding the relationship between chronic proton pump inhibitor (PPI) use and frailty in geriatric patients. The use of visual resources enables a more comprehensive understanding of the mechanisms involved and the clinical outcomes most frequently associated with the long-term use of these medications.

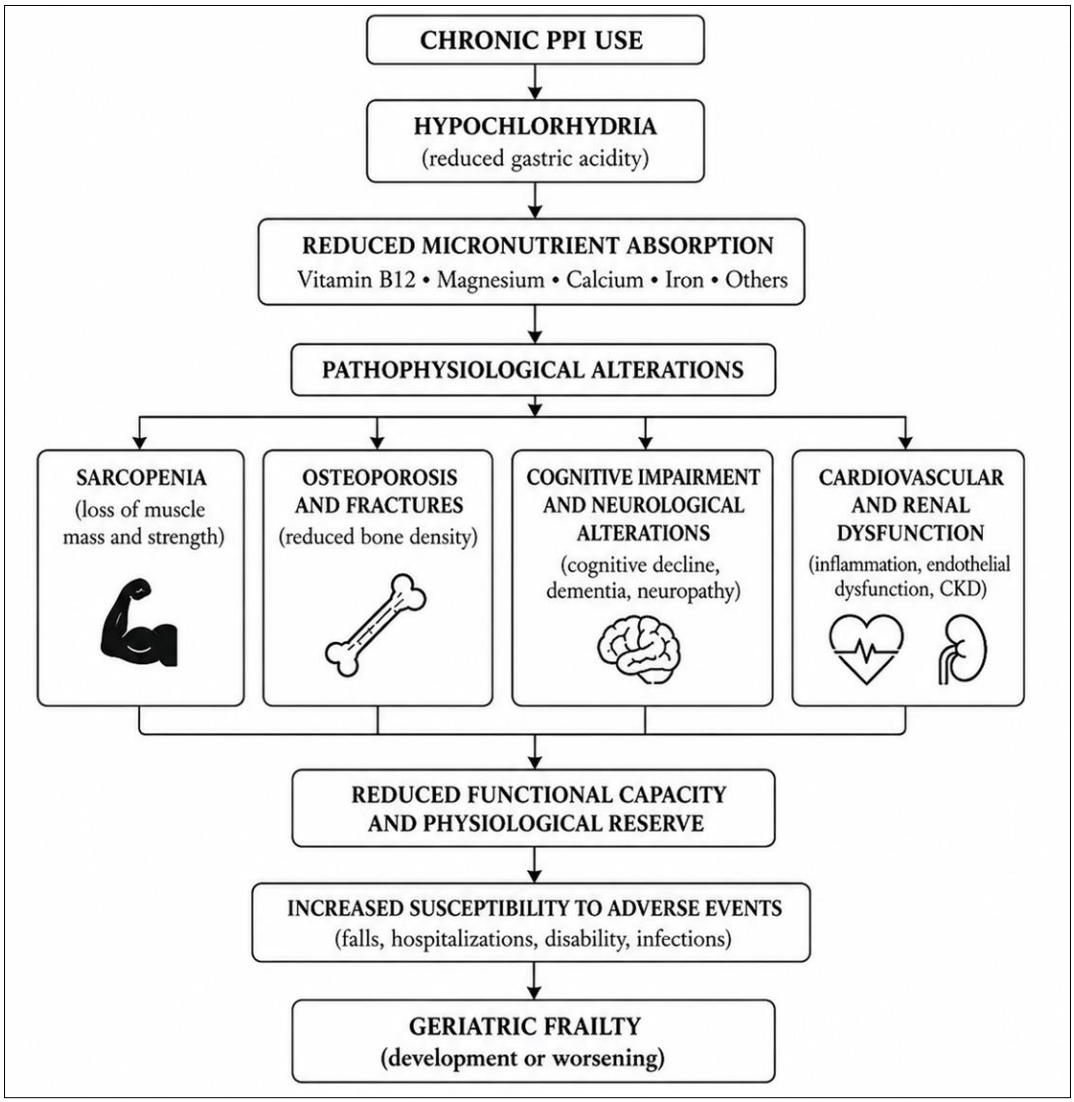
Figure 2 presents the distribution of the main outcomes reported in the studies included in this review, highlighting the areas with the highest concentration of scientific evidence. Among the most frequently observed findings are alterations related to micronutrient deficiency, bone health, cognitive impairment, cardiovascular events, and polypharmacy. These outcomes represent critical factors in the reduction of functional capacity and the increase of clinical vulnerability in the elderly population (SHAHID *et al*., 2025; ROBERT *et al*., 2025; CHAN *et al*., 2023; BELL *et al*., 2021) [61, 53, 13, 11].

Additionally, Figure 3 illustrates the pathophysiological model proposed based on the analyzed studies, demonstrating the sequence of biological events potentially triggered by the long-term use of PPIs. The model highlights how the reduction of gastric acidity can interfere with the absorption of essential nutrients and contribute to metabolic, musculoskeletal, cardiovascular, and neurological alterations, culminating in the development or exacerbation of geriatric frailty (COSTA *et al*., 2021; SILVA *et al*., 2024; WU *et al*., 2025) [19, 63, 71].



Source: Prepared by the authors (2026), based on studies included in the systematic review.

Fig 2: Distribution of the main adverse effects associated with chronic use of proton pump inhibitors in older adults.



Source: Prepared by the authors (2026), based on evidence synthesized from the studies included in the systematic review.

Fig 3: Pathophysiological model illustrating the relationship between chronic proton pump inhibitor use and the development of geriatric frailty.

6. Discussion

The results of this systematic review evidenced a consistent association between chronic proton pump inhibitor (PPI) use and multiple factors related to the development and exacerbation of frailty in geriatric patients (WU *et al*., 2025; DEWI *et al*., 2024; CONDUR *et al*., 2025) [71, 22, 15].

Although PPIs remain among the most widely prescribed medications globally for the treatment of acid-peptic disorders, a growing body of evidence has demonstrated that their long-term use may trigger physiological alterations capable of compromising functional capacity and increasing clinical vulnerability in the elderly. In this context, our findings support the hypothesis that prolonged PPI exposure represents a potentially modifiable factor within the multifactorial process that characterizes frailty syndrome (KAMBOJ *et al*., 2024; LAKSHMISAI *et al*., 2025; SHAHID *et al*., 2025) [33, 36, 61].

Among the primary results, an association was identified between the chronic use of PPIs and increased frailty indices. Wu *et al*. (2025) identified that long-term users of these medications presented significantly higher scores on frailty assessment instruments, suggesting that the cumulative effects of the therapy may contribute to the progressive compromise of physiological reserve. Similar results were observed by Dewi *et al*. (2024), who demonstrated a higher prevalence of frailty syndrome in elderly patients undergoing long-term use of these drugs (WU *et al*., 2025; DEWI *et al*., 2024) [71, 22].

Frailty is recognized as a dynamic condition resulting from the accumulation of biological deficits throughout the aging process. In this regard, Johnson *et al*. (2024) and Pridham, Rockwood, and Rutenberg (2024) highlight that the progressive increase in frailty indices is directly related to functional impairment, a higher incidence of hospitalizations, and increased mortality. Thus, any pharmacological intervention capable of accelerating the accumulation of these deficits must be carefully monitored in the geriatric population (JOHNSON *et al*., 2024; PRIDHAM; ROCKWOOD; RUTENBERG, 2024) [31, 52].

Another aspect widely identified in the analyzed studies refers to nutritional alterations resulting from the long-term use of PPIs. Costa *et al*. (2021) and Silva *et al*. (2022) observed a significant association between the chronic use of these medications and vitamin B12 deficiency, whereas Barbosa *et al*. (2025) and Shahid *et al*. (2025) reported impaired absorption of calcium, iron, and magnesium. These alterations stem primarily from the reduction in gastric acidity promoted by PPIs, a condition that directly interferes with the bioavailability of several essential micronutrients (COSTA *et al*., 2021; SILVA *et al*., 2022; BARBOSA *et al*., 2025; SHAHID *et al*., 2025) [19, 64, 8, 61].

The clinical consequences of these nutritional deficiencies are particularly relevant to the elderly population. Vitamin B12 deficiency is associated with the onset of peripheral neuropathies, cognitive impairment, and reduced functional capacity, whereas hypomagnesemia may favor muscle weakness, cardiac arrhythmias, and clinical instability. Collectively, these factors contribute to the progressive loss of functional autonomy, constituting central elements in the pathophysiology of geriatric frailty (COSTA *et al*., 2021; SERENO *et al*., 2024) [19, 60].

The results of this review also demonstrated an important association between long-term PPI use and alterations in bone health. Marques *et al*. (2021) and Silva *et al*. (2024) reported that reduced calcium absorption secondary to hypochlorhydria may predispose to the development of osteopenia and osteoporosis. These findings are reinforced by the meta-analysis conducted by Robert *et al*. (2025), which identified a significant increase in fracture risk among chronic users of these medications (MARQUES *et al*., 2021; SILVA *et al*., 2024; ROBERT *et al*., 2025) [41, 63, 53].

Fractures represent one of the most impactful events in elderly health, frequently associated with the loss of independence, institutionalization, and increased mortality. Thus, the association between PPIs, bone fragility, and fractures reinforces the need for continuous clinical and laboratory monitoring, especially in elderly patients with additional risk factors for bone mass loss (ROBERT *et al*., 2025; SILVA *et al*., 2024) [53, 63].

Cognitive impairment constitutes another significant outcome identified in this review. Chan *et al*. (2023) demonstrated an association between long-term PPI use and a higher incidence of cognitive decline, while Xie *et al*. (2024) and Peng *et al*. (2026) reinforced the existence of consistent observational evidence linking these medications to an increased risk of dementia. Although causality has not yet been fully established, the results suggest that inflammatory, metabolic, and vascular mechanisms may play a role in this process (CHAN *et al*., 2023; XIE *et al*., 2024; PENG *et al*., 2026) [13, 72, 49].

According to Koundinya *et al*. (2025), micronutrient deficiency, especially of vitamin B12 and magnesium, may represent one of the mechanisms underlying the association between PPIs and cognitive impairment. Considering that cognition is a fundamental component for the maintenance of functional independence, such alterations may significantly contribute to the progression of geriatric frailty (KOUNDINYA *et al*., 2025; SHAHID *et al*., 2025) [34, 61].

Beyond the nutritional and neurological effects, the studies included in this review evidenced potential cardiovascular repercussions associated with the long-term use of PPIs. Bell *et al*. (2021) identified an increased risk of heart failure and cardiovascular disease in chronic users, while Geng *et al*. (2023) observed similar results in patients with type 2 diabetes mellitus. Additionally, Fan *et al*. (2024) demonstrated an association between the use of these medications and QT interval prolongation, a condition potentially related to an increased risk of arrhythmias (BELL *et al*., 2021; GENG *et al*., 2023; FAN *et al*., 2024) [11, 29, 25].

Foresta *et al*. (2024) highlight that cardiovascular alterations may directly contribute to the reduction of functional capacity and to the increase of clinical vulnerability in the elderly. Thus, although the individual absolute risk remains relatively low, the high prevalence of PPI utilization makes these findings particularly relevant in terms of public health (FORESTA *et al*., 2024) [27].

Another significant result identified in this review refers to polypharmacy. Oliveira *et al*. (2023), Moreira and Rodrigues (2025), and Santos *et al*. (2025) demonstrated that chronic PPI users frequently present with multiple comorbidities and high medication consumption, significantly increasing the risk of drug-drug interactions, adverse reactions, and potentially inappropriate prescribing. This condition is recognized as one of the primary factors associated with the development of geriatric frailty (OLIVEIRA *et al*., 2023; MOREIRA; RODRIGUES, 2025; SANTOS *et al*., 2025) [48, 43, 59].

Furtado *et al*. (2021) emphasize that polypharmacy promotes physiological and metabolic overload, favoring the occurrence of adverse events and compromising functional capacity in the elderly. Similarly, Rocha *et al*. (2021) highlight that age-related pharmacokinetic and pharmacodynamic changes potentiate the risks associated with the simultaneous use of multiple medications (FURTADO *et al*., 2021; ROCHA *et al*., 2021) [28, 54].

Given this scenario, deprescribing emerges as a critical strategy to reduce the risks associated with the long-term use of PPIs. Targownik, Fisher, and Saini (2022) published international recommendations advising the periodic reassessment of the clinical necessity for maintaining these medications, especially when used in the absence of a current clinical indication (TARGOWNIK; FISHER; SAINI, 2022) [66].

Similar results were observed by Rossi *et al*. (2024) and Pereira *et al*. (2024), who demonstrated clinical benefits resulting from the safe withdrawal of PPIs in eligible patients (ROSSI *et al*., 2024; PEREIRA *et al*., 2024) [55, 50].

Lai *et al*. (2021) and Ayoub *et al*. (2021) demonstrated that structured deprescribing programs can significantly reduce unnecessary PPI exposure without a significant increase in the recurrence of gastrointestinal symptoms. These findings reinforce the importance of interprofessional practice and longitudinal follow-up in Primary Health Care (LAI *et al*., 2021; AYOUB *et al*., 2021) [35, 7].

Primary Health Care plays a pivotal role in the early identification of frailty, monitoring of polypharmacy, and periodic review of prescriptions. Aragonez (2025) and Corrêa *et al*. (2022) highlight that systematic screening and therapeutic review strategies enable the identification of patients at higher risk of adverse events, favoring preventive interventions and contributing to the maintenance of functional capacity (ARAGONEZ, 2025; CORRÊA *et al*., 2022) [4, 17].

Despite the consistency of the findings observed, this review presents limitations inherent to the included studies, especially regarding the predominance of observational designs, which hinder the establishment of definitive causal relationships. Furthermore, the heterogeneity of the methods used for frailty assessment and the different populations analyzed may influence the comparability of the results.

However, even considering these limitations, the compiled evidence suggests that the chronic use of proton pump inhibitors should be carefully monitored in geriatric patients, particularly in those with multiple comorbidities, polypharmacy, and early signs of frailty. The adoption of strategies for periodic assessment, nutritional monitoring, and deprescribing when clinically indicated may represent an important measure to minimize risks and promote healthier and more functional aging (TARGOWNIK; FISHER; SAINI, 2022; ROSSI *et al*., 2024; PEREIRA *et al*., 2024) [66, 55, 50].

7. Conclusion

This systematic review demonstrated that chronic use of proton pump inhibitors is associated with multiple factors potentially related to the development and exacerbation of frailty in geriatric patients followed up in Primary Health Care. The analyzed evidence demonstrated that the prolonged use of these medications may promote significant pathophysiological alterations, including micronutrient deficiency, compromised bone health, increased risk of fractures, cognitive decline, cardiovascular events, and greater exposure to polypharmacy.

The results indicated that deficiency in vitamin B12, magnesium, calcium, and iron constitutes one of the primary mechanisms involved in this association, contributing to reduced muscle strength, neurological impairment, loss of functional capacity, and increased clinical vulnerability. Concurrently, the higher incidence of osteoporosis, fractures, and cognitive alterations reinforces the influence of PPIs on different components of geriatric frailty.

It was also observed that elderly patients who are chronic PPI users frequently present with multimorbidity and high medication consumption—factors that potentiate the risk of adverse events and accelerate functional decline. In this context, polypharmacy proved to be a significant element associated with the progression of frailty and the occurrence of potentially inappropriate prescribing.

The evidence also demonstrated that strategies for periodic pharmacotherapy review and safe deprescribing of PPIs can contribute to reducing clinical risks and improving medication safety in the elderly population. Thus, Primary Health Care assumes a pivotal role in the early identification of vulnerable patients, in monitoring adverse effects related to the long-term use of these medications, and in implementing preventive interventions aimed at preserving functional capacity.

It is concluded that the chronic use of proton pump inhibitors should be carefully evaluated in geriatric patients, considering their potential impacts on frailty and quality of life. The adoption of evidence-based practices for monitoring, therapeutic reassessment, and deprescribing may represent a relevant strategy to promote healthier aging, reduce adverse events, and optimize comprehensive care for the elderly.

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