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Meta-analysis

The association between polypharmacy and malnutrition(risk) in older people: A systematic review

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SUMMARY

Background & aim: Malnutrition adversely influences a broad range of physical and psychological symptoms. Although polypharmacy is often mentioned to be associated with malnutrition, especially in older people it is unclear to what extent. The aim of this systematic review was to investigate the extent of the association between polypharmacy and malnutrition in older people.

Methods: The methodology followed the guidelines of the Cochrane Collaboration. Literature search was performed in PubMed, CINAHL and Embase. The population of interest for this systematic review were people of 65 years and older with polypharmacy. Because there is ambiguity with regard to the actual definition of malnutrition and polypharmacy, in this systematic review all articles describing malnutrition prevalence rates were included, regardless of the criteria used. Both observational and intervention studies were screened for eligibility. Selection and quality assessment of the included full text studies was assessed by two reviewers independently. A level of evidence and methodological quality score was adjudged to each article based on this assessment.

Results: A total of 3126 studies were retrieved by the literature search, of which seven studies were included in this systematic review. There was considerable variation in the definition of polypharmacy between studies. Two studies defined polypharmacy as the use of five or more drugs, two studies as the use of six or more drugs, two studies provided a mean and standard deviation that corresponded to the minimum of five drugs, and one study distinguished between polypharmacy (five or more drugs) and excessive polypharmacy (ten or more drugs). However, all studies showed a statistically significant association between (the risk) of becoming malnourished and polypharmacy regardless the instrument or criterion used to define risk of malnutrition. Studies presented the associations respectively as OR $\geq$ 1.177, *p*-value $\leq$ 0.028, $\beta \geq -0.62$ and r ≥ -0.31.

Conclusion: This review demonstrated a statistically significant association between polypharmacy and malnutrition. Further research is required to determine the magnitude of the effect by increased number of drugs in combination with the type of drugs, on the risk of malnutrition.

1. Introduction

Polypharmacy has increased substantially over the past 20 years, especially in older people, and has become a global public health concern [1,2]. This is due to the higher susceptibility of the negative effects of polypharmacy in older people because of their altered pharmacokinetics and decreased renal and hepatic drug clearance [3]. It has been demonstrated that polypharmacy affects between 40% and 50% of older adults in high-income countries [2,4–6].

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Older people with polypharmacy take an average of five to nine drugs prescribed for various reasons [7]. The most common indications are diabetes mellitus, lipid metabolism disorder, hypertension, angina pectoris, sleep disturbances and stomach pain [7]. Drug use is associated with numerous side effects, such as diarrhea, stomach pain, nausea, polyuria and hyperhidrosis, decreased feeling of thirst, decreased appetite and dry mouth [8,9]. In addition, an association between a higher intake of fluids and higher number of drugs is demonstrated, resulting in a reduced food intake [8,10]. The use of opiates often causes constipation as a side effect [11].

In the Netherlands, between 265.000 and 375.000 older people were malnourished based on commonly used prevalence rates in 2016. A recent systematic review demonstrates prevalence rates of high malnutrition risk in 28% for hospitalized patients, 17,5% of patients living in residential care, and 8,5% in community dwelling older adults [12]. These rates are expected to increase as older people live longer [13]. However, various side effects of drugs such as loss of appetite, and gastrointestinal complains, contribute to a substantial decrease in food consumption, which leads to a poorer nutritional status or malnutrition [2,14]. To our knowledge it remains unclear to what extent polypharmacy actually increases the risk in of becoming malnourished in older people [15]. The magnitude of this association has not been demonstrated yet.

Malnutrition can cause care dependency, negatively influence the quality of life and increases the risk of mortality in older people [14]. To prevent older people from becoming malnourished it is important to get more insight on how polypharmacy and malnutrition are associated, and to what extent. The aim of the study was to perform a systematic review on the available literature to investigate the magnitude of the association between polypharmacy and malnutrition in older people.

2. Methods

This systematic review was conducted in adherence to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [16].

2.1. Search strategy

The methodology followed the guidelines of the Cochrane Collaboration. PubMed (Medline), Embase, and CINAHL were searched for literature from January 2000 to September 2020. A comprehensive database search strategy with multiple terms and synonyms was conducted in collaboration with a medical information specialist (Appendix 1). The search included indexing terms (MeSH terms and keywords) related to polypharmacy and malnutrition. The search strategy was appropriately modified for each database. Two reviewers independently screened the search results to identify potential eligible studies (WK and EH). Any disagreement between the two reviewers was resolved through discussion with a third review author (KJ). The reference lists of all included publications were checked by hand-searching.

2.2. Selection criteria type of studies

Articles were eligible for inclusion if they described the association of polypharmacy and malnutrition, supplemented with specific observed and described details about the number of drugs and assessment of the nutritional status of participants. A language restriction to English and Dutch was adhered for. Observational and interventional studies were included. Reviews, case reports, expert opinions, conference meetings, summaries, papers, and overviews were excluded. Studies not available in full text were excluded.

2.3. Selection criteria population

The population of interest for this systematic review was people of 65 years or older with polypharmacy. With regard to the study population we set up the following exclusion criteria. First, studies on frailty and sarcopenia were excluded in order to avoid overestimation or underestimation of the actual association between malnutrition and polypharmacy. Both polypharmacy and malnutrition are strongly associated to frailty and they share risk factors [17–21]. In ESPEN guidelines on definitions and terminology of clinical nutrition, sarcopenia and frailty were agreed to be separate conditions often associated with malnutrition, but not fully overlapping [22]. In our systematic review we focussed on the association between polypharmacy and malnutrition without frailty and sarcopenia as possible confounders. Second, given the fact that cancer can also influence the association between malnutrition and polypharmacy, studies with cancer patients only were excluded. Primary, because cancer has a negative influence on human metabolism and finally causes alterations in taste, smell, appetite and weight [23]. Thereby chemotherapy and radiotherapy causes pain, loss of appetite, vomiting, nausea, constipation or diarrhoea. These side effects have a negative influence on the nutritional status [23]. Studies with a mixed population of patients up to 20% cancer patients were included in this systematic review to counteract the influence.A third exclusion criterion was study end stage disease, because in the palliative phase a maintenance of nutritional status is no longer a priority [24]. A fourth exclusion criterion was (complete) enteral or parenteral feeding. Artificial nutrition can mask the unwanted influence of polypharmacy on the nutritional status [25]. Finally, studies wherein people undergoing abdominal surgery were excluded. Surgical operations can negatively influence the functioning of the gastrointestinal tract in terms of reduced peristalsis, digestion, absorption, nausea and vomiting [26]. This makes it difficult to investigate the actual association between polypharmacy and malnutrition.

2.3.1. Definitions polypharmacy and malnutrition

There are various definitions to define polypharmacy. In this systematic review polypharmacy was defined as the daily use of five or more drugs [5]. Similar to polypharmacy, various definitions of malnutrition and different screening tools were used to indicate malnutrition. Malnutrition is usually defined as involuntary weight loss within a certain time frame and/or a low BMI. A Mini Nutritional Assessment (MNA) score of $\leq$23.5 and Mini Nutritional Status Short Form (MNA-SF) score of $\leq$11 were also considered to indicate an increased risk of malnutrition. In this systematic review all articles describing (risk of) malnutrition prevalence rates were included, regardless the criteria used.

2.4. Methodological and statistical heterogeneity

Information with regard to the study design, population and study outcomes was extracted from each study by one of the researchers (WK) and reviewed by a second researcher (EH). Clinical and methodological heterogeneity were both expected beforehand, because of the broad research question, variability in participants, measuring instruments, outcomes and study design.

2.5. Methodological quality assessment

Quality assessment of the included full text articles was independently assessed by two reviewers (WK and EH), using international quality checklists: Joanna Briggs Institute critical appraisal checklist for case–control studies; Joanna Briggs Institute critical appraisal checklist for cohort studies; The Newcastle–Ottawa Scale

(NOS) for cross-sectional studies. A level of evidence and methodological quality score was adjudged to each article based on the assessment. Quality scores were defined as followed: 0–5 poor; 5,6 moderate; 7,8 sufficient; and 9,10 good. Articles with quality score 6 or lower were excluded.

3. Results

3.1. Study selection

The electronic database search resulted in 3126 studies. After removing duplicates, 2489 potential studies remained. Independently screening of titles, abstracts and full text studies by two researchers (WK and EH) resulted in 10 potentially eligible studies (Fig. 1). The exclusion of 2441 studies was based on: polypharmacy was not the aim of study, malnutrition was not the aim of study, frailty or sarcopenia was the aim of study, a substantial part of the population was aged below 65 years.

3.2. Methodological quality

The remaining 10 articles were independently assessed for methodological quality by two reviewers (WK and EH) using both Joanna Briggs Institute critical appraisal checklists and the NOS for cross-sectional studies (Appendix 2). Three studies were excluded due to a NOS methodological quality score 6 or lower. After assessment of the methodological quality, seven studies were included for this systematic review.

3.3. Study characteristics and causality

The characteristics of the included studies are presented in Table 1. Five studies had a cross-sectional design, one was a cohort study and one a case–control study. Due to the design of these studies, no statements can be made about causality. Number of participants ranged from 81 to 1.660 with a total number of 3.368. Six studies were performed in older people living at home, and one study consisted of participants living in a retirement home.

Performing a meta-analysis, pooling or defining subgroups was not possible due to both statistical and clinical heterogeneity.

3.4. Polypharmacy

Two studies defined polypharmacy as the use of five or more drugs [27,28]. However, two studies defined polypharmacy as the use of six or more drugs [29,30]. Two studies did not provide a definition based on the number of drugs used, but a mean and standard deviation that corresponded to the minimum of 5 drugs [31,32]. In their analysis, Jyrkka et al. (2011) distinguished between polypharmacy (five or more drugs) and excessive polypharmacy (ten or more drugs) [33]. Studies where polypharmacy was defined with using fewer drugs were excluded [34–37].

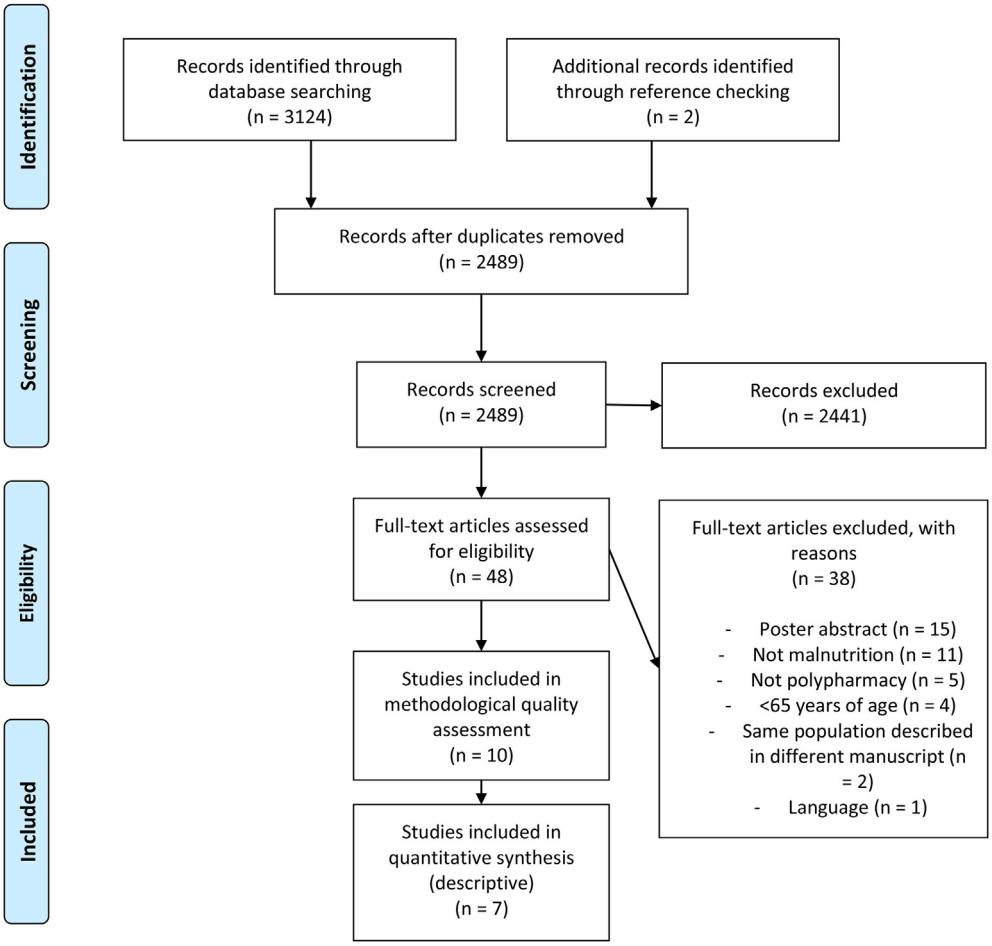

Fig. 1. Flow chart of study selection.

Table 1
General study characteristics table.

First author, year (reference)	Country	Design	Number of participants, (mean) age	Setting	Aim (study on …)	Level of evidence
Farre (2014) [32]	Spain	Cross-sectional	N = 328 ≥85	Community dwelling	The prevalence of risk of being malnourished, and associated study factors	4
Griep (2000) [31]	Belgium	Cross-sectional	N = 81 83.4 ± 6.6	Retirement homes	Age-associated factors on the risk of malnutrition	4
Jyrkkä (2011) [33]	Finland	Prospective cohort study (with yearly follow-ups)	N = 294 80.6 ± 4.2 Polypharmacy group (6−9 drugs): 81.9 ± 5.0 Excessive polypharmacy group (10+ drugs): 81.8 ± 4.6	Community dwelling	The association of polypharmacy with nutritional status, functional ability and cognitive capacity	3
Komiya (2017) [30]	Japan	Cross-sectional	N = 153, 80.4 ± 10.2	Community dwelling with home care	Factors associated with polypharmacy	4
Maseda (2015) [28]	Spain	Cross-sectional	N = 749 75.76 ± 7.2	Community dwelling	Health determinants of (risk of) malnutrition	4
Ramgoolie (2016) [29]	Trinidad	Case-control	N = 103 Cases N = 57 (polypharmacy ≥6 drugs) 74.2 ± 6.6 y Controls N = 46 (non-polypharmacy) 72.5 ± 5.9	Community dwelling	The association of polypharmacy and nutritional status	3
Rodríguez-Sánchez (2020) [27]	Spain	Cross-sectional and longitudinal	N = 1660 75.61 ± 6.29	Community dwelling	The impact of malnutrition risk on healthcare utilization and costs	4

N: Number of patients; M: Mean; y: year; ±: standard deviation
*Level of evidence: 1; Randomized controlled trials, 2; Non-randomized controlled trial, 3; Observational studies with controls, 4; Observational studies without controls.

3.5. Malnutrition

In six studies, malnutrition risk was defined by the Mini Nutritional Assessment (MNA) or Mini Nutritional Assessment Short Form (MNA-SF) [28−33]. Rodrígeuz-Sánchez et al. (2020) defined malnutrition based on the categories defined by the Global Leadership Initiative on Malnutrition (GLIM) criteria [27].

3.6. Polypharmacy associated to malnutrition

An extensive overview of all seven included studies is presented in Table 2.

Different effect measures were reported in the included studies: Odds Ratios, Beta coefficients and correlation coefficients. Adjustments were made in three studies with regard to gender [29,32,33], aspects related to social economic status (higher social risk [32], residential status [33], educational level [29,33], ethnicity and marital status [29]), and indication for disease (prescriptions for cardiovascular drugs, number of drugs and lower Lawton scale score [32], self-reported health status, functional comorbidity index [33], number of disease [29]. In addition, two studies also adjusted for age [29,33] and one study for time of measuring [33].

Seven studies reported Odds Ratios. Ramgoolie et al. (2016) demonstrated that, after adjustment for age, gender, ethnicity, highest educational level achieved, marital status and number of diseases (Diabetes, heart disease, high blood pressure, high cholesterol, arthritis), older people with polypharmacy (six or more drugs) had significantly lower MNA scores than older people without polypharmacy (OR 3.94, 95%CI 1.35−16.77, $p = 0.015$) [29]. After adjustment for sex (female), lower Lawton scale score, higher social risk, number of drugs and prescriptions for cardiovascular drugs, the study of Farre et al. (2014) demonstrated a statistically significant association between (the risk of) malnutrition according to lower MNA-score, and a higher number of drugs ((six or seven drugs (OR 3.23, 95%CI 1.16−8.97, $p = 0.02$), and more than eight drugs (OR 5.58, 95%CI 2.09−14.92, p = 0.001)) [32]. The univariate- and multivariate logistic regression of Komiya et al. (2017) showed that MNA-SF was significantly associated with polypharmacy (six or more drugs). Respectively an OR of 1.177 (95%CI 1.052−1.318, $p = 0.005$) and an OR of 1.238 (95%CI 1.023−1.498, $p = 0.028$) [30] was found. According to Maseda et al. (2015) the use of higher number of prescribed drugs was associated with lower MNA-SF scores and a logistic regression model, including co-morbidity, on polypharmacy was significantly associated with malnutrition/risk of becoming malnourished (β-0.839, $p < 0.001$) [28]. Rodríguez-Sánchez et al. (2020) demonstrated that malnutrition risk, according to the GLIM-criteria, was significantly associated to an increased number of drugs (OR = 2.96, $p < 0.05$) [27].

Two studies reported a Beta coefficient. Both univariate and multivariate analysis by Griep et al. (2000) demonstrated a significant correlation between higher number of drugs taken and lower MNA score (respectively r = −0.34, $p = 0.001$ and β = −0.31, $p = 0.008$) [31]. In addition, Jyrkka et al. (2011) demonstrated lower mean scores for MNA-SF ($p < 0.001$) compared to the non-polypharmacy group at baseline. These differences remained significant ($p < 0.001$) through the three-year follow-up. After adjustment for age, gender, residential status, educational level, modified functional comorbidity index, self-reported health status and time of measuring, excessive polypharmacy (more than ten drugs) remained to be associated with lower MNA-SF scores (β-0.62, SE 0.18, $p < 0.001$, 95%CI -0.98 to −0.27) compared to the non-polypharmacy group [33]. However, the association between polypharmacy (six to nine drugs) and lower MNA-SF scores attenuated (β-0.12, $p = 0.333$).

Two studies reported a correlation coefficient. According to Rodríguez-Sánchez et al. (2020), drugs use increased in case of

Table 2
Overview of outcomes per study.

Author, year (reference)	Definition of polypharmacy	Measurement of malnutrition	Association with malnutrition	Effect size	Additional information on the analysis
Farre (2014) [32]	Mean number of chronic drugs prescriptions: 6.09 ± 3.3	MNA score ≤23.5	Higher number of drugs associated with lower MNA score	6-7 drugs: OR 3.23, 95% CI 1.16–8.97, $p = 0.02$ ≥8 drugs: OR 5.58, 95% CI 2.09–14.92, $p = 0.001$ (ref 0–3 drugs)	Adjustment for sex (female), lower Lawton scale score, higher social risk, number of drugs, prescriptions for cardiovascular drugs
Griep (2000) [31]	Mean number of drugs taken: 4.5 ± 2.9 (MNA >24) 7.0 ± 2.6 (MNA 17–23.3) 12.0 ± 0 (MNA <17)	MNA score ≤23.5	Negative regression coefficient of higher number of drugs and lower MNA score	Univariate: r = −0.34, $p = 0.001$ Multivariate: β = −0.31, $p = 0.008$	Included in multivariate model: MOS scores (mental, social, perceived health, perceived pain), gender, number of teeth, and drugs
Jyrkkä (2011) [33]	Non-polypharmacy (0–5 drugs), polypharmacy (6–9 drugs) and excessive polypharmacy (10+ drugs)	MNA-SF score ≤11	At baseline (2004) and after three year follow-up, excessive polypharmacy showed lower mean MNA-SF scores compared with non-polypharmacy Polypharmacy shows lower MNA-SF scores, but not significant	β-0.62, SE 0.18, p = 0.001, 95%CI -0.98-(-0.27) ($p < 0.001$) β-0.12, $p = 0.333$	Adjustment for age, gender, residential status, educational level, modified FCI, self-reported health status and time of measuring
Komiya (2017) [30]	≥6 different drugs	MNA-SF score ≤11	Higher number of drugs associated with lower MNA score	Univariate: OR 1.177, 95%CI 1.052–1.318, $p = 0.005$ Multivariate: OR 1.238, 95%CI 1.023–1.498, $p = 0.028$	Included in multivariate model: Sex (female), age, CCI, BI, MNA-SF, insurance, premium level, constipation, pollakisuria, insomnia and PIM
Maseda (2015) [28]	≥5 drugs	MNA-SF score ≤11	Significant negative correlation with number of prescribed drugs	r = −0.208; $p < 0.001$ β-0.839, $p < 0.001$, OR 0.432, 95%CI 0.276–0.677	Included in multivariate model: Sex, age categories, educational level, BMI≥25 kg/m2, co-morbidity, presence of cognitive impairment, depressive symptoms, frailty status, self-rated health
Ramgoolie (2016) [29]	≥6 drugs	MNA score ≤23.5	Higher number of drugs associated with lower MNA score	MNA scores ≤23.5: OR 3.94, 95%CI 1.52, 10.13, $p = 0.004$) After adjustment: OR 3.94, 95%CI 1.35, 16.77, $p = 0.015$)	Adjustment for age, gender, ethnicity, highest educational level achieved, marital status and number of diseases
Rodríguez-Sánchez (2020) [27]	Daily use of ≥5 drugs	GLIM criteria	Significant association between higher number of drugs and malnutrition risk Drug use increased in case of (being at risk of) malnutrition	OR 2.96, $p < 0.05$ At risk (r = 0.409) Malnourished (r = 0.49)	Included in multivariate model: Nutritional status, age, sex (female), CCI, depression, and frailty

M: Mean; ±: standard deviation; OR: Odds Ratio; 95% CI: 95% Confidence Interval; p: p-value; r: correlation; β: Beta; BMI: Body Mass Index; MOS: medical outcome study; FCI: Functional comorbidity index; CCI: Charlson Comorbidity Index; BI: Barthel Index; PIM: potentially inappropriate medication; MNA: Mini Nutritional Assessment; MNA-SF: Mini Nutritional Assessment Short Form; GLIM: Global Leadership Initiative on Malnutrition.

being at risk of malnutrition (r = 0.409) and being malnourished (r = 0.49) [27]. In this study, malnutrition or risk of becoming malnourished was always associated with a higher number (five or more drugs) of drugs taken on a daily basis. In addition, longitudinal data indicated that number of drugs increased significantly for both at risk and malnourished groups (r = 0.40 and r = 0.45 more drugs taken daily, respectively $p < 0.05$) [27]. Maseda et al. (2015) presented that well-nourished older people used a significantly lower number of prescribed drugs than those who were (at risk of becoming) malnourished, according to MNA-SF, respectively 4.52 ± 3.17 drugs on average versus 6.51 ± 3.52 drugs on average (r = −0.208: $p < 0.001$) [28].

All studies showed a statistically significant association between (the risk) of becoming malnourished and polypharmacy regardless the instrument or criterion used (MNA, MNA-SF, GLIM criteria, or low fat free mass) and the number of drugs.

3.7. Other risk factors associated to malnutrition, besides polypharmacy

In addition to polypharmacy, five of the included studies also demonstrated significant associations with other risk factors for malnutrition. According to Griep et al. (2000) women had lower MNA scores than men [31]. This association was also demonstrated by Farre et al. (2014) (respectively OR 2.44, 95%CI 1.28–4.54) [32]. The main determinants for malnutrition/risk of malnutrition, besides polypharmacy, were poor self-rated health for women, and overweight or obesity and depressive symptomatology for men according to Maseda et al. (2016) [28]. Rodriguez-Sanchéz et al. (2020) showed that overall, patients at risk of malnutrition or malnourished were older, had lower functional status, and had more comorbidities compared to well-nourished counterparts ($p < 0.05$) [27]. A statistically significant association was also found

with disability according to Lawton Index (OR 1.47, 95% CI 1.29–1.66) and increased social risk (OR 1.15, 95% CI 1.02–1.29) in the study of Farre et al. (2014) [32]. This is supported by Griep et al. (2000) who demonstrated that lower MNA scores were significantly correlated with lower perceived health ($r = 0.19$, $p = 0.047$), social functioning ($r = 0.19$, $p = 0.045$), and mental functioning ($r = 0.29$, $p = 0.003$) [31].

4. Discussion

This systematic review demonstrates statistically significant association between polypharmacy and malnutrition in older people. The seven included studies unanimously demonstrated that older people using five or more drugs, defined as polypharmacy, have a substantially higher risk of (developing) malnutrition. Although the association between polypharmacy and malnutrition was statistically significant in all seven studies, no conclusions about causality could be drawn due to the designs of the included studies.

Polypharmacy is defined in various ways. In this review, all studies where polypharmacy was defined as the daily use of five or more drugs showed a significant association with the risk of malnutrition. However, also studies with fewer drugs have shown a significant association [34–37]. Therefore it remains unclear which number of drugs increases the risk of malnutrition. In addition, from these studies it is not clear whether there is a difference in the type of drug that was used. Many of the drugs used by this group of older people (e.g. for lowering blood pressure or gastric acid inhibitors) cause side effects such as dry mouth or nausea [9]. Xerostomia (dry mouth) is also a known side effect of diabetes medications, antidepressants, psycholeptics, and urological medications [2,14,38,39]. These side effects can in turn lead to eating and drinking problems in these people which results in undernourishment. Subsequently, these people possibly consume too few calories and/or essential nutrients like vitamins, minerals and fibre. There are indications that older people have shortages of vitamin B2, vitamin B12, vitamin D, calcium, iron and zinc [9].

Older patients with polypharmacy are at higher risk of potentially inappropriate medications (PIMs) use [40]. Alhawassi et al. (2019) demonstrated a prevalence of PIMs of 37.5%. The most commonly prescribed PIMs were gastrointestinal agents (35.6%) and endocrine agents (34.3%). PIMs use increases the risk of hospitalization, drug-related problems (DRP) and other adverse health outcomes by two to three folds [41]. A common drug-related problem, especially in older patients with polypharmacy, is overtreatment and undertreatment [42–46]. Overtreatment occurs when the best scientific evidence demonstrates that a treatment provides no benefit for the diagnosed condition. Patients are exposed to treatment harms, and waste of resources is inevitable on a grand scale [47]. Undertreatment is associated with negative clinical outcomes, such as higher risk of cardiovascular events, worsening disability, hospitalization and death [48]. A cross-sectional study based on 3807 Clinical Medication Reviews (CMR) in older patients with polypharmacy demonstrated that overtreatment (25.5%) and undertreatment (15.9%) were the most common drug related problems [46]. Drug classes most frequently involved in overtreatment were drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD, 10.2%), antithrombotic agents (6.7%), lipid modifying agents (5.2%), drugs for constipation (3.5%) and anxiolytics (2.8%). Drug classes most frequently involved in undertreatment were lipid modifying agents (2.9%), antithrombotic agents (2.6%), vitamin A and/or D (2.5%), calcium (1.4%) and blood glucose lowering drugs (excl. insulin 1.3%) [46]. Kuijpers et al. (2017) demonstrated that the highest percentage of undertreatment were found for laxatives to prevent constipation in patients using morphine and for β-adrenoceptor blockers and ACE inhibitors in the treatment of cardiovascular disease. The probability of undertreatment increased significantly with the pre-scribed number of drugs [49]. It is recommended to conduct follow-up research on the number and type of drugs and the association with malnutrition. An unambiguous definition of both polypharmacy and malnutrition would support research and clinical practice, in order to reduce the potential risks of polypharmacy and malnutrition in older people.

Malnutrition can be defined as “a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease” according to ESPEN [50]. In ESPEN guidelines on definitions and terminology of clinical nutrition, sarcopenia and frailty were agreed to be separate conditions often associated with malnutrition [22]. More recently, the Global Leadership Initiative on Malnutrition (GLIM) a core set of diagnostic criteria for malnutrition. GLIM takes a two-step approach; first screening to identify at risk status by the use of any validated screening tool, and second, assessment for diagnosis and grading the severity of malnutrition based on five diagnostic criteria: weight loss, BMI, body composition, food intake and inflammation [51]. Because malnutrition was defined and diagnosed in various ways in the seven included studies, we were unable to provide pooled results of the association between polypharmacy and malnutrition. However, all seven studies showed a significant association regardless of the method of measurement.

By indicating the magnitude of the association between polypharmacy and nutritional status, more awareness can be created among caregivers and health care professionals about the effect and undesirable consequences of polypharmacy and malnutrition. The previous discussion shows that malnutrition has several causes that are also interrelated. Malnutrition is not a causal factor for developing disease, yet malnourished patients are more prone to adverse events which require medication, e.g. (post-operative) infections requiring antibiotics, or more severe side-effects of cancer treatment. In addition, interactions between food (dairy, grapefruit juice, caffeine) and drugs can lead to either decreased bioavailability of a drug, which is prone to treatment failure, or increased bioavailability, which increases the risk of side effects and even toxicity [52]. Finally, changes in body weight may require adaptations of dosages of some drugs. It remains unclear though whether the association is a two-way association, or whether polypharmacy increases the risk of being malnourished, or vice versa: that being malnourished results in polypharmacy in older people.

Polypharmacy increases in old age and people who are malnourished are generally older [53–56]. This could be a possible explanation why malnutrition is more common in older people with polypharmacy. Malnutrition in older people, which is often overlooked by clinicians, is common and increases an individual's risk of developing general poor health or chronic diseases, such as declined muscle function, delayed wound healing or cardiovascular disease [57,58]. Besides malnutrition, polypharmacy also appears to be related to various other factors such as falls and cognitive decline [59–65], drug–drug interactions and food–drug interactions [52,66–69]. In addition, there are several patient groups with renal-, liver-, and heart failure, and diabetes [66,70–75] that deserve extra attention with regard to polypharmacy.

Points for improvement in patient's care include intensifying communication with patient and between health care professionals. For example, patients sometimes do not know why they have to use certain drugs, or experience side effects, such as loss of taste and deviate from the prescription, whether consciously or not, or eat less. Furthermore, the cooperation and communication

between the various health care professionals is not always optimal; there may be no agreements between doctors and pharmacists about the performance of drug checks [76]. Optimizing the exchange of information between the various health care professionals involved about which drugs have been prescribed, changed or stopped is recommended as an intervention. The desired situation is to carry out drug assessment as a cyclical process, in which the total package of drugs used is also (re)assessed in the prescribing and delivery phase [76].

4.1. Methodological limitations of included studies

Firm conclusions based on this systematic review are hampered by the statistical and clinical heterogeneity, as well as the methodological quality of the included studies. The seven studies included a cross-sectional design resulting in a low level of evidence, time point measurements, and no control group. Methodological quality was often inadequate in terms of comparability of the subjects, non-respondents, confounding control and statistical testing. Special importance should be given to the type of studies (methodological quality) in future research, as the studies reviewed in this systematic review were all of insufficient methodological quality.

4.2. Strength and limitations

This systematic review was strengthened by focusing on the association between polypharmacy and malnutrition outside of the group of frail older people. While it is often assumed that the association between malnutrition and polypharmacy mainly occurs in frail older people, a strong association has now been shown outside this group. In addition, it included a large number of older people from different settings, the data analyzed should be reasonably representative of this population. Besides, studies were searched in three different databases and the studies found were independently assessed by two reviewers. In order to achieve an optimal search strategy, the help of a medical information specialist was consulted.

Sarcopenia and frailty were agreed to be separate conditions often associated with malnutrition [50]. Studies on frailty and sarcopenia were excluded in order to avoid overestimation or underestimation of the actual association between malnutrition and polypharmacy. However, “un-diagnosed” frail and/or sarcopenic persons may be included due to the characteristics of the population of interest. A final limitation is that no adjustment could be made for disease burden in general.

4.3. Conclusion and recommendations

All seven included studies in this systematic review demonstrated that polypharmacy is significantly associated with malnutrition. Although the insufficient quality of the reviewed studies makes it difficult to reach firm conclusions, more attention should be given to the nutritional status of older people with polypharmacy and at polypharmacy itself. This underlines that special attention should be paid to the risk of malnutrition in older patients using multiple drugs, as multiple (adverse) interactions between drug use and impaired food intake have been described. Prevention and timely evaluation of polypharmacy, deprescribing, and monitoring of malnutrition, may lead to a reduced risk of malnutrition in older people.

Author contributions

Individual contributions: W.E. Kok contributed to the study design, conceptualized the research question, conducted the studies and data analyses, and conceptualised the manuscript, commissioned by E.B. Haverkort and Y.A. Algra. W.E. Kok developed the search strategy with support of J. Mollema, a medical information specialist, who helped designing the search string and carried out the searches in the databases. W.E. Kok and E.B. Haverkort screened search results, obtained papers, screened retrieved papers against inclusion criteria and carried out quality assessment. W.E. Kok extracted the data from included papers, designed tables and figures and wrote the review. E.B. Haverkort and Y.A. Algra commented on drafts of the review. V.R.Y. Hollaar, E. Naumann, M.A.E. de van der Schueren and K. Jerković-Ćosić participated in the design of the study and assisted in the drafting of the manuscript. K. Jerković-Ćosić supervised the project and was available for advice.

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Declaration of competing interest

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All authors approved the submitted version, agreed to be personally accountable for their contribution to this review, and ensure that questions related to the accuracy or integrity of any part of this work will be appropriately investigated, resolved and documented.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2022.03.007.

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