# An overview of prevalence, determinants and health outcomes of polypharmacy

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***Abstract:*** A high rate of polypharmacy is, in part, a consequence of the increasing proportion of multimorbidity in the ageing population worldwide. Our understanding of the potential harm of taking multiple medications in an older, multi-morbid population, who are likely to be on a polypharmacy regime, is limited. This is a narrative literature review that aims to appraise and summarise recent studies published about polypharmacy. We searched MEDLINE using the search terms *polypharmacy* (and its variations, e.g. multiple prescriptions, inappropriate drug use, etc.) in titles. Systematic reviews and original studies in English published between 2003 and 2018 were included. In this review, we provide current definitions of polypharmacy. We identify the determinants and prevalence of polypharmacy reported in different studies. Finally, we summarise some of the findings regarding the association between polypharmacy and health outcomes in older adults, with a focus on frailty, hospitalisation and mortality. Polypharmacy was most often defined in terms of the number of medications that are being taken by an individual at any given time. Our review showed that the prevalence of polypharmacy varied between 10% to as high as around 90% in different populations. Chronic conditions, demographics, socioeconomics and self-assessed health factors were independent predictors of polypharmacy. Polypharmacy was reported to be associated with various adverse outcomes after adjusting for health conditions. Optimising care for polypharmacy with valid, reliable measures, relevant to all patients, will improve the health outcomes of older adult population.

## Introduction

A high rate of polypharmacy, often defined as taking five or more medications, is in part a consequence of the increasing rate of multimorbidity in the ageing population worldwide.[1] This has direct negative unintended consequences. Investigating the effectiveness and safety as well as side effects of new medications is traditionally achieved mainly through randomised controlled trials, where patients with multiple chronic conditions or frailty are usually excluded.[1,2] Therefore, our understanding of the potential harm of taking multiple medications in an older, multi-morbid population, who are likely to be on a polypharmacy regime, is limited. Improvement in evidence to better understand the relationship between polypharmacy and health outcomes

should be a priority to optimise treatment in frail older people with various chronic conditions.[3] For various reasons, polypharmacy has drawn much attention recently. Polypharmacy is reported to be the main risk for 'potentially inappropriate prescribing (PIP)', with serious implications for healthcare costs.[4–6] It could be used as a quick quality indicator of medication use in older adults.[7] A prospective cohort study found that patients with polypharmacy (6–10 medications) and excessive polypharmacy (⩾11 medications) were significantly more likely to be prescribed anticholinergic drugs,[8] which are known to be linked to several adverse health outcomes.[9–11] Observational studies have shown that polypharmacy is associated with increased side effects, harmful drug interactions,

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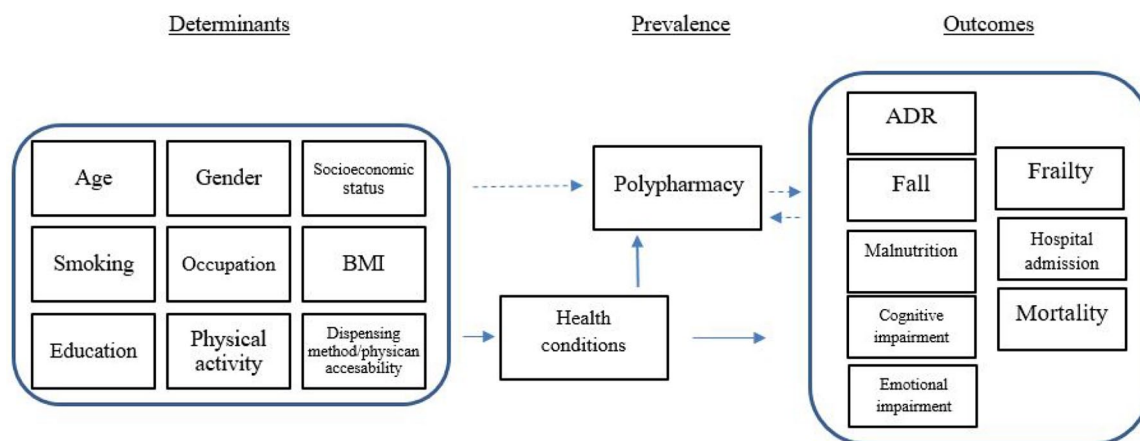
**Figure 1.** Determinants and outcomes associated with polypharmacy. Most of the proposed predictors and outcomes of polypharmacy are also independently associated with health conditions.
ADR, adverse drug reaction; BMI, body mass index.

medication non-adherence, and functional and cognitive decline and frailty.[12] It has also been reported to be associated with other important adverse health outcomes such as increased risk of hospitalisation and mortality.[13]

Although polypharmacy is mostly a consequence of multiple chronic conditions (multimorbidity), there might be other modifiable factors that determine polypharmacy independently of this burden. In addition, the association of polypharmacy and health outcome is a complex relationship. Most outcomes associated with polypharmacy are associated independently with pre-existing multimorbidity. Furthermore, many of these outcomes could also exacerbate the rate of prescription, and therefore it should be considered as a bidirectional relationship (Figure 1). For example, the rate of adverse drug reactions (ADR) is significantly higher in patients taking multiple medications. Counterintuitively, patients might require taking more medications to control or reduce these adverse effects.[14]

In this review, we provide current definitions of polypharmacy. We identify the determinants and prevalence of polypharmacy reported in different studies. Finally, we summarise some of the findings regarding the association between polypharmacy and health outcomes in older adults, with a particular focus on frailty, hospitalisation and mortality.

**Methods**
This is a narrative literature review that aims to appraise and to summarise recent studies published about polypharmacy. We searched MEDLINE using the search terms 'polypharmacy' (and its variations, for example, multiple prescriptions, inappropriate drug use, etc.) in titles. Systematic reviews and original studies in English published between 2003 and 2018 were included. We screened the titles and abstracts of the eligible studies as well as the citations of the articles retrieved during the first search, and selected studies that aimed to address any of our research questions on the definition, prevalence, determinants and outcomes of polypharmacy. We then classified articles based on the results reported. For the health outcomes, we selected articles that reported on the association of polypharmacy and frailty, hospitalisation and mortality.

**Definition of polypharmacy and excessive polypharmacy**
Polypharmacy has no generally accepted definition, though criteria for major and minor polypharmacy have been suggested in the literature. Polypharmacy has been defined using different approaches, including numerical and descriptive methods.

Most often, polypharmacy is defined in terms of the number of medications that are being taken by

an individual at any given time. Many studies have used a numerical method either by using a cut-off point or using a continuous number approach to define polypharmacy. Different cut-off points have been suggested. For example, taking more than four, five or six medications at the same time is categorized as polypharmacy. Though, the most frequent definition that has been used so far is 'taking 5 or more medications concurrently' as polypharmacy and '10 or more medications concurrently' as excessive polypharmacy.[15]

Using a strict cut-off to identify polypharmacy with a view to study the associated health outcomes has raised some concerns. A prospective cohort study showed that the number of drug-related problems was linearly related to the number of medicines used in patients admitted to hospital. This approach accounts for effects of number of medications on a linear scale (e.g. from 1 to 4) and a possible dose response relationship that is not captured through a binary classification.[16]

There are some proposed time-defined methods that considered duration of treatment for diagnose of polypharmacy. 'Taking five or more medications for more than 90 days'[17] or 'five or more medications in 1 month for 6 months or more in a year'[18] are some examples. In a study by Fincke and colleagues,[19] a cumulative and continuous definition was suggested for polypharmacy to allow exploration of various aspects of medication use, such as the effect of chronic medication exposure.

There are a few descriptive only definitions suggested for polypharmacy such as 'patients visiting multiple pharmacies to obtain medications' and 'use of additional medications to correct adverse effects'.[20,21]

It is worth emphasising that taking multiple medications is not necessarily unwise and could be both rational and appropriate in some patients. Therefore, it is important to distinguish between appropriate and inappropriate polypharmacy.[1] Recent studies have suggested a shift towards using the term 'appropriate polypharmacy' rather than simply using the count. By adopting this approach, we would be able to distinguish between the necessary and unnecessary prescription of multiple drugs in older adults and to

justify the outcomes. Different definitions of 'appropriate polypharmacy' have been suggested, but more studies are needed to confirm and validate this approach further.[1,15,22]

## Prevalence of polypharmacy in the elderly

The prevalence of polypharmacy reported in literature varies between 10% to as high as around 90% according to the age group, definition used, healthcare and geographical setting of the study.

A cross-sectional analysis of the Survey of Health, Ageing, and Retirement in Europe (SHARE) database showed that the prevalence of polypharmacy, defined as taking five or more medications concurrently in older adults aged 65 years or more, was between 26.3% and 39.9% among 17 European countries and Israel.[23]

According to 'Stimulating Innovation Management of Polypharmacy and Adherence in the Elderly' (SIMPATHY), a European Union (EU) funded project aimed at managing polypharmacy by 2030, around 20% of people age 70–74 years are prescribed 10 or more medicines and the rate of polypharmacy is significantly higher in the most deprived population (Figure 2).[24]

In the UK, prescribing rates continue to increase because of population ageing. A population database analysis of 310,000 adults resident in the Tayside region of Scotland reported that the proportion of adults dispensed 5 or more medications doubled to 20.8%, and the proportion dispensed 10 or more tripled to 5.8% between 1995 and 2010.[3] In another study, analysis of electronic primary healthcare records in Scotland showed that 16.9% of adults were receiving 4–9 medications.[25]

Analysis of the prescription drug data in the United States showed that polypharmacy rate increased from 6.3% to 10.7% from 1999–2000 through 2007–2008 in the population (Figure 3).[26]

In Switzerland, it was reported that polypharmacy prevalence was 11.8%, as defined by regular use of five or more different pharmacologically active medicines among 4938 subjects aged between 40 and 81 years.[27]
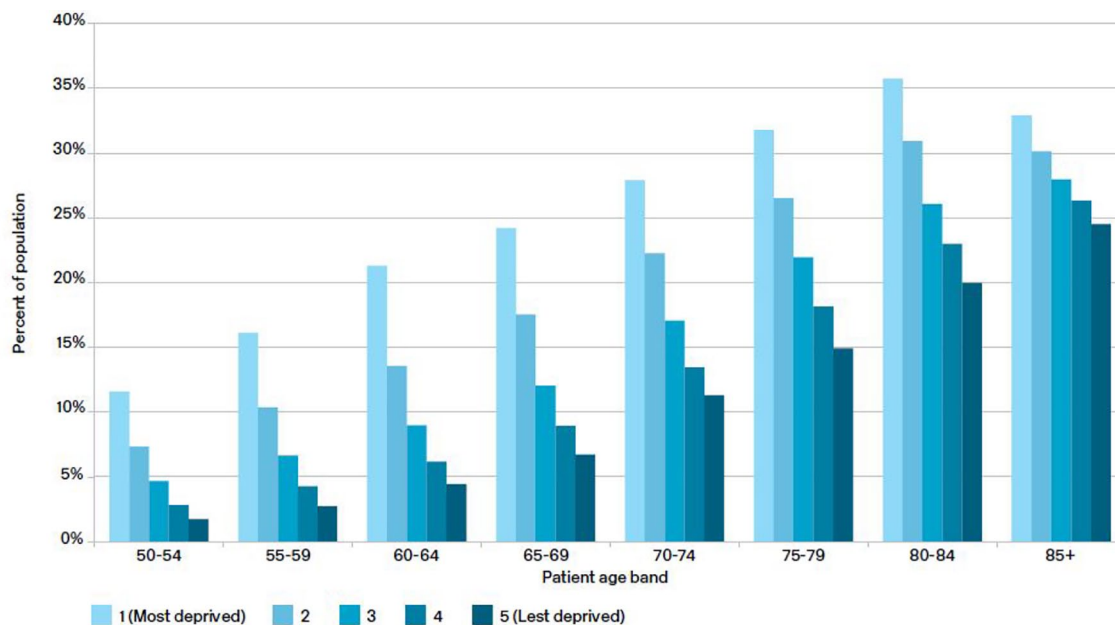
**Figure 2.** Percentage of patients prescribed 10 or more medicines (excessive polypharmacy) by age group and deprivation in Scotland (obtained from the SIMPATHY consortium document available at http://www.simpathy.eu/).[24]
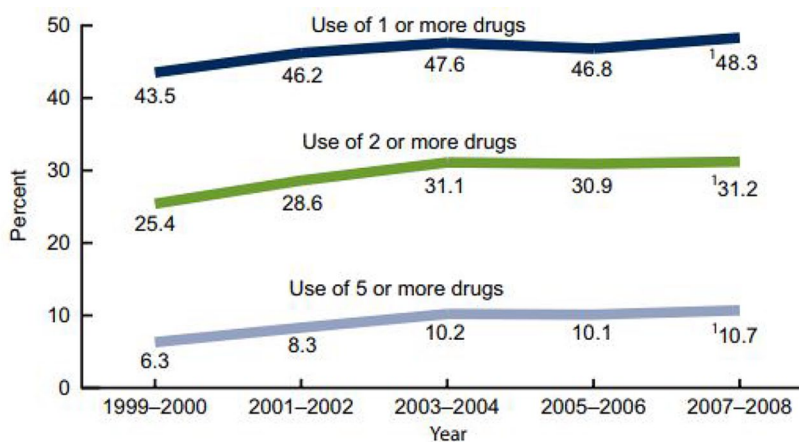


**Figure 3.** Increasing rate of taking prescription medications in the US (obtained from the US prescription drug data for 2007–2008 available at).[26]
[1]Significant linear trend from 1999–2000 through 2007–2008.
Note: Age adjusted by direct method to the year 2000 projected US population.
Source: CDC/NCHS, National Health and Nutrition Examination Survey.
CDC, Centers for Disease Control and Prevention; NCHS, National Center for Health Statistics; US, United States.

Of 2057 participants (60% female; mean age 81.7 years) who visited the emergency department of a geriatric hospital in Italy, 30.3% were taking 6–9 drugs concomitantly, and excessive polypharmacy (≥10 drugs) was presented in 17.8% of the patients.[28]

Between 2010 and 2013, a total of 1,742,336 individuals aged 65 years and older were included and followed until death or by the end of the study in Sweden. The prevalence of polypharmacy (taking five or more medications) was 44.0% and the incidence rate in individuals

without polypharmacy at baseline was 19.9 per 100 person-years.[29]

In an older adult Korean population of 319,185 aged 65 years and older, an 86.4% estimated prevalence of polypharmacy (≥6 medications) was found, of whom 44.9% had excessive polypharmacy (≥11 medications) and 3.0% were taking ≥21 medications.[30] Similarly, Chan *et al.* reported that 83.5% of national samples of 11,338 elderly people in Taiwan were categorised as having polypharmacy defined as taking six or more drugs concomitantly.[31]

A health insurance database analysis compared changes in the rate of polypharmacy over 10 years for different age groups and in men *versus* women. They found that the proportion of patients with polypharmacy was highest in the 75–84 years (32.5%) but the change in the number of drugs used was greatest among patients aged 65–74 years (+2.14, 95% CI 2.10–2.19) compared with older age groups. This study also found that men had a higher increase in the number of medications taken compared with women over the follow up period.[7]

Although the prevalence of polypharmacy reported varies significantly in different countries, prescribing rates continue to increase because of the increase in the older adult population and the availability of many more different medications globally.

## Determinants of polypharmacy

Many studies reported poor health as the main reason for occurrence of polypharmacy in older adults.[5,32–35]

Of all the chronic conditions, obstructive pulmonary disease was the factor most strongly associated with both polypharmacy and excessive polypharmacy in a population-based cohort study in Finland.[32] Diabetes, depression, heart disease, hypertension, being breathless and pain were other conditions and symptoms significantly linked with both polypharmacy and excessive polypharmacy in various observational studies.[32,33]

The neutrophil/lymphocyte ratio, a marker of systemic inflammation, was independently related to higher daily drug consumption after adjusting for chronic conditions. Metabolic syndrome, chronic pain, urinary incontinence, increased creatinine levels and reported gastric disturbances were also

significant risk factors for increased number of medications.[36]

According to the Belgian Health Interview Survey, factors most strongly associated with excessive polypharmacy were having at least one contact with a general practitioner in past 2 months and self-reported depression during the last year. This study reported that 90% of patients in the excessive polypharmacy group were taking cardiovascular system medications.[35]

Studies have shown that demographics, socioeconomic circumstances and self-assessed health factors could also be independently associated with polypharmacy.[3,37] A retrospective cohort study reported that polypharmacy participants were significantly older and more frequently obese, had lower educational attainment and were former smokers.[27]

A cohort study of older adults in a primary care setting in Germany, assessed medication use as reported by older patients and compared it with doctor's perceived medication regimens for their respective patients. This study showed that having a medication disagreement between physicians and patients in terms of the regular intake of prescribed drugs was a significant determinant of polypharmacy.[33] Poor self-assessed health, being dependent on instrumental activities of daily living and having a low perceived health were other significant predictors of polypharmacy.[32,33]

Older adults using multi-dose dispensing, a dose administration aid where medications are supplied into one unit for each dose packed in disposable bags,[29,38] were at significantly higher risk of developing incident polypharmacy compared with those receiving ordinary prescriptions. After adjustment for confounders, living in a nursing home was found to be linked with lower risks of incident polypharmacy and incident excessive polypharmacy in a prospective cohort study of older adults.[29]

## Health outcomes associated with polypharmacy

### *Polypharmacy and frailty*
Frailty is a multidimensional syndrome characterised by a non-resilient state and increased vulnerability in older adults.[39]

Co-existence of multiple chronic diseases is prevalent in frail older people and can significantly increase the use of multiple medications.[40–42] Frailty and polypharmacy are both very prevalent in older adults, although little is known about the impact they might have on each other. In recent years an increasing number of studies have investigated the relationship between frailty and polypharmacy and have tried to explain the mechanisms underlying their association. A recent systematic review about the relationship between polypharmacy and frailty included the results from 25 publications and concluded that polypharmacy could be associated with increased risk of frailty. The casual relationship is still unclear, and it seems to be a bidirectional relationship.[43]

Polypharmacy has been shown to increase the risk of frailty in older adults independently of other risk factors.[44–46] A longitudinal cohort study followed participants over 8 years showed that polypharmacy was associated with higher incidence of frailty in a dose dependent manner.[45]

Co-occurrence of polypharmacy and frailty could increase the risk of poorer health outcomes in older adults. The adjusted association of combined frailty status and polypharmacy with adverse outcome showed that polypharmacy was linked with mortality, incident disability, hospitalisation and emergency department visits in frail and pre-frail, but not in non-frail, elderly.[47]

### Polypharmacy and hospitalisation

A prospective cohort of community dwelling older men investigated the association between polypharmacy, as an indicator of suboptimal medication use, and incident all-cause hospital admissions, and those due to falls, incontinence and delirium. This study showed that the number of medicines used was independently associated with all cause admission to hospital over 4.5 years of follow up.[48]

In the Taiwan Longitudinal Health Insurance Database study, a dose–response relation was found between polypharmacy, all-cause and fracture-specific admission to hospital. The odds for anticholinergic risk scale scores to predict fracture-specific admission to hospital were comparable with polypharmacy in this study.[7]

Polypharmacy and excessive polypharmacy were both independent risk factors for 6-month emergency department return and hospital admission in an observational cohort study conducted in a geriatric hospital in Italy.[28]

Scottish Polypharmacy Guidance reported that up to 11% of unplanned hospital admissions are related to harm from medicines and almost 50% of these are preventable.[1] Several studies have reported the role of polypharmacy in adverse drug reactions with resultant drug-related hospitalisations. A review study by Salvi and colleagues pointed out that polypharmacy, which is often associated with the use of potentially inappropriate prescription, was amongst the main reasons for drug-related hospitalisations in older adults along with other risk factors such as changes in pharmacokinetic and pharmacodynamics with older age and multiple chronic conditions.[49]

Nobili *et al.* examined the relationship between polypharmacy and length of hospital stay, and found that polypharmacy was not related to length of hospital stay though the occurrence of adverse events was a significant predictor of prolonged hospital stay by nearly 4 days.[50]

The rate of unplanned hospitalisation was directly linked to the number of medications, but this association was reduced in patients with several conditions in a retrospective cohort study linking the medication data to national hospital admission data in Scotland. Payne and colleagues showed that multiple prescription was associated with the greatest increased risk of unplanned hospitalisation in those with fewest recorded conditions. This study highlighted the importance of considering polypharmacy in the clinical context for which medications were prescribed.[25]

### Polypharmacy and mortality

A systematic review and meta-analysis of 47 studies demonstrated a significant association between mortality and polypharmacy. When polypharmacy is defined categorically, a dose-response relationship was observed across escalating thresholds for defining polypharmacy using values of one to four medications, five medications, and six to nine medications.[13]

A retrospective cohort study examined the association between polypharmacy and mortality in 12,423 participants' aged 65 years or more in England and Wales over 18 years of follow up. According to this study, the relationship between polypharmacy and mortality changed over time and was different for men and women. Polypharmacy was associated with increased mortality in the short term independently of other confounders reported at baseline. The association remained, although weaker, in women over the medium to long term (5–18 years) but decreased continuously over time in men and become non-significant in the longer term.[51]

The Concord Health and Aging in Men Project aimed to determine an optimal discriminating number of concomitant medications associated with mortality in community-dwelling elderly population. The highest value of Youden Index was obtained for a cut-off of 4.5 medications and for each one increase in number of medications, the adjusted odds ratios was 1.09 [95% confidence interval (CI) = 1.04–1.15] for mortality. This study supported the use of five or more medications in the current definition of polypharmacy to estimate the medication-related adverse health outcomes.[52]

## Conclusion

Populations are ageing rapidly all over the world and the study of polypharmacy has become a priority in recent years. Polypharmacy is one of the most significant public health challenges in the elderly and the burden is set to increase as more people suffer from long-term conditions. The necessity for immediate and effective polypharmacy management has been prioritised to decrease the risks and costs of prescriptions. There is a need for larger studies that follow patients throughout life to improve understanding of factors predicting polypharmacy and allow detection of vulnerable people at earlier stages. The negative health outcomes associated with polypharmacy should be considered particularly in frail elderly people.

The association of polypharmacy and poor outcomes could simply represent that polypharmacy is the marker of increased risk and not the primary cause of it.[53,54] Therefore, correct adjustment for chronic illnesses to avoid indication bias is particularly important to consider.[2] Although most of the studies controlled for the effect of chronic conditions, different co-morbidity indices do not cover all common health conditions, and the severity of chronic disease, which could partly explain some of the observed associations between polypharmacy and poor health outcomes.[48] Therefore, assumptions that polypharmacy represents poor care and is always harmful needs to be reconsidered. It is rational to interpret polypharmacy in the clinical context for the individual patient.[25]

Distinguishing between appropriate and inappropriate polypharmacy is necessary and more studies are needed to apply this approach. The appropriateness of polypharmacy could be identified with relevant indicators.[1,22] According to Scottish Polypharmacy Guidance, polypharmacy could be evaluated in different domains by reviewing 'Aims, Need, Effectiveness, Safety, Cost-effectiveness and Patient centeredness'.[1] Burt and colleagues have recently developed an indicator to measure appropriate polypharmacy applicable in primary care.[22] Use of these indicators in clinical practice could improve policy though, their feasibility and usefulness require further evaluation. Reducing inappropriate polypharmacy can be achieved through various interventions such as educational and regulatory interventions. However, the effectiveness and cost-effectiveness of these interventions to improve health outcomes is still unclear.[5] Optimising care for polypharmacy with valid, reliable measures, relevant to all patients, will improve the health outcomes and reduce substantially the healthcare costs of older adult population.

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