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Review

The patterns and implications of potentially suboptimal medicine regimens among older adults: a narrative review

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Abstract: In the context of an ageing population, the burden of disease and medicine use is also expected to increase. As such, medicine safety and preventing avoidable medicine-related harm are major public health concerns, requiring further research. Potentially suboptimal medicine regimens is an umbrella term that captures a range of indicators that may increase the risk of medicine-related harm, including polypharmacy, underprescribing and high-risk prescribing, such as prescribing potentially inappropriate medicines. This narrative review aims to provide a background and broad overview of the patterns and implications of potentially suboptimal medicine regimens among older adults. Original research published between 1990 and 2021 was searched for in MEDLINE, using key search terms including polypharmacy, inappropriate prescribing, potentially inappropriate medication lists, medication errors, drug interactions and drug prescriptions, along with manual checking of reference lists. The review summarizes the prevalence, risk factors and clinical outcomes of polypharmacy, underprescribing and potentially inappropriate medicines. A synthesis of the evidence regarding the longitudinal patterns of polypharmacy is also provided. With an overview of the existing literature, we highlight a number of key gaps in the literature. Directions for future research may include a longitudinal investigation into the risk factors and outcomes of extended polypharmacy, research focusing on the patterns and implications of underprescribing and studies that evaluate the applicability of tools measuring potentially inappropriate medicines to study settings.

Plain Language Summary

A review on potentially inappropriate medicine regimens

Medicine use in older age is common. Older adults with more than one chronic condition are likely to use multiple medicines to manage their health. However, there are times when taking multiple medicines may be unsafe and the number of medicines, or the combination of medicines used, may increase the risk of poor health outcomes. The term medicine regimens is used to describe all the medicines an individual takes. There are several ways to measure when a medicine regimen may be inappropriate and, therefore, potentially harmful. Much research has been published looking into potentially inappropriate medicine regimens. To bring together the current research, this review provides a background on the different measures of potentially inappropriate medicine regimens. It also summarizes how many people may experience potentially inappropriate medicine regimens, the impact it is having on their health and who may be at greater risk. In doing so, we found a number of gaps in the existing evidence, indicating that our understanding of potentially inappropriate medicine regimens is incomplete. This review highlights gaps in knowledge that can be addressed by future research. With an improved understanding of potentially inappropriate medicine regimens, we may be able to better identify those at greater risk to prevent or minimize the impact of poorer health outcomes related to unsafe medicine use.

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Introduction

Medicine safety and medicine-related harm are major public health concerns. Older adults are particularly vulnerable to adverse events associated with pharmaceutical intervention. Potentially suboptimal medicine regimens is an umbrella term that encompasses a range of tools and indicators for measuring medicine use that may increase the risk of harm in older adults. Medicines safety has become a policy priority in many countries since the World Health Organization (WHO) launched its Medication Without Harm initiative in 2017, which aimed to reduce medicine-related harm by 50% within 5 years.[1] While there is a substantial body of evidence investigating potentially suboptimal medicine regimens internationally, how risk is defined and measured appears to vary across the literature. This narrative review aims to provide an overview of the current evidence of potentially suboptimal medicine regimens, namely, polypharmacy, underprescribing and potentially inappropriate medicines (PIMs). The objective is to highlight key gaps in the literature to inform targets for future research.

Methods

This is a narrative literature review that aims to synthesize the current research on the prevalence and risk factors of potentially suboptimal medicine regimens, longitudinal patterns of polypharmacy and outcomes of polypharmacy, PIMs and underprescribing. We searched MEDLINE (1990–2021) and using manual checking of reference lists for original research. Databases were searched using combinations of free text and Medical Subject Headings (MeSH) terms for polypharmacy, inappropriate prescribing, medication errors, drug prescriptions, age, adults, risk factors, drug interactions, potentially inappropriate medication lists and trends (see Box 1 for a more detailed sample of search terms). This review focused on general populations, excluding populations experiencing specific disease states. Data on population, indicators of suboptimal regimens, prevalence, associations and clinical outcomes were extracted and tabulated for synthesis.

Box 1. Examples of key search terms.

1. Medicines – medic*, drug*, pharma*, prescrib*
2. Suboptimal prescribing – suboptimal*, potential*, inappropriate
3. Polypharmacy – polymed*, polydrug*, multiple medic* overprescrib* over utili*ation, multimed*
4. Potentially inappropriate medicines – explicit criteria, PIM*, inappropriate prescrib*, inappropriate medic*
5. Risk factors – risk factor*, predictor*, association*, relationship*, determinant*, explanat*
6. Clinical outcomes – clinical*, outcome*, consequence*, implication*, adverse, event*, harm*
7. Longitudinal studies – longitudinal*, trend*, pattern*, cohort*, panel*, time

Ageing – epidemiology

Globally, projections suggest the number of older adults, aged 65 years and above, will exceed 1.5 billion by 2050.[2] Multimorbidity is estimated to affect approximately 65% of adults aged 65–84 years and up to 82% among those aged 85 years or older.[3] To manage these morbidities, medicines are one of the most common treatments in health care. However, older adults are a heterogeneous group, encompassing those who are robust and in good health, as well as those with significant frailty and high burden of disease.[4] These factors can make optimal prescribing complex. Ageing is associated with a range of physiological changes, including decreased kidney and liver function and loss of total muscle mass,[5] which can affect the absorption, distribution, metabolism and excretion of medicines, and may increase the risk of adverse events and medicine-related harm.[6,7] Consequently, older adults are regularly excluded from drug trials and dosing is often extrapolated from younger, healthier populations, which may not be appropriate in older age.[8] To further confuse the situation, prescribing guidelines often focus on single diseases and do not consider potentially harmful medicine combinations or disease contradictions associated with

having two or more chronic conditions, which is common in older age.[8] With increasing burden of disease and complexity of medicine regimens, medicine-related harm is increasingly being understood as a new risk factor for disease in older adults.[9,10]

Medicine-related harm

Medicine-related harm is often recognized as a preventable cause of harm, which may occur with an error in the provision or management of therapy.[11] Medicine-related harm has been associated with poor health outcomes, including increased falls and fractures, confusion, loss of appetite, functional decline, hospitalization and mortality.[4] The WHO has projected that medicine errors cost US$42 billion per annum.[1] Estimates suggest that 1 in 10 patients admitted to hospital will have experienced an adverse medicine event, either leading to or during their hospitalization.[12] A recent systematic review indicated that more than half of adverse events could have been prevented with safer prescribing practices.[13] Inability to consider the total impact of age-related changes, burden of disease and the number and type of medicines used by older adults may put them at greater risk of adverse events and medicine-related harm.[14] A such, careful and regular review is essential for identifying risk and preventing avoidable harm. To support this effort, there is an expanding body of research describing and applying a range of tools and indicators for identifying potentially suboptimal medicine regimens among older adults both in the community and higher risk settings.

Table 1. Indicators of potential suboptimal medicine regimens.

Indicator	Description
Intensity of medicine use	
Polypharmacy	A numerical indicator determined according to the number of medicines used. There is no agreed-upon definition for polypharmacy; however, the use of five or more concurrent medicines is the most common cut point applied in the literature.[15]
Quality of medicine use	
Omitted medicines	Underprescribing or the omission of a clearly indicated medicine will likely benefit the older adult.[16]
High-risk prescribing	
PIMs	The use of medicines where the risk outweighs the potential benefit includes inappropriate dose, frequency or duration, the use of medicines with clinically significant interactions with other medicines or that are contraindicated in the context of specific symptoms, conditions or diseases, particularly when safer alternatives exist.[17]
Anticholinergic and sedative medicines	Medicines with anticholinergic or sedative properties have a more prominent effect in older adults, and cumulative burden may lead to adverse events.[18] As a subset of PIMs, these medicines are often measured independently of broader indicators.
Prescribing cascades	The use of medicines to treat the adverse reactions of another medicine has been misinterpreted as a new medical condition requiring treatment.[19]

PIMs, potentially inappropriate medicines.

Potentially suboptimal medicine regimens

Potentially suboptimal medicine regimens is a term that considered an individual's entire regimen and captures a range of indicators that aim to identify medicine use that may increase risk of medicine-related harm. The concept measures the intensity of multiple medicine use, which is called polypharmacy. It also considers the quality of medicine regimens by identifying specific medicines used, or not used, to determine their potential appropriateness. These indicators include underprescribing, and high-risk prescribing, which encompasses the use of PIMs, specific medicines with anticholinergic or sedative properties, which are a subset of PIMs, and prescribing cascades. Table 1 provides a brief outline of the key indicators of potentially suboptimal medicine regimens.

The appropriateness of an individual's medicine regimen is often highly contextual. A range of quality indicators have been developed, including both implicit and explicit measures. Factors including overall health and life expectancy, current diagnoses, which may include multiple comorbidities, previously unsuccessful treatments or intolerances, as well as the patient care goals and values must all be considered to investigate true regimen appropriateness.[17,20] Implicit measures, or qualitative assessments, are judgement-based and capture these contextual factors.

Trained health care professionals provide an individualized assessment of a patient's medicine regimen, which is often informed by a patient interview and/or review of full medical history. While this level of detail is achievable in clinical settings, access to these data is less common in research, particularly in large epidemiological studies. Therefore, research often relies on explicit tools to assess the quality of medicine regimens. These tools are more objective and criteria-based measures, designed to minimize the need for clinical judgement. These features make the application of explicit tools more accessible to a wider range of users and may be appropriate for measuring regimen quality across populations. However, with the ease of application, assumptions must be made on a population level; therefore, explicit measures may only provide an estimate of *potential* inappropriateness.

Polypharmacy (overprescribing)

Polypharmacy, polytherapy or the use of multiple medicines is one of the broadest measures of potentially suboptimal medicine regimens. The intensity of medicine use may be estimated using the number of medicines to indicate where potential overprescribing may be occurring. There is no universally agreed-upon definition for polypharmacy; it may be captured according to a continuous measure of the number of medicines or be defined by a cut point of a specific number of medicines.[21] A recent systematic review investigating polypharmacy definitions found substantial heterogeneity in the cut points applied across the literature, ranging from the use of ⩾2 concurrent medicines up to ⩾21 medicines.[15] Variability has also been observed in the criteria for measuring polypharmacy, including numeric only measures, for example, ⩾10 medicines; numeric measures with conditions, for example, ⩾6 medicines taken in the previous 7 days; or qualitative measures, for example, more medicines than clinically necessary.[15] While qualitative measures may provide the best estimate of whether overprescribing may be occurring, access to quality data is often a limitation. Therefore, the quantitative, ⩾5 medicine cut point is the most common measure of polypharmacy in published research,[15,21] and appears to be the most appropriate cut point for identifying those at possible risk of harm.[22,23] Hyperpolypharmacy or excessive polypharmacy is generally considered to be ⩾10 medicines.

Applying measures of polypharmacy

Point prevalence. Polypharmacy is a commonly applied indicator of potentially suboptimal medicine regimens. Most studies focus on older cohorts, aged 65 years or older, some studies also include middle-aged adults, while the addition of younger cohorts appears less common among general populations (Table 2). Applying a ⩾5 medicine cut point, the prevalence of polypharmacy reported in the literature ranged from 7.0% up to 83.0%;[24,25] however, there was substantial heterogeneity across the literature in terms of study population, age group, methods for counting medicines and geographic locations (Table 2). The inclusion of younger cohorts generally appears to lower the prevalence of polypharmacy across the literature; however, similar estimates were observed between an older sample of community-dwelling men (35.9%)[26] and primary care outpatients aged 20 years or older (39.2%),[27] which suggests in some cases the study context may be just as important a determinant as age (Table 2). Hyperpolypharmacy (⩾10 medicines) was less commonly measured and ranged from 2.0% to 23.8%.[28,29]

Polypharmacy definitions also included more nuanced methods of counting, beyond whether medicines were doctor-prescribed or self-prescribed. While some definitions were non-specific, others counted medicines according to the number of active ingredients or focused on specific administration routes, such as only counting medicines with systemic action (Table 2). Polypharmacy was also defined according to administration frequency, medicines taken regularly or PRN (as required), or used within specific time frames, such as co-prescription, which describes the number of medicines dispensed at one time, the total medicines or mean medicines used daily, weekly, monthly or in the previous year (Table 2). However, because study setting, age group and methodology vary substantially between studies, it is unclear the effect definitions have on overall prevalence measures and whether results can be compared. Furthermore, it should also be acknowledged that quantitative measures of polypharmacy, alone, are unlikely to distinguish between appropriate and inappropriate polypharmacy. Appropriate polypharmacy is possible within the context of multiple comorbidities, where the prescription of several medicines is following the best evidence; while inappropriate polypharmacy occurs when regimens include

Table 2. Summary of studies reporting polypharmacy prevalence estimates.[a]

Authors	Country	Age group	Sample size	Population/setting	Measure	Prevalence
Husson *et al.*[30]	France	60+	2545	Community-dwelling adults receiving an annual health checkup	⩾4 chronic daily medicines (non-specific)	30.0%
Oliveira *et al.*[31]	Brazil	60+	142	Primary care	⩾4 medicines (non-specific)	64.5%
Payne *et al.*[32]	Scotland	20+	180,815	Primary care	4–9 regular or PRN prescriptions	16.9%
Richardson *et al.*[24]	Ireland	50–69	3864	Population-based – advantaged subset	⩾5 medicines (non-specific)	7.0%
Nascimento *et al.*[33]	Brazil	18+	8803	Primary care	⩾5 medicines used in the previous 30 days (including all medicines)	9.4%
Richardson *et al.*[24]	Ireland	50–69	1932	Population-based – disadvantaged subset	⩾5 medicines (non-specific)	22.0%
de Araújo *et al.*[34]	Brazil	60+	418	Community-dwelling adults accessing public health care	⩾5 medicines (non-specific)	27.2%
Beer *et al.*[26]	Australia	70–88	4260	Community-dwelling men	⩾5 medicines (non-specific)	35.8%
San-José *et al.*[35]	Spain	85+	336	Hospitalized older adults	5–9 medicines (non-specific)	37.5%
Chiapella *et al.*[36]	Argentina	65+	2231	Patients attending community pharmacies with ⩾1 dispensed medicine	⩾5 mean number of medicines per month	42.3%
Blanco-Reina *et al.*[37]	Spain	65+	407	Community dwelling	⩾5 medicines (non-specific)	45.0%
Gorup and Šter[38]	Slovenia	65+	503	Primary care, with ⩾1 medicines	⩾5 medicines (non-specific)	62.3%
Roux *et al.*[39]	Canada (Quebec)	66+	1,105,295	Community dwelling, with or at risk of chronic disease	⩾5 medicines (non-specific)	72.5%
Alhawassi *et al.*[40]	Saudi Arabia	65+	4073	Ambulatory care	⩾5 medicines (non-specific)	80.5%
Jankyova *et al.*[25]	Slovakia	65+	459	Nursing home residents	⩾5 daily medicines (non-specific)	83.0%
Valent[41]	Italy	All ages	251,831	Population-based, with a registered chronic condition and prescribed ⩾1 medicines	⩾5 co-prescriptions	10.0%
Castioni *et al.*[42]	Switzerland	40+	4938	Population-based	⩾5 regular prescriptions (active ingredient)	11.4%
Silva *et al.*[43]	Brazil	35–74	14,523	Active/retired public servants employed at a university/research institute	⩾5 regular medicines (non-specific)	11.7%
Blozik *et al.*[44]	Switzerland	18+	1,059,495	Customers from a health insurance company	⩾5 prescriptions	16.7%

(Continued)

Table 2. (Continued)

Authors	Country	Age group	Sample size	Population/setting	Measure	Prevalence
Amorim *et al.*[45]	Brazil	60+	417	Primary care, receiving ⩾1 prescription	⩾5 co-prescriptions received at a general practitioner visit	16.8%
Lockery *et al.*[28]	The United States/ Australia	70+	19,144	Health community dwelling adults	⩾5 regular prescriptions, ⩾1 times per week	27.0%
Turnbull *et al.*[46]	Scotland	16+	23,844	Intensive care unit discharges	⩾5 mean monthly dispensed prescriptions	29.9%
Slater *et al.*[47]	The United Kingdom	50+	7730	Population-based	⩾5 prescriptions used in the previous 7 days	30.5%
Page *et al.*[48]	Australia	70+	2,593,514	Population-based	⩾5 regular subsidized prescriptions (active ingredients)	36.1%
Joung *et al.*[18]	South Korea	70+	388,629	Population-based	⩾5 mean daily prescription (active ingredients)	36.2%
Fujie *et al.*[49]	Japan	75+	8080	Dispensing pharmacies	⩾5 prescriptions	43.1%
Hubbard *et al.*[29]	Australia	70+	1216	General medicines inpatients	5–9 prescriptions	52.2%
Page *et al.*[50]	Australia	45+	273	Aboriginal Australians living in remote communities	⩾5 prescriptions	53.0%
Wauters *et al.*[51]	Belgium	80+	503	Population-based	⩾5 prescriptions used daily	57.7%
Awad and Hanna[52]	Kuwait	65+	420	Primary care	⩾5 prescriptions (excluding dermatological and topical preparations)	69.5%
Al-Dahshan and Kehyayan[53]	Qatar	65+	5639	Patients with completed medication reconciliation	⩾5 prescriptions (excluding dermatological or topical preparations)	75.5%
de Vries *et al.*[54]	Germany	30+	4782	Population-based	⩾5 prescriptions or OTC medicines (active ingredients)	15.9%
Aoki *et al.*[27]	Japan	20+	544	Primary care outpatients	⩾5 prescription (regular or PRN) or OTC medicines (regular only)	39.2%
Haider *et al.*[55]	Sweden	77+	621	Population-based	⩾5 prescription or OTC medicines	42.2%
Jensen *et al.*[56]	Denmark	65+	71	Acutely hospitalized patients	⩾5 regular or PRN prescriptions or OTC medicines	80.0%
Gutiérrez-Valencia *et al.*[57]	Spain	65+	7023	Population-based	⩾5 prescription, OTC or CAMs in the previous 2 weeks	27.3%
Midão *et al.*[58]	Europe	65+	34,232	Survey of Health, Ageing and Retirement in Europe Study	⩾5 prescription, OTC or CAMs on a typical day	32.2%

(Continued)

Table 2. (Continued)

Authors	Country	Age group	Sample size	Population/setting	Measure	Prevalence
Lechevallier-Michel *et al.*[59]	France	65+	9294	Community dwelling	⩾5 self-medicated or prescription medicines	45.0%
Lim *et al.*[60]	Malaysia	55+	1265	Community dwelling	⩾5 prescription, OTC or CAMs	45.9%
Gallagher *et al.*[61]	Europe	65+	900	Patients admitted to geriatric wards with acute illness	⩾6 medicines (non-specific)	58.0%
Baek and Shin[62]	South Korea	20+	953,658	Outpatients with ⩾1 subsidized prescription	⩾6 regular or PRN subsidized prescriptions	42.9%
Schuler *et al.*[63]	Austria	75+	543	Hospital admissions to internal medicine ward	⩾6 regular prescriptions (systemic action only, active ingredients)	58.4%
Baldoni et al.[64]	Brazil	60+	1000	Patients attending an outpatient pharmacy	⩾6 prescription or OTC medicines	60.1%
Hudhra *et al.*[65]	Albania	60+	319	Patients discharged from cardiology or internal medicine wards	⩾6 prescriptions	73.0%
Bongue *et al.*[66]	France	75+	35,259	Population-based	⩾6 different prescriptions per year	90.3%
Jyrkkä *et al.*[67]	Finland	75+	523	Community dwelling	6–9 regular or PRN prescriptions, OTC and CAMs (including minerals, excluding herbal products)	33.8%
Fahrni *et al.*[8]	Malaysia	65+	301	Hospital admissions for acute illness	⩾8 medicines (non-specific)	31.0%
Walckiers *et al.*[68]	Belgium	65+	2835	Population-based	⩾9 regular or PRN prescription or OTC medicines used in the previous 24 h (preparations)	8.2%
Blanco-Reina *et al.*[37]	Spain	65+	407	Community dwelling	⩾10 medicines (non-specific)	6.0%
Gorup and Šter[38]	Slovenia	65+	503	Primary care, with ⩾1 medicines	⩾10 medicines (non-specific)	9.1%
Gallagher *et al.*[61]	Europe	65+	900	Patients admitted to geriatric wards with acute illness	⩾10 medicines (non-specific)	14.0%
Lockery *et al.*[28]	The United States/ Australia	70+	19,144	Health community dwelling adults	⩾10 regular prescriptions, ⩾1 times per week	2.0%
Hubbard *et al.*[29]	Australia	70+	1216	Inpatients, general medicine	⩾10 prescriptions	23.8%

CAMs, complementary and alternative medicines; ICU, intensive care unit; OTC, over the counter; PRN, as required.
[a]The table sorted according to polypharmacy measures.

unnecessary treatments or potentially harmful medicine combinations.[69]

Risk factors for polypharmacy. Identifying the risk factors associated with polypharmacy may highlight who may be disproportionately affected by potential overprescribing. Of the studies investigated, increasing age appears to be a consistent predictor of polypharmacy (Table 3), although there is some evidence risk may decrease slightly among the very old (aged 90 or older).[32,70] The relationship between sex and polypharmacy was mixed; however, being female was a commonly identified risk factor (Table 3). Indicators of poorer health were variably defined across the literature and may include the Charlson comorbidity index,[71] crude number of chronic diseases,[32,41,43,60,62,70] binary indicators of specific chronic conditions[28,30,33,50,67,68] or comorbidity (present/absent),[51,55] frailty[28] or poor self-perceived health.[30,33,67] Poorer health appears to be a strong predictor of polypharmacy and hyperpolypharmacy across a range of age categories and study populations (Table 3), though it remains unclear whether polypharmacy is causing poorer health or polypharmacy is required due to poor health.

Several studies also investigated the relationship between education and polypharmacy, with a growing body of evidence to suggest lower education may be associated with the use of more medicines (Table 3). Of interest, studies finding no association or the inverse relationship tended to apply a definition that included over the counter (OTC) and complementary or alternative medicines (CAMs), in addition to prescription medicines.[55,73] This suggests the predictors of prescription, OTC and CAMs use may differ according to education level. The relationship between polypharmacy and indicators of social disadvantage seems to be less frequently investigated (Table 3). As with measures of poor health, social disadvantage was also defined according to a range of measures, including area-level indicators of relative social advantage and disadvantage,[32,72] household income[43,55,62] and employment status.[55,73] The emerging evidence appears to have been observed among relatively younger cohorts, compared with other risk factors, with inconclusive results (Table 3). Two studies reported models that did not adjust for indicators of poorer health,[72,73] as a likely confounder in the social disadvantage–polypharmacy relationship.[74,75] A single study found greater social disadvantage was protective against polypharmacy in Brazil,[43] though it remains unclear whether the decreased risk may be driven by barriers to accessing health care and subsequent potential underprescribing.

From a broader perspective, the direction of the relationships predicting polypharmacy appears relatively stable among studies investigating associations among older cohorts (Table 3). However, the conflicting results observed for sex,[41,60] education[73] and social disadvantage[43] seem to be occurring in samples that include younger and middle-aged adults, which may suggest the predictors of polypharmacy differ across age groups (Table 3). Two studies conducted age sub-analyses in Australian and South Korean populations. In South Korea, the study found no change in direction of associations between paediatric and adolescent participants (aged <20 years) and adults (aged $\geqslant 20$ years), although the strengths of relationships did vary between the age groups.[62] The Australian study stratified age groups into young baby boomers [aged 43–52: estimated from the year of data collection (2008) and birth year defined as 1956–1965], baby boomers [aged 53–61: estimated from the year of data collection (2008) and birth year defined as 1946–1955] and older adults [aged $\geqslant 62$: estimated from the year of data collection (2008) and birth year defined as born before 1946]. The study found both significant and non-significant associations for sex and education across the three age strata.[73] Despite substantial evidence to support a relationship with increasing age, there is limited research investigating how age interacts with other potential predictors of polypharmacy.

Longitudinal patterns of polypharmacy. Having investigated risk factors cross-sectionally, this section of the review focuses on studies measuring polypharmacy over more than one timepoint. Several studies have investigated the ecological trends in polypharmacy over time, using a repeat cross-sectional study design. Findings indicate the prevalence of polypharmacy and hyperpolypharmacy have increased over the last one to two decades.[9,72,76–78] Studies have detected a near doubling of those using $\geqslant 5$ prescription medicines (8.2–15%; $p < 0.001$) over a 13-year period in the United States[76] and a more than tripling of those who used 10–14 medicines (1.5–4.7%; $p < 0.05$) over 16 years in Scotland.[72] In Australasia, nationwide studies have also observed increases in polypharmacy prevalence.[48,78,79]

Table 3. Direction of association between polypharmacy and commonly reported risk factors.[a]

Authors	Country	Setting	Sample size	Sample age	Measure	Older age	Female	Poorer health	Low education	Social disadvantage
Valent[32]	Italy	Residents with ⩾1 registered chronic disease and prescribed ⩾1 medicines	261,831	All ages	⩾5 co-prescriptions	↑	↓	↑		
Nascimento *et al.*[37]	Brazil	Population-based	8803	18+	⩾5 medicines used in previous 30 days (non-specific)	↑	NA	↑		NA
Baek and Shin[33]	South Korea	Outpatients with ⩾1 prescription	206,668	<20	⩾6 regular or PRN prescriptions	Sub-analysis	↑	↑		NL
			746,980	20+	⩾6 regular or PRN prescriptions	Sub-analysis	↑	↑		NL
Payne *et al.*[28]	Scotland	Primary care	180,815	20+	Number of regular prescriptions	↑	NA	↑		↑
Guthrie *et al.*[43]	Scotland	Population-based	301,019	20+	⩾10 dispensed medicines in previous 84 days	↑	↑			↑
Silva *et al.*[34]	Brazil	Active/retired public servants employed at a university/research institute	14,523	35–74	⩾5 regular medicines (non-specific)	↑	↑	↑		↓
Castioni *et al.*[126]	Switzerland	Population-based	4938	40+	⩾5 daily prescriptions	↑	NA		↑	
Per *et al.*[42]	Australia	Population-based	538	Young baby boomers[b]	⩾5 prescription, OTCs or CAMs	Sub-analysis	NA		↓	↑
Page *et al.*[35]	Australia	Aboriginal Australians living in remote communities	273	45+	⩾5 current prescriptions	NA	NA	↑	↑	
Per *et al.*[42]	Australia	Population-based	463	Baby boomers[c]	⩾5 prescription, OTCs or CAMs	Sub-analysis	NA		NA	↑
Lim *et al.*[31]	Malaysia	Community dwelling using ⩾1 medicine regularly	1265	55+	⩾5 prescription, OTCs or CAMs (preparations)	↑	↓	↑	NA	
Husson *et al.*[38]	France	Community dwelling	2545	60+	⩾4 daily medicines (non-specific)	↑		↑	↑	
Per *et al.*[42]	Australia	Population-based	647	Older adults[d]	⩾5 prescription, OTCs or CAMs	Sub-analysis	↑		NA	↑
Morin *et al.*[29]	Sweden	Population-based	1,742,336	65+	⩾5 dispensed medicines	↑		↑	↑	

(Continued)

Table 3. (Continued)

Authors	Country	Setting	Sample size	Sample age	Measure	Older age	Female	Poorer health	Low education	Social disadvantage
Walckiers *et al.*[36]	Belgium	Population-based	2835	65+	⩾9 regular or PRN prescriptions or OTCs used in previous 25 h	↑	NA	↑		
Lockery *et al.*[25]	Australia and the United States	Healthy community dwelling	19,114	70+	⩾5 prescriptions	↑		↑	↑	
Haider *et al.*[30]	Sweden	Population-based using ⩾1 prescriptions	626,258	75–89	⩾5 prescriptions	↑	↑	↑	↑	
					⩾10 prescriptions	↑	↑	↑	↑	
Jyrkkä *et al.*[39]	Finland	Community dwelling	523	75+	6–9 regular or PRN medicines (excluding herbal supplements)	NA	NA	↑		
					⩾10 regular or PRN medicines (excluding herbal supplements)	↑	↑	↑		
Haider *et al.*[40]	Sweden	Population-based	621	77+	⩾5 prescription or OTCs	NA	NA	↑	NA	NA
Wauters *et al.*[41]	Belgium	Population-based	503	80+	⩾5 medicines (non-specific)	NA		↑		

CAMs, complementary and alternative medicines; NA, no association; NL, non-linear association; OTCs, over the counters; PRN, as required; ↑, positive association; ↓, negative association.
[a]The table sorted according to sample age.
[b]Born between 1956 and 1965.
[c]Born between 1946 and 1955.
[d]Born before 1946.

Between 2005 and 2013, the proportion of New Zealanders aged ⩾65 years experiencing polypharmacy increased from 23.4% to 29.5% ($p < 0.001$),[78] with similar increases in Australia between 2006 and 2014 (33.2–39.8%) among those aged ⩾70 years.[48] However, polypharmacy prevalence among Australians declined over the following 3 years to 36.2% by 2017,[48] with similar patterns of declining rates between 2014 and 2018 among older age groups (⩾60) in New Zealand.[79] While this suggests we may be seeing translational outcomes for the efforts made to reduce unnecessary polypharmacy among older adults, during the same time frame (2014–2018) the prevalence of New Zealanders aged 20–29 taking ⩾5 medicines increased by 30.4%.[79] This highlights the potential importance of broadening research to investigate polypharmacy among all adult age groups.

Changes in prevalence over time. Of the studies investigating polypharmacy over time, following the same cohort, definitions varied. Studies applied binary cut points ranging from ⩾2 to ⩾10 medicines and continuous measures indicating the mean number of medicines (Table 4). Over the study durations, which ranged from 3 to 12 years, both the prevalence of polypharmacy and mean number of medicines use increased (Table 4). While one Swiss population-based study found a significant increase in polypharmacy over 5.5 years among those aged 35–75,[80] studies largely focus on older populations aged ⩾65 years (Table 4). The underlying reason for the growth in the number of medicines used by older adults is likely multifactorial. Proposed explanations have included the availability of new medicines, changes in prescribing recommendations, increased focus on preventive therapies and clinical guidelines for single disease states.[37,54,72] The optimal management of some common chronic conditions may result in the prescription of multiple medicines. Anecdotally, research investigating the development of polypharmacy in younger cohorts tends to focus on specific disease contexts, for example, among patients with HIV,[81] cerebral palsy[82] or mental illness,[83] where the use of multiple medicines may be expected. Studies tracking the development of polypharmacy among the general population before reaching older age appear less common. With findings indicating that medicines use appears to be increasing both in the community and over time, cross-sectional research may be insufficient in

Table 4. Change in polypharmacy prevalence over time.[a]

Authors	Location	Age group	Population	Study duration (years)	Measure	Baseline, *n*	Baseline prevalence/mean medicines	Follow-up, *n*	Baseline prevalence/mean medicines	*p* value
Veehof *et al.*[84]	The Netherlands	65+	Primary care	4	⩾2 medicines used for ⩾250 days	1544	26.40%	1544	41.10%	Not provided
Abolhassani *et al.*[80]	Switzerland	35–75	Population-based	5.5	⩾5 prescription or OTC medicines (preparations)	4679	7.70%	4679	15.30%	<0.001
Lapi *et al.*[85]	Italy	65+	Community dwelling, with ⩾1 medicines	5	⩾5 prescription and non-prescription medicines (1-week window)	568	8.80%	568	21.60%	<0.001
Wastesson *et al.*[86]	Denmark	92–100	Population-based (birth cohort)	7	⩾5 prescription or OTC medicines, excluding CAMs	1998	34%	146	40%	Not provided
Jyrkkä *et al.*[87]	Finland	75+	Population-based	3	6–9 medicines, including vitamins and minerals	294	34.60%	294	39.40%	Not provided
					⩾10 medicines, including vitamins and minerals	294	17.70%	294	25.80%	Not provided
Jyrkkä *et al.*[67]	Finland	75+	Population-based	5	⩾10 regular or PRN medicines, excluding herbal remedies	601	19%	339	28%	Not provided
					Mean regular or PRN medicines, excluding herbal remedies	601	6.3 (95% CI: 5.9, 6.7)	339	7.5 (95% CI: 7.1, 7.9)	<0.001
Haider *et al.*[88]	Sweden	77+	Population-based	11	Mean regular or PRN prescription or OTC medicines (2-week window)	512	2.5 (95% CI: 2.3, 2.7)	561	4.4 (95% CI: 4.1, 4.7)	<0.001
Blumstein *et al.*[89]	Israel	75+	Community dwelling	12	Mean prescription or OTC medicines	160	2.22 (SD: 1.99)	160	2.68 (SD: 1.94)	0.06

CAMs, complementary and alternative medicines; CI, confidence interval; OTC, over the counter; PRN, as required; SD, standard deviation.
[a]The table sorted according to polypharmacy measures.

identifying who may be at risk of polypharmacy in the future.

Associations with changes in polypharmacy. Studies investigating associations with changes in polypharmacy used a range of study designs and polypharmacy measures to analyse longitudinal data. However, the outcome was most defined according to the number of medicines or polypharmacy status at baseline and follow-up (Table 5). Less frequently applied methods included incidence of polypharmacy,[70] exposed to polypharmacy for ⩾80% of the study period (chronic exposure),[90] or a multinomial analysis investigating differences in associations between polypharmacy initiation, reduction or maintenance according to exposure baseline and follow-up.[80] For most studies, the time to follow-up ranged from 3 to 5.5 years (Table 5), except for one study that assessed the long-term predictors of medicine used over 11.7 years.[89] However, with data on only 160 older adults and a substantial number of predictor variables, this study was likely underpowered.

Increasing age was associated with a greater number of medicines, polypharmacy incidence and probability of high exposure time at follow-up (Table 5). One analysis measured time in the study, which is likely to act as a function of age, with similar findings.[85] A reduction in polypharmacy was also associated with increasing age when compared with those with no polypharmacy at baseline or follow-up.[80] The number of medicines used at baseline appears to be a consistent predictor of higher medicine use and polypharmacy at follow-up (Table 5). Evidence also suggests that greater morbidity may increase the likelihood of polypharmacy in the future, particularly among those with diagnosed coronary heart disease, heart failure and diabetes, as well as positive correlations between polypharmacy and total number of comorbidities (Table 5). However, there is limited research investigating the relationship between indicators of socioeconomic status and changes in exposure to medicines or polypharmacy over time (Table 5). Of the three studies considering factors such as education, source of income or whether individuals were living as a couple or alone,[70,80,89] education appears to be the only factor showing any significant association (Table 5).

While longitudinal studies may provide insight into the mechanism driving polypharmacy, there is emerging evidence highlighting that polypharmacy is not a time-stable exposure, rather it may be transient or consistent over time and within-person trajectories may vary.[86,91,92]

Of the research investigating longitudinal associations with polypharmacy, only two studies considered polypharmacy as a time-variant exposure.[80,90] Abolhassani *et al.*[80] measured the maintenance and transitions between states of polypharmacy exposure and non-exposure among adults aged 35–75 years. The study only captured prevalence at two timepoints 5½ years apart. This method is unlikely to be sensitive to person-level fluctuations over time and is unable to distinguish between incidental or acute episodes of increased medicine use and exposure to polypharmacy that is more chronic. Furthermore, the study only investigated transitions and maintenance of polypharmacy with those who have never had polypharmacy and it remains unclear how associations may vary compared with those who maintained polypharmacy across both timepoints. Wastesson *et al.*,[90] on the contrary, address the issue of transient and chronic exposure by measuring monthly medicine use in adults aged ⩾65 years. By calculating the proportion of time exposed over the study duration, chronic polypharmacy is operationalized as spending ⩾80% of the time exposed.[90] While this study offers a rigorous methodology for defining chronic polypharmacy, participants are limited to those with polypharmacy at baseline and the analysis does not investigate transitions between exposure and non-exposure. Research investigating within-person variations in trajectories of polypharmacy may also be limited. One study (not presented in Table 5) tracked the number of medicines used among a birth cohort of nonagenarians over four timepoints.[86] The findings show the gradient, measuring within-person changes in medicine use, was steepest between the first and second timepoints for those who exited the study early and gentler for those who stayed in the study for the full study period.[86] This level of investigation highlights different within-person patterns, though it remains unclear who may be at greater risk an accelerated increases in medicines over time.

Table 5. Associations with change in polypharmacy.[a]

Authors	Location	Age group	Population	Sample size	Study duration (years)	Indicator	Measure of change	Age	Sex	Medicine use	Morbidity	Socioeconomic factors
Abolhassani *et al.*[80]	Switzerland	35–75	Population-based	4679	5.5	⩾5 prescription or over the counter medicines (preparations)	Polypharmacy reduced, compared with no polypharmacy	⩾65 years – OR: 3.58 (95% CI: 1.86, 6.88)	Male – OR: 0.34 (95% CI: 0.21, 0.57)	Controlled for in study design	Obesity: NA Hypertension: NA Dyslipidaemia – OR: 1.69 (95% CI: 1.02, 2.81) Diabetes: NA	Low education: NA Living as a couple: NA
							Polypharmacy initiated, compared with no polypharmacy	⩾65 years – OR: 4.65 (95% CI: 3.36, 6.43)	Male – OR: 0.46 (95% CI: 0.36, 0.59)	Controlled for in study design	Obesity – OR: 1.92 (95% CI: 1.41, 2.63) Hypertension – OR: 2.71 (95% CI: 2.12, 3.46) Dyslipidaemia – OR: 1.40 (95% CI: 1.09, 1.80) Diabetes – OR: 3.35 (95% CI: 1.53, 4.50)	Low education: NA Living as a couple: NA
							Polypharmacy maintained, compared with no polypharmacy	⩾65 years – OR: 8.96 (95% CI: 5.34, 15.05)	Male – OR: 0.50 (95% CI: 0.36, 0.69)	Controlled for in study design	Obesity – OR: 1.96 (95% CI: 1.31, 2.93) Hypertension – OR: 4.75 (95% CI: 3.39, 6.65) Dyslipidaemia – OR: 3.41 (95% CI: 2.43, 4.77) Diabetes – OR: 2.10 (95% CI: 1.03, 4.30)	Low education – OR: 1.91 (95% CI: 1.13, 3.21) Living as a couple: NA
Morin *et al.*[70]	Sweden	65+	Population-based	1,742,336	3	⩾5 prescriptions	Incidence of polypharmacy	⩾95 years – HR: 1.49 (95% CI: 1.42, 1.56)	Female – HR: 1.09 (95% CI: 1.08, 1.09)		⩾5 chronic diseases – HR: 3.78 (95% CI: 3.71, 3.85) Time to death ⩽12 months – HR: 2.41 (95% CI: 2.34, 2.38)	Higher education – HR: 0.92 (95% CI: 0.91, 0.93)
Wastesson *et al.*[90]	Sweden	65+	Population-based, with ⩾5 prescriptions	711,432	3	⩾5 prescriptions (30-day window)	Not measured, predictors of chronic polypharmacy (exposure for ⩾80% of study period)	Increasing age = increased probability of chronic polypharmacy	Male = increased probability of chronic polypharmacy	Higher number of medicines used at baseline = increased probability of chronic polypharmacy	Higher number of chronic conditions = increased probability of chronic polypharmacy	
Veehof *et al.*[84]	The Netherlands	65+	Primary care	1544	4	Number of long-term medicines	Number of long-term medicines at follow-up	Increasing age: β = 0.07 ($p < 0.001$)	Sex: NA	Number of long-term medicines at baseline: β = 0.45 ($p < 0.001$) Used ⩾1 medicines without indication: β = 0.06 ($p = 0.03$)	Diabetes: β = 0.12 ($p < 0.001$) Coronary heart disease: β = 0.13 ($p < 0.001$) Heart failure – OR: 0.05 ($p = 0.01$) Hypertension: β = 0.14 ($p < 0.001$) Asthma/Chronic Obstructive Pulmonary Disease: NA Osteoarthritis: NA Atrial fibrillation: β = 0.06 ($p < 0.001$) Dementia: NA Gastro-oesophageal disease: β = 0.04 ($p = 0.03$) Depression: NA	

(Continued)

Table 5. (Continued)

Authors	Location	Age group	Population	Sample size	Study duration (years)	Indicator	Measure of change	Age	Sex	Medicine use	Morbidity	Socioeconomic factors
Lapi *et al.*[85]	Italy	65+	Community dwelling	568	5	⩾5 prescription and non-prescription medicines (1-week window)	Odds of having polypharmacy at follow-up	Not measured[b]			Number of diseases – OR: 1.3 (95% CI: 1.2, 1.5) Disability: NA Coronary heart disease – OR: 3.1 (95% CI: 2.0, 4.7) Heart failure – OR: 4.2 (95% CI: 2.5, 7.0)	
Blumstein *et al.*[89]	Israel	75+	Population-based	160	11.7	Mean current prescription or over the counter medicines	Not measured, long-term predictors of medicine use adjusting for number of medicines at baseline	Increasing age: NA	Male: NA	Medicines at baseline: NA	High perceived health: NA Number of diseases: $\beta = 0.174$ ($p < 0.05$) Activities of daily living: NA Depression: NA Cognitive impairment: NA	Years of education: NA Marital status: NA Source of income: NA
				620	3.6	Mean current prescription or over the counter medicines	Not measured, short-term predictors of medicine use adjusting for number of medicines at baseline	Increasing age: NA	Male: $\beta = -0.83$ ($p < 0.05$)	Medicines at baseline: $\beta = 0.518$ ($p < 0.001$)	High perceived health: $\beta = -0.94$ ($p < 0.05$) Number of diseases: NA Activities of daily living: NA Depression: $\beta = -0.109$ ($p < 0.05$) Cognitive impairment: NA	Years of education: NA Marital status: NA Source of income: NA

β, coefficient; CI, confidence interval; HR, hazard ratio; NA, no association; OR, odds ratio; OTC, over the counter.
[a]The table sorted according to age group.
[b]Time in study was used.

Clinical implications of polypharmacy. There is a substantial body of research investigating the clinical implications of polypharmacy, including several reviews that have synthesized the existing research.[93–96] Of note, the association between polypharmacy and drug–drug or drug–disease interactions and adverse events is generally accepted across the literature.[97,98] However, research is heterogeneous, often focusing on more sensitive indicators of high-risk prescribing, such as specific drug–drug or drug–disease interactions, rather than considering the broader total number of medicines use. This section provides a brief overview of studies reporting longitudinal outcomes of polypharmacy (Table 6).

There is some evidence to suggest those experiencing polypharmacy (binary ⩾5 medicines) may have a greater probability of mortality, with research also demonstrating a significant dose–response relationship with the number of medicines used (continuous measure; Table 6). While two studies showed no association between polypharmacy and mortality, the null findings were observed among relatively younger cohorts.[46,103] The number of medicines used also appears to be a significant predictor of re-hospitalization post-discharge, with each additional medicine contributing to a 3–11% increase in risk.[46,101] When investigating the relationship between physical function and polypharmacy, capacity was measured using a range of tools and tests, with mixed findings (Table 6). Of interest, using participants with no polypharmacy at baseline or follow-up as the reference group, a UK study found extended exposure may be linked to a significant reduction in sit-to-stand and walking speed, balance and grip strength.[102] However, associations between current or previous exposure to polypharmacy were less consistent across the same indicators of physical function.[102] There is some evidence that polypharmacy may be associated with a decline in cognitive function; however, findings were only significant when a ⩾10 medicine cut point was applied,[87] among those exposed to ⩾5 medicines at more than one follow-up.[102] The findings from an Australian study also suggest that the greater number of medicines used may increase the risk of experiencing a cardiovascular event in the following 4.5 years.[26] While a study in Finland found older adults with hyperpolypharmacy may experience a 38% decline in their nutritional state over a 3-year follow-up, however, no association was observed among those using 5–9 medicines.[87]

Table 6. Outcomes of polypharmacy.[a]

Authors	Location	Age group	Population	Sample size	Study duration (years)	Outcome measure	Polypharmacy measure	Unit of measure	Effect size (95% CI)
Mortality									
De Vincentis *et al.*[99]	Italy	65+	Community-dwelling hospital discharges	2631	0.25	All-cause mortality	Number of medicines	Continuous	HR: 1.05 (1.01, 1.10)
							⩾5 medicines	Binary	HR: 1.70 (1.12, 2.58)
Turnbull *et al.*[46]	Scotland	16+	ICU discharges	23,844	1	All-cause mortality	⩾5 mean dispensed medicines per month (12-month window)	Binary	NA
Beer *et al.*[26]	Australia	70–88	Community-dwelling men	4260	4.5	All-cause mortality	Number of medicines	Continuous	HR: 1.04 (1.00, 1.07)[b]
Huang *et al.*[100]	Japan	45+	Outpatients receiving hospital in the home	196	5	All-cause mortality	⩾5 medicines	Binary	NA
de Araújo *et al.*[34]	Brazil	60+	Community dwelling accessing public health care	418	10	All-cause mortality (12-month)	⩾5 medicines	Binary	HR: 1.98 (1.30, 3.01)
Hospitalization									
De Vincentis *et al.*[99]	Italy	65+	Community-dwelling hospital discharges	2631	0.25	Re-hospitalization	⩾5 medicines	Binary	HR: 1.31 (1.01, 1.71)[b]
							Number of medicines	Continuous	HR: 1.05 (1.01, 1.08)
Brunetti *et al.*[101]	Italy	>65	Hospital discharges	611	0.5	Re-hospitalization (unplanned)	Number of medicines at discharge	Continuous	OR: 1.11 (1.05, 1.18)
Turnbull *et al.*[46]	Scotland	>16	ICU discharges	23,844	1	Re-hospitalization	Mean dispensed medicines per month (12-month window)	Continuous	HR: 1.03 (1.02, 1.03)
Beer *et al.*[26]	Australia	70–88	Community-dwelling men	4260	4.5	Hospitalization – all cause	Number of medicines	Continuous	HR: 1.04 (1.03, 1.06)
Physical function									
De Vincentis *et al.*[99]	Italy	65+	Community-dwelling hospital discharges	2631	0.25	Barthel index[c]	Number of medicines	Mean % variation	NA

(Continued)

Table 6. (Continued)

Authors	Location	Age group	Population	Sample size	Study duration (years)	Outcome measure	Polypharmacy measure	Unit of measure	Effect size (95% CI)
							⩾5 medicines	Mean % variation	NA
Jyrkkä *et al.*[87]	Finland	75+	Population-based	294	3	Instrumental activities of daily living[c]	6–9 medicines	No polypharmacy	β = −0.29 (−0.47, −0.10)
							⩾10 medicines	No polypharmacy	β = −0.53 (−0.81, −0.26)
Rawle *et al.*[102]	The United Kingdom	60–64	Population-based	2149	4	Chair-to-stand speed	⩾5 medicines	No polypharmacy at baseline or follow-up	Previous exposure: β = −1.2 (−2.6, −0.3) Current exposure: NA Extended exposure: β = −2.4 (−3.6, −1.2)
						Walking speed	⩾5 medicines	No polypharmacy at baseline or follow-up	Previous exposure: NA Current exposure: NA Extended exposure: β = −0.1 (−0.2, −0.0)[b]
						Balance	⩾5 medicines	No polypharmacy at baseline or follow-up	Previous exposure: β = NA Current exposure: β = −0.1 (−0.2, 0.0)[b] Extended exposure: β = −0.1 (−0.2, 0.0)[b]
						Grip strength	⩾5 medicines	No polypharmacy at baseline or follow-up	Previous exposure: NA Current exposure: β = −1.6 (−2.7, −0.5) Extended exposure: β = −2.1 (−2.9, −0.9)
Cognitive function									
Jyrkkä *et al.*[87]	Finland	75+	Population-based	294	3	Mini-Mental State Exam[c]	6–9 medicines	No polypharmacy	NA
							⩾10 medicines	No polypharmacy	β = −1.36 (−2.10, −0.63)
Rawle *et al.*[102]	The United Kingdom	60–64	Population-based	2149	4	Word learning	⩾5 medicines	No polypharmacy at baseline or follow-up	Previous exposure: NA Current exposure: NA Extended exposure: β = −0.7 (−1.4, 0.0)[b]
						Verbal search speed	⩾5 medicines	No polypharmacy at baseline or follow-up	Previous exposure: NA Current exposure: NA Extended exposure: β = −9.8 (−19.3, −0.3)

(Continued)

Table 6. (Continued)

Authors	Location	Age group	Population	Sample size	Study duration (years)	Outcome measure	Polypharmacy measure	Unit of measure	Effect size (95% CI)
Cardiovascular events									
Beer *et al.*[26]	Australia	70–88	Community dwelling	4260	4.5	⩾1 cardiovascular event	Number of medicines	Continuous	HR: 1.09 (1.06, 1.12)
Malnourishment									
Jyrkkä *et al.*[87]	Finland	75+	Population-based	294	3	Mini Nutritional Assessment – Short Form[d]	6–9 medicines	No polypharmacy	NA
							⩾10 medicines	No polypharmacy	β = –0.62 (–0.08, –0.01)

CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; NA, no association; OR, odds ratio.
[a]The table sorted according to study duration.
[b]Borderline significant.
[c]Lower score indicates reduced capacity or function.
[d]Lower score indicates a greater degree of malnourishment.

Gaps in the literature. Future polypharmacy research may address several gaps in the literature, including an investigation into the impact of different polypharmacy definitions on polypharmacy prevalence estimates and how the predictors of polypharmacy may vary across the age groups. Studies applying quantitative definitions may also consider qualitative indicators of polypharmacy or broader measures of overall prescribing quality, including exposure to PIMs and potential underprescribing. This distinction may enable an enhanced ability to distinguish between instances of appropriate and inappropriate polypharmacy While cross-sectional research may provide insight into who may be at greater risk of potentially suboptimal medicine regimens at a single timepoint, this design is unable to address the temporal nature of relationships. Current research investigating longitudinal associations with polypharmacy appears to focus on older adults; therefore, future work should include adult and middle-aged populations, with the potential to identify characteristics present in younger age that may predict polypharmacy in older age. Research investigating the transitions between states of polypharmacy exposure and non-exposure is also needed; however, data collection at each timepoint should capture medicine use over a set period to distinguish between chronic and potential transient polypharmacy exposure. Finally, future work should investigate associations between within-person trajectories in medicine use, identifying those who may be at greater risk of more rapid increases in medicine use, further exploring how medicine use in younger age may influence trajectories of medicine use in older age. The implications of these gaps in the literature suggest that polypharmacy research may not be developed enough for clinical application at this time as appropriate cut points remain uncertain.

Omitted medicines (underprescribing)

Underprescribing, prescribing omissions or omitted medicines occurs when an individual is not prescribing a potentially beneficial medicine, indicated for the treatment or prevention of a disease or condition.[37] Paradoxically, polypharmacy has been identified as a risk factor for underprescribing.[37,104,105] In the context of an already complex medicine regimen, clinicians may hesitate to prescribe preventive therapies or contribute to the overall medicine burden and choose to prioritize the management of current conditions.[38] In some instances, particularly in end-stage care, the rationale for underprescribing is valid; however, avoiding essential pharmacotherapy can also pose a risk to patients' safety and may reduce quality of life.[8,20]

Tools have been developed to assist clinicians and researchers to evaluate when potential underprescribing may be occurring. One of the most common tools is the Screening Tool to Alert doctors to the Right Treatment (START), an explicit list of criteria that considers common instances of potential underprescribing, where no contraindications exist and where life expectancy and functional status justify the prescription.[17] While implicit tools, such as the Assessment of Underutilization (AOU) tool, will likely provide a more accurate estimate of potential underprescribing, the AOU requires a detailed medical history, a complete list of current medicines and the clinical judgement of a trained health care professional, which are not always available in population-based research.[17]

Applying measures of underprescribing

Point prevalence. Studies measuring underprescribing were less commonly reported in the literature than polypharmacy. Most studies were sampled from a patient population, with only four studies reporting prevalence estimates for community-dwelling or population-based samples (Table 7). This pattern may reflect the challenges associated with collecting complete data on current medicines and diagnoses, both of which are required to determine when a potentially beneficial medicine may have been omitted. Prevalence estimates ranged from 12% to 64.2%;[50,104] however, study settings varied substantially between studies (Table 7).

Risk factors for underprescribing. Evidence investigating the risk factors for underprescribing is limited and appears inconclusive (Table 8). While there is some evidence to support an association between older age and polypharmacy, a greater number of studies reported no significant relationship with these risk factors (Table 8). Education and income do not appear to be associated with underprescribing (Table 8), except for one study, which found a non-linear relationship with educational attainment among primary care patients in Kuwait.[52]

Clinical implications of underprescribing. Research investigating clinical outcomes of underprescribing is also limited (Table 9). Evidence suggests that underprescribing may be linked to increased risk of cardiovascular events in a sample of older Australian men.[26] While the odds of all-cause hospitalization were greater among Māori New Zealanders with underprescribing, however, no association was observed in the non-Māori study sample.[106] No association between underprescribing and mortality was observed in either study (Table 9).

Gaps in the literature. There is a paucity of research investigating the risk factors and clinical outcomes of potential underprescribing. It remains unclear whether there is a relationship between underprescribing and social disadvantage, and whether it is possible to distinguish between underprescribing resulting from the receipt of potentially suboptimal care or a lack of access to health care more generally. It is also challenging to interpret underprescribing at a population level and whether instances may be inappropriate or conscious, in the context of shared decision making. Likewise, in clinical practice, clear documentation regarding the reasons not to prescribe would be beneficial across transitions of care.

High-risk prescribing: PIMs

Indicators captured under the banner of high-risk prescribing evaluate the medicines used by older adults to provide a more sensitive assessment of potential inappropriateness. PIMs are medicines that are known to be potentially harmful when used by older adults, where the potential risk outweighs the anticipated benefit, particularly when safer or more effective alternatives for the same condition are available.[110,111] To assist clinicians, pharmacists and researchers to evaluate the potential appropriateness of a regimen, a range of tools have been developed to monitor, prevent and minimize the use of PIMs in older populations. As with underprescribing, screening tools may be implicit (judgement-based) or explicit (criterion-based) by design. Implicit tools, (e.g. Medication Appropriate Index (MAI)) can be applied to any medicine and score their appropriateness according to a set of questions to evaluate factors such as indication, effectiveness, potential for interactions and duration.[112] This patient-level assessment is an effective quality assessment and may be applied to any regimen, in any setting or population.[112]

Table 7. Summary of studies reporting prevalence estimates for underprescribing.[a]

Authors	Location	Age group	Sample size	Population/setting	Indicator	Prevalence
Page *et al.*[50]	Australia	45+	273	Aboriginal Australians in remote communities	Self-defined	12.0%
Blanco-Reina *et al.*[37]	Spain	65+	407	Community dwelling	START	41.8%
Ryan *et al.*[106]	New Zealand	80+	267	Community dwelling – Māori subset	START v2	58.1%
		85+	404	Community dwelling – non-Māori subset	START v2	49.0%
Beer *et al.*[26]	Australia	70–88	4260	Community-dwelling men	Self-defined	57.0%
Ma *et al.*[104]	China	65+	662	Discharges from internal medicine wards	START v2	64.2%
Fahrni *et al.*[8]	Malaysia	65+	100	Hospital admission for acute illness	START	37.9%
Gallagher *et al.*[61]	Europe	65+	900	Hospital admission to geriatric wards with acute illness	START	59.4%
Barry *et al.*[16]	Ireland	65+	600	Hospital admissions with acute illness	START	57.8%
Dalleur *et al.*[107]	Belgium	75+	302	Hospital admissions with frailty	START	62.9%
San-José *et al.*[35]	Spain	85+	336	Hospitalized older adults	ACOVE3	59.4%
					START	53.7%
Galvin *et al.*[105]	Ireland	65+	3507	Population-based	START	30.0%
Awad and Hanna[52]	Kuwait	65+	420	Primary care	START v2	19.8%
Gorup and Šter[38]	Slovenia	65+	503	Primary care, with ⩾1 medicines	START	42.9%
Ubeda *et al.*[108]	Spain	65+	85	RACF	START	44.0%

RACF, residential aged care facility.
[a]The table sorted according to study population/setting.

PIMs can also be measured using explicit tools, which are generally developed through literature review, expert opinion and consensus panels of health care professionals. The tools can range from simple lists of medicines and medicine classes that should be avoided in older adults, to more complex lists that may also consider dosage, duration, other medicines, current diagnoses and functional state to assess regimens.[113–115] PIMs tools may also vary in their target population, some developed for community-dwelling older adults, while others focus on specific settings or disease states.[113–115] With minimal clinical judgement required, PIMs tools are often appropriate

Table 8. Direction of association between potentially underprescribing and commonly reported risk factors.[a]

Authors	Country	Setting	Sample size	Sample age	Indicator	Older age	Female	Poorer health	Polypharmacy	Low education	Income
Gallagher *et al.*[61]	Europe	Acutely ill and hospitalized	900	65+	START	↑	NA	↑	NA		
Projovic *et al.*[109]	Serbia	Chronically ill outpatients	324	65+	START v2	NA	NA	↑	NA	NA	NA
Blanco-Reina *et al.*[37]	Spain	Community dwelling	407	65+	START	NA	NA	↑	↑		
San-José *et al.*[35]	Spain	Hospitalized older adults	336	85+	START	NA	NA	↑		NA	
Ma *et al.*[104]	China	Patients discharged from internal medicine wards	662	65+	START v2	↑	NA	↑	↑		
Galvin *et al.*[105]	Ireland	Population-based	3507	65+	START	NA	↓		↑		
Awad and Hanna[52]	Kuwait	Primary care	420	65+	START v2	NA	NA	↑	NA	NL	
Gorup and Šter[38]	Slovenia	Primary care, with ⩾1 prescription	503	65+	START	↑	NA	↑	NA	NA	

NA, no association; NL, non-linear association; ↑, positive association; ↓, negative association.
[a]The table sorted according to study setting.

Table 9. Outcomes of underprescribing – associations with hospitalization and emergency department visits.

Authors	Location	Age group	Population	Sample size	Study duration (years)	Outcome measure	Underprescribing tool	Unit of measure	Effect size (95% CI)
Ryan *et al.*[106]	New Zealand	85+	Community dwelling – non-Māori subset	404	1	Mortality – all cause	START 2	Binary	NA
						Hospitalization – all cause	START 2	Binary	NA
		80+	Community dwelling – Māori subset	267	1	Mortality – all cause	START 2	Binary	NA
						Hospitalization – all cause	START 2	Binary	OR: 2.80 (1.54, 5.10)
Beer *et al.*[26]	Australia	70–88	Community-dwelling men	4260	4.5	Mortality – all cause	Self-defined	Binary	NA
						Hospitalization – all cause	Self-defined	Binary	NA
						⩾1 cardiovascular event	Self-defined	Binary	HR: 1.20 (1.03, 1.40)

CI, confidence interval; HR, hazard ratio; NA, no association; OR, odds ratio.

for application to a range of users and data, including routinely collected administrative data.[8] There has been a proliferation of PIMs tools over the past decade, developed internationally to capture country-specific approved medicines, local treatment practices and specific therapeutic, and prescribing guidelines.[113,114] Two of the most common explicit tools are the US-developed Beers criteria, which is updated approximately every 3 years,[116] and the European consensus Screening Tool of Older Persons' Prescriptions (STOPP), which is currently in its second iteration.[116,117] While PIMs tools may be considered appropriate for application in the country of origin, their refection of national formularies is often recognized as a limitation to translation to other contexts.[113,115]

Applying measures of PIMs

Point prevalence. The prevalence of PIMs appears to be a widely reported statistic. Estimates range from 10.3% to 90.6%;[25,44] however, the tools used to measure prevalence varied across study populations (Table 10). It was common for authors to acknowledge the differences between the tools by investigating more than one PIMs tool in the same study sample.[36,44,52,64,65,100,103,108,118–125] Two studies were of particular interest, applying an implicit tool, the MAI, as a more sensitive indicator of inappropriate prescribing, alongside a selection of explicit tools to investigate their ability to accurately diagnose PIMs within a defined population.[52,125] With the MAI as the reference tool, Table 11 provides a summary of the explicit tools' accuracy according to sensitivity and specificity statistics. Across both studies, the explicit tools used do not appear to discriminate between those with and without PIMs well (Table 11). While the STOPP version 2 appears relatively consistent across both studies, with moderate sensitivity and good specificity (Table 11), variability in the overall results does highlight the potential for imprecision between the tools and the likelihood for error in identifying PIMs according to explicit criteria.

Risk factors for PIMs. There also appears to be a substantial body of research investigating associations with PIMs use. The association between age and PIMs appears inconsistently across the literature (Table 12). Of interest, two studies reported conflicting associations between age and PIMs using two different tools in the same population.[100,118] Both studies, conducted in China and Taiwan, found the risk of PIMs use decreased with age when PIMs were identified according to locally developed tools (the Chinese criteria 2017 and the Taiwan criteria, respectively); inversely, when PIMs were measured using US-developed Beers criteria, there was a positive association with increasing age.[100,118] These findings further highlight potential variability in the applicability of tools in different study settings. The female sex was often associated with an increased risk of PIMs use; however, no association with sex was also just as common (Table 12). One study presented age sub-analyses looking at younger–older adults (65–74 years) and older adults (⩾75 years) and found being female was associated with an increased risk of PIMs use among the younger–old, while no association was observed among older adults.[146] These variable results suggest the risk factors of PIMs use may change with age and that sub-analyses may be an important consideration.

The relationship between poorer health and the use of PIMs also appears mixed (Table 12). Studies that applied a modified version of a PIMs list, for example, excluding any criteria where diagnoses were required to assess potential appropriateness, tended to find an association between increased risk of PIMs use and poorer hea lth.[28,39,134,137,149] Alternatively, those that appeared to apply the full criteria, as published, were more likely to find no association with poorer health (Table 12). This suggests that accounting for diagnoses when identifying PIMs may, in part, be controlling for potential confounding by indication. Compared with indicators of poorer health, polypharmacy appears to be a more reliable predictor of PIMs use (Table 12). While the debate continues around the distinction between appropriate and inappropriate polypharmacy, this well-established link between polypharmacy and PIMs suggests even considered polypharmacy may contain specific drug–drug or drug–disease interactions that are suboptimal. Of interest, only a handful of studies that focused on measuring associations with PIMs provided a detailed definition of polypharmacy;[28,45,52,64,66] however, it remains unclear whether associations vary between doctor-prescribed and self-prescribed medicines. The relationship between education and PIMs use appears to have been less extensively researched, relative to the polypharmacy literature (Table 12). Studies reporting an association between lower education appear to have

Table 10. Summary of studies reporting PIMs prevalence estimates.[a]

Authors	Location	Age group	Sample size	Population/setting	PIMs tool	Prevalence
Page *et al.*[50]	Australia	45+	273	Aboriginal Australians living in remote communities	Beers 2015	20.0%
Alhmoud *et al.*[126]	Qatar	65+	501	Care in the home patients	Beers 2012	38.2%
Chang *et al.*[118]	Taiwan	65+	25,187	Care in the home patients	Beers 2012 (independent of diagnoses)	63.0%
					PRISCUS	68.5%
					Taiwan (independent of diagnoses)	82.7%
Blanco-Reina *et al.*[120]	Spain	65+	582	Community dwelling	Beers 2015	54.0%
					STOPP v2	66.8%
Muhlack *et al.*[119]	Germany	60+	2011	Community dwelling	PRISCUS	13.7%
					Beers 2015	26.4%
					EU(7) PIM list	37.5%
Ryan *et al.*[106]	New Zealand	80+	267	Community dwelling – Māori subset	STOPP v2	24.3%
		85+	404	Community dwelling – non-Māori subset	STOPP v2	28.0%
de Araújo *et al.*[34]	Brazil	60+	418	Community dwelling accessing public health care	Beers 2019	50.1%
Blozik *et al.*[44]	Switzerland	65+	1,059,495	Community-dwelling health insurance users	Beers 2003 (independent of diagnoses)	10.3%
					PRISCUS (independent of diagnoses)	16.0%
Patel *et al.*[127]	The United States	65+	703	Community-dwelling Medicare beneficiaries with ⩾1 prescriptions	Beers 2015	29.0%
Beer *et al.*[26]	Australia	70–88	4260	Community-dwelling men	Beers 2003 (modified)	48.7%
Li *et al.*[128]	The United States	65–79	2949	Community-dwelling older drivers	Beers 2015	18.5%
Cahir *et al.*[129]	Ireland	75+	931	Community-dwelling primary care patients	STOPP	42.0%
Lockery *et al.*[28]	The United States/ Australia	70+	19,114	Community-dwelling healthy adults	Beers 2019 (independent of diagnoses)	39.0%
Huang *et al.*[100]	China	65+	1874	Community dwelling, self-referred to clinic	Beers 2019	35.0%

(Continued)

Table 10. (Continued)

Authors	Location	Age group	Sample size	Population/setting	PIMs tool	Prevalence
					Chinese criteria 2017	50.6%
Novaes *et al.*[121]	Brazil	60+	368	Community dwelling, with ⩾1 prescriptions	Taiwan (independent of diagnoses)	31.3%
					STOPP v2	46.2%
					Beers 2015	50.0%
					EU(7) PIM list	59.5%
Nyborg *et al.*[10]	Norway	70+	445,900	Community dwelling, with ⩾1 prescriptions	NORGEP-HP	34.8%
Roux *et al.*[39]	Canada	66+	1,105,295	Community dwelling, with or at risk of chronic disease	Beers 2015 (independent of diagnoses)	48.3%
Hudhra *et al.*[65]	Albania	60+	319	Discharges from cardiology and internal medicine wards	Beers 2012	34.5%
					STOPP	34.5%
					STOPP v2	63.0%
Magalhães *et al.*[130]	Brazil	60+	255	Discharges from clinical or geriatric wards	Brazilian criteria	58.4%
He *et al.*[122]	China	65+	6424	Discharges from geriatric ward	Beers 2015	64.3%
					Beers 2019	64.8%
Ma *et al.*[104]	China	65+	662	Discharges from internal medicine ward	STOPP v2	47.7%
Ni Chroinin *et al.*[131]	Australia	65+	534	Hospital admissions	STOPP	54.8%
Johansen *et al.*[123]	Norway	65+	715	Hospital admissions to geriatric ward	EU(7) PIM list	49.9%
					NORGEP-HP	62.4%
Gallagher *et al.*[61]	Europe	65+	900	Hospital admissions to geriatric ward for acute illness	STOPP	51.3%
Wahab *et al.*[132]	Australia	65+	100	Hospital admissions to hospital (general)	STOPP	60.0%
Schuler *et al.*[63]	Austria	75+	543	Hospital admissions to internal medicine ward	Beers 2003 (modified)	30.1%
Fahrni *et al.*[8]	Malaysia	65+	301	Hospital admissions with acute illness	STOPP	34.9%
Jensen *et al.*[56]	Denmark	65+	71	Inpatients, with acute illness	Red–Yellow–Green List	85.0%
Alhawassi *et al.*[40]	Saudi Arabia	65+	4073	Inpatient, ambulatory care	Beers 2015 (independent of diagnoses)	57.5%

(Continued)

Table 10. (Continued)

Authors	Location	Age group	Sample size	Population/setting	PIMs tool	Prevalence
San-José *et al.*[35]	Spain	85+	336	Inpatients	Beers 2003	47.3%
					STOPP	63.4%
Tosato *et al.*[124]	Italy	65+	871	Inpatients	Beers 2012	58.4%
					STOPP	50.4%
Sharma *et al.*[133]	India	65+	323	Inpatients, with ⩾1 medicines	Beers 2019	61.9%
Skaar and O'Connor[134]	The United States	65+	19 million (approximately)	Medicare beneficiaries visiting the dentist	Beers 2015	56.9%
Holmes *et al.*[135]	The United States	66+	677,580	Outpatient Medicare beneficiaries	Beers 2003	31.9%
Lopez-Rodriguez *et al.*[125]	Spain	65–74	593	Outpatient, with multimorbidity and polypharmacy, accessing primary care in previous 12 months	Beers 2015	70.8%
					Beers 2019	68.8%
					STOPP	43.3%
					STOPP v2	57.4%
Huang *et al.*[103]	Japan	45+	196	Outpatients receiving hospital in the home	Beers 2015	71.9%
					STOPP-J	67.3%
Maio *et al.*[137]	Italy	65+	849,425	Outpatients with ⩾1 prescription claims	Beers 2003	18.0%
Morgan *et al.*[138]	Canada	65+	660,679	Outpatients with ⩾1 prescription claims – men	Beers 2012	31.0%
				Outpatients with ⩾1 prescription claims – women	Beers 2012	26.0%
Al-Azayzih *et al.*[139]	Jordan	65+	4356	Outpatients with ⩾1 prescriptions	Beers 2015	62.5%
Al-Dahshan and Kehyayan[53]	Qatar	65+	5639	Patients with completed medication reconciliation	Beers 2015	76.0%
Saboor *et al.*[140]	Iran	60+	1591	Pharmacy referrals	Beers 2012	26.0%
Chiapella *et al.*[36]	Argentina	65+	2231	Pharmacy, community with ⩾1 prescriptions	Beers 2015 (independent of diagnoses)	72.8%

(Continued)

Table 10. (Continued)

Authors	Location	Age group	Sample size	Population/setting	PIMs tool	Prevalence
					IFAsPIAM List (Argentinian List) (independent of diagnoses)	71.1%
Fujie *et al.*[49]	Japan	75+	8080	Pharmacy, dispensing	STOPP-J	26.7%
Baldoni et al.[64]	Brazil	60+	1000	Pharmacy, outpatients	Beers 2003	48.0%
					Beers 2012	59.2%
Miller *et al.*[141]	The United States	65+	16,588	Population-based	Beers 2012	30.9%
Bongue *et al.*[66]	France	75+	35,259	Population-based	Laroche PIMs list	53.5%
Galvin *et al.*[105]	Ireland	65+	3507	Population-based	STOPP	14.6%
Nishtala *et al.*[142]	New Zealand	75+	316	Population-based, with ⩾1 prescriptions	Beers 2012 (independent of diagnoses)	42.7%
Oliveira *et al.*[31]	Brazil	60+	142	Primary care	Beers 2003	34.5%
Awad and Hanna[52]	Kuwait	65+	420	Primary care	Beers 2015	53.1%
					FORTA 2014	44.3%
					STOPP v2	55.7%
Bradley *et al.*[143]	Northern Ireland	70+	166,108	Primary care	STOPP	34.0%
Amorim *et al.*[45]	Brazil	60+	417	Primary care (urban), with ⩾1 prescriptions	Brazilian criteria	45.3%
Ubeda *et al.*[108]	Spain	65+	85	RACF	STOPP	48.0%
					Beers 2003	25.0%
Jankyova *et al.*[25]	Slovakia	65+	459	RACF	EU(7) PIM list	90.6%
Lau *et al.*[144]	The United States	65+	3372	RACF residents for ⩾3 months	Beers 1991 and 1997 (modified)	50.3%
Shade *et al.*[145]	The United States	65+	141	Rural community dwelling, with ⩾3 medicines	Beers 2012	49.0%

PIMs, potentially inappropriate medicines; RACF, Residential aged care facilities; STOPP, Screening Tool of Older Persons' Prescriptions; STOPP-J, Japanese adaptation of Euro-developed STOPP; STOPP v2, STOPP version 2; (EU)(7)-PIM list, European Union 7 Potentially Inappropriate Medicine list; PRISCUS, Latin for "old and venerable"; IFAsPIAM, List of explicit criteria for Potencialmente Inapropiados en Adultos Mayores (translation: potentially inappropriate medications in older people.
[a]The table sorted according to study population/setting.

Table 11. Diagnostic test accuracy of explicit tools, using an implicit tool as the reference standard.

Authors	**Lopez-Rodriguez *et al.*[125]**		**Awad and Hanna[52]**	
Prevalence according to the MAI – reference tool	94.1%		73.6%	
Index tool	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**
STOPP	45.3%	82.9%		
STOPP v2	60.1%	80.0%	68.6%	80.2%
Beers 2019	68.8%	31.4%		
Beers 2015	71.8%	42.9%	58.3%	61.3%
FORTA			52.4%	78.4%

MAI: Medication Appropriate Index; STOPP, Screening Tool of Older Persons' Prescriptions; STOPP v2, STOPP version 2. Sensitivity/specificity interpretation: 91–100% – Excellent, 81–90% – Good, 71–80% – Moderate, 61–70% – Fair, 51–60% – Poor, <50% – Very poor.

Table 12. Direction of association between PIMs and commonly reported risk factors.[a]

Authors	**Country**	**Setting**	**Sample size**	**Sample age**	**Measure**	**Older age**	**Female**	**Poorer health**	**Polypharmacy**	**Low education**	**Social disadvantage**
Page *et al.*[50]	Australia	Aboriginal Australians living in remote communities	273	45+	Beers 2015	NA	NA	↑ and NA~		NA	
Gallagher *et al.*[61]	Europe	Acutely ill and hospitalized	900	65+	STOPP	NA	NA	NA	NA		
Chang *et al.*[118]	Taiwan	Care in the home recipients	25,187	65+	Beers 2012 (independent of diagnoses)	↑	↓	↑	↑		
					Taiwan criteria (independent of diagnoses)	↓	↓	↑	↑		
Projovic *et al.*[109]	Serbia	Chronically ill outpatients	364	65+	STOPP v2	NA	NA	↑	↑	NA	NA
Blanco-Reina *et al.*[120]	Spain	Community dwelling	582	65+	STOPP v2	NA	NA	NA	↑		
Bongue *et al.*[147]	France	Community dwelling	30,683	65+	Laroche criteria	↑	↑	↑	↑	↑	
Roux *et al.*[39]	Canada	Community dwelling	1,105,295	66+	Beers 2015 (independent of diagnoses)	↑	↑	↑			↑
Huang *et al.*[100]	China	Community-dwelling outpatients	1874	65+	Beers 2019	↑	↑	↓	↑		
					Chinese criteria 2017	↓	NA	↓	↑		
Lockery *et al.*[28]	Australia and the United States	Healthy community dwelling	19,114	70+	Beers 2019 (independent of diagnoses)	↑	Adjusted	↑	↑		

(Continued)

Table 12. (Continued)

Authors	Country	Setting	Sample size	Sample age	Measure	Older age	Female	Poorer health	Polypharmacy	Low education	Social disadvantage
Skaar and O'Connor[134]	The United States	Medicare beneficiaries visiting the dentist	19 million (approximately)	65+	Beers 2015 (independent of diagnoses)	NA	↑	↑		↑	
Al-Azayzih *et al.*[139]	Jordan	Outpatients	4356	65+	Beers 2015	NA	↑		↑		
Baldoni et al.[64]	Brazil	Outpatients	1000	60+	Beers 2012	↓	↑		↑	NA	NA
Maio *et al.*[137]	Italy	Outpatients with ⩾1 prescriptions	849,425	65+	Beers 2002 (independent of dose, duration or diagnoses)	↑	↓	↑	↑		↑
Ma *et al.*[104]	China	Patients discharged from internal medicine wards	662	65+	STOPP v2	↑	↑	NA	↑		
Galvin *et al.*[105]	Ireland	Population-based	3507	65+	STOPP	↑	NA	NA	↑		
Holmes *et al.*[135]	The United States	Population-based	677,580	66+	Beers 2003	NA	↑	↓	↑		↑
Miller *et al.*[141]	The United States	Population-based	16,588	65+	Beers 2012	↓	NA	NA	↑	↑	NA
Haider *et al.*[71]	Sweden	Population-based using ⩾1 prescriptions	626,258	75–89	Swedish indicators	Adjusted	Adjusted	Adjusted		↑	
Hyttinen *et al.*[146]	Finland	Population-based, with ⩾1 prescription	15,080	65–74	Med75+	Sub-analysis	↑		↑		↓
			13,064	75+	Med75+	Sub-analysis	NA		↑		NA
Price *et al.*[148]	Australia	Population-based, with ⩾1 prescription	251,305	65+	Beers 2003 (modified)	NL	↑		↑		↓
Nishtala *et al.*[142]	New Zealand	Population-based, with ⩾1 prescriptions	316	75+	Beers 2012	NA	NA		↑	NA	
Awad and Hanna[52]	Kuwait	Primary care	420	65+	STOPP v2	NA	NA	NA	↑	NA	
Amorim *et al.*[45]	Brazil	Primary care patients with ⩾1 prescription	417	65+	Brazilian criteria	NA	NA	NA	↑		NA

NA, no association; NL, non-linear association; PIMs, potentially inappropriate medicines; STOPP, Screening Tool of Older Persons' Prescriptions; STOPP v2, STOPP version 2; ↑, positive association; ↓, negative association.
~ stroke = NA; diabetes = ↑.
[a]The table sorted according to study population.

been measured among community-dwelling or population-based samples,[66,71,134,141] while those who found no association tended to be observed among patient populations.[52,64,109]

Evidence of an association between indicators of social disadvantage and PIMs use is mixed (Table 12). However, the relationship with social disadvantage is likely to be highly contextual and variability in the tools used to measure PIMs and the social, economic and political settings in which these findings were observed may have influenced the inconsistent results.

Clinical implications of PIMs use. One of the major limitations of published PIMs tools is that they have been developed *via* expert consensus and their clinical significance remains unclear. Several studies have investigated associations between PIMs and clinical outcomes cross-sectionally;[8,121,150–153] however, without establishing a temporal relationship between the predictor and outcome, the ability to make inference is limited. Therefore, this review has focused on studies measuring the exposure and outcomes at different timepoints. A range of cross-sectional research has investigated the association between PIMs, specific drug–drug or drug–disease contraindications and adverse events.[97] With a well-established link between PIMs and polypharmacy (Table 12), polypharmacy may be a mediating factor in the association between PIMs and medicine-related adverse events.

Mortality. There is some evidence to suggest older adults using one or more PIMs have an increased probability of mortality (Table 13). However, it would appear studies investigating a longer survival time (⩾5 years) were more likely to find an association, compared with those with a shorter study duration (Table 13). Of interest, studies applying locally developed PIMs tools appear more likely to have significant associations with mortality, relative to their internationally imported counterparts. For example, participants exposed to medicines listed on the Finnish-developed Med75+ criteria for 1, 3 and 6 months in Finland experienced an increased probability of mortality.[154] Similarly, adults with a disability receiving hospital in the home in Japan who used ⩾1 PIMs, defined according to the STOPP-J, the Japanese adaptation of Euro-developed STOPP, also saw a positive association with mortality. Yet when the US-developed Beers 2015 criteria were applied to the same Japanese sample, no association was observed.[103] This suggests that when applied within the intended geographic location, PIMs tools may be more precise in detecting clinically significant PIMs. Furthermore, looking back at the prevalence of PIMs, the same Japanese study[103] reported a higher PIMs prevalence for the Beers 2015 criteria (71.9%) compared with the STOPP-J (67.3%) (Table 10). This may highlight an issue of discrimination where utilization alone may be a misleading indicator of risk.

Hospitalization. The use of PIMs has been linked to an increased risk of hospitalization, re-hospitalization and emergency department visits (Table 14). A novel study method was used in Germany among a population-based sample of older adults, where a case control–type design grouped exposed individuals, who used medicines on the German-developed PRISCUS list, and unexposed individuals, who used medicines that were considered to be the safer alternative to PIM on the PRISCUS list.[155] The study found that compared with those taking a safer alternative, those using ⩾1 PRISCUS PIMs were 38% more likely to be hospitalized in the proceeding 6 months.[155] In Japan, Huang *et al.*[103] reported a similar pattern of association for hospitalization than what was observed for mortality, finding a borderline association with the locally developed STOPP-J but no relationship with the Beers 2015 criteria. In Australia, Beer and colleagues modified Beers 2003 criteria to the Australian setting, finding community-dwelling older men using >1 PIM within a 12-month window were 16% more likely to experience all-cause hospitalization within the next 4¼ years.[26]

Falls, fractures, physical function and frailty. There is also some evidence linking the use of PIMs with an increased risk of falls and fractures (Table 15). Both studies considered degrees of exposure, defined according to the number of months with a PIM or whether PIMs use was classified as regular or occasional use.[154,158] When considering specific subclasses within a PIMs tool, it would appear some medicines are more likely to be associated with falls,[158] which suggests applying a complete list, in its entirety, may be a blunt tool for assessing some outcomes. The evidence to support an association between PIMs use and a decline in physical function or incidence of

Table 13. Outcomes of PIMs – associations with mortality.[a]

Authors	Location	Age group	Population	Sample size	Study duration (years)	PIMs tool	Unit of measure	Effect size (95% CI)
De Vincentis *et al.*[99]	Italy	65+	Community-dwelling hospital discharges	2631	0.25	Beers 2019	Binary	NA
						STOPP v2	Binary	NA
Ryan *et al.*[106]	New Zealand	80+	Community dwelling – Māori subset	267	1	STOPP v2	Binary	NA
		85+	Community dwelling – non-Māori subset	404	1	STOPP v2	Binary	NA
Beer *et al.*[26]	Australia	70–88	Community-dwelling men	4260	4.5	Beers 2003 (modified) (12-month window)	Binary	NA
Huang *et al.*[103]	Japan	45+	Outpatients receiving hospital in the home	196	5	Beers 2015	Binary	NA
						STOPP-J	Binary	HR: 3.01 (1.37, 6.64)
de Araújo *et al.*[34]	Brazil	60+	Community dwelling accessing public health care	418	10	Beers 2019	Binary	NA
Hyttinen *et al.*[154]	Finland	65+	Community dwelling (2-year PIMs washout period)	20,666	12	Med75+ (6-month exposure to PIMs)	Binary	HR: 1.81 (1.71, 1.92)
						Med75+ (3-month exposure to PIMs)	Binary	HR: 1.67 (1.56, 1.78)
						Med75+ (1-month exposure to PIMs)	Binary	HR: 1.38 (1.24, 1.54)
Nascimento *et al.*[33]	Brazil	60+	Community dwelling	1371	14	Beers 2012	Binary	HR: 1.44 (1.21, 1.71)

CI, confidence interval; HR, hazard ratio; NA, no association; PIMs, potentially inappropriate medicines; STOPP-J, Japanese adaptation of Euro-developed STOPP; STOPP v2, STOPP version 2.
[a]The table sorted according to study duration.

Table 14. Outcomes of PIMs – associations with hospitalization and emergency department visits.[a]

Authors	Location	Age group	Population	Sample size	Outcome measure	Study duration (years)	PIMs tool	Reference/unit of measure	Effect size (95% CI)
De Vincentis *et al.*[99]	Italy	65+	Community-dwelling hospital discharges	2631	Re-hospitalization	0.25	Beers 2019	Binary	NA
							STOPP v2	Binary	NA
Brunetti *et al.*[101]	Italy	65+	Hospital discharges	611	Re-hospitalization – unplanned	0.5	STOPP v2	Continuous	OR: 1.23 (1.03, 1.46)
Endres *et al.*[155]	Germany	65+	Population-based	392,337	Hospitalization – all cause	0.5	PRISCUS	Binary – patients using a safer PIMs alternative (reference)	HR: 1.38 (1.35, 1.41)

(Continued)

Table 14. (Continued)

Authors	Location	Age group	Population	Sample size	Outcome measure	Study duration (years)	PIMs tool	Reference/unit of measure	Effect size (95% CI)
Ryan *et al.*[106]	New Zealand	85+	Community dwelling – non-Māori subset	404	Hospitalization – all cause	1	STOPP v2	Binary	NA
		80+	Community dwelling – Māori subset	267	Hospitalization – all cause	1	STOPP v2	Binary	NA
Beer *et al.*[26]	Australia	70–88	Community-dwelling men	4260	Hospitalization – all cause	4.5	Beers 2003 (modified) (12-month window)	Binary	HR: 1.16 (1.08, 1.24)
Chu *et al.*[156]	Taiwan	65+	Population-based	42,912	Emergency department visits	5	Beers 2003 (independent of diagnoses)	Binary	OR: 1.36 (1.33, 1.40)
					Hospitalization – all cause	5	Beers 2003 (independent of diagnoses)	Binary	OR: 1.29 (1.25, 1.32)
Huang *et al.*[103]	Japan	45+	Outpatients receiving hospital in the home	196	Hospitalization – all cause	5	Beers 2015	Binary	NA
							STOPP-J	Binary	HR: 1.70 (1.01, 2.84)[b]
Moriarty *et al.*[157]	Ireland	45–64	Community dwelling – socially disadvantaged	808	Emergency department visits	12	PROMPT	Multilevel	NA

CI, confidence interval; HR, hazard ratio; NA, no association; OR, odds ratio; PIMs, potentially inappropriate medicines.
[a]The table sorted according to study duration.
[b]Borderline significant.

Table 15. Outcomes of PIMs – associations with falls and fractures.

Authors	Location	Age group	Population	Sample size	Outcome measure	Study duration (years)	PIMs tool	Reference/ unit of measure	Effect size (95% CI/*p* value)
Berdot *et al.*[158]	France	65+	Community dwelling	6343	Self-reported falls (⩾2 falls during 4-year follow-up)	4	Full list – Beers 1991 and Laroche (combined)	Never used defined PIM	Occasional user – OR: 1.23 (1.04, 1.45) Regular user – NA
							Full list excluding cerebral vasodilators[a]	Never used defined PIM	Occasional user – OR: 1.22 (1.02, 1.45) Regular user – OR: 1.19 (1.00, 1.41)[b]
							Long-acting benzodiazepines[a]	Never used defined PIM	Occasional user – OR: 1.40 (1.10, 1.79) Regular user – OR: 1.41 (1.12, 1.79)
							Inappropriate psychotropic drugs[a]	Never used defined PIM	Occasional user – NA Regular user – OR: 1.74 (1.14, 2.66)

(Continued)

Table 15. (Continued)

Authors	Location	Age group	Population	Sample size	Outcome measure	Study duration (years)	PIMs tool	Reference/ unit of measure	Effect size (95% CI/*p* value)
							Medicines with anticholinergic properties[a]	Never used defined PIM	Occasional user – NA Regular user – OR: 1.57 (1.18, 2.10)
							Short- or intermediate-half-life benzodiazepines[a]	Never used defined PIM	Occasional user – NA Regular user – NA
Hyttinen *et al.*[154]	Finland	65+	Community dwelling (2-year PIMs washout period)	20,666	Registered fall-related fractures	12	Med75+ (6-month exposure to PIMs)	Binary	HR: 1.30 (1.17, 1.43)
							Med75+ (3-month exposure to PIMs)	Binary	HR: 1.30 (1.16, 1.46)
							Med75+ (1-month exposure to PIMs)	Binary	HR: 1.20 (1.01, 1.44)

CI: confidence interval; HR, hazard ratio; NA, no association; OR, odds ratio; PIMs, potentially inappropriate medicines.
[a]Subset of a combined list using the Beers 1991 criteria and the Laroche PIMs list.
[b]Borderline significant.

frailty, however, is less compelling. Of the three studies investigating these outcomes, each looked at more than one PIMs list to investigate associations, often with mixed findings (Table 16). Of note, a study from Germany found no association between the locally developed PRISCUS list and 6-year incidence of frailty; however, an increased probability was observed when PIMs were measured using the Beers 2015 criteria from the United States.[159] This appears to go against the trend observed in the Japanese study reporting associations with mortality and hospitalization using a locally developed tool.[103] A possible explanation is that the PRISCUS tool was published in 2010 and may no longer reflect the current challenges associated with inappropriate prescribing in Germany, and while the Beers 2015 criteria are not native to the study population, a more recently updated tool may be the sharper instrument for detecting clinically significant PIMs.

Other clinically significant outcomes. In addition to the outcome discussed above, associations with quality of life and risk of cardiovascular events have also been considered (Table 17). There is some evidence that the use of two PIMs may be associated with a decrease in quality of life, according to the EuroQoL 5-Dimension (EQ-5D) utility, among a sample of community-dwelling older adults.[129] However, there is limited research investigating this outcome. One study investigated cardiovascular events as an outcome in Australia, finding no association.[26]

Gaps in the literature. There is evidence to indicate that PIMs are likely associated with poorer outcomes, which validates the tools beyond the expert opinion or consensus in which they were developed. However, it was not uncommon for studies to report conflicting results within the same study population when different PIMs tools were applied. While this suggests not all tools are equal in any given study setting, there is limited research available and it was not possible to compare the outcomes associated with specific tools across different study contexts. Research investigating the patterns and implications of PIMs use among the population must consider the applicability of the explicit tool(s) to the study setting. The most well-known PIMs tools may not be the most appropriate for all clinical contexts, and tool selection should be mindful of the intended purpose of the tool as well as the country in which it was developed.[115]

Table 16. Outcomes of PIMs – associations with physical function and frailty.[a]

Authors	Location	Age group	Population	Sample size	Outcome measure	Study duration (years)	PIMs tool	Unit of measure	Effect size (95% CI)
Tosato *et al.*[124]	Italy	65+	Inpatients	871	Decline in physical function – activities of daily living	11 days (mean length of admission)	Beers 2012	Binary	NA
							STOPP	Binary	OR: 2.00 (1.10, 3.64)
De Vincentis *et al.*[99]	Italy	65+	Community-dwelling hospital discharges	2631	Physical function – Barthel index	0.25	Beers 2019	Mean % variation	NA
							STOPP v2	Mean % variation	NA
Muhlack *et al.*[119]	Germany	60+	Community dwelling	2011	Incidence of frailty – fried frailty phenotype	6	PRISCUS	Binary	NA
							EU(7) PIMs list	Binary	NA
							Beers 2015	Binary	HR: 1.34 (1.08, 1.66)

CI, confidence interval; HR, hazard ratio; NA, no association; OR, odds ratio; PIMs, potentially inappropriate medicines; STOPP, Screening Tool of Older Persons' Prescriptions; STOPP-J, Japanese adaptation of Euro-developed STOPP; STOPP v2, STOPP version 2.
[a]The table sorted according to study duration.

Table 17. Outcomes of potential suboptimal medicine regimens – other clinically significant outcomes.

Quality of life									
Authors	**Location**	**Age group**	**Population**	**Sample size**	**Outcome measure**	**Study duration (years)**	**PIMs tool**	**Reference**	**Effect size (95% CI/*p* value)**
Cahir *et al.*[129]	Ireland	75+	Community dwelling	931	Health-related quality of life – EQ-5D utility (lower score indicating reduced QoL)	0.5	STOPP	No PIMs	1 PIM: NA 2 PIMs: $\beta = -0.09$ ($p < 0.05$)
Moriarty *et al.*[157]	Ireland	45–64	Community dwelling, socially disadvantaged	808	QoL – CASP-19 (lower score indicating reduced QoL)	2	PROMPT	No PIMs	1 PIM: NA ⩾2 PIMs: NA
Beer *et al.*[26]	Australia	70–88	Community dwelling men	4260	⩾1 cardiovascular event	4.5	Beers 2003 (modified) (12-month window)	Binary	NA

β, coefficient; CI, confidence interval; NA, no association; PIMs, potentially inappropriate medicines; QoL, quality of life; STOPP, Screening Tool of Older Persons' Prescriptions.

Conclusion

There is a need for further research that distinguishes between transient and chronic exposure to polypharmacy and longitudinal studies that determine the trajectories of polypharmacy through adulthood into older age to better identify people at greatest risk. Research investigating underprescribing is limited and future research is warranted; however, it may be important to also consider indicators of health care utilization to better differentiate between instances of potential suboptimal prescribing and confounding by SES. Within PIMs research, substantial heterogeneity in tools, study contexts and populations of interest make it challenging to synthesize the evidence. It remains unclear how well PIMs tools developed internationally transfer to local settings, and thus the validity of many studies remains uncertain when applied internationally. As such, an evaluation of the applicability of tool(s) to specific contexts should be considered before the patterns and implications of PIMs are investigated. Addressing these gaps in the existing literature would contribute to the growing body of research on potentially suboptimal medicine regimens and build knowledge that may reduce the risk of medicine-related harm among older adults.

Key points

Potentially suboptimal medicine regimens is an umbrella term that considers an individual's entire regimen.

Indicators of a potentially suboptimal medicine regimen may include polypharmacy, underprescribing or potentially inappropriate medicines (PIMs).

Polypharmacy

- Polypharmacy is prevalent among older adults, but varying definitions make it difficult to compare research.
- There is substantial evidence to suggest older age and indicators of poorer health are risk factors for polypharmacy.
- It is unclear whether the risk factors for polypharmacy are the same for younger and middle-aged cohorts as they are for older cohorts.
- Exposure to polypharmacy can be transient or chronic.
- Polypharmacy research may not be developed enough to define a specific number of medicines to measure exposure in clinical settings at this time.

Underprescribing

- Complete data on current medicines and medical histories are required to measure underprescribing.
- More is known about underprescribing among patient populations than in community settings.
- There is limited research investigating the risk factors of underprescribing and findings appear mixed.
- Few studies have measured the clinical implications of underprescribing over time.

PIMs

- Explicit tools to measure PIMs are diverse, which may explain some of the variability observed across the literature.
- There is a strong body of evidence supporting the association between polypharmacy and PIMs.
- There is some evidence to suggest PIMs are associated with premature mortality and increased risk of hospitalization, falls and fractures.

PIMs tools applied to populations from the country in which they were developed may be more precise in detecting clinically significant PIMs.

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Consent for publication

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References

1. World Health Organization. Medication without harm, https://www.who.int/initiatives/medication-without-harm (2022, accessed January 2022).
2. United Nations Department of Economic and Social Affairs: Population Division. *World population ageing 2019: highlights*. New York: United Nations, 2019.
3. Barnett K, Mercer SW, Norbury M, *et al*. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012; 380: 37–43.
4. Hilmer SN, Gnjidic D and Le Couteur DG. Thinking through the medication list: appropriate prescribing and deprescribing in robust and frail older patients. *Aust Fam Physician* 2012; 41: 924–928.
5. Gould H, Brennan SL, Kotowicz MA, *et al*. Total and appendicular lean mass reference ranges for Australian men and women: the Geelong osteoporosis study. *Calcif Tissue Int* 2014; 94: 363–372.
6. Gallagher P and O'Mahony D. Inappropriate prescribing in older people. *Rev Clin Gerontol* 2008; 18: 65–76.
7. Kouladjian O'Donnell L, Gnjidic D, Nahas R, *et al*. Anticholinergic burden: considerations for older adults. *J Pharm Pract Res* 2017; 47: 67–77.
8. Fahrni ML, Azmy MT, Usir E, *et al*. Inappropriate prescribing defined by STOPP and START criteria and its association with adverse drug events among hospitalized older patients: a multicentre, prospective study. *PLoS ONE* 2019; 14: e0219898.
9. Page AT, Potter K, Clifford R, *et al*. Deprescribing in older people. *Maturitas* 2016; 91: 115–134.
10. Nyborg G, Straand J and Brekke M. Inappropriate prescribing for the elderly – a modern epidemic? *Eur J Clin Pharmacol* 2012; 68: 1085–1094.
11. Nebeker JR, Barach P and Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. *Ann Intern Med* 2004; 140: 795–801.
12. Alhawassi TM, Krass I, Bajorek BV, *et al*. A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting. *Clin Interv Aging* 2014; 9: 2079–2086.
13. Yadesa TM, Kitutu FE, Deyno S, *et al*. Prevalence, characteristics and predicting risk factors of adverse drug reactions among hospitalized older adults: a systematic review and meta-analysis. *SAGE Open Med* 2021; 9: 20503121211039099.
14. Parekh N, Ali K, Page A, *et al*. Incidence of medication-related harm in older adults after hospital discharge: a systematic review. *J Am Geriatr Soc* 2018; 66: 1812–1822.
15. Masnoon N, Shakib S, Kalisch-Ellett L, *et al*. What is polypharmacy? A systematic review of definitions. *BMC Geriatr* 2017; 17: 230.
16. Barry PJ, Gallagher P, Ryan C, *et al*. START (Screening Tool to Alert doctors to the Right Treatment) – an evidence-based screening tool to detect prescribing omissions in elderly patients. *Age Ageing* 2007; 36: 632–638.
17. O'Connor MN, Gallagher P and O'Mahony D. Inappropriate prescribing: criteria, detection and prevention. *Drugs Aging* 2012; 29: 437–452.
18. Joung K-I, Shin J-Y and Cho S-I. Features of anticholinergic prescriptions and predictors of high use in the elderly: population-based study. *Pharmacoepidemiol Drug Saf* 2019; 28: 1591–1600.
19. Kalisch LM, Caughey GE, Roughead EE, *et al*. The prescribing cascade. *Aust Prescr* 2011; 34: 162–166.

20. Cherubini A, Corsonello A and Lattanzio F. Underprescription of beneficial medicines in older people: causes, consequences and prevention. *Drugs Aging* 2012; 29: 463–475.
21. Sirois C, Simard M, Gosselin E, *et al*. Mixed bag 'polypharmacy': methodological pitfalls and challenges of this exposure definition. *Curr Epidemiol Rep* 2019; 6: 390–401.
22. Turner JP, Jamsen KM, Shakib S, *et al*. Polypharmacy cut-points in older people with cancer: how many medications are too many? *Support Care Cancer* 2016; 24: 1831–1840.
23. Gnjidic D, Hilmer SN, Blyth FM, *et al*. Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. *J Clin Epidemiol* 2012; 65: 989–995.
24. Richardson K, Kenny RA and Bennett K. The effect of free health care on polypharmacy: a comparison of propensity score methods and multivariable regression to account for confounding. *Pharmacoepidemiol Drug Saf* 2014; 23: 656–665.
25. Jankyova S, Rubintova D and Foltanova T. The analysis of the use of potentially inappropriate medications in elderly in the Slovak Republic. *Int J Clin Pharm* 2020; 42: 100–109.
26. Beer C, Hyde Z, Almeida OP, *et al*. Quality use of medicines and health outcomes among a cohort of community dwelling older men: an observational study. *Br J Clin Pharmacol* 2011; 71: 592–599.
27. Aoki T, Ikenoue T, Yamamoto Y, *et al*. Attributes of primary care in relation to polypharmacy: a multicenter cross-sectional study in Japan. *Int J Qual Health Care* 2017; 29: 378–383.
28. Lockery JE, Ernst ME, Broder JC, *et al*. Prescription medication use in older adults without major cardiovascular disease enrolled in the Aspirin in Reducing Events in the Elderly (ASPREE) clinical trial. *Pharmacotherapy* 2020; 40: 1042–1053.
29. Hubbard RE, Peel NM, Scott IA, *et al*. Polypharmacy among inpatients aged 70 years or older in Australia. *Med J Aust* 2015; 202: 373–377.
30. Husson N, Watfa G, Laurain MC, *et al*. Characteristics of polymedicated (⩾ 4) elderly: a survey in a community-dwelling population aged 60 years and over. *J Nutr Health Aging* 2014; 18: 87–91.
31. Oliveira MG, Amorim WW, de Jesus SR, *et al*. Factors associated with potentially inappropriate medication use by the elderly in the Brazilian primary care setting. *Int J Clin Pharm* 2012; 34: 626–632.
32. Payne RA, Avery AJ, Duerden M, *et al*. Prevalence of polypharmacy in a Scottish primary care population. *Eur J Clin Pharmacol* 2014; 70: 575–581.
33. Nascimento RCRMD, Álvares J, Guerra AA, *et al*. Polypharmacy: a challenge for the primary health care of the Brazilian Unified Health System. *Rev Saude Publica* 2017; 51: 19s.
34. de Araújo NC, Silveira EA, Mota BG, *et al*. Potentially inappropriate medications for the elderly: incidence and impact on mortality in a cohort ten-year follow-up. *PLoS ONE* 2020; 15: e0240104.
35. San-José A, Agustí A, Vidal X, *et al*. Inappropriate prescribing to the oldest old patients admitted to hospital: prevalence, most frequently used medicines, and associated factors. *BMC Geriatr* 2015; 15: 42.
36. Chiapella LC, Montemarani Menna J, Marzi M, *et al*. Prevalence of potentially inappropriate medications in older adults in Argentina using Beers criteria and the IFAsPIAM List. *Int J Clin Pharm* 2019; 41: 913–919.
37. Blanco-Reina E, Ariza-Zafra G, Ocaña-Riola R, *et al*. Optimizing elderly pharmacotherapy: polypharmacy vs. undertreatment. Are these two concepts related? *Eur J Clin Pharmacol* 2015; 71: 199–207.
38. Gorup EC and Šter MP. Number of medications or number of diseases: what influences underprescribing? *Eur J Clin Pharmacol* 2017; 73: 1673–1679.
39. Roux B, Sirois C, Simard M, *et al*. Potentially inappropriate medications in older adults: a population-based cohort study. *Fam Pract* 2020; 37: 173–179.
40. Alhawassi TM, Alatawi W and Alwhaibi M. Prevalence of potentially inappropriate medications use among older adults and risk factors using the 2015 American Geriatrics Society Beers criteria. *BMC Geriatr* 2019; 19: 154.
41. Valent F. Polypharmacy in the general population of a Northern Italian area: analysis of administrative data. *Ann Ist Super Sanita* 2019; 55: 233–239.
42. Castioni J, Marques-Vidal P, Abolhassani N, *et al*. Prevalence and determinants of polypharmacy in Switzerland: data from the CoLaus study. *BMC Health Serv Res* 2017; 17: 840.

43. Silva IR, Gonçalves LG, Chor D, *et al.* Polypharmacy, socioeconomic indicators and number of diseases: results from ELSA-Brasil. *Rev Bras Epidemiol* 2020; 23: e200077.

44. Blozik E, Rapold R, von Overbeck J, *et al.* Polypharmacy and potentially inappropriate medication in the adult, community-dwelling population in Switzerland. *Drugs Aging* 2013; 30: 561–568.

45. Amorim WW, Passos LC, Gama RS, *et al.* Physician and patient-related factors associated with inappropriate prescribing to older patients within primary care: a cross-sectional study in Brazil. *Sao Paulo Med J* 2021; 139: 107–116.

46. Turnbull AJ, Donaghy E, Salisbury L, *et al.* Polypharmacy and emergency readmission to hospital after critical illness: a population-level cohort study. *Br J Anaesth* 2021; 126: 415–422.

47. Slater N, White S and Frisher M. Central nervous system (CNS) medications and polypharmacy in later life: cross-sectional analysis of the English Longitudinal Study of Ageing (ELSA). *BMJ Open* 2020; 10: e034346.

48. Page AT, Falster MO, Litchfield M, *et al.* Polypharmacy among older Australians, 2006–2017: a population-based study. *Med J Aust* 2019; 211: 71–75.

49. Fujie K, Kamei R, Araki R, *et al.* Prescription of potentially inappropriate medications in elderly outpatients: a survey using 2015 Japanese Guidelines. *Int J Clin Pharm* 2020; 42: 579–587.

50. Page A, Hyde Z, Smith K, *et al.* Potentially suboptimal prescribing of medicines for older Aboriginal Australians in remote areas. *Med J Aust* 2019; 211: 119–125.

51. Wauters M, Elseviers M, Vaes B, *et al.* Polypharmacy in a Belgian cohort of community-dwelling oldest old (80+). *Acta Clin Belg* 2016; 71: 158–166.

52. Awad A and Hanna O. Potentially inappropriate medication use among geriatric patients in primary care setting: a cross-sectional study using the Beers, STOPP, FORTA and MAI criteria. *PLoS ONE* 2019; 14: e0218174.

53. Al-Dahshan A and Kehyayan V. Prevalence and predictors of potentially inappropriate medication prescription among older adults: a cross-sectional study in the state of Qatar. *Drugs Real World Outcomes* 2021; 8: 95–103.

54. de Vries FM, Stingl JC and Breteler MMB. Polypharmacy, potentially inappropriate medication and pharmacogenomics drug exposure in the Rhineland Study. *Br J Clin Pharmacol* 2021; 87: 2732–2756.

55. Haider SI, Johnell K, Thorslund M, *et al.* Analysis of the association between polypharmacy and socioeconomic position among elderly aged ⩾77 years in Sweden. *Clin Ther* 2008; 30: 419–427.

56. Jensen LD, Andersen O, Hallin M, *et al.* Potentially inappropriate medication related to weakness in older acute medical patients. *Int J Clin Pharm* 2014; 36: 570–580.

57. Gutiérrez-Valencia M, Herce PA, Lacalle-Fabo E, *et al.* Prevalence of polypharmacy and associated factors in older adults in Spain: data from the National health survey 2017. *Med Clín* 2019; 153: 141–150.

58. Midão L, Giardini A, Menditto E, *et al.* Polypharmacy prevalence among older adults based on the survey of health, ageing and retirement in Europe. *Arch Gerontol Geriatr* 2018; 78: 213–220.

59. Lechevallier-Michel N, Gautier-Bertrand M, Alpérovitch A, *et al.* Frequency and risk factors of potentially inappropriate medication use in a community-dwelling elderly population: results from the 3C Study. *Eur J Clin Pharmacol* 2005; 60: 813–819.

60. Lim LM, McStea M, Chung WW, *et al.* Prevalence, risk factors and health outcomes associated with polypharmacy among urban community-dwelling older adults in multi-ethnic Malaysia. *PLoS ONE* 2017; 12: e0173466.

61. Gallagher P, Lang PO, Cherubini A, *et al.* Prevalence of potentially inappropriate prescribing in an acutely ill population of older patients admitted to six European hospitals. *Eur J Clin Pharmacol* 2011; 67: 1175–1188.

62. Baek Y-H and Shin J-Y. Trends in polypharmacy over 12 years and changes in its social gradients in South Korea. *PLoS ONE* 2018; 13: e0204018.

63. Schuler J, Dückelmann C, Beindl W, *et al.* Polypharmacy and inappropriate prescribing in elderly internal-medicine patients in Austria. *Wien Klin Wochenschr* 2008; 120: 733–741.

64. Baldoni AdO, Ayres LR, Martinez EZ, *et al.* Factors associated with potentially inappropriate medications use by the elderly according to Beers criteria 2003 and 2012. *Int J Clin Pharm* 2014; 36: 316–324.

65. Hudhra K, Beçi E, Petrela E, *et al.* Prevalence and factors associated with potentially

inappropriate prescriptions among older patients at hospital discharge. *J Eval Clin Pract* 2016; 22: 707–713.

66. Bongue B, Laroche ML, Gutton S, *et al.* Potentially inappropriate drug prescription in the elderly in France: a population-based study from the French National Insurance Healthcare system. *Eur J Clin Pharmacol* 2011; 67: 1291–1299.

67. Jyrkkä J, Enlund H, Korhonen MJ, *et al.* Patterns of drug use and factors associated with polypharmacy and excessive polypharmacy in elderly persons. *Drugs Aging* 2009; 26: 493–503.

68. Walckiers D, Van der Heyden J and Tafforeau J. Factors associated with excessive polypharmacy in older people. *Arch Public Health* 2015; 73: 50.

69. Duerden M, Avery T and Payne R. *Polypharmacy and medicines optimisation. Making it safe and sound*. London: The King's Fund, 2013.

70. Morin L, Johnell K, Laroche ML, *et al.* The epidemiology of polypharmacy in older adults: register-based prospective cohort study. *Clin Epidemiol* 2018; 10: 289–298.

71. Haider SI, Johnell K, Weitoft GR, *et al.* The influence of educational level on polypharmacy and inappropriate drug use: a register-based study of more than 600,000 older people. *J Am Geriatr Soc* 2009; 57: 62–69.

72. Guthrie B, Makubate B, Hernandez-Santiago V, *et al.* The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995–2010. *BMC Med* 2015; 13: 74.

73. Per BL, Taylor AW and Gill TK. Prescription medicines, over-the-counter medicines and complementary and alternative medicines use: a comparison between baby boomers and older South Australians. *AIMS Public Health* 2019; 6: 380–395.

74. Marmot M. Social determinants of health inequalities. *Lancet* 2005; 365: 1099–1104.

75. Kyriacou DN and Lewis RJ. Confounding by indication in clinical research. *JAMA* 2016; 316: 1818–1819.

76. Kantor ED, Rehm CD, Haas JS, *et al.* Trends in prescription drug use among adults in the United States from 1999-2012. *JAMA* 2015; 314: 1818–1830.

77. Linjakumpu T, Hartikainen S, Klaukka T, *et al.* Use of medications and polypharmacy are increasing among the elderly. *J Clin Epidemiol* 2002; 55: 809–817.

78. Nishtala PS and Salahudeen MS. Temporal trends in polypharmacy and hyperpolypharmacy in older New Zealanders over a 9-year period: 2005-2013. *Gerontology* 2015; 61: 195–202.

79. Nind J, Smith A, Devananda M, *et al.* A whole of population retrospective observational study on the rates of polypharmacy in New Zealand 2014 to 2018 Polypharmacy in New Zealand: what is the current status? *Health Sci Rep* 2021; 4: e263.

80. Abolhassani N, Castioni J, Marques-Vidal P, *et al.* Determinants of change in polypharmacy status in Switzerland: the population-based CoLaus study. *Eur J Clin Pharmacol* 2017; 73: 1187–1194.

81. Ware D, Palella FJ Jr, Chew KW, *et al.* Examination of polypharmacy trajectories among HIV-positive and HIV-negative men in an ongoing longitudinal cohort from 2004 to 2016. *AIDS Patient Care STDS* 2019; 33: 354–365.

82. Whitney DG, Schmidt M and Haapala H. Polypharmacy is a risk factor for mortality, severe chronic kidney disease, and liver disease among privately insured adults with cerebral palsy. *J Manag Care Spec Pharm* 2021; 27: 51–63.

83. Veereschild HM, Noorthoorn EO, Nijman HLI, *et al.* Diagnose, indicate, and treat severe mental illness (DITSMI) as appropriate care: a three-year follow-up study in long-term residential psychiatric patients on the effects of re-diagnosis on medication prescription, patient functioning, and hospital bed utilization. *Eur Psychiatry* 2020; 63: e47.

84. Veehof L, Stewart R, Haaijer-Ruskamp F, *et al.* The development of polypharmacy. A longitudinal study. *Fam Pract* 2000; 17: 261–267.

85. Lapi F, Pozzi C, Mazzaglia G, *et al.* Epidemiology of suboptimal prescribing in older, community dwellers. *Drugs Aging* 2009; 26: 1029–1038.

86. Wastesson JW, Oksuzyan A, von Bornemann Hjelmborg J, *et al.* Changes in drug use and polypharmacy after the age of 90: a longitudinal study of the Danish 1905 cohort. *J Am Geriatr Soc* 2017; 65: 160–164.

87. Jyrkkä J, Enlund H, Lavikainen P, *et al.* Association of polypharmacy with nutritional status, functional ability and cognitive capacity over a three-year period in an elderly population. *Pharmacoepidemiol Drug Saf* 2011; 20: 514–522.

88. Haider SI, Johnell K, Thorslund M, *et al.* Trends in polypharmacy and potential drug-drug interactions across educational groups in elderly patients in Sweden for the period 1992-2002. *Int J Clin Pharmacol Ther* 2007; 45: 643–653.

89. Blumstein T, Benyamini Y, Chetrit A, *et al.* Prevalence and correlates of psychotropic medication use among older adults in Israel: cross-sectional and longitudinal findings from two cohorts a decade apart. *Aging Ment Health* 2012; 16: 636–647.

90. Wastesson JW, Morin L, Laroche ML, *et al.* How chronic is polypharmacy in old age? A longitudinal nationwide cohort study. *J Am Geriatr Soc* 2019; 67: 455–462.

91. Falster MO, Charrier R, Pearson SA, *et al.* Long-term trajectories of medicine use among older adults experiencing polypharmacy in Australia. *Br J Clin Pharmacol* 2021; 87: 1264–1274.

92. Wang Y-J, Chiang S-C, Lee P-C, *et al.* Is excessive polypharmacy a transient or persistent phenomenon? A nationwide cohort study in Taiwan. *Front Pharmacol* 2018; 9: 120.

93. Davies LE, Spiers G, Kingston A, *et al.* Adverse outcomes of polypharmacy in older people: systematic review of reviews. *J Am Med Dir Assoc* 2020; 21: 181–187.

94. Wastesson JW, Morin L, Tan ECK, *et al.* An update on the clinical consequences of polypharmacy in older adults: a narrative review. *Expert Opin Drug Saf* 2018; 17: 1185–1196.

95. Maher RL, Hanlon J and Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf* 2014; 13: 57–65.

96. Khezrian M, McNeil CJ, Murray AD, *et al.* An overview of prevalence, determinants and health outcomes of polypharmacy. *Ther Adv Drug Saf* 2020; 11: 2042098620933741.

97. Rodrigues MCS and de Oliveira C. Drug-drug interactions and adverse drug reactions in polypharmacy among older adults: an integrative review. *Rev Lat Am Enfermagem* 2016; 24: e2800.

98. Shah BM and Hajjar ER. Polypharmacy, adverse drug reactions, and geriatric syndromes. *Clin Geriatr Med* 2012; 28: 173–186.

99. De Vincentis A, Gallo P, Finamore P, *et al.* Potentially inappropriate medications, drug–drug interactions, and anticholinergic burden in elderly hospitalized patients: does an association exist with post-discharge health outcomes? *Drugs Aging* 2020; 37: 585–593.

100. Huang Y, Zhang L, Huang X, *et al.* Potentially inappropriate medications in Chinese community-dwelling older adults. *Int J Clin Pharm* 2020; 42: 598–603.

101. Brunetti E, Aurucci ML, Boietti E, *et al.* Clinical implications of potentially inappropriate prescribing according to STOPP/START version 2 criteria in older polymorbid patients discharged from geriatric and internal medicine wards: a prospective observational multicenter study. *J Am Med Dir Assoc* 2019; 20: 1476.e1–1476.e10.

102. Rawle MJ, Cooper R, Kuh D, *et al.* Associations between polypharmacy and cognitive and physical capability: a British birth cohort study. *J Am Geriatr Soc* 2018; 66: 916–923.

103. Huang C-H, Umegaki H, Watanabe Y, *et al.* Potentially inappropriate medications according to STOPP-J criteria and risks of hospitalization and mortality in elderly patients receiving home-based medical services. *PLoS ONE* 2019; 14: e0211947.

104. Ma Z, Tong Y, Zhang C, *et al.* Potentially inappropriate medications and potentially prescribing omissions in Chinese older patients: comparison of two versions of STOPP/START. *J Clin Pharm Ther* 2020; 45: 1405–1413.

105. Galvin R, Moriarty F, Cousins G, *et al.* Prevalence of potentially inappropriate prescribing and prescribing omissions in older Irish adults: findings from The Irish LongituDinal Study on Ageing study (TILDA). *Eur J Clin Pharmacol* 2014; 70: 599–606.

106. Ryan C, Teh R, Moyes S, *et al.* Quality of prescribing predicts hospitalisation in octogenarians: life and living in advanced age: a cohort study in New Zealand (LiLACS NZ). *BMC Geriatr* 2019; 19: 357.

107. Dalleur O, Boland B, Losseau C, *et al.* Reduction of potentially inappropriate medications using the STOPP criteria in frail older inpatients: a randomised controlled study. *Drugs Aging* 2014; 31: 291–298.

108. Ubeda A, Ferrándiz L, Maicas N, *et al.* Potentially inappropriate prescribing in institutionalised older patients in Spain: the STOPP-START criteria compared with the Beers criteria. *Pharm Pract* 2012; 10: 83–91.

109. Projovic I, Vukadinovic D, Milovanovic O, *et al.* Risk factors for potentially inappropriate

prescribing to older patients in primary care. *Eur J Clin Pharmacol* 2016; 72: 93–107.

110. Hill-Taylor B, Sketris I, Hayden J, *et al.* Application of the STOPP/START criteria: a systematic review of the prevalence of potentially inappropriate prescribing in older adults, and evidence of clinical, humanistic and economic impact. *J Clin Pharm Ther* 2013; 38: 360–372.

111. Spinewine A, Schmader KE, Barber N, *et al.* Appropriate prescribing in elderly people: how well can it be measured and optimised? *Lancet* 2007; 370: 173–184.

112. Hanlon JT, Schmader KE, Samsa GP, *et al.* A method for assessing drug therapy appropriateness. *J Clin Epidemiol* 1992; 45: 1045–1051.

113. Kaufmann CP, Tremp R, Hersberger KE, *et al.* Inappropriate prescribing: a systematic overview of published assessment tools. *Eur J Clin Pharmacol* 2014; 70: 1–11.

114. Motter FR, Fritzen JS, Hilmer SN, *et al.* Potentially inappropriate medication in the elderly: a systematic review of validated explicit criteria. *Eur J Clin Pharmacol* 2018; 74: 679–700.

115. Lee G, Lim JF, Page AT, *et al.* Applicability of explicit potentially inappropriate medication lists to the Australian context: a systematic review. *Australas J Ageing*. Epub ahead of print 13 January 2022. DOI: 10.1111/ajag.13038.

116. Fick DM, Semla TP, Steinman M, *et al.* American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2019; 67: 674–694.

117. O'Mahony D, O'Sullivan D, Byrne S, *et al.* STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing* 2014; 44: 213–218.

118. Chang C-B, Lai H-Y, Yang S-Y, *et al.* Patient- and clinic visit-related factors associated with potentially inappropriate medication use among older home healthcare service recipients. *PLoS ONE* 2014; 9: e94350.

119. Muhlack DC, Hoppe LK, Saum KU, *et al.* Investigation of a possible association of potentially inappropriate medication for older adults and frailty in a prospective cohort study from Germany. *Age Ageing* 2019; 49: 20–25.

120. Blanco-Reina E, Valdellós J, Aguilar-Cano L, *et al.* 2015 Beers Criteria and STOPP v2 for detecting potentially inappropriate medication in community-dwelling older people: prevalence, profile, and risk factors. *Eur J Clin Pharmacol* 2019; 75: 1459–1466.

121. Novaes PH, da Cruz DT, Lucchetti ALG, *et al.* Comparison of four criteria for potentially inappropriate medications in Brazilian community-dwelling older adults. *Geriatr Gerontol Int* 2017; 17: 1628–1635.

122. He D, Zhu H, Zhou H, *et al.* Potentially inappropriate medications in Chinese older adults: a comparison of two updated Beers criteria. *Int J Clin Pharm* 2021; 43: 229–235.

123. Johansen JS, Halvorsen KH, Svendsen K, *et al.* The impact of hospitalisation to geriatric wards on the use of medications and potentially inappropriate medications – a health register study. *BMC Geriatr* 2020; 20: 190.

124. Tosato M, Landi F, Martone AM, *et al.* Potentially inappropriate drug use among hospitalised older adults: results from the CRIME study. *Age Ageing* 2014; 43: 767–773.

125. Lopez-Rodriguez JA, Rogero-Blanco E, Aza-Pascual-Salcedo M, *et al.* Potentially inappropriate prescriptions according to explicit and implicit criteria in patients with multimorbidity and polypharmacy. MULTIPAP: a cross-sectional study. *PLoS ONE* 2020; 15: e0237186.

126. Alhmoud E, Khalifa S and Bahi AA. Prevalence and predictors of potentially inappropriate medications among home care elderly patients in Qatar. *Int J Clin Pharm* 2015; 37: 815–821.

127. Patel R, Zhu L, Sohal D, *et al.* Use of 2015 Beers criteria medications by older Medicare beneficiaries. *Consult Pharm* 2018; 33: 48–54.

128. Li Y, Hu J, Gao Y-Z, *et al.* Prevalence and determinants of potentially inappropriate medications prescribing in elderly patients in Chinese communities. *Ann Palliat Med* 2021; 10: 2072–2079.

129. Cahir C, Bennett K, Teljeur C, *et al.* Potentially inappropriate prescribing and adverse health outcomes in community dwelling older patients. *Br J Clin Pharmacol* 2014; 77: 201–210.

130. Magalhães MS, Santos FSD and Reis AMM. Factors associated with the use of potentially inappropriate medication by elderly patients prescribed at hospital discharge. *Einstein* 2019; 18: eAO4877.

131. Ni Chroinin D, Neto HM, Xiao D, *et al.* Potentially inappropriate medications (PIMs) in older hospital in-patients: prevalence,

contribution to hospital admission and documentation of rationale for continuation. *Australas J Ageing* 2016; 35: 262–265.

132. Wahab MS, Nyfort-Hansen K and Kowalski SR. Inappropriate prescribing in hospitalised Australian elderly as determined by the STOPP criteria. *Int J Clin Pharm* 2012; 34: 855–862.

133. Sharma R, Bansal P, Garg R, *et al*. Prevalence of potentially inappropriate medication and its correlates in elderly hospitalized patients: a cross-sectional study based on Beers criteria. *J Family Community Med* 2020; 27: 200–207.

134. Skaar DD and O'Connor H. Using the Beers criteria to identify potentially inappropriate medication use by older adult dental patients. *J Am Dent Assoc* 2017; 148: 298–307.

135. Holmes HM, Luo R, Kuo YF, *et al*. Association of potentially inappropriate medication use with patient and prescriber characteristics in Medicare Part D. *Pharmacoepidemiol Drug Saf* 2013; 22: 728–734.

136. Parodi López N, Villán Villán YF, Granados Menéndez MI, *et al*. Potentially inappropriate prescribing in patients over 65 years-old in a primary care health centre. *Aten Primaria* 2014; 46: 290–297.

137. Maio V, Yuen EJ, Novielli K, *et al*. Potentially inappropriate medication prescribing for elderly outpatients in Emilia Romagna, Italy: a population-based cohort study. *Drugs Aging* 2006; 23: 915–924.

138. Morgan SG, Weymann D, Pratt B, *et al*. Sex differences in the risk of receiving potentially inappropriate prescriptions among older adults. *Age Ageing* 2016; 45: 535–542.

139. Al-Azayzih A, Alamoori R and Altawalbeh SM. Potentially inappropriate medications prescribing according to Beers criteria among elderly outpatients in Jordan: a cross sectional study. *Pharm Pract* 2019; 17: 1439.

140. Saboor M, Kamrani A-AA, Momtaz YA, *et al*. Prevalence and associated factors of potentially inappropriate medications among Iranian older adults. *Med Glas* 2019; 16: 121–127.

141. Miller GE, Sarpong EM, Davidoff AJ, *et al*. Determinants of potentially inappropriate medication use among community-dwelling older adults. *Health Serv Res* 2017; 52: 1534–1549.

142. Nishtala PS, Bagge ML, Campbell AJ, *et al*. Potentially inappropriate medicines in a cohort of community-dwelling older people in New Zealand. *Geriatr Gerontol Int* 2014; 14: 89–93.

143. Bradley MC, Fahey T, Cahir C, *et al*. Potentially inappropriate prescribing and cost outcomes for older people: a cross-sectional study using the Northern Ireland Enhanced Prescribing Database. *Eur J Clin Pharmacol* 2012; 68: 1425–1433.

144. Lau DT, Kasper JD, Potter DE, *et al*. Potentially inappropriate medication prescriptions among elderly nursing home residents: their scope and associated resident and facility characteristics. *Health Serv Res* 2004; 39: 1257–1276.

145. Shade M, Berger AM and Chaperon C. State of the science on potentially inappropriate medications in community-dwelling older adults. *West J Nurs Res* 2014; 36: 1380–1381.

146. Hyttinen V, Jyrkkä J, Saastamoinen LK, *et al*. Patient- and health care-related factors associated with initiation of potentially inappropriate medication in community-dwelling older persons. *Basic Clin Pharmacol Toxicol* 2019; 124: 74–83.

147. Bongue B, Naudin F, Laroche ML, *et al*. Trends of the potentially inappropriate medication consumption over 10 years in older adults in the East of France. *Pharmacoepidemiol Drug Saf* 2009; 18: 1125–1133.

148. Price SD, Holman CD, Sanfilippo FM, *et al*. Are older Western Australians exposed to potentially inappropriate medications according to the Beers criteria? A 13-year prevalence study. *Australas J Ageing* 2014; 33: E39–E48.

149. Chang CB, Lai HY, Hwang SJ, *et al*. The updated PIM-Taiwan criteria: a list of potentially inappropriate medications in older people. *Ther Adv Chronic Dis* 2019; 10: 2040622319879602.

150. Andersen CU, Lassen PO, Usman HQ, *et al*. Prevalence of medication-related falls in 200 consecutive elderly patients with hip fractures: a cross-sectional study. *BMC Geriatr* 2020; 20: 121.

151. Hamilton H, Gallagher P, Ryan C, *et al*. Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients. *Arch Intern Med* 2011; 171: 1013–1019.

152. Bolina AF, Gomes NC, Marchiori GF, *et al*. Potentially inappropriate medication use and frailty phenotype among community-dwelling

older adults: a population-based study. *J Clin Nurs* 2019; 28: 3914–3922.

153. Akkawi ME, Nik Mohamed MH and Md Aris MA. Does inappropriate prescribing affect elderly patients' quality of life? A study from a Malaysian tertiary hospital. *Qual Life Res* 2019; 28: 1913–1920.

154. Hyttinen V, Jyrkkä J, Saastamoinen LK, *et al.* The association of potentially inappropriate medication use on health outcomes and hospital costs in community-dwelling older persons: a longitudinal 12-year study. *Eur J Health Econ* 2019; 20: 233–243.

155. Endres HG, Kaufmann-Kolle P, Steeb V, *et al.* Association between potentially inappropriate medication (PIM) use and risk of hospitalization in older adults: an observational study based on routine data comparing PIM use with use of PIM alternatives. *PLoS ONE* 2016; 11: e0146811.

156. Chu H-Y, Chen C-C and Cheng S-H. Continuity of care, potentially inappropriate medication, and health care outcomes among the elderly: evidence from a longitudinal analysis in Taiwan. *Med Care* 2012; 50: 1002–1009.

157. Moriarty F, Cahir C, Bennett K, *et al.* Potentially inappropriate prescribing and its association with health outcomes in middle-aged people: a prospective cohort study in Ireland. *BMJ Open* 2017; 7: e016562.

158. Berdot S, Bertrand M, Dartigues J-F, *et al.* Inappropriate medication use and risk of falls – a prospective study in a large community-dwelling elderly cohort. *BMC Geriatr* 2009; 9: 30.

159. Muhlack DC, Hoppe LK, Stock C, *et al.* The associations of geriatric syndromes and other patient characteristics with the current and future use of potentially inappropriate medications in a large cohort study. *Eur J Clin Pharmacol* 2018; 74: 1633–1644.