Review Article

Adverse Outcomes of Polypharmacy in Older People: Systematic Review of Reviews

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A B S T R A C T

Objective: Polypharmacy is widespread among older people, but the adverse outcomes associated with it are unclear. We aim to synthesize current evidence on the adverse health, social, medicines management, and health care utilization outcomes of polypharmacy in older people.
Design: A systematic review, of systematic reviews and meta-analyses of observational studies, was conducted. Eleven bibliographic databases were searched from 1990 to February 2018. Quality was assessed using AMSTAR (A Measurement Tool to Assess Systematic Reviews).
Setting and participants: Older people in any health care setting, residential setting, or country.
Results: Twenty-six reviews reporting on 230 unique studies were included. Almost all reviews operationalized polypharmacy as medication count, and few examined medication classes or disease states within this. Evidence for an association between polypharmacy and many adverse outcomes, including adverse drug events and disability, was conflicting. The most consistent evidence was found for hospitalization and inappropriate prescribing. No research had explored polypharmacy in the very old (aged ≥85 years), or examined the potential social consequences associated with medication use, such as loneliness and isolation.
Conclusions and implications: The literature examining the adverse outcomes of polypharmacy in older people is complex, extensive, and conflicting. Until polypharmacy is operationalized in a more clinically relevant manner, the adverse outcomes associated with it will not be fully understood. Future studies should work toward this approach in the face of rising multimorbidity and population aging.

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Polypharmacy describes the situation where multiple medications are prescribed for an individual, and it is most commonly defined as the concomitant use of 5 or more medicines.[1,2] Polypharmacy among older people has become more common in recent years[3,4] because of disease-specific prescribing guidelines,[5–7] rising levels of multimorbidity due to population ageing,[7,8] and a lack of evidence to support deprescribing approaches.[9] Indeed, the proportion of older people taking 10 or more medicines—so-called hyper-polypharmacy—more than tripled between 1995 (4.9%) and 2010 (17.2%).[3]

Polypharmacy in older people may be appropriate[7] but it also has potential negative effects including reduced adherence, adverse drug events, increased health care utilization, falls, cognitive impairment, and mortality.[10,11] The literature relating to polypharmacy has expanded over the past 2 decades, with many groups exploring its adverse outcomes through systematic review.[12–14] Despite this progress and the growing literature base, the data relating to the spectrum of polypharmacy-related adverse effects is conflicting in people aged ≥65 years, and even less clearly defined in the very old (aged ≥85 years), or across a range of health care and residential settings. This is problematic as the very old are the fastest-growing section of the population[15,16] whose needs have the potential to reshape clinical practice. In addition, polypharmacy is likely to generate more adverse outcomes for older people, especially when combined with functional decline, rising levels of multimorbidity, and frailty.[17]

It is, therefore, timely that we establish the consequences of polypharmacy in older people, so as to identify and target interventions that may optimize prescribing-related outcomes in later life. The aim of this study was to synthesize evidence from existing systematic reviews on the adverse outcomes of polypharmacy in older people.

Methods

Protocol, Registration, and Study Design

To meet our aim, we employed a systematic review of systematic reviews approach. This methodology builds a comprehensive picture of a broad topic to inform policy, practice, patients, and the public.

The protocol for this review was registered with PROSPERO (registration number: CRD42018088949). A PRISMA statement is also included within the Supplementary Material 1.

Search Strategy

Eleven bibliographic databases were searched from 1990[18,19] to February 2018 without language, setting, or geographical restrictions (Supplementary Material 2). These included Database of Abstracts of Reviews of Effects (DARE), Cochrane Database of Systematic Reviews (CDSR), Health Technology Assessment Database (HTA), MEDLINE, EMBASE, CINAHL, PsycINFO, Epistemonikos, PubMed, Scopus, and Web of Science (SCI-Expanded, SSCI, CPCI-S, CPCI-SSH, ESCI). Gray literature was searched via Google Scholar (first 300 results),[20] TRIP, NICE Evidence Search, and PROSPERO to reduce publication bias. Key journals along with reference lists of included reviews were hand-searched, and topic experts contacted to inquire about ongoing studies. Titles and abstracts were screened by 1 reviewer (L.E.D.), and a random sample of 10% screened by a second reviewer (G.S.). The full texts of potentially relevant papers were then examined independently by the 2 reviewers (L.E.D. and G.S.) and discrepancies resolved through discussion.

Selection Criteria

Following standard evidence synthesis approaches, the inclusion criteria for this review were determined a priori in terms of PICOS (Population, Intervention, Comparison, Outcome and Study Design).

Population: older people from any health care or residential setting. For the purposes of this review, we defined older people as 80% aged ≥55 years, or stratified data for the ≥55-year age group.

Intervention: polypharmacy (multiple medicines).[2]

Comparison: none.

Outcome: adverse health (eg, disability), social (eg, loneliness), medicines management (eg, nonadherence) or health care utilization outcomes (eg, hospital admission) of polypharmacy.

Study design: systematic reviews and/or meta-analyses of observational studies.

We excluded records that did not meet the quality standard (≥4 DARE criteria),[21–23] did not consider the concept of polypharmacy, did not relate adverse outcomes to polypharmacy, were not in older people, or did not include observational studies. Irretrievable full texts and randomized controlled trials or intervention studies were also excluded.

Data Extraction

Information from eligible reviews was extracted by 1 reviewer (L.E.D.) using a bespoke form adapted from the Cochrane Collaboration[24] (Supplementary Material 3) and a random sample of 10% extracted by a second reviewer (G.S.). Extracted items included the following: (1) first author, year of publication, search restrictions, and databases searched; (2) aim and review type; (3) primary study design, setting, country, participant characteristics, and measures of polypharmacy; and (4) outcomes, statistics, number of primary studies, and number of participants (Supplementary Material 4). Reviews were grouped under the adverse health, social, medicines management, and health care utilization outcomes of polypharmacy, with adverse health outcomes further categorized under geriatric syndrome subheadings[25,26] to help detect patterns in the data.[27]

Quality Assessment

Quality assessment was performed independently by 2 reviewers (L.E.D. and G.S.) using AMSTAR, and consensus reached through discussion.[28] Included reviews had a median quality score of 4 (range 2-6). Overall scores were presented under the categories of low (0-3), medium (4-7), or high quality (8-11), alongside individual item scores (Supplementary Material 5).[29] No records were excluded following quality assessment in order to present the evidence in context.

Overlapping Primary Studies

Reviews with overlapping primary studies were removed[30] to avoid bias from double counting[22,31] and provide a complete picture of the relevant evidence from which to examine conflicting findings.[32] If 2 or more reviews considered the same adverse outcome(s) from different primary studies, all outcomes were reported. However, if 2 or more reviews considered the same adverse outcome(s) from the same primary studies, we selected the most recent review.[33] If this had low AMSTAR quality, we proceeded to earlier review if it was of higher AMSTAR quality and published within 5 years of the first.[31] If the excluded review reported additional adverse outcome(s) from unique primary studies, these data were still reported so as to capture all relevant evidence. When updated systematic reviews were encountered, only the most recent review was included. The degree of overlap was also presented using the Corrected Coverage Area Index (5.00%).[34]

Data Synthesis

The adverse health, social, medicines management, and health care utilization outcomes from each included review were presented narratively with accompanying summary of evidence tables,[18,22] forest plots, and harvest plots (Supplementary Materials 6-9). Summary of evidence tables were annotated with the review number and AMSTAR quality score.[22] Forest plots were ordered by effect size to highlight the strength of associations and aid the detection of heterogeneity.[35] Outcomes were reported dependent on analytical technique. Odds ratio, hazard ratio, relative risk, and β-coefficients (95% confidence interval) were presented when single outcomes were reported per review. When multiple results for the same adverse outcomes were reported within the same review, the range of these metrics was presented as a means to summarize the unsynthesized heterogeneous information.

Harvest plots were used to highlight patterns, research gaps, and publication bias within the narrative data, and reduce quantitative bias.[36,37] The height of each bar is proportional to the AMSTAR score, with the number of primary studies and combined sample size overlaid above to address discordance. These results were plotted under categories of "no evidence," "inverse association," and "positive effect" to avoid vote counting and value judgments.[38]

Both forest plots and harvest plots were annotated with the type of observational study design per outcome, to highlight temporal relationships.
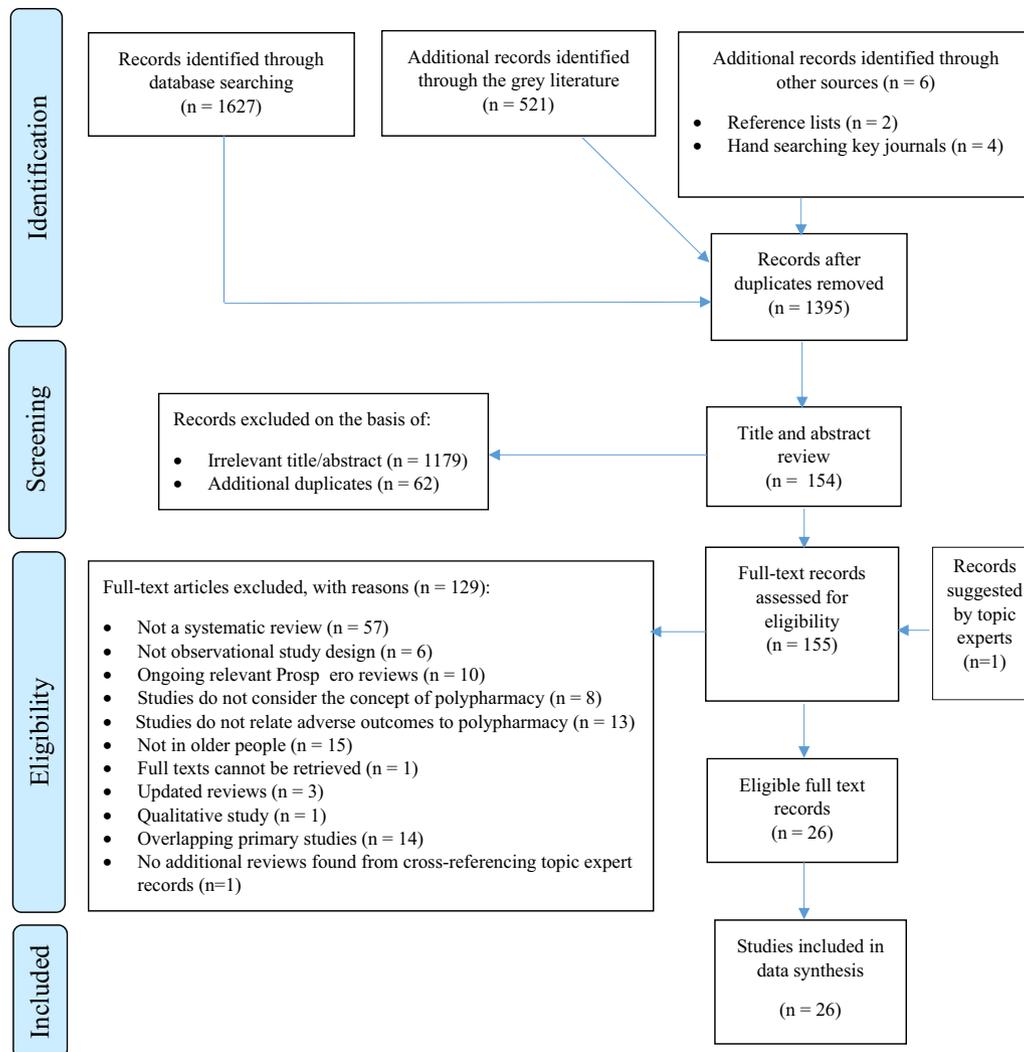
Fig. 1. PRISMA flow diagram of study selection.

Patient and Public Involvement (PPI)

Six members of the Newcastle University–supported public and patient engagement organization VOICE (Valuing Our Intellectual Capital and Experience) with experience of polypharmacy discussed the implications of this work in a specifically convened meeting.

Results

Study Selection and Characteristics

Twenty-six reviews reporting on 230 unique studies from North America, Europe, Asia, and Australia, published between 2002 and 2018, were included (Figure 1). Five reviews[12–14,39,40] had a distinct polypharmacy focus and 21 contributed relevant data. These 5 reviews operationalized polypharmacy as medication count, and only 1 adequately examined medication classes within this.[39] Four reviews focused on specific conditions—cancer, chronic kidney disease, dementia, and Parkinson's disease[41–44]—and 2 specific countries.[45,46] Eleven reviews also reported the adverse outcomes associated with specific medication classes,[42,44,47–55] but synthesis of this data was beyond the scope of this review. Sample sizes ranged from 51 to more than 90,000, and participants were aged from 16 to 108 years. Studies were included from community,[12,41,46,56,57] hospital,[47,52–54,58–60] long-term care facilities,[39,51,55,61] home care,[49] or a mixture of settings.[13,40,42–45,48,50] In 1 review, setting was not reported.[14] Most reviews included studies of cross-sectional and longitudinal design (Supplementary Material 4). Outcomes considered included adverse health (n = 16), health care utilization (n = 11), medicines management (n = 7), and social consequences of polypharmacy (n = 1). Eighteen reviews[40–48,51,52,54–59,61] reported 1 adverse outcome of polypharmacy and 8 reported multiple outcomes.[12–14,39,49,50,53,60]

Summary of Evidence Tables, Forest Plots, and Harvest Plots

Adverse Health Outcomes

Figure 2 summarizes the evidence for the adverse health outcomes of polypharmacy, with more detailed information found within forest plots and harvest plots (Supplementary Material 6). Positive associations were found for frailty, malnutrition, and selected chronic disease areas. However, the evidence for adverse drug events, adverse drug reactions, depression, cognitive impairment, falls, fractures, weight loss, functional decline, disability, and mortality was conflicting.

Adverse Social Outcomes

Evidence for the adverse social outcomes of polypharmacy was sparse. One review reported a negative association between

Adverse outcome	No association	Mixed evidence	Negative association	Positive association
Adverse drug events		52 Δ, 12 □		13 ‡, 53 Δ, 49 ‡
Adverse drug reactions		12 □		39 ‡
Anxiety				51 ‡
BMI	39 ‡			
Circulatory diseases				39 ‡
Cognitive impairment		12 □	39 ‡	14 ‡
Delirium		58 □		47 Δ
Depression		39 ‡		12 □ *
Disability and functional decline		39 ‡, 12 □		49 ‡, 13 ‡, 59 ‡
Dizziness		12 □		39 ‡
Dry mouth				50 □
Endocrine and metabolic disorders				39 ‡
Falls	42 ‡			48 Δ
Fear of falling		12 □		
Fractures		12 □		
Frailty				12 Δ **, 49 ‡
Gastrointestinal symptoms				39 ‡, 12 □
Genitourinary disorders				39 ‡, 14 ‡
Impaired balance				12 Δ
Malnutrition				13 ‡, 12 Δ
Mortality		60 □		40 Δ
Multimorbidity		39 ‡		49 ‡
Pain				39 ‡
Pressure ulcers	39 ‡			
Pulmonary diseases				39 ‡
Self-perceived health status				12 □
Weight loss	39 ‡			12 Δ

Δ = quantitative data only   □ = quantitative and narrative data   ‡ = narrative data only   * = women only   * = men only**

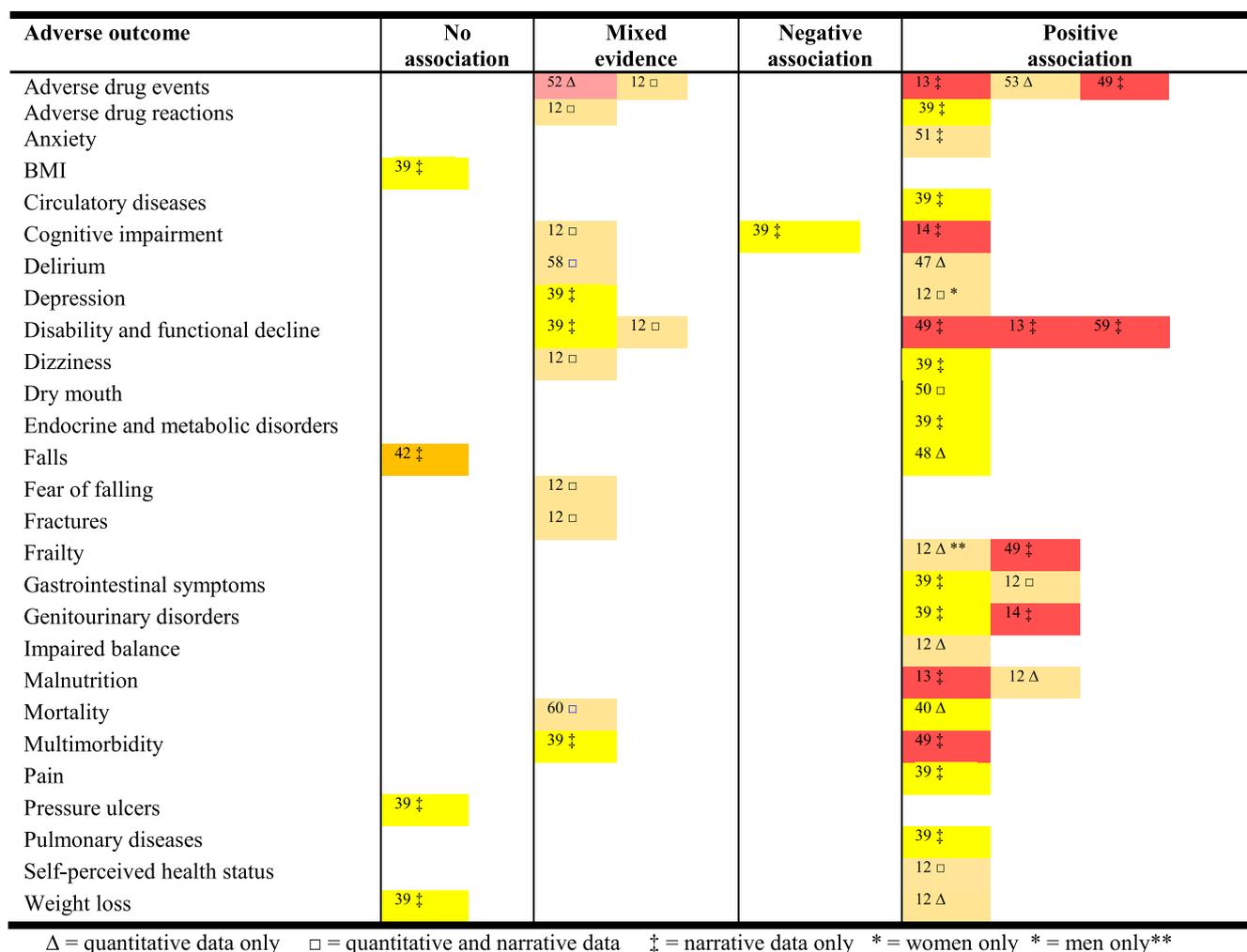| AMSTAR Score 2	AMSTAR Score 3	AMSTAR Score 4	AMSTAR Score 5	AMSTAR Score 6

Fig. 2. Summary of evidence for the adverse health outcomes of polypharmacy. The numbers in the figure refer to the numbered cited literature.

polypharmacy and physical activity participation in dementia (Supplementary Material 7).[41] No other potential social consequences such as loneliness or isolation were reported.

Adverse Medicines Management Outcomes

Medicines management describes the safe and effective use of medicines by patients and the NHS in terms of prescribing, dispensing, and administration. In this domain, 5 reviews[13,43,46,49,61] reported associations between polypharmacy and "service provider issues" such as inappropriate prescribing. Three[13,44,45] reported "patient issues" such as nonadherence to medications (Figure 3 and Supplementary Material 8).

Adverse Health Care Utilization Outcomes

Polypharmacy was associated with many adverse health care utilization outcomes including hospitalization, unplanned admissions, and the number of prescribers (Figure 4 and Supplementary Material 9). However, the evidence for length of stay[39,60] and nursing home placement[57,60] was conflicting.

Discussion

Principal Findings

This review identified an extensive literature of conflicting evidence for the association between polypharmacy and many adverse outcomes including adverse drug reactions, adverse drug events, and disability. A majority of reviews operationalized polypharmacy as medication count, and of those that specifically focused on polypharmacy,[12–14,39,40] few adequately examined medication classes or comorbidities.[39] We identified a dearth of research exploring the harms of polypharmacy in the very old (aged ≥85 years) and the potential social consequences associated with it.

Comparison With Other Work

Our review identified many adverse outcomes of polypharmacy in older people, in keeping with policy initiatives.[62,63,64] However in contrast to previous work,[65,66] the evidence for an association with adverse drug reactions and adverse drug events was conflicting, which may reflect differences in appropriate vs inappropriate
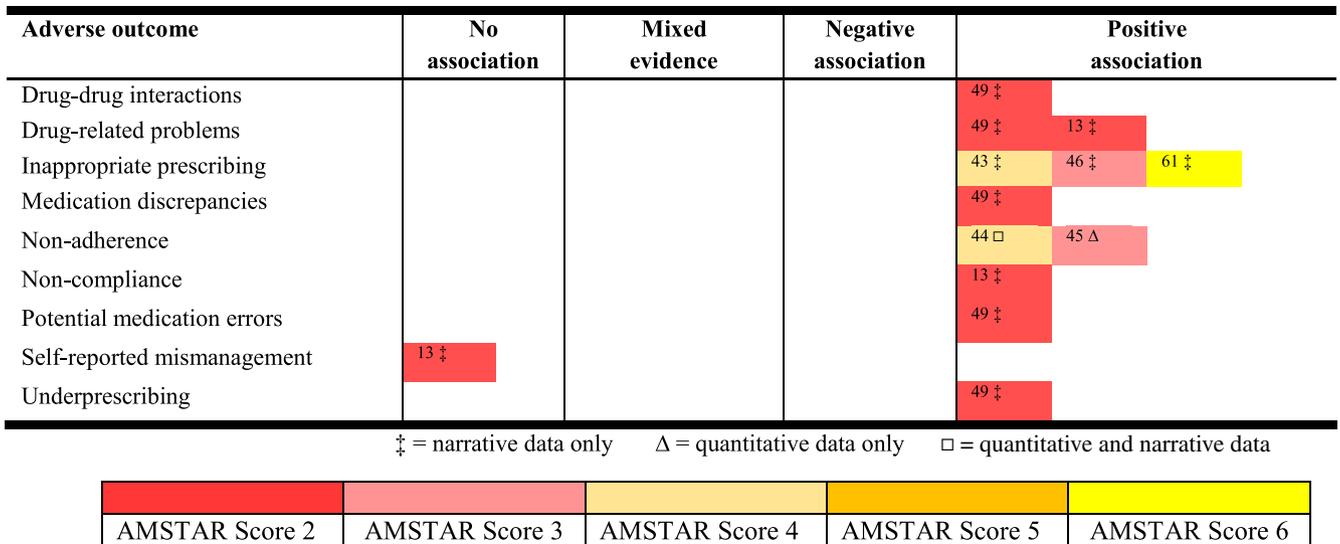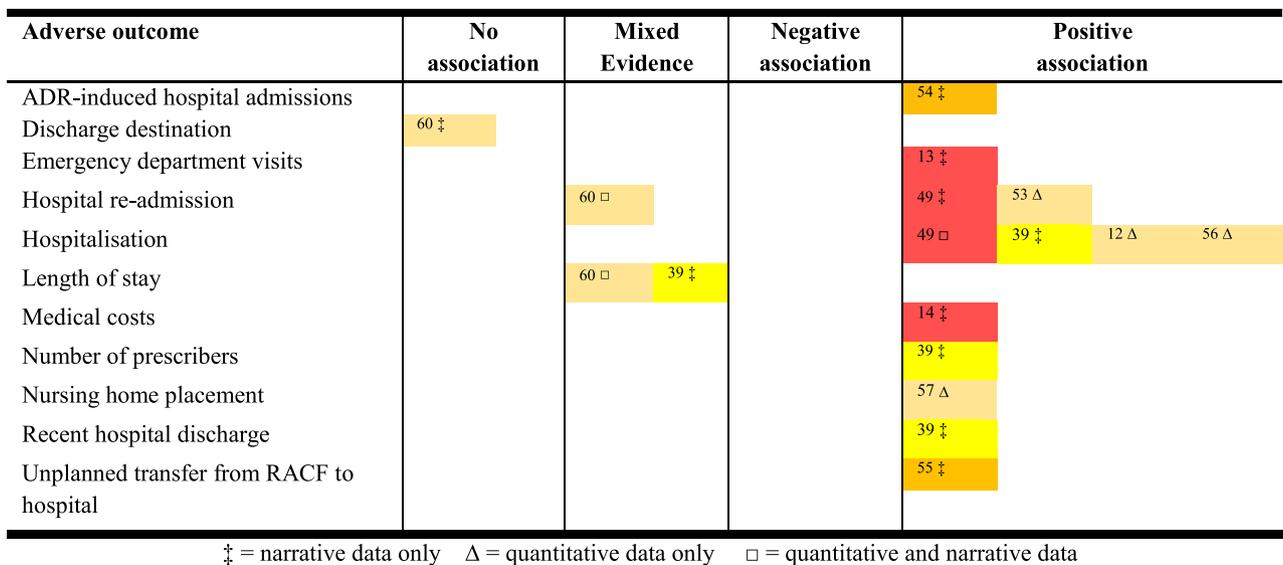
Fig. 3. Summary of evidence for the adverse medicines management outcomes of polypharmacy. The numbers in the figure refer to the numbered cited literature.

polypharmacy within the primary studies.[7,67] The mixed picture surrounding disability and functional decline is unsurprising, given the lack of international consensus on their definition and measurement.[68] The evidence gap for the adverse social outcomes of polypharmacy can be explained by the limited primary research in this area,[69,70] despite plausible pathways. For example, polypharmacy may lead to loneliness and social isolation through cumulative side effects that limit the ability to interact, such as impaired balance.[12]

Many of the associations between polypharmacy and symptoms or diseases can be explained by the prevalence of different conditions in later life and established patterns of prescribing. Circulatory, pulmonary, and endocrine diseases[39] are, for example,

commonly found in multimorbidity clusters in the very old.[71] Other associations are more likely to reflect inappropriate prescribing. Polypharmacy among residents of aged care facilities with anxiety[51] may be due to anxiolytic and hypnotic prescribing, for example. We identified many adverse medicines management outcomes of polypharmacy, notably, the association between polypharmacy and inappropriate prescribing in chronic kidney disease.[43] The association between polypharmacy and an increased risk of malnutrition[12,13] is in keeping with a recent literature review, with several drug classes implicated in drug-nutrient interactions.[72] The unclear evidence for body mass index and weight loss may also suggest that malnutrition is a hidden problem among

Fig. 4. Summary of evidence for the adverse health care utilization outcomes of polypharmacy. The numbers in the figure refer to the numbered cited literature. ADR, adverse drug reaction; RACF, residential aged care facility.

older people taking multiple medications. Polypharmacy and frailty[12,49] have been highlighted in recent UK clinical guidance,[73] but the pathogenesis of this relationship is unclear,[74] and we could not determine how polypharmacy or specific drug classes may influence frailty transitions. Our results appear to support the widely held belief that polypharmacy is associated with admissions to hospital, particularly unscheduled, and the number of prescribers. However, the association between polypharmacy and nursing home placement is unclear, and we could not determine whether this conflicting evidence is related to long-term stays or short-term admissions after hospital discharge.[57,60] We found more evidence supporting an association between polypharmacy and mortality than not, with meta-analytic associations increasing with medication count.[40,60] However, confounding factors such as health inequalities and specific anticholinergic medications may have influenced this association.[75,76]

Strengths and Limitations

This was a comprehensive review, produced using established methods.[18,19,22,77] The use of data from observational studies allowed us to explore the adverse outcomes of polypharmacy in "real world" scenarios, and over longer time scales than is possible in randomized controlled trials. Adverse outcomes were grouped in a novel matrix and presented graphically to clearly communicate complex information.[38,78,79] PPI viewpoints helped to shape the interpretation of the findings.

However, despite these strengths, we acknowledge that this work has a number of limitations. First, as this was a review of reviews, we did not search for, extract from, or assess the quality of the original primary studies. Instead, we relied on information provided by the authors of the included systematic reviews, but acknowledge that reporting varied in style and quality. Most reviews operationalized polypharmacy as multiple medicines, so we could not draw the distinction between appropriate and inappropriate prescribing in terms of medication classes, indications, doses, and durations. The measurement of polypharmacy through different numerical cut-points also could have led to variable effect sizes. All observational studies may be liable to confounding, and this is a particular concern in reviews where polypharmacy was not the main focus. Because of the challenges of residual confounding and collinearity, polypharmacy could also be a proxy for morbidity. A number of the reviews included cross-sectional studies that provide no information on the direction of any associations. Their inclusion is justified by our intention to produce a review of reviews that could be a useful platform for further longitudinal research to inform prescribing decisions. Several outcomes also came from a small number of primary studies but were reported in line with our review protocol. The influence of gender and socioeconomic position on the adverse outcomes of polypharmacy were also seldom studied. Lastly, the use of inconsistent or unclear measurement instruments for outcomes such as disability, cognitive impairment, and depression reflects international variation, and limited cross-study comparison.

Conclusions and Implications

The literature examining the adverse outcomes of polypharmacy in older people is complex, extensive, and conflicting. The majority of studies used medication counting as a way of assessing polypharmacy, which has the potential to aggregate very different medication and disease profiles. Future work should seek to operationalize polypharmacy in a more clinically relevant manner lest the adverse outcomes associated with it, and deprescribing strategies, will not be fully understood. At the very minimum, future studies of polypharmacy

should report medication classes and comorbidities to help untangle conflicting associations and identify the medication and disease clusters with the greatest risk of adverse outcomes. With this approach, researchers should investigate medication utilization outcomes in the very old (aged ≥85 years). Doing so is imperative in the face of rising multimorbidity and population aging.

Supplementary Data

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.jamda.2019.10.022.

References

1. 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.
2. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr 2017;17:230.
3. Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: Population database analysis 1995–2010. BMC Med 2015;13:74.
4. Melzer D, Tavakoly B, Winder RE, et al. Much more medicine for the oldest old: Trends in UK electronic clinical records. Age Ageing 2015;44:46–53.
5. Smith SM, Soubhi H, Fortin M, et al. Managing patients with multimorbidity: Systematic review of interventions in primary care and community settings. BMJ 2012;345:e5205.
6. Hughes LD, McMurdo MET, Guthrie B. Guidelines for people not for diseases: The challenges of applying UK clinical guidelines to people with multimorbidity. Age Ageing 2013;42:62–69.
7. Duerden AT, Payne R. Polypharmacy and Medicines Optimisation. Making It Safe and Sound. London: The King's Fund; 2013.
8. 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.
9. Ailabouni NJ, Nishtala PS, Mangin D, Tordoff JM. Challenges and enablers of deprescribing: A general practitioner perspective. PLoS One 2016;11:e0151066.
10. Hilmer SN, Gnjidic D. The effects of polypharmacy in older adults. Clin Pharmacol Ther 2009;85:86–88.
11. Maher RL, Hanlon JT, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf 2014;13:57–65.
12. Fried T, O'Leary J, Towle V, et al. Health outcomes associated with polypharmacy in community-dwelling older adults: A systematic review. J Am Geriatr Soc 2014;62:2261–2272.
13. Frazier SC. Health outcomes and polypharmacy in elderly individuals: An integrated literature review. J Gerontol Nurs 2005;31:4–11.
14. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. Am J Geriatr Pharmacother 2007;5:345–351.
15. Office for National Statistics. How the population of England is projected to age; 2016.
16. Collerton J, Davies K, Jagger C, et al. Health and disease in 85 year olds: Baseline findings from the Newcastle 85+ cohort study. BMJ 2009;339:b4904.
17. Gnjidic D, Husband A, Todd A. Challenges and innovations of delivering medicines to older adults. Adv Drug Deliv Rev 2018;135:97–105.
18. Aromataris E, Fernandez R, Godfrey CM, et al. Summarizing systematic reviews: Methodological development, conduct and reporting of an umbrella review approach. Int J Evid Based Healthc 2015;13:132–140.
19. Smith V, Devane D, Begley CM, Clarke M. Methodology in conducting a systematic review of systematic reviews of healthcare interventions. BMC Med Res Methodol 2011;11:15.
20. Haddaway NR, Collins AM, Coughlin D, Kirk S. The role of Google Scholar in evidence reviews and its applicability to grey literature searching. PLoS One 2015;10:e0138237.
21. University of York. Database of Abstracts of Reviews of Effects (DARE): Quality-assessed reviews 2014. Available at: https://www.ncbi.nlm.nih.gov/books/NBK285222/. Accessed January 19, 2018.
22. Pollock A, Campbell P, Brunton G, et al. Selecting and implementing overview methods: Implications from five exemplar overviews. Syst Rev 2017;6:145.

23. Pussegoda K, Turner L, Garritty C, et al. Systematic review adherence to methodological or reporting quality. Syst Rev 2017;6:131.
24. The Cochrane Collaboration. Data Collection Form for Intervention Reviews: RCTs and Non-RCTs. Version 3. London: The Cochrane Collaboration; 2014.
25. Olde Rikkert MG. Conceptualizing geriatric syndromes. In: Michel J, Beattie B, Martin F, et al., editors. Oxford Textbook of Geriatric Medicine. Oxford: Oxford University Press; 2018. p. 355–362.
26. Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric syndromes: Clinical, research and policy implications of a core geriatric concept. J Am Geriatr Soc 2007;55:780–791.
27. Popay J, Roberts H, Sowden A, et al. Guidance on the Conduct of narrative synthesis in systematic Reviews. A product from the ESRC methods programme. Version 1; 2006.
28. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: A measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol 2007;7:10.
29. Shea BJ, Hamel C, Wells GA, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol 2009;62:1013–1020.
30. Lunny C, Brennan SE, McDonald S, McKenzie JE. Toward a comprehensive evidence map of overview of systematic review methods: Paper 1—purpose, eligibility, search and data extraction. Syst Rev 2017;6:231.
31. Pieper D, Antoine S-L, Neugebauer EAM, Eikermann M. Up-to-dateness of reviews is often neglected in overviews: A systematic review. J Clin Epidemiol 2014;67:1302–1308.
32. McKenzie JE, Brennan SE. Overviews of systematic reviews: Great promise, greater challenge. Syst Rev 2017;6:185.
33. Jepson RG, Harris FM, Platt S, Tannahill C. The effectiveness of interventions to change six health behaviours: A review of reviews. BMC Public Health 2010; 10:538.
34. Pieper D, Antoine S-L, Mathes T, et al. Systematic review finds overlapping reviews were not mentioned in every other overview. J Clin Epidemiol 2014; 67:368–375.
35. Schriger DL, Altman DG, Vetter JA, et al. Forest plots in reports of systematic reviews: A cross-sectional study reviewing current practice. Int J Epidemiol 2010;39:421–429.
36. Mark C, Alison A, Graeme M, Graham M. A further use for the harvest plot: A novel method for the presentation of data synthesis. Res Synth Methods 2011; 2:79–83.
37. Ogilvie D, Fayter D, Petticrew M, et al. The harvest plot: A method for synthesising evidence about the differential effects of interventions. BMC Med Res Methodol 2008;8:8.
38. Pieper D, Li L, Buchter R. Avenues for further research. In: Biondi-Zoccai G, editor. Evidence Synthesis With Overviews of Reviews and Meta-epidemiologic Studies. London: Springer International; 2016.
39. Jokanovic N, Tan ECK, Dooley MJ, et al. Prevalence and factors associated with polypharmacy in long-term care facilities: A systematic review. J Am Med Dir Assoc 2015;16:e1–e12.
40. Leelakanok N, Holcombe AL, Lund BC, et al. Association between polypharmacy and death: a systematic review and meta-analysis. J Am Pharm Assoc 2017;57: 729–738.e10.
41. Stubbs B, Eggermont L, Soundy A, et al. What are the factors associated with physical activity (PA) participation in community dwelling adults with dementia? A systematic review of PA correlates. Arch Gerontol Geriatr 2014;59: 195–203.
42. Wildes TM, Dua P, Fowler SA, et al. Systematic review of falls in older adults with cancer. J Geriatr Oncol 2015;6:70–83.
43. Tesfaye W, Castelino R, Wimmer B, Zaidi S. Inappropriate prescribing in chronic kidney disease: A systematic review of prevalence, associated clinical outcomes and impact of interventions. Int J Clin Pract 2017;71:e12960.
44. Daley DJ, Myint PK, Gray RJ, Deane KH. Systematic review on factors associated with medication non-adherence in Parkinson's disease. Parkinsonism Relat Disord 2012;18:1053–1061.
45. Gellad WF, Grenard JL, Marcum ZA. A systematic review of barriers to medication adherence in the elderly: Looking beyond cost and regimen complexity. Am J Geriatr Pharmacother 2011;9:11–23.
46. Tommelein E, Mehuys E, Petrovic M, et al. Potentially inappropriate prescribing in community-dwelling older people across Europe: A systematic literature review. Eur J Clin Pharmacol 2015;71:1415–1427.
47. Ahmed S, Leurent B, Sampson EL. Risk factors for incident delirium among older people in acute hospital medical units: A systematic review and meta-analysis. Age Ageing 2014;43:326–333.
48. Seppala LJ, van de Glind EMM, Daams JG, et al. Fall-risk-increasing drugs: A systematic review and meta-analysis: III. Others. J Am Med Dir Assoc 2018;19: 372.e1–372.e8.
49. Meyer-Massetti C, Meier CR, Guglielmo BJ. The scope of drug-related problems in the home care setting. Int J Clin Pharm 2018;40:325–334.
50. Tan E, Lexomboon D, Sandborgh-Englund G, et al. Medications that cause dry mouth as an adverse effect in older people: A systematic review and meta-analysis. J Am Geriatr Soc 2018;66:76–84.
51. Creighton AS, Davison TE, Kissane DW. The correlates of anxiety among older adults in nursing homes and other residential aged care facilities: A systematic review. Int J Geriatr Psychiatry 2017;32:141–154.
52. Boeker E, Ram K, Klopotowska J, et al. An individual patient data meta-analysis on factors associated with adverse drug events in surgical and non-surgical inpatients. Br J Clin Pharmacol 2015;79:548–557.
53. Morath B, Mayer T, Send AFJ, et al. Risk factors of adverse health outcomes after hospital discharge modifiable by clinical pharmacist interventions: A review with a systematic approach. Br J Clin Pharmacol 2017;83:2163–2178.
54. Oscanoa TJ, Lizaraso F, Carvajal A. Hospital admissions due to adverse drug reactions in the elderly. A meta-analysis. Eur J Clin Pharmacol 2017;73: 759–770.
55. Dwyer R, Stoelwinder J, Gabbe B, Lowthian J. Unplanned transfer to emergency departments for frail elderly residents of aged care facilities: A review of patient and organizational factors. J Am Med Dir Assoc 2015;16:551–562.
56. Wang SY, Shamliyan TA, Talley KM, et al. Not just specific diseases: Systematic review of the association of geriatric syndromes with hospitalization or nursing home admission. Arch Gerontol Geriatr 2013;57:16–26.
57. Luppa M, Luck T, Weyerer S, et al. Prediction of institutionalization in the elderly. A systematic review. Age Ageing 2010;39:31–38.
58. Oh ES, Li M, Fafowora TM, et al. Preoperative risk factors for postoperative delirium following hip fracture repair: A systematic review. Int J Geriatr Psychiatry 2015;30:900–910.
59. McCusker J, Kakuma R, Abrahamowicz M. Predictors of functional decline in hospitalized elderly patients: A systematic review. J Gerontol A Biol Sci Med Sci 2002;57:M569–M577.
60. Campbell S, Seymour D, Primrose W, Project A. A systematic literature review of factors affecting outcome in older medical patients admitted to hospital. Age Ageing 2004;33:110–115.
61. Storms H, Marquet K, Aertgeerts B, Claes N. Prevalence of inappropriate medication use in residential long-term care facilities for the elderly: A systematic review. Eur J Gen Pract 2017;23:69–77.
62. Scottish Government Polypharmacy Model of Care Group. Polypharmacy Guidance. Realistic Prescribing. Edinburgh, UK: Scottish Government; 2018.
63. All Wales Medicines Strategy Group. Polypharmacy: Guidance for Prescribing. Llandough, Wales, UK: All Wales Therapeutics and Toxicology Centre; 2014.
64. National Institute for Health and Care Excellence. Multimorbidity and Polypharmacy. Key Therapeutic Topic [KTT18]. London: National Institute for Health and Care Excellence; 2018.
65. Prybys K, Melville K, Hanna J, et al. Polypharmacy in the elderly: Clinical challenges in emergency practice: Part 1 overview, etiology, and drug interactions. Emerg Med Rep 2002;23:145–153.
66. Field TS, Gurwitz JH, Avorn J, et al. Risk factors for adverse drug events among nursing home residents. Arch Intern Med 2001;161:1629–1634.
67. Burt J, Elmore N, Campbell SM, et al. Developing a measure of polypharmacy appropriateness in primary care: Systematic review and expert consensus study. BMC Med 2018;16:91.
68. Leonardi M, Bickenbach J, Ustun TB, et al. The definition of disability: What is in a name? Lancet 2006;368:1219–1221.
69. Liu BC, Chi I. The moderating effect of medication review on polypharmacy and loneliness in older Chinese adults in primary care. J Am Geriatr Soc 2013;61: 290–292.
70. Wenger C, Davies R, Shahtahmasebi S, Scott A. Social isolation and loneliness in old age: Review and model refinement. Aging Society 1996;16:333–358.
71. Collerton J, Jagger C, Yadegarfar ME, et al. Deconstructing complex multimorbidity in the very old: Findings from the Newcastle 85+ study. Biomed Res Int 2016;2016:8745670.
72. Little MO. Updates in nutrition and polypharmacy. Curr Opin Clin Nutr Metab Care 2018;21:4–9.
73. British Geriatrics Society. Fit for frailty. Part 1: Consensus best practice guidance for the care of older people living in community and outpatient settings. London: British Geriatrics Society; 2017.
74. Bonaga B, Sánchez-Jurado PM, Martínez-Reig M, et al. Frailty, polypharmacy, and health outcomes in older adults: The frailty and dependence in Albacete study. J Am Med Dir Assoc 2018;19:46–52.
75. Schöttker B, Saum K-U, Muhlack DC, et al. Polypharmacy and mortality: New insights from a large cohort of older adults by detection of effect modification by multi-morbidity and comprehensive correction of confounding by indication. Eur J Clin Pharmacol 2017;73:1041–1048.
76. Ruxton K, Woodman RJ, Mangoni AA. Drugs with anticholinergic effects and cognitive impairment, falls and all-cause mortality in older adults: A systematic review and meta-analysis. Br J Clin Pharmacol 2015;80:209–220.
77. Pollock M, Fernandes RM, Becker LA, et al. What guidance is available for researchers conducting overviews of reviews of healthcare interventions? A scoping review and qualitative metasummary. Syst Rev 2016;5:190.
78. Howard W. Understanding graphs and tables. ETS Res Rep Series 1992;1992: 4–20.
79. Schild A, Voracek M. Less is less: A systematic review of graph use in meta-analyses. Res Synth Methods 2013;4:209–219.