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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 hyperpolypharmacy—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]

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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.

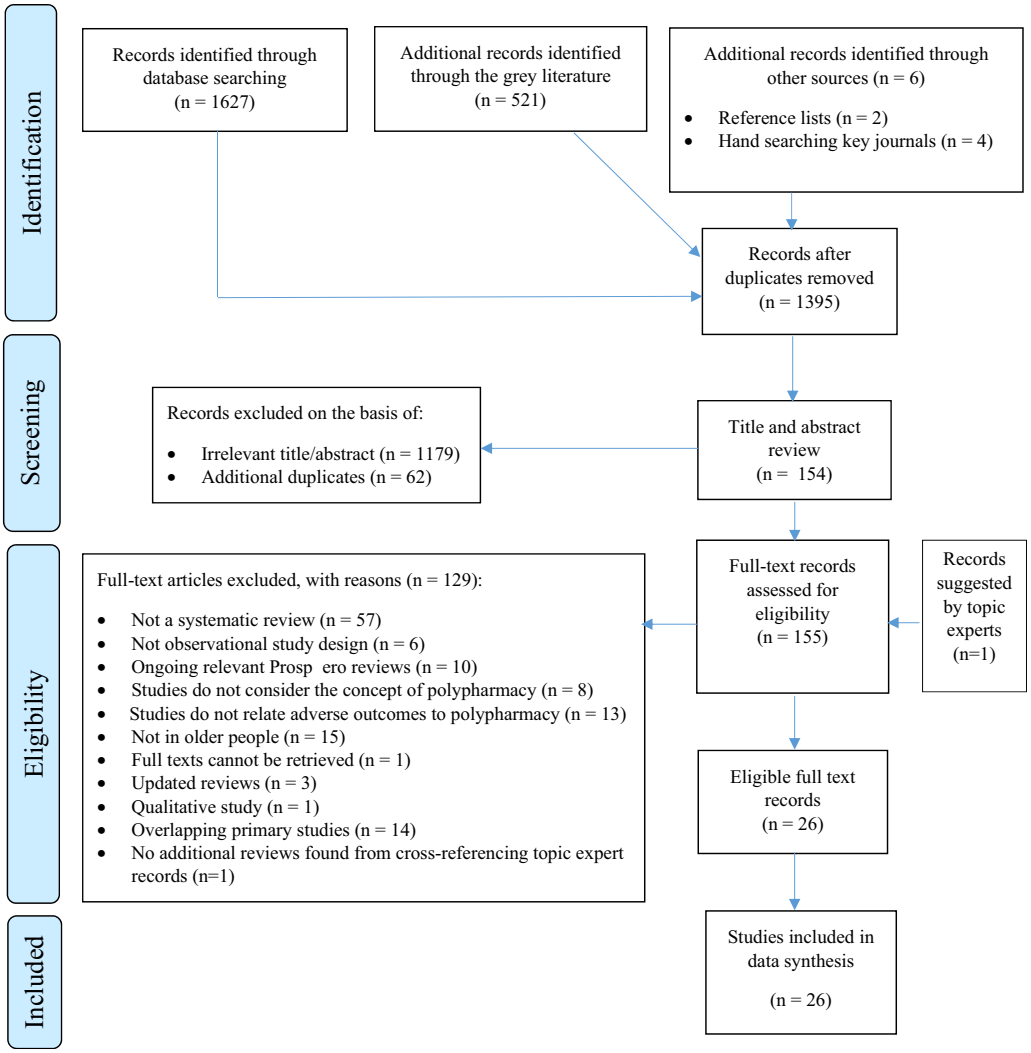

Fig. 1. PRISMA flow diagram of study selection.

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

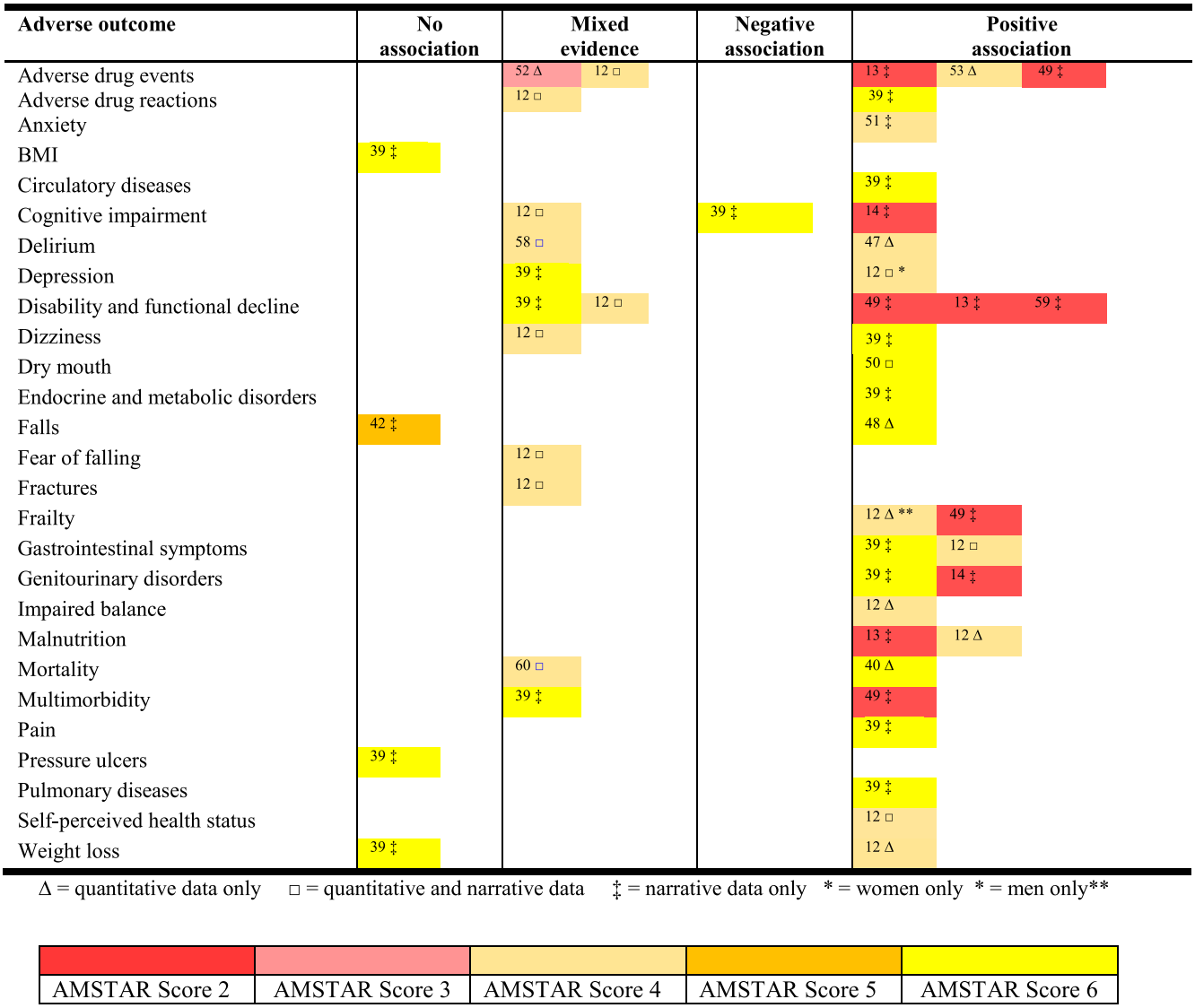

Fig. 2. Summary of evidence for the adverse health outcomes of polypharmacy. The numbers in the figure refer to the numbered cited literature.

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

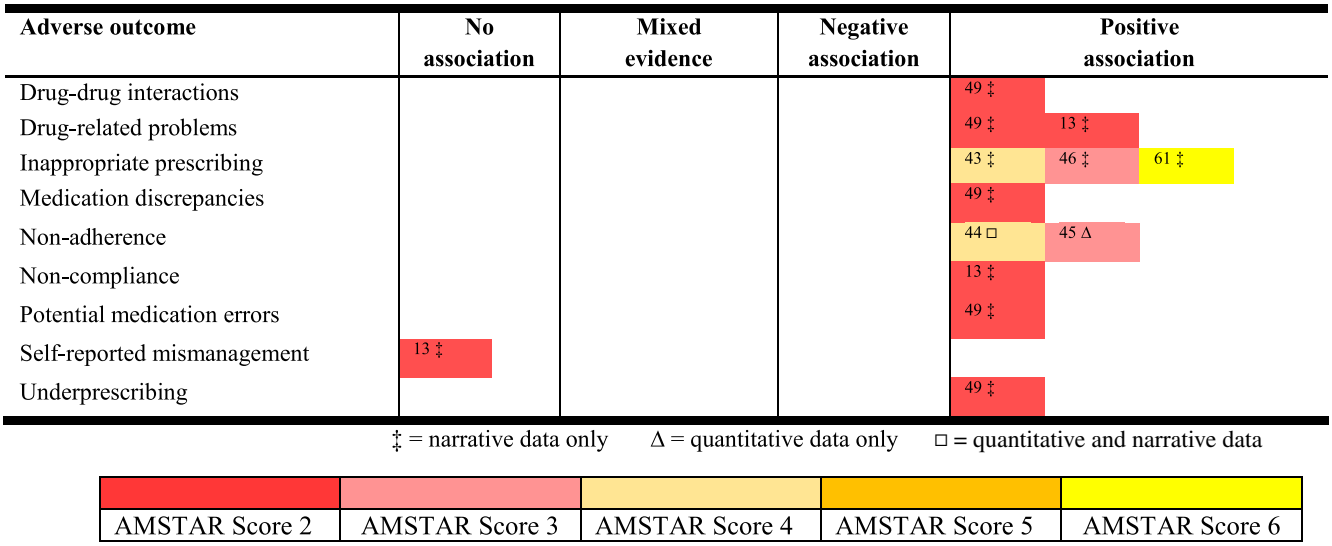

Fig. 3. Summary of evidence for the adverse medicines management outcomes of polypharmacy. The numbers in the figure refer to the numbered cited literature.

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

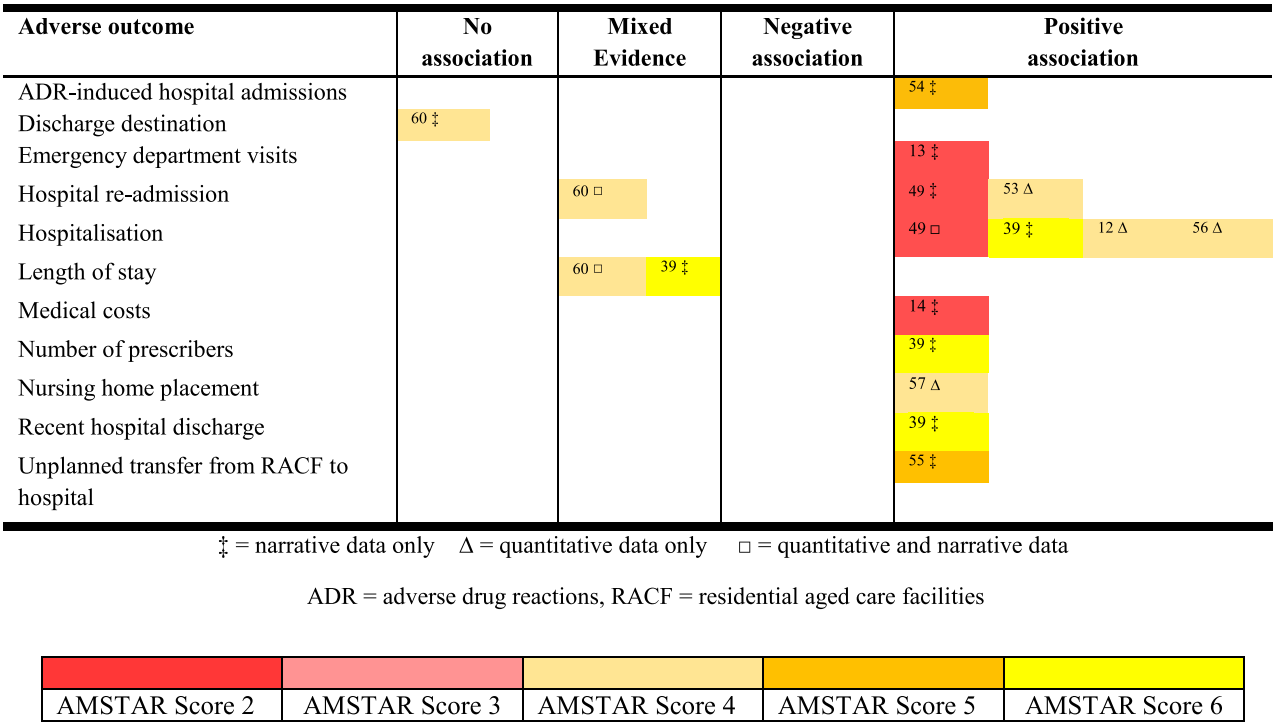

Fig. 4. Summary of evidence for the adverse health care utilization outcomes of polypharmacy. The numbers in the figure refer to the numbered cited literature. ADR, adverse drug reaction; RACF, residential aged care facility.

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 $\geq$85 years). Doing so is imperative in the face of rising multimorbidity and population aging.

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Supplementary Data

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

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