In-hospital adverse drug reactions in older adults; prevalence, presentation and associated drugs – *a systematic review and meta-analysis*

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Abstract

Background: The prevalence of adverse drug reactions (ADRs) in hospitalised older patients, their clinical presentations, causative drugs, severity, preventability and measurable outcomes are unclear, ADRs being an increasing challenge to older patient safety.

Methods: We systematically searched PubMed, Embase, EBSCO-CINAHL, the Cochrane Library, 'grey' literature and relevant systematic review bibliographies, published from database inception to March2020. We included any study reporting occurrence of in-hospital ADRs as primary or secondary outcomes in hospitalised older adults (mean age ≥65 years). Two authors independently extracted relevant information and appraised studies for bias. Study characteristics, ADR clinical presentations, causative drugs, severity, preventability and clinical outcomes were analysed. Study estimates were pooled using random-effects meta-analytic models.

Results: From 2399 abstracts, we undertook full-text screening in 286, identifying 27 studies (29 papers). Final analysis yielded a pooled ADR prevalence of 16% (95%CI 12%-22%, I^2 98%,τ^2 0.8585), in a population of 20153 hospitalised patients aged ≥ 65 years of whom 2479 patients experienced ≥1 ADR. ADR ascertainment was highly heterogeneous. 48.3% of all ADRs involved five presentations: fluid/electrolyte disturbances (17.3%), gastrointestinal motility/defaecation disorders (13.3%), renal disorders (8.2%), hypotension/blood pressure dysregulation disorders/shock (5.5%) and delirium (4.1%). Four drug classes accounted for 57.8% of causative medications i.e. diuretics (19.8%), anti-bacterials (14.8%), antithrombotic agents (12.2%) and analgesics (10.9%). Pooled analysis of severity was not feasible. Four studies reported the majority of ADRs as preventable (55%-95%).

Conclusion: On average, 16% of hospitalised older patients experience significant ADRs, varying in severity and mostly preventable, with commonly prescribed drug classes accounting for most ADRs.

Keywords: Older people, adverse drug reaction, polypharmacy, multimorbidity, inpatient, iatrogenic

Key points:

- Adverse drug reactions (ADRs) are highly prevalent in hospitalised older inpatients, with commonly prescribed drug classes accounting for the majority ADRs.
- Cumulatively, twenty ADR presentations represent 90% of all ADRs.
- Twenty therapeutic drug classes accounted for 94% of all ADRs in older people.
- There is marked heterogeneity in ADR studies pointing to a need for standardisation of ADR ascertainment and assessment.
- Patient outcomes from ADRs were inadequately and infrequently measured, indicating the need for a standardised ADR core outcome set.

INTRODUCTION:

The World Health Organisation (WHO) defines an adverse drug reaction (ADR) as "a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man".[1] An adverse drug event or experience (ADE) is defined as "any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment".[1] Since 1960, studies have focused on ADR prevalence, with recent emphasis on predictive models, associated risk factors, preventability and methods to reduce ADR occurrence. Female gender, comorbid complexity and increased number of daily medications are significant risk factors for ADRs, particularly in older adults (≥65 years).[2]

ADRs and ADEs represent a significant proportion of older adult acute hospital admissions (8.7%[3] - 16.6%[4]) and increase the cost of care by almost one fifth per patient i.e. €2200, more so in patients aged over 65.[5] Hospital-acquired ADEs prolong length of stay (LOS),[5-8] particularly in older patients[5,8] and greater ADE severity incurs greater hospitalisation costs.[9] In hospitalised patients of all ages 6-7% will experience serious incident ADRs,[10] cognitively impaired older adults being at particular risk.[11] Preventable ADEs cost almost 50% more than non-preventable ADEs[12] and importantly tend to occur more frequently in older adults.[13,14] Thus, reducing *preventable* ADRs and ADEs in hospitalised older adults could potentially offer substantial economic dividends.

Several systematic reviews (SRs) have focused on ADRs in hospital,[15] yet few deal with ADRs in older adults specifically,[2,3,11,16,17] or as a subset.[4,18,19] Reported ADE/ADR frequency varies widely depending on sex, age, time-point (i.e. at admission versus discharge), study setting (i.e. in-hospital versus community-acquired), and specific-disease cohorts. Furthermore, SRs examining older adults in isolation report lower ADR frequencies than those reporting older age as a subgroup of all ages.[2-4,18]

Estimates indicate that hospital-acquired ADRs occur frequently, irrespective of age; up to 1 in 4 hospitalised adults experience ADRs (10.9%[10]- 23.4%[20]). Alhawassi *et al.*[2] estimated that 11.5%

(95% CI, 0 – 27%)[2] of older people experience hospital-acquired ADRs. However, the confidence interval for this estimate was wide and the number of studies considered and the overall patient population size represented by this estimate are unclear.

It is evident that ADRs in general occur more frequently in hospital than in other settings and that older people are more at risk, yet a dedicated pooled estimate of ADR prevalence in this population is lacking. Therefore, the objectives of this systematic review and meta-analysis were: (i) to calculate the pooled prevalence of hospital-acquired ADRs in older people (≥65 years), (ii) to identify the common clinical presentations of these ADRs, and (iii) to identify associated causative medications.

Materials and methods

This study was registered (PROSPERO CRD42018079095 2018)[21] and reported as per PRISMA (Preferred Reporting Items For Systematic Reviews And Meta-Analyses)[22] and MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines[23] (***Appendix 1***). Two investigators conducted each step independently, results were compared for agreement, identified discrepancies were discussed and consensus reached.

Search Strategy

PubMed, Embase, Ebsco-CINAHL and Cochrane Library databases were searched from inception until March 2020, without language restriction, using terms 'aged', 'adverse drug reaction', 'hospitalised', 'multi-morbid', 'polypharmacy' and 'hospital-acquired' (***Appendix 1-Search terms***).

Data extraction

Two researchers [EJ, KM] extracted data using a pre-specified template. Authors were contacted for further information when insufficient data were reported. Only control arm data were extracted in randomised control trials (RCTs).

Eligibility Criteria

Studies were included if they reported on:

i) *Population:* Human participants aged ≥ 65 years.

ii) *Outcome:* Proportion of ADRs/ADEs occurring during acute hospitalisation reporting methodology for identifying ADRs; details of clinical presentations of ADRs and/or causative medications; specifics of severity and/or preventability of ADRs; description of ADR assessment methods; evaluation or ADR-related clinical outcomes.

iii) *Design:* Any design, with the exception of review publications or case reports (bibliographic hand search undertaken).

In cases of missing or ambiguous data reporting author(s) were contacted seeking clarification.

Assessment of Study Quality

Included studies were critically appraised using the Cochrane risk of bias tool[24] (randomised interventional studies) and the modified Newcastle-Ottawa scale (NOS)[25] (observational studies).

Statistical Analysis

i) *ADR Prevalence:* this was defined as the proportion of participants aged ≥ 65 years experiencing ≥ 1 ADR during hospitalisation.

ii) *ADR clinical presentations:* were classified according to the Medical Dictionary for Regulatory Activities terminology[26] using BioPortal©[27,28] reported as the proportion of overall number of ADR presentations and validated by sensitivity analysis (***Appendix 2***).

iii) *Causative drugs:* were reported as a proportion of the total count of all reported agents using the WHO Anatomical Therapeutic Chemical [ATC] classification system.[2931]

All analyses were conducted using the R Language for Statistical Programming.[30] Meta-analysis models and plots were produced using the Metafor® package.[31] For meta-analysis models, generalized linear mixed effects model for logit transformed proportions (i.e. metafor::rms.glmm (measure = "PLO")) were used. Forest plots summarise weighted proportions and associated confidence intervals (CI).

RESULTS

Characteristics of identified studies

Of 2399 retrieved articles, 29 publications involving 27 studies with a combined total of 128580 patients aged ≥ 65 years met inclusion criteria[32-60] (**Figure 1**). Publications spanned 6 decades (1965-2020) and study size varied enormously (97-108548 patients) (**Table 1**). Only 10 studies reported sex for 5704 patients (28.47%) aged ≥ 65 years, of whom 3090 (54%) were female.[37,38,40,49,50,54,55,57-60]

Quality of studies and risk of bias assessment

Detailed descriptions of study quality and risk of bias (RoB) are outlined in ***appendices 3***, ***4, 5, 6, 7, 8***. After appraisal, analysis of its impact on pooled estimates (***appendix 6***) and funnel plot (***appendix 8***), the study by Liao *et al.*[51] was excluded due to concerns regarding the accuracy of their ADR proportion estimation methodology (data mining of a hospital ADR reporting system), which was inherently prone to underreporting.[61] Two studies[44,56] of good quality, provided 10065 (49.9%) of

patients included in the final analysis, Giardina et al. [44] being 1 of 7 studies (29%) meeting all domains of NOS.[33,38,39,42,49,58] Onder *et al.'s*[56] description of assessment and evaluation of ADRs was deemed inadequate, but it met all other inclusion criteria. ADRs were clearly incident in eleven (44%) observational studies (***appendix7***). Both included RCTs[55,57] had potential bias relating to randomisation and blinding (***appendix 9***).

ADR Prevalence

The pooled proportion of ADR prevalence by random effects model was 16% (n=20153, 95%CI 12%-22%, I^2 = 98%, τ^2 0.8585) indicating substantial heterogeneity **(Figure 2)**. Comparison of ADR proportions pooled by specialist service setting was just below statistical significance (p=0.051). Reporting limitations prevented evaluation by surgical or medical specialty (***appendix 10***).

ADR Methodologies

ADR identification and ascertainment methodologies varied widely between studies, only 4 studies (15%)[34,39,42,59] described methodologies across all assessment domains (***appendix 11 and 16***). Five ADR definitions and four causality tools were utilised. The WHO ADR definition and Naranjo ADR causality algorithm were concomitantly applied in 8 studies (30%)[32,41-43,46,47,53,56] (***appendices 11 and 15***). ADR severity was predominantly author-defined in 8 studies (30%).[34,38,41,43,45,54-56] Five ADR classification methods were described; the Rawlins & Thompson method was solely used for 7 studies (26%).[32,33,39,46,48,50,59] Only 6 studies[34,39,42,44,55,59] reported preventable-ADRs, four studies[39,42,55,59] used Hallas criteria.

Subgroup Analyses

We interrogated heterogeneity via a subgroup meta-analysis of studies recruiting all ages[32-34,39,41-48,52,53] versus solely ≥65 years at baseline.[35-38,40,49,50,54-58,60] While still heterogeneous, ADR prevalence was higher in this subgroup i.e. 19% (95% CI 13%-27%, I^2=98%, τ^2 0.86, p=0.299) (***appendix 12***).

Grouping by ADR definition (***appendix 13)*** did not reduce heterogeneity nor was there a significant difference between groups i.e. WHO definition 14%, author-defined 19%, Bates definition 12%, Edwards & Aronson definition 17%, local therapeutic committee definition 30%, and undefined in 23% (p = 0.806).

Meta-analysis by ADR causality (***appendix 14***) criteria did not influence prevalence estimation i.e. Naranjo criteria 15%, Hallas criteria 12%, Kramer criteria 19%, undefined criteria 15%, WHO-UMC 22% (p = 0.8094).

Interrogation by overlapping definition/causality methodologies (***appendix 15***) did not reduce heterogeneity, nor was there a significant difference between definition/causality groups (p=0.383) i.e. WHO/WHO-UMC criteria 22%, WHO/Naranjo criteria 10% Edwards & Aronson/Naranjo criteria 21%.

Reported ADR Presentation

Nineteen studies (70%)[32-39,41-43,45,46,48,50,54-58] reported 2728 ADR presentations in 1886 patients aged ≥ 65 years. After sensitivity analysis, 3251 ADRs were classified and ranked (***appendix 2***). Cumulatively, twenty clinical presentations represented 90% of all ADRs (**Table 2**). Details of ADRs by MedDRA-SOC® classification (***appendix 17***) and ADR details (***appendix 18)*** is available in the ***supplementary data.***

ADR Drugs

Nineteen studies[34,36-41,43-45,47,49,51,54,55,57-59,3,4] reported medications related to hospital-acquired ADRs, by drug name[32,39,41-43,45,46,58] or by drug class.[32,34-39,41-43,45,46,48,50,51,54,55,57,59] One study only reported drugs as causing ADRs when experienced by a pre-defined number of participants.[37] One study reported grouped ATC drug classes.[37,51] Cumulatively, 2428 causative entities were analysed, with ATC classification applicable in 2385 cases across 49 therapeutic subgroups. Twenty therapeutic subgroups incorporated 94% of all ADRs (**Table 3** and ***appendix 19***). The breakdown of causative entities by ATC classification is available in appendices 20 and 21.

The top five anatomical systems affected by ADR-causing drugs were: (i) cardiovascular system (769, 32.24%), (ii) central nervous system (415, 17.40%), (iii) anti-infectives for systemic use (410, 17.19%), (iv) blood and blood forming organs (329, 13.79%) and (v) alimentary tract and metabolism (169, 7.09%). Eleven studies[32,34,37-39,41-43,45,46,48] reported ADR-drug relationship; 3 published, 8 author-provided data, further synthesis was not feasible.

ADR Severity

Moderate to severe ADR detection ranged from 24% to 100% as reported in eighteen studies.[33,34,37-39,41-43,46,48,50,51,54-59] (***appendices 22 and 23***).

ADR Preventability

Seven studies[34,39,42,44,46,55,59] reported preventable ADRs; 4 studies had extractable data and used Hallas criteria.[39,42,44,55,59] (***appendices 24 and 25***).

Polypharmacy

Details describing medication-burden were reported in 18 studies.[32,38,40,43-51,54-57,59,60] Polypharmacy (i.e. a mean/median of ≥ 5 daily medications) was present in 11 studies (***appendix 26***).[32,38,40,43,49,50,54-57,59,60] In three studies, patients experiencing ADRs had higher numbers of daily medications at baseline compared to those who did not.[38,56,59] Onder *et al.* reported that prescription of ≥8 drugs daily was strongly associated with ADRs (odds ratio 4.07).[56] Giardina *et al.* studied 4802 patients, 48% of whom had polypharmacy at baseline; 3646 patients (76%) were aged ≥ 65 years. In this cohort, the adjusted odds ratio for in-hospital ADRs was 1.46 (95% CI 1.06-2.03, p<0.05) in patients taking ≥4 medications at admission.[44]

Multi-morbidity

Baseline multi-morbidity (i.e. a mean/median of ≥ 3 chronic conditions) was reported in 10 studies.[32,38,40,49,51,54,56,59,60] Eleven studies examined co-morbidity as an ADR-associated variable (***appendix 27***).[32,38,40,43,46,49,51,54,56,59,60] Three studies reported no significant association between ADR risk and degree of multi-morbidity.[32,54,59] Corsonello *et al.* reported higher Cumulative Illness Rating Scale scores in the ADR cohort compared to non-ADR cohort i.e. 4.5 versus 3.6 (p<0.05).[38] Similarly, Onder *et al.* observed that a significantly higher proportion of older patients with ≥ 4 comorbidities experienced ADRs compared to patients with fewer comorbidities.[56] Liao *et al.* observed that patients experiencing ADRs had a higher mean Charlson co-morbidity index score than the non-ADR cohort (4.06 versus 3.53 p = <0.001.)[51]

ADR Outcomes

Clinical outcomes following ADRs were infrequently reported, only 9 papers[37,39,43,48,51,54,55,57,59] commented on mortality and/or LOS. (***Appendix 28***) Patient groups experiencing hospital-acquired ADRs tended to have longer LOS, pooled analysis was not feasible.

DISCUSSION

This study presents the first meta-analysis of hospital-acquired ADRs in older adults. The principal findings are: (i) approximately 1 in 6 older patients experienced an ADR during hospitalisation, (ii) 20 clinical presentations accounted for 90% of reported ADRs, (iii) 16 routinely prescribed medications or medication classes accounted for 90% of all reported ADRs, (iv) ADR detection methodologies were highly heterogeneous with resultant large variation in reported prevalence, and (v) tangible clinical outcomes following hospital-acquired ADRs are infrequently reported.

ADR presentations and causative drug agents were explored in isolation given the high level of heterogeneity precluding analysis of drug specific ADR associations. However, our findings provide focus and some specific targets for future studies of ADR interventions that could benefit older patients. For example, the most common ADR presentation was fluid/electrolyte imbalance and the most common drug class causing ADRs was diuretics.

Our estimate of 17.0% of older-patients experiencing ADRs during hospitalisation is comparable to Miguel *et al*. for all ages i.e. 16.9%.[62] However, it exceeds previously reported estimations of proportions of older patient populations experiencing ADRs during hospitalisation (11.5%)[2] and contributing to hospitalisation (8.7%[4] – 10.7%[2,17]). Two Italian studies[44,56] where ADR prevalence estimates were 3%[44] and 7%[56] provided almost half (49.9%) of patients included in our overall analysis, an established pharmacovigilance culture of underreporting of ADRs may account for this.[63]

Reported ADR presentations in this study overlap with those described by Laatikainen *et al.* in all ages[20] i.e. dizziness, sedation, delirium (neurological events), electrolyte disturbances (renal dysfunction), hypo- and hyperglycaemia (endocrine disorders), constipation (GI events) and bleeding (haematological events). As Oscanoa *et al.*[3] did not differentiate ADR-presentations leading to

hospitalisation in older adults a comparison is not possible. Not surprisingly, these presentations are heterogeneous and often non-specific, being easily misinterpreted as new intrinsic geriatric conditions by unsuspecting physicians and thereby increasing risk of prescribing cascades.[64]

Similar to Wolfe *et al.*[15], Kongkaew *et al.*[18] and Alhawassi *et al.*[2], cardiovascular system medications caused most ADRs. Medications affecting the central nervous system had a higher propensity for hospital-acquired ADRs compared to those *leading to* hospitalisation (17.42% versus 13.8%[18]), possibly due to differing prescribing patterns and practices between hospital and community settings. Equally, patients' recent frailty, change in baseline activities of daily living and overall health status from the insult leading to hospitalisation could account for these differences.

Our study shares six of the top ten drug classes that caused ADR-related hospitalisations in older people in the study by Oscanoa et al.[3] i.e. antibiotics, oral anticoagulants, digoxin, ACE-Inhibitors, opioids and oral anti-diabetics.[3] NSAIDs and beta-blockers ranked 15th and 21st respectively in the present study, compared to 1st and 2nd suggesting that medications causing in-hospital ADRs differ to those *leading to* hospitalisation in older adults. Six drug classes i.e. antibiotics, anticoagulants, digoxin, diuretics, hypoglycaemic agents and NSAIDs account for two-thirds of ADRs *in all ages* [65] Our estimates attribute 54% of hospital-acquired ADRs to the same drug classes with different ranking by prevalence. The time interval between studies and our focus being entirely on patients aged ≥ 65 years may account for these differences. Our analysis found that hospital-acquired ADRs are infrequently caused by NSAIDs i.e. 1.68%. Nevertheless, NSAIDs commonly contribute to ADR-related hospitalisations with an overall higher risk in older patients than younger patients (18.8%[18], 2.3% - 33%[3] versus 7%[15] - 11%[66]).

Surprisingly, Oscanoa et *al.*[3] did not associate diuretics with ADR-related hospitalisations in older patients. Yet, regardless of age, 1 in 6 preventable ADR induced hospitalisations[66] and 1 in 10 of hospital-acquired ADRs are diuretic-related.[15] Our estimate of diuretic-related ADR prevalence

was of 19.86% , likely because diuretic prescription is considerably more common in older people than in younger age groups.

Our study found that anti-bacterials were more frequently associated with hospital-acquired ADRs in older adults than those of all ages i.e. 14.82% versus 11.0%.[15] By comparison, Oscanoa *et al.* reported that antibiotics may have accounted for 1.1% - 22.2% of ADR-associated hospitalisations in older adults.[3] The availability of newer antibiotics, greater use of broad-spectrum antibiotics and evolving resistance patterns may contribute to these differences.

Irrespective of age, antithrombotic drugs cause more ADR-associated hospitalisations than hospital-acquired ADRs i.e. 24%[66] versus 12.5%.[15] This pattern persists for older patients, where 3.3% - 55.6%[3] of ADR-related hospitalisations and 12.17% of hospital-acquired ADRs are associated with antithrombotic agents.

Like Gray *et al.*[16], notable heterogeneity existed across our analyses, relating to the variance in the studies themselves. Studies spanned several decades, had varying design, heterogeneous populations and differing ADR assessment methodologies. Equally, there was global spread of study location, such that international differences in health care systems (e.g. licensed medications and mandatory national ADR reporting) could contribute to variable results. This heterogeneity is significant in itself as it indicates the need for an internationally standardised ADR assessment methodology and core outcome set to lessen study variation and ambiguity. Such tools would improve future study quality and facilitate meaningful conclusions from multiple studies to support improvements in patient outcomes.

Our study has some limitations, principally examining heterogeneous studies which are mostly retrospective and observational and more prone to bias. Wolfe *et al.*[15] reported the highest rates of preventable ADRs in prospective observational studies. Thus, there is potential reporting bias due to underreporting of some ADRs. Hence, our results may underestimate true ADR prevalence in this population. Our study highlights the most frequent ADR presentations and the

most frequent causative drugs independently, we could not generate strong recommendations for preventing ADRs due to insufficient information of the circumstances of the ADR occurrence. Hence, we could not define groupings of "preventable ADR-Drug pairs" which would support targeted intervention. Additionally, pooled estimates for clinical outcomes were not feasible given reporting limitations. Finally, it is likely that there are missing data relating to identified studies that could not be included, as efforts to contact some study authors seeking to obtain missing data were unsuccessful.

Overall, relatively low quality of reporting of patient-centred clinical outcomes was evident from our analysis. Where reported, although not suitable for meta-analysis, patient groups experiencing ADRs in-hospital had longer LOS than their non-ADR counterparts. Lack of robust outcome reporting prohibits evaluation of these ADRs from a health economic standpoint and therefore makes estimation of ADR impact on health-care systems difficult. More concerning is the absence of patient-centred ADR-related outcomes such as quality of life. We contend that defining ADR incidence and prevalence in specific patient populations is no longer sufficient and that a validated reproducible core outcome set for measuring the impact of ADRs on morbidity, quality of life, mortality, health resource utilisation and rehospitalisation for older patients and healthcare systems is needed.

Considering the high proportion of older people experiencing clinically significant ADRs during hospitalisation, this study confirms the need to predict and prevent ADRs in this high-risk patient population. Greater focus on those medications that most frequently cause ADRs leading to and occurring during hospitalisation in older people is needed. Routine surveillance of older patients prescribed higher risk drug classes represents one way of minimizing ADRs in older patients. Careful review of the need for such drugs, consideration of safer alternatives and awareness of the common and often non-specific nature of ADR manifestations in older people should, in theory, minimize ADRs and their effects in older hospitalised patients.

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A complete list of all 66 references is available in the online appendix 30

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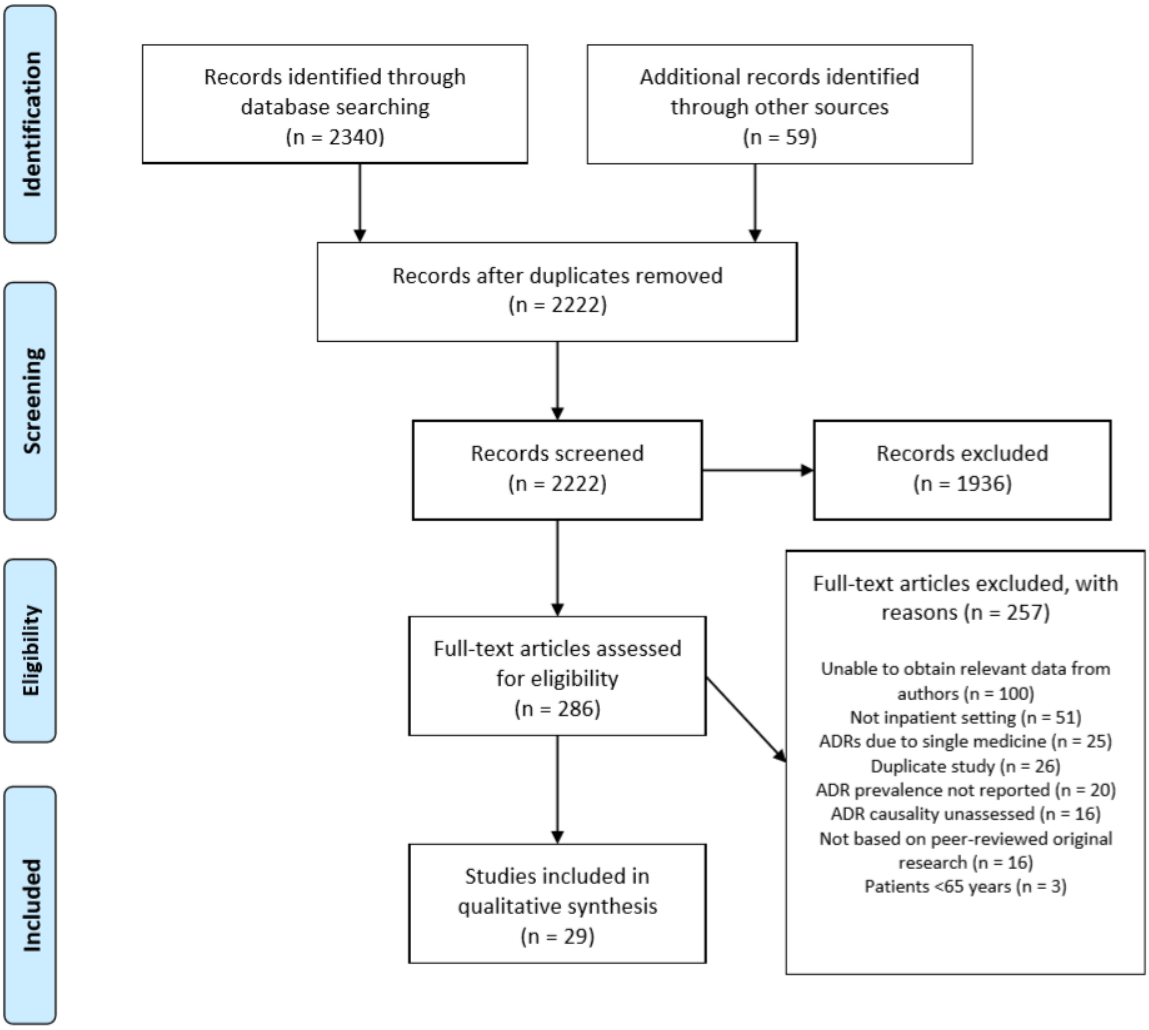


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of systematic literature search and final study selection process.

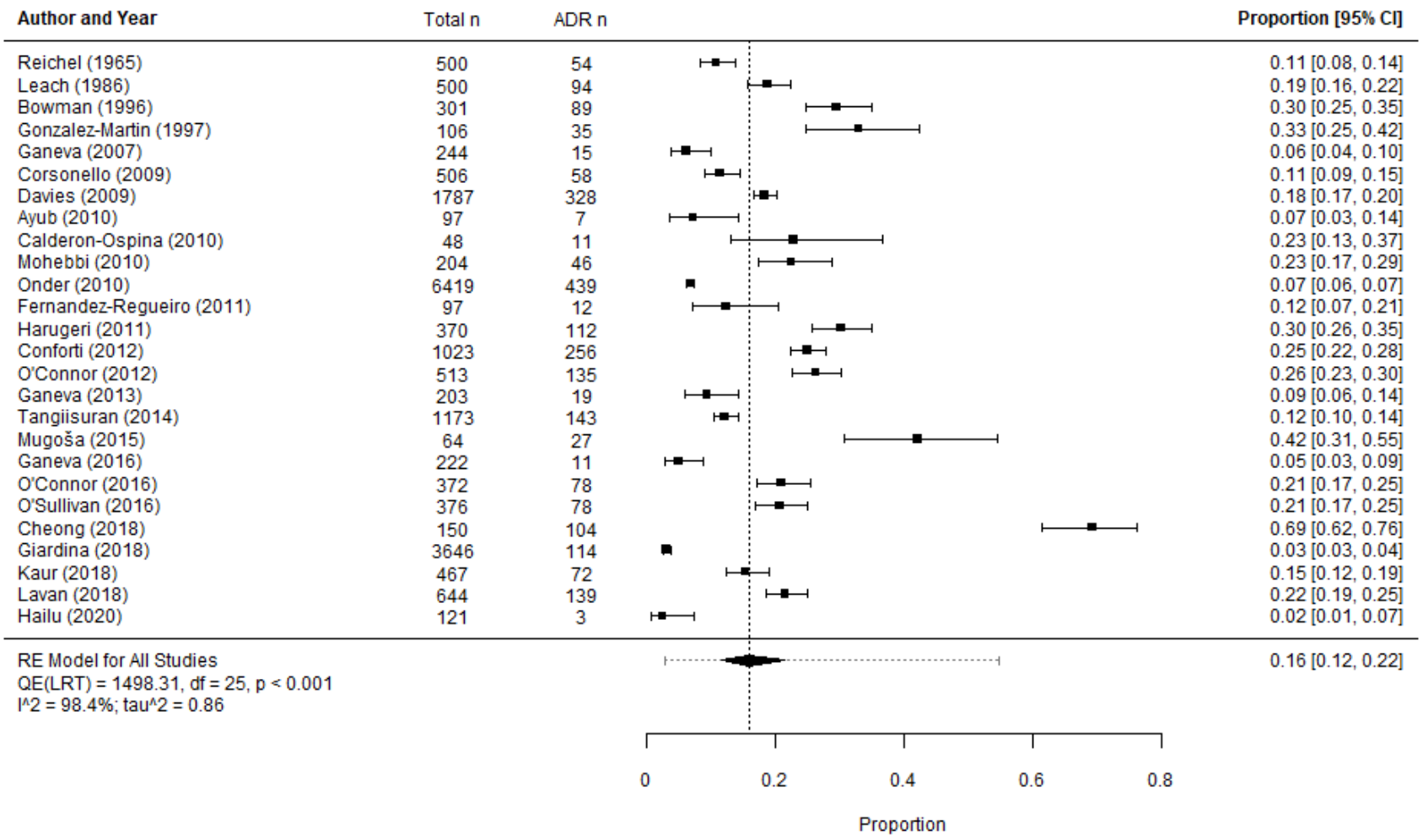


Figure 2. Forrest plot showing proportion of patients aged 65 years or older experiencing an in-hospital ADR. (Liao *et al.*[51] excluded, forest plot illustrating inclusion available in ***appendix 6***)

Table 1. Summary of characteristics of the 29 papers (27 studies) included in systematic review.

Source	Country	Language	Design	Hospital / Ward Setting	Population	Duration *(months)*	Total N	N ≥ 65 yrs	Age *(yrs)*	Sex *(% M)*
Ayub[32]	Brazil	English	Pro	ICU	Adults	6	270	97	57.3 ± 16.3[c]	57
Bowman[33]	U.S.A.	English	Post-H	GIM & ICU	Adults	4	1024	301	54 ± 18 [c]	-
Caldron-Ospina[34]	Colombia	English	Pro	UH, ward setting not described	Adults	1	104	48	-	54
Cheong[35,36]	Singapore	English	Retro	TH, geriatric wards	Older adults	1	150	150	89.7 ± 4.0 [c]	-
Conforti[37]	Italy	English	Pro	UH, geriatric wards	≥ 65 yrs with ADRs[§]	6	1023	1023	81.9 ± 7.1 [c]	49
Corsonello[38]	Italy	English	Pro	Collaborative group, medical	≥ 65 yrs	3	506	506	80.1 ± 6 [c]	46
Davies[39]	U.K.	English	Pro	UH, medical and surgical wards	Adults	6	3322	1787	-	-
Fernandez-Regueiro[40]	Spain	Spanish	Pro	Internal medical service	≥ 65 yrs ≥ 1 PIM <48[o]	5	97	97	81.3 ± 6.6 [c]	45
Ganeva[41]	Bulgaria	English	Pro	UH, acute dermatology service	Adults	24	1041	244	48.9 ± 18.9 [c]	42
Ganeva[43]	Bulgaria	English	Pro	UH, acute dermatology service	Adults	18	674	203	-	47
Ganeva[42]	Bulgaria	English	Pro	UH, acute dermatology service	Adults	60	750	222	-	-
Giardina[44]	Italy	English	Pro	2 hospitals, 6 wards[◊]	Adults	24	4802	3646	-	-
Gonzalez-Martin[45]	Chile	Spanish	Pro	UH, internal medicine	Adults ≥ 65 yrs ¥	8	201	106	-	47
Hailu[46]	Ethiopia	English	Pro	UH, medical and surgical wards	≥ 60 yrs	4	200	121	67.3 ± 7.3 [c]	67.5
Harugeri[47]	India	English	Pro	TH, medical wards	In-patient, ≥ 60 yrs	18	920	370	-	59
Kaur[48]	India	English	Pro	TH, geriatric wards	Adults > 50 yrs	21	658	467	-	59
Lavan[49]	Ireland	English	Pro	SENATOR 6 European trial sites	≥65 yrs multi-morbid ≤72[o]	18	644	644	77.8 ± 7.4 [c]	48
Leach[50]	U.K.	English	Pro	District hospital, geriatric unit	Consecutive admissions	5	500	500	78.3[c]	46
Liao[51]	Taiwan	English	Retro	ADR reporting system analysis	Older inpatients	72	108548	108548	-	-
Mohebbi[52]	Iran	English	Pro	2 CCU wards	Adults, ≥ 1 CVS drug	8	677	204	-	65
Mugosa[53]	Montenegro	English	Pro	Critical care, cardiology centre	Adults ≥ 72[o]	6	200	64	60.5 ± 10 [c]	69
O'Connor[54]	Ireland	English	Pro	UH, medical & surgical	ED admissions ≥ 65yrs†	12	513	513	77 (72-82)[d]	44
O'Connor[55]	Ireland	English	RCT	UH, medical & surgical	Admissions ≥ 65 yrs†	4	372	372	78 (72-84)[d]	50
Onder[56]	Italy	English	Pro	83 centres, 4 European sites	≥ 65 yrs hospitalised	19**	6419	6419	78 ± 7.9 [c]	-
O'Sullivan[57]	Ireland	English	RCT	UH, medical & surgical	Admissions ≥ 65 yrs	13	376	376	78 (72-84) [d]	51
Reichel[58]	U.S.A.	English	Pro	County general hospital	Admissions ≥ 65 yrs	8	500	500	77.9[c]	43
Tangiisuran[59]	U.K.	English	Pro	UHs, 4 care of elderly wards	≥ 80 yrs***	6	560***	560***	87 ± 5.6 [c]	37
Tangiisuran[60]	U.K.	English	Pro	UHs, 4 care of elderly wards	≥ 65 yrs	6	1173 *690[d], 483[v]*	1173 *690[d], 483[v]*	80(75-86)[dD] 85(81-89) [dv]	39[d] 42.2[v]

***Legend**: yrs – years; M – Male; Pro – prospective observational; ICU – Intensive care unit; [c] – mean ± standard deviation; Post-H – Post-hoc analysis; GIM – general internal medicine; UH – University Hospital; Retro – retrospective observational; TH – Tertiary Hospital; ADRs – adverse drug reactions; § - ADRs at presentation and in-hospital; PIM – Potentially inappropriate medication; [o] – hours since admission; ◊ - GIM, geriatrics, metabolic diseases; ¥ - excluded physical and cognitive impairment; SENATOR - Software ENgine for the Assessment & optimization of drug and non-drug Therapy in Older peRsons; CCU – coronary care unit; CVS – cardiovascular system; ED – Emergency department; † – excluded ICU, palliative, clinical pharmacology, psychiatry, geriatric medicine; [d] – median (Interquartile range); RCT – randomised control trial; ** combined duration over (1988, 1991, 1993, 1995, 1997); ***subset of population described in 2014 paper; [D] – development cohort, [v] – validation cohort.*

Table 2. Most frequently reported ADR presentations.

Rank	MedDRA-SOC® ADR Classification	n	% Of (3251)	ADR Presentation Details†
1	Electrolyte and fluid balance conditions	561	17.26%	*Potassium imbalance* 325 (9.99%) – hypokalaemia 275 (8.46%), hyperkalaemia 50 (1.54%) *Sodium imbalance* 29 (0.89%) – hyponatraemia 27 (0.83%), hypernatraemia 2 (0.06%) *Fluid volume* 5 (0.15%) – increased 3 (0.09%), decreased 2 (0.06%)
2	Gastrointestinal motility and defaecation conditions	480	14.76%	*Constipation* 334 (10.27%) *Diarrhoea* 146 (4.49%)
3	Renal disorders (excl. nephropathies)	267	8.21%	*Acute kidney injury* 265 (8.15%) *Renal failure complications* 2 (0.06%)
4	Decreased and nonspecific blood pressure disorders and shock	179	5.51%	*Vascular hypotensive disorders* 179 (5.51%) – postural hypotension 98 (3.02%), hypotension 81 (2.49%)
5	Delirium (incl. confusion)	132	4.06%	*Confusion* 132 (4.06%)
6	Injuries NEC	123	3.78%	*Fall* 123 (7.8%)
7	Cardiac rate and rhythm disorders	122	3.75%	*Bradycardia* 102 (3.14%), *AV Block* 12 (0.37%), *tachycardia* 8 (0.24%)
8	Unspecified / unclassifiable cardiovascular disorders*	110	3.38%	*Cardiovascular complications** 97 (2.98%) *"Cardiovascular System"** 13 (0.40%)
9	Haematology investigations – deranged coagulation and bleeding analyses	98	3.01%	*INR increase* 97 (2.98%) *Low prothrombin time* 1 (0.03%)
10	Unspecified / unclassifiable gastrointestinal disorders*	90	2.77%	*"Gastrointestinal"** 90 (2.77%)
11	Vascular haemorrhagic disorders	89	2.74%	*Haemorrhages NEC* 89 (2.74%) – Bleeding 69 (2.13%), haematoma 20 (0.62%)
12	Gastrointestinal haemorrhages NEC	85	2.61%	*Gastrointestinal bleeding* 85 (2.61%)
13	Unspecified / unclassifiable nervous system disorders*	80	2.46%	*"Neurologic"** 68 (2.09%) *"Central nervous system"** 12 (0.37%)
14	Glucose metabolism disorders (incl. diabetes mellitus)	74	2.28%	*Hypoglycaemia* 51 (1.57%) *Hyperglycaemia* 23 (0.71%)
15	Epidermal and dermal conditions	72	2.21%	*Rashes, eruptions and exanthems* NEC 72 (2.21%)
16	Gastrointestinal signs and symptoms	71	2.18%	*Nausea/vomiting* 68 (2.09%), *dyspepsia* 2 (0.06%), *abdominal pain* 1 (0.03%)
17	Grouped unspecified / unclassifiable neuropsychiatric disorders*	68	2.09%	*"Neuropsychiatric"** 68 (2.09%)

18	Fungal infectious disorders - candida infections	67	2.06%	*Thrush* 67 (2.06%)
19	Neurological disorders NEC	63	1.94%	*Disturbances in consciousness NEC* 63 (1.94%)
20	Allergic conditions	54	1.66%	*Allergy* 54 (1.66%)

†reporting most common presentation per MedDRA-SOC® description, further details of subgroup / breakdown available in ***appendix 18.*** *Breakdown of ADR presentations by ADR detail.*

*Excl. – excluding, Incl. – including, * indicates that papers did not classify further, NEC – not elsewhere classified, INR – international normalised ratio*

Table 3. Most frequently reported ADR culprit drugs.

Rank	ATC 2nd Level Therapeutic Subgroup	n	% (2385)	***Most Frequently Reported Pharmacological Subgroup**** –chemical subgroup** (drug name/chemical substance***)
1	Diuretics	473	19.83%	*High ceiling diuretics* 234 (9.81%) – sulfonamides 232 (9.73%) (furosemide 194), (bumetanide 32) *Potassium sparing* 47 (1.97%) *Low ceiling diuretics* 27 (1.13%) – thiazides 24 (1.01%), excl. thiazides 13 (0.55%) *Combinations* 5 (0.21%)
2	Antibacterials for systemic use	354	14.84%	*Beta-lactams penicillins* 106 (4.44%) *Cephalosporins* 54 (2.26%) *Macrolides, lincosamides and streptogramins* 46 (1.93%) – macrolides 43 (1.80%) *Quinolones* 29 (1.22%) – fluoroquinolones 29 (1.22%) *Imidazole derivatives, glycopeptides, polymixins* 26 (1.09%) (metronidazole 16) *Sulfonamides and trimethoprim* 23 (0.96%) *Aminoglycosides* 6 (0.25%) *Tetracyclines* 1 (0.04%)
3	Antithrombotic agents	292	12.24%	*Vitamin K antagonists* 82 (3.44%) *Heparin group* 84 (3.52%) *Platelet aggregation inhibitors* 77 (3.23%) *Enzymes* 3 (0.13%)
4	Analgesics	260	10.90%	*Opioids* 205 (8.60%) – natural opium alkaloids 44 (1.84%) (Morphine 40), tramadol 28 (1.17%), phenylpiperidine derivatives 6 (0.25%), combination with non-opioid analgesics 4 (0.17%) *Other analgesics and antipyretics* 55 (2.31%) – anilides 34 (1.43%) (co-codamol 31)
5	Drugs for obstructive airway diseases (OAD)	113	4.74%	*Adrenergics, inhalants* 78 (3.27%) – beta-2-adrenoceptor agonists 62 (salbutamol 60) *Other drugs used for OAD* 23 – xanthines 23 (theophylline 12)
6	Agents acting on the renin-angiotensin system	98	4.11%	*ACE inhibitors*, plain 39 (1.63%) – (Ramipril 14) *Angiotensin II receptor blockers (ARBs)*, plain 12 (0.50%)
7	Psycholeptics	92	3.86%	*Anxiolytics* 61 (2.56%)– benzodiazepine derivatives 60 *Antipsychotics* 18 (0.76%) *Hypnotics and sedatives* 13 (0.55%)
8	Corticosteroids for systemic use	77	3.23%	*Glucocorticoids* 60 (2.52%) – (prednisolone 41)
9	Cardiac therapy	71	2.98%	*Cardiac glycosides* 44 (1.85%) – (digoxin 39) *Vasodilators used in cardiac diseases* 12 (0.50%) *Antiarrhythmics, class I and III* 10 (0.42%) – (Amiodarone 10)
10	Drugs used in diabetes	61	2.56%	*Insulins and analogues* 39 (1.64%) – intermediate of long acting combined with fast acting 27, fast acting 8

				Blood glucose lowering drugs excl. insulin 20 (0.84%)
11	Antimycobacterials	54	2.26%	*Drugs for treatment of tuberculosis* 54 (2.26%)
12	Antihypertensives	52	2.18%	*Not specified by paper* 52 (2.18%)
13	Mineral supplements	50	2.10%	*Calcium* 41 (1.72%) *Potassium* 9 (0.38%)
14	Calcium channel blockers	41	1.72%	*Not specified by paper* 30 (1.26%) *Selective with direct cardiac effects* 7 (0.29%) *Selective with mainly vascular effects* 4 (0.17%)
15	Anti-inflammatory and antirheumatic products	40	1.68%	*Antiinflammatory and antirheumatic products, non-steroids* 40 (1.68%)
16	Antiepileptics	30	1.26%	*Barbituates and derivatives* 18 (0.76%) – (phenobarbital 18) *Carboxamide derivatives* 9 (0.38%)
17	Drugs for acid related disorders	26	1.09%	*Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)* 26 (1.09%)
18	Drugs for constipation	24	1.01%	*Drugs for constipation* 10 (0.42%) – (Enemas 10)
19	Anti-anaemic preparations	22	0.92%	*Iron preparations* 20 (0.84%) – (ferrous sulphate 16) *Vitamin B12 and folic acid* 1
20	Psychoanaleptics	20	0.84%	*Anti-depressants* 19 (0.80%) – (selective serotonin reuptake inhibitors 10) *Anti-dementia drugs* 1 (0.04%)

** - ATC 3rd level, ** - ATC 4th level, *** - ATC 5th level (only reported when n ≥10). Additional information / level breakdown available in* ***appendix 22*** *"Breakdown by ATC Classification in descending reported frequency"*

In-hospital adverse drug reactions in older adults; prevalence, presentation and associated drugs. A systematic review and meta-analysis

SUPPLEMENTARY DATA

Table of Contents

Appendix 1. MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Described	Location in document
Reporting of background should include			
1	Problem definition	✓	Introduction
2	Hypothesis statement	✓	Introduction and Methods
3	Description of study outcome(s)	✓	Introduction and Methods
4	Type of exposure or intervention used	NA	-
5	Type of study designs used	✓	Methods
6	Study population	✓	Methods
Reporting of search strategy should include			
7	Qualifications of searchers (eg, librarians and investigators)	✓	Methods
8	Search strategy, including time period included in the synthesis and key words	✓	Methods and eSupplement
9	Effort to include all available studies, including contact with authors	✓	Methods
10	Databases and registries searched	✓	Methods
11	Search software used, name and version, including special features used (eg, explosion)	✓	Methods and eSupplement
12	Use of hand searching (eg, reference lists of obtained articles)	✓	Methods
13	List of citations located and those excluded, including justification	✓	Figure 1. PRISMA diagram
14	Method of addressing articles published in languages other than English	✓	Methods
15	Method of handling abstracts and unpublished studies		
16	Description of any contact with authors	✓	Methods
Reporting of methods should include			
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	✓	Methods
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	✓	Methods
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	✓	Methods
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	NA	NA
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	✓	Methods and eSupplement
22	Assessment of heterogeneity	✓	Methods, Results and eSupplement
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	✓	Methods

Item No	Recommendation	Described	Location in document
24	Provision of appropriate tables and graphics	✓	Results and eSupplements
Reporting of results should include			
25	Graphic summarizing individual study estimates and overall estimate	✓	Figure 2. Overall Forest plot and eSupplement
26	Table giving descriptive information for each study included	✓	Table 1.
27	Results of sensitivity testing (eg, subgroup analysis)	✓	Results and eSupplement
28	Indication of statistical uncertainty of findings	✓	Results and discussion
Reporting of discussion should include			
29	Quantitative assessment of bias (eg, publication bias)	✓	eSupplement
30	Justification for exclusion (eg, exclusion of non-English language citations)	✓	Figure 1. PRSIMA diagram and methods
31	Assessment of quality of included studies	✓	Results, Table 1. and eSupplement
Reporting of conclusions should include			
32	Consideration of alternative explanations for observed results	✓	Discussion
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	✓	Discussion
34	Guidelines for future research	✓	Discussion, future directions
35	Disclosure of funding source	✓	Funding

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

Supplemental Materials – ***In-hospital adverse drug reactions in older adults; prevalence, presentation and associated drugs – a systematic review and meta-analysis***

Methods

Search terms

A trained biomedical academic librarian assisted with the search strategy design. Two clinically trained investigators (EJ as a senior resident in geriatric medicine and KM as a pharmacist with expertise in geriatric pharmacotherapy) screened papers identified from the search for inclusion, firstly by title and abstract, and then full-text screening of shortlisted papers.

PubMed

old* OR aged OR ageing OR aging OR elderly OR geriatric* OR "Aged"[Mesh] OR "Aged, 80 and over"[Majr] OR "Aged, 80 and over"[Mesh]

AND

Adverse drug effect OR Adverse drug effects OR Adverse drug event OR Adverse drug events OR Adverse drug reaction OR Adverse drug reactions OR Drug induced disease OR Drug induced diseases OR Drug induced morbidity OR Drug induced injury Drug related morbidity OR Drug related problem OR Drug related problems OR Medication error OR Medication errors OR Medication related problem OR Medication related injury OR Medication related disease OR Medication related toxicity OR Toxicity OR Adverse event OR adverse reaction OR drug reaction OR drug event OR adverse outcome OR adverse drug outcome OR adverse drug outcomes OR adverse medication outcome OR adverse medication outcomes OR Side effect OR unintended effect OR unintended effects OR Unintended reaction OR Unintended reactions OR Unintended outcome OR Unintended outcomes OR Unintended event OR Unintended events OR Unintended morbidity OR Unintended problem OR Unintended injury OR Adverse drug OR "Drug-Related Side Effects and Adverse Reactions"[Mesh]

AND

admis* OR admit* OR inpatient OR in-patient OR ward OR Ward-based OR hospitali* OR Hospital OR In hospital OR In-hospital OR "Inpatients"[Mesh]

AND

Multimorbid OR Multi-morbid OR Multimorbidity OR Multi-morbidity OR Multimorbid* OR Comorbid OR co-morbid OR morbid* OR co-morbid* OR "Comorbidity"[Majr] OR "Comorbidity"[Mesh]

AND

Polypharmacy OR drug combinations OR multiple drugs OR multiple medications OR multiple medication OR multiple medicines OR "Polypharmacy"[Mesh]

AND

Nosocomial OR Iatrogenic OR Hospital-acquired OR Hospital acquired OR Post-admission OR Post admission OR During admission OR During-admission OR Avoidable OR Avoided OR Avoid* OR Preventable OR prevented OR Prevent* OR "Iatrogenic Disease"[Mesh] OR "Secondary Prevention"[Mesh]

EMBASE

old OR aged OR ageing OR aging OR elderly OR geriatric OR 'aged'/exp OR Old*

AND

adverse AND ('drug'/exp OR drug) AND effect OR adverse AND drug AND effects OR adverse AND drug AND event OR adverse AND drug AND events OR adverse AND drug AND reaction OR adverse AND drug AND reactions OR drug AND induced AND disease OR drug AND induced AND diseases OR drug AND induced AND morbidity OR drug AND induced AND injury OR drug AND related AND morbidity OR drug AND related AND problem OR drug AND related AND problems OR medication AND error OR medication AND errors OR 'medication'/exp OR medication) AND related AND problem OR medication AND related AND injury OR medication AND related AND disease OR medication AND related AND toxicity OR Toxicity OR adverse AND event OR adverse AND reaction OR drug AND reaction OR drug AND event OR adverse AND outcome OR adverse AND drug AND outcome OR adverse AND drug AND outcomes OR adverse AND medication AND outcome OR adverse AND medication AND outcomes OR side AND effect OR unintended AND effect OR unintended AND effects OR unintended AND reaction OR unintended AND reactions OR unintended AND outcome OR unintended AND outcomes OR unintended AND event OR unintended AND events OR unintended AND morbidity OR unintended AND problem OR unintended AND injury OR adverse AND drug OR 'adverse event'/exp OR 'adverse drug reaction'/exp

AND

admis* OR admit* OR inpatient OR “In patient” OR Ward OR 'ward based' OR hospitali* OR Hospital OR In hospital OR 'in hospital' OR inpatient* OR 'hospital patient'/exp

AND

Multimorbid OR 'multi morbid' OR Multimorbidity OR 'multi morbidity' OR Multimorbid* OR Comorbid OR 'co morbid' OR morbid* OR 'co morbid*' OR 'multiple chronic conditions'/exp OR 'comorbidity'/exp

AND

Polypharmacy OR drug AND combinations OR multiple AND drugs OR multiple AND medications OR multiple AND medication OR multiple AND medicines OR 'polypharmacy'/exp

AND

Nosocomial OR Iatrogenic OR 'hospital acquired' OR hospital AND acquired OR 'post admission' OR post AND admission OR during AND admission OR 'during admission' OR Avoidable OR Avoided OR Avoid* OR Preventable OR prevented OR Prevent* OR 'iatrogenic disease'/exp OR 'secondary prevention'/exp

CINAHL

old* OR aged OR ageing OR aging OR elderly OR geriatric* OR (MH "Aged+")

AND

Adverse drug effect OR Adverse drug effects OR Adverse drug event OR Adverse drug events OR Adverse drug reaction OR Adverse drug reactions OR Drug induced disease OR Drug induced diseases OR Drug induced morbidity OR Drug induced injury OR Drug related morbidity OR Drug related problem OR Drug related problems OR Medication error OR Medication errors OR Medication related problem OR Medication related injury OR Medication related disease OR Medication related toxicity OR Toxicity OR Adverse event OR adverse reaction OR drug reaction OR drug event OR adverse outcome OR adverse drug outcome OR adverse drug outcomes OR adverse medication outcome OR adverse medication outcomes OR Side effect OR unintended effect OR unintended effects OR Unintended reaction OR Unintended reactions OR Unintended outcome OR Unintended outcomes OR Unintended event OR Unintended events OR Unintended morbidity OR Unintended problem OR Unintended injury OR Adverse drug OR (MH "Adverse Drug Event+")

AND

admis* OR admit* OR inpatient OR in-patient OR ward OR Ward-based OR Ward based OR hospitali* OR Hospital OR In hospital OR In-hospital OR (MH "Inpatients") OR (MH "Aged, Hospitalized")

AND

Multimorbid OR Multi-morbid OR Multimorbidity OR Multi-morbidity OR Multimorbid* OR Comorbid OR co-morbid OR morbid* OR co-morbid* OR comorbid* OR (MH "Comorbidity")

AND

Polypharmacy OR drug combinations OR multiple drugs OR multiple medications OR multiple medication OR multiple medicines OR (MH "Polypharmacy")

AND

Nosocomial OR Iatrogenic OR Hospital-acquired OR Hospital acquired OR Post-admission OR Post admission OR During admission OR During-admission OR Avoidable OR Avoided OR Avoid* OR Preventable OR prevented OR Prevent* OR (MH "Iatrogenic Disease") OR (MH "Preventive Health Care+")

Study Eligibility Criteria

Studies that examined or as a subset reported on hospital-acquired ADRs/ADEs were included. If ADR data could not be extracted or ambiguity existed regarding methodologies the author(s) were contacted for further clarification.

Studies were included if they reported on (a) human participants aged ≥ 65 years, (b) ADR occurrence during acute hospitalization, and (c) the methodology used to identify the occurrence of an ADR.

Studies were excluded if (i) all participants were under 65 years, (ii) ADRs occurred in outpatient, community or primary care settings, (iii) the setting of ADR occurrence was unclear, (iv) they described a single drug or particular ADR presentation in isolation (as not representative of our cohort), (v) they were review publications or case reports (bibliographic hand search undertaken), (vi) they related to medication errors (included if reported ADR subset), (vii) they related to intentional overdoses, or (viii) they solely related to ADRs/ADEs occurring prior to, or leading to hospitalisation.

Statistical analysis

All analysis were conducted using the R Language for Statistical Programming.[1] Meta-analysis models and plots were produced using the Metafor® package.[2] For meta-analysis models we used a generalized linear mixed effects model for logit transformed proportions (i.e. metafor::rms.glmm(measure = "PLO")).

ADR Prevalence

ADR prevalence was defined as the proportion of participants aged ≥ 65 years experiencing ≥ 1 ADR during hospitalisation. Prevalence was chosen over incidence as details pertaining to the duration of each hospital admission was poorly reported in included studies i.e. prevalence is the proportion of cases in the population at a given time rather than rate of occurrence of new cases. As

the admission durations were not comparable or standardised across studies (duration of hospitalisations poorly reported) we chose point prevalence as the most appropriate epidemiological measure to represent pooled proportions. Pooled prevalence estimates were calculated using the random-effects meta-analytic model implying that studies come from different populations i.e. there is no one single "true" estimate. Forest plots summarise weighted proportions and associated 95% CIs.

Culprit Drugs

Causative drugs were classified according to the WHO Anatomical Therapeutic Chemical [ATC] coding system.[3] When more than one drug was accountable per ADR, each drug was counted individually. Therapeutic subgroups were reported as a proportion of the total count of all reported causative drugs. This strategy allows for comparison across studies given the lack of a common reporting system between studies.

ADR Presentation

ADR clinical presentations were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology[4] using BioPortal©.[5,6] When studies grouped ADRs involving multiple MedDRA®[4] subgroups, equal weighting was applied to each subgroup and validated by sensitivity analysis to results when grouped ADRs were excluded (see ***eSupplement-eTable 2***).

The absolute number of ADR presentations was indeterminable as some studies only reported ADRs when a predetermined threshold was met. Proportions of ADR presentations were calculated with the number of ADRs specific to the individual presentation as the numerator and overall number of reported ADR presentations as the denominator.

Appendix 2. Sensitivity Analysis of ADR Presentations

Rank	Sens. Rank	ADR details	Class. n	% Class.	Cumul. Class.	Sens. n	% Sens.	Cumul. sens.
1	1	Electrolyte and fluid balance conditions	461	19.78%	19.78%	561	17.26%	17.26%
2	2	Gastrointestinal motility and defaecation conditions	392	16.82%	36.59%	432	13.29%	30.54%
3	3	Renal disorders (excl. nephropathies)	150	6.44%	43.03%	267	8.21%	38.76%
4	4	Decreased and nonspecific blood pressure disorders and shock	126	5.41%	48.43%	179	5.51%	44.26%
15	5	Deliria (incl. confusion)	52	2.23%	50.66%	132	4.06%	48.32%
16	6	Injuries NEC	34	1.46%	52.12%	123	3.78%	52.11%
10	7	Rate and rhythm disorders	74	3.17%	55.30%	122	3.75%	55.86%
11	8	Epidermal and dermal conditions	72	1.07%	59.46%	118	3.63%	59.49%
19	9	Neurological disorders NEC	25	4.72%	64.18%	111	3.41%	62.90%
5	10	Unspecified / Unclassifiable Cardiovascular	110	4.20%	68.38%	110	3.38%	66.29%
6	11	Haematology investigations - Coagulation and bleeding analyses	98	3.86%	72.24%	98	3.01%	69.30%
7	12	Unspecified / unclassifiable Gastrointestinal disorders	90	3.82%	76.06%	90	2.77%	72.07%
8	13	Vascular haemorrhagic disorders	89	2.87%	78.94%	89	2.74%	74.81%
13	14	Gastrointestinal haemorrhages NEC	67	0.47%	79.41%	85	2.61%	77.42%
26	15	unspecified / unclassifiable nervous system disorders	11	3.17%	82.58%	80	2.46%	79.88%
9	16	Glucose metabolism disorders (incl. diabetes mellitus)	74	2.62%	85.20%	74	2.28%	82.16%
14	17	Gastrointestinal signs and symptoms	61	0.00%	85.20%	71	2.18%	84.34%
63	18	Unspecified / unclassifiable neuropsychiatric disorder	0	2.87%	88.07%	68	2.09%	86.43%
12	19	Fungal infections disorders - Candida infections	67	0.34%	88.42%	67	2.06%	88.50%
29	20	Allergic conditions	8	1.16%	89.58%	54	1.66%	90.16%
17	21	Anaemias nonhaemolytic and marrow depression	27	1.12%	90.69%	27	0.83%	90.99%
18	22	Unspecifed / unclassifiable - Metabolism and nutrition disorders	26	5.41%	48.43%	26	0.80%	91.79%
65	23	"Other"	0	0.00%	90.69%	23	0.71%	92.49%
20	24	Urinary tract signs and symptoms	22	0.94%	91.63%	22	0.68%	93.17%
21	25	Respiratory disorders NEC	20	0.86%	92.49%	20	0.62%	93.79%

Contd. Rank	Sens. Rank	ADR details	Class. n	% Class.	Cumul. Class.	Sens. n	% Sens.	Cumul. sens.
22	26	Bacterial infectious disorders - Clostridia infections	19	0.30%	93.61%	19	0.58%	94.37%
32	27	Gastrointestinal inflammatory conditions	7	0.69%	94.29%	17	0.52%	94.89%
23	28	Hepatobiliary investigations - liver function analyses	16	0.69%	94.98%	16	0.49%	95.39%
24	29	Platelet disorders	16	0.64%	95.62%	16	0.49%	95.88%
25	30	Unspecified / Unclassifiable Blood and lymphatic system disorders	15	0.43%	96.05%	16	0.49%	96.37%
27	31	Gastrointestinal stenosis and obstruction	10	0.39%	96.44%	10	0.31%	96.68%
28	32	Headaches	9	0.34%	96.78%	9	0.28%	96.95%
30	33	Joint disorders - Crystal arthropathic disorders	8	0.34%	97.13%	8	0.25%	97.20%
31	34	Toxicity to various agents	8	0.26%	97.38%	8	0.25%	97.45%
33	35	Disturbances in thinking and perception	6	0.13%	97.51%	6	0.18%	97.63%
39	36	Movement disorders (incl parkinsonism)	3	0.00%	97.51%	6	0.18%	97.82%
62	37	Cognitive and attention disorders and disturbances NEC	0	0.21%	97.73%	6	0.18%	98.00%
34	38	Neurological signs and symptoms NEC	5	0.21%	97.94%	5	0.15%	98.15%
35	39	Unspecified / unclassifiable Hepatobiliary disorders	5	0.13%	98.07%	5	0.15%	98.31%
36	40	Body temperature conditions	3	0.13%	98.20%	4	0.12%	98.43%
42	41	unspecified / unclassifiable respiratory system	3	0.00%	90.69%	4	0.12%	98.55%
37	42	Bone disorders (excl. congenital and fractures) - metabolic bone disorders	3	0.13%	98.33%	3	0.09%	98.65%
38	43	Bone, calcium, magnesium and phosphorus metabolism disorders	3	0.13%	98.46%	3	0.09%	98.74%
40	44	Nephropathies	3	0.13%	98.71%	3	0.09%	98.92%
41	45	Procedural related injuries and complications NEC - Cardiac and vascular procedural complications	3	0.13%	98.84%	3	0.09%	99.02%
43	46	White blood cell disorders	3	0.00%	98.84%	3	0.09%	99.11%
64	47	Missing	0	0.09%	98.93%	3	0.06%	99.17%
44	48	Anterior eye structural change, deposit and degeneration	2	0.09%	99.01%	2	0.06%	99.23%
45	49	Bone and joint injuries	2	0.09%	99.10%	2	0.06%	99.29%
46	50	Cardiac failure	2	0.09%	99.18%	2	0.06%	99.35%

47	51	General system disorders NEC	2	0.09%	99.27%	2	0.06%	99.42%
Contd. Rank	**Sens. Rank**	**ADR details**	**Class. n**	**% Class.**	**Cumul. Class.**	**Sens. n**	**% Sens.**	**Cumul. sens.**
48	52	Glaucoma and ocular hypertension	2	0.04%	99.31%	2	0.06%	99.48%
56	53	Muscle disorders	1	0.09%	99.40%	2	0.06%	99.54%
49	54	Oral soft tissue conditions	2	0.09%	99.49%	2	0.06%	99.60%
50	55	Seizures (incl. subtypes)	2	0.09%	99.57%	2	0.06%	99.66%
51	56	Toxicology and therapeutic drug monitoring - antibiotic level	2	0.04%	99.61%	2	0.03%	99.69%
52	57	Asthenic conditions	1	0.04%	99.66%	1	0.03%	99.72%
53	58	Chest pain	1	0.04%	99.70%	1	0.03%	99.75%
54	59	Gait disturbances	1	0.04%	99.74%	1	0.03%	99.78%
55	60	Inflammations	1	0.04%	99.79%	1	0.03%	99.82%
57	61	Purine and pyrimidine metabolism disorders	1	0.04%	99.83%	1	0.03%	99.85%
58	62	Therapeutic and nontherapeutic effects (excl. toxicity)	1	0.04%	99.87%	1	0.03%	99.88%
59	63	Vascular hypertensive disorders	1	0.13%	98.33%	1	0.09%	98.65%
60	64	Viral infectious disorders - herpes viral infections	1	0.04%	99.91%	1	0.03%	99.91%
61	65	Failure	0	0.00%	99.91%	1	0.03%	99.94%
61	66	Exposures, chemical injuries and poisoning	1	0.04%	99.96%	1	0.03%	99.97%
62	67	CNS Vascular disorder	1	0.04%	100.00 %	1	0.03%	100.00%
			2385*	100.00 %		3251	100.00%	

Sens. – sensitivity, Class. – classifiable by MedDRA-SOC®, cumul. – Cumulative count, excl. – excluding, Incl. – including, NEC – not elsewhere classified.

**2728 ADR presentations reported in nineteen papers,[7-26] 397 reported by papers were not classifiable by MedDRA-SOC® classification, resulting in 2385 ADRs being accounted for in "classifiable" count. Sensitivity analysis applied equal weighting to all presentations in "grouped" reporting therefore overall 3251 presentations accounted for in sensitivity analysis count.*

Green shading represents direct agreement between MedDRA-SOC® classifiable and sensitivity analysis by ranking. Yellow highlights presentation falls in top 10 ranking in either classifiable or sensitivity rankings, and red highlights top 15 in either classifiable of sensitivity rankings. The top 15 in both cases were highlighted within top 20 across two ranking systems.

Risk of Bias (RoB) and Quality Assessment

Appendix 3. Descriptive summary of RoB / Quality justification and judgements of domains of NOS of included observational Studies (provided in alphabetical order)

Ayub 2009, Bowman 1996

Domain description	Ayub [7] 2009 Judgement	Ayub [7] 2009 Justification	Bowman [8] 1996 Judgement	Bowman [8] 1996 Justification
Representativeness of the exposed cohort	1	Description of population, setting, duration of study, selection of participants and sample size calculation.	1	Description of population, setting and duration of study and selection of participants.
Selection of the non exposed cohort	1	Description of population, setting, duration of study and sample size calculation.	1	Description of population, setting and duration of study and selection of participants.
Ascertainment of exposure	1	Description of patient/episode review; personnel conducting review, timing of review, data sources used and data extraction method.	1	Description of patient/episode review; personnel conducting review, timing of review and data sources used.
Demonstration that outcome of interest was not present at start of study	0	Inadequate - no mention of assessment of ADRs prior to admission.	1	Description of review for ADR at admission.
E1 - Assessment of outcome	1	Description of ADR identification, collection of pertaining details, and use of Naranjo algorithm to assess.	1	Description of ADR identification, collection of pertaining details, and evaluation.
E2 - Was follow-up (FUP) long enough for outcomes to occur	1	Description of FUP from admission until discharge / deceased (Intensive Care Unit)	1	Description of FUP from admission, throughout hospital stay until discharge.
E3 - Adequacy of follow up of cohorts	1	All patients followed for duration of ICU admission Missing data - some outcome data missing but accounted for by author	1	Patients adequately followed. No evidence of loss to FUP during hospitalisation (i.e. missing data)

Calderon-Ospina 2010, Cheong 2018

Description	Calderon-Ospina [9] 2010 Judgement	Calderon-Ospina [9] 2010 Justification	Choeng[10,11] 2018 Judgement	Choeng [10,11] 2018 Justification
S1 - Representativeness of the exposed cohort	1	Description of population, setting, selection of participants and sample size calculation.	?	Inadequate – unclear as to how 150 participants were selected.
S2 - Selection of the non exposed cohort	1	Description of population, setting, selection of participants and sample size calculation.	?	Inadequate – unclear as to how 150 participants were selected.
S3 - Ascertainment of exposure	1	Description of patient/episode review; personnel conducting review, timing of review, data	0	Inadequate - Unable to determine method of attainment of exposure

		sources used and data extraction method.		
Contd. **Description**	**Calderon-Ospina [9] 2010 Judgement**	**Calderon-Ospina [9] 2010 Justification**	**Choeng[10,11] 2018 Judgement**	**Choeng [10,11] 2018 Justification**
S4 - Demonstration that outcome of interest was not present at start of study	1	Description of exclusion of patients hospitalized because of an ADR.	0	Inadequate - no mention of assessment of ADRs prior to admission.
E1 - Assessment of outcome	1	Description of method of ADR identification, collection of pertaining details, and independent evaluation (WHO causality).	?	Inadequate – unclear as to the source and method of assessment of outcome.
E2 - Was follow-up (FUP) long enough for outcomes to occur	?	Inadequate – unclear as to duration of FUP.	0	Inadequate - Unable to determine period of follow-up
E3 - Adequacy of follow up of cohorts	1	All data accounted for, no evidence of inadequate FUP.	0	Inadequate- insufficient information to determine adequacy of follow-up of cohorts

Conforti 2012, Corsonello 2009

Description	**Conforti [12] 2012 Judgement**	**Conforti [12] 2012 Justification**	**Corsonello[13] 2009 Judgement**	**Corsonello [13] 2009 Justification**
S1 - Representativeness of the exposed cohort	1	Description of population, setting, duration of study and selection of participants.	1	Description of population, setting, duration of study and selection of participants.
S2 - Selection of the non exposed cohort	1	Description of population, setting, duration of study and selection of participants.	1	Description of population, setting, duration of study and selection of participants.
S3 - Ascertainment of exposure	?	Inadequate – Unclear as to where information for ADR was obtained from	1	Description of patient/episode review; personnel conducting review, timing of review, data sources used and data extraction method.
S4 - Demonstration that outcome of interest was not present at start of study	1	Description of review for ADR at admission.	1	Description of review for ADR at admission.
E1 - Assessment of outcome	?	Inadequate – unclear of how outcomes were assessed.	1	Description of method of ADR identification, collection of pertaining details, and attending physician evaluation.
E2 - Was follow-up (FUP) long enough	1	Description of FUP from admission until discharge.	1	Description of FUP from admission until discharge,

for outcomes to occur				patients were followed up every 3 months for 1 year.
Contd. **Description**	**Conforti [12] 2012 Judgement**	**Conforti [12] 2012 Justification**	**Corsonello[13] 2009 Judgement**	**Corsonello [13] 2009 Justification**
E3 - Adequacy of follow up of cohorts	1	All data accounted for, no evidence of inadequate FUP.	1	All patients followed for duration of admission, then up to 1 year. Missing data - some outcome data missing but accounted for by author

Davies 2009, Fernandez-Regueiro 2011

Description	**Davies [14] 2009 Judgement**	**Davies [14] 2009 Justification**	**Fernandez-Regueiro [27] 2011 Judgement**	**Fernandez-Regueiro [27] 2011 Justification**
S1 - Representativeness of the exposed cohort	1	Description of population, setting, duration of study and selection of participants.	?	Description of population, setting, duration of study. However selection of participants was unclear.
S2 - Selection of the non exposed cohort	1	Description of population, setting, duration of study and selection of participants.	1	Description of population, setting, duration of study.
S3 - Ascertainment of exposure	1	Description of patient/episode review; personnel conducting review, timing of review, data sources used and data extraction method.	?	Detailed description of variables of interest. However, unclear as to how information was obtained, by whom and from which source
S4 - Demonstration that outcome of interest was not present at start of study	1	Description of review for ADR at admission.	1	Description of review for ADR at admission.
E1 - Assessment of outcome	1	Description of method of ADR identification, collection of pertaining details, method of assessment and independent evaluation.	0	Details pertaining to AR scoring systems are listed. However, there is inadequate detail as to by whom and from which source the assessment was conducted.
E2 - Was follow-up (FUP) long enough for outcomes to occur	1	Description of FUP from admission until discharge.	1	Description of FUP from admission until discharge.
E3 - Adequacy of follow up of cohorts	1	All data accounted for, no evidence of inadequate FUP.	1	All data accounted for, no evidence of inadequate FUP.

Ganeva 2016, Ganeva 2013

Description	Ganeva [16] 2016 Judgement	Ganeva [16] 2016 Justification	Ganeva [17] 2013 Judgement	Ganeva [17] 2013 Justification
S1 - Representativeness of the exposed cohort	1	Description of population, setting, duration of study and selection of participants.	1	Description of population, setting, duration of study and selection of participants.
S2 - Selection of the non exposed cohort	1	Description of population, setting, duration of study and selection of participants.	1	Description of population, setting, duration of study and selection of participants.
S3 - Ascertainment of exposure	1	Description of patient/episode review; personnel conducting review, timing of review, data sources used and data extraction method.	1	Description of patient/episode review; timing of review, data sources used and data extraction method.
S4 - Demonstration that outcome of interest was not present at start of study	1	Additional data provided to authors demonstrates differentiation between pre-hospital and in-hospital ADRs.	1	Additional data provided to authors demonstrates differentiation between pre-hospital and in-hospital ADRs.
E1 - Assessment of outcome	1	Description of method of ADR identification, collection of pertaining details, method of assessment and independent evaluation.	?	Unclear - scoring systems are mentioned, no information in paper or the supplied additional data explains how the outcomes were assessed.
E2 - Was follow-up long enough for outcomes to occur	1	Description of FUP from admission until discharge.	0	Inadequate - no mention in methods
E3 - Adequacy of follow up of cohorts	1	All data accounted for, no evidence of inadequate FUP.	1	All data accounted for, no evidence of inadequate FUP.

Ganeva 2007, Giardina 2018

Description	Ganeva [15] 2007 Judgement	Ganeva [15] 2007 Justification	Giardina [28] 2018 Judgement	Giardina [28] 2018 Justification
S1 - Representativeness of the exposed cohort	1	Description of population, setting, duration of study and selection of participants.	1	Description of population, setting, duration of study and selection of participants.
S2 - Selection of the non exposed cohort	1	Description of population, setting, duration of study and selection of participants.	1	Description of population, setting, duration of study and selection of participants.
S3 - Ascertainment of exposure	1	Description of patient/episode review; personnel conducting review, timing of review, data sources used and data extraction method.	1	Description of patient/episode review; personnel conducting review, data sources used and data extraction method.
S4 - Demonstration that outcome of interest was not	1	Description of review for ADR at admission.	1	Description of review for ADR at admission.

present at start of study				
Contd. **Description**	**Ganeva [15] 2007 Judgement**	**Ganeva [15] 2007 Justification**	**Giardina [28] 2018 Judgement**	**Giardina [28] 2018 Justification**
E1 - Assessment of outcome	1	Description of method of ADR identification, collection of pertaining details, method of assessment and independent evaluation.	1	Description of method of ADR identification, collection of pertaining details, method of assessment and independent evaluation.
E2 - Was follow-up long enough for outcomes to occur	0	Inadequate - no mention in methods	1	Description of FUP from admission until discharge.
E3 - Adequacy of follow up of cohorts	1	All data accounted for, no evidence of inadequate FUP.	1	All data accounted for, no evidence of inadequate FUP.

Gonzalez-Martin 1997, Hailu 2020

Description	**Gonzalez-Martin [18] 1997 Judgement**	**Gonzalez-Martin [18] 1997 Justification**	**Hailu [19] 2020 Judgement**	**Hailu [19] 2020 Justification**
S1 - Representativeness of the exposed cohort	1	Description of population, setting, duration of study and selection of participants.	1	Description of population, setting, duration of study and selection of participants.
S2 - Selection of the non exposed cohort	1	Description of population, setting, duration of study and selection of participants.	1	Description of population, setting, duration of study and selection of participants.
S3 - Ascertainment of exposure	1	Description of patient/episode review; personnel conducting review, timing of review, data sources used and data extraction method. (source was referenced)	1	Description of patient/episode review; data sources used and data extraction method.
S4 - Demonstration that outcome of interest was not present at start of study	0	Inadequate - no mention of assessment of ADRs prior to admission.	0	Inadequate - no mention of assessment of ADRs prior to admission.
E1 - Assessment of outcome	1	Description of method of ADR identification, collection of pertaining details, method of assessment and evaluation. (source was referenced)	1	Description of method of ADR identification, collection of pertaining details, method of assessment and evaluation.
E2 - Was follow-up long enough for outcomes to occur	0	Inadequate - No description of period of follow-up reported.	0	Inadequate - No description of period of follow-up reported.
E3 - Adequacy of follow up of cohorts	1	All data accounted for, no evidence of inadequate FUP.	1	All data accounted for, no evidence of inadequate FUP.

Harugeri 2011, Kaur 2018

Description	Harugeri [29] 2011 Judgement	Harugeri [29] 2011 Justification	Kaur [20] 2018 Judgement	Kaur [20] 2018 Justification
S1 - Representativeness of the exposed cohort	1	Description of population, setting, duration of study and selection of participants.	1	Description of population, setting, duration of study and selection of participants.
S2 - Selection of the non exposed cohort	1	Description of population, setting, duration of study and selection of participants.	1	Description of population, setting, duration of study and selection of participants.
S3 - Ascertainment of exposure	1	Description of patient/episode review; personnel conducting review, timing of review, data sources used and data extraction method.	1	Description of patient/episode review; personnel conducting review, timing of review, data sources used and data extraction method.
S4 - Demonstration that outcome of interest was not present at start of study	0	Inadequate - no mention of assessment of ADRs prior to admission.	0	Inadequate - no mention of assessment of ADRs prior to admission.
E1 - Assessment of outcome	1	Description of method of ADR identification, collection of pertaining details, method of assessment and independent evaluation.	1	Description of method of ADR identification, collection of pertaining details, assessment and evaluation.
E2 - Was follow-up long enough for outcomes to occur	1	Description of FUP from admission until discharge.	1	Description of FUP from admission until discharge.
E3 - Adequacy of follow up of cohorts	1	All data accounted for, no evidence of inadequate FUP.	1	All patients followed until discharge. Missing data - some outcome data missing but accounted for by author

Lavan 2017, Leach 1986

Description	Lavan [30] 2017 Judgement	Lavan [30] 2017 Justification	Leach [21] 1986 Judgement	Leach [21] 1986 Justification
S1 - Representativeness of the exposed cohort	1	Description of population, setting, duration of study and selection of participants.	1	Description of population, setting, duration of study and selection of participants.
S2 - Selection of the non exposed cohort	1	Description of population, setting, duration of study and selection of participants.	1	Description of population, setting, duration of study and selection of participants.
S3 - Ascertainment of exposure	1	Description of patient/episode review; personnel conducting review, timing of review, data sources used and data extraction method.	1	Description of patient/episode review; personnel conducting review, timing of review,

				data sources used and data extraction method.
Contd. **Description**	**Lavan [30] 2017 Judgement**	**Lavan [30] 2017 Justification**	**Leach [21] 1986 Judgement**	**Leach [21] 1986 Justification**
S4 - Demonstration that outcome of interest was not present at start of study	1	Events were classified as prevalent if they occurred prior to enrolment and as incident if they occurred after enrolment.	0	Inadequate - no mention of assessment of ADRs prior to admission.
E1 - Assessment of outcome	1	Description of method of ADR identification, collection of pertaining details, method of assessment and independent evaluation.	?	Unclear - methods outline a definition, probability of causality and severity criteria for ADRs. However, there it is unclear as to who conducted the assessment.
E2 - Was follow-up long enough for outcomes to occur	1	Description of FUP from admission until discharge or within 14 days of enrolment, whichever came first.	0	Inadequate - No description of period of follow-up reported.
E3 - Adequacy of follow up of cohorts	1	All data accounted for, no evidence of inadequate FUP.	1	All data accounted for, no evidence of inadequate FUP.

Liao 2019, Mohebbi 2010

Description	**Liao [31] 2019 Judgement**	**Liao [31] 2019 Justification**	**Mohebbi [32] 2010 Judgement**	**Mohebbi [32] 2010 Justification**
S1 - Representativeness of the exposed cohort	1	Retrospective identification from established database* Description of population, setting, duration of study and selection of participants.	1	Description of population, setting, duration of study and selection of participants.
S2 - Selection of the non exposed cohort	1	Retrospective identification from established database. Description of population, setting, duration of study and selection of participants.	1	Description of population, setting, duration of study and selection of participants.
S3 - Ascertainment of exposure	1	Description of established mandated ADR reporting system.	1	Description of patient/episode review; personnel conducting review, timing of review, data sources used and data extraction method.
S4 - Demonstration that outcome of interest was not present at start of study	0	Inadequate - no mention of assessment of ADRs prior to admission.	0	Inadequate - no mention of assessment of ADRs prior to admission.

E1 - Assessment of outcome	1	Description of method of ADR identification, collection of pertaining details, method of assessment and independent evaluation.	?	Unclear – methods outline ADR scoring systems. Inadequate detail as to by whom the assessment was conducted
Contd. **Description**	**Liao [31] 2019 Judgement**	**Liao [31] 2019 Justification**	**Mohebbi [32] 2010 Judgement**	**Mohebbi [32] 2010 Justification**
E2 - Was follow-up long enough for outcomes to occur	1	Description of FUP from admission until discharge.	0	Inadequate - No description of period of follow-up reported.
E3 - Adequacy of follow up of cohorts	1	All data accounted for, no evidence of inadequate FUP.	1	All data accounted for, no evidence of inadequate FUP.

**Liao et al. was subsequently excluded from analyses based on concerns regarding potential reporting bias in the accuracy of the reported ADR rates in the database it was conducted from*

Mugosa 2015, O'Connor 2012

Description	**Mugosa [33] 2015 Judgement**	**Mugosa [33] 2015 Justification**	**O'Connor [22] 2012 Judgement**	**O'Connor [22] 2012 Justification**
S1 - Representativeness of the exposed cohort	?	Description of population, setting, duration of study. However, selection of 200 participants is unclear.	1	Description of population, setting, duration of study and selection of participants.
S2 - Selection of the non exposed cohort	1	Description of population, setting, duration of study.	1	Description of population, setting, duration of study and selection of participants.
S3 - Ascertainment of exposure	0	Inadequate – solely patient reported ADRs. No Description of objective patient/episode review; personnel conducting review, timing of review, data sources used and data extraction method.	1	Description of patient/episode review; personnel conducting review, timing of review, data sources used and data extraction method.
S4 - Demonstration that outcome of interest was not present at start of study	0	Inadequate - no mention of assessment of ADRs prior to admission.	0	Inadequate - no mention of assessment of ADRs prior to admission.
E1 - Assessment of outcome	?	Methods detail "discussion" between researcher and doctor after patient reports ADR. Unclear method of assessment and evaluation.	1	Description of method of ADR identification, collection of pertaining details, method of assessment and independent evaluation.
E2 - Was follow-up long enough for outcomes to occur	0	Inadequate - No description of period of follow-up reported.	0	Inadequate – FUP on day 5 and day 10. Potential for ADRs to occur after this and prior to discharge.
E3 - Adequacy of follow up of cohorts	1	All data accounted for, no evidence of inadequate FUP.	1	All data accounted for, no evidence of inadequate FUP.

Onder 2010, Reichel 1965

Description	Onder [24] 2010 Judgement	Onder [24] 2010 Justification	Reichel [26] 1965 Judgement	Reichel [26] 1965 Justification
S1 - Representativeness of the exposed cohort	1	Description of population, setting, duration of study and selection of participants.	1	Description of population, setting, duration of study and selection of participants.
S2 - Selection of the non exposed cohort	1	Description of population, setting, duration of study and selection of participants.	1	Description of population, setting, duration of study and selection of participants.
S3 - Ascertainment of exposure	1	Description of patient/episode review; personnel conducting review, timing of review, data sources used and data extraction method.	1	Description of patient/episode review; timing of review, data sources used and data extraction method.
S4 - Demonstration that outcome of interest was not present at start of study	1	Description of review for ADR at admission. ADRs that were observed at hospital admission or that caused hospital admission were excluded.	1	Description of review for ADR at admission. "the development of a new problem that was not present at the time of admission. "
E1 - Assessment of outcome	0	Inadequate – methods detail ADR scoring systems. Inadequate detail as to by whom the assessment was conducted and evaluation.	1	Description of method of ADR identification, method of assessment and evaluation.
E2 - Was follow-up long enough for outcomes to occur	1	Description of FUP from admission until discharge.	1	Description of FUP from admission until discharge.
E3 - Adequacy of follow up of cohorts	1	All data accounted for, no evidence of inadequate FUP.	1	All data accounted for, no evidence of inadequate FUP.

Tangiisuran 2012, Tangiisuran 2014

Description	Tangiisuran[34] 2012 Judgement	Tangiisuran [34] 2012 Justification	Tangiisuran [35] 2014 Judgement	Tangiisuran [35] 2014 Justification
S1 - Representativeness of the exposed cohort	1	Description of population, setting, duration of study and selection of participants.	1	Description of population, setting, duration of study and selection of participants.
S2 - Selection of the non exposed cohort	1	Description of population, setting, duration of study and selection of participants.	1	Description of population, setting, duration of study and selection of participants.
S3 - Ascertainment of exposure	1	Description of patient/episode review; personnel conducting review, timing of review, data	1	Description of patient/episode review; personnel conducting review, timing of review,

		sources used and data extraction method.		data sources used and data extraction method.
Contd. Description	**Tangiisuran[34] 2012 Judgement**	**Tangiisuran [34] 2012 Justification**	**Tangiisuran [35] 2014 Judgement**	**Tangiisuran [35] 2014 Justification**
S4 - Demonstration that outcome of interest was not present at start of study	0	Inadequate - no mention of assessment of ADRs prior to admission.	0	Inadequate - no mention of assessment of ADRs prior to admission.
E1 - Assessment of outcome	1	Description of method of ADR identification, collection of pertaining details, method of assessment and independent evaluation.	1	Description of method of ADR identification, collection of pertaining details, method of assessment and independent evaluation.
E2 - Was follow-up long enough for outcomes to occur	1	Description of FUP from admission until discharge.	1	Description of FUP from admission until discharge.
E3 - Adequacy of follow up of cohorts	1	All data accounted for, no evidence of inadequate FUP.	1	All data accounted for, no evidence of inadequate FUP.

Appendix 4. Summary of Observational Studies Quality Assessment

Quality / Risk of Bias assessment based on Modified Newcastle-Ottawa Scale [NOS] domains.

		NOS Domain								
Author	**Year**	**S1 -Representativeness of the exposed cohort**	**S2 - Selection of the non exposed cohort**	**S3 - Ascertainment of exposure**	**S4 - Demonstration that outcome of interest was not present at start of study**	**E1 - Assessment of outcome**	**E2 - Was follow-up long enough for outcomes to occur**	**E3 - Adequacy of follow up of cohorts**	**NOS Score Total**	**ADR proportion (95% CI)**
Ayub[7]	2009	+	+	+	-	+	+	+	6	0.07 (0.03-0.14)
Bowman[8]	1996	+	+	+	+	+	+	+	7	0.30 (0.24-0.35)
Calderon-Ospina[9]	2010	+	+	+	+	+	?	+	6	0.23 (0.12-0.37)
Choeng[10,11]	*2018*	?	+	-	-	?	-	-	*1*	*0.69 (0.61-0.77)*
Conforti[12]	*2012*	+	+	?	+	?	+	+	*5*	*0.25 (0.22-0.28)*
Corsonello[13]	*2009*	+	+	+	+	+	+	+	*7*	*0.11 (0.09-0.15)*
Davies[14]	2009	+	+	+	+	+	+	+	7	0.18 (0.17-0.20)
Fernandez-Regueiro[27]	*2011*	?	+	?	+	-	+	+	*4*	*0.12 (0.07-0.21)*
Ganeva[16]	2016	+	+	+	+	+	+	+	7	0.05 (0.02-0.09)
Ganeva[17]	2013	+	+	+	+	?	-	+	5	0.09 (0.06-0.14)
Ganeva[15]	2007	+	+	+	+	+	-	+	6	0.06 (0.03-0.10)
Giardina[28]	2018	+	+	+	+	+	+	+	7	0.03 (0.03-0.04)
Gonzalez-Martin[18]	1997	+	+	+	-	+	-	+	5	0.33 (0.24-0.43)
Hailu[19]	*2020*	+	+	+	-	+	-	+	*5*	*0.02 (0.01-0.07)*
Harugeri[29]	2011	+	+	+	-	+	+	+	6	0.30 (0.26-0.35)
Kaur[20]	2018	+	+	+	-	+	+	+	6	0.15 (0.12-0.19)

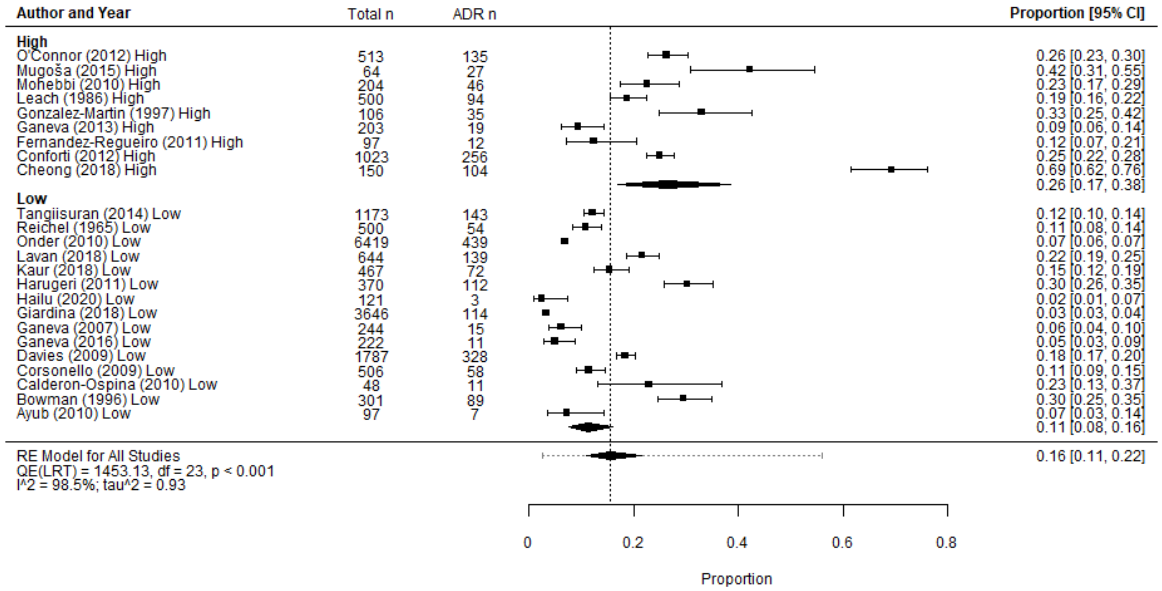
Supplemental Materials – ***In-hospital adverse drug reactions in older adults; prevalence, presentation and associated drugs – a systematic review and meta-analysis***

Author	Year	S1 -Representativeness of the exposed cohort	S2 - Selection of the non exposed cohort	S3 - Ascertainment of exposure	S4 - Demonstration that outcome of interest was not present at start of study	E1 - Assessment of outcome	E2 - Was follow-up long enough for outcomes to occur	E3 - Adequacy of follow up of cohorts	NOS Score Total	ADR proportion (95% CI)
Lavan[30]	*2017*	+	+	+	+	+	+	+	*7*	*0.22 (0.18-0.25)*
Leach[21]	*1986*	+	+	+	-	?	-	+	*4*	*0.19 (0.15-0.23)*
Liao*[31]	*2019*	+	+	+	-	+	+	+	*6*	*0.01 (0.01-0.01)*
Mohebbi[32]	2010	+	+	+	-	?	-	+	4	0.23 (0.17-0.29)
Mugosa[33]	2015	?	+	-	-	?	-	+	2	0.42 (0.30-0.55)
O'Connor[22]	*2012*	+	+	+	-	+	-	+	*5*	*0.26 (0.23-0.30)*
Onder[24]	*2010*	+	+	+	+	-	+	+	*6*	*0.07 (0.06-0.07)*
Reichel[26]	1965	+	+	+	+	+	+	+	7	0.11 (0.08-0.14)
Tangiisuran[34]	*2012*	+	+	+	-	+	+	+	*6*	*0.13 (0.11-0.16)*
Tangiisuran[35]	*2014*	+	+	+	-	+	+	+	*6*	*0.12 (0.10-0.14)*

+ green indicates study was awarded item on assessment low risk of bias; ? yellow indicates description of the item was unclear unclear risk of bias; - red - indicates the item was not described high risk of bias; *italics* identifies studies where all participants were ≥ 65 years.

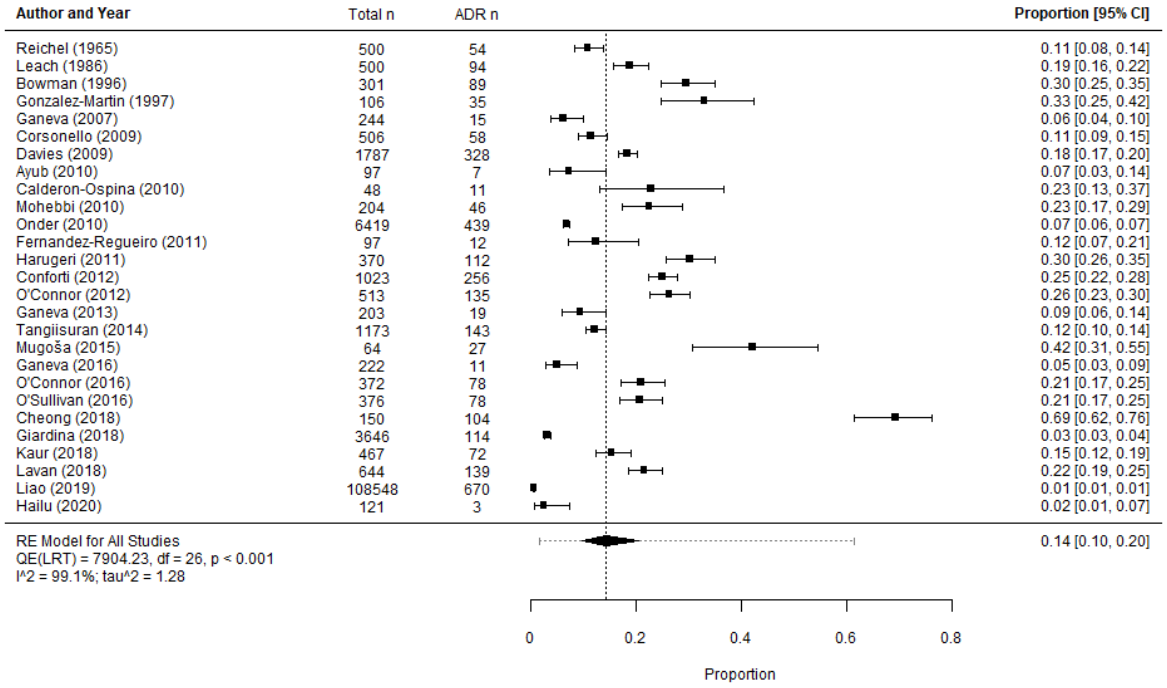
*Liao et al. was subsequently excluded from analyses based on concerns regarding potential reporting bias in the accuracy of the reported ADR rates in the database it was conducted from i.e. retrospective study retrospective based on all reported ADR cases over 6 year period in a single medical centre. It is well established that ADRs are consistently underreported and potentially only 6% of true ADRs are recorded in reporting systems.[36]

Appendix 5. Observational studies grouped by study quality (p=0.003)



Low – low risk of bias/good quality. High – high risk of bias/poor quality

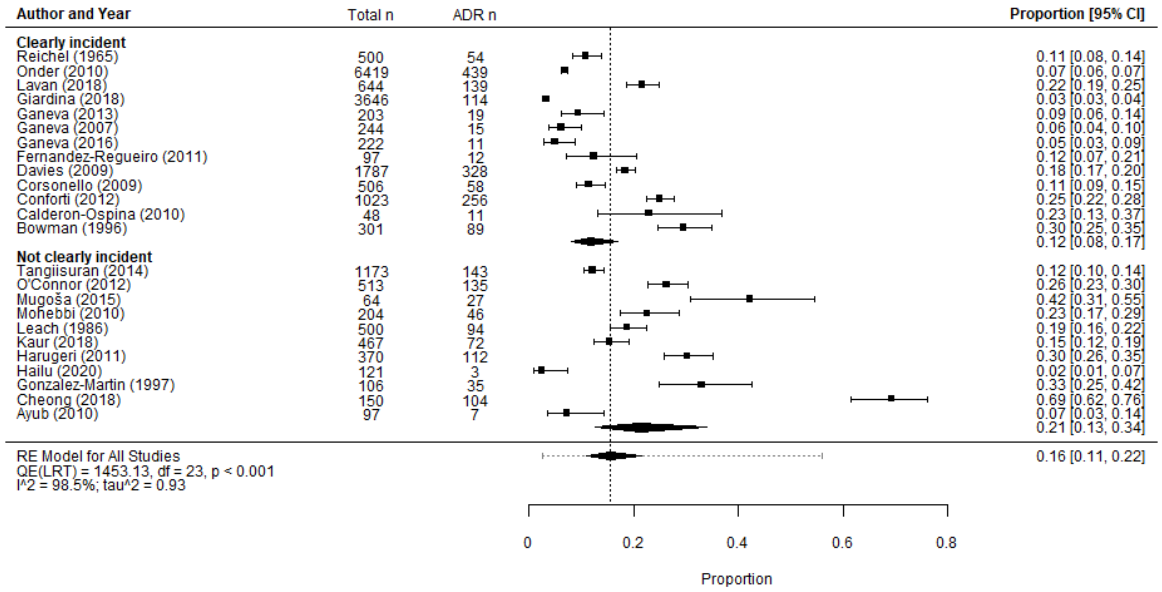
Appendix 6. Forrest plot showing proportion of patients aged 65 years or older experiencing an in-hospital ADR - including Liao *et al.** [31]



Pooled estimate by random effects (RE) model 0.1423 (0.0970-0.2039) I^2=99.15% τ^2=1.28

*Liao et al. was subsequently excluded from analyses based on concerns regarding potential reporting bias in the accuracy of the reported ADR rates in the database it was conducted from i.e. retrospective study retrospective based on all reported ADR cases over a 6 year period in a single medical centre. It is well established that ADRs are consistently underreported and potentially only 6% of true ADRs are recorded in reporting systems.[36]

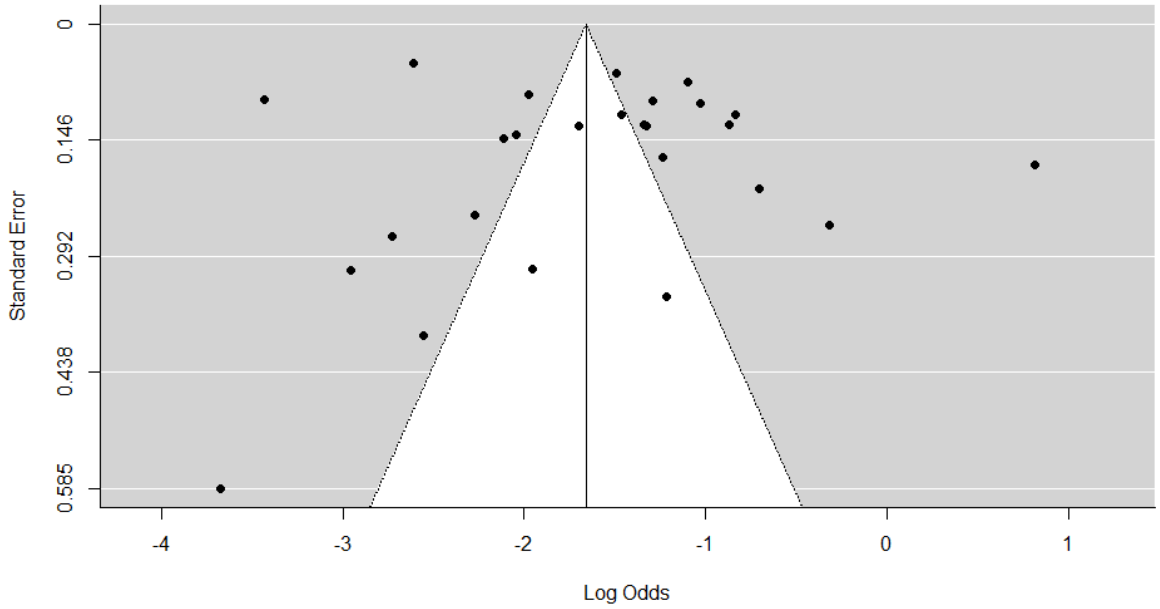
Appendix 7. Observational studies grouped according to NOS Domain S4 - demonstration that outcome of interest (ADR) was not present at start of study



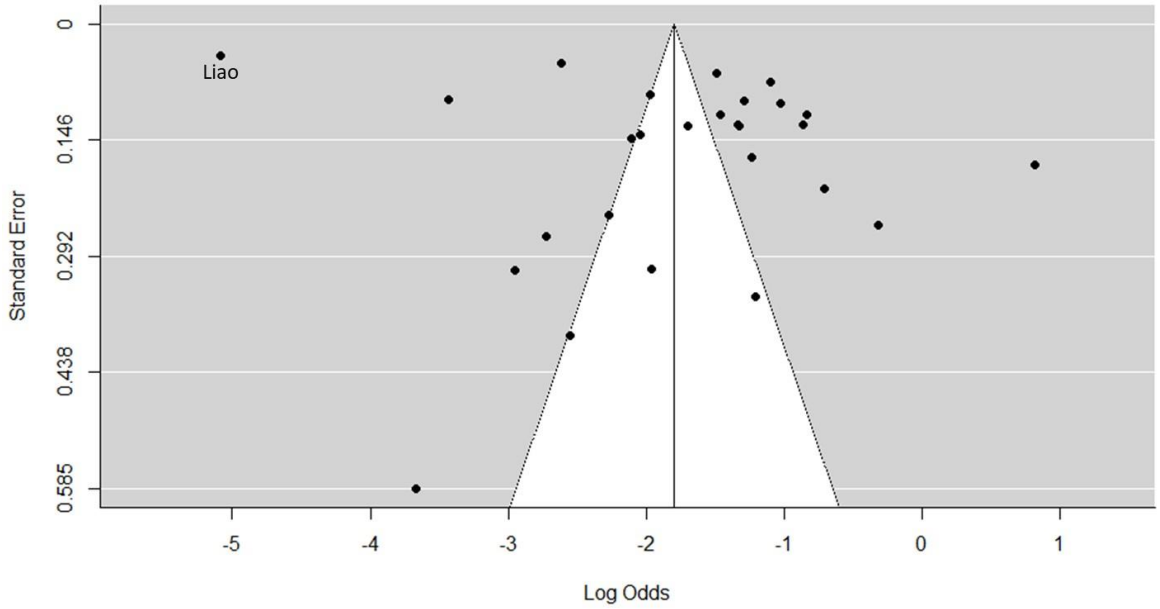
Clearly incident – study illustrated that ADRs were not present at admission/enrolment into study; Not clearly incident – study did not adequately describe if ADRs were present at admission/enrolment

Appendix 8. Funnel plots of included studies

Funnel plot excluding Liao *et al.*[31]



Funnel plot including Liao *et al.*[31]

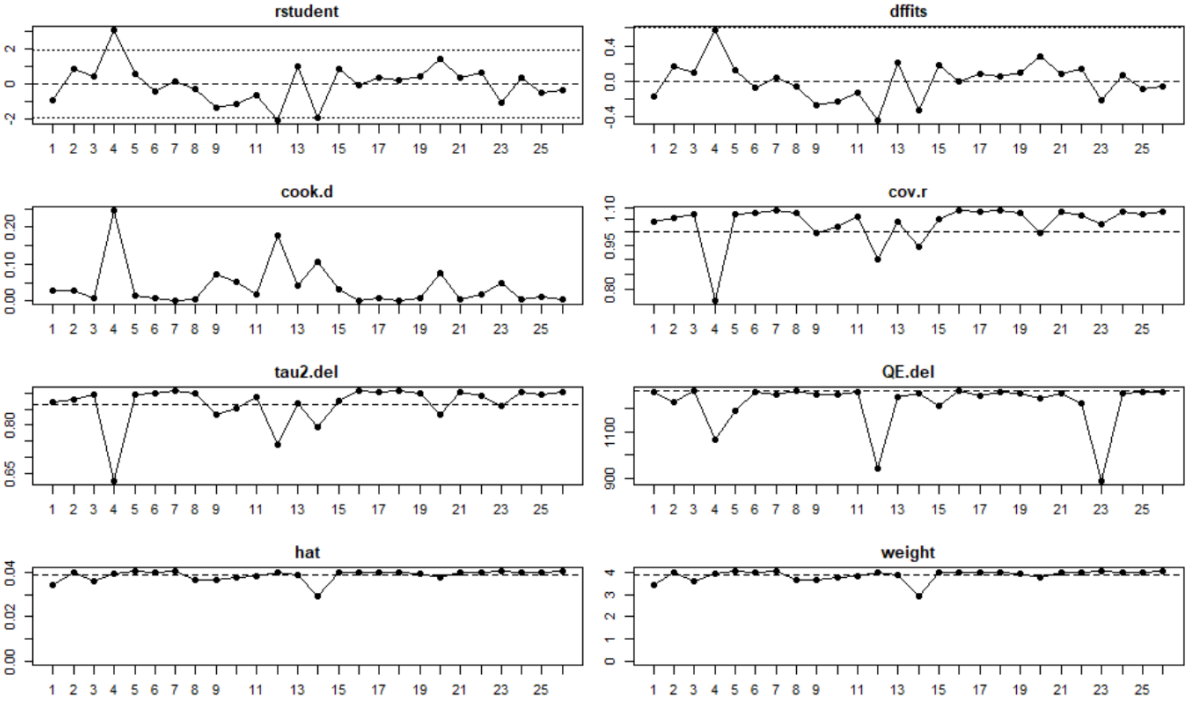


Appendix 9. Cochrane Risk of Bias (RoB) 2.0 Assessment of Randomised Control Trials (RCT).

Description	O'Connor [23] 2016 Judgement	Justification (O'Connor[23])	O'Sullivan[25] 2016 Judgement	Justification (O'Sullivan[25])
Random sequence generation	Unclear risk of bias	Quote: Two lists of attending consultants were generated such that the combined rates of ADRs in these groups were known to be comparable from an ADR assessment study completed shortly before the initiation of the present clinical trial. Having finalized the composition of the lists, one list of specialist consultants was assigned as the intervention arm of the study and the other list of specialist consultants as the control arm. Comment: no evidence of random sequence generation	Unclear risk of bias	Quote: we generated two clusters of attending consultants… one group (cluster) of specialist consultants was allocated the intervention arm of the study while the other group (cluster) of specialist consultants was allocated the control arm. Comment: no evidence of random sequence generation
Allocation concealment	Low risk of bias	Quote: to avoid potentially biased selection of subjects into either arm of the study, we approached prospective trial participants in the order of their admission to the hospital Comment:	Low risk of bias	Quote: to avoid potentially biased selection of subjects into either arm of the study, the primary researcher approached prospective trial participants in the order of their admission to the hospital Comment:
Blinding of participants and personnel. Assessments should be made for each main outcome (or class of outcomes).	High risk of bias	Quote: cluster RCT design was chosen for two reasons, namely the intervention could not be double blinded (because of its nature) and the need to avoid possible "training effect". MNO'C recruited and conducted intervention and then screened for outcome.	High risk of bias	Primary researcher who recruited patients was the same researcher who carried out the intervention, so researcher was not blinded
Blinding of outcome assessment. Assessments should be made for each main outcome (or class of outcomes).	Low risk of bias	Quote: The primary researcher judged whether an ADR had occurred… and corroboration of the clinical event or observation by a second researcher who was blinded to the randomization group of the participant	Unclear risk of bias	Quote: the research pharmacist performed ADR ascertainment… a physician trained in geriatric pharmacology / therapeutics reviewed and verified all putative ADRs… subsequently two experienced pharmacists verified ADRs. Comment: unclear of blinding
Incomplete outcome data. Assessments should be made for each main outcome (or class of outcomes).	Low risk of bias	All patients included in reporting including those who died during their hospitalisation	Low risk of bias	All patients included in reporting including those who died during their hospitalisation
Selective reporting	Low risk of bias	Authors reported data on each outcome from the aims	Low risk of bias	Authors reported data on each outcome from the aims
Other sources of bias	N/A	-	N/A	-

Green – low risk of bias, yellow – unclear of risk of bias, red high risk of bias

Regression diagnostics



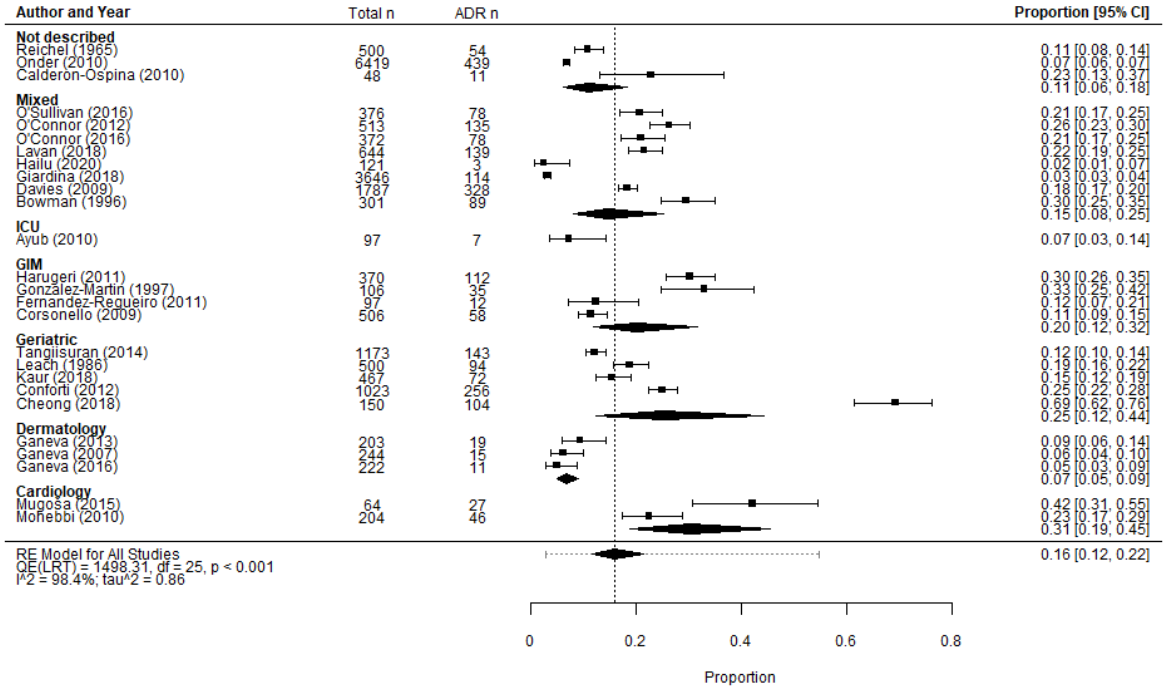

```
##
##    estimate    zval  pval ci.lb ci.ub        Q    Qp  tau2     I2     H2
## 1     0.167  -8.438 0.000 0.121 0.225 1273.542 0.000 0.870 98.492 66.309
## 2     0.158  -8.708 0.000 0.114 0.215 1228.850 0.000 0.879 98.457 64.821
## 3     0.160  -8.566 0.000 0.115 0.218 1275.527 0.000 0.896 98.534 68.194
## 4     0.150 -10.596 0.000 0.113 0.196 1066.445 0.000 0.627 97.887 47.335
## 5     0.159  -8.594 0.000 0.114 0.217 1190.604 0.000 0.893 98.367 61.234
## 6     0.164  -8.374 0.000 0.118 0.223 1272.939 0.000 0.898 98.499 66.627
## 7     0.161  -8.452 0.000 0.116 0.220 1259.183 0.000 0.906 98.325 59.702
## 8     0.164  -8.407 0.000 0.118 0.223 1277.368 0.000 0.899 98.536 68.311
## 9     0.169  -8.516 0.000 0.124 0.227 1262.344 0.000 0.831 98.420 63.273
## 10    0.168  -8.455 0.000 0.122 0.226 1264.054 0.000 0.852 98.454 64.682
## 11    0.165  -8.389 0.000 0.120 0.224 1272.956 0.000 0.886 98.510 67.111
## 12    0.173  -8.813 0.000 0.129 0.229  941.909 0.000 0.742 98.126 53.372
## 13    0.157  -8.796 0.000 0.114 0.213 1252.662 0.000 0.867 98.472 65.466
## 14    0.171  -8.686 0.000 0.126 0.227 1266.920 0.000 0.793 98.352 60.671
## 15    0.158  -8.727 0.000 0.114 0.214 1211.473 0.000 0.876 98.439 64.058
## 16    0.162  -8.409 0.000 0.117 0.221 1277.795 0.000 0.906 98.504 66.863
## 17    0.160  -8.517 0.000 0.115 0.218 1254.712 0.000 0.901 98.454 64.692
## 18    0.161  -8.463 0.000 0.116 0.219 1271.864 0.000 0.905 98.490 66.208
## 19    0.160  -8.541 0.000 0.115 0.218 1268.650 0.000 0.899 98.515 67.322
## 20    0.155  -9.055 0.000 0.113 0.210 1246.010 0.000 0.831 98.414 63.044
## 21    0.160  -8.506 0.000 0.115 0.218 1267.109 0.000 0.902 98.497 66.549
## 22    0.159  -8.625 0.000 0.114 0.216 1225.292 0.000 0.889 98.443 64.206
## 23    0.168  -8.421 0.000 0.122 0.226  885.258 0.000 0.858 98.119 53.160
## 24    0.160  -8.501 0.000 0.115 0.219 1267.775 0.000 0.903 98.498 66.570
## 25    0.165  -8.373 0.000 0.119 0.224 1271.008 0.000 0.895 98.497 66.535
## 26    0.164  -8.373 0.000 0.118 0.223 1270.401 0.000 0.901 98.439 64.045
```

Regression diagnostics illustrating the pooled estimates when excluding one study at a time – these values do not change considerably therefore no one study is highly influential.

4 = Cheong (2018)[10,11], 12 = Giardina (2018)[28], 23 = Onder (2010)[24]

Subgroup Analyses

Appendix 10. Reported ADR events and ADR proportions for all included papers/studies, grouped by specialist service setting (p=0.051)



Description of ADR Identification and Assessment Methodologies Employed by all Included Papers/studies

Appendix 11. Description of ADR Identification and Assessment Methodologies Employed by all Included Papers/studies

Author	Year	ADR Definition	Identification Method	Causality	Severity	Classification	Preventability
Ayub[7]	2009	WHO	Pharmacist, chart review at 3 TPs, adapted from National Health Surveillance Agency	Naranjo	Not documented	Rawlins & Thompson	Not documented
Bowman[8]	1996	Local therapeutic committee	2 x Pharmacist, chart review, ≥ 3 TPs, indicator flag list and spontaneous reporting	Naranjo	Venulet	Rawlins & Thompson	Not documented
Calderon-Ospina[9]	2010	WHO	2 x two internal physicians, daily assessment, patient questioning and panel adjudication	WHO-UMC	Author defined	DoTS	Schumock & Thornton
Cheong[10,11]	2018	Not Documented	Retrospective chart review	Naranjo	Hartwig	Not documented	Not documented
Conforti[12]	2012	Edwards & Aronson	Nurse and Physician, "patients were monitored"	Not documented	WHO-ART	WHO-ART	Not documented
Corsonello[13]	2009	WHO	Physician, daily review of chart, laboratory results, discussion with nurse and attending physician.	Not documented	Author defined	Not documented	Not documented
Davies[14]	2009	Edwards & Aronson	Research pharmacist, daily review patients' drug charts, medical and nursing notes.	Naranjo	Hartwig	Rawlins & Thompson	Hallas

Contd. Author	Year	ADR Definition	Identification Method	Causality	Severity	Classification	Preventability
Fernandez-Regueiro[27]	2011	Bates reference	Not documented	Naranjo	Spanish system of pharmacovigilance	Not documented	Not documented
Ganeva[15]	2007	WHO	3 x Dermatologist and pharmacologist, Structured review past medical and drug history, laboratory tests, clinical description of adverse event and outcome.	Naranjo	Author defined	WHO-ART & Rawlins	Not documented
Ganeva[17]	2013	WHO	Medical chart review	Naranjo	author defined – "clinical judgement" mild, moderate, severe"	WHO-ART	Not documented
Ganeva[16]	2016	WHO	Screened during clinical rounds, analysis of laboratory data.	Naranjo	Hartwig	WHO-ART	Hallas
Giardina[28]	2018	Not documented	Medical records screened by pharmacist, then research team review	Naranjo	EMA	MedDRA-SOC®	Schumock & Thornton
Gonzalez-Martin[18]	1997	Author defined - prior publication	The pharmacovigilance described by the Boston Collaborative Drug Surveillance Program	Naranjo	Author defined - lethal, severe, moderate	Not documented	Not documented
Hailu[19]	2020	WHO	Four MSc clinical pharmacists identified and documented DRPs (patient questionnaire and chart review.	Naranjo	Hartwig	Rawlins & Thompson	Not documented
Harugeri[29]	2011	WHO	Pharmacist, daily review of chart, laboratory and nursing notes.	Naranjo	Hartwig	WHO-ART	Not documented

Contd. Author	Year	ADR Definition	Identification Method	Causality	Severity	Classification	Preventability
Kaur[20]	2018	Edwards & Aronson's	Spontaneous reporting, chart and laboratory results review then geriatrician physician and pharmacologist assessment	Naranjo	Hartwig	Rawlins & Thompson	Not documented
Lavan[30]	2017	WHO	Application of trigger list at recruitment and then retrospectively at D14/DC, all cases adjudicated	WHO-UMC	Hartwig	Not documented	Not documented
Leach[21]	1986	WHO	Patient interview and notes review	Kramer	Hurwitz	Rawlins & Thompson	Not documented
Liao[31]	2019	Edwards & Aronson's	Interrogation of ADR reporting database (ADRs approved by senior pharmacist)	Naranjo	Not documented	Not documented	Not documented
Mohebbi[32]	2010	WHO	Pharmacist; daily patient interview, chart and lab results review; confirmatory discussion with physicians	WHO-UMC	WHO-ART	Not documented	Not documented
Mugosa[33]	2015	WHO	SPC/ADR specific questionnaire and patient interview, discussion between interviewer and physician	Naranjo	WHO-ART	Meyboom, Rawlins and System organ	Not documented
O'Connor[22]	2012	Not Documented	Physician; review of medications labs and notes at D5 & D10; patient and physician consultation	WHO-UMC	Author defined - severe, moderate, mild	Not documented	Not documented

Contd. Author	Year	ADR Definition	Identification Method	Causality	Severity	Classification	Preventability
O'Connor[23]	2016	WHO	Not documented	WHO-UMC	Author defined	Not documented	Hallas
Onder[24]	2010	WHO	Physician; daily review of nursing and medical notes	Naranjo	Author defined	Not documented	Not documented
O'Sullivan[25]	2016	WHO	Pharmacist; D7-10/DC interview with patient or NOK; review of notes, labs, Kardex® and trigger list. ADRs adjudicated by geriatrician.	WHO-UMC	Hartwig	Not documented	Not documented
Reichel[26]	1965	Author defined - "new problem"	Physician; daily chart review - labs, medical and nursing notes, Kardex®, investigations, autopsy reports	Not documented	Not documented	Not documented	Not documented
Tangiisuran[34]	2012	Edwards & Aronson	3 step process – identify, confirm and classify; daily review of labs, notes, prescriptions	Hallas	Morimoto	Rawlins & Thompson	Hallas
Tangiisuran[35]	2014	Edwards & Aronson [D] Not documented [V]	Primary investigator trigger tool and review of medical and nursing notes, labs, drug charts and incident forms	Hallas [D] Naranjo [V]	Not documented	Not documented	Not documented

WHO – World Health Organisation, TP – Time point WHO-UMC – World Health Organisation Uppsala Monitoring Centre, DoTs – Dose, time and susceptibility classification, WHO-ART – World Health Organisation Adverse Drug Reaction Terminology, EMA - European Medicines Agency, MedDRA-SOC® - Medical Dictionary for Regulatory Activities

Supplemental Materials – ***In-hospital adverse drug reactions in older adults; prevalence, presentation and associated drugs – a systematic review and meta-analysis***

System Organ Classes, D – Day, DC – Discharge, SPC – Summaries of Product Characteristics, NOK – next of kin, [D] – development group, [V] – validation group, DoTs –.; DRPs – drug related problems.

Definitions

WHO[37] *"a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."*

Edwards and Aronson[38] *"an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product."*

Bates[39] *"Adverse drug event - An injury resulting from medical intervention related to a drug."*

Causality

Naranjo[40] *definite, probable, possible, doubtful. Event scored across 10 questions (answers Yes, No, Don't Know) Total scores range from -4 to +13; ≥9 indicates a definite adverse drug reaction (ADR); a score of 5 to 8 indicates a probable ADR; a score of 1 to 4 indicates a possible ADR; a score of ≤ 0 indicates that an ADR is doubtful. Q1 Are there previous conclusive reports on this reaction? (+1, 0, 0) Q2 Did the adverse event occur after the suspected drug was administered? (+2, -1, 0) Q3 Did the adverse reaction improve when the drug was discontinued or an antagonist was administered? (+1, 0, 0) Q4 Did the adverse reaction reappear when the drug was re-administered? (+2, -1, 0) Q5 Are there alternative causes (other than the drug) that could have on their own caused the reaction? (-1, +2, 0) Q6 Did the reaction reappear when a placebo was given? (-1, +1, 0) Q7 Was the drug detected in the blood (or other fluids) in concentrations known to be toxic? (+1, 0, 0) Q8 Was the reaction more severe when the drug was increased or less severe when the drug was decreased? (+1, 0, 0) Q9 Did the patient have a similar reaction to the same or similar drugs in any previous exposure? (+1, 0, 0) Q10 Was the adverse event confirmed by any objective evidence? (+1, 0, 0)*

WHO-UMC[41] *Certain, probable, possible, unlikely, conditional/ unclassified, unassessable/ unclassifiable. Certain – event / laboratory test abnormality with plausible time relationship to intake of a drug, cannot be explained by disease or other drugs, response to withdrawal plausible, event definitive pharmacologically or phenomenologically, rechallenge satisfactory, if necessary. Probable – event or laboratory test abnormality, with reasonable time relationship to drug intake, unlikely to be attributed to disease*

or other drugs, response to withdrawal clinically reasonable, re-challenge not required. Possible – event or laboratory test abnormality, with reasonable time relationship to drug intake, could also be explained by disease or other drugs, information on drug withdrawal may be lacking or unclear. Unlikely – Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable Disease or other drugs provide plausible explanations. Conditional/ Unclassified – event or laboratory test abnormality, more data for proper assessment needed, or additional data under examination. Unassessable/ Unclassifiable – report suggesting an adverse reaction, cannot be judged because information is insufficient or contradictory, data cannot be supplemented or verified.

Hallas[42] *Definite (all five criteria were satisfied), probable (criteria (l), (2), (3) and (4) were satisfied), possible (criteria (1), (2) and (3) were satisfied) and unlikely/unevaluable (The relevant information required for evaluation could not be obtained, or the temporal sequence was atypical, or other conditions or dispositions were considered far more likely to have caused the symptoms); Criteria – (1) known ADR or toxic reaction: (2) a reasonable temporal relationship between commencement of drug therapy and onset of adverse reaction : (3) the adverse reaction disappeared upon dis- continuation or dose reduction: (4) the symptom or event could not be explained by any other known condition or predisposition of the patient: (5) the symptoms reappeared upon re-exposure, or laboratory tests showed toxic drug levels or drug-induced metabolic disturbances that explained the symptom.*

Kramer[43] *definite (score 6-7), probable (score 4-5), possible (0-3), unlikely (<0) based on a multi-axis algorithm, six axes are scored and the individual scores are added to get a total score, which corresponds to an overall probability that the clinical manifestation represents an ADR. The total score can range from -7 to +7.*

Severity

Hartwig[44] *seven level scale, mild (levels 1 & 2), moderate (levels 3 & 4) and severe (levels 5, 6 & 7); 1 An ADR occurred but no change in treatment with suspected drug 2 The ADR required that treatment with the suspected drug be held, discontinued or otherwise changes. No antidote or other treatment required. No increase in length of stay. 3 The ADR required that treatment with the suspected drug be held, discontinued or otherwise changed, or an antidote or other treatment. No increase in length of stay. 4 Any level 3 ADR which increases length of stay by at least one day or the ADR was the reason for admission. 5 Any level 4 ADR which required intensive medical care. 6 Any ADR causing permanent harm to the patient. 7a The ADR was indirectly linked to the death of the patient. 7b The ADR was directly linked to the death of the patients.*

Hurwitz[45] *Severe: fatal or life threatening, (2) moderate: required treatment, admission to hospital, or prolonged the stay in hospital by at least one day, (3) mild: incidental, required no treatment.*

Morimoto[46] *four discrete categories: (a) fatal, i.e. leading to death; (b) life threatening, i.e. prolonging hospitalization, leading to permanent defects or life-threatening complications; (c) serious, i.e. demanding a dosage reduction, therapy cessation etc.; or (d) significant, i.e. any ADR that does not meet the above criteria, not usually requiring a change in therapy.*

Venulet[47] *Severe: Fatal or life threatening, lowers the patient's life expectancy. A severe impairment of a vital organ-system, even if transient. Persisting for more than one month period. Moderate: Symptoms are marked but involvement of vital organ-systems is moderate. No loss of consciousness, no cardiovascular failure. Antidote drugs or hospizalization required or hospitalization prolonged by at least one day. Development of definite biochemical or structural changes could justify assigning to this category. Minor: Incidental, no antidote required, suspected drug mayor may not be stopped. Do not complicate significantly the primary disease.*

WHO-ART[48] *Non-serious or Serious: An adverse event or reaction that results in death; requires hospitalization or extension of hospital stay; results in persistent or significant disability or incapacity; is life-threatening.*

European Medicines Agency[49] *serious if fatal, life-threatening, required or prolonged hospitalization, caused serious or permanent disability, or congenital anomaly/birth defect.*

Spanish system of pharmacovigilance[50] *Mild (no additional measures required), moderate (motivates hospital admission), severe (threatens the patient's life) and deadly (contributes directly or indirectly to Patient's death).*

Classification

DoTs[9] *three-dimensional classification - Dose, timing and susceptibility classification; Dose – (1) supratherapeutic reactions (occurring at doses higher than are recommended), (2) collateral reactions (which usually occur at the recommended dose) or (3) hypersensitivity reactions (occurring at lower doses than are recommended); Timing - : (1) fast reactions (on administration of a drug, which is usually given intravenously), (2) the first dose, (3) early, (4) intermediate, (5) late and (6) delayed; Susceptibility – factors of genetic susceptibility, age (paediatric and older population), gender and the presence of exogenous factors (e.g. drug interactions) or disease (e.g. hepatic or renal disease).*

MedDRA-SOC®[6] *five level hierarchy from very specific (lowest level terms of which there are 70,000) to very general (system organ class).*

Rawlins and Thompson[51] *divided into two categories: reactions that are common, predictable, and that may occur in any individual (type A); and reactions that are uncommon, not predictable, and that occur only in susceptible individuals (type B).*

WHO-ART[48] *four level hierarchy from general system organ classes (32), high level terms, preferred terms, and included terms (no longer actively maintained, last release WHO-UMC 2015, and superseded by MedDRA-SOC® in 2008).*

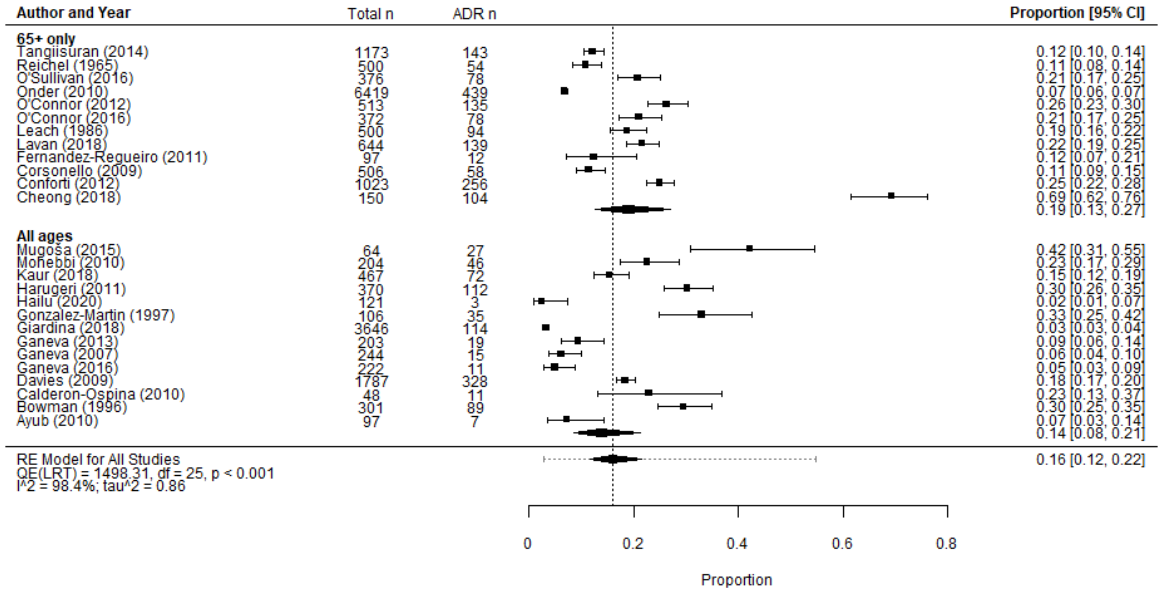
Meyboom[52] *type A ("drug actions"), type B ("patients reactions") and type C ("statistical ").*

Preventability

Hallas[42] *definitely avoidable, possibly avoidable, unavoidable and unclassifiable – 'Definitely avoidable'. The drug event was due to a drug treatment procedure inconsistent with present- day knowledge of good medical practice or was clearly unrealistic, taking the known circumstances into account. 'Possibly avoidable '. The prescription was not erroneous, but the drug event could have been avoided by an effort exceeding the obligatory demands. 'Not avoidable'. The drug event could not have been avoided by any reasonable means, or it was an unpredictable event in the course of a treatment fully in accordance with good medical practice. 'Unevaluable'. The data for rating could not be obtained or the evidence was conflicting.*

Schumock & Thornton[53] *certainly preventable, probably preventable, unavoidable/not preventable; yes to any question in any category. Definitely preventable 1. Was there a history of allergy or previous reactions to the drug? 2. Was the drug involved inappropriate for the patient's clinical condition? 3. Was the dose, route or frequency of administration inappropriate for the patient's age, weight or disease state? 4. Was a toxic serum drug concentration (or laboratory monitoring test) documented? 5. Was there a known treatment for the Adverse Drug Reaction? Probably preventable 6. Was required Therapeutic drug monitoring or other necessary laboratory tests not performed? 7. Was a drug interaction involved in the ADR? 8. Was poor compliance involved in the ADR? 9. Were preventative measures not prescribed or administered to the patient? Unavoidable/Not preventable If all above criteria not fulfilled*

Appendix 12. Meta-analysis of Studies Where all Participants Were ≥65 Years at Baseline (p=0.299)

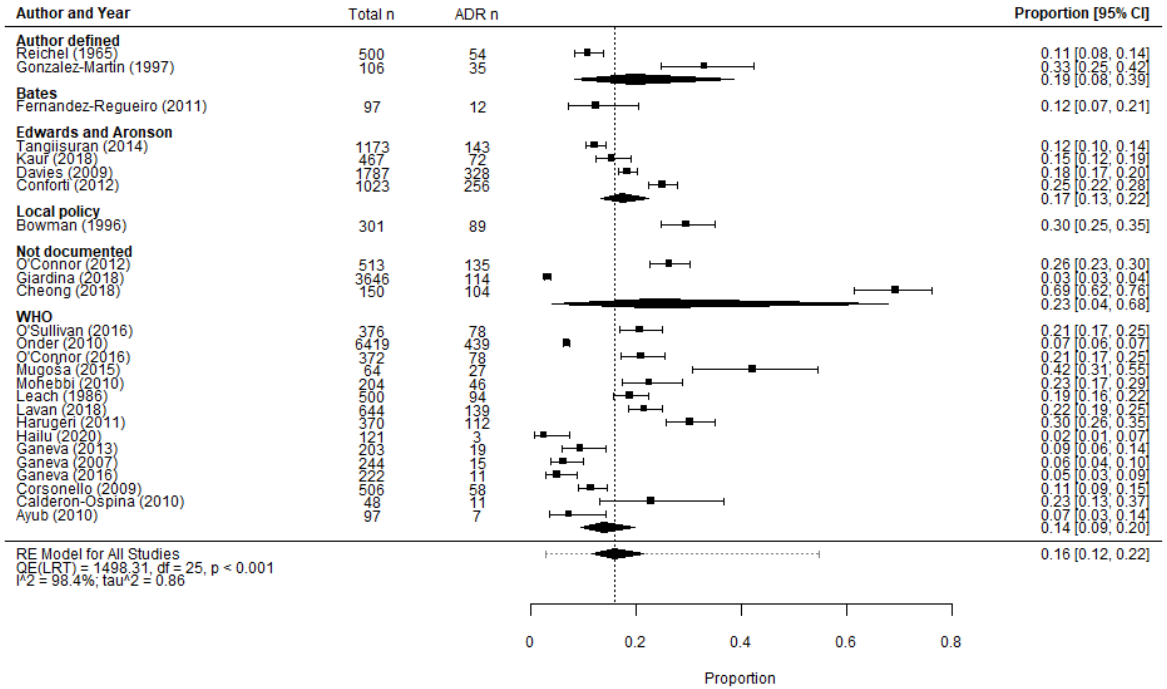


RE – Random effects model

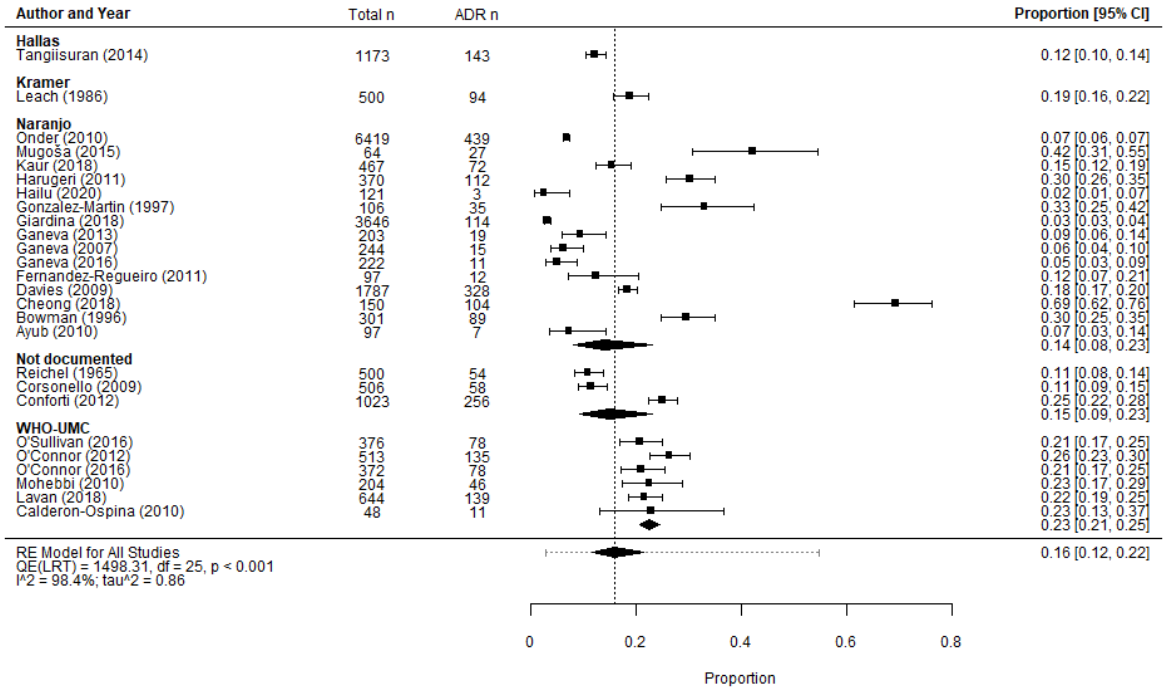
eFigure 2: Subgroup analysis of patients experiencing at least one in-hospital ADR in studies recruiting all ages[7-9,14-20,28,29,32,33] versus solely ≥65 years.[10-13,21-27,30,35]

RE – Random effects model, n – number of patients aged ≥65 years, n ADR – number of patients ≥65 years experiencing at least 1 ADR during hospitalisatio

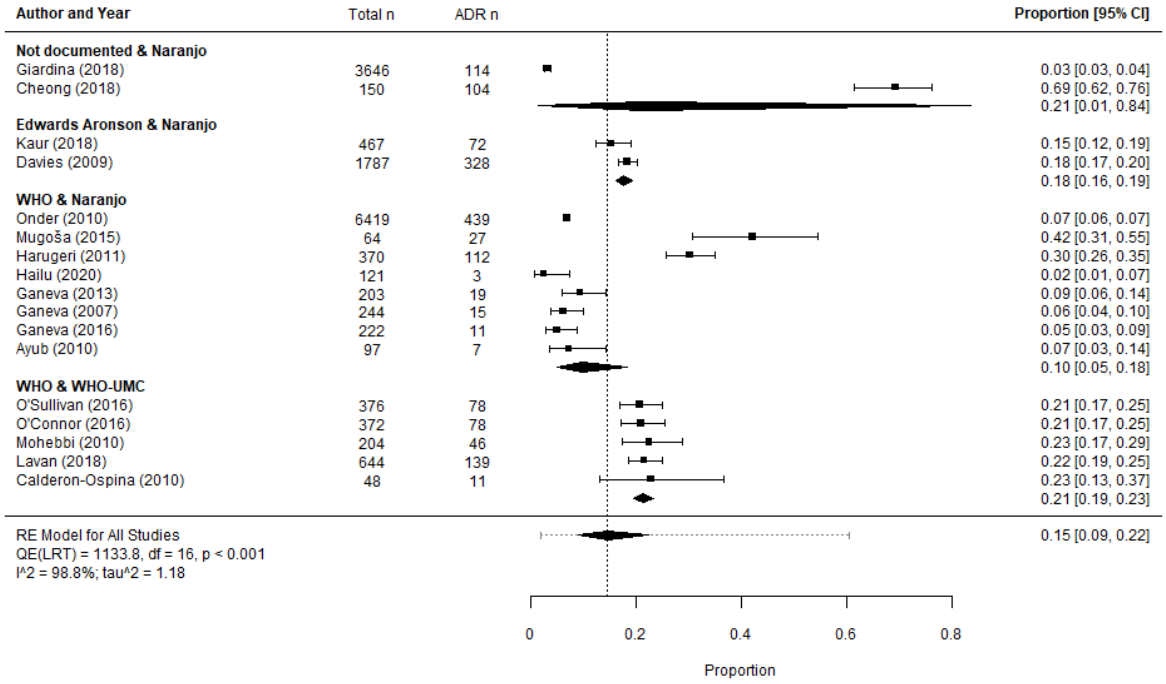
Appendix 13. Meta-analysis of studies grouped by ADR definition (p=0.806)



Appendix 14. Meta-analysis of studies grouped by ADR causality (p=0.78)

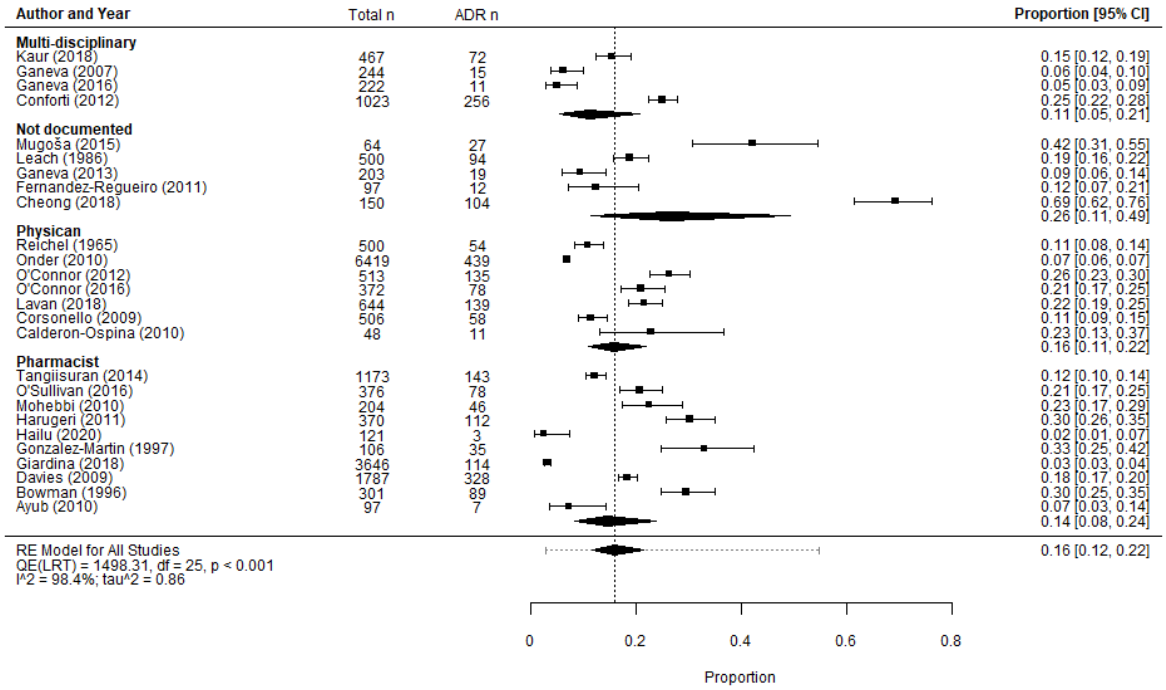


Appendix 15. Meta-analysis of studies grouped by comparable overlapping ADR methodologies (p=0.383)



eFigure: Forest plot showing subgroup analysis of prevalence of in hospital ADRs reported by studies grouped by matching assessment methods

Appendix 16. Pooled estimates of ADR proportions grouped by ADR identification methods (p =0.31)



ADR Presentations

Appendix 17. Ranking of ADR Presentations by MedDRA-SOC® Classification

Rank	MedDRA® SOC Classification	n	% of 2728	cumulative
1	Gastrointestinal Disorders	629	23.05%	23.06%
2	Metabolism and Nutrition Disorders	565	20.73%	43.77%
3	Unclassifiable - Unclassifiable (Grouped Presentations / "Other")	397	14.57%	58.32%
4	Vascular Disorders	216	7.93%	66.24%
5	Cardiac Disorders	187	6.86%	73.09%
6	Renal and Urinary Disorders	175	6.42%	79.51%
7	Investigations	116	4.26%	83.76%
8	Infections and Infestations	87	3.19%	86.95%
9	Skin and Subcutaneous Tissue Disorders	72	2.64%	89.59%
10	Blood and Lymphatic System Disorders	61	2.24%	91.83%
11	Psychiatric Disorders	58	2.13%	93.95%
12	Nervous System Disorders	56	2.02%	96.00%
13	Injury, Poisoning and Procedural Complications	48	1.72%	97.76%
14	Respiratory, Thoracic and Mediastinal Disorders	23	0.84%	98.61%
15	Musculoskeletal and Connective Tissue Disorders	12	0.44%	99.05%
16	General Disorders and Administration Site Conditions	9	0.33%	99.38%
17	Immune System Disorders	8	0.29%	99.67%
18	Hepatobiliary Disorders	5	0.18%	99.85%
19	Eye Disorders	4	0.15%	100.00%
		2728	100.00%	

Appendix 18. Breakdown of ADR Presentations by ADR Detail (In Descending Frequency).

MedDRA® SOC Classification	**% (2728)**	***n***	**Description (High-Level Group Term)**	***n***	**Further ADR Description**	***n***	**Lowest Level ADR Detail (when available)**	***n***
Gastrointestinal disorders	23.06%	*629*	Gastrointestinal motility and defaecation conditions	*392*	Constipation	*254*	-	-
					Diarrhoea	*138*	-	-
			Unspecified / unclassifiable Gastrointestinal disorders	*90*	Gastrointestinal	*88*	-	-
					Vomiting and diarrhoea	*2*	-	-
			Gastrointestinal haemorrhages NEC	*67*	GI Bleed	*60*	-	-
					Gastrointestinal bleeding	*7*	-	-
			Gastrointestinal signs and symptoms	*61*	Nausea / vomiting	*59*	-	-
					Dyspepsia	*2*	-	-
			Gastrointestinal stenosis and obstruction	*10*	Ileus	*10*	-	-
			Gastrointestinal inflammatory conditions	*7*	Haemorrhage / gastritis	*6*	-	-
					Gastritis	*1*	-	-
			Oral soft tissue conditions	*2*	Oral ulcers	*2*	-	-
Metabolism and nutrition disorders	20.71%	*565*	Electrolyte and fluid balance conditions	*461*	Potassium imbalance	*299*	Hypokalaemia	*275*
							Hyperkalaemia	*24*
					Sodium imbalance	*29*	Hyponatraemia	*27*
							Hypernatraemia	*2*
					Total fluid volume decreased	*2*	Dehydration	*2*
					Total fluid volume increased	*3*	Oedema	*3*
					Unspecified / unclassifiable - Electrolyte and fluid balance conditions	*128*	Electrolyte disturbance	*78*
							Electrolytic	*50*

Contd. **MedDRA® SOC Classification**	**% (2728)**	***n***	**Description (High-Level Group Term)**	***n***	**Further ADR Description**	***n***	**Lowest Level ADR Detail (when available)**	***n***
Metabolism and nutrition disorders contd.					Hypercalcaemia	*2*	-	-
			Bone, calcium, magnesium and phosphorus metabolism disorders	*3*	Unspecified / unclassifiable - Bone, calcium, magnesium and phosphorus metabolism disorders	*1*	Hypokalaemia / Hypocalcaemia	*1*
			Unspecified / unclassifiable - Metabolism and nutrition disorders	*26*	Electrolyte / metabolic abnormality	*26*	-	-
			Glucose metabolism disorders (incl. diabetes mellitus)	*74*	Hyperglycaemic conditions NEC	*23*	Hyperglycaemia	*21*
							Steroid diabetes	*2*
					Hypoglycaemic conditions NEC	*51*	Hypoglycaemia	*51*
			Purine and pyrimidine metabolism disorders	*1*	Disorders of purine metabolism	*1*	Hyperuricemia	*1*
Unclassifiable	14.55%	*397*	Unclassifiable into MedDRA® SOC grouping from extractable ADR data	*397*	Multiple presentations grouped	*370*	-	-
					Reported as "other" or "missing"	*27*	-	-
Vascular disorders	7.92%	*216*	Decreased and nonspecific blood pressure disorders and shock	*126*	Vascular hypotensive disorders	*126*	Hypotension	*81*
							Postural hypotension	*45*
			Vascular haemorrhagic disorders	*89*	Haemorrhages NEC	*89*	Haematoma	*20*
							Bleeding	*58*
							Bleeding requiring transfusion with or without hemostasis intervention	*11*

			Vascular hypertensive disorders	*1*	Hypertension	*1*	-	-
Contd. **MedDRA® SOC Classification**	**% (2728)**	***n***	**Description (High-Level Group Term)**	***n***	**Further ADR Description**	***n***	**Lowest Level ADR Detail (when available)**	***n***
Cardiac disorders	6.85%	*187*	Rate and rhythm disorders	*74*	Bradycardia	*55*	-	-
					Tachycardia	*7*	-	-
					AV Block	*12*	-	-
			Unspecified / Unclassifiable Cardiovascular	*110*	Cardiovascular and arrhythmic complications	*97*	-	-
					Cardiovascular system	*13*	-	-
			Cardiac failure	*2*	Left ventricular failure / overload	*2*	-	-
			Chest pain	*1*	Chest pain	*1*	-	-
Renal and urinary disorders	6.41%	*175*	Renal disorders (excl. nephropathies)	*150*	AKI	*148*	AKI	*148*
					Renal failure complications	*2*	Hyperazotaemia	*2*
			Urinary tract signs and symptoms	*22*	Bladder and urethral symptoms	*22*	Haematuria	*18*
							Urine retention	*4*
			Nephropathies	*3*	Nephritis	*3*	-	-
Investigations	4.25%	*116*	Haematology investigations - Coagulation and bleeding analyses	*98*	INR increase	*97*	-	-
					Low prothrombin time	*1*	-	-
			Toxicology and therapeutic drug monitoring - antibiotic level	*2*	Elevated vancomycin level	*2*	-	-
			Hepatobiliary investigations - liver function analyses	*16*	Elevated liver enzymes	*16*	-	-
Infections and infestations	3.19%	*87*	Fungal infectious disorders - Candida infections	*67*	Thrush	*67*	-	-

Contd. **MedDRA® SOC Classification**	**% (2728)**	***n***	**Description (High-Level Group Term)**	***n***	**Further ADR Description**	***n***	**Lowest Level ADR Detail (when available)**	***n***
Infections and infestations contd.					Clostridium difficile +ve w/o diarrhoea	*7*	-	-
					Clostridium difficile diarrhoea	*5*	-	-
			Bacterial infectious disorders - Clostridia infections	*19*	Clostridium difficile diarrhoea, vancomycin-resistant enterococci, gentamicin-induced acute kidney injury	*4*	-	-
					C. Diff Colitis	*3*	-	-
			Viral infectious disorders - herpes viral infections	*1*	Herpes zoster	*1*	-	-
Skin and subcutaneous tissue disorders	2.64%	*72*	Epidermal and dermal conditions	*72*	Rashes, eruptions and exanthems NEC	*72*	Cutaneous Rash	*60*
							Prurigo	*2*
							Urticaria	*10*
Blood and lymphatic system disorders	2.24%	*61*	Anaemias nonhaemolytic and marrow depression	*27*	Anaemia	*26*	-	-
					Pancytopaenia	*1*	-	-
			Platelet disorders	*16*	Thrombocytopaenia	*16*	-	-
			Unspecified / Unclassifiable Blood and lymphatic system disorders	*15*	Haematological disturbance	*14*	-	-
					Coagulation	*1*	-	-
			White blood cell disorders	*3*	Neutropenia	*2*	-	-
					Leukopaenia	*1*	-	-
Psychiatric disorders	2.13%	*58*	Deliria (incl. confusion)	*52*	Confusion	*52*	-	-
			Disturbances in thinking and perception	*6*	Hallucination	*6*	-	-

Contd. **MedDRA® SOC Classification**	**% (2728)**	***n***	**Description (High-Level Group Term)**	***n***	**Further ADR Description**	***n***	**Lowest Level ADR Detail (when available)**	***n***
Nervous system disorders	2.05%	*56*	Neurological disorders NEC	*25*	Disturbances in consciousness NEC	*25*	Unconscious	*1*
							Drowsiness / Somnolence / sleepiness	*24*
			Headaches	*9*	-	-	-	-
			Unspecified / unclassifiable nervous system disorders	*11*	Central nervous system	*11*	-	-
			Neurological signs and symptoms NEC	*5*	Dizziness	*5*	-	-
			Movement disorders (incl. parkinsonism)	*3*	Tremor	*2*	-	-
					Extra-pyramidal SEs	*1*	-	-
			Seizures (incl. subtypes)	*2*	Non-convulsive epileptic crisis	*1*	-	-
					Seizure	*1*	-	-
			CNS Vascular disorder	*1*	CNS Haemorrhage & cerebrovascular accident	*1*	Haemorrhagic transformation stroke	*1*
Injury, poisoning and procedural complications	1.76%	*48*	Injuries NEC	*34*	Fall	*34*	-	-
			Bone and joint injuries	*2*	Fracture	*2*	-	-
			Toxicity to various agents	*8*	Digitalis intoxication	*6*	-	-
					Lithium toxicity	*1*	-	-
					Opioid toxicity	*1*	-	-
			Procedural related injuries and complications NEC - Cardiac and vascular procedural complications	*3*	Phlebitis	*3*	-	-
			Exposures, chemical injuries and poisoning	*1*	Poisoning and toxicity	*1*	Toxic epidermal necrolysis	*1*

Respiratory, thoracic and mediastinal disorders	0.84%	*23*	Respiratory disorders NEC	*20*	Respiratory failures (excl. neonatal)	*16*	-	-
					Cough	*4*	-	-
			Unspecified / unclassifiable respiratory system	*3*	Respiratory system	*3*	-	-
***Contd.* MedDRA® SOC Classification**	**% (2728)**	***n***	**Description (High-Level Group Term)**	***n***	**Further ADR Description**	***n***	**Lowest Level ADR Detail (when available)**	***n***
Musculoskeletal and connective tissue disorders	0.44%	*12*	Joint disorders - Crystal arthropathic disorders	*8*	Gout	*8*	-	-
			Bone disorders (excl. congenital and fractures) - metabolic bone disorders	*3*	Osteoporosis	*3*	-	-
			Muscle disorders	*1*	Muscular necrosis	*1*	-	-
General disorders and administration site conditions	0.33%	*9*	Body temperature conditions	*3*	Hyperthermia	*3*	-	-
			General system disorders NEC	*2*	Hyperhidrosis	*2*	-	-
			Asthenic conditions	*1*	Asthenia	*1*	-	-
			Gait disturbances	*1*	Ataxia	*1*	-	-
			Inflammations	*1*	Local inflammation	*1*	-	-
			Therapeutic and nontherapeutic effects (excl. toxicity)	*1*	Signs of withdrawal	*1*	-	-
Immune system disorders	0.29%	*8*	Allergic conditions	*8*	Allergy or drug sensitivity	*7*	-	-
					Bronchospasm	*1*	-	-
Hepatobiliary disorders	0.18%	*5*	Unspecified / unclassifiable Hepatobiliary disorders	*5*	Jaundice	*1*	-	-
					Hepatic	*4*	-	-
Eye disorders	0.15%	*4*	Glaucoma and ocular hypertension	*2*	Glaucoma	*2*	-	-
			Anterior eye structural change, deposit and degeneration	*2*	Cataract	*1*	-	-
					Corneal deposits	*1*	-	-

NEC – Not elsewhere classified, AV – atrioventricular, AKI – Acute Kidney Injury, INR – International Normalised Ratio, +ve – positive, w/o – without, C. Diff – Clostridium Difficile, Incl. – including, SEs – Side effects, excl. – excluding

ADR Drugs

Appendix 19. Causative Drug Agents Ranked by Descending Frequency as per Therapeutic Subgroup (ATC 2nd Level).

Rank	ATC 2nd	Therapeutic subgroup	n	% of 2385
1	C03	Diuretics	473	19.83%
2	J01	Antibacterials for systemic use	354	14.84%
3	B01	Anti-thrombotic agents	292	12.24%
4	N02	Analgesics	260	10.90%
5	R03	Drugs for obstructive airway diseases	113	4.74%
6	C09	Agents acting on the renin-angiotensin system	98	4.11%
7	N05	Psycholeptics	92	3.86%
8	H02	Corticosteroids for systemic use	77	3.23%
9	C01	Cardiac therapy	71	2.98%
10	A10	Drugs used in diabetes	61	2.56%
11	J04	Anti-mycobacterials	54	2.26%
12	C02	Anti-hypertensives	52	2.18%
13	A12	Mineral supplements	50	2.10%
14	C08	Calcium channel blockers	41	1.72%
15	M01	Anti-inflammatory and anti-rheumatic products	40	1.68%
16	N03	Antiepileptics	30	1.26%
17	A02	Drugs for acid related disorders	26	1.09%
18	A06	Drugs for constipation	24	1.01%
19	B03	Antianemic preparations	22	0.92%
20	N06	Psychoanaleptics	20	0.84%
21	C07	Beta blocking agents	19	0.80%
22	B05	Blood substitutes and perfusion solutions	15	0.63%
23	R01	Nasal preparations	15	0.63%
24	S02	Otologicals	11	0.46%
25	M04	Antigout preparations	10	0.42%
26	C****	Not specified by paper	8	0.34%
27	C10	Lipid modifying agents	7	0.29%
28	M05	Drugs for treatment of bone diseases	6	0.25%
29	N07	Other nervous system drugs	6	0.25%
30	L01	Antineoplastic agents	5	0.21%
31	A03	Drugs for functional gastrointestinal disorders	4	0.17%
32	G04	Urologicals	3	0.13%
33	N04	Anti-parkinson drugs	3	0.13%
34	A07	Antidiarrheals, intestinal antiinflammatory/antiinfective agents	2	0.08%
35	J02	Antimycotics for systemic use	2	0.08%
36	M03	Muscle relaxants	2	0.08%
37	N****	"Psychotropics" unspecified	2	0.08%
38	N01	Anaesthetics	2	0.08%
39	R05	Cough and cold preparations	2	0.08%

Contd. Rank	ATC 2nd	Therapeutic subgroup	n	% of 2385
40	R06	Antihistamines for systemic use	2	0.08%
41	A04	Antiemetics and antinauseants	1	0.04%
42	A11	Vitamins	1	0.04%
43	D01	Antifungals for dermatological use	1	0.04%
44	D06	Antibiotics and chemotherapeutics for dermatological use	1	0.04%
45	H01	Pituitary and hypothalamic hormones and analogues	1	0.04%
46	L04	Immunosuppressants	1	0.04%
47	P01	Antiprotozoals	1	0.04%
48	P02	Anthelmintics	1	0.04%
49	V04	Diagnostic agents	1	0.04%

Appendix 20. Reported Causative Drugs Grouped by Anatomical Group (ATC 1st Level) in Descending Order.

Overarching ATC Anatomical System (1st level, anatomical main group)	overall n (organ)	overall % (2385)
C – Cardiovascular System	769	32.24%
N – Central nervous system	415	17.40%
J – General anti-infectives, systemic	410	17.19%
B – Blood and blood forming organs	329	13.79%
A - Alimentary tract and metabolism	169	7.09%
R – Respiratory system	132	5.54%
H – Systemic hormonal preparations, excl. sex hormones	78	3.27%
M – Musculo-skeletal system	58	2.43%
S - Sensory organs	11	0.46%
L - Antineoplastic and immunomodulating agents	6	0.25%
G – Gentino-urinary system and sex hormones	3	0.13%
D – Dermatologics	2	0.08%
P - Antiparasitic products, insecticides and repellents	2	0.08%
V – Various	1	0.04%
	2385	100.00%

Excl. - excluding

Appendix 21. Breakdown of Causative Drugs by ATC Classification in Descending Frequency – Grouped by Anatomical (ATC 1st) Level to Chemical Substance/Drug (ATC 5th); n = 2385.

Cardiovascular system

Cardiovascular 769 (32.24%)										
ATC 2nd	**Therapeutic Subgroup**	**n**	**ATC 3rd**	**Pharmacological Subgroup**	**n**	**ATC 4th**	**Chemical Subgroup**	**n**	**ATC 5th / drug (when n ≥ 10)**	**n**
C03	Diuretics	473	C03C	High-ceiling diuretics	234	C03CA	Sulfonamides, plain	232	Furosemide	194
									Bumetanide	32
			C03D	Potassium-sparing agents	47	-	-	-	-	-
			C03A	Low-ceiling diuretics, thiazides	24	-	-	-	-	-
			C03B	Low-ceiling diuretics, excl. Thiazides	13	-	-	-	-	-
			C03E	Diuretics and potassium-sparing agents in combination	5	-	-	-	-	-
			C03*	Not specified by paper	39	-	-	-	-	-
C09	Agents Acting On The Renin-Angiotensin System	98	C09A	ACE inhibitors, plain	39	C09AA	ACE inhibitors, plain (ramipril)	14	Ramipril	14
			C09*	Not specified by paper	34	-	-	-	-	-
			C09C	Angiotensin II receptor blockers (ARBs), plain	12	-	-	-	-	-
			C09D	ARB II, combinations	1	-	-	-	-	-

Contd. ATC 2nd	Therapeutic Subgroup	n	ATC 3rd	Pharmacological Subgroup	n	ATC 4th	Chemical Subgroup	n	ATC 5th / drug (when n ≥ 10)	n
C01	Cardiac Therapy	71	C01A	Cardiac glycosides	44	C01AA	Digitalis glycosides	39	Digoxin	39
			C01D	Vasodilators used in cardiac diseases	12	-	-	-	-	-
			C01B	Antiarrhythmics, class I and III	10	C01BD	Antiarrhythmics, class III	10	Amiodarone	10
			C01*	Not specified by paper	3	-	-	-	-	-
			C01E	Other cardiac preparations	2	C01EB	Other cardiac preparations	2	-	-
C02	Antihypertensives	52	C02*	Not specified by paper	52	-	-	-	-	-
C08	Calcium Channel Blockers	41	C08*	Not specified by paper	30	-	-	-	-	-
			C08D	Selective calcium channel blockers with direct cardiac effects	7	-	-	-	-	-
			C08C	Selective calcium channel blockers with mainly vascular effects	4	-	-	-	-	-
C07	Beta Blocking Agents	19	C07A	Beta blocking agents	18	C07AB	Beta blocking agents, selective	15	-	-
						C07AA	Beta blocking agents, non-selective	2	-	-
						C07AG	Alpha and beta blocking agents	1	-	-
			C07C	Beta blocking agents and other diuretics	1	-	-	-	-	-

Contd. ATC 2nd	Therapeutic Subgroup	n	ATC 3rd	Pharmacological Subgroup	n	ATC 4th	Chemical Subgroup	n	ATC 5th / drug (when n ≥ 10)	n
C****	Not specified by paper	8	-	-	-	-	-	-	-	-
C10	Lipid Modifying Agents	7	C10*	Not specified by paper	7	-	-	-	-	-

Central nervous system

Central Nervous System 415 (17.40%)										
ATC 2nd	Therapeutic subgroup	n	ATC 3rd	Pharmacological Subgroup	n	ATC 4th	Chemical Subgroup	n	ATC 5th/ drug (when n ≥ 10)	n
N02	Analgesics	260	N02A	Opioids	205	N02A*	Unspecified "Opioids"	123	-	-
						N02AA	Natural opium alkaloids	44	Morphine	40
						N02AX	Other opioids	28	Tramadol	28
						N02AB	Phenylpiperidine derivatives	6	-	-
						N02AJ	Opioids in combination with non-opioid analgesics	4	-	-
			N02B	Other analgesics and antipyretics	55	N02BE	Anilides	34	Co-codamol	31
						N02B*	Not specifed by the paper	18	-	-
N05	Psycholeptics	92	N05B	Anxiolytics	61	N05BA	Benzodiazepine derivatives	60	Unspecified "benzodiazepines"	54
						N05BB	Diphenylmethane derivatives	1	-	-
			N05A	Antipsychotics	18	N05A*	Unspecified "Antipsychotics"	7	-	-

Contd. ATC 2nd	**Therapeutic subgroup**	**n**	**ATC 3rd**	**Pharmacological Subgroup**	**n**	**ATC 4th**	**Chemical Subgroup**	**n**	**ATC 5th/ drug (when n ≥ 10)**	**n**
Contd. N05	*Contd.* Psycholeptics		*Contd.* N05A	*Contd.* Antipsychotics		N05AD	Butyrophenone derivatives	2	-	-
						N05AF	Thioxanthene derivatives	2	-	-
						N05AH	Diazepines, oxazepines, thiazepines and oxepines	2	-	-
						N05AA	Phenothiazines with aliphatic side-chain	1	-	-
						N05AB	Phenothiazines with piperazine structure	1	-	-
						N05AC	Phenothiazines with piperidine structure	1	-	-
						N05AN	Lithium	1	-	-
						N05AX	Other antipsychotics	1	-	-
			N05C	Hypnotics and sedatives	13	N05C*	Unspecified "benzodiazepines"	10	-	-
						N05CD	Benzodiazepine derivatives	2	-	-
						N05CA	Barbiturates, plain	1	-	-
N03	Antiepileptics	30	N03A	Antiepileptics	30	N03AA	Barbiturates and derivatives	18	phenobarbital	18
						N03AF	Carboxamide derivatives	9	-	-

						N03AX	Other antiepileptics	3	-	-
Contd. ATC 2nd	**Therapeutic subgroup**	**n**	**ATC 3rd**	**Pharmacological Subgroup**	**n**	**ATC 4th**	**Chemical Subgroup**	**n**	**ATC 5th/ drug (when n ≥ 10)**	**N**
N06	Psychoanaleptics	20	N06A	Antidepressants	19	N06AB	Selective serotonin reuptake inhibitors	10	-	-
						N06AA	Non-selective monoamine reuptake inhibitors	7	-	-
						N06A*	Unspecified by paper	2	-	-
			N06D	Anti-dementia drugs	1	-	-	-	-	-
N07	Other nervous system drugs	6	-	-	-	-	-	-	-	-
N****	"Psychotropics" unspecified	2	-	-	-	-	-	-	-	-
N01	Anaesthetics	2	-	-	-	-	-	-	-	-
N04	Anti-parkinson drugs	3	-	-	-	-	-	-	-	-

Anti-infectives for systemic use

Ant-infectives for systemic use 410 (17.19%)										
ATC 2nd	**Therapeutic subgroup**	**n**	**ATC 3rd**	**Pharmacological Subgroup**	**n**	**ATC 4th**	**Chemical Subgroup**	**n**	**ATC 5th/ drug (when n ≥ 10)**	**n**
J01	Antibacterials For Systemic Use	354	J01C	Beta-lactam antibacterials, penicillins	106	J01CA	Penicillins with extended spectrum	32	Ampicillin	16
									Amoxicillin	16
						J01CR	Combinations of penicillins, incl.	28	Co-amoxiclav	28

							Beta-lactamase inhibitors			
Contd. ATC 2nd	**Therapeutic subgroup**	**n**	**ATC 3rd**	**Pharmacological Subgroup**	**n**	**ATC 4th**	**Chemical Subgroup**	**n**	**ATC 5th/ drug (when n ≥ 10)**	**n**
Contd. J01	*Contd.* Antibacterials For Systemic Use		*Contd.* J01C	*Contd.* Beta-lactam antibacterials, penicillins		J01CG	Beta-lactamase inhibitors	16	Sulbactam	16
						J01C*	Not specified by paper	11	-	-
						J01CE	Beta-lactamase sensitive penicillins	10	Penicillin G	5
						J01CF	Beta-lactamase resistant penicillins	9	-	-
			J01*	Not specified by paper	63	-	-	-	-	-
			J01D	Other beta-lactam antibacterials	54	J01DD	Third-generation cephalosporins	27	Ceftriaxone	26
						J01DC	Second-generation cephalosporins	20	Cefuroxime	15
						J01DB	First-generation cephalosporins	6	-	-
						J01DE	Fourth-generation cephalosporins	1	-	-
			J01F	Macrolides, lincosamides and streptogramins	46	J01FA	Macrolides	43	Erythromycin	24
									Clarithromycin	18
						J01FF	Lincosamides	3	-	-
			J01M	Quinolone antibacterials	29	J01MA	Fluoroquinolones	29	Ciprofloxacin	28
			J01X	Other antibacterials	26	J01XD	Imidazole derivatives	16	Metronidazole	16
						J01XA	Glycopeptide antibacterials	8	-	-

Contd. ATC 2nd	Therapeutic subgroup	n	ATC 3rd	Pharmacological Subgroup	n	ATC 4th	Chemical Subgroup	n	ATC 5th/ drug (when n ≥ 10)	n
Contd. J01	*Contd.* Antibacterials For Systemic Use		*Contd.* J01X	*Contd.* Other antibacterials		J01XB	Polymyxins	1	-	-
						J01XX	Other antibacterials	1	-	-
			J01E	Sulfonamides and trimethoprim	23	J01EE	Combinations of sulfonamides and trimethoprim, incl. derivatives	23	Trimethoprim	22
			J01G	Aminoglycoside antibacterials	6	-	-	-	-	-
			J01A	Tetracyclines	1	-	-	-	-	-
J04	Antimycobacterials	54	J04A	Drugs for treatment of tuberculosis	54	J04AB	Drugs for treatment of tuberculosis, antibiotics	54	Not specified by the paper	49
J02	Antimycotics for systemic use	2	J02A	Antimycotics for systemic use	2	-	-	-	-	-

Blood and blood forming organs

Blood and blood forming organs 329 (13.79%)										
ATC 2nd	**Therapeutic subgroup**	**n**	**ATC 3rd**	**Pharmacological Subgroup**	**n**	**ATC 4th**	**Chemical Subgroup**	**n**	**ATC 5th/ drug (when n ≥ 10)**	**n**
B01	Antithrombotic Agents	291	B01A	Antithrombotic agents	250	B01AA	Antithrombotic agents vitamin K antagonists	82	Warfarin	81
						B01AB	Antithrombotic agents heparin group	84	Enoxaparin	40
									Dalteparin	32
									Heparin	12

Contd. ATC 2nd	Therapeutic subgroup	n	ATC 3rd	Pharmacological Subgroup	n	ATC 4th	Chemical Subgroup	n	ATC 5th/ drug (when n ≥ 10)	n
Contd. B01	*Contd.* Antithrombotic Agents		*Contd.* B01A	*Contd.* Antithrombotic agents		B01AC	Antithrombotic agents platelet aggregation inhibitors excl. heparin	77	Aspirin	23
									Unspecified antiplatelets	36
									Clopidogrel	10
						B01AD	Enzymes	3	-	-
			B01*	Not specified by paper	18	-	-	-	-	-
B03	Antianemic Preparations	22	B03A	Iron preparations	20	B03AA	Iron bivalent, oral preparations	16	Ferrous sulphate	16
						B03A*	Unspecified Iron preparations	4	-	-
			B03*	Not specified by paper	1	-	-	-	-	-
			B03B	Vitamin B12 and folic acid	1	-	-	-	-	-
B05	Blood Substitutes And Perfusion Solutions	15	B05B	I.V. SOLUTIONS	8	-	-	-	-	-

Alimentary tract and metabolism

Alimentary tract and metabolism 169 (7.09%)										
ATC 2nd	**Therapeutic subgroup**	**n**	**ATC 3rd**	**Pharmacological Subgroup**	**n**	**ATC 4th**	**Chemical Subgroup**	**n**	**ATC 5th/ drug (when n ≥ 10)**	**n**
A10	Drugs Used In Diabetes	61	A10A	Insulins and analogues	39	A10AD	Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting	27	Unspecified insulin or analogues	17

Contd. ATC 2nd	Therapeutic subgroup	n	ATC 3rd	Pharmacological Subgroup	n	ATC 4th	Chemical Subgroup	n	ATC 5th/ drug (when n ≥ 10)	n
Contd. A10	*Contd.* Drugs Used In Diabetes		*Contd.* A10A	*Contd.* Insulins and analogues		A10AB	Insulins and analogues for injection, fast-acting	8	-	-
						A10AE	Insulins and analogues for injection, long-acting	4	-	-
			A10B	Blood glucose lowering drugs, excl. Insulins	20	-	-	-	-	-
			A10*	Not specified	1	-	-	-	-	-
A12	Mineral Supplements	50	A12A	Potassium	9	-	-	-	-	-
			A12A	Calcium	41	A12AA	Calcium	41	-	-
A02	Drugs for Acid Related Disorders	26	A02B	Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)	26	-	-	-	-	-
A06	Drugs for Constipation	24	A06A	Drugs for constipation	24	A06AG	Enemas	10	-	-
						A06AD	Osmotically acting laxatives	9	-	-
						A06AB	Contact laxatives	4	-	-
A03	Drugs for Functional Gastrointestinal Disorders	4	-	-	-	-	-	-	-	-
A07	Antidiarrheals, Intestinal Antiinflammatory / Antiinfective Agents	2	-	-	-	-	-	-	-	-
A04	Antiemetics and Antinauseants	1	-	-	-	-	-	-	-	-
A11	Vitamins	1	-	-	-	-	-	-	-	-

Respiratory system

Respiratory System 132 (5.53%)										
ATC 2nd	**Therapeutic subgroup**	**n**	**ATC 3rd**	**Pharmacological Subgroup**	**n**	**ATC 4th**	**Chemical Subgroup**	**n**	**ATC 5th / drug (when n ≥ 10)**	**n**
R03	Drugs For Obstructive Airway Diseases	113	R03A	Adrenergics, inhalants	78	R03AC	Selective beta-2-adrenoreceptor agonists	62	Salbutamol	60
						R03AK	Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics	12	Salmeterol/Fluticasone	12
						R03AL	Adrenergics in combination with anticholinergics incl. triple combinations with corticosteroids	4	-	-
			R03D	Other systemic drugs for obstructive airway diseases	23	R03DA	Xanthines	23	Theophylline	12
			R03B	Other drugs for obstructive airway diseases, inhalants	8	-	-	-	-	-
			R03*	Not specified by paper	4	-	-	-	-	-
R01	Nasal Preparations	15	R01A	Decongestants and other nasal preparations for topical use	15	R01AD	Corticosteroids	14	Beclomethasone	14
R05	Cough And Cold Preparations	2	-	-	-	-	-	-	-	-
R06	Antihistamines For Systemic Use	2	-	-	-	-	-	-	-	-

Systemic hormonal preparations, excluding sex hormones

Systemic hormonal preparations, excluding sex hormones 78 (3.27%)										
ATC 2nd	**Therapeutic subgroup**	**n**	**ATC 3rd**	**Pharmacological Subgroup**	**n**	**ATC 4th**	**Chemical Subgroup**	**n**	**ATC 5th / drug (when n ≥ 10)**	**n**
H02	Corticosteroids For Systemic Use	77	H02A	Corticosteroids for systemic use, plain	61	H02AB	Glucocorticoids	60	Prednisolone	41
						H02AA	Mineralocorticoids	1	-	-
			H02*	Not specified by paper	16	-	-	-	-	-
H01	Pituitary And Hypothalamic Hormones And Analogues	1	-	-	-	-	-	-	-	-

Musculoskeletal system

Musculo-skeletal system 58 (2.43%)										
ATC 2nd	**Therapeutic subgroup**	**n**	**ATC 3rd**	**Pharmacological Subgroup**	**n**	**ATC 4th**	**Chemical Subgroup**	**n**	**ATC 5th / drug (when n ≥ 10)**	**n**
M01	Antiinflammatory and Antirheumatic Products	40	M01A	Antiinflammatory and antirheumatic products, non-steroids	40	M01A*	Not specified by the paper	25	-	-
M04	Antigout Preparations	10	M04A	Antigout preparations	10	-	-	-	-	-
M05	Drugs For Treatment of Bone Diseases	6	M05B	Drugs affecting bone structure and mineralization	6	M05BA	Bisphosphonates	6	-	-
M03	Muscle Relaxants	2	-	-	-	-	-	-	-	-

Sensory organs

Sensory organs 11 (0.46%)

ATC 2nd	Therapeutic Subgroup	n	ATC 3rd	Pharmacological Subgroup	n	ATC 4th	Chemical Subgroup	n	ATC 5th / drug (when n ≥ 10)	n
S02	Otologicals	11	S02B	Corticosteroids	11	S02BA	Corticosteroids	11	Dexamethasone	11

Antineoplastic and immunomodulating agents

Antineoplastic and immunomodulating agents 6 (0.25%)										
ATC 2nd	**Therapeutic subgroup**	**n**	**ATC 3rd**	**Pharmacological Subgroup**	**n**	**ATC 4th**	**Chemical Subgroup**	**n**	**ATC 5th / drug (when n ≥ 10)**	**n**
L01	Antineoplastic Agents	5	-	-	-	-	-	-	-	-
L04	Immunosuppressants	1	-	-	-	-	-	-	-	-

Genitourinary system and sex hormones

Genito-urinary system and sex hormones 3 (0.13%)										
ATC 2nd	**Therapeutic Subgroup**	**n**	**ATC 3rd**	**Pharmacological Subgroup**	**n**	**ATC 4th**	**Chemical Subgroup**	**n**	**ATC 5th / drug (when n ≥ 10)**	**n**
G04	Urologicals	3	-	-	-	-	-	-	-	-

Dermatologics

Dermatologics 2 (0.08%)										
ATC 2nd	**Therapeutic Subgroup**	**n**	**ATC 3rd**	**Pharmacological Subgroup**	**n**	**ATC 4th**	**Chemical Subgroup**	**n**	**ATC 5th / drug (when n ≥ 10)**	**n**
D01	Antifungals for Dermatological Use	1	-	-	-	-	-	-	-	-
D06	Antibiotics and Chemotherapeutics for Dermatological Use	1	-	-	-	-	-	-	-	-

Antiparasitic products, insecticides and repellents

Antiparasitic products, insecticides and repellents 2 (0.08%)										
ATC 2nd	**Therapeutic Subgroup**	**n**	**ATC 3rd**	**Pharmacological Subgroup**	**n**	**ATC 4th**	**Chemical Subgroup**	**n**	**ATC 5th / drug (when n ≥ 10)**	**n**
P01	Antiprotozoals	1	-	-	-	-	-	-	-	-
P02	Anthelmintics	1	-	-	-	-	-	-	-	-

Various

Various: 1 (0.04%)										
ATC 2nd	**Therapeutic Subgroup**	**N**	**ATC 3rd**	**Pharmacological Subgroup**	**n**	**ATC 4th**	**Chemical Subgroup**	**n**	**ATC 5th / drug (when n ≥ 10)**	**n**
V04	Diagnostic Agents	1	-	-	-	-	-	-	-	-

Appendix 22. ADR Reported Severity.

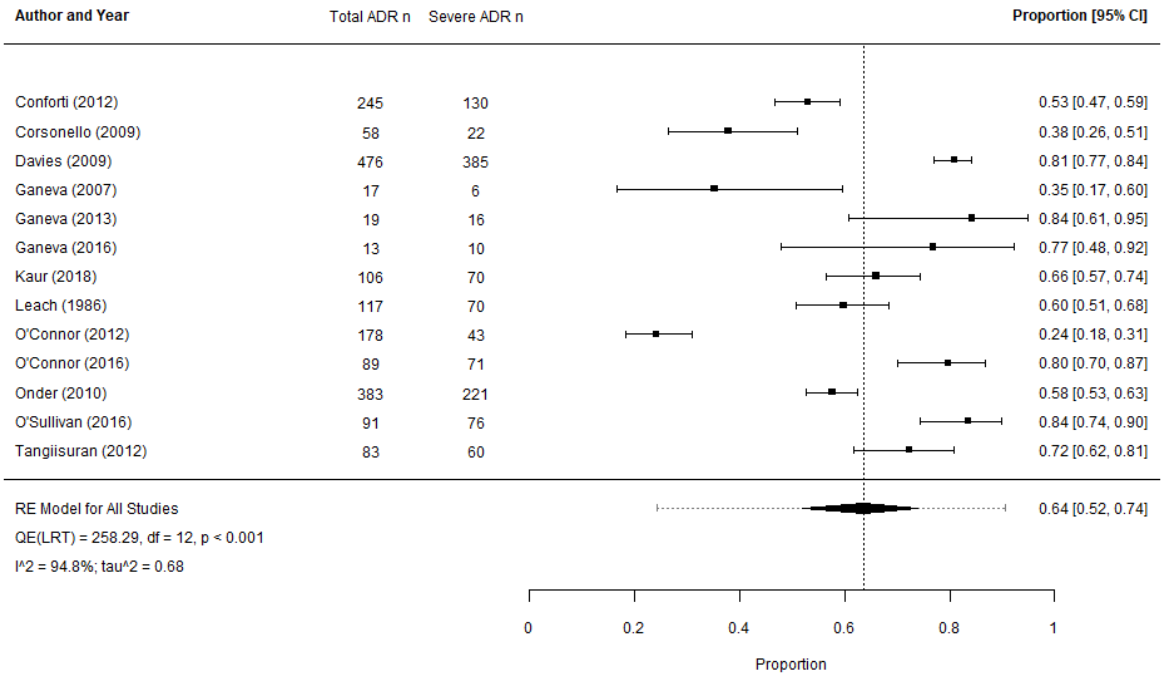
Eighteen studies reported details pertaining to ADR severity.[8,9,12-17,19-26,31,34]

Author	**Population**	**n ≥ 65**	**# ≥ 65 ADRs**	**Severity Tool**	**n ADRs***	**% Severe***
Conforti (2012)[12]	Population ≥ 65 years	1023	245	Not described	130	53.30
Corsonello (2009)[13]	Population ≥ 65 years	506	99	Not described	22/58pts	37.93
Leach (1986)[21]	Population ≥ 65 years	500	117	Hurwitz	70	59.83
Liao (2020)[31]	Population ≥ 65 years	108548	670 (539 reported)	Not described	347	64.38
O'Connor (2016)[23]	Population ≥ 65 years	513	89	Author defined	71	79.78
O'Connor (2012)[22]	Population ≥ 65 years	372	178	Author defined	43	24.00
Onder (2010)[24]	Population ≥ 65 years	6419	383	Author defined	221	64.00
O'Sullivan (2016)[25]	Population ≥ 65 years	376	91	Hartwig Scale	76	83.52
Tangiisuran (2012)[34]	Population ≥ 65 years	560	83	Hallas	60	72.29
Kaur (2018)[20]	All ages author supplied	467	106	Hartwig Scale	70	66.06
Davies (2009)[14]	All ages author supplied	1787	476	Hartwig Scale	385	80.88
Ganeva (2016)[16]	All ages author supplied	97	13	Hartwig Scale	10	76.92
Ganeva (2013)[17]	All ages author supplied	203	19	Self-described clinical judgement	16	84.21
Ganeva (2007)[15]	All ages author supplied	222	17	Author defined	6	54.55
Hailu[19]	All ages author supplied	121	3	Hartwig Scale	3	100
Bowman (1996)[8]	*All ages (29.39% ≥ 65 years)*	301	89	Venulet	64	72.00
Calderon-Ospina (2010)[9]	*All ages (48.15% ≥ 65 years)*	48	13	Author defined	13	100.00

Gonzalez-Martin (1997)[18]	*All ages (52.74% ≥ 65 years)*	244	35	Author defined - lethal, severe, moderate	9	25.71

**Reporting ADRs that are moderate, severe, serious or life threatening*

Appendix 23. Meta-analysis ADR Reported Severity



Appendix 23. Forest plot of pooled estimate (binomial-normal random effects model) of proportion of severe ADRs across eighteen studies.[8,9,12-17,19-26,31,34]

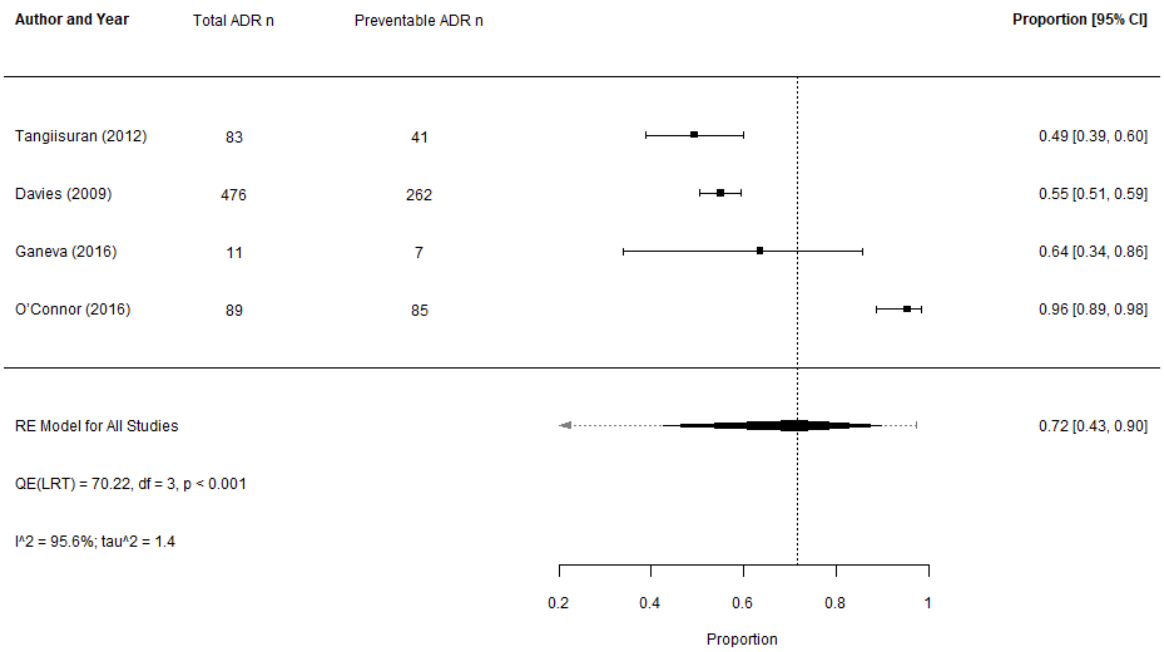
This estimate is limited by the high level of heterogeneity and substantial variability across included studies (as evidenced by I^2 and τ^2 value). Hence, the estimate should be interpreted with caution as rather than considered as a "true" estimate.

Appendix 24. Preventability

ADRs preventability was assessed in 7 studies.[9,14,16,19,23,28,34] Preventable in this instance is as defined by the various study methodologies. Studies did not report on the details of which ADR presentations or ADR-Drug pairs were "preventable". Four studies[14,16,23,28,34] had extractable data and used the same tool (Hallas).

Source	Population	Tool	Details of Preventability
O'Connor (2016)[23]	Population ≥ 65 years	Hallas	78 patients 89 ADRs 85 ADRs (95.5%) definitely or possibly avoidable
Tangiisuran (2012)[34]	Population ≥ 65 years	Hallas	74 patients 83 ADR *"69% of life-threatening or serious deemed preventable"* Life-threatening = 3 Serious = 57 41 (59%) ADRs preventable
Davies (2009)[14]	All ages author supplied	Hallas	328 patients 476 ADRs 262 (55.04%) preventable 25 definitely 237 possibly 214 unavoidable
Ganeva (2016)[16]	All ages author supplied	Hallas	11 patients ADRs 7 (63.63%) preventable 1 definitely 6 possibly 4 unavoidable
Hailu (2020)[19]	All ages author supplied	Not specified	3 patients ADRs 2 preventable
Calderon-Ospina (2010)[9]	*All ages* *(48.15% ≥ 65 years)*	Schumock & Thornton	50% (33.1-66.9%) of ADRs were considered preventable (all ages)
Giardina[28]	*All ages* *(75.93%≥ 65 years)*	Schumock & Thornton	Probably preventable in 69.4% (all ages) unavoidable 24.2% 6.4% certainly preventable

Appendix 25. Meta-analysis of pooled estimate of "preventable" ADRs in studies (n=4) using Hallas tool



Appendix 25. Forest plot of pooled estimate (binomial-normal random effects model) of proportion of preventable ADRs across four studies using comparable reporting. [14,16,23,28,34]

In addition to being a small sample-size in context of overall pooled population, this estimate is limited by the high level of heterogeneity and substantial variability across included studies (as evidenced by I^2 and τ^2 value). Hence, the estimate should be interpreted with caution as rather than considered as a "true" estimate.

Appendix 26. Reported Polypharmacy

Details pertaining to medication-burden were reported in 18 studies.[7,13,17-25,27-31,34,35] (11 whose population was ≥65 years, 6 whose population was all ages author supplied data for cohort of interest and 4 studies reported data for all ages). Polypharmacy (i.e. ≥ 5 daily medications at baseline reported as a mean/median) was present in 11 studies.[7,13,17,21-25,27,30,34,35]

Source	Population	Medication burden	Comments/further details
Corsonello[13]	Population ≥ 65 years	10.6 ± 5.5 [a]	# drugs per stay (excl. PIMs) ADR group vs non-ADR 15.2±7.9 [a] vs 9.9±4.8 [a]p=0.001
Fernandez – Regueiro[27]	Population ≥ 65 years	9 IQR 3-16[b]	81 patients (84%) ≥ 6 drugs
Lavan[30]	Population ≥ 65 years	9.9 ± 3.8 [a]	-
Leach[21]	Population ≥ 65 years	Mean 6.1 mode 4	Incidence ADRs increased with number of drugs 6% 1-

			3 drugs to 52% >8 drugs p<0.001
Contd. Source	**Population**	**Medication burden**	**Comments/further details**
Liao[31]	Population ≥ 65 years	Medications measured by number of drug classes during whole hospital stay	ADR 14.98 ± 0.43 [a] Non-ADR 14.95 ± 0.22[a] P = <0.01
O'Connor (2016)[23]	Population ≥ 65 years	8 IQR 6-11[b]	291 (78%) ≥ 5 drugs
O'Connor (2012)[22]	Population ≥ 65 years	7 IQR 1-10[b]	345 (67%) ≥ 6 drugs ADR median 10 Non-ADR median 7 p<0.001
Onder[24]	Population ≥ 65 years	3911 (66%) GIFA study ≥ 5 drugs 425 (88%) val. Study ≥ 5 drugs	ADR group 3579 (64%) ≥ 5 drugs Non-ADR group 332 (87%) ≥ 5 drugs 5-7 drugs OR 1.9 (1.35-2.68) ≥8 drugs OR 4.07 (2.93-5.65) ADR group 52 (93%) ≥ 5 drugs Non-ADR group 373 (87%) ≥ 5 drugs p=0.001
O'Sullivan[25]	Population ≥ 65 years	8 IQR 6-11[b]	321 (85.4%) ≥ 5 drugs control arm
Tangiisuran (2012)[34]	Population ≥ 65 years	5 IQR 3-7[b]	Baseline, total ADR 6 IQR 3-8 [b] Non-ADR 5 IQR 3-7 [b] p<0.05 On ward, total ADR 10 (7.75-13)[b] Non-ADR 7 (5-10) [b] P<0.05
Tangiisuran (2014)[35]	Population ≥ 65 years	Dev. 6 IQR 3-8[b] Val. 5 IQR 4-8[b]	Dev. Range 0-18
Ayub[7]	All ages, author supplied	17.2 ± 2.4[a]	Min 13 Max 20
Ganeva (2013)[17]	All ages author supplied	6.1 ± 2.4 [a]	-
Harugeri[29]	*Population >60 years (40% >70 years)*	Overall not described	Overall medications higher in ADR group median 10 (range 3-22) non-ADR group median 9 (range 1-21) p<0.001
Giardina[28]	*All ages (75.93% ≥ 65 years)*	Overall 48% ≥ 5 medications	-
Gonzalez-Martin[18]	*All ages (52.74% ≥ 65 years)*	Overall not described	Number of medications administered: A significant difference was observed between the patients > 65

			years, in relation to the number of medications received during hospitalization and the frequency of ADR (9.0 ± 2.3[a] medications vs. 5.5 ± 2.2 [a] medications) (t = 7.6, p <0.05).
Contd. Source	**Population**	**Medication burden**	**Comments/further details**
Hailu[19]	*All ages (60.5% ≥ 65 years)*	Overall 3.9 ± 2.108 [a]	Overall, 71 (35.5%) had polypharmacy (defined ≥5)
Kaur[20]	*All ages (70.97% ≥ 65 years)*	98% experiencing ADRs had polypharmacy	Population (>50 years) Polypharmacy ≥ 3 drugs 467 (71%) ≥ 65 years

[a] - *Mean ± standard deviation; # - number;* excl. – excluded; *PIMs – potentially inappropriate medications;* [b] - *Median IQR; IQR – interquartile range; ADRs – Adverse drug reaction; GIFA – gruppo Italiano di farmacovigilanza nell'Anziano; OR – Odds Ratio; Val. – validation; Dev. – development*

Appendix 27. Reported multi-morbidity

Eleven studies examined the degree of co-morbidity as an ADR-associated variable.[7,13,17,19,22,24,27,30,31,34,35] Baseline multi-morbidity (defined as a mean/median of ≥ 3 chronic conditions) was reported in 10 studies.[7,13,22,24,27,30,31,34,35]

Source	**Population**	**Multi-morbidity**	**Comments/further details**
Corsonello[13]	Population ≥ 65 years	3.7 ±1.9[a]	Based on CIRS ADR vs non ADR CIRS 4.5±1.8[a] vs 3.6±1.9 [a] p=0.001
Fernandez – Regueiro[27]	Population ≥ 65 years	8 ± 3[a]	Range 1-17
Lavan[30]	Population ≥ 65 years	5.4 ± 1.9[a] 5 IQR 4-6[b]	Range 2-13 10% ≥ 8 conditions
Liao[31]	Population ≥ 65 years	1831 of 2393 (76%) ≥4 comorbidities	ADR 4.06 ± 1.48 [a] Non-ADR 3.53 ±1.08 [a] p = <0.001
O'Connor (2012)[22] *	Population ≥ 65 years	412 (80%) ≥ 4 comorbidities	ADR 115 (85%) ≥ 4 comorbidities Non-ADR 301 (79.6%) ≥ 4 comorbidities p=0.157
Onder[24]	Population ≥ 65 years	2996 (50%) GIFA≥ 4 comorbidities 347 (72%) val. ≥ 4 comorbidities	ADR group 252 (66%) ≥ 4 comorbidities Non-ADR group 2744 (49%) ≥ 4 comorbidities p=<0.001 ADR group 49 (88%) ≥ 4 comorbidities

			Non-ADR group 298 (70%) ≥ 4 comorbidities p=0.006
Contd. Source	**Population**	**Multi-morbidity**	**Comments/further details**
Tangiisuran (2012)[34]	Population ≥ 65 years	8 IQR 6-10[b] ADR 8 IQR 6-10[b] Non-ADR	-
Tangiisuran (2014)[35]	Population ≥ 65 years	8 IQR 6-10[b] Dev. Val. Not documented	-
Ayub[7]	All ages author supplied	4.71 ± 1.6[a]	Range 2-7 ADR 4.8 ± 1.3[a] Non-ADR 3.6 ± 1.7[a] p=0.475
Ganeva (2013)[17]	All ages author supplied	2.7 ± 1.8[a]	-
Hailu[19]	*All ages* *(60.5% ≥ 65 years)*	2.20 ± 1.157 [a]	Adjusted odds ratio (all ages) 1.588 (1.03–2.45) p = 0.04

[a] - *Mean ± standard deviation; CIRS – cumulative illness rating score; ADRs – Adverse drug reaction; * - identified from subsequent publication[51];* [b] - *Median IQR; IQR – interquartile range; GIFA – gruppo Italiano di farmacovigilanza nell'Anziano; Dev. – development; Val. – validation*

Appendix 28. Reported ADR outcomes

Clinical outcomes following ADRs were infrequently reported, only 9 papers[12,14,17,20,22,23,25,31,34] commented on mortality and/or LOS. Pooled analysis was not feasible.

Source	**Population**	**Outcome details**
Conforti[12]	Population ≥ 65 years	ADR LOS 18.7 (95% CI 17.2-20.1)[a] Non-ADR LOS 12.6 (95% CI 11.9-12.3)[a] No comment on statistical significance.
Corsonello[13]	Population ≥ 65 years	ADRs impact on functional decline Increasing # ADRs = loss of ADLs 1 ADR OR 11.1(4.18-29.5) p=0.001 loss ≥1ADLs Increasing severity of ADR = loss of ADLs Moderate to severe ADR OR 8.11(2.67-24.6) p=<0.01
Liao[31]	Population ≥ 65 years	ADR group had increased length of stay (days). 30.8±30.2 [a] vs 16.9±14.7 [a] p = <0.01 ADR group had higher total medical expenses. US$ 9531.3±13634.5 [a] vs 4108.9±5180.1 [a] p=<0.01 ADR group had higher drug expenses. US$ 2276.4±4244.1 [a] vs 817.0±1806.8 [a] p=<0.01
O'Connor (2016)[23]	Population ≥ 65 years	ADR LOS 10 IQR 6-17 [b] Non-ADR LOS 7 IQR 4-14 [b] Death 9 (control arm; unknown if ADR related)
O'Connor (2012)[22]	Population ≥ 65 years	ADR LOS 12 [b] Non-ADR LOS 7 [b] Death 29 (5.64%)

Contd. Source	**Population**	**Outcome details**
O'Sullivan[25]	Population ≥ 65 years	ADR LOS 11 IQR 7-18 [b] Non-ADR LOS 8 IQR 5-13 [b] p<0.001 Death 17 (4.5% control arm; unknown if ADR related)
Tangiisuran (2012)[34]	Population ≥ 65 years	ADR LOS 14 IQR 10-26.5[b] Non-ADR LOS 12 IQR 7-19 [b]
Davies[14]	All ages author supplied	ADR LOS 22 IQR 14-37[b] Non-ADR 10 IQR 6-17[b] Death 165 (11 ADR related)
Ganeva (2013)[17]	All ages author supplied	ADR LOS 9.2 ± 3.4[a]
Harurgeri[29]	Population >60 years (40% >70 years)	Overall ADR group had longer LOS ADR LOS median 7 (range 1-43) Non-ADR 6 (range 1-20) p=0.02
Gonzalez-Martin[18]	*All ages* *(52.74% ≥ 65 years)*	Patients> 65 years with ADRs had a longer hospital stay than those without ADRs (9.57 ± 7.55 [a] days vs. 5.21 ± 3.21 [a] days) p <0.05
Kaur[20]	*All ages* *(70.97% ≥ 65 years)*	ADR LOS +2 days Death 3 ≥ 65 (unknown if ADR related)

LOS – length of stay in days; CI – Confidence Interval; [a] *- Mean ± standard deviation; ADL – Activities of Daily Living; OR – Odds Ratio;* [b] *- Median IQR; IQR – interquartile range; ADRs – Adverse drug reaction; GIFA – gruppo Italiano di farmacovigilanza nell'Anziano; Dev. – development; Val. – validation*

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APPENDIX 27 – Full list of references from main manuscript

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