Received: 21 September 2018 | Revised: 24 October 2018 | Accepted: 28 October 2018

DOI: 10.1002/agm2.12045

ORIGINAL ARTICLE

WILEY Aging Medicine Open Access

Factors associated with medication adherence in older patients: A systematic review

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Abstract

Objective: Medication adherence is a major challenge in the treatment of older patients; however, they are under-represented in research. We undertook a systematic review focused on older patients to assess the reasons underlying non-adherence in this population.

Methods: We searched multiple electronic databases for studies reporting reasons for non-adherence to medication regimens in patients aged 75 years and over. Our results were not limited to specific diseases, health-care settings, or geographical locations. The quality of eligible studies was assessed using the Newcastle-Ottawa Scale. A narrative synthesis of findings was performed.

Results: A total of 25 publications were included, all of which were in community settings. Frequent medication review and knowledge regarding the purpose of the medication were positively associated with adherence. Factors associated with poor adherence were multimorbidity, cognitive impairment, complex regimens with multiple prescribing physicians, and problems with drug storage or formulation.

Conclusion: These findings suggest that interventions to improve adherence could focus on medication review aimed at simplifying regimens and educating patients about their treatment. Groups with poor adherence that may benefit most from such a model include patients with multiple comorbidities and cognitive impairment.

KEYWORDS

drug prescriptions, geriatric medicine, polypharmacy

1 | INTRODUCTION

Medication adherence—where prescribed medications are taken at the right doses and times in the manner specified—has been shown to improve health outcomes and reduce health-care costs.[1,2] Indeed, a recent Cochrane review concluded that "increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments."[3] Non-adherence, which can take the form of non-initiation and non-persistence, is closely linked with treatment efficacy and disease progression,[4] as well as inappropriate up-titration, with subsequent risk of interactions and adverse drug reactions.[5] Adherence is a particular concern in older persons, with the prevalence of factors associated with poor adherence, such as multimorbidity and greater regimen complexity, increasing with age.[6–8]

Multiple factors at the drug, patient, provider, and institutional levels may explain non-adherence in the specific population of older people, including: (a) increased vulnerability to drug-related

problems through pharmacodynamic and pharmacokinetic changes[9]; (b) high prevalence of comorbidity with subsequent polypharmacy and functional impairment[10–12]; (c) elevated risk of drug interactions with increasing medication burden[13,14]; and (d) high rates of service use across settings, leading to multiple providers and regimen complexity.[15] These problems rarely occur in isolation and can be both the cause and effect of non-adherence, leading to a cycle of escalating adversity. Despite this, studies that explicitly consider this older population appear to be under-represented, and those that do tend to focus on a single disease. We set out to quantify the factors potentially associated with adherence by undertaking a systematic review of studies addressing these issues specifically in persons aged ≥75 years, enabling synthesis of results across different diseases and health-care settings.

2 | METHODS

2.1 | Search strategy and selection criteria

We used the following search terms in PubMed, adapting them for EMBASE and Web of Science: (Complia*/Non-complia*) (Adher*/Non-adher*) (Concordan*/Non-concordan*) (Elder*/Old*/Geriatr*/Aged/Senior). References for included articles and relevant literature reviews were also hand-searched for additional relevant publications. The search was completed in November 2017.

After screening title and abstract, the full text was reviewed. The majority of screening was carried out by A.S., with a sample independently carried out by a second reviewer (R.R.) and cross-checked to ensure validity and reproducibility. Any uncertainty was resolved following discussion with a third reviewer (D.D.). Screening and full-text review was undertaken using Covidence.[16]

We used the following inclusion criteria:

- Population—Studies that only included participants aged 75 or over; studies in which the mean age of participants was ≥75 years; or studies that reported data separately for participants aged ≥75.
- Intervention—Both interventional and non-interventional studies were considered.
- Outcomes—Studies with an operational definition of *adherence*.
- Analysis—Studies quantifying associations between any measured factors and adherence.

We applied the following exclusion criteria: non-English publications; articles that had not undergone full peer review, such as conference abstracts/posters; publications relating solely to the cost of medicines or cost analysis; and studies published prior to 2000 due to evolutions in prescribing practice over the last two decades.

2.2 | Data extraction

Data were extracted and entered into a custom template made by the first author. Data were extracted twice by two independent reviewers (A.S. and M.W.C.). Any inconsistencies were resolved by a third reviewer (D.D.). Extracted data included basic information about the study (timing, design, location/setting, sample size, and demographics of the

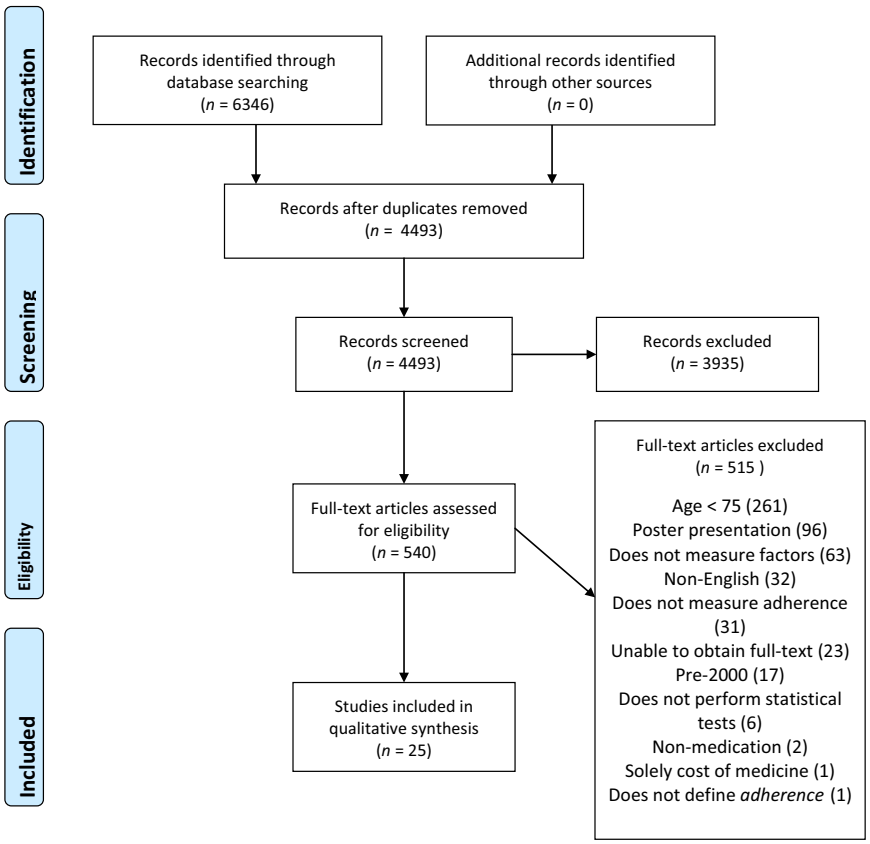

FIGURE 1 PRISMA flowchart describing search and selection of studies

TABLE 1 Characteristics of included studies

Citation	Study design	Sample	Setting	Data collection
Barat et al 2001[18]	Cross-sectional Random sample from population register	Patients aged 75 prescribed medication by GP Size = 348 Mean age = 75 M:F = 43:57	Denmark Patients living in own homes	Structured interview with medical, cognitive and functional assessment
Borah et al 2010[19]	Cohort All eligible members of health plan included	All new initiators of Alzheimer's disease medication Size = 3091 Mean age = 80 M:F = 36:64	USA Members of large health plan	Baseline information from electronic health record 1-year follow-up of pharmacy fill data
Bourcier et al 2017[20]	Cross-sectional All eligible patients within geographical area invited	Patients aged > 75 with a GP prescription Size = 1206 Mean age = 82 M:F = 35:65	France Community pharmacy in Greater Paris	Structured interview and access to pharmacy record
Choudhry et al 2008[21]	Cohort All eligible members from health plan included	All patients discharged from hospital following first myocardial infarction Size = 33 646 Mean age = 81 M:F = 25:75	USA Members of large health plan	Medicare PACE and PAAD records
Cooper et al 2005[22]	Cross-sectional Participants of AdHOC study	Participants invited from a "representative area" judged by national lead Size = 3881 Mean age = 82 M:F = 25:75	Europe (11 countries)	Structured interview
Fallis et al 2013[23]	Cohort Consecutive discharges from hospital	All discharges who were prescribed a new medication Size = 232 Mean age = 78 M:F = 49:51	Canada Consecutive discharges from hospital followed into the community	Review of electronic pharmacy record and discharge summary
Foebel et al 2012[24]	Cross-sectional Patients assessed under RAI-HC	Patients with heart failure assessed for care needs Size = 140 822 All aged >75 M:F not stated	Canada Community based	Review of RAI-HC validated against medical records
Garcia-Sempere et al 2017[25]	Cohort Patients discharged from hospital	Patients admitted with hip fracture and prescribed bone protection Size = 4856 84% aged ≥ 75 M:F = 13:87	Spain Cohort identified from hospital discharges followed into the community	Review of electronic health record

Adherence assessments	Covariates	Summary findings	Quality	Comments
Drug score, dose score and regimen score calculated Self-report for missed doses	Dementia* Depression Sex Alcohol consumption Knowledge* Years of schooling Living alone Number of prescribing physicians* Number of drugs* Number of OTC drugs Use of compliance aids	Positive association: Not having dementia, Knowledge of purpose of treatment and consequences of omission, Living with spouse Negative association: Increasing number of prescribers, Increasing number of drugs	Random sample from population register Structured interview with verification from GP record N-O score = 6	
MPR calculated for dementia medication Non-adherent if MPR < 80%	Charlson Comorbidity Index* Age* Sex* Pill burden*	Positive association: Younger age Male sex Higher pill burden Negative association: Higher comorbidity score	All eligible patients included from large register Retrospective cohort therefore no dropouts N-O score = 8	For every one under increase in pill burden, likelihood of adherence if increased by 19%. Did not control for caregiver support
Girerd score Poorly adherent if score ≥ 3	Age Social isolation* Satisfaction with formulation* Use of generic name* Complete written regimen Need to split tablets Use of MCA	Positive association: Satisfaction with formulation Negative association: Social isolation Use of generic name	Reports "adjusted odds ratios" but does not state which variables were controlled for N-O score = 3	
PDC calculated	COPD* Hospitalization in previous year Age Male* Ethnicity* Nursing home* Pill burden	Positive association: White race Nursing home resident Negative association: COPD Male sex	Large retrospective cohort study Odds ratios adjusted for several important factors N-O score = 8	Many diseases were assessed; COPD was the only one to have a statistically significant association with adherence
Self-reported adherence plus comparison with available prescriptions	Cognitive impairment* Dementia diagnosis Psychiatric diagnosis Depression Impaired vision/hearing Age Sex Being unmarried* Alcohol screen positive* Abusive Socially inappropriate Resisting care* Wandering Living situation Living alone/in care Resident caregiver ADLs/iADLs Medications Number of medications No medication review in last 6 months*	Positive association: Cognitive impairment Being unmarried Medication review Negative association: Alcohol overuse Resisting care	Each sample judged to be representative of that country Participants derived from other study so perhaps represent motivated individuals N-O score = 6	Cohort identified from participants of the AdHOC study
Failure to fill prescription (non-initiation)	Age Sex Discharge to long-term care* Number of medications Inclusion of primary care physician's name on script	Negative association: Discharge to long-term care	Representative cohort Data sourced from electronic health record N-O score = 8	
Medication use in past 7 days Deemed non-adherent if use <100%	Caregiver stress level* Caregiver residence*	Negative association: Stressed caregiver Caregiver does not live with client	Very large sample size with multivariate regression N-O score = 6	Highest impact on adherence if caregiver is stressed and does not live with client
PDC for bone protection medication at 1 year and 4 years	Comorbidity* Emergency attendance History of stroke* History of diabetes Age* Sex* Sedatives* Polypharmacy	Negative association: Charlson score > 2 History of stroke Increasing age Male sex Sedatives	Representative cohort of this population 4-year follow-up period Attrition rate not stated N-O score = 7	Only considered adherence to bone protection. As age increased, risk of non-adherence also increased.

(Continues)

TABLE 1 (Continued)

Citation	Study design	Sample	Setting	Data collection
Hayes et al 2009[26]	Cross-sectional Retirement village residents given additional vitamin C tablet	Recruited from 2 retirement villages Size = 38 Mean age = 82 M:F = 32:68	USA Community based All residents invited from the 2 villages	Electronic pill box measurement for additional tablet
Jerant et al 2011[27]	Cohort Pill count every 6 months	Sample derived from Ginkgo biloba trial Size = 771 Mean age = 78 M:F = 58:42	USA. Community based	Pill count
Lee et al 2013[28]	Cohort Interviews via social work outreach team	Sample recruited via social workers Size = 86 Mean age = 81 M:F = 37:63	Hong Kong Community based	Structured interview with MMAS score
Li et al 2008[29]	Cross-sectional Questionnaire given to sample of Mandarin speakers	Convenience sample from Asian health clinic Size = 144 Mean age = 75 M:F = 52:48	USA Community based via Asian health clinic	Self-report questionnaire With MMAS score
Lindquist et al 2012[30]	Cross-sectional Interview following admission to hospital	Recruited from acute admissions ward Size = 254 Mean age = 79 M:F = 47:53	USA Community following recruitment on acute admissions ward	Interview
Mansur et al 2008[31]	Cohort Follow-up of discharges from hospital	Recruited from acute geriatric ward Size = 198 Mean age = 81 M:F = 38:62	Israel Follow-up acute geriatric admissions	Telephone interview ± verification with GP
Marcum et al 2013[32]	Cross-sectional Questionnaire with subset of large population cohort.	Participants of Health, Ageing and Body Composition Study with HTN ± DM ± CHD Size = 897 Mean age = 82 M:F = 47:53	USA Community	Self-report questionnaire
Márquez-Contreras et al 2016[33]	Cohort Primary care patients	Patients taking NOAC in primary care Size = 370 Mean age = 75 M:F = 47:53	Spain Patients recruited via primary care and specialized researchers	Electronic pill counts and structured interviews
Moisan et al 2002[34]	Cross-sectional Interviews with patients recruited via ambulatory care	Cohort recruited via ambulatory care Size = 325 Mean age = 78 M:F = 17:83	Canada Community follow-up of patients recruited via ambulatory care	Interview with MMAS score
Ownby et al 2006[35]	Cross-sectional Interview with users of memory disorder clinic	Convenience sample from memory clinic Size = 63 Mean age = 76 M:F = 29:71	USA Recruited via memory clinic	Interview plus verification with carers and medical records

Adherence assessments	Covariates	Summary findings	Quality	Comments
Dose count and timing of dose measured Non-adherent if < 80%	Cognitive function*	Positive association: Higher cognitive function	Very small study Only controlled for number of drugs N-O score = 4	Effect of cognitive function persisted after adjustment for number of medications
Non-adherent if < 80%	Cognitive function* Comorbidity BMI Self-rated health* Age* Sex Ethnicity Income Personality trait* Smoking Years of schooling Social visits	Positive association: High self-rated health Negative association: Cognitive impairment Age Neuroticism	Median follow-up 6.1 years Cohort predominantly well-educated white males N-O score = 8	1 standard deviation in 3MSE score increases non-adherence by 3%. 5-year increment in age increased non-adherence by 1.3%.
Non-adherent if MMAS score ≥ 2	Comorbidity Sex* Health-related knowledge Adverse drug reaction Polypharmacy* Drug storage problems*	Negative association: Female sex Polypharmacy Accumulation of drugs Scattered storage Any storage problem	Small sample of specific group Does not control for other variables N-O score = 6	Defined polypharmacy as ≥ 9 drugs
Non-adherent if ≤80%	Sex* Perceived susceptibility to disease Belief about medicines Social support Length of time since immigration*	Positive association: Female sex Longer time since immigration	Small sample of very specific group Self-report with no verification N-O score = 4	Beliefs regarding Western and Chinese medicine were not significant
Comparison of self-report with discharge summary	Cognitive impairment Age Sex Health literacy* Marital status	Poor health literacy increases risk of unintentional non-adherence Good health literacy increases risk of intentional non-adherence	Relies on self-report during interview N-O score = 5	Mini-Mental State Examination cutoff for cognitive impairment determined by level of education
Self-report	Contact with GP* Polypharmacy* Medication regimen changes*	Negative association: No contact with GP Polypharmacy High number of regimen changes	Verification of self-report with GP N-O score = 8	Polypharmacy defined as ≥7 drug types
MMAS-4 and Cost-Related Nonadherence-2	Comorbidity* Physical function Falls* Sleep disturbance* Flu vaccination Hospitalization* Age Sex Race* Education/literacy Marital status	Positive association: 3 of DM/CHD/HTN Cancer Negative association: 2 of DM/CHD/HTN Sleep disturbance Hospitalization in previous 6 months Black race	Representative sample from large population cohort Outcome assessed by self-report N-O score = 4	All patients had at least one of DM/CHD/HTN. With reference to 1 of 3, 2 of 3 worsened adherence and 3 of 3 improved adherence.
Compliance percentage from pill count Adherent if ≥80%	Comorbidity* Bodyweight* Polypharmacy*	Negative association: Increasing number of current diseases Bodyweight Polypharmacy	1-year follow-up period N-O score = 7	Definitions of current diseases, bodyweight and polypharmacy not given.
Non-adherent if ≥1 "yes" on MMAS questionnaire.	Age Sex Ability to read/understand script Belief* Perception of health Satisfaction Living alone Help to take medication Sufficient funds Treatment complexity Pill organizer	Negative association: Belief drugs have little/no effect	Predominantly female sample N-O score = 5	Reports only crude odds ratios
Park and Jones model used	Cognition Age* Sex Memory strategy Knowledge* Seriousness of disease Education Side effects* Total number of drugs	Positive association: Knowledge of outcome of disease if not treated Age Negative association: Relies on self to remember doses Side-effects	Adherence based on self-report with verification with carers N-O score = 5	*P*-values given but no odds ratios

(Continues)

TABLE 1 (Continued)

Citation	Study design	Sample	Setting	Data collection
Ownby et al 2012[36]	Randomized controlled trial	Cohort recruited via memory clinic Size = 27 Mean = 79.9 M:F = 59:31	USA Recruited via memory clinic	Interview with cognitive testing and electronic pill monitoring
Pasina et al 2014[37]	Cohort Interview with patients recruited from acute medical ward and followed into the community	First 100 patients discharged from ward with polypharmacy Size = 100 Mean age = 78 M:F = N/A	Italy Recruited via acute medical unit and followed into the community	Structured interview
Piper et al 2017[38]	Cross-sectional Random sample of Medicare beneficiaries	5% sample of Medicare beneficiaries with epilepsy Size = 36 912 Median age >75 M:F = 39:61	USA Community	Access to medical record
Salter et al 2014[39]	Cohort Interviews in a subset of the MRC SCOOP trial over 18 months	Geographical subset selected from SCOOP trial Size = 30 Median age > 75 M:F = 0:100	UK Community	Structured interview
Sheer et al 2016[40]	Cohort Evaluation of pharmacy record of Medicare beneficiaries	Patients in receipt of Medicare prescription for an intra-ocular hypotensive agent Size = 73 256 Mean age = 76 M:F = 42:58	USA Community	Access to electronic pharmacy record
Turner et al 2009[41]	Cross-sectional Interviews with patients identified in primary care	"Representative sample" from primary care record Size = 202 Mean age = 77 M:F = 34:66	USA Community	Structured interview
Ulfvarson et al 2007[42]	Cross-sectional Hospital discharges followed into the community	All eligible admissions to the acute medical ward invited Size = 200 Mean age = 79 M:F = 48:52	Sweden Sample identified in hospital and assessed in the community	Interview with medical record linkage

Abbreviations: 3MSE, modified Mini-Mental State Examination; ADLs, activities of daily living; BMI, body mass index; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, hypertension; iADLs, instrumental activities of daily living; MCA, medication compliance aid; MMAS, Morisky Medication Adherence Scale; MPR, medication possession ratio; N-O score, Newcastle-Ottawa score; NOAC, novel oral anticoagulant; OTC, over-the-counter; PAAD, New Jersey Pharmaceutical Assistance for the Aged and Disabled; PACE, Pennsylvania Pharmaceutical Assistance Contract for the Elderly; PDC, proportion of days covered; RAI-HC, Resident Assessment Instrument – Home Care.
*Statistically significant association.

participants), method of data collection, definition of *adherence*, and any measured associations (if any). Study quality was assessed by the same independent reviewers using the Newcastle-Ottawa Scale[17] rating: selection, comparability, and outcome (maximum score = 9 points).

3 | RESULTS

Of the 6346 publications identified, 540 were eligible for full-text review and 25 met the criteria for inclusion (Figure 1). The

Adherence assessments	Covariates	Summary findings	Quality	Comments
Continuous scale based on electronic monitoring No cutoff for "non-adherent"	Cognition Presence of caregiver*	Positive association: Presence of caregiver	Very small sample N-O score = 7	Participants all have clinical diagnosis of memory problem and treated with cholinesterase inhibitor or memantine. Poor adherence predicted cognitive decline, but cognition did not predict adherence. Effect of caregiver presence attenuated over time
Medication level: mean adherence of each patient Patient level: % of patients who are 100% adherent	Age Sex Marital status Presence of caregiver Number of medications*	Non-adherent had higher number of prescriptions than adherent (9.5 vs. 8.2, $P = 0.043$)	Length of study = 3 months Does not control for other variables Odds ratios not given N-O score = 5	
PDC from electronic health record Non-adherent if PDC < 0.8	Comorbidity* Seeing specialist* Ethnicity* Sex* Age* Income*	Positive association: Being eligible for low-income subsidy Negative association: Comorbid conditions: 1-3 = OR 1.09, 4+ = OR 1.31 Seeing neurologist close to diagnosis African American/Hispanic/Asian ethnicity (ref. White) Female sex Age over 85 Below poverty line	Random sample of largest US electronic health database Multivariate logistic regression N-O score = 6	Large well-designed study specific to patients with epilepsy
Self-report during interview Non-adherent if <80% doses taken	Medical history History of falls Family history Response to screening Acceptance of risk	No factors had significant association	Very small sample Only female participants Does not control for other variables N-O score = 5	As such a small sample size, the study may be under-powered.
PDC specifically for intra-ocular agents Non-adherent if PDC <¯ 80%	Sex* Age* Income subsidy* New prescription*	Positive association: Increasing age Low income subsidy Negative association: Male sex New prescription	Cohort identified retrospectively therefore no dropouts Large cohort Multivariate logistic regression N-O score = 8	Study specific to intra-ocular agents
Non-adherent if any dose missed in the last 3 months	Mood disorder Self-rated health Age Ethnicity Checks blood pressure at home Trouble following advice Polypharmacy* Runs out of medication*	Negative association: ≥4 antihypertensive medications Runs out of medication	Adjustment made for demographics, treatment regimen, and sampling weights N-O score = 5	Primary focus of study was antihypertensive medications
Self-report verified against medical record	Self-rated health Sex Age Education/knowledge Marital status Experience of side-effects Polypharmacy Use of OTC/herbal meds Sufficient information Sufficient time with doctor/nurse Use of compliance aid	No factors had significant association	Multivariate logistic regression N-O score = 6	Relatively small sample. Perhaps the study was under-powered

majority of those eligible for inclusion were observational studies (one randomized controlled trial, 11 cohort, and 13 cross-sectional) based in Europe or North America. Participants were community dwelling (range n = 27 to n = 140 000), although some studies assessed specific groups within the community, such as those post-hospitalization or memory clinic users (Table 1[18–42]). Operational definitions of *non-adherence* varied, even when the method of data collection was the same.

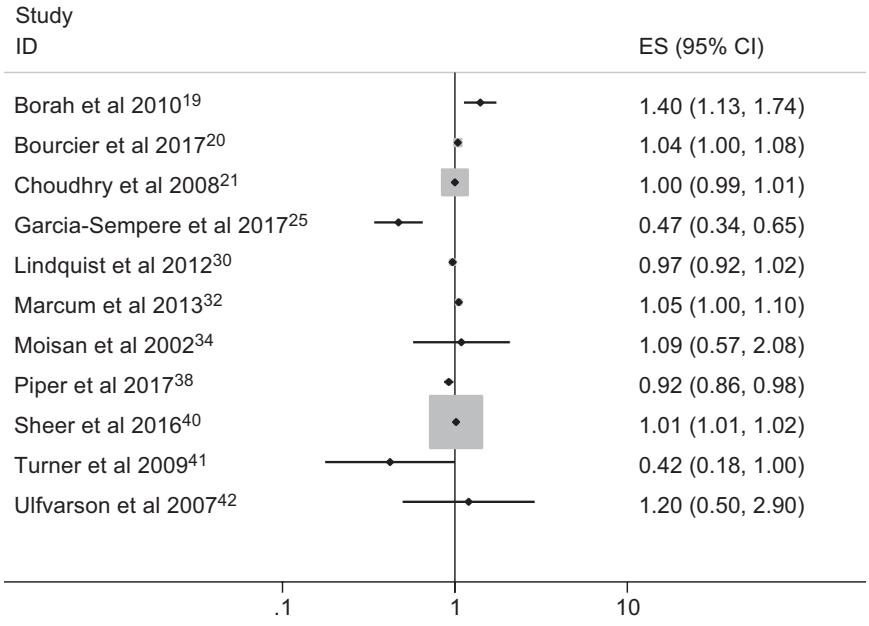

FIGURE 2 Effect of older age on adherence. Forest plot showing the association of age on adherence in selected studies reporting comparable age relationships. No pooled estimate is shown due to substantial heterogeneity across studies. CI, confidence interval; ES, effect size

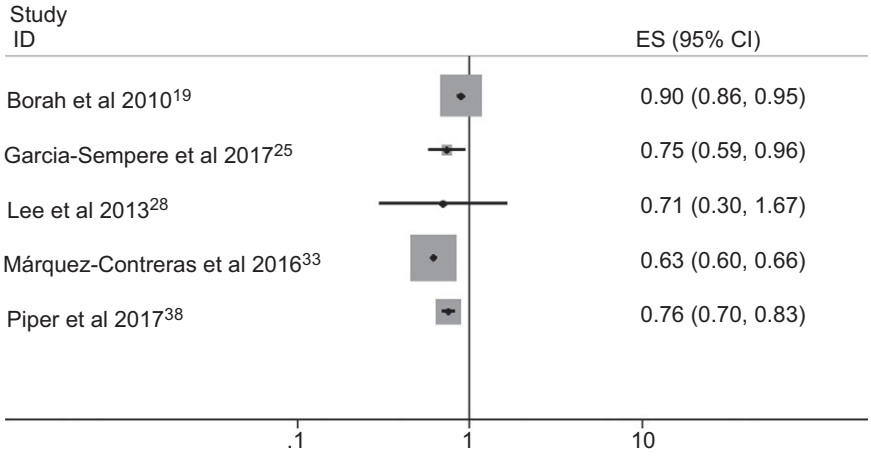

FIGURE 3 Effect of multimorbidity on adherence. Forest plot showing the association of multimorbidity on adherence in selected studies reporting comparable multimorbidity measures. No pooled estimate is shown due to substantial heterogeneity across studies. CI, confidence interval; ES, effect size

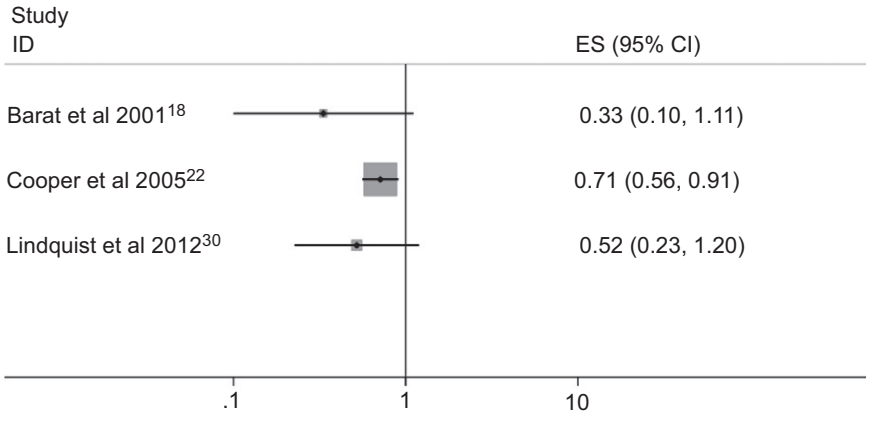

FIGURE 4 Effect of cognitive impairment on adherence. Forest plot showing the association of cognitive impairment on adherence in selected studies reporting comparable measures of cognitive impairment. No pooled estimate is shown due to substantial heterogeneity across studies. CI, confidence interval; ES, effect size

Methods for ascertaining adherence included: (a) data collected from electronic monitoring systems; (b) information from medical records, such as prescription fill data and insurance claims; and (c) data from interviews or self-report questionnaires. These differences were considered when drawing broader conclusions.

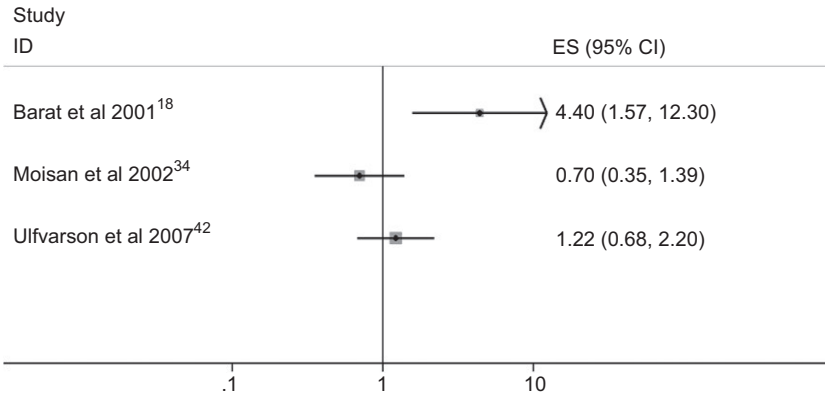

FIGURE 5 Effect of compliance aids on adherence. Forest plot showing the association of age on adherence in selected studies reporting comparable measures of use of compliance aids. No pooled estimate is shown due to substantial heterogeneity across studies. CI, confidence interval; ES, effect size

3.1 | Patient factors

Factors positively associated with adherence included being of European descent,[21,32,38] and having high health literacy and information about the treatment purpose and consequences of omission.[18,30] With regard to specific diseases, only cancer was shown to have a positive association with adherence.[32]

Demographic factors negatively associated with adherence included older age[19,25,27,35,38] and being male,[21,25,28,29,40] although these associations were weak (Figure 2). Health behaviors negatively associated with adherence were excessive alcohol consumption.[22] Other factors negatively associated with adherence included the neurotic personality trait (other personality traits did not have a significant impact),[27] recent hospitalization, and lack of contact with a general practitioner.[31,32] Higher levels of comorbidity were also associated with poorer adherence (Figure 3).[9,25,33,38] Compared with people who did not have these diseases, stroke,[25] falls,[32] sleep disturbance,[32] and chronic obstructive pulmonary disease[21] were all found to have an independent negative effect on adherence due to their presence. There was a suggestion that cognitive impairment shares a negative association with adherence[18,22,26,27] (Figure 4), although these results contrasted findings from two smaller studies. Both of these studies not demonstrating any association featured small sample sizes, one of which recruited patients from a memory clinic (i.e., without a healthy control comparator).[30,35]

General education did not appear to be associated with adherence,[18,27,32,35,42] and nor were psychiatric diagnoses.[18,22,41] The two studies reporting body mass index associations had discordant results.[27,33]

3.2 | Medication factors

The only medication factor positively associated with adherence was having had a medication review in the last 6 months, although this was only assessed in one study.[22] Factors negatively associated with adherence included recently changed medication regimens[31] and those regimens that had been formulated through involvement of greater numbers of prescribing physicians.[18] Patient dissatisfaction with the drug formulation and difficulties with drug storage, such as accumulation of drugs and scattered drug storage, were also negatively associated with adherence.[20,28,41]

In general, adherence was negatively associated with larger numbers of prescribed drugs, but this was not consistent. Where reports defined polypharmacy with a higher cutoff (such as greater than seven or even nine drugs), polypharmacy was more likely to have a negative association with adherence.[28,31,37] The studies that used a continuous scale of overall pill burden were less likely to find an association between polypharmacy and adherence.[21,22,35] One study reported improved adherence with increasing pill burden.[19]

Compliance aids were not consistently associated with adherence (Figure 5).[18,20,34,42] One study found that compliance aids were associated with medications being taken on a given day but not improved adherence to the correct dosage or regimen.[18]

3.3 | Institutional factors

Six studies reported on the presence of a caregiver, five of which found no association with adherence.[22,27,29,34,37] One study found that a resident caregiver improved adherence focused on patients with mild cognitive impairment.[34] There was no consensus between studies that reported the setting in which the patient lived, and similarly whether the patient lived alone or with someone else.[18,20–23,34]

4 | DISCUSSION

Factors most consistently negatively associated with adherence in this older population were related to complex regimens with multiple prescribing physicians, and problems with medication storage and formulation. Multimorbidity and cognitive impairment were also negatively associated with adherence. In contrast, recent medication review and knowledge about the purpose of the treatment and consequences of omission were positively associated with adherence. However, the use of medication compliance aids and, in the absence of cognitive impairment, the presence of a caregiver did not appear to be associated with adherence. Although we sought to examine this question specifically in older populations, we found only a weak negative association with adherence at these ages. Taken together, our findings suggest that interventions for improving adherence should be aimed at patients with multimorbidity and cognitive impairment,

with the goal of improving knowledge about the treatment and simplifying regimens.

This review goes beyond the findings of an earlier systematic review by considering studies conducted outside of the USA and focusing solely on patients aged over 75 years.[43] Previous work found it difficult to draw broad conclusions due to differences in the definition and measurement of adherence and the limited number of publications that were included. Our findings support the conclusions that health-related knowledge, cognitive impairment, and polypharmacy have an impact on adherence. However, our analysis adds uncertainty to the notion that medication compliance aids are effective. This suggests that future investigations into other forms of adherence support are merited. The utility of compliance aids has been debated in a recent European Medicines Agency Reflection Paper, in which problems relating to the recognition of medicines due to removal from their original packaging were specifically highlighted.[44] We found that external reminders (such as caregivers and phone call reminders) were more effective in older adults with cognitive impairment.[45]

Our results should be treated with caution. As with previous research in this area,[43] the primary limitation relates to the quantity of available research. Though we used broad inclusion criteria, we only identified 25 eligible publications. Most of these were observational, with very few randomized controlled trials having been undertaken. A further limitation concerns the lack of a clear consensus definition of *adherence* and *polypharmacy*. As such, studies relating to the administration of medications are heterogenous, both in the populations studied and in their outcome definition. Nonetheless, the strongest associations hold despite these operational differences. The major strengths of our approach have been our specific focus on older populations, a previously unexplored group with a high prevalence of adherence issues, and inclusion of studies across a range of English-language health-care systems.

The mechanisms underlying factors with an impact on adherence are strongly interlinked. An individual with multiple medical problems is likely to see several health-care practitioners, all of whom may make changes to their regimen. This is likely to be confusing, thereby leading to poor adherence. Cognitive impairment across domains such as episodic memory and executive function will have consequences that include both intentional and unintentional non-adherence. The prevalence of multimorbidity and cognitive impairment increases with age, and appears to become more important for adherence than age *per se*. As such, medication review with the opportunity to clarify and simplify prescription regimens and for the patient to ask questions might be most effective in this group. This is consistent with having fewer prescribing physicians and knowledge about the treatment being positively associated with adherence, and should be considered in light of our finding that neither the presence of a carer (in the absence of cognitive impairment) nor compliance aids showed any association with adherence. A recent case report discussed the potential utility of knowing a patient's medication schedule so that the pill burden is not unnecessarily increased when changes need to be made, something that could be achieved with this single-point-of-care model.[46] Ultimately, it may be that the most effective interventions focus on patient empowerment rather than the influence of external factors, even if individuals are living with cognitive impairment or dementia.[47]

Overall, this review supports our understanding that non-adherence is prevalent amongst older patients and is multifactorial in origin. We suggest that interventions to improve adherence in this population might be most effective if delivered in the form of a medication review, with the aim of simplifying prescription regimens and providing patient education on the indications of individual therapies. If provided from a single point of care, this would reduce the number of prescribing physicians and monitor the frequency of regimen changes. In addition, switching formulation to that preferred by the patient and screening for drug storage problems could also be effective in optimizing adherence. In particular, it would seem that specific targeting of those with cognitive impairment and multimorbidity would address an at-risk group with unmet needs.

ACKNOWLEDGMENTS

This study received no specific funding. A.S. is funded by a CEO Clinical Research Fellowship from University College London Hospital NHS Trust. D.D. is funded by a Wellcome Trust Intermediate Clinical Researcher Fellowship (WT107467).

CONFLICT OF INTEREST

No conflicts of interest were reported by the authors.

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How to cite this article: Smaje A, Weston-Clark M, Raj R, Orlu M, Davis D, Rawle M. Factors associated with medication adherence in older patients: A systematic review. *Aging Med*. 2018;1:254–266. https://doi.org/10.1002/agm2.12045