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.\(^6\)\(^7\)\(^8\)

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; (b) high prevalence of comorbidity with subsequent polypharmacy and functional impairment; (c) elevated risk of drug interactions with increasing medication burden; and (d) high rates of service use across settings, leading to multiple providers and regimen complexity. 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. 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              | Cross-sectional               | Patients aged 75 prescribed medication by GP                         | Denmark                                      | Structured interview with medical, cognitive and functional assessment         |
|                               | Random sample from population | Size = 348                                                             |                                              |                                                                                  |
|                               | register                      | Mean age = 75                                                          |                                              |                                                                                  |
|                               |                               | M:F = 43:57                                                            |                                              |                                                                                  |
| Borah et al 2010              | Cohort                        | All new initiators of Alzheimer’s disease medication                   | USA                                          | Baseline information from electronic health record                             |
|                               | All eligible members of health| Size = 3091                                                             | Members of large health plan                 | 1-year follow-up of pharmacy fill data                                         |
|                               | plan included                 | Mean age = 80                                                          |                                              |                                                                                  |
|                               |                               | M:F = 36:64                                                            |                                              |                                                                                  |
| Bourcier et al 2017           | Cross-sectional               | Patients aged >75 with a GP prescription                              | France                                       | Structured interview and access to pharmacy record                              |
|                               | All eligible patients within  | Size = 1206                                                             | Community pharmacy in Greater Paris          |                                                                                  |
|                               | geographical area invited     | Mean age = 82                                                          |                                              |                                                                                  |
|                               |                               | M:F = 35:65                                                            |                                              |                                                                                  |
| Choudhry et al 2008           | Cohort                        | All patients discharged from hospital following first myocardial      | USA                                          | Medicare PACE and PAAD records                                                  |
|                               | All eligible members from     | infarction                                                             | Members of large health plan                 |                                                                                  |
|                               | health plan included          | Size = 3364                                                             |                                              |                                                                                  |
|                               |                               | Mean age = 81                                                          |                                              |                                                                                  |
|                               |                               | M:F = 25:75                                                            |                                              |                                                                                  |
| Cooper et al 2005             | Cross-sectional               | Participants invited from a "representative area" judged by national | Europe (11 countries)                        | Structured interview                                                           |
|                               | Participants of AdHOC study   | lead                                                                    |                                              |                                                                                  |
|                               |                               | Size = 3881                                                             |                                              |                                                                                  |
|                               |                               | Mean age = 82                                                          |                                              |                                                                                  |
|                               |                               | M:F = 25:75                                                            |                                              |                                                                                  |
| Fallis et al 2013             | Cohort                        | All discharges who were prescribed a new medication                   | Canada                                       | Review of electronic pharmacy record and discharge summary                      |
|                               | Consecutive discharges from   | Size = 232                                                              | Consecutive discharges from hospital         |                                                                                  |
|                               | hospital                      | Mean age = 78                                                          | followed into the community                  |                                                                                  |
|                               |                               | M:F = 49:51                                                            |                                              |                                                                                  |
| Foebel et al 2012             | Cross-sectional               | Patients with heart failure assessed for care needs                   | Canada                                       | Review of RAI-HC validated against medical records                              |
|                               | Patients assessed under RAI-  | Size = 140,822                                                         | Community based                              |                                                                                  |
|                               | HC                            | All aged >75                                                           |                                              |                                                                                  |
|                               |                               | M:F not stated                                                         |                                              |                                                                                  |
| Garcia-Sempere et al 2017     | Cohort                        | Patients admitted with hip fracture and prescribed bone protection    | Spain                                        | Review of electronic health record                                              |
|                               | Patients discharged from      | Size = 4856                                                             | Cohort identified from hospital discharges   |                                                                                  |
|                               | hospital                      | Mean age = 75                                                          | followed into the community                  |                                                                                  |
|                               |                               | M:F = 13:87                                                            |                                              |                                                                                  |
| Adherence assessments                                      | Covariates                                              | Summary findings                                                                                     | Quality                                                                                     | Comments                                                                                     |
|-----------------------------------------------------------|---------------------------------------------------------|-------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
| Drug score, dose score and regimen score calculated       | Dementia*                                               | Positive association:                                                                                  | Random sample from population register Structured interview with verification from GP record | For every one under increase in pill burden, likelihood of adherence if increased by 15%. Did not control for caregiver support |
| Self-report for missed doses                              | Depression                                              | Not having dementia, Knowledge of purpose of treatment and consequences of omission, Living with spouse | N-O score = 6                                                                              |                                                                                               |
|                                                           | Sex                                                     | Negative association:                                                                                  |                                                                                               |                                                                                               |
|                                                           | Alcohol consumption                                     | Increasing number of prescribers, Increasing number of drugs                                          |                                                                                               |                                                                                               |
|                                                           | Knowledge                                              |                                                                                                       |                                                                                               |                                                                                               |
|                                                           | Years of schooling                                      |                                                                                                       |                                                                                               |                                                                                               |
|                                                           | Living alone                                            |                                                                                                       |                                                                                               |                                                                                               |
|                                                           | Number of prescribing physicians                        |                                                                                                       |                                                                                               |                                                                                               |
|                                                           | Number of drugs*                                        |                                                                                                       |                                                                                               |                                                                                               |
|                                                           | Number of OTC drugs                                     |                                                                                                       |                                                                                               |                                                                                               |
|                                                           | Use of compliance aids                                  |                                                                                                       |                                                                                               |                                                                                               |
| MPR calculated for dementia medication                    | Charlson Comorbidity Index*                             | Positive association:                                                                                  |                                                                                               |                                                                                               |
| Non-adherent if MPR < 80%                                 | Age*                                                    | Younger age                                                                                           | All eligible patients included from large register                                          |                                                                                               |
|                                                           | Sex*                                                    | Male sex                                                                                              | Retrospective cohort therefore no dropouts                                                   |                                                                                               |
|                                                           | Pill burden*                                            | Higher comorbidity score                                                                               | N-O score = 8                                                                              |                                                                                               |
| Gired score                                              | Age                                                     | Positive association:                                                                                  |                                                                                               |                                                                                               |
| Poorly adherent if score ≥ 3                             | Social isolation*                                       | Satisfaction with formulation*                                                                        | Reports “adjusted odds ratios” but does not state which variables were controlled for        |                                                                                               |
|                                                           | Use of generic name*                                    | Negative association:                                                                                  | N-O score = 3                                                                              |                                                                                               |
|                                                           | Complete written regimen                                | Social isolation                                                                                        |                                                                                               |                                                                                               |
|                                                           | Need to split tablets                                   | Use of generic name                                                                                    |                                                                                               |                                                                                               |
|                                                           | Use of MCA                                              |                                                                                                       |                                                                                               |                                                                                               |
| MDC calculated                                           | COPD*                                                   | Positive association:                                                                                  | Large retrospective cohort study Odds ratios adjusted for several important factors            | Many diseases were assessed; COPD was the only one to have a statistically significant association with adherence |
|                                                           | Hospitalization in previous year                        | White race                                                                                           |                                                                                               |                                                                                               |
|                                                           | Age                                                     | Nursing home resident                                                                                  |                                                                                               |                                                                                               |
|                                                           | Male*                                                   | Negative association:                                                                                  |                                                                                               |                                                                                               |
|                                                           | Ethnicity*                                              | COPD                                                                                                  |                                                                                               |                                                                                               |
|                                                           | Nursing home*                                           | Male sex                                                                                                |                                                                                               |                                                                                               |
|                                                           | Pill burden*                                            |                                                                                                       |                                                                                               |                                                                                               |
| Self-reported adherence                                  | Cognitive impairment*                                    | Positive association:                                                                                  |                                                                                               |                                                                                               |
| plus comparison with available prescriptions              | Dementia diagnosis                                      | Cognitive impairment                                                                                    |                                                                                               |                                                                                               |
|                                                           | Psychiatric diagnosis                                   | Being unmarried                                                                                        |                                                                                               |                                                                                               |
|                                                           | Depression                                              | Alcohol screen positive                                                                                 |                                                                                               |                                                                                               |
|                                                           | Impaired vision/hearing                                 | Abusive                                                                                               |                                                                                               |                                                                                               |
|                                                           | Age                                                     | Socially inappropriate                                                                                  |                                                                                               |                                                                                               |
|                                                           | Sex                                                     | Resisting care                                                                                        |                                                                                               |                                                                                               |
|                                                           | 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*                   |                                                                                                       |                                                                                               |                                                                                               |
| Failure to fill prescription (non-initiation)             | Age                                                     | Negative association:                                                                                  |                                                                                               |                                                                                               |
|                                                          (non-initiation)                                    | Sex                                                     | Discharge to long-term care                                                                            |                                                                                               |                                                                                               |
|                                                           | Discharge to long-term care*                            | Inclusion of primary care physician’s name on script                                                  |                                                                                               |                                                                                               |
|                                                           | Number of medications                                   |                                                                                                       |                                                                                               |                                                                                               |
|                                                           | Inclusion of primary care physician’s name on script     |                                                                                                       |                                                                                               |                                                                                               |
| Medication use in past 7 days Deemed non-adherent if use | Caregiver stress level*                                 | Negative association:                                                                                  |Very large sample size with multivariate regression                                           | Highest impact on adherence if caregiver is stressed and does not live with client          |
| <100%                                                     | Caregiver residence*                                    | Stressed caregiver                                                                                    |                                                                                               |                                                                                               |
|                                                            |                                                        | Caregiver does not live with client                                                                   |                                                                                               |                                                                                               |
| PDC for bone protection medication at 1 year and 4 years | Comorbidity*                                            | Negative association:                                                                                  |                                                                                               |                                                                                               |
|                                                           | Emergency attendance                                    | Charlson score > 2                                                                                    |                                                                                               | Only considered adherence to bone protection. As age increased, risk of non-adherence also increased. |
|                                                           | History of stroke*                                      | History of stroke                                                                                     |                                                                                               |                                                                                               |
|                                                           | History of diabetes                                     | Increasing age                                                                                        |                                                                                               |                                                                                               |
|                                                           | Age*                                                    | Male sex                                                                                              |                                                                                               |                                                                                               |
|                                                           | Sex*                                                    | Sedatives                                                                                             |                                                                                               |                                                                                               |
|                                                           | Sedatives*                                              |                                                                                                       |                                                                                               |                                                                                               |
|                                                           | Polypharmacy                                            |                                                                                                       |                                                                                               |                                                                                               |
|                                                           |                                                                 |                                                                                                       |                                                                                               |                                                                                               |
| (Continues)                                              |                                                                 |                                                                                                       |                                                                                               |                                                                                               |
| Citation | Study design | Sample | Setting | Data collection |
|----------|--------------|--------|---------|----------------|
| Hayes et al 2009 | Cross-sectional | Retired village residents given additional vitamin C tablet | Recruited from 2 retirement villages, size = 88, 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 | 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 | 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 | 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 | 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 | 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 | 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 | Cohort | Patients taking NOAC in primary care | 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 | 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 | 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 | Cognitive function*                                                        | Positive association: Higher cognitive function                                    | Very small study                                                        | Effect of cognitive function persisted after adjustment for number of medications |
| Non-adherent if < 80%                 | 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 2%. 5-year increment in age increased non-adherence by 1.3%. |
| Non-adherent if MMAS score ≥ 2        | Comorbidity, Sex*, Perceived susceptibility to disease, Belief about medicines, Social support, Length of time since immigration* | Negative association: Female sex, Polypharmacy, Accumulation of drugs, Scattered storage, Any storage problem | Small sample of specific group N-O score = 4                            | Defined polypharmacy as ≥ 9 drugs                                         |
| Non-adherent if ≤80%                  | Sex*, Age, Current smoking, Health literacy*, Marital status                 | Positive association: Female sex, Longer time since immigration                     | Small sample of very specific group 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                  | 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 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             | Cognitive function*, 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)
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 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                                      | Cognition                                                                 | 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                                      | Age Sex Marital status                                                    | 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 | Random sample of largest US electronic health database Multivariate logistic regression N-O score = 6 Large well-designed study specific to patients with epilepsy |
| Patient level: % of patients who are 100% adherent                                     | Comorbidty* 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 1.91 Seeing neurologist close to diagnosis African American/Hispanic/Asian ethnicity (ref. White) Female sex Age over 85 Below poverty line | | |
| PDC from electronic health record Non-adherent if PDC < 0.8                          |                                                                                                                                 |                                                                                                                                 |                                                                                                                                 |                                                                                                                                 |
| 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). Operational definitions of non-adherence varied, even when the method of data collection was the same.
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, and having high health literacy and information about the treatment purpose and consequences of omission. With regard to specific diseases, only cancer was shown to have a positive association with adherence.

Demographic factors negatively associated with adherence included older age, and being male, although these associations were weak (Figure 2). Health behaviors negatively associated with adherence were excessive alcohol consumption. Other factors negatively associated with adherence included the neurotic personality trait (other personality traits did not have a significant impact), recent hospitalization, and lack of contact with a general practitioner. Higher levels of comorbidity were also associated with poorer adherence (Figure 3). Compared with people who did not have these diseases, stroke, falls, sleep disturbance, and chronic obstructive pulmonary disease 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 (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).

General education did not appear to be associated with adherence, and nor were psychiatric diagnoses. The two studies reporting body mass index associations had discordant results.

### 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. Factors negatively associated with adherence included recently changed medication regimens and those regimens that had been formulated through involvement of greater numbers of prescribing physicians. 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.

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. The studies that used a continuous scale of overall pill burden were less likely to find an association between polypharmacy and adherence. One study reported improved adherence with increasing pill burden.

Compliance aids were not consistently associated with adherence (Figure 5). 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.

### 3.3 Institutional factors

Six studies reported on the presence of a caregiver, five of which found no association with adherence. One study found that a resident caregiver improved adherence focused on patients with mild cognitive impairment. 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.

### 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. 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. We found that external reminders (such as caregivers and phone call reminders) were more effective in older adults with cognitive impairment.

Our results should be treated with caution. As with previous research in this area, 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. 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.

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.

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CONFLICT OF INTEREST

No conflicts of interest were reported by the authors.

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