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

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Conflict of Interest
No conflicts of interest were reported by the authors.
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 healthcare costs.\textsuperscript{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.”\textsuperscript{3} Non-adherence, which can take the form of non-initiation and non-persistence, is closely linked with treatment efficacy and disease progression,\textsuperscript{4} as well as inappropriate uptitration, with subsequent risk of interactions and adverse drug reactions.\textsuperscript{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.\textsuperscript{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\textsuperscript{9}; (b) high prevalence of comorbidity with subsequent polypharmacy and functional impairment\textsuperscript{10–12}; (c) elevated risk of drug interactions with increasing medication burden\textsuperscript{13,14}; and (d) high rates of service use across settings, leading to multiple providers and regimen complexity.\textsuperscript{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 healthcare 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.\textsuperscript{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 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\textsuperscript{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 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\textsuperscript{18–42}). 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.

3.1 Patient factors

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

Demographic factors negatively associated with adherence included older age,\textsuperscript{19,25,27,35,38} and being male,\textsuperscript{21,25,28,29,40} although these associations were weak (Figure 2). Health
behaviors negatively associated with adherence were excessive alcohol consumption.\textsuperscript{22} Other factors negatively associated with adherence included the neurotic personality trait (other personality traits did not have a significant impact),\textsuperscript{27} recent hospitalization, and lack of contact with a general practitioner.\textsuperscript{31,32} Higher levels of comorbidity were also associated with poorer adherence (Figure 3).\textsuperscript{9,25,33,38} Compared with people who did not have these diseases, stroke,\textsuperscript{25} falls,\textsuperscript{32} sleep disturbance,\textsuperscript{32} and chronic obstructive pulmonary disease\textsuperscript{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,\textsuperscript{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).\textsuperscript{30,35} General education did not appear to be associated with adherence,\textsuperscript{18,27,32,35,42} and nor were psychiatric diagnoses.\textsuperscript{18,22,41} The two studies reporting body mass index associations had discordant results.\textsuperscript{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.\textsuperscript{22} Factors negatively associated with adherence included recently changed medication regimens\textsuperscript{31} and those regimens that had been formulated through involvement of greater numbers of prescribing physicians.\textsuperscript{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.\textsuperscript{20,28,41} One study reported improved adherence with increasing pill burden.\textsuperscript{19} Compliance aids were not consistently associated with adherence (Figure 5).\textsuperscript{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.\textsuperscript{18}

3.3 Institutional factors

Six studies reported on the presence of a caregiver, five of which found no association with adherence.\textsuperscript{22,27,29,34,37} One study found that a resident caregiver improved adherence focused on patients with mild cognitive impairment.\textsuperscript{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.\textsuperscript{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. 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 heterogeneous, 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.\textsuperscript{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.\textsuperscript{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

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References

3. Haynes RB, McDonald H, Garg AX, Montague P. Interventions for helping patients to follow prescriptions for medications. Cochrane Database Syst Rev. 2002; (2)doi: 10.1002/14651858.cd000011


Figure 1.
PRISMA flowchart describing search and selection of studies

- Records identified through database searching (n = 6346)
- Additional records identified through other sources (n = 0)

Records after duplicates removed (n = 4493)

Records excluded (n = 3935)

Full-text articles excluded (n = 515)
  - Age < 75 (261)
  - Poster presentation (96)
  - Does not measure factors (63)
  - Non-English (32)
  - Does not measure adherence (31)
  - Unable to obtain full-text (23)
  - Pre-2000 (17)
  - Does not perform statistical tests (6)
  - Non-medications (2)
  - Solely cost of medicine (1)
  - Does not define adherence (1)

Studies included in qualitative synthesis (n = 25)
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.
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
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
### Table 1
Characteristics of included studies

<table>
<thead>
<tr>
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<th>Study design</th>
<th>Sample</th>
<th>Setting</th>
<th>Data collection</th>
<th>Adherence assessments</th>
<th>Covariates</th>
<th>Summary findings</th>
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<th>Comments</th>
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<tbody>
<tr>
<td>Barat et al 2001&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Cross-sectional Random sample from population register</td>
<td>Patients aged 75 prescribed medication by GP Size = 348 Mean age = 75 M:F = 43:57</td>
<td>Denmark Patients living in own homes</td>
<td>Structured interview with medical, cognitive and functional assessment</td>
<td>Drug score, dose score and regimen score calculated Self-report for missed doses</td>
<td>* 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</td>
<td>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</td>
<td>Random sample from population register</td>
<td>Structured interview with verification from GP record N-O score = 6</td>
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<tr>
<td>Borah et al 2010&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Cohort All eligible members of health plan included</td>
<td>All new initiators of Alzheimer’s disease medication Size = 3091 Mean age = 80 M:F = 36:64</td>
<td>USA Members of large health plan</td>
<td>Baseline information from electronic health record 1-year follow-up of pharmacy fill data</td>
<td>MPR calculated for dementia medication Non-adherent if MPR &lt; 80%</td>
<td>Charlson Comorbidity Index * Age * Sex * Pill burden</td>
<td>Positive association: Younger age Male sex Higher pill burden Negative association: Higher comorbidity score</td>
<td>All eligible patients included from large register Retrospective cohort therefore no dropouts N-O score = 8</td>
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<tr>
<td>Bourcier et al 2017&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Cross-sectional All eligible patients within geographical area invited</td>
<td>Patients aged &gt; 75 with a GP prescription Size = 1206 Mean age = 82 M:F = 35:65</td>
<td>France Community pharmacy in Greater Paris</td>
<td>Structured interview and access to pharmacy record</td>
<td>Ginerd score Poorly adherent if score &gt; 3</td>
<td>Age Social isolation Satisfaction with formulation Use of generic name Complete written regimen Need to split tablets Use of MCA</td>
<td>Positive association: Satisfaction with formulation Negative association: Social isolation Use of generic name</td>
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<tr>
<td>Choudhry et al 2008&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Cohort All eligible members from health plan included</td>
<td>All patients discharged from hospital following first myocardial infarction Size = 33 646 Mean age = 81 M:F = 25:75</td>
<td>USA Members of large health plan</td>
<td>Medicare PACE, and PAAD records</td>
<td>PDC calculated</td>
<td>COPD Hospitalization in previous year Age * Male * Ethnicity Nursing home * Pill burden</td>
<td>Positive association: White race Nursing home resident Negative association: COPD Male sex</td>
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<tr>
<td>Cooper et al 2005&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Cross-sectional Participants of AdHOC study</td>
<td>Participants invited from a “representative area” judged by national lead Size = 3881 Mean age = 82 M:F = 25:75</td>
<td>Europe (11 countries)</td>
<td>Structured interview</td>
<td>Self-reported adherence plus comparison with available prescriptions</td>
<td>Cognitive impairment Dementia diagnosis Psychiatric diagnosis Depression Impaired vision/hearing Age Sex Being unmarried</td>
<td>Positive association: Cognitive impairment Being unmarried Medication review Negative association: Alcohol overuse Resisting care</td>
<td>Each sample judged to be representative of that country Participants derived from other study so perhaps represent motivated individuals N-O score = 6</td>
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*A: *Statistically significant

Aging Med (Milton). Author manuscript; available in PMC 2019 August 13.
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<tr>
<td>Fallis et al 2013</td>
<td>Cohort</td>
<td>All discharges who were prescribed a new medication</td>
<td>Canada Consecutive discharges from hospital followed into the community</td>
<td>Review of electronic pharmacy record and discharge summary</td>
<td>Failure to fill prescription (non-initiation)</td>
<td>Age Sex Discharge to long-term care Number of medications Inclusion of primary care physician’s name on script</td>
<td>Negative association: Discharge to long-term care Representative cohort Data sourced from electronic health record N-O score = 8</td>
<td></td>
<td>Highest impact on adherence if caregiver is stressed and does not live with client</td>
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<td></td>
<td>Consecutive discharges from hospital</td>
<td>Patients admitted with hip fracture and prescribed bone protection</td>
<td>Canada Community based</td>
<td>Review of RAI-IC validated against medical records</td>
<td>Medication use in past 7 days Deemed non-adherent if use &lt;100%</td>
<td>Caregiver stress level Caregiver residence</td>
<td>Negative association: Stressed caregiver Caregiver does not live with client Very large sample size with multivariate regression N-O score = 6</td>
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<td></td>
<td>Patients assessed under RAI-IC</td>
<td>Patients admitted with hip fracture and prescribed bone protection</td>
<td>Spain Cohort identified from hospital discharges followed into the community</td>
<td>Review of electronic health record</td>
<td>PDC for bone protection medication at 1 year and 4 years</td>
<td>Comorbidities Emergency attendance History of stroke History of diabetes Age Sex</td>
<td>Negative association: Charlson score &gt; 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</td>
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<td></td>
<td>Cohort</td>
<td>Patients admitted with hip fracture and prescribed bone protection</td>
<td>USA Community based</td>
<td>Review of electronic health record</td>
<td>Dose count and timing of dose measured Non-adherent if &lt; 80%</td>
<td>Cognitive function</td>
<td>Positive association: Higher cognitive function Very small study Only controlled for number of drugs N-O score = 4</td>
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<td></td>
<td>Patients discharged from hospital</td>
<td>Recruited from 2 retirement villages</td>
<td>USA Community based</td>
<td>Electronic pill box measurement for additional tablet</td>
<td>Cognitive function Comorbidity BMI Self-rated health Age Ethnicity Income Personality trait</td>
<td>Positive association: High self-rated health Negative association: Cognitive impairment Age Neuroticism</td>
<td>Median follow-up 6.1 years Cohort predominantly well-educated white males N-O score = 8</td>
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<td>Cohort</td>
<td>Sample derived from Ginkgo biloba trial</td>
<td>USA Community based</td>
<td>Pill count</td>
<td>Non-adherent if &lt; 80%</td>
<td>Cognitive function</td>
<td>Positive association: High self-rated health Negative association: Cognitive impairment Age Neuroticism</td>
<td>1 standard deviation in 3MSE score increases non-adherence by 3%. 5-year increment in age increased non-adherence by 1.3%.</td>
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<tr>
<td>Lee et al 2013</td>
<td>Cohort Interviews via social work outreach team</td>
<td>Sample recruited via social workers Size = 86 Mean age = 81 M:F = 37.63</td>
<td>Hong Kong Community based</td>
<td>Structured interview with MMAS score</td>
<td>Non-adherent if MMAS score ≥ 2</td>
<td>Comorbidity * Sex Health-related knowledge Adverse drug reaction * Polypharmacy Drug storage problems *</td>
<td>Negative association: Female sex Polypharmacy Accumulation of drugs Scattered storage Any storage problem</td>
<td>Small sample of specific group Does not control for other variables N-O score = 6</td>
<td>Defined polypharmacy as ≥9 drugs</td>
</tr>
<tr>
<td>Li et al 2008</td>
<td>Cross-sectional Questionnaire given to sample of Mandarin speakers</td>
<td>Convenience sample from Asian health clinic Size = 144 Mean age = 75 M:F = 52.48</td>
<td>USA Community based via Asian health clinic</td>
<td>Self-report questionnaire With MMAS score</td>
<td>Non-adherent if ≥80%</td>
<td>Cognitive impairment Age Sex Health literacy Marital status</td>
<td>Positive association: Female sex Longer time since immigration</td>
<td>Small sample of very specific group Self-report with no verification N-O score = 4</td>
<td>Beliefs regarding Western and Chinese medicine were not significant</td>
</tr>
<tr>
<td>Lindquist et al 2012</td>
<td>Cross-sectional Interview following admission to hospital</td>
<td>Recruited from acute admissions ward Size = 254 Mean age = 79 M:F = 47.53</td>
<td>USA Community following recruitment on acute admissions</td>
<td>Interview Comparison of self-report with discharge summary</td>
<td>Self-report</td>
<td>Contact with GP * Polypharmacy Medication regimen * changes</td>
<td>Poor health literacy increases risk of unintentional non-adherence Good health literacy increases risk of intentional non-adherence</td>
<td>Relies on self-report during interview N-O score = 5</td>
<td>Mini-Mental State Examination cutoff for cognitive impairment determined by level of education</td>
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<td>Mansur et al 2008</td>
<td>Cohort Follow-up of discharges from hospital</td>
<td>Recruited from acute geriatric ward Size = 198 Mean age = 81 M:F = 38.62</td>
<td>Israel Follow-up acute geriatric admissions</td>
<td>Telephone interview &amp; verification with GP</td>
<td>Self-report</td>
<td>Negative association: No contact with GP Polypharmacy High number of regimen changes</td>
<td>Verification of self-report with GP N-O score = 8</td>
<td>Polypharmacy defined as ≥2 drug types</td>
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<td>Marquez-Contreras et al 2013</td>
<td>Cross-sectional Questionnaire with subset of large population Cohort.</td>
<td>Participants of Health, Ageing and Body Composition Study with HTN &amp; DM ± CHD Size = 897 Mean age = 82 M:F = 47.53</td>
<td>USA Community</td>
<td>Self-report questionnaire MMAS-4 and Cost-Related Nonadherence-2</td>
<td>Self-report</td>
<td>Positive association: 3 of DM/CHD/HTN Cancer Negative association: 2 of DM/CHD/HTN Sleep disturbance Hospitalization Age Sex Race Education/ literacy Marital status</td>
<td>Representative sample from large population cohort Outcome assessed by self-report N-O score ≥ 4</td>
<td>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</td>
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<td>Moisan et al 2002</td>
<td>Cross-sectional Interviews with patients recruited via</td>
<td>Cohort recruited via ambulatory care Size = 325 Mean age = 78</td>
<td>Canada Community follow-up of patients recruited via</td>
<td>Interview with MMAS score</td>
<td>Non-adherent if ≥7 of MMAS questionnaire.</td>
<td>Age Sex Ability to read/understand Beliefs about drugs Drug reaction Drug storage problems</td>
<td>Negative association: Belief drugs have little/no effect</td>
<td>Predominantly female sample N-O score ≥ 5</td>
<td>Reports only crude odds ratios</td>
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<tr>
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<tr>
<td>Ownby et al 2006</td>
<td>Cross-sectional Interview with users of memory disorder clinic</td>
<td>Convenience sample from memory clinic Size = 63 Mean age = 76 M:F = 29:71</td>
<td>USA Recruited via memory clinic</td>
<td>Interview plus verification with carers and medical records</td>
<td>Park and Jones model used</td>
<td>Positive association: Knowledge of outcome of disease if not treated</td>
<td>Adherence based on self-report with verification of carers N-O score = 5</td>
<td>3</td>
<td>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</td>
</tr>
<tr>
<td>Ownby et al 2012</td>
<td>Randomized controlled trial</td>
<td>Cohort recruited via memory clinic Size = 27 Mean = 79.9 M:F = 59:31</td>
<td>USA Recruited via memory clinic</td>
<td>Interview with cognitive testing and electronic pill monitoring</td>
<td>Continuous scale based on electronic monitoring No cutoff for “non-adherent”</td>
<td>Positive association: Presence of caregiver</td>
<td>Very small sample N-O score = 7</td>
<td>3</td>
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<tr>
<td>Pasina et al 2014</td>
<td>Cohort Interview with patients recruited from acute medical ward and followed</td>
<td>First 100 patients discharged from ward with polypharmacy Size = 100 Mean age = 78 M:F = N/A</td>
<td>Italy Recruited via acute medical unit and followed into the community</td>
<td>Structured interview</td>
<td>Medication level: mean adherence of each patient Patient level: % of patients who are 100% adherent</td>
<td>Non-adherent had higher number of prescriptions than adherent (9.5 vs. 8.2, P = 0.043)</td>
<td>Length of study = 3 months Does not control for other variables Odds ratios not given N-O score = 5</td>
<td>3</td>
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<tr>
<td>Piper et al 2017</td>
<td>Cross-sectional Random sample of Medicare beneficiaries</td>
<td>5% sample of Medicare beneficiaries with epilepsy Size = 36 912 Median age &gt; 75 M:F = 39:61</td>
<td>USA Community</td>
<td>Access to medical record</td>
<td>PDC from electronic health record Non-adherent if PDC &lt; 0.8</td>
<td>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</td>
<td>Random sample of largest US electronic health database Multivariate logistic regression N-O score = 6</td>
<td>3</td>
<td>Large well-designed study specific to patients with epilepsy</td>
</tr>
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</table>

**Adherence:** Adherence assessments included in the studies varied, with most using a combination of self-report and客观 monitoring methods. **Covariates:** Covariates such as age, sex, marital status, presence of caregiver, number of medications, and comorbidity were assessed. **Summary findings:** Positive associations were found for knowledge of outcomes of disease if not treated and presence of caregiver, while negative associations were observed for side-effects and number of medications. **Quality:** The studies varied in their methodologies and data collection methods, with some studies recruiting larger samples and using more sophisticated adherence assessment tools. **Comments:** The studies highlight the importance of adherence in managing chronic conditions, particularly in the context of memory disorders and epilepsy.
<table>
<thead>
<tr>
<th>Citation</th>
<th>Study design</th>
<th>Sample</th>
<th>Setting</th>
<th>Data collection</th>
<th>Adherence assessments</th>
<th>Covariates</th>
<th>Summary findings</th>
<th>Quality</th>
<th>Comments</th>
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<tr>
<td>Salter et al 2014</td>
<td>Cohort Interviews in a subset of the MRC SCOOP trial over 18 months</td>
<td>Geographical subset selected from SCOOP trial Size = 30 Median age &gt; 75 M/F = 0.100</td>
<td>UK Community</td>
<td>Structured interview</td>
<td>Self-report during interview Non-adherent if &lt;80% doses taken</td>
<td>Medical history History of falls Family history Response to screening Acceptance of risk</td>
<td>No factors had significant association</td>
<td>Below poverty line</td>
<td>Very small sample Only female participants Does not control for other variables N-O score = 5</td>
</tr>
<tr>
<td>Sheer et al 2016</td>
<td>Cohort Evaluation of pharmacy record of Medicare beneficiaries</td>
<td>Patients in receipt of Medicare prescription for an intra-ocular hypotensive agent Size = 73 256 Mean age = 76 M/F = 42.58</td>
<td>USA Community</td>
<td>Access to electronic pharmacy record</td>
<td>PDC specifically for intra-ocular agents Non-adherent if PDC &lt; 80%</td>
<td>Positive association: Increasing age Low income subsidy Negative association: Male sex New prescription</td>
<td>No factors had significant association</td>
<td>Below poverty line</td>
<td>Very small sample Only female participants Does not control for other variables N-O score = 5</td>
</tr>
<tr>
<td>Turner et al 2009</td>
<td>Cross-sectional Interviews with patients identified in primary care</td>
<td>&quot;Representative sample&quot; from primary care record Size = 202 Mean age = 77 M/F = 34.66</td>
<td>USA Community</td>
<td>Structured interview</td>
<td>Non-adherent if any dose missed in the last 3 months</td>
<td>Mood disorder Self-rated health Age Ethnicity Checks blood pressure at home Trouble following advice Polypharmacy Runs out of medication</td>
<td>No factors had significant association</td>
<td>Below poverty line</td>
<td>Very small sample Only female participants Does not control for other variables N-O score = 5</td>
</tr>
<tr>
<td>Ulfvarson et al 2007</td>
<td>Cross-sectional Hospital discharges followed into the community</td>
<td>All eligible admissions to the acute medical ward invited Size = 200 Mean age = 79 M/F = 48:52</td>
<td>Sweden Sample identified in hospital and assessed in the community</td>
<td>Interview with medical record linkage</td>
<td>Self-report verified against medical record</td>
<td>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</td>
<td>No factors had significant association</td>
<td>Below poverty line</td>
<td>Very small sample Only female participants Does not control for other variables N-O score = 5</td>
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</tbody>
</table>

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.