

BMJ Open Prevalence and predictors of medication non-adherence among people living with multimorbidity: a systematic review and meta-analysis

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To cite: Foley L, Larkin J, Lombard-Vance R, *et al*. Prevalence and predictors of medication non-adherence among people living with multimorbidity: a systematic review and meta-analysis. *BMJ Open* 2021;**11**:e044987. doi:10.1136/bmjopen-2020-044987

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2020-044987>).

Received 21 September 2020
Accepted 06 August 2021



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ABSTRACT

Objectives This systematic review aimed to describe medication non-adherence among people living with multimorbidity according to the current literature, and synthesise predictors of non-adherence in this population.

Methods A systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses. PubMed, EMBASE, CINAHL and PsycINFO were searched for relevant articles published in English language between January 2009 and April 2019. Quantitative studies reporting medication non-adherence and/or predictors of non-adherence among people with two or more chronic conditions were included in the review. A meta-analysis was conducted with a subgroup of studies that used an inclusive definition of multimorbidity to recruit participants, rather than seeking people with specific conditions. Remaining studies reporting prevalence and predictors of non-adherence were narratively synthesised.

Results The database search produced 10 998 records and a further 75 were identified through other sources. Following full-text screening, 178 studies were included in the review. The range of reported non-adherence differed by measurement method, at 76.5% for self-report, 69.4% for pharmacy data, and 44.1% for electronic monitoring. A meta-analysis was conducted with eight studies ($n=8949$) that used an inclusive definition of multimorbidity to recruit participants. The pooled prevalence of non-adherence was 42.6% (95% CI: 34.0 - 51.3%, $k=8$, $I^2=97%$, $p<0.01$). The overall range of non-adherence was 7.0%–83.5%. Frequently reported correlates of non-adherence included previous non-adherence and treatment-related beliefs.

Conclusions The review identified a heterogeneous literature in terms of conditions studied, and definitions and measures of non-adherence used. Results suggest that future attempts to improve adherence among people with multimorbidity should determine for which conditions individuals require most support. The variable levels of medication non-adherence highlight the need for more attention to be paid by healthcare providers to the impact of multimorbidity on chronic disease self-management.

PROSPERO registration number CRD42019133849.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Criteria for inclusion did not specify particular chronic conditions, permitting inclusion of a wide variety of disease combinations.
- ⇒ Studies were not excluded on the basis of design, setting or method of non-adherence measurement, generating a comprehensive overview of the literature.
- ⇒ Due to considerable heterogeneity between studies, meta-analysis and synthesis of predictors was restricted to studies that did not recruit participants with prespecified combinations of conditions.
- ⇒ Quantitative subgroup analysis was not conducted to determine the influence of participant or study characteristics on non-adherence estimates.

INTRODUCTION

Multimorbidity is broadly defined as the coexistence of two or more chronic conditions¹ and has been described as the most common chronic condition experienced by adults.² In a Scottish study of 1.75 million people, the prevalence of multimorbidity was estimated to be 23.3%, increasing to 65% among those aged 65–84 years.³ People living with multimorbidity attend more medical consultations, experience higher rates of hospital admissions, and face increased healthcare costs.⁴ People with multimorbidity are also expected to engage with complex self-management regimens which can include monitoring symptoms, changing lifestyle behaviours, and adhering to prescribed medications.⁵

Adherence refers to the extent to which a person's behaviours correspond with agreed recommendations from their healthcare provider.⁶ Multimorbidity is closely associated with polypharmacy,⁷ and it has been reported previously that the risk of medication non-adherence can increase as people are prescribed more medicines.⁸ The extent of non-adherence among people

with multimorbidity is poorly understood, attributable to challenges in measuring multiple medication adherence.⁹ However, it is recognised that medication non-adherence in multimorbidity can exacerbate the burden experienced by individuals through increased morbidity and mortality.¹⁰ Medication adherence can be influenced by many factors, including treatment characteristics, condition-related factors, and illness and medication beliefs.¹¹ Identifying significant correlates of non-adherence among people self-managing multiple conditions will contribute to an evidence base for developing behavioural treatments which support adherence in the context of multimorbidity.

Much intervention development to improve medication adherence has focused on single-disease populations.¹² Such a focus may produce an artificial underestimation of the complexity of chronic disease self-management when, in reality, most people with a chronic condition have additional morbidity(s).³ This, in turn, may lead to policies and interventions which are not designed with ‘the most common chronic condition’² in mind. In order to develop interventions to improve medication adherence among people living with multimorbidity, it is first necessary to understand the extent of non-adherence in this population, as well as factors that might influence adherence. To our knowledge, a synthesis of the prevalence and predictors of medication non-adherence among people with multimorbidity has not been previously reported. This review therefore aims to (1) describe the prevalence of medication non-adherence among people living with multimorbidity and (2) describe previously identified correlates of non-adherence in this population.

METHODS

A systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement¹³ (online supplemental file 1). The review was prospectively registered on PROSPERO and a peer-reviewed protocol was published.¹⁴ Prior to finalising our aims, we searched in PROSPERO¹⁵ to determine if an equivalent review had been conducted or was currently being conducted.

Inclusion and exclusion criteria

Original peer-reviewed articles and doctoral theses produced in English from 2009 to 2019 were reviewed. A 10-year range was chosen to reflect the marked increase in multimorbidity literature in recent years.¹⁶ Opinion pieces, conference presentations, books, letters, editorials, and abstracts were not reviewed. Quantitative studies including adults aged 18 years or older, living with two or more chronic conditions (including physical and/or mental health conditions) reporting medication non-adherence and/or predictors of non-adherence in an extractable format were considered. Presence of multimorbidity was required to be part of study aims and/or inclusion criteria. Polypharmacy was not used as a

definition of multimorbidity; however, studies referring to use of two or more medications that could be inferred as treatment for two or more chronic conditions were considered. Studies were not excluded based on design, however only observational data were extracted for review. Therefore, clinical trials that did not report baseline non-adherence were excluded. Studies including any participants under 18 years were excluded.

Search strategy and study selection

An electronic database search of PubMed, EMBASE, CINAHL and PsycINFO from January 2009 to April 2019 was conducted using a predefined search strategy combining terms related to ‘multimorbidity’ and ‘medication adherence’ (online supplemental file 2). Reference lists of included studies were screened for relevant articles. Records were exported to EndNote X8 to remove duplicates. Two reviewers (LF, RL-V) each screened 50% of titles and abstracts in Covidence.¹⁷ Twenty per cent of each reviewer’s records were chosen at random for cross-checking by the other reviewer. Studies meeting inclusion criteria were moved forward for full-text screening by two independent reviewers (LF and JL or EG). Where disagreements arose, a third reviewer (GJM or AWM) was consulted.

Data extraction and quality assessment

A data extraction form was developed to extract relevant data from each included study (online supplemental file 3). Where studies reported medication adherence, this was converted to medication *non*-adherence by subtracting the number of adherent participants from the total sample. One reviewer (LF) extracted data from all included studies, and a second reviewer (JL) cross-checked 20%.

The quality of included studies was assessed using criteria for observational studies¹⁸ previously adapted for medication adherence reviews.¹⁹ Criteria include 11 items related to selection methods, measurement, sources of bias, control for confounding, and use of statistics. Each item was answered with ‘yes’, ‘no’, ‘don’t know’ or ‘not applicable’. All included studies were assessed using these criteria, including intervention studies as only baseline observational data were reviewed. One reviewer (LF) assessed the quality of all studies and a second reviewer (EG) cross-checked a random sample of 20%. No studies were excluded based on quality.

Data analysis

Due to between-study heterogeneity relating to study population, design, setting, and measurement and definition of medication non-adherence, a quantitative synthesis involving all studies was not considered appropriate. Meta-analysis was conducted with studies which recruited participants as ‘people living with ≥ 2 chronic conditions’. This group of studies was considered to be most focused in addressing a universal experience of multimorbidity—albeit a multifaceted and complex

experience across individuals—offering results that can be used in future attempts to address non-adherence in this population. Studies which recruited participants with pre-specified conditions were therefore not included in the meta-analysis. Meta-analysis was conducted in R²⁰ using the meta²¹ and metafor²² packages (online supplemental file 4). A random-effects model was used to estimate the pooled prevalence of non-adherence. Between-study heterogeneity was assessed using I^2 .²³

Remaining studies were narratively synthesised to describe medication non-adherence in multimorbidity, informed by Popay and colleagues' guidelines.²⁴ The study characteristics table was preliminarily analysed to identify and count patterns of results. This was followed by an exploration of relationships within and between results of individual studies. Predictors of non-adherence were also synthesised in this way with studies which recruited participants using an inclusive definition of multimorbidity. Predictors were not extracted from studies which recruited participants with pre-specified combinations of diseases due to potential confounding associated with specific conditions, for example, a study of people living with bipolar disorder and depression assessing severity of depressive symptoms and psychological disability as predictors of non-adherence.²⁵

Patient and public involvement

A panel of people with experience of living with multimorbidity were consulted to advise on appropriate methods

for disseminating findings from the review to patients and the public.

RESULTS

Overview of studies

After removing duplicates, 10998 studies were identified from the database search and 75 from reference lists of included studies. Following screening of titles and abstracts, 449 full-texts were reviewed. Of these, 271 were excluded with reasons (figure 1), with 178 studies included in the final synthesis.^{9 25-201} The study selection process is outlined in the PRISMA flow diagram in figure 1.

Study quality

Results of study quality assessment are summarised in figure 2.

Study characteristics

One hundred and thirty-three studies included participants with ≥ 2 specific conditions, for example, Gibson *et al* recruited participants self-managing type 2 diabetes and hypertension⁷⁹; 26 studies included participants with one specific condition and ≥ 1 other condition(s), for example, Puyat *et al* recruited participants living with depression and an additional chronic health condition¹⁵⁶; and 19 studies recruited participants using an inclusive definition of multimorbidity, for example, Schüz and

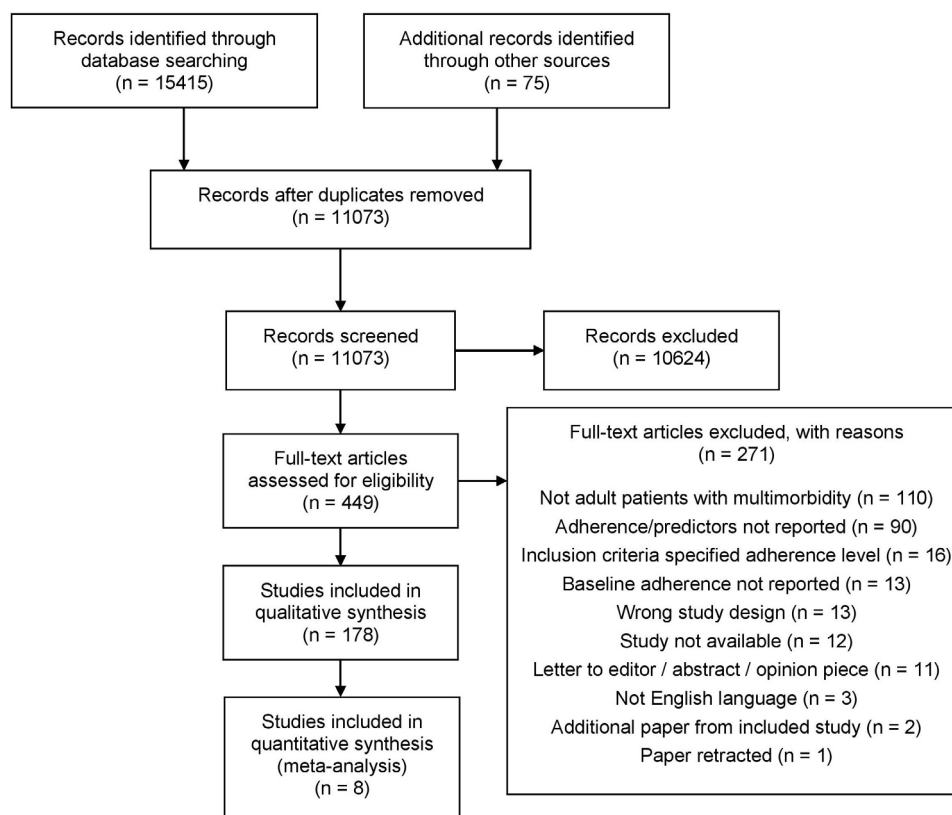


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

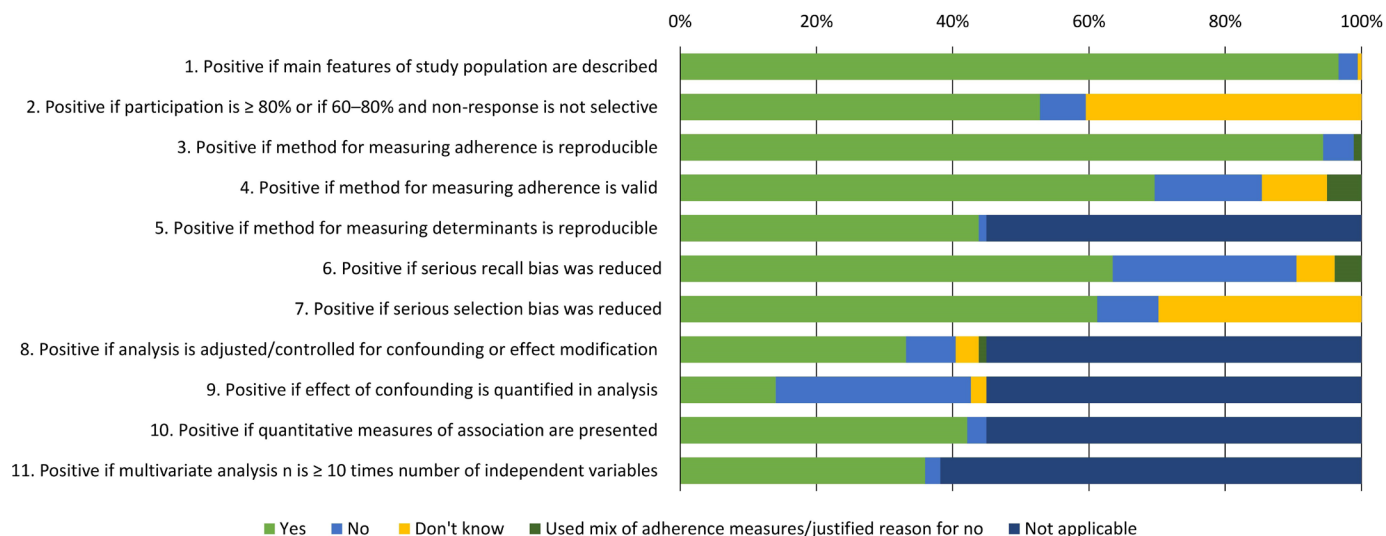


Figure 2 Methodological quality graph.

colleagues¹⁷⁰ recruited people living with ≥ 2 conditions from the Charlson Comorbidity Index²⁰² or Functional Comorbidity Index.²⁰³

Eighty-four studies measured non-adherence using pharmacy data, for example, Kim *et al*¹⁰⁷ used pharmacy claims data to assess non-adherence among people living with hypertension and a psychiatric condition; 81 used self-report, for example, Moore *et al*¹³⁵ measured adherence to medications for HIV and bipolar disorder using a visual analogue scale; and 20 used electronic monitoring, for example, Safren *et al*⁶³ assessed non-adherence to antiretroviral medication among people living with HIV and a depressive mood disorder using a Medication Event Monitoring System (MEMS). Three studies used pill counts,^{59 101 176} two involved reports by a healthcare provider^{80 83} and one did not report the method used.⁶⁴ Ten of these studies used more than one method to measure adherence, for example, Bogner *et al*⁴⁵ used electronic monitoring and self-report to measure non-adherence for diabetes and depression. Forty-seven studies reported average non-adherence only. The characteristics of all included studies are summarised in online supplemental files 5 and 6.

Participant characteristics

The number of participants with multimorbidity in each study ranged from 22¹³⁰ to 599141.²⁰¹ Among 135 studies reporting the mean (SD) age of participants, the average age ranged from 32.4 (9.6)¹⁰⁵ to 80.8 (9.1) years.¹⁵⁸ Ninety-three (52.2%) study samples were majority female, while three studies did not report gender.^{98 117 126}

Prevalence of medication non-adherence

A meta-analysis was conducted with eight studies reporting prevalence of non-adherence and using an inclusive definition of multimorbidity, that is, without seeking people with ≥ 1 specific condition(s).^{56 71 115 137 138 184 189 193} The pooled prevalence of non-adherence was 42.6% (95% CI: 34.0% to 51.3%, $k=8$, $I^2=97\%$, $p<0.01$) (figure 3). The range of non-adherence among studies in the meta-analysis was 16.4%⁷¹–61.4%.¹⁹³ The range among all reviewed studies was 7.0%⁴²–83.5%.¹⁹⁹ Remaining studies were narratively synthesised to describe prevalence and predictors of medication non-adherence.

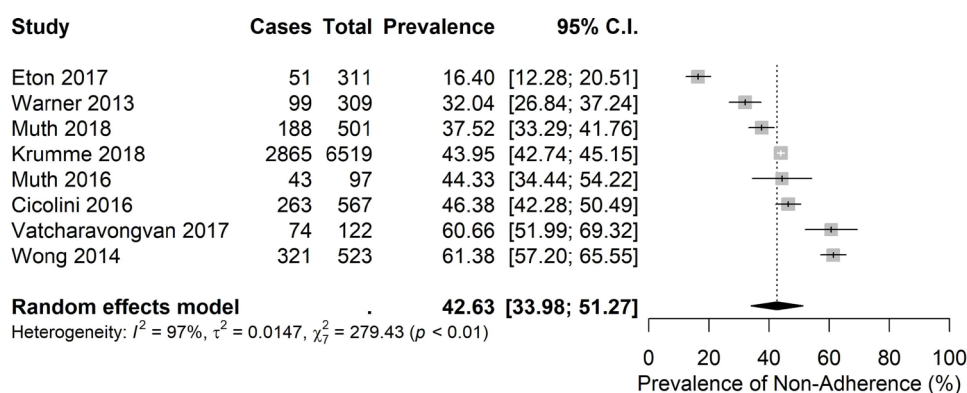


Figure 3 Results of random effects meta-analysis.

Narrative synthesis findings

Medication non-adherence over time

The direction and extent of change in medication non-adherence over time was variable between studies. Among studies reporting prevalence of non-adherence over time, respective lengths of follow-up were three months,⁹⁶ six months,¹⁸⁹ 48 weeks,¹²¹ one year,^{26 36} 16 months,¹⁶¹ two years,⁶⁰ three years,⁴⁸ and five years.¹⁹⁸ Of these, four studies measured change in non-adherence following a recent diagnosis or treatment for an additional condition,^{36 48 96 161} four measured change following medication initiation^{26 60 121 198} and one reported change not related to specific patient or treatment characteristics.¹⁸⁹ Three studies reported decreased non-adherence,^{36 96 161} with the greatest decrease being 9.6% after 3 months.⁹⁶ Four studies reported increased non-adherence,^{26 121 189 198} with the greatest increase being 41.2% after 12 months.²⁶ One study reported variation in how non-adherence changed over time depending on the class of medication,⁶⁰ while another reported an initial 13.9% increase after 2 years, followed by a 14.9% decrease 1 year later.⁴⁸

Assessment of multiple medications

Within individual studies, the extent of non-adherence for one condition did not always correspond with non-adherence for another condition among people taking medications for multimorbidity. Twenty-six studies reported non-adherence prevalence estimates separately for each condition, for example, Foguet-Boreu *et al* reported that, among people living with both diabetes and hypertension, 39.8% were non-adherent to medication for diabetes, while 23.8% were non-adherent to medications for hypertension.⁷⁵ Differences in non-adherence between conditions ranged from 0.8% measured by a 1-item self-report measure in a study of people living with HIV and tuberculosis,¹³⁹ to 33.6% measured by pharmacy data in a study of people with greater non-adherence to medications for Chronic Obstructive Pulmonary Disease (COPD) than depression.²⁷ Four studies reported a difference of $\leq 5\%$,^{45 79 88 139} five reported a difference of 5%–9.9%,^{95 110 129 135 177} eleven reported a difference of 10%–19.9%^{38 57 65 75 84 90 102 133 177 180 191} and six reported a difference of $\geq 20\%$.^{27 66 80 90 105 185}

Physical and mental multimorbidity

Differences in non-adherence between physical and mental health conditions were not consistent across the literature. Among studies of people living with a physical condition and depression and/or anxiety, four reported non-adherence prevalence for both the physical and mental health condition, for example, Gupte-Singh and colleagues reported non-adherence to medications for asthma (62.0%) and depression (74.3%).⁸⁴ Non-adherence was higher for depression in three studies,^{45 84 185} and higher for the physical condition in one study.²⁷

Among studies of people living with a psychiatric condition and a physical condition, seven reported

non-adherence prevalence for both conditions, for example, Moore *et al* reported non-adherence among people living with HIV (52.3%) and bipolar disorder (64.1%).¹³³ Non-adherence was higher for the psychiatric condition in three studies^{90 133 135} and higher for the physical condition in four studies.^{66 88 111 129}

Characteristics of multiple medication regimens

Two studies compared prevalence of non-adherence according to characteristics of multiple medication regimens.^{26 93} Starting medications for two conditions simultaneously resulted in lower non-adherence versus not starting simultaneously (24.8% vs 55.0% at 2 months; 66.0% vs 69.0% at 12 months).²⁶ Hussein and colleagues assessed the difference between a single-pill versus two-pill antihypertensive, lipid-lowering regimen.⁹³ Results concluded that a single-pill regimen improved adherence compared with a two-pill regimen, and improvements were greater among people with previous experience taking either an antihypertensive or lipid-lowering medication.⁹³

Method of non-adherence measurement

Different methods of measuring non-adherence produced differences in the range of non-adherence estimates, with self-report measures producing the widest range, and observed adherence producing the narrowest range. Among 64 studies using pharmacy data, non-adherence prevalence ranged from 10.6% among women with breast cancer and osteoporosis¹⁴⁴ to 80.0% among people with COPD and depression.²⁸ Among 50 studies using self-report, non-adherence prevalence ranged from 7.0% among people with anxiety and cardiac disease⁴² to 83.5% among people with depression and an additional chronic condition(s).¹⁹⁹ Among 10 studies using MEMS, non-adherence prevalence ranged from 20.0% among people living with HIV and hypertension or chronic kidney disease¹⁹¹ to 64.1% among people living with HIV and bipolar disorder.¹³³ Two studies reported prevalence of non-adherence assessed by a healthcare provider⁸³ or a mix of healthcare providers, patients and relatives,⁸⁰ with non-adherence ranging from 8.6%⁸³ to 52.5%.⁸⁰ Two studies used observed medication adherence to identify discrepancies between medications taken and medications prescribed,^{137 138} with non-adherence prevalence ranging from 37.5%¹³⁸ to 44.3%.¹³⁷ among people with three or more chronic conditions. Two studies used pill counts, with non-adherence ranging from 46.3%¹⁰¹ to 70.0%.¹⁷⁶

Nine studies reporting prevalence of non-adherence used more than one measure.^{34 45 51 114 122 137 138 181 194} Among studies using self-report and MEMS, two studies reported lower non-adherence using self-report,^{45 114} one study reported higher non-adherence using self-report¹⁸¹ and one study reported a 1% difference.³⁴ Another study reported no difference between self-report and pharmacy data.⁵¹ Stack and colleagues used self-report to measure prevalence of intentional non-adherence (e.g., deliberately choosing not to take medicines) and unintentional



non-adherence (e.g., forgetting to take medications) to three medications.¹⁷⁷ For each medication, unintentional non-adherence was more prevalent (62.9%, 47.1%, 46.9%) than intentional non-adherence (13.1%, 19.2%, 18.1%).

Predictors of medication (non-)adherence

Eleven studies using an inclusive definition of multimorbidity reported predictors of adherence (see online supplemental file 7).^{40 56 62 71 94 106 168–170 189} Nine used self-report to measure adherence,^{56 62 71 94 106 168–170 189} and two used pharmacy data.^{40 68} The mean age of participants was <65 years in four studies^{40 62 68 94} and >65 in seven studies.^{56 71 106 168–170 189} Five studies assessed demographic variables as predictors,^{56 106 168 169 189} including age, sex, marital status, education and deprivation. No demographic variables significantly predicted non-adherence.

One study assessed health status, which was associated with adherence - that is, poorer health status was associated with stronger motivation to take medications.¹⁰⁶ Other factors assessed included number of prescribed medications,^{56 62 168 169 189} number of chronic conditions,^{62 68 106 168 169} physical fitness¹⁸⁹ and functional health status,¹⁶⁸ as well as presence of other conditions.^{56 68 106} Schüz and colleagues¹⁶⁸ found lower intentional non-adherence among people prescribed more medications and higher intentional non-adherence among people with more conditions; number of conditions and medications did not predict unintentional non-adherence.¹⁶⁸ Domino and colleagues⁶⁸ reported lower non-adherence among those with more comorbidities. Depression was associated with lower adherence, while schizophrenia was linked to both higher and lower adherence, depending on other physical conditions present.⁶⁸

A number of studies explored beliefs about conditions and medications as predictors of adherence. One study reported that better adherence was associated with both stronger necessity beliefs and stronger concern beliefs.⁵⁶ Two studies using the same sample reported more intentional non-adherence among those with increasing beliefs that medications are harmful,¹⁶⁸ and more unintentional non-adherence among those with increasing beliefs that medications are overused.^{168 169} Changes in necessity beliefs predicted intentional non-adherence, with increasing beliefs about necessity associated with improved adherence.^{168 169} Beliefs about consequences, treatment control and timeline were also explored.^{106 170} Kenning and colleagues did not report significant relationships between beliefs and adherence.¹⁰⁶ Schüz and colleagues found higher adherence was predicted by stronger control beliefs, stronger beliefs about negative consequences, and beliefs about a shorter illness timeline.¹⁷⁰ One study assessed beliefs about multimorbidity itself, reporting no significant relationship with adherence.¹⁰⁶

Three studies using the same sample reported an association between previous and later unintentional non-adherence,^{168 169 189} two of which also reported

an association between previous and later intentional non-adherence.^{168 169} Previous medication motivation predicted adherence, with participants with higher motivation at baseline reporting higher adherence at follow-up.¹⁰⁶ Other factors assessed included attitudes towards medications,¹⁸⁹ medication knowledge¹⁰⁶ and medication adherence self-efficacy,⁶² none of which predicted non-adherence. One study assessed general received social support and medication specific-support,¹⁸⁹ with higher medication-specific social support associated with lower adherence; this relationship was moderated by social conflict. General received social support did not predict adherence. Other factors assessed included chronic disease self-efficacy, medication assistance, health literacy and functional health literacy,⁶² none of which predicted non-adherence.

Lower adherence was associated with lower physical ($r = -0.44$) and environmental ($r = -0.57$) quality of life.⁶² Lower prospective memory performance was related to more omission errors of adherence ($r = -0.29$), while lower retrospective memory performance was related to more commission errors ($r = -0.24$).⁹⁴ Other factors positively associated with adherence were medical home enrolment,⁴⁰ better health provider relational quality ($r = 0.22$)⁷¹ and fewer hassles during healthcare system encounters.¹⁰⁶ Self-help behaviours did not predict adherence,¹⁰⁶ better self-monitoring and insight predicted higher motivation to adhere to medications,¹⁰⁶ and a more impulsive/careless problem-solving style was associated with lower adherence ($r = -0.49$).⁶²

DISCUSSION

Our systematic review identified a heterogeneous literature reporting medication non-adherence among people living with multimorbidity. Variation in study design, population, and measurement and definitions of both multimorbidity and non-adherence was observed between studies. Among studies using an inclusive definition of multimorbidity ($k = 11$), correlates of non-adherence included treatment related beliefs and previous non-adherence. From eight studies considered suitable for meta-analysis, 43% (95% CI: 34% - 51%) of participants with multimorbidity were non-adherent to medications. Non-adherence ranged from 16.4%⁷¹ to 61.4%,¹⁹³ with the lowest estimate arising from a single-item self-report measure,⁷¹ and the highest derived from pharmacy data.¹⁹³ One study in the meta-analysis contributed to 76% of the total sample.¹¹⁵ These characteristics of individual studies should be considered when interpreting findings of the quantitative synthesis.

Among studies reporting non-adherence prevalence for more than one condition, results highlighted disparities in non-adherence between conditions. It was previously reported that people with multimorbidity prioritise certain conditions over others,^{204 205} with our results suggesting this prioritisation may be reflected in self-management behaviours. Other factors known to

predict adherence in general may also explain disparities within an individual, including differences in regimen complexity and differences in the expected efficacy of medications.²⁰⁶ Inauen and colleagues⁹ have reported that adherence within an individual can differ between medications, and emphasise the need to assess adherence for multiple medications separately in order to focus interventions appropriately. Despite such calls, a recent systematic review suggested there are no standard criteria for measuring multiple medication adherence, as well as no agreement on how existing measures developed for measuring adherence to monotherapy can be adapted to multiple medications.²⁰⁷ A number of studies reviewed here, including those in the quantitative synthesis, reported a single prevalence estimate representing average non-adherence across conditions, potentially resulting in a concealment of those conditions for which non-adherence is highest. This should be considered when interpreting the meta-analysis.

Among participants with a physical condition and depression, non-adherence was higher for antidepressants in three of four studies. This somewhat supports previous findings that non-adherence to antidepressants is higher than to medications for physical conditions,²⁰⁸ and may extend this observation to instances where both occur in one individual; however, further research is necessary to draw stronger conclusions. Among participants with a psychiatric and physical condition, prevalence of non-adherence to psychiatric medications was higher than non-adherence to medications for physical conditions in three of seven studies. Previous literature has reported that adherence to antipsychotic medications may be lower than adherence to medications for physical conditions,²⁰⁸ while others have found antipsychotic adherence to be higher.²⁰⁹ These discrepancies further highlight the heterogeneity that is inherent in multimorbidity, as well as the importance of considering between-condition medication adherence within individuals. Moreover, it has previously been reported that the condition people with multimorbidity prioritise most can differ over time as conditions and treatments change.²⁰⁵ Considering the cyclical nature of some mental health conditions,²¹⁰ it is important to consider whether self-management behaviours, such as medication taking, fluctuate over time as a result of changing priorities in response to symptoms.

Among the variables frequently tested as predictors were number of chronic conditions and number of prescribed medications. Surprisingly, the strength and direction of association with non-adherence was not consistent across studies. A recent systematic review concluded that deprescribing interventions do not consistently improve adherence,²¹¹ suggesting an equivocal relationship between medication burden and non-adherence. This highlights the clinical dilemma faced by clinicians where deprescribing may be a necessary but not sufficient therapeutic response. It has been suggested previously that the frequency of medication administration has a greater

influence on adherence than number of tablets,²¹² which may have particular relevance in multimorbidity considering some people take medications for different conditions throughout the day while others take multiple medications together.²¹³ Indeed, it has been reported that particular combinations of conditions are associated with higher dosing frequencies in multimorbidity, with potential implications for treatment burden,²¹³ and therefore possibly influencing medication adherence. Mode of drug delivery may also be an influencing factor, with different modes of delivery varying in convenience and, therefore, adherence.²¹⁴ Due to lack of individual patient data regarding treatment regimens, it is beyond the scope of this review to explore this further.

Illness and medication beliefs were among the most frequently explored predictors of adherence. Schüz and colleagues¹⁷⁰ results suggest medication adherence in the context of multimorbidity may be influenced by perceptions of unique conditions as well as the effect of multiple combined illness perceptions. A scale to measure multimorbidity illness perceptions has been developed,²¹⁵ accounting for domains such as treatment burden, emotional impact and prioritisation. When tested within a study reviewed here, this measure did not predict adherence,¹⁰⁶ however, authors note the measure was in early stages of development at the time of administration.¹⁰⁶ Nonetheless, illness perceptions—and how they present in the context of multimorbidity—appear to be of relevance to both intentional and unintentional non-adherence in the context of multimorbidity.^{168–170} This tendency to be influenced by illness beliefs may position intentional non-adherence as a rational judgement for some people self-managing chronic conditions; how this transpires as selective non-adherence among people self-managing multiple conditions should be explored in future research.²¹⁶

Analysis of pharmacy data was the most frequently used method to measure non-adherence, followed by self-report and electronic monitoring. Variation in measurement methods contributed to the heterogeneity that prevented a larger meta-analysis—a limiting factor that has previously been identified in reviews of non-adherence to multiple medications.²¹⁷ While also noting variance due to different combinations of conditions within individual studies, the range of reported non-adherence differed by measurement method (77% for self-report, 69% for pharmacy data, and 44% for MEMS). Results from 10 studies using multiple methods to report prevalence of non-adherence emphasised this variability further, extending to multimorbidity the recommendation to use subjective and objective measures of non-adherence in combination to allow the strengths of each to compensate for the limitations of others.²¹⁸

We did not stratify our analysis of prevalence by age, potentially limiting interpretation of our findings. Notably, age was not found to be a significant correlate in our synthesis of predictors, and it has been suggested previously that there is no consensus on age as a predictor



of non-adherence.²¹⁹ Nevertheless, it may be plausible that variables are differentially associated with non-adherence at different life stages. For example, among reviewed studies, Domino and colleagues⁶⁸ reported lower levels of non-adherence in people with more conditions, with a mean age among participants of 43 years; Schüz and colleagues found higher intentional non-adherence among participants with more conditions, with a mean age of 73 years.¹⁶⁸ Exploring how non-adherence is variably predicted by clinical and psychosocial influences across the lifespan could inform intervention development which is appropriately targeted according to life stage.

The quality assessment produced a number of recommendations for future research exploring non-adherence among people with multimorbidity. Of note, while almost all studies (94%) were judged to have used non-adherence measures that were reproducible, 16% of studies used methods that were not considered to be valid. The validity of non-adherence assessment methods should be a priority for future related investigations. Furthermore, almost 30% of studies were judged not to have reduced serious recall bias. It has been suggested that the appropriate period for retrospective self-report of non-adherence should be balanced between optimising recall and capturing instances of infrequent non-adherence.²²⁰ The optimum recall period for measures of multiple medication non-adherence should be determined.

The methods used to conduct this systematic review have limitations. First, only 20% of titles and abstracts were screened by two reviewers and authors were not contacted for full-text articles or data that was not accessible, both of which increased the risk of excluding relevant studies. Second, criteria for inclusion in the review were limited to English language studies produced between 2009 and 2019. While this date range may exclude relevant articles, the review aimed to synthesise evidence produced since the proliferation of the multimorbidity literature over the last decade,¹⁶ as well as a call for the careful design of adherence research in multimorbidity that uses reliable and consistent adherence measurement and details adherence for multiple conditions.¹² Non-English language articles were not reviewed for feasibility reasons. Third, studies of people with depression or anxiety were eligible for inclusion if the condition was identified through a self-report measure. As a result, it is possible that not all participants had a clinical diagnosis. This decision was made to account for the overrepresentation and underdiagnosis of depression among people with chronic conditions due to incomplete recording in medical records,²²¹ and has been made previously when reviewing the multimorbidity literature.²²² Finally, while the study adopted ‘two or more chronic conditions’ to define multimorbidity, studies were also included if participants were prescribed medications that could be inferred as treatment for a chronic condition. While this extended the definition of multimorbidity beyond clinical diagnoses, to exclude

these studies would have underrepresented the burden that is characteristic of multimorbidity.

CONCLUSION

This review summarises the complexity of non-adherence in multimorbidity, as well as factors that should be considered for the development of interventions to support adherence for ‘the most common chronic condition’. While the review did not identify specific combinations of conditions producing the highest levels of non-adherence, results suggest that non-adherence in multimorbidity varies both between and within studies. Management of multimorbidity demands integration across conditions and clinical guidelines, requiring practitioners and researchers to focus on individual people as opposed to individual diseases.² While the move towards this multi-disease focus is welcomed, attempts by researchers and clinicians to improve medication adherence should determine for which conditions individuals require most support. The use of measures designed to assess multiple medication adherence will be central to achieving this aim.

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Acknowledgements We thank members of the Patient and Public Involvement panel working with the Multimorbidity Collaborative Doctoral Award PhD students for their contribution to plans for disseminating the results of this research to patients and members of the public.

Contributors LF is the guarantor of the review and contributed to study design, data collection, data analysis and original draft preparation. JL, RL-V and EG contributed to data collection and draft review and editing. LH contributed to supervision and draft review and editing. AM and GJM contributed to study design, supervision and draft review and editing.

Funding This research was funded by a Health Research Board Ireland Collaborative Doctoral Award, grant number CDA-2018-003.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. All data relevant to the study are included in the article or uploaded as supplementary information. All data relevant to the study are included in the article, uploaded as supplementary information or deposited on Open Science Framework: <https://osf.io/nym7v/>. Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CCO 1.0 Public domain dedication). Our systematic review produced a large amount of information and the arising database is available for future collaboration on additional analyses. Please contact the corresponding author with any inquiries.

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Correction: *Prevalence and predictors of medication non-adherence among people living with multimorbidity: a systematic review and meta-analysis*

Foley L, Larkin J, Lombard-Vance R, *et al.* Prevalence and predictors of medication non-adherence among people living with multimorbidity: a systematic review and meta-analysis. *BMJ Open* 2021;11:e044987. doi: 10.1136/bmjopen-2020-044987

This article was previously published with an error.

Currently on Page 6 under 'Predictors of medication (non-)adherence', paragraph 3 reads:

A number of studies explored beliefs about conditions and medications as predictors of adherence. Two studies using the same sample reported less non-adherence among those with stronger beliefs about the necessity of medications,^{168 169} less non-adherence among those with greater concerns about medications,¹⁶⁹ more intentional non-adherence among those with increasing beliefs that medications are harmful,¹⁶⁸ and more unintentional non-adherence among those with increasing beliefs that medications are overused.¹⁶⁸ Changes in necessity beliefs predicted intentional non-adherence, with increasing beliefs about necessity associated with improved adherence.¹⁶⁹ Beliefs about overuse of medications predicted unintentional non-adherence, with stronger beliefs associated with higher unintentional non-adherence.^{168 169}

This should actually read:

A number of studies explored beliefs about conditions and medications as predictors of adherence. One study reported that better adherence was associated with both stronger necessity beliefs and stronger concern beliefs.⁵⁶ Two studies using the same sample reported more intentional non-adherence among those with increasing beliefs that medications are harmful,¹⁶⁸ and more unintentional non-adherence among those with increasing beliefs that medications are overused.^{168 169} Changes in necessity beliefs predicted intentional non-adherence, with increasing beliefs about necessity associated with improved adherence.^{168 169}

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BMJ Open 2022;12:e044987corr1. doi:10.1136/bmjopen-2020-044987corr1

