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META-ANALYSIS

A systematic review of medication adherence and mortality in chronic disease: Implications for clinical guidelines and policy

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Objectives: This systematic review aims to investigate whether good medication adherence in adults with chronic conditions is associated with a lower mortality risk compared to poor adherence within published literature, and the extent to which this relationship is represented within South African policy and legislation.

Methods: A systematic search of three electronic databases—PubMed, MEDLINE (Ovid) and Scopus—was conducted. Only primary research articles published in English after March 2004 and with study populations >18 years of age were considered.

South African health legislation and professional guidelines from 2014 onwards were sourced using search terms aligned with the systematic review strategy and systematically analysed.

Results: Twenty-six articles were included in the systematic review. Effect measures included hazard ratios (HR), incidence rate ratios (IRRs) and odds ratios (OR), where values greater than 1 indicate a higher risk of mortality. The effect measures from individual studies were categorized according to adherence levels: good, intermediate, poor and non-adherent. A total of 17 effect measures were reported for good adherence, only one of which was greater than 1. There were 44 effect measures reported for intermediate, poor and non-adherence categories, all of which were greater than 1. Pooled estimates for poor adherence and non-adherence had the highest HRs (HR = 1.63; 95% confidence interval [CI]: 1.36–1.96 and HR = 2.77; 95% CI: 2.3–3.34 respectively).

Review of South African health legislation and professional guidelines showed a dominance of mortality-related terms (1.323 and 2.98 matches per 1000 words for 'mortality' and 'death', respectively) compared with adherence-related terms (0.053–2.98 matches per 1000 words). Co-occurrence between medication adherence-related search terms (MARS, adherence, medication adherence, adhere, non-adherence and medication compliance) and mortality-related search terms (death, mortality and survival) was low within all documents analysed.

Conclusion: The systematic review demonstrates a clear relationship between good adherence to chronic medication and a lower mortality risk. However, the review of legislative and policy documents suggests that government efforts are focused primarily on surveillance, rather than strategy or preventative measures. This strong evidence should motivate incorporating adherence-based risk assessments into clinical and legal frameworks.

KEYWORDS

chronic diseases, chronic medication, death, medication adherence, medication compliance, mortality, survival rate

1 | INTRODUCTION

Poor adherence to chronic medication is a global problem.[1] Adherence to long-term therapy is estimated to average around 50% in high-income countries, and rates are likely to be even lower in developing countries, such as those in Africa.[1–4] Recent studies highlight persistently low medication adherence rates across Africa, with a 2024 systematic review reporting 43.5% non-adherence to blood pressure-lowering medications in Sub-Saharan Africa, driven by socioeconomic barriers and high pill burden.[5]

The terms 'compliance' and 'adherence' are often used interchangeably and describe behaviour related to the use of medication.[6] They differ mainly in the way in which they portray the doctor-patient relationship. Compliance is defined as 'the extent to which the patient's behaviour matches the prescriber's recommendations'.[6,7] This definition disregards the role that the patient plays in determining the most appropriate treatment regimen for their own context. It creates the impression of a one-sided relationship in which the patient has no choice but to conform to the prescriber's instructions, irrespective of their suitability. Adherence is defined as 'the extent to which the patient's behaviour matches agreed recommendations from the prescriber'.[6,8] The focus here is on collaboration between the doctor and patient, meaning that the patient plays a more active role in determining treatment recommendations. Importantly, the patient cannot be held solely responsible for treatment failure, as responsibility for the proper use of medication is shared between both parties. For this review, 'adherence to medication' is defined according to the Ascertaining Barriers to Compliance (ABC) taxonomy proposed by Vrijens et al. as 'the process by which patients take their medication as prescribed'.[9] The ABC taxonomy also describes three components of adherence to medications: initiation, implementation and discontinuation. Initiation refers to a patient taking the first dose of their medication; implementation is the extent to which a patient's actual dosing corresponds to the prescribed regimen; and discontinuation signifies the end of therapy, whereafter no more doses are taken.

Seven of the top 10 natural causes of death in South Africa (diabetes mellitus, cerebrovascular diseases, heart disease, human immunodeficiency virus, hypertensive diseases, ischaemic heart disease and chronic lower respiratory diseases)[10] are chronic diseases with established pharmacological treatments. Deviation from the intended dosage and frequency of medication use may limit the therapeutic effect and allow for increased disease progression.[11,12] The efficacy of pharmaceutical therapies for treating disease is typically reported based on outcomes of randomized controlled clinical trials. However, much of this benefit is negated due to high non-adherence rates in the real world.[13] For example, the decline in the number of deaths due to coronary heart disease (CHD) in the United States may be strongly attributed to evidence-based medical therapies.[14] Considering that only half of CHD patients are estimated to be adherent to their medication,[13,15] full realization of this benefit is being significantly impeded.

In the United States, the pharmaceutical industry spends 17.7% of total revenue on research and development, including clinical trials.[16] The annual cost of non-adherence per person ranges from $949 to $52 341.[17] Inpatient expenses are the primary cost driver, while outpatient and pharmacy costs may be lower among individuals with low adherence.[18] This demonstrates the long-term effect of non-adherence and the associated consequences of poor clinical outcomes over time.

Previous systematic reviews have explored the link between chronic medication adherence and mortality for specific types of medication (statins[19,20] and cardiovascular medications[21,22]) or specific conditions (type 2 diabetes mellitus,[11] metastatic breast cancer[23] and coronary artery disease[12]). However, no review to date has synthesized findings across the broader spectrum of chronic diseases. Adherence should be viewed as a public health issue, and understanding the universal implications of poor adherence supports the design of interventions on a system level rather than in condition-specific silos.

Although many studies demonstrate a correlation between poor medication adherence and mortality,[24–30] the use of medication adherence rates in assessing clinical risk has been limited by challenges regarding its assessment and interpretation. Using different formulae for calculating adherence rates[31] makes comparing results challenging and using different metrics[32–34] to report on adherence can influence the observed relationship to mortality. The threshold to distinguish between adherent and non-adherent individuals (typically 80%)[31] has seldom been linked to clinical effects and has recently been questioned.[31,33] Furthermore, patients and healthcare providers tend to overestimate adherence when providing a subjective rating of the problem.[35,36] Despite these limitations, the authors contend that

there remains significant value in investigating the association between adherence and mortality. Medication adherence is a modifiable risk factor and may have substantial implications not only for individual patient outcomes but also for the broader South African healthcare system.

An improvement in adherence and a resultant decrease in mortality rates would greatly alter the profitability of industries which effectively 'pay' for death, such as life insurers. The Association for Savings and Investment South Africa (ASISA) reported payouts worth R39.9 billion rand to cover 900 000 death claims in 2023.[37] The insurance gap is defined as the difference between the insurance needs and actual cover and, therefore, represents the total net additional cover that active earners in South Africa should purchase to achieve adequate coverage.[38] By increasing the risk of mortality, non-adherence is a likely contributing factor to higher claims on private insurance products, increasing premiums to cover aggregate risks.[39] This makes insurance unaffordable for many people, resulting in an insurance gap of more than R34 trillion in South Africa.[38] A clear understanding of how poor adherence drives increased mortality should incentivize capital allocation to fund relevant interventions.

Incorporating medication adherence into the prediction of outcomes could play a role in value-based reimbursement structures for healthcare providers.[40] New methods to improve cost efficiencies will be essential as South Africa prepares to implement National Health Insurance (NHI).[41,42] The head of Public Sector Assurance in South Africa, Yugen Pillay, referenced the potential unaffordability of NHI within the current fiscal landscape when he said, 'the prospect of financing the NHI through conventional means appears increasingly untenable' .[43] The R39.9 billion paid in death claims by South African insurers in 2023 (representing 95.9% of all claims processed)[37] underscores the systemic cost of premature mortality driven by preventable conditions, a burden NHI must absorb as it transitions to universal coverage. Integrating adherence interventions into the NHI framework could offset fiscal strain by reducing mortality-linked costs and reallocating savings to primary care expansion, making the goal of universal health care more achievable. Adherence interventions could reduce NHI costs by up to 32%, as demonstrated by multifaceted programs combining SMS reminders and counselling.[44]

Considering the high mortality rates associated with various chronic conditions,[10] there is a pressing need to evaluate the current landscape regarding the relationship between medication adherence and mortality risk. The primary aim of this systematic review is to investigate whether good medication adherence in adults with chronic conditions is associated with a lower mortality risk than poor adherence. Using the PICO framework, we examine the relationship between adherence (intervention) and mortality risk (outcome) in this population. The secondary aim is to investigate the extent to which this relationship is represented within South African policy and legislation. The goal is to provide critical insights for healthcare providers, policymakers and researchers to improve patient outcomes and reduce mortality rates. By synthesizing existing evidence through rigorous systematic review methodology, this study builds on previous efforts to optimize medication use and adherence, ultimately informing strategies to mitigate rising mortality rates among patients with chronic conditions.

2 | METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[45] In accordance with the guidelines, a protocol for this review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 25/02/2024 (CRD42024512459).

2.1 | Literature search strategy

The systematic review included studies published between 1 March 2004 and 31 March 2024. To capture any newly published literature, the databases were re-searched manually in April 2025. We conducted a comprehensive search of three electronic databases: PubMed, MEDLINE (Ovid) and Scopus. The search strategy was developed systematically and documented transparently to ensure reproducibility and completeness. The detailed search strategy is outlined in DataS1. Our search strategy combined specific keywords and Medical Subject Headings (MeSH) terms related to medication adherence, chronic medication and mortality. The search terms included phrases such as 'medication adherence', 'chronic medication' and 'mortality', using Boolean operators 'OR' and 'AND' to combine or exclude keywords. The search strategy was supplemented by examining the reference lists of included studies to ensure a thorough coverage of relevant literature. A web-based systematic review platform was used to assist with the screening and management of articles. Duplicate studies were removed using the platform's automated removal process.

2.2 | Eligibility criteria

This systematic review aims to explore the relationship between medication adherence and mortality risk in adult patients with chronic conditions. The study focuses on patients aged 18 years or older using medication for chronic diseases and past the initiation phase of medication adherence.[9] There was no restriction placed on the type of chronic condition. Examples of chronic conditions include, but are not limited to hypertension, chronic heart failure, chronic liver disease, coronary artery disease, type 2 diabetes mellitus, osteoporosis and metastatic breast cancer. The review includes randomized controlled trials (RCTs), non-RCTs (non-RCTs), and observational studies that assess medication adherence using metrics like medication possession ratio (MPR) or proportion of days covered (PDC). All adherence measurement methods were considered eligible, including but not limited to self-reporting, pill counts, pharmacy claims data and electronic monitoring. These studies must define a clear threshold for distinguishing between different levels or categories of adherence.

The review seeks to compare the risk of mortality or hazard ratio (HR) between individuals with good *vs*. poor medication adherence. Only primary research articles published in English were considered. The search strategy involved databases such as PubMed, MEDLINE (Ovid) and Scopus, using specific keywords related to medication adherence, chronic medication, and mortality.

Two authors (J. B. and N. S.) independently screened titles and abstracts, applying the eligibility criteria. The authors were blinded to each other's selections until they arrived at their respective list of studies for full-text review. Subsequently, the authors independently reviewed the full-text articles and selected the final set of studies for inclusion in the review. The authors were blinded to each other's selections until they arrived at their respective list of studies for inclusion. A third author (A. J. v. R.) acted to resolve any discrepancies following unblinding.

2.3 | Quality assessment

The modified Downs and Black Checklist[46] was used to assess methodological quality and risk of bias of both RCTs and non-RCTs. Other widely used tools, such as the Cochrane Risk of Bias Tool for Randomized Trials,[47] Risk of Bias in Non-Randomized Studies of Interventions[48] and Newcastle-Ottawa Scale,[49] are better suited to evaluate either RCTs or non-randomized studies, not both. The modified Downs and Black Checklist contains 27 items and is grouped into five key domains (reporting, external validity, internal validity–bias, internal validity–confounding and power). This checklist allows for a maximum score of 28 points. Studies with scores of 20 and above were considered to be of good quality with a low to moderate risk of bias and were deemed eligible for inclusion in the review. Studies with scores lower than 20 were considered poor quality, with a high risk of bias and were excluded from the review.

The Joanna Briggs Institute (JBI) critical appraisal tool[50] was used to assess methodological quality and risk of bias of observational studies according to five domains (selection and comparability, exposure or outcome measure, confounding, follow-up and statistical analysis). This tool does not use a formal numerical scoring system and relies on a qualitative judgement on the proportion of criteria met. For this review, observational studies meeting ≥70% of criteria were eligible for inclusion.

The 2011 Oxford Centre for Evidence-based Medicine (OCEBM) Levels of Evidence[51] was used to grade the quality of the articles. This framework ranks evidence from Level 1 (highest quality) to Level 5 (lowest quality) based on study design and methodological rigour.

Two authors (J. B. and N. S.) independently scored the studies using these tools and frameworks. Any disagreements were resolved through discussion with a third author (A. J. v. R.).

2.4 | Study selection and data extraction

The data obtained from the studies that met the inclusion criteria was consolidated into an MS Excel spreadsheet. The dataset encompasses various variables such as: study details (level of evidence,[52] authors, study title, year of publication, study design, aim), sample details (sample size, country of study), disease area, adherence measurement, outcomes (effect of adherence on specific causes of mortality, effect of adherence on all-cause mortality, non-mortality related outcomes) and source of funding.

One reviewer (J. B.) extracted the data, and a second reviewer (N. S.) verified the accuracy of the extracted data. Any disagreements were resolved through consensus with the intervention of a third reviewer (A. J. v. R.). Missing data were noted accordingly.

TABLE 1 Adherence categories.

Adherence category	Description
Good adherence	Adherence rate ≥80% OR 'good' adherence as defined by the study where a specific threshold value was not provided.
Intermediate adherence	50 ≤ adherence rare <80% OR 'intermediate' or 'moderate' adherence as defined by the study where a specific threshold value was not provided.
Poor adherence	Adherence rate <50% OR 'poor' adherence as defined by the study where a specific threshold value was not provided.
Non-adherence (binary definition)	As defined in studies where 'adherence' and 'non-adherence' were viewed as binary categories. Non-adherence referred to any deviation occurring during the implementation phase of adherence (as per the ABC taxonomy).[9]

2.5 | Effect measures

The effect measures used in the synthesis of the results were HRs, incidence rate ratios (IRR) and odds ratios (OR). This study used these effect measures and 95% confidence intervals, to analyse the relationship between adherence categories (good, intermediate, poor and non-adherence) and mortality risk. The effect measures are used to indicate how much the risk of mortality changes with improved adherence rates. For example, for the purpose of this study, a HR of 1.5 with a 95% CI of 1.2 to 1.8 suggests that poor adherence categories increase the risk of mortality by 50%, and this effect is statistically significant since the CI does not include 1.0.

2.6 | Synthesis methods and data preparation

The effect measures from each study were recorded in a spreadsheet according to the adherence category (Table 1). The adherence categories were operationalized based on commonalities across the studies, with the aim to ensure consistency and maximize inclusivity. These categories were defined for the purposes of this study, and reflect both quantitative cut-offs and qualitative author designations. Where

studies reported more than one effect measure, each one was recorded as a separate item. Certain studies[53,54] reported combined effect sizes related to more than one adherence category, necessitating the introduction of a fifth category: 'poor and intermediate adherence'. This was done to preserve data integrity without over-extrapolation. Results of individual studies were represented in a forest plot.

2.7 | Data synthesis

This study aimed to investigate whether adherence categories predict mortality risk in patients with chronic conditions. A meta-analysis of time-to-event data (using the direct method with HRs and confidence intervals) was conducted to calculate HRs for each adherence category. The results were adjusted for potential confounders such as age and sex. The HRs provided insight into the relative risk of mortality for each adherence category compared with the reference group.

2.8 | Document analysis for convergence

A review of eight key South African health legislation and professional guidelines relevant to chronic disease management was conducted to analyse regulatory approaches to medication adherence, prescribing practices, chronic disease management and their relationship to mortality. Document analysis is a qualitative method commonly used in health policy analysis, which aims to synthesize and appraise textual data to gain understanding and develop empirical knowledge.[55,56] The authors drew on the findings of Kayesa and Shung-King[55] who described key steps in a document analysis process: adopting clear inclusion criteria, coding of documents, extracting data, applying a clear analytical framework for analysis and presentation of the findings.

Legislative documents, guidelines and grey literature (e.g., policy briefs and organizational reports)[57–64] published after 2014 were sourced using search terms aligned with the systematic review strategy. Key search terms representing the core concepts of mortality (e.g., 'death' and 'mortality'), adherence (e.g., 'adherence', 'MARS' and 'medication compliance') and chronic disease (e.g., 'non-communicable disease' and 'chronic disease') were used.

A coding framework was developed to categorize core concepts such as mortality, chronic disease and medication adherence with MAXQDA software, enabling systematic analysis. Data S2 details the coding framework and included documents. This analysis identified gaps in how regulatory frameworks address adherence-mortality linkages. Findings were triangulated with systematic review data through thematic comparison, assessing convergences between empirical adherence measures and policy priorities. This convergence analysis assessed how regulatory frameworks reflect the adherence-mortality relationship, evaluating the extent to which the validity of adherence scores in predicting mortality risk is present within policy decision making.

The analytical framework use was a relational analysis (set to a window of a maximum of two paragraphs) to identify contextual relationships between mortality and adherence terms. Furthermore, results were normalized per 1000 words to account for document length.

3 | RESULTS

3.1 | Results of study selection

The literature search resulted in 1809 hits. Cohen's Kappa statistic following the independent screening of abstracts and titles was 0.29 (approximate significance <0.001), indicating a fair level of agreement between the raters.[65] Following discussion of the discrepancies by the two authors (J. B. and N. S.), full agreement was reached (Cohen's Kappa statistic = 1). Twenty-five articles were eligible for full-text screening.

Initial inter-rater agreement ($\kappa = 0.29$) reflected challenges in applying broad inclusion criteria to heterogeneous abstracts. Reviewers achieved consensus through iterative discussions and criterion refinement, ensuring consistent full-text screening ($\kappa = 1$). This process aligns with best practices for resolving ambiguity in complex systematic reviews.[45,66]

Sixteen articles remained following full-text screening, with no discrepancies between the two reviewers. An additional 10 articles were identified through the bibliographies of the included reports. These were screened in full and met the same eligibility criteria. This left 24 articles from which data were extracted.

3.2 | Risk of bias scores

Two studies[67,68] were evaluated using the modified Downs and Black Checklist.[46] Both had scores >20 and were subsequently included in the review. The remaining studies were evaluated using the JBI critical appraisal tool.[50] Two observational studies[26,34] used a single-item patient-reported scale to measure adherence, which introduced a disproportionate risk of measurement bias compared with the other studies. Furthermore, there were insufficient strategies to address incomplete follow-up. This, together with the relatively small sample sizes ($n = 130$ and $n = 592$, respectively), resulted in these studies being excluded from the review. Data S3 provides the detailed scoring for each study.

The flow diagram of the literature search and screening process, based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) template, is shown in Figure 1.

3.3 | Study characteristics

Table 2 shows the study characteristics. There was no missing data noted. Most of the study designs were retrospective cohort studies (87.5%) with Level 2b evidence (91.7%). Most studies included all adults over 18 years (69.2%) and investigated both males and females (83.3%). Most studies used PDC as the measure of adherence (58.3%). Various disease categories were represented, with cardiac

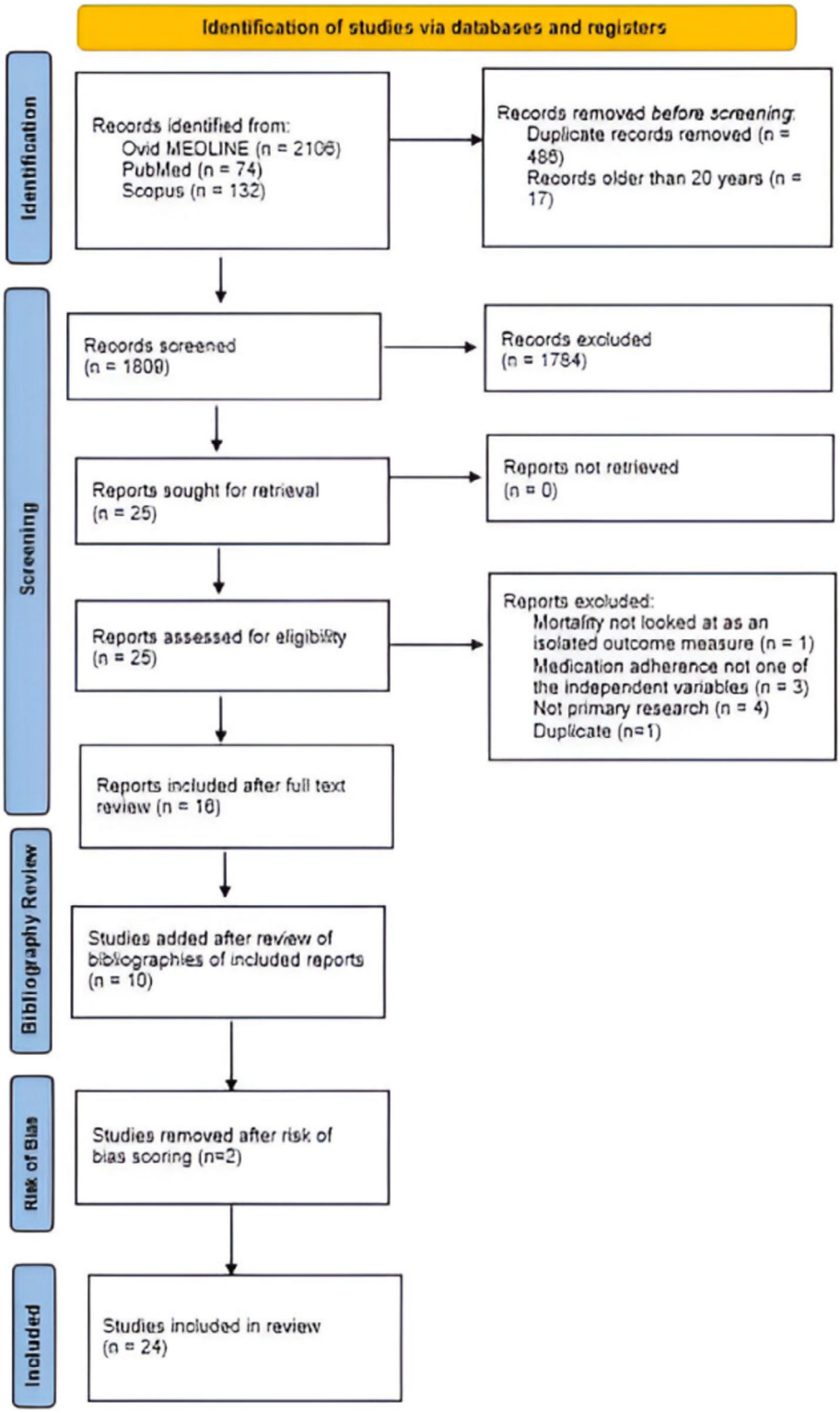

FIGURE 1 PRISMA flow diagram of study selection process.

disease seen as the most frequently investigated category (33.3%). Some studies (12.5%) reported only on specific causes of death, such as cardiovascular mortality. A further 16.7% studies reported on both specific causes of death and all-cause mortality (i.e., death resulting any cause) (16.7%). The majority of studies (70.8%) reported on all-cause mortality without referencing any specific causes (70.8%),

Since all included studies involved participants who had already commenced treatment, they did not examine the initiation phase of adherence (as per the ABC taxonomy[9]) but rather focused on the implementation phase. They tracked and identified treatment gaps or deviations from the prescribed regimen and, in some cases, discontinuation.

TABLE 2 Study characteristics ($n = 24$ articles).

Characteristic		Number of studies (%)
Study design		
	Retrospective cohort study	21 (87.5%)
	Randomized controlled trial	2 (8.3%)
	Case–control study	1 (4.2%)
Level of evidence		
	1b	2 (8.3%)
	2b	22 (91.7%)
Age of participants		
	≥18 years	17 (70.8%)
	40–80 years	1 (4.2%)
	≥65 years	4 (16.7%)
	Not specified	2 (8.3%)
Sex of participants		
	Male and female	20 (83.3%)
	Female only	4 (16.7%)
Disease category		
	Cardiac	8 (33.3%)
	Cancer	3 (12.5%)
	Hepatic	2 (8.3%)
	Metabolic	6 (25%)
	Neurological	1 (4.2%)
	Renal	1 (4.2%)
	Respiratory	1 (4.2%)
	>1 category	2 (8.3%)
Adherence metric		
	PDC	14 (58.3%)
	MPR	7 (29.2%)
	MPR and PDC	3 (12.5%)
Mortality outcome measure		
	Specific causes only	3 (12.5%)
	All-cause only	17 (70.8%)
	Specific and all-cause	4 (16.7%)

Note: Level of evidence 1b = individual randomized controlled trial. Level of evidence 2b = individual cohort study. All-cause mortality = death from any cause. Specific cause mortality = death attributed to a defined condition or disease. Details on the characteristics of the included articles are provided in Data S4.
Abbreviations: MPR, medication possession ratio; PDC, proportion of days covered.

3.4 | Results of individual studies

Effect measures included HRs, IRRs and ORs, where values greater than 1 indicate a higher risk of mortality. A total of 61 effect measures were reported across all included studies: 17 for good adherence and 44 for intermediate, poor and non-adherence categories. Only 1 of the 17 effect measures reported for good adherence was >1.[69] All of the 44 effect measures reported for intermediate, poor and non-adherence categories were >1. Figure 2 presents the effect measures for the different adherence categories. Two HRs, which evaluated the effect of intermediate levels of adherence to entecavir treatment on mortality (Shin et al.)[70] were excluded from Figure 2 to aid visualization and comparison across the adherence categories. This was because the effect measures reported were substantially higher than all other studies included in this adherence category. The HR (CI 95%) for liver-related mortality was 14.9 (3.49–58.47), and all-cause mortality was 4.96 (2.19–11.27). The relatively large confidence intervals suggest less precision in the estimate, but still suggest a greater risk of mortality with intermediate adherence rates.

3.5 | Results of synthesis

The effect measure for the good adherence category showed a decreased mortality risk compared with other adherence categories (HR = 0.71). All other adherence categories showed an increased risk of mortality. Greater HRs were observed with lower rates of adherence. Figure 3 shows the synthesized effect measures.

3.6 | Document analysis for convergence

The document with the highest number of search term matches was the South African Department of Statistics 2017 statistical release, with 822 matches (Table 3). The South African legislative documents[58,59] had the lowest frequency of matches (0.2 and 0.7 per 1000 words), whereas the large-scale validation study of the Medication Adherence Rating Scale (MARS) had the highest frequency of matches (15.5 per 1000 words). The search terms 'death', 'mortality' and 'non-communicable disease' appeared the most frequently within the documents with 2.98, 1.323 and 1.184 matches per 1000 words, respectively (Table 4). Comparatively, there were only 0.053 to 0.162 matches per 1000 words for all terms related to the medication adherence core concept (MARS, adherence, medication adherence, adhere, non-adherence and medication compliance). It must be noted that roughly three-quarters of these instances occurred within the large-scale validation study of the MARS—a study focusing on an adherence rating scale. This demonstrates that the occurrence of adherence-related terms across all other documents was extremely low.

None of the search terms related to the mortality risk core concept appeared in any of the documents, suggesting that while the mortality core concept was fairly well-represented within the documents, the factors driving increased risk have been poorly considered.

Data S2 shows detailed results of the document review and coding visualizations. The number of intersections between the mortality core concept and the medication adherence terms was low. The strongest relationship in terms of co-occurrence was between 'non-communicable disease' and 'mortality'. Co-occurrence between

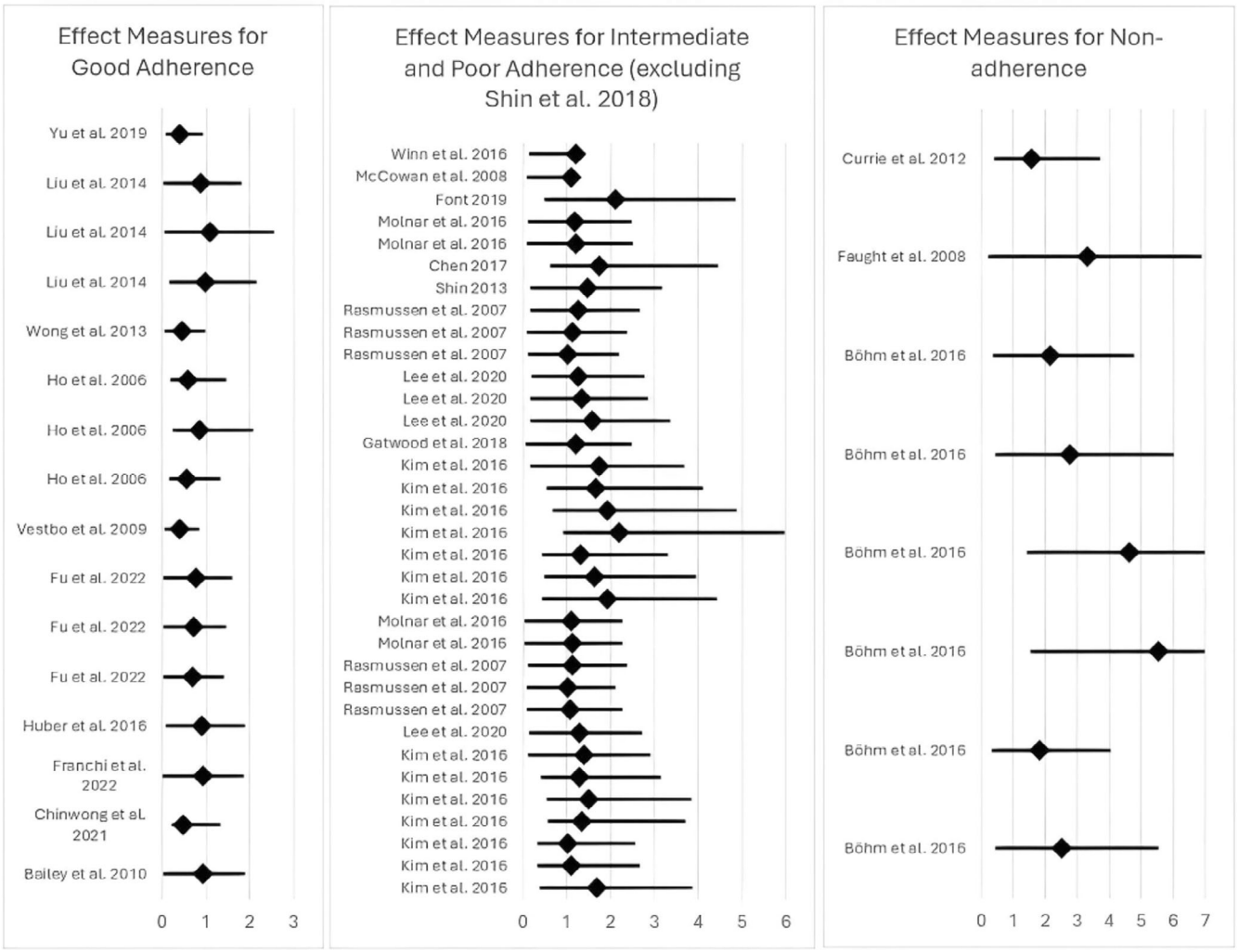

FIGURE 2 Effect measures per adherence category.

FIGURE 3 Synthesized mortality effect measures per adherence category.

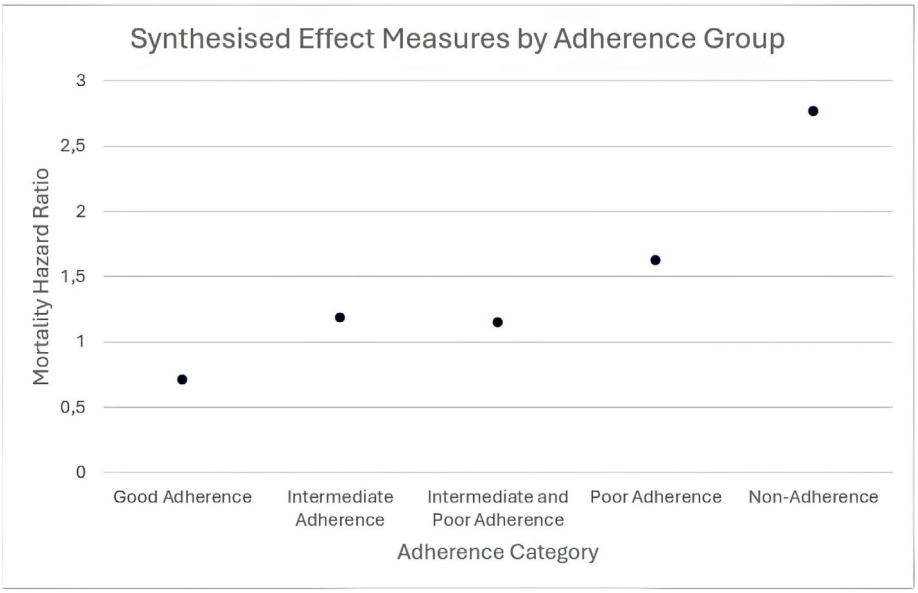

TABLE 3 Total search term matches per document.

Document	Number of search term matches	Document length (number of words)	Total matches per 1000 words
Large-scale validation study of the MARS[63]	73	4719	15.5
StatsSA Mortality Stats 2017[62]	822	65 224	12.6
Strategic plan for prevention and control of NCDs[60]	233	23 621	9.9
WHO global action plan[64]	93	30 467	3.1
SA comparative risk assessment study	5	1726	2.9
Adherence guidelines for HIV, TB and NCDs[61]	58	36 691	1.6
National Health Act[59]	14	21 057	0.7
NHI-Bill-2023[58]	6	25 918	0.2

TABLE 4 Total search term matches across all documents (terms not shown did not appear in any of the documents).

Search terms	Number of matches	Total matches per 1000 words
Death	624	2.98
Mortality	277	1.323
Non-communicable disease	248	1.184
Chronic disease	35	0.167
MARS	34	0.162
Adherence	27	0.129
Medication adherence	22	0.105
Adhere	13	0.062
Non-adherence	11	0.053
Survival	4	0.019
Medication compliance	2	0.01
Lifestyle disease	1	0.005

medication adherence-related search terms (MARS, adherence, medication adherence, adhere, non-adherence and medication compliance) and mortality-related search terms (death, mortality and survival) was low within all documents analysed. This suggests a systemic disconnect between adherence frameworks and mortality risk.

The strongest relationship in terms of proximity was between 'non-communicable disease', 'death' and 'mortality'. Proximity between medication adherence-related search terms and mortality-related search terms was substantially lower. This further emphasizes the lack of a meaningful connection between these concepts.

4 | DISCUSSION

4.1 | Systematic review

This review adds to the existing body of literature by synthesizing evidence on the association between chronic medication adherence and mortality across a broad range of chronic conditions, rather than limiting the focus to a single disease or drug class. Although previous systematic reviews have examined this relationship in condition-specific contexts (such as cardiovascular disease,[12,21,22] type 2 diabetes mellitus\[11] or cancer[23]), this review is, to the best of our knowledge, the first to explore the consistency of this association across the chronic disease spectrum. By doing so, it highlights adherence not only as a clinical issue within individual disease domains but as a broader public health challenge. The findings demonstrate that the link between poor adherence and increased mortality risk is consistently observed across diverse conditions and settings, supporting the need for health system-level interventions that move beyond siloed, condition-specific approaches. This broader perspective contributes novel insights into how adherence is conceptualized and measured, and it underscores the importance of developing scalable, generalizable strategies to improve medication adherence across chronic care pathways.

The results of the synthesis showed a clear association between adherence categories and mortality risk, with lower adherence rates linked to increased mortality. Poor adherence and non-adherence had the highest HRs (HR = 1.63; 95% CI: 1.36–1.96; and HR = 2.77; 95% CI: 2.3–3.34, respectively). This relationship was consistent across the varying disease areas and whether all-cause or specific causes of mortality were investigated. The single instance where a study showed a HR > 1 (HR = 1.1; 95% CI: 1.04–1.44) for good adherence was within a specific racial group (South Asian) where race was assigned based on surname algorithms (rather than self-reported).[69] This was also by far the smallest racial sample included in the study (6099 compared with 16 495 for Chinese patients and 126 320 for White patients).

Studies were critically appraised using the modified Downs and Black Checklist for RCTs and non-randomized trials and the JBI critical appraisal tool for observational studies. The two studies[67,68] assessed using the Downs and Black tool, demonstrated sufficient methodological rigour and were included. However, two observational studies[26,34] evaluated with the JBI tool were excluded due to a combination of methodological limitations. Specifically, both studies relied on a single-item, patient-reported measure of adherence, which introduced a high risk of measurement bias relative to other included studies that employed more robust methods. In addition, they lacked adequate

strategies to address incomplete follow-up and were based on relatively small sample sizes, limiting the reliability and generalizability of their findings. These exclusions aim to maintain a consistent standard of evidence quality throughout the review and minimize the impact of methodological weaknesses on the overall synthesis.

This addresses the research question and shows that in adult patients using medication for chronic conditions, a good medication adherence rate indicates a lower mortality risk than a poor medication adherence rate. It is important to note that this relationship held true irrespective of the adherence metric used. Although standardizing how adherence is measured and reported would be advantageous, using different metrics should not be a reason to overlook the significance of this association. This relationship was also consistent irrespective of the disease category or specific condition that was investigated. The researchers note that risk of mortality for some conditions may be greater than for other conditions, independently of adherence category. Furthermore, the authors were not able to adjust for the severity of disease. Patients with more severe conditions may have had a higher risk of mortality with the same adherence level. However, the consistency of the results supports the conclusion that a good medication adherence rate is associated with a lower risk of mortality.

These findings are further supported by literature demonstrating the relationship between medication adherence and disease control measures, for example, blood pressure[71] and blood glucose levels.[3] Furthermore, systematic reviews[72–75] and RCTs[76] have shown that interventions to improve medication adherence can improve disease markers and reduce hospital admissions. Although the evidence favouring improving mediation adherence is strong given its effect on clinical outcomes, assessing the potential economic impact is also prudent. Available evidence does suggest that adherence interventions are cost-effective or cost-saving,[77] further reiterating the value of focusing on this aspect of chronic disease management.

4.2 | Document analysis for convergence

Despite the strength of the relationship between medication adherence and mortality risk observed in the meta-analysis results, the concept of medication adherence was underrepresented in the review of related guidelines and legislation. Medication adherence was observed least frequently among the three core concepts represented in the documents (medication adherence, mortality and chronic disease). This indicates that the notion of adherence and clinical impact is not sufficiently documented, despite the clear evidence demonstrating its importance. The document with the highest representation of adherence search terms was the large-scale validation study of the MARS.[63] This study investigated the validity of a particular adherence scale in estimating real-world adherence rates. It did not aim to draw any associations between the MARS and clinical outcomes, such as mortality. Even in this instance, no relationship between the adherence and the mortality concepts was established.

The dominance of the mortality-related terms in the legislative and policy documents suggests that government efforts are focused primarily on surveillance, rather than strategy or preventative measures. This is also evidenced by the relatively high co-occurrence and proximity of mortality-related search terms (death, mortality and survival) and the 'non-communicable disease' search term. This supports the view that the association between chronic diseases and mortality is appreciated and has been clearly documented. However, the proximity and co-occurrence of these terms with any adherence-related codes was low. This suggests that the relationship between adherence rates and mortality as an outcome is not well described. Although we apparently clearly understand how poor adherence drives increased mortality, this does not seem to have influenced policy or clinical guidelines. In a resource-limited setting such as South Africa, this highlights an area where further attention is needed. Given the supporting evidence, there should be a move towards developing and funding appropriate interventions to improve adherence to chronic medication.

The legislative documents, particularly, had few matches to any search terms, including the adherence-related terms. This is a noteworthy gap considering South Africa's plan to implement NHI. Concerns about the affordability and feasibility of NHI have been raised,[41–43] highlighting the importance of driving cost efficiencies and value-based care. The current legislative framework does not adequately support the use of adherence-based scores in assessing mortality risk. This gap is concerning, and the systematic review and meta-analysis suggest that it should be addressed.

4.3 | Study limitations

Different effect measures (HR, OR and IRR) were used within the data synthesis. Although these measures reflect similar concepts, they are not identical, which may have introduced inconsistencies. Additionally, the consistency of the definition of the adherence categories used in the synthesis cannot be guaranteed. Where studies gave a clear quantitative definition for an adherence category, this was used. Where studies provided only a qualitative definition of a category, this had to be categorized in the most appropriate way, which may have introduced subjectivity. Furthermore, the absence of a standardized adherence metric constitutes a limitation which may have affected the comparability of adherence assessments.

Heterogeneity between the studies must be acknowledged. This review intentionally did not restrict the type of chronic condition or adherence measurement method. However, these broad inclusion criteria would have led to variability, which may limit direct comparability of results across studies. Such heterogeneity highlights the need for more standardized reporting and methodology in future adherence research.

The use of only three databases may have limited the scope of the review, as the inclusion of additional sources could have captured a broader range of relevant studies. Furthermore, the findings of the document analysis may not be generalizable to all contexts, given the focus on South African legislative and regulatory documents.

Despite these limitations, the consistency of findings across the different studies lends credibility to the overall conclusions.

The observed association between medication adherence and mortality was repeatedly demonstrated, suggesting a robust and meaningful relationship that holds across a wide range of chronic conditions and methodological approaches.

4.4 | Implications of results and recommendations for future research

The strong evidence showing that good adherence to chronic medication is associated with a lower mortality risk compared with poor adherence should motivate incorporating adherence-based risk assessments into clinical and legal frameworks. The authors have noted that the lack of standardized reporting and methodology in adherence research introduces heterogeneity that limits comparability across studies. Although this review showed that the effect measures across different adherence metrics were consistent, a standardized measure of adherence should be developed to allow for more consistent assessment. A standardized metric also has the advantage of transferability and scalability, essentially remaining agnostic of patient, provider or institution. This would enhance the feasibility of applying adherence measures in real-world applications and support broader implementation at scale. Ideally, this measure should not rely on self-reporting and should be as objective as possible. Where datasets related to health consumption (e.g., medication purchasing) are used, ethical and legal considerations must be taken into account to ensure that personal information is adequately protected.

Once a standardized metric is developed, further research will be required to validate its credibility and relevance. Its relationship with clinical outcomes, such as mortality, must be clearly demonstrated through an appropriate statistical analysis.

In addition to finding a standardized way of assessing adherence, steps should be taken to develop and test interventions that can improve adherence to chronic medication. This will necessitate future research investigating the most effective and cost-friendly methods. It is important to note that, should evidence support any particular intervention, policy must be updated to enforce correct implementation.

5 | CONCLUSION

This systematic review demonstrates that good adherence to chronic medication is consistently associated with a significantly lower risk of mortality in adults with chronic conditions, with non-adherence increasing mortality risk by up to 45% in some populations. Despite this robust evidence, the critical role of medication adherence remains underrepresented in both clinical guidelines and health policy frameworks in South Africa. To address this gap, there is a pressing need to standardize adherence assessment methods and to develop and evaluate cost-effective interventions that improve adherence rigorously. Furthermore, South African policymakers should prioritize integrating adherence metrics and interventions into national clinical guidelines and relevant legislation, ensuring that evidence-based strategies are implemented to reduce preventable mortality and enhance the sustainability of healthcare systems. Future research should focus on identifying scalable, context-appropriate adherence interventions and evaluating their impact on both patient outcomes and health system costs.

AUTHOR CONTRIBUTIONS

Jessica Hamuy Blanco: conceptualization; methodology; literature search; screening and selection; data extraction; risk of bias assessment; data curation; project administration; writing the original draft; writing review and editing. Dina C. Janse van Rensburg: conceptualization; methodology; supervision; writing review and editing. Audrey Jansen van Rensburg: conceptualization; methodology; screening and selection; supervision; writing review and editing. Corrie Uys: Formal analysis; data curation; writing review and editing. Natalie Schellack: conceptualization; methodology; screening and selection; data extraction; risk of bias assessment; supervision; writing review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

No additional data are available. All data relevant to the study are included in the article.

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REFERENCES

1. Chauke GD, Nakwafila O, Chibi B, Sartorius B, Mashamba-Thompson T. Factors influencing poor medication adherence amongst patients with chronic disease in low-and-middle-income countries: a systematic scoping review. *Heliyon*. 2022;8(6):e09716. doi:10.1016/j.heliyon.2022.e09716
2. Mekonnen GB, Gelayee DA. Low medication knowledge and adherence to oral chronic medications among patients attending community pharmacies: a cross-sectional study in a low-income country. *Biomed Res Int*. 2020;2020(1):4392058. doi:10.1155/2020/4392058
3. Sendekie AK, Netere AK, Kasahun AE, Belachew EA. Medication adherence and its impact on glycemic control in type 2 diabetes mellitus patients with comorbidity: a multicenter cross-sectional study in Northwest Ethiopia. *PLoS ONE*. 2022;17(9):e0274971. doi:10.1371/journal.pone.0274971
4. Jackson IL, Adibe MO, Okonta MJ, Ukwe CV. Medication adherence in type 2 diabetes patients in Nigeria. *Diabetes Technol Ther*. 2015;17(6):398-404. doi:10.1089/dia.2014.0279
5. Aminde LN, Agbor VN, Fongwen NT, et al. High burden and trend in nonadherence to blood pressure-lowering medications: meta-analysis of data from over 34 000 adults with hypertension in sub-Saharan Africa. *J Am Heart Assoc*. 2025;14(9):e037555. doi:10.1161/JAHA.124.037555

6. Chakrabarti S. What's in a name? Compliance, adherence and concordance in chronic psychiatric disorders. *World J Psychiat*. 2014;4(2):30-36. doi:10.5498/wjp.v4.i2.30
7. Jin J, Sklar G, Min Sen Oh V, Chuen Li S. Factors affecting therapeutic compliance: a review from the patient's perspective. *Ther Clin Risk Manag*. 2008;4(1):269-286. doi:10.2147/tcrm.s1458
8. van Dulmen S, Sluijs E, van Dijk L, de Ridder D, Heerdink R, Bensing J. Patient adherence to medical treatment: a review of reviews. *BMC Health Serv Res*. 2007;7(1):55. doi:10.1186/1472-6963-7-55
9. Vrijens B, De Geest S, Hughes DA, et al. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol*. 2012;73(5):691-705. doi:10.1111/j.1365-2125.2012.04167.x
10. Africa DoSS. Mortality and causes of death in South Africa: findings from death notification. 2018 [cited 2024 24 August]. Available from: https://www.statssa.gov.za/publications/P03093/P030932018.pdf
11. Khunti K, Seidu S, Kunutsor S, Davies M. Association between adherence to pharmacotherapy and outcomes in type 2 diabetes: a meta-analysis. *Diabetes Care*. 2017;40(11):1588-1596. doi:10.2337/dc16-1925
12. Du L, Cheng Z, Zhang Y, Li Y, Mei D. The impact of medication adherence on clinical outcomes of coronary artery disease: a meta-analysis. *Eur J Prev Cardiol*. 2017;24(9):962-970. doi:10.1177/2047487317695628
13. Bosworth HB, Granger BB, Mendys P, et al. Medication adherence: a call for action. *Am Heart J*. 2011;162(3):412-424. doi:10.1016/j.ahj.2011.06.007
14. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980–2000. *N Engl J Med*. 2007;356(23):2388-2398. doi:10.1056/NEJMsa053935
15. Organization WH. *Adherence to Long-Term Therapies: Evidence for Action*. World Health Organization; 2003.
16. Sertkaya A, Beleche T, Jessup A, Sommers BD. Costs of drug development and research and development intensity in the US, 2000–2018. *JAMA Netw Open*. 2024;7(6):e2415445. doi:10.1001/jamanetworkopen.2024.15445
17. Cutler RL, Fernandez-Llimos F, Frommer M, Benrimoj C, Garcia-Cardenas V. Economic impact of medication non-adherence by disease groups: a systematic review. *BMJ Open*. 2018;8(1):e016982. doi:10.1136/bmjopen-2017-016982
18. Egede LE, Gebregziabher M, Dismuke CE, et al. Medication nonadherence in diabetes: longitudinal effects on costs and potential cost savings from improvement. *Diabetes Care*. 2012;35(12):2533-2539. doi:10.2337/dc12-0572
19. De Vera MA, Bhole V, Burns LC, Lacaille D. Impact of statin adherence on cardiovascular disease and mortality outcomes: a systematic review. *Br J Clin Pharmacol*. 2014;78(4):684-698. doi:10.1111/bcp.12339
20. Basios A, Chatzi CA, Markozannes G, et al. Adherence to statins and development of atherosclerosis-related events. A systematic review and meta-analysis. *J Diabetes Complications*. 2025;39(8):109040. doi:10.1016/j.jdiacomp.2025.109040
21. Liu M, Zheng G, Cao X, et al. Better medications adherence lowers cardiovascular events, stroke, and all-cause mortality risk: a dose-response meta-analysis. *J Cardiovasc Dev Dis*. 2021;8(11):146. doi:10.3390/jcdd8110146
22. Peng X, Wan L, Yu B, Zhang J. The link between adherence to antihypertensive medications and mortality rates in patients with hypertension: a systematic review and meta-analysis of cohort studies. *BMC Cardiovasc Disord*. 2025;25(1):145. doi:10.1186/s12872-025-04538-6
23. Inotai A, Ágh T, Maris R, et al. Systematic review of real-world studies evaluating the impact of medication non-adherence to endocrine therapies on hard clinical endpoints in patients with non-metastatic breast cancer. *Cancer Treat Rev*. 2021;100:102264. doi:10.1016/j.ctrv.2021.102264
24. Kim S, Shin DW, Yun JM, et al. Medication adherence and the risk of cardiovascular mortality and hospitalization among patients with newly prescribed antihypertensive medications. *Hypertension (Dallas, Tex: 1979)*. 2016;67(3):506-512. doi:10.1161/HYPERTENSIONAHA.115.06731
25. Kim YY, Lee JS, Kang HJ, Park SM. Effect of medication adherence on long-term all-cause-mortality and hospitalization for cardiovascular disease in 65,067 newly diagnosed type 2 diabetes patients. *Sci Rep*. 2018;8(1):12190. doi:10.1038/s41598-018-30740-y
26. Asher D, Halen N, Cukor D. Depression and non-adherence predict mortality in hemodialysis treated ESRD patients. *Haemodial Int*. 2012;16(3):387-393. doi:10.1111/j.1542-4758.2012.00688.x
27. Shin S, Song H, Oh S, Choi KE, Kim H, Jang S. Effect of antihypertensive medication adherence on hospitalization for cardiovascular disease and mortality in hypertensive patients. *Hypertens Res*. 2013;36(11):1000-1005. doi:10.1038/hr.2013.85
28. Wong MC, Tam WW, Cheung CS, et al. Drug adherence and the incidence of coronary heart disease- and stroke-specific mortality among 218,047 patients newly prescribed an antihypertensive medication: a five-year cohort study. *Int J Cardiol*. 2013;168(2):923-933. doi:10.1016/j.ijcard.2012.10.048
29. Molnar MZ, Gosmanova EO, Sumida K, et al. Predialysis cardiovascular disease medication adherence and mortality after transition to dialysis. *Am J Kidney Dis*. 2016;68(4):609-618. doi:10.1053/j.ajkd.2016.02.051
30. Font R, Espinas JA, Barnadas A, et al. Influence of adherence to adjuvant endocrine therapy on disease-free and overall survival: a population-based study in Catalonia, Spain. *Breast Cancer Res Treat*. 2019;175(3):733-740. doi:10.1007/s10549-019-05201-3
31. Baumgartner P, Haynes R, Hersberger K, Arnet I. A systematic review of medication adherence thresholds dependent of clinical outcomes. *Front Pharmacol*. 2018;9:1290. doi:10.3389/fphar.2018.01290
32. Prieto-Merino D, Mulick A, Armstrong C, et al. Estimating proportion of days covered (PDC) using real-world online medicine suppliers' datasets. *J Pharmaceut Pol Pract*. 2021;14(1):113. doi:10.1186/s40545-021-00385-w
33. Stauffer M, Hutson P, Kaufman A, Morrison A. The adherence rate threshold is drug specific. *Drugs R D*. 2017;17(4):645-653. doi:10.1007/s40268-017-0216-6
34. Wu JM, Moser DK, De Jong MJ, et al. Defining an evidence-based cutpoint for medication adherence in heart failure. *Am Heart J*. 2009;(2):285-291. doi:10.1016/j.ahj.2008.10.001
35. Schaefer M, Wagoner S, Young M, et al. Subjective versus objective measures of medication adherence in adolescents/young adults with attention-deficit hyperactivity disorder. *J Dev Behav Pediatr*. 2019;40(1):54-59. doi:10.1097/DBP.0000000000000602
36. Shi L, Liu J, Fonseca V, Walker P, Kalsekar A, Pawaskar M. Correlation between adherence rates measured by MEMS and self-reported questionnaires: a meta-analysis. *Health Qual Life Outcomes*. 2010;8(1):99. doi:10.1186/1477-7525-8-99
37. Africa AfSIS. Life insurers paid close to 900 000 death claims worth R39.9 billion in 2023. 2024 [cited 2024 24 August]. Available from: https://www.asisa.org.za/media-releases/life-insurers-paid-close-to-900-000-death-claims-worth-r39-9-billion-in-2023/
38. Consultants TSAa. *The South African Insurance Gap (2022)*. Association for Savings & Investment South Africa; 2022. [cited 2024 24 August]. Available from: https://www.asisa.org.za/media/m0pnw3ow/the-south-african-insurance-gap-2022.pdf
39. Fitzgerald C, Ryan D. *Impact on Insurance of Medication Adherence*. Swiss Re Institute; 2019.
40. van den Staalduinen DJ, Bekerom P, Groeneveld S, Kidanemariam M, van Stiggelbout AM, van den Akker- Marle ME. The implementation of value-based healthcare: a scoping review. *BMC Health Serv Res*. 2022;22(1):270. doi:10.1186/s12913-022-07489-2
41. Moosa S, Luiz JM, Carmichael T. Introducing a national health insurance system in South Africa: a general practitioner's bottom-up approach to costing. *S Afr Med J*. 2012;102(10):794-797. doi:10.7196/samj.6072

42. Rice N, Smith PC. Capitation and risk adjustment in health care. *Health Care Manag Sci*. 2000;3(2):73-75. doi:10.1023/a:1019076920736
43. Citizen, T. R1.4 billion in budget for NHI: what does that mean? *The Citizen*. @TheCitizen_News; 2024 [updated 2024-03-08; cited 2024 7 September]. Available from: https://www.citizen.co.za/business/personal-finance/r1-4-billion-in-budget-for-nhi-what-does-that-mean/
44. Muthuri RNDK, Nzinga J, Tsofa B, et al. A mixed methods study examining the impact of primary health care financing transitions on facility functioning and service delivery in Kenya: a study protocol. *Wellcome Open Res*. 2024;9:220. doi:10.12688/wellcomeopenres.21173.1
45. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*. 2021;372:n160. doi:10.1136/bmj.n160
46. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*. 1998;52(6):377-384. doi:10.1136/jech.52.6.377
47. Sterne JA, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ (Clinical Research Ed)*. 2019;366:l4898. doi:10.1136/bmj.l4898
48. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ (Clinical Research Ed)*. 2016;355:i4919. doi:10.1136/bmj.i4919
49. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25(9):603-605. doi:10.1007/s10654-010-9491-z
50. Hilton M. JBI critical appraisal checklist for systematic reviews and research syntheses. *J Can Health Libr Assoc*. 2025;45(3):180. doi:10.29173/jchla29801
51. Howick, J, Chalmers, I, Glasziou, P, Greenhalgh, T, Heneghan, C, Liberati, A, et al.. OCEBM Levels of Evidence Working Group. The Oxford 2011 levels of evidence. 2020.
52. Group OLoEW. Oxford centre for evidence-based medicine: levels of evidence. 2009 [27 May 2024]. Available from: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence
53. McCowan C, Shearer J, Donnan PT, et al. Cohort study examining tamoxifen adherence and its relationship to mortality in women with breast cancer. *Br J Cancer*. 2008;99(11):1763-1768. doi:10.1038/sj.bjc.6604758
54. Winn AN, Dusetzina SB. The association between trajectories of endocrine therapy adherence and mortality among women with breast cancer. *Pharmacoepidemiol Drug Saf*. 2016;25(8):953-959. doi:10.1002/pds.4012
55. Kayesa NK, Shung-King M. The role of document analysis in health policy analysis studies in low and middle-income countries: lessons for HPA researchers from a qualitative systematic review. *Health Policy Open*. 2020;15(2):100024. doi:10.1016/j.hpopen.2020.100024
56. Bowen G. Document analysis as a qualitative research method. *Qual Res J*. 2009;9(2):27-40. doi:10.3316/QRJ0902027
57. Group SACRAC. Second comparative risk assessment for South Africa (SACRA2) highlights need for health promotion and strengthened surveillance. *S Afr Med J*. 2022. [cited 2025 1 February]. Available from: https://www.samrc.ac.za/sites/default/files/attachments/2022-10/ComparativeRiskFactorStudy.pdf
58. Africa RoS. *National Health Insurance Bill [B11–2019]*. Pretoria; 2019. [cited 2025 1 February]. Available from: https://www.parliament.gov.za/bill/1233734
59. Africa RoS. *National Health Act No. 61 of 2003*. Government Gazette; 2004. [cited 2025 1 February]. Available from: https://www.gov.za/documents/national-health-act
60. Africa RoS. *Strategic Plan for the Prevention and Control of Non-Communicable Diseases 2013–17*. National Department of Health; 2013. [cited 2025 1 February]. Available from: https://www.health.gov.za/wp-content/uploads/2022/05/NCDs-SP-2020-2025.pdf
61. Africa RoS. *Adherence Guidelines for HIV, TB and NCDs*. National Department of Health; 2016. [cited 2025 1 February]. Available from: https://www.knowledgehub.org.za/elibrary/adherence-guidelines-hiv-tb-and-ncds-policy-and-service-delivery-guidelines
62. Africa RoS. *Mortality and Causes of Death in South Africa, 2017: Findings From Death Notification*. National Department of Stat; 2017. [cited 2025 1 February]. Available from: https://www.statssa.gov.za/publications/P03093/P030932017.pdf
63. Fialko L, Garety PA, Kuipers E, et al. A Large-Scale Validation Study of the Medication Adherence Rating Scale (MARS). *Schizophr Res*. 2008;100(1–3):53-59. doi:10.1016/j.schres.2007.10.029
64. Organization WH. *Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2020*. World Health Organization; 2013. [cited 2025 1 February]. Available from: https://apps.who.int/iris/handle/10665/94384
65. McHugh ML. Interrater reliability: the kappa statistic. *Biochem Med*. 2012;22(3):276-282. doi:10.1016/j.jocd.2012.03.005
66. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): an R package and shiny web app for visualizing risk-of-bias assessments. *Res Synth Methods*. 2021;12(1):55-61. doi:10.1002/jrsm.1411
67. Bohm M, Lloyd SM, Ford I, et al. Non-adherence to ivabradine and placebo and outcomes in chronic heart failure: an analysis from SHIFT. *Eur J Heart Fail*. 2016;18(6):672-683. doi:10.1002/ejhf.493
68. Vestbo J, Anderson JA, Calverley PM, et al. Adherence to inhaled therapy, mortality and hospital admission in COPD. *Thorax*. 2009;64(11):939-943. doi:10.1136/thx.2009.113662
69. Liu Q, Quan H, Chen G, Qian H, Khan N. Antihypertensive medication adherence and mortality according to ethnicity: a cohort study. *Can J Cardiol*. 2014;30(8):925-931. doi:10.1016/j.cjca.2014.04.017
70. Shin JWMDP, Jung SWMDP, Lee SBMD, et al. Medication nonadherence increases hepatocellular carcinoma, cirrhotic complications, and mortality in chronic hepatitis B patients treated with entecavir. *Am J Gastroenterol*. 2018;113(7):998-1008. doi:10.1038/s41395-018-0093-9
71. Kjeldsen SE, Narkiewicz K, Burnier M, Oparil S. Better drug adherence improves blood pressure control and lowers cardiovascular disease outcomes—from single pill combinations to monitoring of a nationwide health insurance database. *Blood Press*. 2021;30(3):143-144. doi:10.1080/08037051.2021.1917192
72. Ruppar TM, Cooper PS, Mehr DR, Delgado JM, Dunbar-Jacob JM. Medication adherence interventions improve heart failure mortality and readmission rates: systematic review and meta-analysis of controlled trials. *J Am Heart Assoc*. 2016;5(6):e002606. doi:10.1161/JAHA.115.002606
73. Reeves L, Robinson K, McClelland T, Adedoyin CA, Broeseker A, Adunlin G. Pharmacist interventions in the management of blood pressure control and adherence to antihypertensive medications: a systematic review of randomized controlled trials. *J Pharm Pract*. 2021;34(3):480-492. doi:10.1177/0897190020903573
74. Conn VS, Ruppar TM, Chase JD. Blood pressure outcomes of medication adherence interventions: systematic review and meta-analysis. *J Behav Med*. 2016;39(6):1065-1075. doi:10.1007/s10865-016-9730-1
75. Presley B, Groot W, Pavlova M. Pharmacy-led interventions to improve medication adherence among adults with diabetes: a systematic review and meta-analysis. *Res Soc Admin Pharm: RSAP*. 2019;15(9):1057-1067. doi:10.1016/j.sapharm.2018.09.021
76. Hale TM, Jethwani K, Kandola MS, Saldana F, Kvedar JC. A remote medication monitoring system for chronic heart failure patients to reduce readmissions: a two-arm randomized pilot study. *J Med Internet Res*. 2016;18(5):e91. doi:10.2196/jmir.5256

77. Simon-Tuval T, Neumann PJ, Greenberg D. Cost-effectiveness of adherence-enhancing interventions: a systematic review. *Expert Rev Pharmacoecon Outcomes Res*. 2016;16(1):67-84. doi:10.1586/14737167.2016.1138858

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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