Patient Preference and Adherence

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REVIEW

A Systematic Review Uncovering Modifiable Influences on Statin Adherence

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Abstract: Statins are effective in reducing cardiovascular disease (CVD) risk, but adherence rates remain low globally. Understanding and addressing modifiable influences on adherence is key to improving outcomes. Existing reviews have methodological limitations, often failing to integrate qualitative and quantitative data or consider specific barriers to statin adherence. This systematic review aimed to identify modifiable barriers and facilitators to statin adherence using the Theoretical Domains Framework (TDF). A comprehensive search of Embase, MEDLINE, PsycINFO, and CINAHL was conducted, covering studies from January 1998 to November 2023. Data were coded to TDF domains and synthesized to identify specific influences on adherence. The nature of the evidence (qualitative or quantitative) was recorded for each influence, and variations among patient groups were noted. Seventy studies from 20 countries were included, with only one focused on ethnic minorities. The most commonly identified domains affecting adherence were "Beliefs about Consequences", "Knowledge", 'Environmental Context and Resources', and "Social Influences". Key factors included knowledge of disease, perceived disease threat, perceived benefits of statins, and patient-provider communication and trust. While side effects had inconsistent associations with adherence, forgetfulness was mainly addressed in quantitative studies, and social influences were highlighted in qualitative research. This review identified modifiable factors that could improve statin adherence. Future research should focus on addressing barriers faced by under-represented groups to create more inclusive and effective interventions that enhance patient support and communication for better health outcomes.

Plain language summary: People are prescribed statins to prevent strokes and heart attacks. This study combines findings from previous studies to understand why many people do not take statins as prescribed.

- Common barriers to taking statins included not thinking being at risk of strokes and heart attacks, believing statins are harmful, experiencing side effects and poor communication and trust with healthcare professionals.
- Common things encouraging statin taking included thinking statins have benefits, having cholesterol levels checked, routines and methods to remember statin intake and having ways of dealing with side effects.

Keywords: medication adherence, psychological determinants, dyslipidaemia, theoretical domains framework

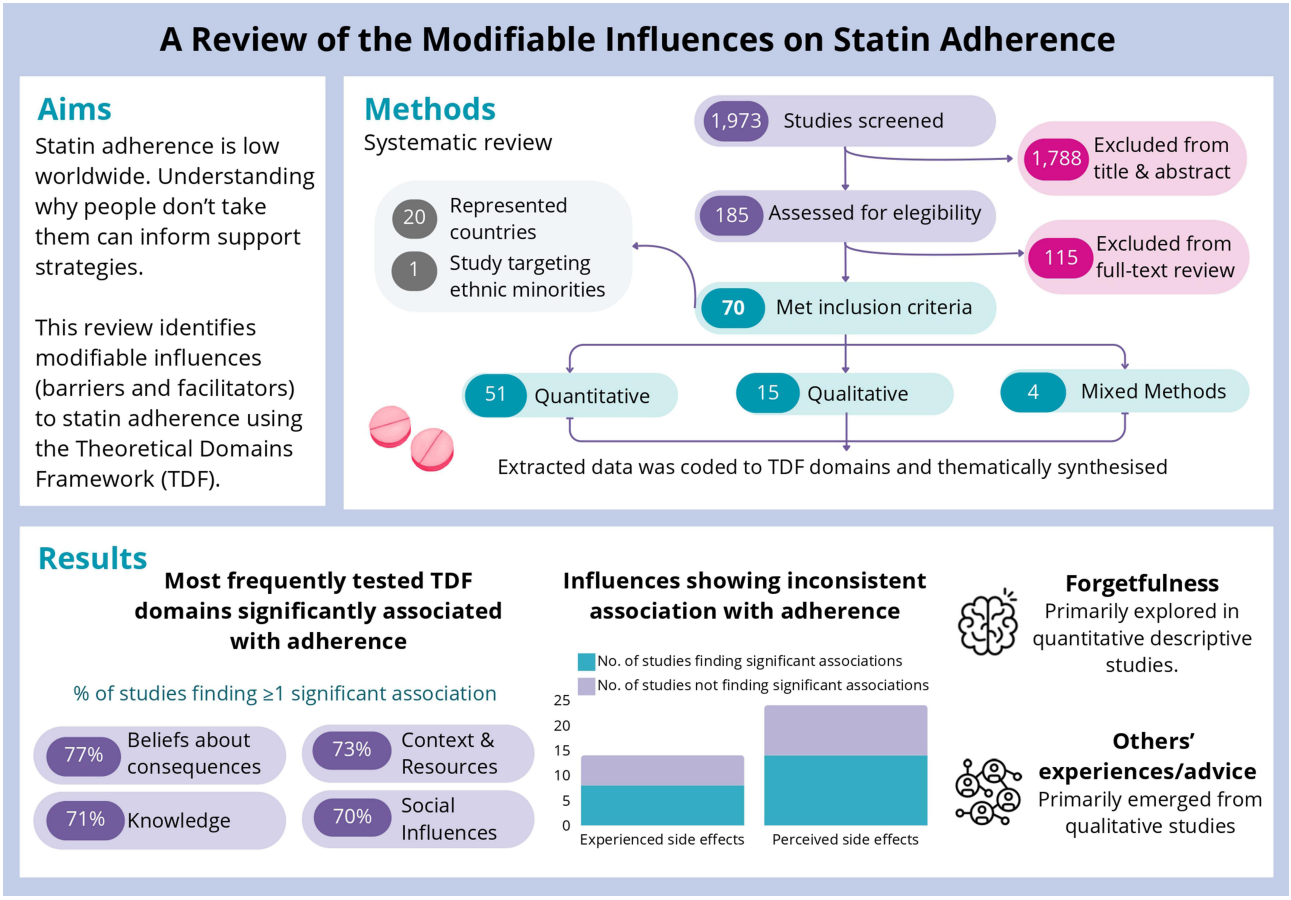
Introduction

Cardiovascular disease (CVD) was responsible for over 20.5 million deaths worldwide in 2021, making it one of the leading causes of mortality.[1] Elevated low-density lipoprotein cholesterol (LDL-C) significantly contributes to such deaths.[2] Statins are highly effective at reducing LDL-C and, therefore, have the potential to significantly reduce the burden of CVD when adherence to the prescribed regimen is high.[3]

Despite their benefits, statin non-adherence remains a major barrier to improving outcomes. Non-adherence is prevalent, approaching 50% within the first year following prescription and declining further beyond this time,[4,5]

Received: 5 November 2024
Accepted: 13 December 2024
Published: 4 January 2025

Graphical Abstract



resulting in increased cardiovascular events, mortality, and avoidable healthcare costs.[6,7] Non-adherence can be categorized as failing to initiate (initiation), stopping early (discontinuation), or taking prescribed medication less than 80% of the time[8] (implementation).

Understanding factors influencing statin adherence is crucial for developing effective interventions.[9] While some factors, like sociodemographic (eg, age, gender) and clinical characteristics (eg, type of prevention, comorbidities), are unchangeable (non-modifiable) and can help identify patients at risk of non-adherence, other modifiable factors present opportunities for improvement.[9] Modifiable influences of statin adherence that have been investigated in prior research include concerns about statins' side effects, lack of perceived benefits, or distrust in healthcare providers.[10]

Behavioral theory offers valuable tools to understand these modifiable influences and their impact on adherence and can also guide intervention design.[11] The Theoretical Domains Framework (TDF),[12] is a synthesis of 33 theories of behavior, and offers a structured and comprehensive approach for assessing the influences that shape individual behavior. This comprehensive framework encompasses 14 theoretical domains covering individuals' social and physical environment, motivation, and capabilities. These domains are: Knowledge, Skills, Social/Professional Role and Identity, Beliefs about Capabilities, Beliefs about Consequences, Optimism, Reinforcement, Intentions, Goals, Memory/ Attention/ Decision Processes, Environmental Context and Resources, Social Influences, Emotion, Behavioral Regulation (see Supplementary Material 1 for definitions). By applying the TDF, researchers can identify the influences on behavior that need to be targeted, thus supporting the development of more effective interventions. While other theoretical frameworks, such as the Perceptions and Practicalities Approach (PaPA)[13] and the Necessity-Concerns Framework (NCF),[14] have also

been used to understand medication adherence, the TDF's strength lies in its practicality as can be mapped to Behavior Change Techniques (BCTs), evidence-based active components that can bring about change.[15] It is also a more comprehensive framework, so it is expected to lead to different and potentially more nuanced categorization of influences on adherence.

While previous reviews[16,17] have explored medication adherence in CVD using the TDF, they have not described barriers to statin adherence separately from other medications. Patients taking statins experience unique challenges. For instance, negative media portrayals[18] questioning their safety profile can lead patients to misattribute symptoms not actually caused by statins and lead to discontinuation. Furthermore, existing reviews on modifiable influences on statin adherence have methodological limitations. A review was rated critically low quality because of an uncomprehensive search strategy, lack of detail of included studies and no quality assessment, among other factors.[10,19] Other reviews lack integration between quantitative[20] and qualitative[21] data, limiting understanding of the complex interplay of influences affecting adherence. The present study addresses this knowledge gap by utilizing the TDF to systematically synthesize quantitative and qualitative evidence on modifiable influences on statin adherence. As part of an intervention development focused on improving communication with patients about statins, and supporting patients to take their statins, this review aims to identify and consolidate modifiable influences (barriers/facilitators) to statin adherence from the published literature, categorize modifiable influences into the TDF, and explore how these influences vary between patient groups.

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[22] The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42023386842). Three modifications were made to enhance the scope and depth of the analysis while preserving the review's objectives. Firstly, studies in all languages were included to increase inclusivity. Secondly, quantitative data were mapped to the TDF irrespective of statistical significance, ensuring a thorough assessment of the evidence of the impact of each variable on adherence. Finally, theoretical domains were not prioritized, meaning the analysis did not focus on a subset of domains deemed the most important. This allowed for a more granular exploration of all domains, to better inform the development of future tailored interventions.

We included all primary studies published in any language that assessed modifiable influences (defined as factors potentially modifiable through behavior change interventions) of statin adherence reported by patients. Factors such as age or comorbidities were deemed non-modifiable based on the lack of direct intervention potential. We excluded studies solely reporting the perspectives of healthcare professionals or caregivers, as our focus was on patient-perceived factors, and excluded studies solely focusing on patients with an advanced life-limiting condition (eg, patients with a life expectancy of less than one year due to advanced illness or significant functional decline) as these individuals are unlikely to participate in a statin adherence intervention. Studies including other medications where statin-specific data could not be isolated were also excluded. Additionally, interventions, systematic reviews, case reports, theses, secondary analyses of surveys, conference abstracts, and prospective studies were excluded.

Four databases (Embase, MEDLINE, PsycINFO, and CINAHL) were searched from January 1st, 1998, to November 11th, 2023. This search timeframe captures studies published since the publication of the first official guidelines recommending statin use in the United Kingdom (UK)[23] and aligns with the broader adoption of similar guidelines in the United States (US).[24] The search strategy, available in the Supplementary Material 2, combined search terms and synonyms with subject headings grouped into four categories: 1) Statins, 2) Medication adherence, 3) Modifiable influences and 4) Study design. Pilot testing optimized results and Boolean operators combined search concepts and subject headings. Citation tracking and reference list searches of included studies were used to identify additional studies. Grey literature was excluded.

References were imported and de-duplicated in Covidence software. Two reviewers (JR, AM) independently screened all titles and abstracts against inclusion/exclusion criteria (Cohen's K = 0.55), and discrepancies were discussed until achieving consensus. Full texts of potentially eligible studies were retrieved. JR screened all full texts, and a second

reviewer (RP) randomly re-screened 25% for inter-rater reliability (Cohen's K = 0.84). Disagreements were resolved by a third reviewer (GJ).

Data Extraction

A data extraction form was developed in Covidence by JR, with feedback from GJ on its structure, leading to adjustments. Two reviewers (JR, SL) independently extracted data from eligible studies. JR extracted data from all studies, while SL independently extracted data from a 25% random sample to ensure reliability. Disagreements were resolved through discussion and consensus with a third reviewer (GJ).

For qualitative studies, extracted data included theme headings, descriptions, participant quotes with context, and author interpretations. For quantitative studies, data were extracted related to descriptive statistics on adherence (eg, medication possession ratio), predictors, and correlates with effect sizes and p-values. For mixed-method studies, these approaches were combined. Authors of the included studies were contacted for missing information.

Quality Assessment

The Mixed Methods Appraisal Tool (MMAT)[25] was used to assess studies given relevance to different study designs. The MMAT evaluates studies using five key criteria: the clarity of research questions, the suitability of the study design to address those questions, the appropriateness of the methods used, the validity of the findings, and the alignment between data collection and analysis. Importantly, the MMAT discourages calculating an overall score by summing ratings across these criteria. Instead, it advocates for a more detailed reporting of individual ratings to provide a clearer picture of the quality of each included study.[25] The first reviewer appraised all studies, and a second reviewer (SL) randomly assessed 25% with a proportion of agreement of 0.71. Discrepancies were resolved by a third reviewer (GJ). The use of solely objective measures (eg, prescription refills) and subjective measures (eg, validated questionnaires, self-reported discontinuation) as classified by the World Health Organization (WHO)[26] was considered inappropriate. A combination of subjective and objective measures is recommended to yield more precise outcomes since researchers can capitalize on the strengths and address the limitations of each method.[27] The Morisky Medication Adherence Scale (8-item) (MMAS-8)[7] was considered inappropriate due to its retraction in 2023.[28] A 70% cut-off was determined to be sufficient for data completeness, and studies below this threshold were categorized as having a "No" rating for data completeness. Studies were not excluded based on MMAT scores.

Synthesis

The included studies were highly heterogeneous in data collection methods and outcome measures, with substantial differences in the phases of statin adherence assessed (eg, initiation, implementation, discontinuation), which made a meta-analysis unfeasible. To address these challenges, we applied analysis methods used in similar reviews involving the TDF[29,30] to integrate both qualitative and quantitative findings. The approach combined deductive coding within the TDF framework and inductive thematic analysis to synthesize the data. Our analysis consisted of four steps: (1) Deductive analysis, (2) Inductive analysis, (3) Evidence level assessment, and (4) Patient group comparison.

1. Deductive Analysis: Extracted data from each study consisted of data fragments, representing specific factors influencing statin adherence. These fragments included direct quotes or author interpretations from qualitative studies, as well as statistical findings from quantitative studies. Each fragment was coded into the most relevant TDF domain based on the nature of the influence it described. To ensure consistency and reliability, two independent reviewers (JR and SL) coded fragments from five studies, discussing and resolving any discrepancies. This led to the development of TDF-informed coding guidelines, providing a consistent framework for analysis. Using these guidelines, one reviewer (JR) then coded the remaining data from all other studies. If a fragment pertained to more than one domain—such as both "Social Influences" and "Environmental Context"—it was coded into multiple domains to fully capture its implications.
2. Inductive Analysis: This process involved thematic analysis,[31] in which all data fragments within a TDF domain were organised into patterns of meaning or subthemes that reflected common views or experiences. In cases where

the data presented opposing perspectives—such as patients expressing a strong perceived need for treatment versus those who felt no such need—these contrasting views were grouped together under the same subtheme to capture the full range of perspectives on a particular influence. Each subtheme was then categorized as either a barrier, facilitator, or both, depending on how it affected statin adherence. For example, financial constraints were categorized as a barrier, as they impeded adherence, while treatment satisfaction was identified as a facilitator. In some cases, subthemes were classified as both barriers and facilitators, such as knowledge about treatment, which could either promote adherence if accurate or hinder it if incomplete. Consensus meetings between the two coders (JR and ML) and two experts (GJ and SG) were held throughout the analysis to refine coding. These discussions resolved any disagreements or ambiguities, resulting in a more reliable and nuanced representation of the data.

3. Evidence Level Assessment: To provide a more nuanced understanding of the evidence base for modifiable influences, the first reviewer (JR) systematically documented the number of studies offering qualitative evidence, quantitative descriptive data, or testing associations with statin adherence (both significant and non-significant) for each subtheme. This approach not only helped identify subthemes with stronger support—such as those backed by a high proportion of significant quantitative associations or consistent qualitative findings—but also clarified the nature of the evidence. For instance, while subthemes were supported by quantitative evidence showing statistical significance, others were supported by qualitative evidence.
4. Patient Group Comparison: Subthemes were compared across different patient groups (primary vs secondary prevention, diabetes, multimorbidity) to explore variations in modifiable influences on statin adherence. This involved examining how subthemes and TDF Domains manifested differently in each group and identifying unique barriers and facilitators to some groups. This analysis allowed for a more tailored understanding of influences affecting adherence within specific patient populations.

Results

The search identified 2734 studies (Figure 1). After removing duplicates (n=761) and screening titles and abstracts, 185 full-text reports were assessed for eligibility, and 70 met the inclusion criteria. The Supplementary Material 3 lists excluded studies.

Study Characteristics

Table 1 presents characteristics of the 70 included studies. 51 studies were quantitative, 15 were qualitative, and four were mixed-methods studies. The complete characteristics of each included study are detailed in the Supplementary Material 4.

The highest proportion of studies (n=25, 36%) were from the US. Other well-represented countries were Turkey (n=7, 10%) and the UK (n=6, 9%). Sixteen studies (22%) targeted individuals undergoing secondary CVD prevention, while seven (10%) focused on primary prevention. Fewer studies (n=8, 11%) investigated statin adherence in specific conditions, including diabetes mellitus and familial hypercholesterolaemia. While three studies explored adherence exclusively in older adults (4%), only one (1%) addressed ethnic minorities.

Most studies focused solely on analyzing influences affecting statins (n=58, 83%). Twelve studies (17%) investigated modifiable influences on other medications, such as cardiovascular medications and other cholesterol-lowering medications, where at least one modifiable influence specific to statins was reported.

Among quantitative studies, 37 solely used self-report to measure statin adherence. Of these, 18 utilised validated scales, most commonly the Morisky Medication Adherence Scale (MMAS) (n=10). The remaining 19 used non-validated measures primarily to measure statin discontinuation. Ten studies exclusively used measures based on medication refill data, such as Proportion of Days Covered (PDC) and discontinuation rates. Only four studies adopted a combined approach, using self-reported adherence measures and refill data.

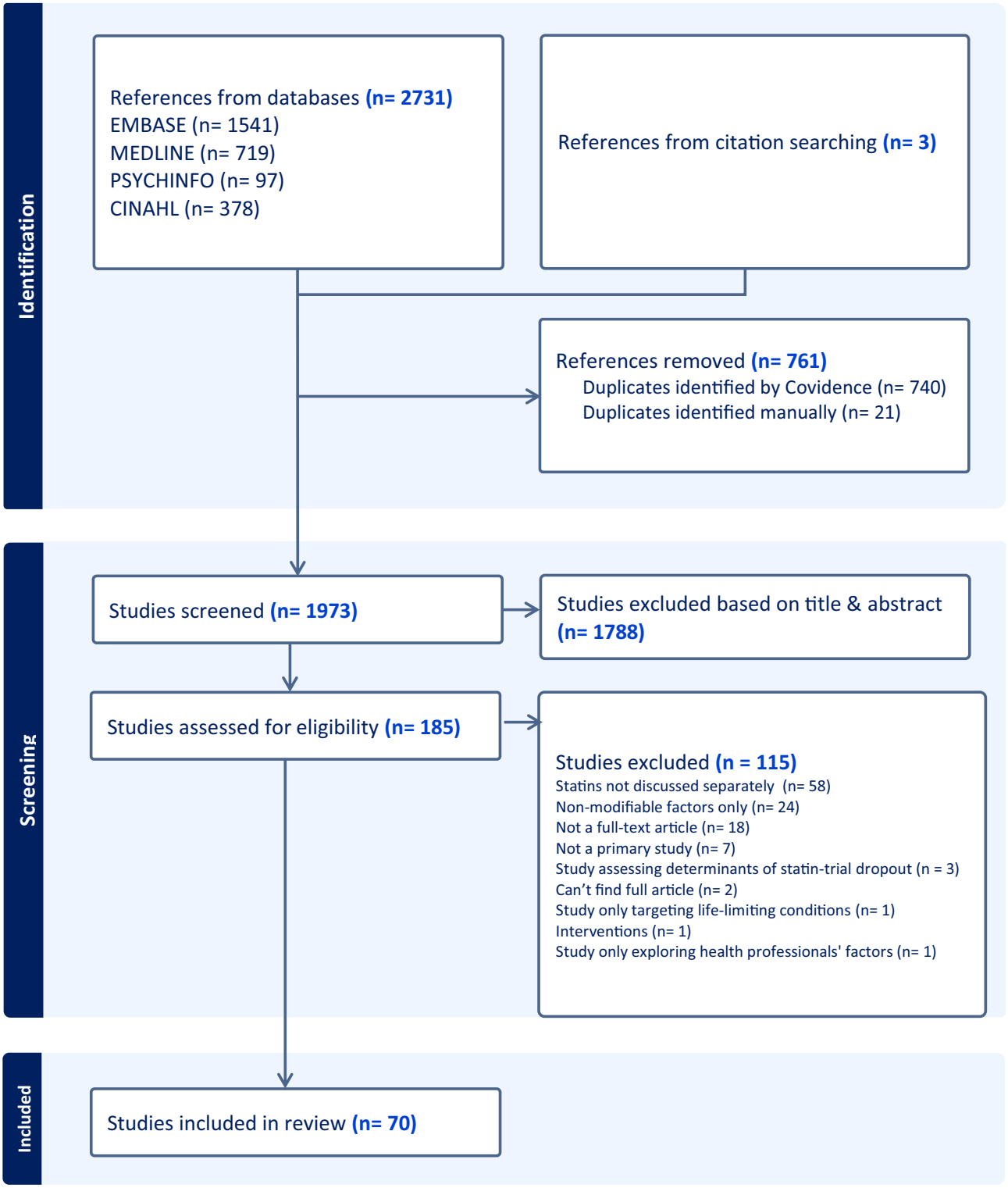


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Diagram.
Notes: The diagram shows the systematic review process, starting with 2734 references. After removing 761 duplicates, 1973 studies were screened, with 1788 excluded. Of 185 full-text studies assessed, 115 were excluded. The final review included 70 studies.

Table 1 Summary of Studies Characteristics

Study Characteristics	Frequencies (Total 70 Studies)
Study methods	51 (72.9%) Quantitative (eg, surveys/questionnaires); 15 (21.4%) Qualitative (eg, interviews/focus group) 4 (5.7%) Mixed methods
Study location	25 (35.7%) United States (US)* 7 (10%) Turkey 6 (8.6%) United Kingdom (UK)* 5 (7.1%) Denmark 5 (7.1%) Netherlands 4 (5.7%) China 2 (2.9%) Canada 2 (2.9%) Brazil 2 (2.9%) Russia 2 (2.9%) Sweden 2 (2.9%) Korea 2 (2.9%) Malaysia 1 (1.4%) India 1 (1.4%) Finland 1 (1.4%) Australia 1 (1.4%) Switzerland 1 (1.4%) Jordan 1 (1.4%) Ireland 1 (1.4%) Lebanon 1 (1.4%) Estonia
Type of prevention	7 (10%) Primary 16 (22.9%) Secondary 47 (67.1%) Both or unspecified type of prevention
Targeted populations	5 (7.1%) Diabetes Mellitus 3 (4.3%) Familial Hypercholesterolemia 3 (4.3%) Older Patients 1 (1.4%) Ethnic minorities (Southeast Asian) 1 (1.4%) Women 1 (1.4%) Rural population 56 (80%) Not targeted populations identified

Notes: (*) indicates that one study was conducted both in the UK and the US. Therefore, each country was credited with one additional study.

Quality of Studies

The quality appraisal of the included studies is provided in the Supplementary Material 5. Five qualitative[32–36] and one quantitative[37] rated positively on all criteria. Three studies[38–40] (4%) received critically low scores due to unclear research questions. The remaining studies showed variability in methodological quality. Most quantitative studies struggled with measurement appropriateness, often using only subjective or objective measures of adherence (n=47, 92%). Efforts to achieve a representative sample were only stated in 17 quantitative studies (33%). Outcome data completeness and low non-response varied, with some studies having large gaps or not reporting withdrawal/dropout rates (n=26, 51%). Confounder management was accounted for in more than half of quantitative non-randomized studies (n=30, 64%). Qualitative studies without perfect scores often had poor coherence between data sources, collection, analysis, and interpretation (n=7, 46%) or inadequate data collection methods (n=6, 40%). Common reasons for this were the lack of quotes to support generated themes or limited descriptions of analytical procedures. Mixed-methods studies

faced challenges in triangulating findings (n=2, 50%) or addressing discrepancies between quantitative and qualitative results (n=2, 50%).

Modifiable Influences Mapping

46 subthemes were identified within the data across all 14 TDF domains. The domains tested in more than four studies with the highest proportion of significant associations were "Beliefs about Consequences", "Knowledge", "Environmental Context and Resources" and "Social Influences" (Table 2). Further information on subthemes and evidence can be found in Table 3 and Supplementary Material 6. The following sections provide a thematic synthesis of the subthemes found in the different TDF domains.

Table 2 Frequencies of Studies and Type of Evidence Identified on Each TDF Domain

TDF Domain	No of Identified Studies	No (%) of Qualitative or Mixed-methods Studies	No (%) of Quantitative Studies Providing only Descriptive Evidence	No (%) of quantitative Studies Testing for Associations within TDF Domain	No of Quantitative Studies Finding ≥1 Significant Association (% of those Testing for Associations)
Beliefs about consequences	63	18 (29%)	19 (30%)	26 (41%)	20 (77%)
Reinforcement	46	14 (30%)	18 (40%)	14 (30%)	8 (57%)
Environmental context and resources	45	11 (24%)	23 (52%)	11 (24%)	8 (73%)
Social influences	44	19 (43%)	15 (34%)	10 (23%)	7 (70%)
Emotions	43	16 (37%)	10 (23%)	17 (40%)	11 (65%)
Knowledge	43	17 (40%)	12 (28%)	14 (32%)	10 (71%)
Memory, attention, and decision processes	36	15 (42%)	16 (44%)	5 (14%)	2 (40%)
Behavioral regulation	29	18 (62%)	4 (14%)	7 (24%)	4 (57%)
Goals	25	9 (36%)	13 (52%)	3 (12%)	3 (100%)
Social professional role and identity	23	11 (48%)	8 (35%)	4 (17%)	3 (75%)
Intention	21	9 (43%)	9 (43%)	3 (14%)	3 (100%)
Beliefs about capabilities	14	6 (43%)	3 (21%)	5 (36%)	4 (80%)
Skills	5	1 (20%)	4 (80%)	0 (0%)	0 (0%)
Optimism	4	3 (75%)	0 (0%)	1 (25%)	1 (100%)

Abbreviation: TDF, Theoretical Domains Framework.

Table 3 Frequencies of Subthemes Cited in Over 10% of Studies and Their Evidence Type Categorized by TDF

TDF Domain	Subtheme	No of Identified Studies	No (%) of Qualitative or Mixed Method Studies	No (%) of Quantitative Studies Providing only Descriptive Evidence	No (%) of Quantitative Studies Testing Associations	No of Quantitative Studies Finding ≥1 Significant Association (% of those Testing for Associations)
Beliefs about consequences	Believing statins are safe/ detrimental	62	18 (29%)	20 (32%)	24 (39%)	14 (58%)
	Believing statins have benefits	33	13 (39%)	10 (30%)	10 (30%)	8 (80%)
	Perceived need for treatment	27	9 (33%)	11 (41%)	7 (26%)	5 (71%)
	Believing there are alternative options	23	11 (48%)	8 (35%)	4 (17%)	2 (50%)
	Perceived threat of disease	16	7 (44%)	3 (18%)	6 (38%)	5 (83%)
Reinforcement	Experiencing statins' side effects	46	14 (30%)	18 (40%)	14 (30%)	8 (57%)
Emotions	Being afraid or uncertain	38	14 (37%)	9 (24%)	15 (39%)	9 (60%)
	Feeling overwhelmed or frustrated	7	7 (100%)	0 (0%)	0 (0%)	0
Knowledge	Knowledge about statin therapy	36	16 (44%)	12 (33%)	8 (22%)	5 (63%)
	Knowledge about disease	21	12 (57%)	2 (10%)	7 (33%)	6 (86%)
	Knowledge about treatment options	17	11 (65%)	6 (35%)	0 (0%)	0
Social Influences	Patient-provider communication and trust	35	18 (51%)	10 (29%)	7 (20%)	5 (71%)
	Media coverage	18	8 (44%)	7 (39%)	3 (17%)	2 (67%)
	Experiences and advice from others	18	10 (56%)	7 (38%)	1 (6%)	1 (100%)

(*Continued*)

Table 3 (Continued).

TDF Domain	Subtheme	No of Identified Studies	No (%) of Qualitative or Mixed Method Studies	No (%) of Quantitative Studies Providing only Descriptive Evidence	No (%) of Quantitative Studies Testing Associations	No of Quantitative Studies Finding ≥1 Significant Association (% of those Testing for Associations)
Environmental context and resources	Financial constraints	30	7 (23%)	16 (53%)	7 (23%)	4 (57%)
	Regimen complexity and convenience	19	6 (32%)	8 (42%)	5 (26%)	3 (60%)
	Problems related to drug access	15	3 (20%)	10 (67%)	2 (13%)	1 (50%)
Social professional role and identity	Skepticism towards pharmaceuticals	21	9 (43%)	9 (43%)	3 (14%)	2 (67%)
Intention	Intention to take statins as prescribed	21	9 (43%)	9 (43%)	3 (14%)	3 (100%)
Memory, attention and decision processes	Seeking information to help decision-making	17	11 (65%)	2 (12%)	4 (23%)	2 (50%)
	Forgetfulness	15	4 (27%)	11 (73%)	0 (0%)	0
	Absence of physical signals	12	7 (58%)	4 (33%)	1 (9%)	0 (0%)
	Cognitive strain of treatment	10	2 (20%)	8 (80%)	0 (0%)	0
Behavioral Regulation	Strategies to manage side effects	19	15 (79%)	3 (16%)	3 (16%)	2 (67%)
	Receiving follow up and monitoring	19	12 (63%)	2 (11%)	5 (26%)	3 (60%)
	Techniques and plans to enable intake	9	6 (67%)	1 (11%)	2 (22%)	1 (50%)
Goals	Statins' importance or priority	17	8 (47%)	7 (41%)	2 (12%)	2 (100%)
	Achievement of cholesterol targets	10	2 (22%)	6 (60%)	2 (22%)	1 (50%)

(*Continued*)

Table 3 (Continued).

TDF Domain	Subtheme	No of Identified Studies	No (%) of Qualitative or Mixed Method Studies	No (%) of Quantitative Studies Providing only Descriptive Evidence	No (%) of Quantitative Studies Testing Associations	No of Quantitative Studies Finding ≥1 Significant Association (% of those Testing for Associations)
Beliefs about capabilities	Perceived control over health	9	6 (67%)	1 (11%)	2 (22%)	2 (100%)
	Perceived capability to take statins	7	2 (29%)	1 (14%)	4 (57%)	3 (75%)

Abbreviation: TDF, Theoretical Domains Framework.

Beliefs About Consequences

Within this domain, "threat of disease" had the highest proportion of significant associations, identified in five studies (83%). A higher perceived CVD risk or worse illness perceptions were significant predictors of statin adherence. Risk perceptions were commonly discussed among participants with family or personal histories of CVD.[34,41] Conversely, a low perceived risk of heart attack and good health perceptions were significantly related to low adherence.[42,43]

"Believing statins have benefits" had a significant relationship with adherence in most (n=8, 80%) studies that tested for associations. In one study, patients who strongly believed taking statins reduced their risk of having heart attacks or strokes were more than twice as likely to report high adherence.[44] In another study, current statin users were significantly more likely to agree that statins were effective than those who discontinued their use.[45] In turn, nonadherent patients were more likely to be of the view that statins provided limited benefit or perceived them as futile than adherent patients.[46,47] Some patients identified that this was because they did not physically feel any difference before and after taking statins.[48,49]

"Perceived personal need for statins" was significantly associated with adherence in 71% (n=5) of studies. Most quantitative studies found that a low perceived need was significantly related to poor adherence. In qualitative findings, participants were unsure of their perceived need if they were implementing lifestyle changes or had borderline high cholesterol levels.[50] Furthermore, adherent patients were more likely to report a high perceived need for statins than nonadherent patients.[51–53] Participants frequently presented themselves as needing statins because healthcare professionals (HCPs) had highlighted this necessity.[41]

"Believing statins are safe/detrimental" was the subtheme most frequently tested for significant impact on adherence, but only over half (n=14, 58%) of the studies identified a significant link with statin adherence. Participants mentioned that statins caused negative health consequences and were even described as a critical threat.[54] On the contrary, believing statins were safe facilitated adherence. In one study, 70.4% of current users agreed statins were safe vs 37.4% who stopped treatment.[45]

"Believing there are alternative options to reduce cholesterol" was tested in a minority of studies, but it was often discussed qualitatively. A preference for lifestyle changes such as diet or exercise over statins was often reported.[34,50,55] Still, no statistically significant links were found between the perceived effectiveness of these changes and adherence.[42,44] The use of supplements, homoeopathy, and natural remedies such as garlic, ginger, cinnamon, and red yeast rice was also described.[36,56] Qualitative studies reported that trusting these alternative options influenced some patients to stop or avoid starting statin treatment.[36,57]

Knowledge

"Knowledge about the disease" had the highest proportion of significant associations with adherence among all subthemes, found in 86% (n=7) of studies. While awareness of hyperlipidaemia and its risks[58] was associated with

better statin adherence,[59] confusion about cholesterol[60] or the connection between hyperlipidaemia and CVD was associated with lower adherence.[45] In some studies, patients generally had good knowledge about their disease antecedents and implications.[50,61] However, cholesterol misconceptions (eg, that high cholesterol could be cured, was innocuous or was unrelated to CVD) were also identified.[35,57,62]

Patients generally had good knowledge about statins' purpose and importance.[46,49] However, being poorly informed about treatment significantly influenced nonadherence[63] - over half (63%, n=5) of studies found significant associations between "knowledge of statin therapy" and adherence. Common knowledge gaps included being unaware of statins' mechanism of action,[62] treatment duration, appropriate use,[47,57] benefits and side effects.[64] For instance, some patients believed that statins were addictive,[36] curative[42] or lowered blood pressure.[56]

While patients were aware of treatment options (eg, lifestyle changes, complementary products), their understanding was not always accurate. Often, patients overestimated the effectiveness of these alternatives, believing they could cure high cholesterol or were superior to statin therapy for cholesterol reduction.[41,56] There was also a need for better information, as in some studies, participants expressed a desire for more details about these options.[50] "Knowledge about treatment options" was mostly supported by qualitative evidence.

Environmental Context & Resources

Issues related to medication expenses, or the lack/cost of insurance were barriers to adherence, particularly in the US, where three studies reported significant associations between "financial constraints" and adherence.[43,59,65] In India,[56] China,[66] and Brazil,[64] 13% to 38% of patients stopped taking statins for financial reasons. Some studies highlighted the impact of financial constraints on patients with multiple medications, who struggled to afford their total expenses.[49,67]

Problems with "regimen characteristics and inconvenience", including unwanted statin type,[68] packaging problems,[69] and treatment complexity,[43] were barriers to adherence. Sixty per cent of the five studies testing this found a significant negative relationship between this subtheme and statin adherence. While inconvenient intake times did not affect most patients,[47,70] a few participants reported struggling to take multiple medications at separate times and missing doses due to conflicts between medication schedules.[59,71] In one study, convenience score was significantly and positively associated with statin adherence.[69]

"Medication access issues", such as difficulties obtaining prescription renewals, travelling to the pharmacy, and medication deliveries,[64,71] were barriers that varied across countries. In the Netherlands, poor access to statins was not related to adherence[70] and discontinuation rates due to pharmacies not dispensing statins were as low as 0.5% in Turkey.[72] However, in the US, 33% of patients discontinued statin use due to running out of medication.[42]

"Inefficient healthcare system" was another barrier, qualitatively described in five studies. Participants referred to long appointment waiting times,[57,64] complications in performing blood tests,[64] time pressures during consultations[57,73] and discoordination between stakeholders (eg, pharmacies, health centers).[71] These experiences hindered adherence by limiting patients' ability to monitor cholesterol levels, discuss treatment concerns with HCPs, and access medication.

Social Influences

"Patient-provider communication/trust" significantly influenced adherence in 71% (n=5) of studies. While poor treatment explanation significantly increased the risk of nonadherence,[74] satisfaction with treatment explanations increased statin need and decreased concerns about adverse effects, which positively impacted adherence.[51] Open discussions on risks, benefits, and side effect management (eg, dosage adjustments) facilitated adherence.[73] Communication breakdowns and conflicts occurred when patients disagreed with treatment plans or felt their side effects were ignored. Trust in HCPs played a key role, with some patients distrusting HCPs due to perceived financial motives or overprescribing,[34,57] while others trusted their HCPs' knowledge and skills.[35]

"Media coverage" both deterred and helped adherence. Two studies (67%) found a significant association between this subtheme and statin adherence. Statins' negative portrayal in newspapers and television often focused on side effects and affected patients' decisions to adhere.[34,75] Negative media coverage was the main reason (87.5%) for statin discontinuation[40] in a study conducted in Turkey. Patients from a study in Malaysia also mentioned trusting social

media influencers promoting alternative medicine and advising against statins.[35,50] However, in one study, exposure to positive media coverage significantly increased the likelihood of continued statin use.[18]

"Experiences and advice from others" significantly influenced statin adherence in the only study testing for associations. Most evidence for this subtheme was descriptive or qualitative. Hearing others' side effects increased anxieties,[73] and in some studies, between 4% and 5% reported discontinuing statins because of receiving friends' or relatives' advice.[38,45] Social comparisons also played a role, with some feeling "healthier" than others and thus less at risk.[41] Observing healthy individuals avoiding statins deterred some patients while seeing CVD outcomes in others prompted medication use.[71]

"Family support" was both practical[33,71] (eg, administering medication or providing transport to pharmacies) and emotional (eg, reminding intake, advocating for patients experiencing side effects).[34] The presence of family support was an enabler,[33] and its absence or difficulties in their role (eg not obtaining a change in treatments) was a barrier.[34,71] Social support was positively associated with adherence in the only study testing associations.[43]

Emotions

"Fear and uncertainty" were barriers for many participants who were concerned about statins' negative effects. These emotions were fueled by information sources that highlighted the side effects of statins, including media reports, internet discussions, medication leaflets, and conversations with other patients.[49,50] For others, fearing CVD events was an incentive to take their medications.[64] This subtheme was significantly related to adherence in nine (60%) studies testing for associations.

The feeling of "being overwhelmed and frustrated" primarily appeared when failing to eliminate side effects,[73] experiencing CVD despite "good health behavior" or feeling disbelieved by HCPs.[41,54,64] Other negative emotions related to taking medicines also emerged. Some participants described feeling helpless due to a perceived lack of control over their disease,[36] embarrassed by taking pills,[41] and guilty when not adhering.[57]

"Satisfaction with treatment" was positively associated with adherence in three (75%) testing studies. Those expressing satisfaction often highlighted statins' benefits, such as effectiveness and convenience.[69]

Reinforcement

"Experiencing side effects" was one of the most frequent influences explored, but only 57% of the 12 testing studies reported significant findings. Side effects included muscle/joint pain, digestive issues, headaches, fatigue, and memory problems, sometimes impacting daily activities and quality of life.[34,75] The proportion of participants citing side effects as a reason for discontinuation varied greatly across studies, from 2.1%[72] to 67%.[76] Interestingly, a qualitative study found that even when some patients proposed side effects as a reason for nonadherence, they also acknowledged using these as reasons to merely justify their behavior.[57] The study indicated that other influences, such as internal conflicts between participants' preferred solutions and recommended treatment, played a more critical role.[57]

Other Identified TDF Domains

Table 2 presents subthemes identified in seven or more studies from other TDF domains. Within "Memory, Attention and Decision Processes", "seeking information to aid decision-making" (n=17) was significantly associated with adherence in two studies (50%).[60,74] Participants often consulted online sources that emphasised statin risks over benefits, raising doubts and leading to seek alternative treatments. "Forgetfulness" (n=15) was the most frequent reason for inadequate implementation across studies, though not statistically tested.[37,59,68] Qualitative evidence linked forgetfulness to managing multiple comorbidities and the "absence of physical signals" of cholesterol (n=12),[49] which was reported to diminish attributed statins' priority.[50] The "cognitive strain of treatment" (n=10) was also a barrier mentioned by patients on multiple medications.[49]

"Behavioral Regulation" subthemes such as "receiving follow-up/monitoring" (n=19) and "strategies to manage side effects" (n=19) were significantly linked to better adherence.[77,78] These strategies fostered treatment buy-in and a sense of being heard by HCPs.[49] "Techniques and plans to enable statin intake" (n=8), such as setting routines or placing tablets in specific locations, were described as helpful in addressing forgetfulness.[34,71]

Within "Goals", "statins" importance and priority' (n=17) positively impacted adherence in two studies.[68,79] Still, some patients described that statins could lose priority in favour of more pressing competing health and personal demands.[57,80] "Achieving cholesterol targets" (n=10) was significantly associated with increased adherence in one study,[81] but it could backfire if patients thought the treatment was no longer necessary.[7,46]

In "Social/Professional Role and Identity", "skepticism towards pharmaceuticals" (n=21) was significantly associated with worse adherence in two studies (67%).[52,61] Many patients described having a general aversion to medications fuelled by distrust of the healthcare system and pharmaceutical companies, along with cultural and religious beliefs.[61] "Intention to take statins as prescribed" (n=21) showed a significant positive association in all studies testing associations,[46,65,79] with many patients willing to restart treatment.[76] Within "Beliefs about Capabilities", the presence of "perceived control over health" (n=9) promoted autonomy but hindered adherence, while its absence increased reliance on HCPs and adherence.[33,57]

A limited number of studies addressed skills (n=5) (eg, difficulties with cutting[50] or swallowing tablets[67]), and Optimism (n=4) (a positive outlook, and confidence of staying healthy without statins[41]).

Comparison Between Groups of Patients

Patients on primary and secondary prevention for CVD had different perspectives across "Beliefs about Consequences", "Knowledge", "Social/Professional Role and Identity", and "Social Influence". Primary prevention patients frequently discussed relying on non-prescription products and lifestyle changes over statins[82,83] and expressed a weaker perceived threat from their disease.[83] They reported fewer perceived benefits from statins and held more negative beliefs about medications,[61,82] often distrusting HCPs.[60]

Patients with diabetes faced distinct influences on statin adherence, particularly within "Beliefs about Consequences", "Knowledge", and "Emotions". Nonadherent patients in this group struggled with low perceived necessity and benefits of treatment, limited knowledge about statins, and fears regarding statins' impact on glucose levels.[48,80]

Patients with multimorbidity encountered specific barriers in "Environmental Context and Resources", "Memory, Attention and Decision Processes", and "Goals". They perceived their medication regimens as complex and were burdened by costs, coordination of multiple medications, and forgetfulness.[59,71] They sometimes discontinued statins due to interactions and viewed cholesterol as less critical than other health issues (eg, cancer, liver disease).[57,71]

Discussion

This systematic review of 70 studies from 20 countries identified 46 subthemes within 14 TDF domains, highlighting statin adherence's complexity and multifaceted nature. While "Beliefs about Consequences", "Knowledge", "Environmental Context & Resources", and "Social Influences" showed strong evidence, "Reinforcement" and "Emotions" were frequently tested but had less evidence of associations. Fewer tested domains included "Memory, Attention & Decision Processes", "Behavioral Regulation", and "Social/Professional Role & Identity".

Many studies quantitatively tested the influence of perceived or experienced side effects. However, only a moderate link between these and statin adherence was found. Conversely, influences such as experiences/advice from others or family support, were primarily identified through qualitative research, with limited quantitative data available. Other influences, such as forgetfulness, cognitive strain of regimen or techniques/plans to enable statin intake, lacked quantitative testing of associations and potentially in-depth qualitative exploration. Notably, 14 of 19 qualitative and mixed method studies lacked theoretical frameworks to inform their research design, thus risking omitting influences that can be important in adherence.

Study findings are consistent with earlier CVD medication adherence reviews using the TDF. Crayton et al[16] identified that "Beliefs about Consequences", "Knowledge", and "Emotions" were the strongest TDF domains influencing adherence in stroke survivors. This study supports some of these findings, with certain subthemes within these domains showing over 80% significant relationships with adherence. However, "Emotions" seem less influential in this review than Crayton et al,[16] which identified 75% of studies linked with adherence. Crayton et al's[16] reduced sample size (only four samples investigating the impact of Emotions on adherence) may explain this disparity. Easthall et al's[17] review on CVD prevention also identified similar barriers to ours. However, they omitted "Social/Professional Role and

Identity" and "Behavioral Regulation" domains. Their focus solely on identifying barriers likely explains the exclusion of "Behavioral Regulation", which we primarily identified as containing enablers. Similarly, their mapping of pill-taking identity under "Social Influences" instead of "Social/Professional Role and Identity" contributes to the omission of the latter domain.

Previous reviews specifically exploring statin adherence have been conducted, but none have utilized the TDF. Among these, two[19,20] identified some modifiable influences, including lack of communication with HCPs, concerns about side effects, preference for lifestyle changes, low perceived benefit and need, and costs. However, they overlooked critical influences identified in this study, such as "Social Influences" (eg, family support, media coverage), "Emotions" (eg, feeling frustrated or overwhelmed), and "Social/Professional Role and Identity" (eg, skepticism toward pharmaceuticals). By employing the TDF, this review offers a more comprehensive and nuanced understanding of the different modifiable influences of statin adherence that previous research has not achieved.

Strengths and Limitations

This review is the first to use the TDF to integrate quantitative and qualitative evidence on modifiable influences of statin adherence, providing a rich understanding. While some findings align with the NCF,[14] our study identified influences related to the social and physical environment, which the NCF overlooks. The PaPA[13] addresses this by integrating practicalities (eg, resources and capabilities) but categorizes non-adherence as intentional or unintentional. Our findings challenge this distinction, as factors like forgetfulness can stem from intentional influences, such as prioritizing other health demands. This suggests that intention to adhere is dynamic and changes within individuals over time. We also employed a deductive-inductive analysis, generating granular subthemes that can inform the development of future intervention content. While other studies have focused only on the most influential domains,[16] we explored the broad range of modifiable influences to ensure the coverage of all potential barriers and facilitators, reducing the chance of omitting influences relevant to less studied populations (which may have greater rates of low adherence).

We recognise that many of the included quantitative studies relied on one type of measure, small and nonrepresentative samples, and limited control of confounding factors, which limits the validity and generalizability of results. Furthermore, high heterogeneity between studies precluded a meta-analysis to determine the strength of associations between modifiable influences and adherence. Previous reviews have faced similar problems.[84] Focusing solely on patient perspectives also introduces potential bias. Incorporating other key informants, such as HCPs, could have enhanced the validity of the present findings. Additionally, some qualitative studies lacked detail, making it difficult to isolate statin-specific influences from broader cardiovascular medication influences. We may have missed relevant findings by only extracting data that explicitly mentioned statins.

Applying the TDF presented challenges due to overlapping domains, necessitating careful and nuanced coding decisions. While we adhered to TDF principles by assigning text excerpts to the domain with the best fit,[85] this occasionally resulted in a related concept appearing across multiple domains, as exemplified by the multiple dimensions of statin side effects (eg, beliefs, physical experiences, and associated fears). However, we are confident in this approach due to the need for distinct intervention strategies targeting different influences, which is supported using the TDF with other frameworks.[15,86]

Recommendations for Practice

This study highlights that improving support and communication with patients about statins is a crucial component of future interventions.

First, it is essential to emphasize the necessity of statins and address patient concerns. Limited awareness of cholesterol's risks and a low perceived threat of CVD were identified as barriers to adherence, while understanding the benefits of statins facilitated it. Providing clear and accessible information about statin effectiveness and the dangers of untreated cholesterol can help patients better appreciate the importance of treatment. Analogies, such as comparing statins to unclogging pipes, may make the consequences of statin use—or non-use—more tangible. Additionally, informing patients about statin safety, potential side effects, and appropriate steps to take if side effects occur can

alleviate uncertainty. By framing mild side effects in comparison to the more severe risks of untreated CVD, patients may be more likely to continue treatment.

Second, building trust and fostering collaboration with HCPs is critical. Poor interactions and distrust of HCPs were key barriers, while HCPs' encouragement of statin use, support and shared decision-making promoted adherence. To improve adherence, communication should focus on engaging patients in discussions about their concerns, actively listening, and tailoring statin recommendations to their needs, preferences, and lifestyles. Discussing complementary approaches, such as diet and exercise, can further support adherence. HCPs should communicate openly and empathetically, adjusting treatments based on patient feedback to build trust and mitigate side effects.

Lastly, reducing treatment burden is vital. Many patients felt overwhelmed by complex medication regimens, forgetfulness, and competing priorities. Clear communication about practical solutions can help alleviate these barriers. For example, informing patients about automatic refills and coordinating refill dates can simplify medication management. Providing guidance on medication interactions, supporting habit formation, addressing routine disruptions, and encouraging family support were identified as effective strategies. Effectively communicating these solutions in future interventions will empower patients to feel more confident in managing their treatment and adhering to statins.

Recommendations for Research

Prioritizing understudied groups is vital. This review identified a critical lack of research on ethnic minorities and socioeconomically disadvantaged populations – groups most vulnerable to non-adherence and poorer cardiovascular outcomes.[20,87] Quantitative studies should aim for representative samples that accurately reflect population diversity, while qualitative research should explore the lived experiences and specific barriers these groups face. By understanding the modifiable influences affecting different patient groups, targeted interventions focused on improving support for and communication with patients about statins can be developed to address the unique needs of each group. Future research on statin adherence needs a broader approach to strengthen the evidence base. This includes utilizing theoretical frameworks to explore all potential influences on statin adherence. Quantitative and qualitative research methodologies should both prioritize increasing the validity of their findings. Quantitative studies can achieve this by combining prescription refill data with self-reported data to mitigate the limitations of each measure. Qualitative research can be enhanced by clearly reporting methods and steps taken to ensure validity and reliability alongside relevant participant quotes to substantiate interpretations.

Conclusion

Our study identified several prominent barriers to adherence, including knowledge gaps, perceived low threat of disease and poor communication and trust with HCPs. This highlights the need for multifaceted interventions across multiple TDF domains to enhance support with statin treatment, tailored at the individual level and specific patient groups (eg, primary vs secondary prevention, presence of diabetes/polypharmacy). Future research should further explore the unique challenges faced by high-risk patient groups. Addressing these gaps is crucial for developing effective interventions that ultimately improve cardiovascular health outcomes for all.

Abbreviations

TDF, Theoretical Domains Framework; PaPA, Perceptions and Practicalities Approach; NCF, Necessity-Concerns Framework; BCTs, Behavior Change Techniques; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MMAT, Mixed Methods Appraisal Tool; MMAS-8, Morisky Medication Adherence Scale (8-item); PDC, Proportion of Days Covered.

Data Sharing Statement

The data used in this systematic review are derived from previously published studies and are, therefore, de-identified. As this is a systematic review, no new primary data were collected. The data underlying the presented analyses are publicly available from the original published sources.

Acknowledgments

The authors thank Rachel Perowne and Jasmin Begum for helping during title and abstract screening and full-text review.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This research was funded by the National Institute for Health and Care Research (NIHR) Research for Patient Benefit (RfPB) Programme (Ref. NIHR205407) and infrastructure support for this study was provided by the NIHR North-West London Patient Safety Research Collaboration (NIHR NWL PSRC, Ref. NIHR204292); The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. Additionally, this work was supported by the Economic and Social Research Council (ESRC) through the London Interdisciplinary Social Science Doctoral Training Partnership (LISS DTP). The first author's role on this work is also funded by the National Agency for Research and Development (ANID) / Scholarship Program / DOCTORADO BECAS CHILE/2022 - 72220048. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Disclosure

The authors report no conflicts of interest in this work.

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