



OPEN Prevalence and associated factors of non-adherence to antihyperlipidemic medication: a nationwide cross sectional survey in Pakistan

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Hyperlipidemia significantly contributes to the risk of developing cardiovascular diseases. However, about half of the patients do not adhere to their antihyperlipidemic medications, leading to healthcare costs and premature mortality. This study's objective was to determine the prevalence and associated factors of non-adherence to antihyperlipidemic medications. The study covered hypertensive patients (21,451) aged 21–75 years, presenting to the primary and secondary healthcare facilities across Pakistan (covering 21 divisions) from January 2022 to April 2023. The outcome intended was non-adherence to antihyperlipidemic medication, which was assessed by SEAMS and pill-counting methods (non-adherence < 80%). The study found overall non-adherence to antihyperlipidemic medication of 60.6% across Pakistan, with the highest non-adherence rates found in Azad Jammu and Kashmir (71.9%) and the lowest in Islamabad (47.7%). Multivariable logistic regression analysis revealed that female, no health card (Sehat Sahulat Program government insurance), < 5 years of illness, < 5 daily medications, and dose frequency of twice daily revealed a positively significant association with non-adherence. While monthly income 51,000–100,000, graduation level of education, Muhajir, and hyperlipidemia with one comorbid condition had a significant negative association with the non-adherence. Antihyperlipidemic non-adherence is a multifaceted, multifactorial, profound problem requiring a multipronged approach.

Keywords Non-adherence, Antihyperlipidemic medications, Compliance, Lipid lowering drugs

Abbreviations

AJ&K	Azad Jammu and Kashmir
AOR	Adjusted odds ratio
BHU	Basic health unit
CI	Confidence interval
CVD	Cardiovascular diseases
DHQ	District head quarter
FATA	Federally administered tribal areas
GLM	Generalized linear model

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GIS	Geographic information system
KP	Khyber Pakhtunkhwa
LDL	Low-density lipoprotein
MOs	Medical officers
OPD	Outpatient department
RHC	Rural healthcare center
SEAMS	Self-efficacy for appropriate medication scale
THQ	Tehsil head quarter
WHO	World Health Organization

The most prevalent kind of dyslipidemia is hyperlipidemia, a crucial risk factor for cardiovascular diseases (CVDs) and the leading cause of morbidity and mortality worldwide¹. Hyperlipidemia accounts for one-third of all ischemic heart disorders worldwide, and the mortality rate is 2.6 million/year². As a result, controlling hyperlipidemia is paramount for lowering cardiovascular disease risks. Lipid-lowering drugs like statins are frequently prescribed to reduce the risk of micro- and macro-cardiovascular problems linked to hyperlipidemia^{3–5}.

Statins are the unambiguous first choice for treating hyperlipidemia⁶ and have been used widely as a medication to treat hyperlipidemia, specifically lowering low-density lipoprotein (LDL)^{7,8}. The pharmacoeconomic studies have demonstrated that statins are the most cost-effective therapy for treating CVDs^{9,10} and reducing CVDs-related mortality^{11,12}. Statins are a medication class that lowers cholesterol levels by blocking the HMG-CoA reductase enzyme. Statins are widely advised for the primary and secondary prevention of cardiovascular diseases¹³. Statins have been incorporated into WHO clinical practice guidelines for CVD prevention and control¹⁴ and have become the first-line therapy for reducing the risk of CVD mortality and morbidity¹³.

Medication adherence is the act or extent of conforming to a provider's recommendation/prescription based on timing, dosage, and frequency of medication use¹. "A ratio of the number of drug doses taken to the number of doses prescribed over a given time period"¹⁵ is another definition. Medication non-adherence can be divided into two categories: primary and secondary non-adherence. Primary non-adherence is when the medication is not adhered to the first time it was prescribed. Prescription refills among patients who have previously finished their initial prescriptions are measured by secondary non-adherence¹⁶.

Good adherence is based on various factors such as the patient's socioeconomic and demographic factors, physician's and health system factors (cost and accessibility), and managing the drug side effects^{17,18}. Patient behavior, such as ignoring medical advice, skipping doses, missing appointments, etc., may diverge from the guidelines established during therapy. Whether on purpose or accidentally, this could result in non-adherence. Therefore, non-adherence is the patient's refusal or resistance to adequately following any medical regimen or therapy^{19,20}. Poor medication adherence refers to the amount of prescribed medication a patient takes and the time between starting and stopping a drug¹⁶.

Statin adherence in clinical practice remained below ideal even though the favorable effects of statin therapy have been documented over the previous 30 years^{21,22}. Research shows that about half of CVD patients do not adhere to their healthcare provider's prescriptions, leading to reduced treatment efficacy²³. It was found that 40–75% of patients stopped taking their statin therapy within the first year of starting it^{24,25}. The effectiveness of statin medication was constrained by poor adherence²⁶. Medication is not desirably effective for non-adherent patients²⁷. It has been established that early termination of therapy shortly after treatment initiation contributes to non-adherence²⁵. According to several studies, non-adherence to statin therapy was linked to an increased risk of cardiovascular and cerebrovascular morbidity, events, and mortality, considerably raising medical expenses^{21,22,28,29}.

Positive health outcomes are primarily dependent on medication compliance. However, statin users' adherence patterns in Pakistan have not been thoroughly examined. Little information is available on the potential link between statin non-adherence among adult Pakistani patients. To attain therapeutic goals, it is necessary to understand the obstacles to drug adherence³⁰.

Evidence is scarce regarding the non-adherence to antihyperlipidemic medication in the local context of Pakistan. With a nationally representative sample, the current study tried to fill this knowledge gap. The study aimed to find out the prevalence of non-adherence to antihyperlipidemic medication and the potential factors associated with this non-adherence in Pakistan.

Methods

Study design, settings, and participants

A cross-sectional study was carried out in Pakistan from January 2022 to April 2023. The study was a population-based national survey that included hyperlipidemic patients across Pakistan. This was a multi-hospital (multiple healthcare facilities were involved $n = 205$) study conducted in the public sector primary (Basic Health Unit (BHU)/Rural Healthcare Center (RHC)) and secondary (Tehsil Head Quarter (THQ)/District Head Quarter (DHQ) level health care facilities of all the provinces of Pakistan, namely; Punjab, Sindh, Baluchistan, and Khyber Pakhtunkhwa (KP) along with Pakistan's autonomous region Azad Jammu and Kashmir (AJ&K) and the federal capital Islamabad. All these regions will be called as provinces hereafter. Further sub-divisions of these provinces are termed divisions in Pakistan (further smaller sub-divisions are called districts, tehsils, and union councils). Our study included healthcare facilities at the divisional level in Pakistan. Included divisions were Lahore, Multan, Rawalpindi, Islamabad, Sahiwal, Sargodha, Gujranwala, Faisalabad, Dera Ghazi Khan (Punjab province), Karachi, Hyderabad, Larkana, Sukkar, and Mir pur Khas (Sindh province), Quetta (Baluchistan province), Peshawar, Bannu, Kohat and Dera Ismail Khan (KP province), AJ&K province and Islamabad (Fig. 1)³¹. Sahiwal is not shown separately; it is merged with Multan on the map; otherwise, it is a separate division. The

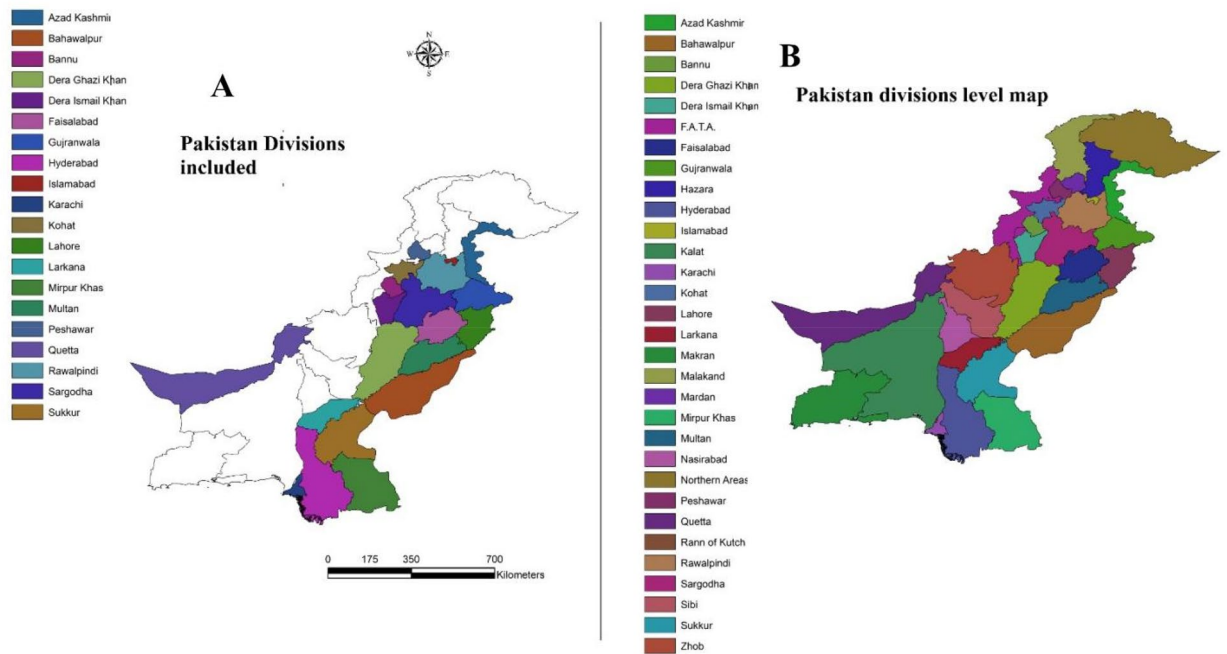


Fig. 1. Sampled health facilities from the divisions across Pakistan. (Figure constructed through Geoda subversion 1.16.0 (<https://geodacenter.github.io/download.html>)³²).

Geographic Information System (GIS) basic map with Sahiwal as a separate division was inaccessible. Some divisions of Baluchistan and Federally Administered Tribal Areas (FATA) were not included due to the law and order/security situation there. See Fig. 1 below for the overall representations of the hospitals from the country. As evident, the sampled hospitals are from the entire country, which is a good representation of Pakistan.

Sampling procedure

The sampling procedure for the current study covered the entire country, where accessibility was not an issue. For this purpose, a multi-stage sampling technique was applied. In the first stage, all those accessible divisions were selected for the study. Within those divisions, the list of the hospitals was retrieved (see supplementary file for hospital links). The hospitals in each of the divisions were then stratified as primary-level healthcare facilities and secondary-level healthcare facilities. Random selection was made from these in each of the tiered healthcare facilities. During the last stage of sampling, consecutive patients in the daily outpatient department of the hospital fulfilling the inclusion criteria were selected and referred by the medical officer to the study team for a detailed interview.

Inclusion and exclusion criteria

Eligible participants were those already diagnosed with hyperlipidemia, taking lipid-lowering treatment/statins for at least six months for the primary or secondary prevention of CVD, in the age group 21–75 years, who can communicate in the Urdu language in any primary or secondary care setting. Participants aged less than 21 years or more than 75 years, self-reported pregnant females, participants with any mental disorder such as psychosis or dementia, history of cancer, and those who do not communicate in Urdu were excluded from the study.

Study outcome

The outcome of the current study was non-adherence to antihyperlipidemic medication in Pakistan. Non-adherence was measured using the Self-Efficacy for Appropriate Medication Scale (SEAMS) and pill count as self-reported measures. Self-reported pill count was the primary outcome, and SEAMS supported the outcome variable in the current study. Measuring medicine adherence involved two approaches: SEAMS score and pill counts, which enhanced the credibility of the assessment technique and produced more accurate results. A body of prior research on the topic has supported these methods^{33,34}.

SEAMS is the most popular and valid tool used in health sciences to measure adherence/non-adherence. It is a proven cost and time-effective measure. The SEAMS is a 13-item medication adherence measure scale. The SEAMS uses a three-point response scale, with 1 representing a lack of confidence, 2 a moderate level of confidence, and 3 a high level of confidence. The Likert scale was used to evaluate the questionnaire. As a result, there were 13 questions and 3 viable options for each. The minimum score was 13, while the maximum was 39. Higher scores were linked to greater medication adherence and vice versa. In previous literature, no cut-off points were used for SEAMS scores^{33,35,36}. The SEAMS tool was translated using the traditional “forward–backward” method from English into Urdu (SEAMS-U) in Pakistan. The translated version was validated using a practical sample of 1011 hyperlipidemic patients receiving treatment at a tertiary care hospital in Lahore, Pakistan. The

internal consistency of the translated SEAMS-U was good (Cronbach's alpha = 0.897). Cronbach's alpha (Part 1) was 0.838, and (Part 2) was 0.789 by split-half reliability. The test-retest reliability was (Spearman's $P = 0.686$, $P < 0.001$), and the intraclass correlation coefficient (ICC) score was 0.814. All ethical concerns pertaining to validity, dependability, and forward-backward translation were suitably and meticulously handled. The SEAMS Urdu-version is in the publication process.

The primary outcome of non-adherence to antihyperlipidemic medication in the current study was based on self-reported pill counting. In this method, participants were asked how many pills they had been prescribed for a specific period of time and how many pills they had actually taken. Based on this information, the non-adherence rates were computed using the pills consumed over a certain period divided by the pills prescribed for that period²⁷. Based on the calculations, those with an adherence percentage of less than 80% were declared non-adherent, while those equal to or above 80% were classified as adherent. This cut-off is reported in the literature as well^{27,33,37}, and this approach has a better accuracy³⁸.

Additionally, sociodemographic variables were added to obtain information regarding age (in years), gender, ethnicity, education, income, and occupation; health-related factors were concomitant disease, duration of illness, number of daily medications, comorbidities and dose (mg), and per-day frequency of medication. Number of prescribed medicines, time of intake as either morning, afternoon, or evening, any side-effect, number of pills prescribed for the last fifteen days, number of pills taken, and any missed dose in the last fifteen days.

Data collection and statistical analysis

Data collection was preceded by administrative approvals from the concerned health facility in-charge. Data was collected after informed consent from the patients. Patients were consecutively approached from the outpatient department of the participating hospitals. For this purpose, the concerned doctors in the hospitals referred the patients to the study team after evaluating the inclusion and exclusion criteria. The interview was then conducted with the concerned patients in a separate room.

Data was entered in Microsoft Excel and later analyzed in Statistical Package for Social Sciences (SPSS) version 26 and R studio. Study variables were first evaluated using descriptive statistics. Continuous data is reported as mean (\pm standard deviation) and categorical variables as numbers (percentages). The generalized linear model (GLM) using multivariable binary regression analysis was employed to evaluate the effect of various sociodemographic and health-related factors on non-adherence to antihyperlipidemic medication. Multivariable binary regression analysis was applied to observe the predictors of non-adherence. The enter method was employed, and statistically significant variables (p -value < 0.05) from the Pearson product-moment correlation coefficient, t -test, and one-way analysis of variance (ANOVA) were retained in the logistic regression model. The significance level was kept at 5%.

Training/calibration and quality control

Medical Officers (MOs) from respective healthcare settings were recruited as master trainers on data collection. MO is a professional doctor with an MBBS degree and is responsible for delivering curative/preventive services in healthcare settings and often renders administrative duties at these facilities. MOs were trained through a web-based session (Zoom application), which in turn trained the research assistants on-site. The research assistants (RAs) were medical students (4th year MBBS), paid monthly throughout this project. Two RAs were assigned for every 20 facilities, and MOs were responsible for training/calibration and supervision of the data collection process. A joint refresher training (via Zoom application) of all the research assistants as well as MOs was also done once all MOs completed all the formal training sessions of their RAs. A qualified epidemiologist performed all these training sessions using a standard training module duly validated before these training sessions. The training module included two-day on-site training of all recruited staff on medication adherence and how to respond to the common questions related to adherence/non-adherence. The training module also addressed the counseling and support to the participants in filling out the adherence/non-adherence to medication questionnaires.

Training protocols were efficiently maintained throughout, ensuring that all surveyors had a standardized understanding of survey objectives, procedures, and ethical considerations and were proficient in data collection methods to minimize variability. During the data collection, the supervisors (MOs) ensured that the same standardized tools were being used for interviews and that accurate and consistent responses were being recorded with no incomplete data. This was done by immediate data checking and validation by the MOs by conducting spot checks and random re-interviews. Real-time feedback and troubleshooting were done wherever required.

Ethics approval

Rehmatul-Lil-Almeen Institute of Cardiology's Institutional Ethical Review Board (Reference Number: RAIC-PESSI-963) and Employers Social Security Tertiary Hospital Lahore (PESSI-1026) approved the study protocol. However, we obtained administrative approval from the concerned health facility before data collection. Written informed consent was obtained from all participants. Furthermore, the study and all applied methods followed the relevant guidelines and regulations.

Results

A total of 51,902 patients were approached for the study. After excluding patients (17,210) and those refusing participation (13,241) the remaining patients (21,451) were retained and interviewed regarding their medication adherence (Fig. 2).

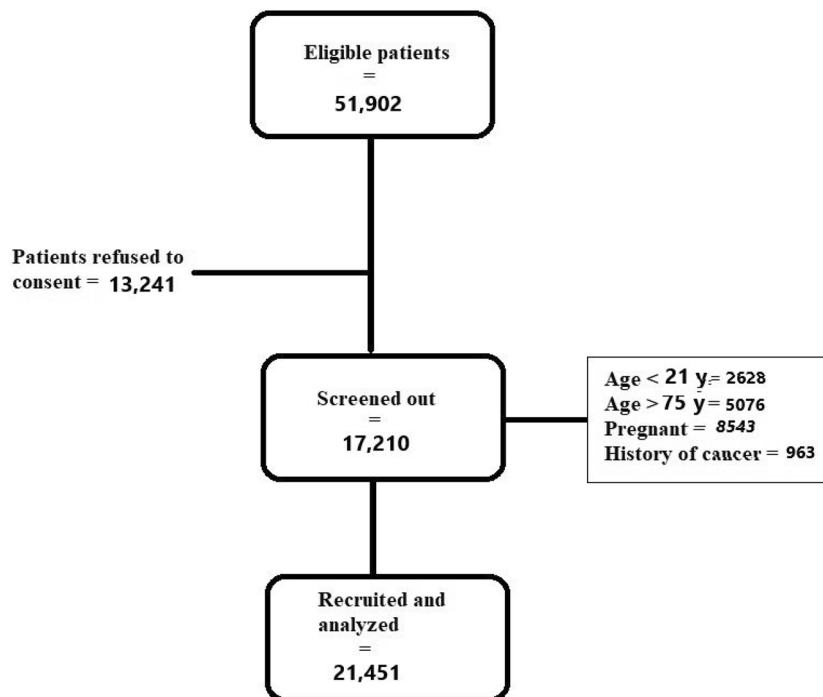


Fig. 2. Study flow diagram.

Respondents' demographic profile

The sociodemographic details of the sample are presented in Table 1. The table below shows that around half of the participants were 50–75 years of age (51.1%), had 51,000–100,000 PKR monthly income (44.7%), and had an illness duration of > 5 years (53.2%). Moreover, more than two-thirds of males (69.8%) had graduate-level education (37.7%) and Punjabi ethnic identity (34.3%). Health-related factors included one comorbid condition (88.7%), half of the participants were with obesity as a type of comorbidity, less than five medications (43.6%), and having a once-daily dose (85.3%). The rest of the demographic information is provided in Table 1.

Respondents' spatial and health facility level distribution

Pakistan has four provinces, Punjab, Sindh, Baluchistan, and Khyber Pakhtunkhwa, and one Capital territory, “Islamabad.” Pakistan also includes one autonomous region: Azad Jammu & Kashmir, which was included in this study. Most of the participants were from the province of Punjab 9471 (44.2%), while the lowest number was from Islamabad 703 (3.3%) (Table 2). Division-level data is fairly similarly distributed across Pakistan, with a similar representation from the primary and secondary healthcare facilities.

The SEAMS responses on non-adherence to medications

The SEAMS questionnaire and the response percentages are depicted in Table 3. As can be seen, the non-adherence to antihyperlipidemic medication was measured through the 13 questions, and their different responses are shown. The frequency of non-adherent respondents to antihyperlipidemic medication using SEAMS score was mean (SD) 26.79 (7.44), whereas the frequency of non-adherent respondents to antihyperlipidemic medication using pill-counting was 12,949 (60.3%).

Non-adherence to antihyperlipidemic medication in the provinces and divisions of Pakistan

Our study depicted that non-adherence was prevalent in Azad Jammu & Kashmir and Khyber Pakhtunkhwa provinces of Pakistan (72% and 69%, respectively), while the least prevalent were Islamabad and Punjab (47% and 55%, respectively). Sindh and Baluchistan provinces had intermediate non-adherence to antihyperlipidemic medication compared to the rest. Division-wise results of non-adherence to antihyperlipidemic medication revealed that the most prevalent divisions were Mirpur Khas (80.2%), Bannu (78.3%), Dera Ghazi Khan (77.5%) and Kohat (76.1%), while Lahore (38.9%) and Karachi (42.3%) were amongst the least non-adherent ones. (Fig. 3). Additional details of the non-adherence in the provinces and the divisions can be found in the supplementary data.

Factors affecting non-adherence to antihyperlipidemic medications

The generalized linear model (GLM) logit model utilizing multivariable logistic regression revealed eight significant variables associated with the probability of having non-adherence to antihyperlipidemic medication. The female gender (AOR = 1.275, 95% CI [0.881–1.845], $P < 0.001$), no health card (Sehat Sahulat

Variables	Sub-categories	Frequency	Percent (%)
Age	50–75	10,951	51.1
	30–49	8040	37.5
	21–29	2460	11.5
Gender	Female	6477	30.2
	Male	14,974	69.8
Education	Primary & secondary	6817	31.8
	Graduate	8092	37.7
	Postgraduate	6542	30.5
Ethnicity	Muhajir	1885	8.8
	Punjabi	7365	34.3
	Suraiki	3314	15.4
	Sindhi	4318	20.1
	Pashtun	3834	17.9
	Baloch	337	1.6
	Hazaras	28	0.1
	Brahui	30	0.1
	Kashmiri	212	1.0
	Pahari	128	0.6
Monthly income (PKR)	< 10,000	46	0.2
	10,000–25,000	1541	7.2
	26,000–50,000	2787	13.0
	51,000–100,000	9598	44.7
	> 100,000	7479	34.9
Health card (Sehat Sahulat program) covered	No	6688	31.2%
	Yes	14,764	68.8%
Duration of disease (hyperlipidemia)	< 5 years	10,042	46.8
	≥ 5 years	11,409	53.2
Comorbid conditions	1	19,028	88.7
	> 1	2423	11.3
Type of comorbidity	Obesity (BMI ≥ 30 kg/m ²)	10,996	51.2
	Diabetes	8043	37.5
	CVDs	2421	11.3
Number of daily medication	< 5	9359	43.6
	5–9	8848	41.2
	≥ 10	3244	15.1
Frequency of dose	Once daily	18,288	85.3
	Twice daily	1368	6.4
	Thrice daily	1795	8.4

Table 1. Sociodemographic characteristics of patients (N = 21,451). PKR: Pakistani Rupee = 0.0036 USD.

Program government insurance) coverage (AOR = 2.802, 95% CI [1.948–4.032], $P < 0.001$), less than five-year of illness (AOR = 1.216, 95% CI [1.132–1.306], $P < 0.001$), less than 5 daily medications (AOR = 1.699, 95% CI [1.535–1.882], $P < 0.001$) and dose frequency of twice daily (AOR = 4.729, 95% CI [2.998–7.458], $P < 0.001$) were positively associated with non-adherence. While the 51,000–100,000 monthly income (AOR = 0.623, 95% CI [0.577–0.672], $P < 0.001$), graduation level of education (AOR = 0.875, 95% CI [0.809–0.946], $P < 0.001$), Muhajir (AOR = 0.415, 95% CI [0.250–0.689], $P < 0.001$) and hyperlipidemia with one comorbid condition (AOR = 0.108, 95% CI [0.094–0.124], $P < 0.001$) were negatively associated with the non-adherence with very strong evidence against the model hypothesis at the sample size (Table 4).

Discussion

The study investigated the prevalence of non-adherence to antihyperlipidemic medication across the country, covering the four provinces and most of the divisions (around two-thirds). Overall, non-adherence to antihyperlipidemic medication in Pakistan was 60.6%. The non-adherence rates at the provincial level were highest in AJK (71.9%) and Khyber Pakhtunkhwa (68.8%) and the lowest in Islamabad (47.7%). Punjab, Sindh, and Baluchistan had non-adherence rates of 55.5%, 63.0%, and 60.5% respectively. Additionally, the study found that the prevalence of non-adherence varied within each province across the divisions.

Regions/level of care	Level	Frequency	Percent (%)
Province	Punjab	9471	44.2
	Sindh	5844	27.2
	Baluchistan	1196	5.6
	Khyber Pakhtunkhwa	2961	13.8
	Islamabad	703	3.3
	Azad Jammu and Kashmir	1276	5.9
Divisions	Bahawalpur	1513	7.1
	Dera Ghazi Khan	480	2.2
	Lahore	1413	6.6
	Multan	1147	5.3
	Rawalpindi	1387	6.5
	Sahiwal	566	2.6
	Sargodha	1148	5.4
	Faisalabad	1296	6.0
	Gujranwala	523	2.4
	Karachi	1564	7.3
	Hyderabad	1286	6.0
	Larkana	1257	5.9
	Sukkur	909	4.2
	Mirpurkhas	828	3.9
	Quetta	1196	5.6
	Peshawar	1021	4.8
	Dera Ismail Khan	721	3.4
	Kohat	591	2.8
	Bannu	628	2.9
	Islamabad	703	3.3
Azad Jammu and Kashmir	1276	5.9	
Type of hospital	RHC/BHU	11,601	54.1
	DHQ/THQ	9850	45.9

Table 2. Spatial and health facility distribution of patients (N = 21,453).

Our study discovered various statistically significant factors linked with non-adherence to antihyperlipidemic medication. Out of these, factors positively associated with non-adherence were the female gender, having less than five years of illness, having fewer than five daily medications, no health card (Sehat Sahulat Program) coverage, and having a dose frequency of twice daily. Meanwhile, the 51,000–100,000 PKR monthly income, graduation level of education, Muhajir, and hyperlipidemia with one comorbid condition were found to be negatively associated with non-adherence to antihyperlipidemic medication.

Existing literature representing isolated parts of the country supports the evidence generated through our findings; however, our analysis signifies national-level data, which is logically not analogous to the findings of those small-scale studies. Depending on their assessment methods and patient demographics, previous research estimated that the prevalence of antihyperlipidemic medication non-adherence ranged from 20 to 80%²⁹. However, some recent literature stated that non-adherence to cardiovascular treatment has been stretched between 40 and 80%^{39–41}. Another study mentioned that the prevalence of good adherence to these medications has improved to 54%⁴². One of the systematic reviews (done from 2012 to 2016) on older people (> 65 years) showed adherence rates ranged between 28 and 60% for the antihyperlipidemic medication users of 2–10 years, respectively; hence, adherence rates were observed to be declining with years of usage⁴³. A relatively recent systematic review described adherence to antihyperlipidemic medications as prevalent between 17.8 and 79.2%.⁴⁴ The most recent evidence from the American region states that the pooled prevalence of antihyperlipidemic medication adherence has been around 78.9%, while non-adherence is around 21%⁴⁵. As adherence is associated with many sociodemographic characteristics, therefore pooled prevalence comparisons will have vast heterogeneity.

Adherence and/or non-adherence measurement

Although it is challenging to measure adherence and/or non-adherence, both direct and indirect methods for measuring adherence (or non-adherence in some cases) have benefits and drawbacks²⁷. Directly monitored therapies are impractical for everyday use and can be compromised by patients who “cheek” or conceal their tablet intake. The same is true for objective measurements of the drug or its metabolites, which are often expensive, have different degrees of value, and do not take into consideration “white-coat adherence” (better adherence) just before and after a medical interaction. On the other hand, indirect methods often include surveys, self-reporting, and pill counts and are simple but prone to deceit⁴⁶.

Questions	Options	Frequency	Percent (%)
How confident are you that you can take your medicines correctly?			
Q1: When you take several different medicines each day	Not confident	541	2.5
	Somewhat confident	5093	23.7
	Very confident	15,817	73.7
Q2: When you take medicines more than once a day	Not confident	1249	5.8
	Somewhat confident	6869	32.0
	Very confident	13,333	62.1
Q3: When you are away from home	Not confident	3816	17.8
	Somewhat confident	6535	30.5
	Very confident	11,100	51.8
Q4: When you have a busy day planned	Not confident	5630	26.2
	Somewhat confident	6511	30.3
	Very confident	9310	43.4
Q5: When they cause some side effects	Not confident	13,882	64.7
	Somewhat confident	4120	19.2
	Very confident	3449	16.1
Q6: When no one reminds you to take the medicine	Not confident	8167	38.1
	Somewhat confident	6078	28.3
	Very confident	7206	33.6
Q7: When the schedule to take the medicine is not convenient	Not confident	5376	25.1
	Somewhat confident	6989	32.6
	Very confident	9086	42.4
Q8: When your normal routine gets messed up	Not confident	10,481	48.9
	Somewhat	2188	10.2
	Very confident	8782	40.9
Q9: When you are not sure how to take the medicine	Not confident	13,637	63.6
	Somewhat confident	4529	21.1
	Very confident	3285	15.3
Q10: When you are not sure what time of the day to take your medicine	Not confident	8680	40.5
	Somewhat confident	6209	28.9
	Very confident	6562	30.6
Q11: When you are feeling sick (you know, like having a cold or the flu)	Not confident	9617	44.9
	Somewhat confident	3073	14.3
	Very confident	8761	40.8
Q12: When you get a refill of your old medicines and some of the pills look different than usual	Not confident	12,825	59.8
	Somewhat confident	5442	25.4
	Very confident	3184	14.8
Q13: When a doctor changes your medicines	Not confident	1630	7.6
	Somewhat	7145	33.3
	Very confident	12,676	59.1
Mean SEAMS score for non-adherence to medication (SD)	26.79 (7.44)		
Pills count non-adherence to medication	< 80% adherence on pills count	12,949	60.3

Table 3. SEAMS responses on non-adherence to medications (N = 21,451).

Rates of prescription refills also act as a substitute for adherence as such data are readily available from pharmacies. Still, it is not deemed the same as the ingestion of medication. Most statin adherence trials used an arbitrary cut-off of 80% while defining adherence. However, clinicians should note that those with greater than 80% adherence may derive even further benefits from reduced LDL-C levels⁴⁶. The current study used the SEAMS questionnaire and pill counting to assess statin non-adherence. The prevalence of medication non-adherence measured by both approaches did not differ significantly, providing triangulation for our findings to be dependable.

The current study found that non-adherent respondents to antihyperlipidemic medication using SEAMS score was mean (SD) 26.79 (7.44). Prior research has employed SEAMS to assess drug adherence in long-term conditions such as cardiovascular diseases (CVDs), hypertension, and other chronic illnesses, and different findings of SEAMS scores were revealed^{33,36,47}. The median (IQR) SEAMS score was reported in earlier research to be 19.5 (5) and 21 (6), respectively³³.

Non-adherence to antihyperlipidemic medications in Pakistan

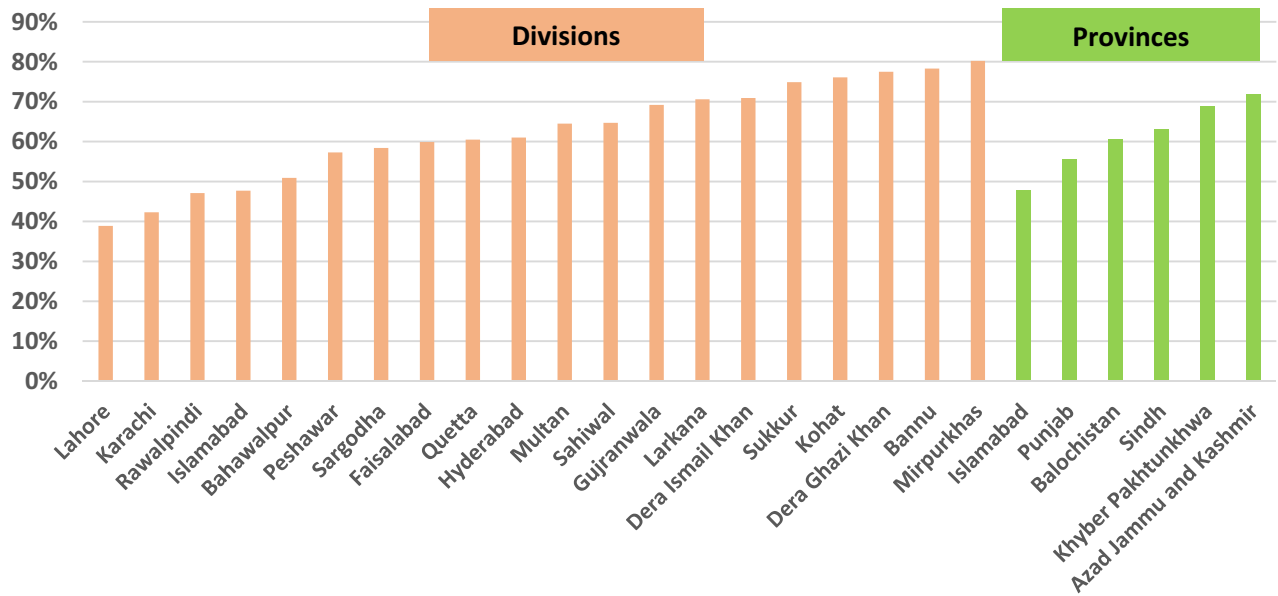


Fig. 3. Provincial and division-level prevalence of antihyperlipidemic medications in Pakistan.

Potential predictors affecting non-adherence to antihyperlipidemic medication

Medication non-adherence is a complicated, multifaceted healthcare issue. Even the most effective treatment will fail if the patient refuses to take it²⁷. The ability of patients to adhere to treatment regimen suggestions is referred to as adherence. On the other side, inadequate implementation of the dosing schedule, non-initiation of the prescribed therapy, or early termination of the treatment may result in non-adherence to medication^{48–50}. During various phases of their treatment, patients may not adhere owing to various factors, including gender, education level, income status, duration of illness, presence, and type of comorbidities, number of prescribed medicines, dose frequency, and relation with the physician. It is well-established that non-adherence to antihyperlipidemic medication is linked to increased cardiovascular mortality^{21,22,28,29}. Improvement in adherence to antihyperlipidemic medication results in cost savings in overall healthcare (an increase in drug expenses but a considerable decrease in hospitalization and outpatient care expenditures)⁵¹; hence, adherence is a vital element of the drug and cost efficacy. Our study identifies several factors that affect medication non-adherence in hyperlipidemia patients. Statistically significant variables negatively associated with non-adherence to antihyperlipidemic medication were female gender, graduation level of education, good income status, health card (Sehat Sahulat Program) coverage, more than five years of illness, hyperlipidemia with one comorbid condition, up to five prescribed medicines, and dose frequency of once daily. Various factors of treatment adherence in patients receiving antihyperlipidemic medication were elaborated in prior studies. Some of them align with our findings, while others differ.

In the current study, the female gender was found to be less likely to default to antihyperlipidemic medication than males. Previous literature supports our findings^{52,53}. Although age was not a significant contributor to non-adherence to antihyperlipidemic medication in this research, previous studies established that non-adherence to antihyperlipidemic medications declines with an increase in age^{54,55}, and another study quantified this decline, stating that non-adherence probability falls by roughly 5–11% for every decade of age⁵⁶. In the current study, education had a mixed association with non-adherence; compared to postgraduate education, primary and secondary education had more odds of being non-adherent, while the graduates were less likely to be non-adherent to antihyperlipidemic medications. In the current study, Muhajir's ethnicity was found to be less likely non-adherent than that of other groups. This could be due to the fact that the majority of these Urdu-speaking participants (Muhajir) are well-educated, which could improve their adherence. Although further studies on different races were in line with our study, some ethnicities are linked with non-adherence, such as African American patients^{55,57} and the Hispanic population have been linked to the worst drug non-adherence^{57,58}.

In our study, income status remained statistically significant for medication adherence. The participants with a monthly income of 51,000–100,000 rupees demonstrated fewer odds of being non-adherent to antihyperlipidemic medication, while lesser income levels were positively associated with the outcome. A study by Osborn et al. investigated the connections between financial stress and medication compliance and found higher income was significantly correlated with less non-adherence in adjusted models ($P < 0.001$). Still, this association disappeared when financial stress was observed. Financial stress positively impacts the association of income with non-adherence ($r = -0.17$, $P < 0.001$) and worse self-rated health ($r = -0.23$, $P < 0.001$)⁵⁹. Income has been more strongly connected with adherence among men than women⁴⁴, and it was also found that patients having health insurance exhibited less non-adherence⁵⁷.

Factors	Categories	Adjusted OR	95% confidence interval		P value
			Lower	Upper	
Age	21–29 years	Reference			
	30–49 years	1.002	0.925	1.085	0.965
	≥ 50 years	1.002	0.927	1.084	0.953
Gender	Female	1.275	0.881	1.845	< 0.001*
Education	Postgraduate education	Reference			
	Primary & Secondary	8.048	7.233	8.955	< 0.001*
	Graduate	0.875	0.809	0.946	< 0.001*
Ethnicity	Pahari	Reference			
	Muhajir	0.415	0.250	0.689	< 0.001*
	Punjabi	1.134	0.855	1.503	0.383
	Suraiki	0.998	0.751	1.327	0.989
	Sindhi	0.840	0.633	1.117	0.230
	Pashtun	0.834	0.628	1.109	0.211
	Baloch	1.281	0.927	1.770	0.133
	Hazaras	0.736	0.332	1.631	0.451
	Brahui	0.621	0.329	1.172	0.141
	Kashmiri	1.166	0.823	1.653	0.388
Monthly income (PKR)	> 100,000 monthly income	Reference			
	10,000–25,000 monthly income	3.896	3.149	4.821	< 0.001*
	26,000–50,000 monthly income	1.407	1.243	1.593	< 0.001*
	51,000–100,000 monthly income	0.623	0.577	0.672	< 0.001*
Health card (Sehat Sahulat Program) covered	No health card coverage	2.802	1.948	4.032	< 0.001*
Duration of disease (hyperlipidemia)	< 5 years of illness	1.216	1.132	1.306	< 0.001*
Comorbid conditions	Comorbid conditions > 1	Reference			
	1	0.108	0.094	0.124	< 0.001*
Number of daily medication	Daily medication ≥ 10	Reference			
	< 5	1.699	1.535	1.882	< 0.001*
	5–9	1.206	1.090	1.334	< 0.001*
Frequency of dose	Thrice daily dosage	Reference			
	Once daily	0.213	0.176	0.257	< 0.001*
	Twice daily	4.729	2.998	7.458	< 0.001*

Table 4. Factors affecting non-adherence to antihyperlipidemic medication (N = 21,451). Significant values are in bold.

In the current study, the majority of the sociodemographics were linked to non-adherence to antihyperlipidemic medication. Sociodemographic variables like education levels might be too broad to accurately predict a person's medication use. This is consistent with a prior study that found that treatment comprehension matters more than educational attainment⁶⁰.

Previous studies have demonstrated that non-adherence to antihyperlipidemic medication is also linked to several medication-related factors. In the current study, the participants with less than five years of illness showed higher odds of non-adherence than patients with a history of more than five years, depicting that the recent adoption of antihyperlipidemic medications contributed to non-adherence. This might be due to the appearance of adverse effects of the medicines in users of these chronic disease patients, making them more likely to purposefully break their medication regimen. However, the literature also suggests that non-adherence was more prevalent in patients with newly prescribed lipid-lowering drugs^{52,61}. Additionally, non-adherence to prescribed treatments is more common among patients who experience side effects or have concerns about potential side effects⁶². These individuals exhibit a 2.89 times higher odds ratio of non-adherence compared to those without side effects⁶³. This highlights the substantial influence of drug-related side effects on patients' adherence behavior.

Studies showed that various comorbid disorders were also related to non-adherence to antihyperlipidemic medication. Participants in the current study who had more comorbid conditions exhibited higher non-adherence than those with fewer comorbid diseases. Our study opposed the findings from previous studies, revealing that a higher number of comorbidities is associated with a lower non-adherence rate. The probability of non-adherence decreases by 4% for each comorbidity that is present⁵⁸. This has been evident since the initial comorbidity, which has resulted in a 5% reduction in non-adherence^{64,65}. On the other hand, the absence of concurrent illnesses is associated with a 59% increase in the likelihood of non-adherence⁶⁶.

We also looked at the correlation between medication adherence and other comorbidities, such as obesity, CVDs, and type 2 diabetes, but we were unable to uncover any statistically significant correlations. Further investigation into the various co-occurring conditions could elucidate the fundamental causes of these results. Previous studies revealed that lower non-adherence is linked to cardiovascular disease event history^{67,68}, patients receiving antiplatelet medication⁶⁹, and patients having hypertension⁷⁰. Similarly, less frequent follow-ups and taking medication at night or odd times negatively impact adherence to antihyperlipidemic medication⁷¹. Also, it has been demonstrated that patients taking beta-blockers had decreased non-adherence rates. On the other hand, Diabetes has been found to be linked to higher rates of non-adherence⁵². Furthermore, it was found that various comorbidities had different effects on non-adherence; individuals with the comorbidities experienced increased non-adherence rates, including Alzheimer's disease⁵⁷, depression⁵⁷, anxiety⁷², and chronic obstructive pulmonary disease⁶⁹.

To the best of our knowledge, there is little information on hyperlipidemia medication non-adherence in Pakistan. The current study attempted to fill this information gap by using a large, nationally representative sample. The current research assessed a range of factors (sociodemographics to medication-related and health-related) associated with non-adherence to antihyperlipidemic medication that had not been thoroughly explored in the preexisting body of literature. The findings of the current study offer important insights on how to improve medication adherence in the local settings, which can be extrapolated to other regions with similar demographics.

Final note and clinical implications

Patients may not adhere to various explanations, including practical, emotional, or perceptual ones, and we cannot tackle these issues without exploring these issues for each particular patient⁷³. Despite the different measurements, each attribute is connected to considerable variance in non-adherence, allowing for adjustment and customization of the therapeutic choice for these individuals. The more of these disorders patients have, the more likelihood of non-adherence is anticipated, and, therefore, healthcare providers should be more concerned.

Despite the lack of systematic counseling in a resource-constrained setting like Pakistan, doctors, at the very least, can direct patients toward dependable services, including pharmacies, health programs, and trustworthy online resources. A recent systematic review recommended additional studies with more sophisticated designs to determine non-adherence predictors and efficient interventions to enhance adherence in CVDs⁷⁴.

Pakistan is a developing country with many limitations in providing quality health services to its population. In many countries, improving patients' medication adherence has been a significant outcome of quality pharmaceutical services. Non-adherence to the therapy may lead to different problems as a consequence of non-adherence at four levels: individual, institutional, social, and national. Adherence to medications is an essential indicator of the quality of medication management and impacts health outcomes. Moreover, patients' customized challenges to adherence must be addressed and acknowledged to move patients from the preparation stage to the action stage. This critical stage necessitates questioning patients about their worries regarding statin therapy and what obstacles to statin medication need to be removed. For instance, beginning with a generic statin could be sensible if cost is a concern.

Our findings suggest the prevalence of non-adherence to antihyperlipidemic medication in Pakistan, with significant variation across its provinces and divisions. These results call for tailored interventions to improve medication adherence, especially in provinces and their divisions with high non-adherence rates. Further research is needed to explore the factors contributing to non-adherence in different regions of Pakistan and develop effective strategies to address the issue. Our findings provide baseline statistics for policymakers, healthcare practitioners, and other service providers to plan their future goals and objectives accordingly to cater to the medical needs of this specific population group.

Limitations

Self-reporting was employed to measure non-adherence, which may have led to an underestimation of drug compliance. However, we chose to use the SEAMS questionnaire because it was deemed appropriate for people with low reading levels^{35,36}. The self-reporting pill-counting method was similarly linked to increased adherence measurement validity. An objective evaluation of adherence could be made using pill counts or pharmacy databases, but these tools could not be used in the context of Pakistan. Additionally, data from pharmacy databases and pill counts cannot reveal the kinds of non-adherence (deliberate or otherwise).

Moreover, no causal conclusions can be drawn regarding the relationship between medicine-taking attitudes and non-adherence due to the cross-sectional methodology of the study. The overall relationship of our logit model was relatively high, indicating several potent predictors of non-adherence.

Conclusion

We determined non-adherence among patients taking antihyperlipidemic for primary or secondary prevention of CVDs in a country with constrained resources. Patients with hyperlipidemia generally had high non-adherence rates. We also examined the elements that affect non-adherence to antihyperlipidemic medication among various ethnic groups; some highlighted operational flaws in the healthcare system that require immediate attention. Since non-adherence shouldn't be viewed as the patient's fault but rather as a critical warning indicator that needs to be addressed for this significant illness, patients and professionals need to collaborate to address some of the other unknown factors immediately. Antihyperlipidemic medication non-adherence is a multifaceted, multifactorial problem that is abundant and has no simple solution.

Recommendations

There are significant, observable factors that contribute to non-adherence in hyperlipidemic individuals. Health-care professionals should recognize these traits to approach patients individually and devote more effort to enhancing adherence. Finding the optimum frequency of adherence and exploring factors of non-adherence further, comprehending the particular individual and community behaviors that encourage non-adherence, and examining the generalizability of these predicted factors across contexts and demographics are critical next steps in building on the current work. There is also a need to create new instructional approaches to increase drug adherence. A recent study compared an innovative mHealth strategy to peer counseling to improve non-adherence⁴⁷.

Moreover, patients with hyperlipidemia generally had high non-adherence rates. Targeting people who were classified as non-adherent and their suggestions will help increase adherence. Therefore, high-quality qualitative designs mixed with new horizons of quantitative research are needed to explore factors in depth.

Data availability

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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Author contributions

Conceptualization, M.A., M.F.U.; Methodology, M.A., M.F.U., M.N.K.; Validation, M.A. and A.F.; formal analysis, M.A.; Investigation, Data collection and Data curation, M.A., M.K., A.H.G., A.B.K., S.Z., A.M.A.; writing—original draft preparation, M.A., M.F.U.; Writing—Review and Editing, M.F.U., M.N.K., A.F. and M.K.; supervision, M.A., M.F.U., M.N.K. All authors have read and agreed to the published version of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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