Cardio-Protective Medication Adherence among Patients with Coronary Heart Disease in China: A Systematic Review, Short title: Medication Adherence among Patients with CHD in China

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Abstract: Aims: In China, poor cardio-protective medication adherence is a key reason for the high mortality rates of coronary heart disease (CHD). The purpose of this systematic review is to 1) describe and synthesize factors that influence medication adherence among Chinese people with CHD, 2) evaluate the current status of the intervention studies, and 3) discuss directions of future research to improve medication adherence. **Methods and Results**: A comprehensive search using PubMed, CINAHL, Embase, Scopus, Global Health, and PSYCINFO was undertaken to describe the poor adherence in China. Thirty-three eligible articles were included in the study. The review shows that there are multiple contributing factors to the poor medication adherence, including patients' socio-demographic characteristics, health status, and medication characteristics. In addition, from patients' perspective, lack of medication-related knowledge, such as the name, function, dosage, and frequency contributes to poor adherence. From physicians' perceptive, a gap exists between CHD secondary prevention guidelines and clinical practice in China. Follow-up phone calls**,** educational lectures, booklets, and reminder cards were common methods found to be effective in improving medication adherence. **Discussion**: This systematic review revealed that cardio-protective medications are commonly prescribed as secondary prevention medication to patients with CHD in China, but the adherence to these medications gradually decrease during a follow-up period. Therefore, more research should be conducted on how to establish high quality health educational programs aimed at increasing patients' medication adherence.

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1. Introduction

Poor medication adherence among patients with coronary heart disease (CHD) is a global public health concern [1]. This is particularly the case in China [2, 3] given the large size of the patient population and significant health disparities in access to care across its regions [4]. CHD is the second leading cause of death in China [5, 6] leading to over 1.5 million deaths each year [5]. Cardio-protective medications, including antiplatelet drugs, beta-blockers, statins, and angiotensin-converting enzyme inhibitors are an essential treatment modality for CHD [7] and can significantly reduce the mortality rate of this disease [3, 8, 9, 10, 11, 12]. However, poor adherence to cardio-protective medications is a public health threat in China [2, 13]. A deeper understanding of the interplay of factors related to adherence to cardio-protective medications among the Chinese population is needed in order to develop interventions that will appropriately target this phenomenon [14, 15]. Therefore, the purpose of this systematic review is to 1) describe and synthesize factors that influence medication adherence among Chinese people with CHD, 2) evaluate the current status of the intervention studies, and 3) discuss directions of future research to improve medication adherence. The findings from this review may provide insights to improve the issue of medication adherence globally.

2. Methods

2.1. Search strategy

We chose the databases PubMed, the Cumulative Index for Nursing and Allied Health Literature (CINAHL), Embase, Scopus, Global Health, and PSYCINFO as primary data sources for this review, as together they provide a comprehensive coverage of research in health-related disciplines. Two authors (ZN and LD) searched each database using key words and algorithms that included (coronary heart disease OR coronary artery disease), and (China OR Chinese), and (adherence OR compliance OR persistence OR discontinue OR underuse OR non-adherence OR non-compliance OR comply OR compliant OR adhere). An academic health center reference librarian

provided key assistance in building the combination of index and search terms, that were applied to each database (Table 1). No restrictions were applied on publication date. The first author (ZN), who is a native Chinese speaker, ran another search within a Chinese database, the China National Knowledge Infrastructure (CNKI), and used the Chinese key words 'yao wu yi cong xing' and 'guan xin bing', meaning medication adherence and coronary heart disease.

2.2 Inclusion and exclusion criteria

We included articles that met the following criteria: (1) focus on the adherence to at least one of the following cardio-protective medications: antiplatelet drugs, beta-blockers, statins, and angiotensin-converting enzyme inhibitors/angiotensin receptor blocker; (2) Chinese samples with CHD living in China; and (3) peer-reviewed articles published in English or Chinese. Studies that included samples of Chinese patients living in Hong Kong, Taiwan, and Macao were excluded, as these areas are historically dominated by foreign cultures and thus, their social structures and healthcare systems are different from that in mainland China.

3. Search Outcomes

Our search resulted in the following: 173 articles from PubMed, 23 from CINAHL, 320 from Embase, 54 from Scopus, 56 from Global Health, and 8 from PSYCINFO. From the resulting 634 articles, 168 duplicates were removed, yielding 466 results. Afterwards, the first and the second authors (ZN and LD) screened the 466 titles independently and compared and discussed their results until agreement was reached, yielding 134 articles for subsequent abstract screening. After evaluating the abstracts of the 134 articles, 54 articles were excluded based on the preset inclusion criteria. The full text of the remaining 54 articles were then examined and 26 articles met the full inclusion criteria (Figure 1). The search of Chinese literature in CNKI yielded 100 related articles. After screening the titles, abstracts, and full texts, 7 articles were included (Figure 2). Together, a total of 33 articles were used in this study.

4. Findings

4.1 Study characteristics

The 33 articles included in this systematic review came from the medical, nursing, and pharmacological disciplines. A range of study designs were employed from cross-sectional studies (N=22), longitudinal studies (N=2), to randomized controlled trials (N=9) (Table 2). In total, 56,786 participants were included in this systematic review, with only 19,997 (35.21%) female. Importantly, participants were from over 560 medical institutions located in over 17 Chinese provinces (out of a total of 34 provincial-level administrative units), with almost all studies were conducted in hospitals located in urban areas of China. Only two studies were conducted in rural areas. There was significant heterogeneity between the studies in terms of instruments used to measure medication adherence, making a robust meta-analysis or statistical analysis difficult to conduct. Thus, a qualitative summary of the findings is presented. We organized our findings with three core themes: (1) Patient and healthcare provider lack of knowledge as barrier to medication adherence; (2) Patients' socio-demographic characteristics, health status, and medication characteristics influencing adherence; (3) Various intervention methods used for the improvement of medication adherence. Subthemes are presented within each of these three core themes.

4.2 Patient and healthcare provider lack of knowledge as barrier to medication adherence (12 articles)

***4.2.1 Patients' lack of knowledge* (5 articles)**

Our systematic review revealed that patients' lack of knowledge about their medications was a substantial barrier to adherence. For example, Wang and Li [16] investigated the adherence to statins among 1,368 elderly patients with CHD over 80 years of age, and found that lack of knowledge of CHD and statins was the main factor influencing their adherence to statins. Participants did not understand the importance of taking medications over the long term, did not know the morbidities of CHD, and did not understand that statins can prevent CHD [16]. Similarly, Li [17] found that lack of knowledge of CHD was significantly related to poor adherence to statins among patients. Lack of knowledge was also a barrier to adherence among patients with uncontrolled cholesterol levels. Ding et al. [18] found that of 903 patients with CHD, 18.2% did not take statins or did not know whether they were taking stains**.** Finally, Zhao, Zhao, Wang, Du, & Qin [19] conducted a descriptive correlational study among 159 participants with CHD and revealed that up to 38% of the participants were non-adherent and that lack of knowledge about medication and disease were significantly associated with non-adherence. Patients with good knowledge of the medication and disease were more likely to adhere to medication instructions [19]. Patients in the study of Zhao et al. [19] reported difficulty accessing information about their medication, especially from pharmacists. Dai [20] surveyed 200 CHD patients living in a Chinese rural area and found that medication adherence was low among those patients living in rural China, with only 6.4% of the participants adhering to their cardio-protective medications. Factors that contributed to poor medication adherence included poor

communication between healthcare providers and patients, healthcare providers not fully explaining CHD and medications, and patients lack of clarity on factors to pay attention to while taking medications [20].

4.2.2 Healthcare providers' lack of knowledge **(10 articles)**

In China, healthcare providers can significantly impact CHD patients' adherence to medications. Yet there is a significant gap in knowledge among healthcare providers regarding the current guidelines for CHD medication protocols. Bi et al. [2] investigated 2,973 patients with acute coronary syndromes in 49 hospitals in China on their medication-taking behavior at the time of hospitalization and one year after hospital discharge. They found that physician compliance with guideline recommendations and sustained use of medical therapy was suboptimal [2]. In addition, more than 20% of the non-adherent participants reported that physicians did not tell them to use medications after discharge [2]. In support of these findings, Jiang et al. [13] studied 837 physicians from cardiology departments in 35 tertiary hospitals in China and found that a gap between guideline requirements (American Heart Association/American College of Cardiology Guidelines for Secondary Prevention for Patients with Coronary and Other Atherosclerotic Vascular Disease) and clinical practice in coronary heart disease secondary prevention, contributing to poor medication adherence in China. Similarly, Hu, Li, & Li [21] conducted a large multicenter study surveying statin usage in CHD outpatients and found that there is a significant gap between the guideline (National Cholesterol Education Program Adult Treatment Panel III) and clinical practice in China. In a more recent study, Jiang, Wang, Jia, & Huo [22] found that 40% of outpatients with stable angina were not taking beta blockers because physicians did not prescribe beta blockers, although beta blockers were the recommended first-choice medication to treat stable angina. Ding et al. [18] also found that cardiologists had poor adherence to lipid lowering guidelines, leading to poor medication adherence in patients. Overall, our review showed that physicians' prescribing practices and patterns of adherence to guidelines for CHD medications were a consistent barrier to medication adherence among Chinese patients with CHD [12, 23, 24, 25, 26].

4.3 Patients' socio-demographic characteristics, health status, and medication characteristics influencing adherence

4.3.1 Socio-demographic characteristics that are associated with adherence

4.3.1.1 Age **(5 articles)**

Several studies [3, 16, 17, 27, 28] have demonstrated a link between older adults and poor adherence to cardio-protective medication. For example, Jin et al. [3] found that among Chinese patients with acute coronary syndrome, medication non-adherence was common among older patients age 65 and above. Li et al. [27] also found that adherence to statins was low among older adults. To further analyze the adherence to statins in elderly patients, Wang and Li [16] chose 1,368 elderly patients aged over 80 years with CHD and found that older patients have poor medication adherence and the authors surmised that memory loss or inability to remember medication name, dosage, route, and time, may be a key explanatory factor. More recently, two studies [17, 28] found older age (>60) to be a main influencing factor contributing to Chinese patients' poor adherence to cardio-protective medications.

4.3.1.2 Gender **(1 article)**

Medication adherence can be different among male and female CHD patients. Yang, Li, Yuan, & Dong [29] compared medication adherence between male and female CHD patients and found that female participants had better adherence in aspirin, beta-blockers, and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; while there was no significant difference between female and male participants in adherence to statins.

4.3.1.3 Education **(8 articles)**

Seven out of eight studies [3, 16, 17, 20, 22, 28, 30, 31] revealed a low educational level is a main influencing factor that contributes to poor medication adherence. Wang and Li [16] investigated the reasons behind this relationship and found patients with a high educational level (> high school) are more likely to gather information about their medications; therefore, they have a better understanding and knowledge of statins. This better understanding contributed to better medication adherence [16]. However, Jiang et al. [22] surveyed 5,047 outpatients with stable angina from 298 hospitals in 15 Chinese provinces and found that patients with a high school or lower education level had higher beta-blockers adherence than those with a college degree. This result is different from our general finding that patients with a higher educational level are more likely to have better medication adherence.

4.3.1.4 Income **(6 articles)**

Our review shows that low income was consistently found to be a factor related to medication non-adherence [3]. Li [32] explored cardio-protective medications adherence among 271 CHD patients and revealed that patients with high family income (>50,000 yuan/year) have significantly better medication adherence. Further, studies [16, 17] investigated CHD patients on their adherence to

statins and found that finances are an influencing factor to medication adherence. Studies [30, 33] on adherence to other cardio-protective medication such as antiplatelet also found the same result. Huang et al. [30] investigated the factors influencing medication adherence among 262 CHD patients who received percutaneous coronary intervention, and found that poor adherence to antiplatelets a year after hospital discharge was correlated with low economic status. Liu et al. [33] investigated the main cause of the non-adherence to ticagrelor, an antiplatelet decreasing the risk of myocardial infarction [34], and found that low economic status is a main cause of non-adherence.

4.3.2 Health status in relationship with adherence

4.3.2.1 Comorbidity **(4 articles)**

Our review suggests that CHD patients with comorbidity are more likely to have poor medication adherence. Zhang & Chen [31] studied 547 CHD patients on their adherence to dual antiplatelet therapy one year after they underwent percutaneous coronary intervention, and revealed that having comorbidities contributed to low medication adherence. Similarly, Chen et al. [35] studied the association between heart function and medication adherence and found that CHD patients with reduced left ventricular ejection fraction had lower medication adherence. Furthermore, Jin et al. [3] found that the higher the number of comorbidities, the greater the chance of medication non-adherence. Li et al. [27] found that statin use was low among certain high-risk CHD patients, including those with hypertension or diabetes, even though the benefits of statin are great among this population.

4.3.2.2 Discharge **(7 articles)**

Medication adherence among Chinese CHD patients often drops significantly after discharge from the hospital. Zhuang et al. [28] studied 348 discharged CHD patients about their adherence to antiplatelet therapy and revealed that medication adherence gradually decreased after patient discharge. Similarly, Li et al. [27] found that among 13,150 CHD patients, continued use of statin dropped substantially over time. Atkins et al. [36] also found that among 236 CHD patients, continued use of cardio-protective medications declined over time. This result is similar to findings from two previous studies [3, 32]. The two studies found that recommended cardio-protective medications were commonly underused among Chinese CHD patients one year after hospital discharge. To further investigate the relationship between discharge and medication adherence, Zhang and Chen [31] and Huang et al. [30] investigated the factors influencing medication adherence among CHD patients who received percutaneous coronary intervention. They found the same results; adherence to antiplatelet dropped over time [30, 31]. In summary, our review found that the longer the time after discharge, the poorer the medication adherence was.

4.3.3 Medication characteristics that are related to adherence

4.3.3.1 Adverse effects **(5 articles)**

Adverse effects are associated with decreased medication adherence among CHD patients. This was supported by several studies in our review [3, 17, 20, 27, 33]. Dai [20] surveyed 200 Chinese CHD patients and found that the fear of adverse effects of cardio-protective medication was a barrier to adherence. Jin et al. [3] investigated main influencing factors to medication non-adherence among CHD patients and found the fear of adverse effects such as sexual dysfunction, depression, and fatigue was a confirmed factor. Similarly, Liu et al. [33] investigated the main cause of the non-adherence to ticagrelor, an oral antiplatelet drug decreasing the risk of myocardial infarction [34], and found that adverse effect of ticagrelor, such as hemorrhage is one main cause. Li [17] studied 138 CHD patients on their adherence to statins and found that adverse effects of statins are indeed a factor contributing to poor adherence. Taking statins over time can influence the musculoskeletal system, neurological system, and liver dysfunction [17]. To further study the association of adverse effects and non-adherence to statins, Li et al. [27] categorized 16,860 patients into different risk levels. They found that statin use was low among high risk CHD patients even though the absolute benefits of using statins are high among this population. Li and colleagues thought this might be because of a treatment-risk paradox [27]. Treatment-risk paradox is a phenomenon in which patients at high risk for adverse events receive less-intensive treatment than do patients at lower risk [37].

4.3.3.2 Number of discharge medications **(2 articles)**

Two studies in our review found that the greater the number of discharge medications patients received, the greater the chance of medication non-adherence it occurred. Li [17] studied 138 CHD patients on their adherence to statins and found that using multiple medications was an influencing factor that contributed to poor adherence. Also, Dai [20] surveyed 200 CHD patients living in a Chinese rural area and found that using multiple medications was a factor that contributed to poor medication adherence.

4.3.3.3 Medication cost/insurance **(4 articles)**

Many studies [3, 17, 30, 31] in our review found that high medication cost was related to poor medication adherence. For example, Zhang and Chen [31] investigated 500 CHD patients on their adherence to antiplatelet therapy and revealed that high medical payment was related to poor adherence. Specifically,

patients having public medical insurance had higher medication adherence than patients who had rural cooperative medical care or needed to pay medical care out of own pocket [30, 31]. Similarly, Jin et al. [3] and Li [17] found that medication cost was an influencing factor that contributed to poor adherence. Participants with no insurance or who had to pay medication out of pocket had poorer medication adherence [17].

4.4 Interventions to improve medication adherence vary in methods

Our systematic review found that researchers explored various interventions to improve CHD patients' adherence to cardio-protective medication. Follow-up phone calls**,** educational lectures, booklets, and reminder cards were common methods found to be effective in improving medication adherence. Education and reminders are two key components of all interventions.

4.4.1 Follow-up phone calls **(7 articles)**

Making follow-up phone calls to remind patients to take medications or give consultations on medication usage is the most common method we found in the review. Du et al. [38] randomized 964 CHD patients into an intervention or control group. Participants in the intervention group received medical consultations from cardiologist through phone calls at three, six, 12 and 36 months post-discharge. The study found that the intervention group had significantly better medication adherence [38]. Similarly, Li et al. [39] used phone-call interviews to educate participants with myocardial infarction on relevant knowledge after discharge and found this intervention was effective in improving medication adherence. Telephone follow-up was used in many randomized controlled trials [40, 41, 42, 43, 45]. For example, Jiang et al. [41] tested the effectiveness of a nurse-led cardiac rehabilitation educational program in improving health behaviors among 167 randomly selected CHD patients. In the program, an experienced cardiac nurse provided patients with professional follow-up through telephone calls to monitor, facilitate and reinforce self-management practice of the patients. Patients who received the intervention demonstrated a significantly better performance in medication adherence [41]. Similarly, Cao et al. [40] conducted a randomized controlled trial to test the effectiveness of a hospital–community partnership transitional program on medication adherence. In the program, family physicians and home nurses made structured telephone calls after patient discharge to reinforced health self-management behaviors and remind timely outpatient visits to hospital. Whereas, patients in the control group received routine care. Cao et al. [40] found that intervention group had significantly higher medication adherence scores than control group at 30 days and 90 days after discharge.

Zhao et al. [43] examined the impact of using a clinical pharmacist support program on medication adherence among patients receiving multidrug therapy for coronary heart disease in China. Compared to a usual care control group, the intervention group received pharmacist support that included medication review, patient education, lifestyle management, discharge guidance, and telephone follow-up. Patients in the intervention group showed better medication adherence [43]. Zhao and Wong [42] tested the effectiveness of a nurse-led post-discharge transitional care program for CHD patients that included a community nurse who followed up with participants' adherence behavior for 4 weeks. Compared to the control group, which received routine care, the intervention group had significantly better adherence to their medications [42].

4.4.2 Booklet **(3 articles)**

Giving a booklet for patients to refer important information of CHD and their medication was found to be effective in our review. However, none of the three studies used booklet alone; booklet was used with other interventions to improve medication adherence, such as follow-up phone calls, educational session, or individual face-to-face education. Wu et al. [44] found patients in an intensive management group had better medication adherence than patients who received routine care. A booklet of CHD was provided to participants in the intensive management group. With such a booklet, patients can learn CHD-relevant knowledge from it. The booklet increased participants' awareness of taking medications. Similarly, Jiang et al. [41] provided a healthy heart booklet that covered medication management to CHD patients to facilitate and reinforce their medication adherence. Zhao, Zhao, Du, Qin [45] investigated whether a pharmaceutical care intervention can improve medication adherence. In this intervention, an instructional list of each medication was provided to patients.

4.4.3 Medication memo card **(1 article)**

A medication memo card was found to be an effective method to improve medication adherence. Li et al. [39] conducted a randomized controlled trial to improve CHD patients' medication adherence. Intervention in the study included giving a medication memo card to participants with a physician's prescription and time of taking medications [39]. This method improved patients' medication adherence.

4.4.4 Short message service **(1 article)**

Using a sample of 280 outpatients, Fang and Li [46] examined the effectiveness of an electronic messaging support service program as means of providing discharged patients with reminders and

coronary artery disease-related health information. Fang and Li [46] found that compared to the control group who received phone calls, the group that received medication reminders via short message service (SMS) had better cumulative adherence to lipid-lowering therapy after 6 months of the program.

***4.4.5 Mobile app* (1 article)**

Fang and Li [46] built a public platform on one of the most popular mobile apps in China called WeChat. From a computer, healthcare providers regularly released to the WeChat platform CHD-related information of cardio-protective medication including its function, method of use, and side effects. Patients in the experimental group had open access to all information on the WeChat platform [46]. Fang and Li [46] found that compared to the control group, the experimental group had better cumulative adherence to lipid-lowering therapy after six months of the program.

***4.4.6 Educational session/ individual face-to-face education* (5 articles)**

Jiang et al. [41] tested the effectiveness of a nurse-led, hospital-initiated, cardiac-rehabilitation educational program to improve 167 CHD patients' health behaviors, including medication adherence. The cardiac rehabilitation program of this study was started in the hospital and maintained to 12 weeks after discharge, consisting of seven educational sessions covering (1) CHD and self-management principles, (2) medication management, (3) angina prevention and management, (4) physical exercise, (5) dietary management, (6) smoking cessation and (7) family support. Patients who received this intervention demonstrated a significantly better performance in medication adherence [41]. In addition, educating participants' family members improved medication adherence. Li et al. [39] conducted a randomized controlled trial to improve medication adherence. Interventions for the experimental group included educating participants' family members on how to care for patients with myocardial infarction at months one, three, six, nine and 12 post-discharge [39]. Individual face-to-face education provided by healthcare providers also can improve medication adherence [43]. Zhao et al. [43] examined the impact of using a clinical pharmacist support program on medication adherence among patients receiving multi-drug therapy for coronary heart disease in China. Compared to a usual care control group, the intervention group received pharmacist support that included individual face-to-face patient education. As a result, patients in the intervention group showed significantly better understanding of the importance of medication adherence and improved medication adherence [43]. Similarly, in the study conducted by Zhao et al. [45] and Cao et al. [40], healthcare providers gave medical directions and explained the importance of taking cardio-protective medications to patients. The result was that the medication adherence rate was higher in the pharmaceutical care group [45].

In addition to investigating the advantages of each intervention, disadvantages of the interventions were rarely mentioned in the reviewed studies. Only one study [46] discussed that mobile apps and short message services require patients to have access to a cellular data network; therefore, these interventions may be less applicable to patients in rural areas who do not have access to smart phones or cellular networks or who are illiterate.

5. Discussion

In this systematic review we found that cardio-protective medications were commonly prescribed as secondary prevention medication to patients with CHD in mainland China, but that adherence to these medications gradually decreased during a follow-up period. This finding is a critical public health issue in China because it affects the quality of healthcare and negatively impacts CHD patients' health. In this review we synthesized the findings to provide a clearer understanding of factors related to poor adherence which we organized into several key themes. The impact of the lack of medication-related knowledge among CHD patients cannot be underemphasized and served as a barrier to medication adherence and programs aimed to improve medication-related knowledge. Also, our review showed that, in China, there is a significant gap in knowledge among healthcare providers regarding the current guidelines for CHD medication protocols; Physicians' prescribing practices and patterns of adherence to guidelines for CHD medications were found to be a barrier to medication adherence among Chinese patients with CHD [12, 23, 24, 25, 26]. One possible reason for this gap could be the poor and slow dissemination of current guidelines. To improve this gap, a Chinese translation of current international guidelines could be helpful. Because most updated guidelines are made in the United States and Europe, they are written in English. Most Chinese physicians cannot read English or do not have time to read English guidelines. Finally, hospitals in mainland China should provide cardiologists, particularly young cardiologists, with further training opportunities on cardiology prevention and rehabilitation. It is also possible that physicians' poor adherence to practice guidelines is related to healthcare system in China. Under the current system, most physicians are required to see a great number of patients each day and they may not have sufficient amount of time to provide advice to patients on medication adherence.

We found that adherence is contingent upon patients' health and demographic characteristics including age, education, comorbidities, number of medications prescribed, adverse effects, and insurance. Patients from more affluent backgrounds and with access to care were likely to have better medication adherence overall. Finally, we found that interventions to improve medication adherence varied in methods, but that education and reminder were the consistent key components of all interventions.

We used a set of criteria to assess quality of evidence provided by each of the included 33 studies. These criteria included study design, sample selection and size, measures, control for confounding variables, length of follow-up period, attrition rate, and statistical analyses [47]. Our review revealed a significant variation in the quality of reviewed studies. Overall, studies published in English journals provided more methodological details than those published in Chinese journals. Major limitations to some of the 33 studies included using non-representative samples, unstandardized assessment measures, and an insufficient number of longitudinal findings. Therefore, findings from this review are not conclusive. However, they provide a foundation from which to conduct future research. In particular, findings suggest more research should be conducted on how to establish high quality health educational programs aimed to increasing patients' medication adherence.

In China, educating patients to take medications is the responsibility of healthcare providers. However, this review found that many Chinese physicians did not provide patients advice on the importance of medication adherence. This might be due to physicians' insufficient or not-up-to-date knowledge of cardio-protective medications or due to physicians' lack of time allocated for each patient. Further, no articles in this review explored nurses' and pharmacists' knowledge of cardio-protective medications. To further explore the reasons for poor cardio-protective medication adherence among patients with CHD in mainland China, future studies should focus on the roles of all healthcare providers on patient education. Improving discharge prescription of cardio-protective medications and promoting long-term patient adherence is critically needed in China. Many studies in the review were conducted in urban areas of China. Given that there is a big difference in medical care between urban areas and rural areas of China, future research should study the medication adherence among patients with CHD living in rural China. In the meantime, income and cost are consistently found to be associated with medication adherence. China is in the process of undergoing healthcare reform and extending health insurance coverage in rural areas. Demonstration projects are needed to examine the cost effectiveness of health insurance extension on medication adherence. More robust studies are needed to examine the mediator and moderator factors associated with medication adherence using longitudinal data.

6. Competing Interests

None

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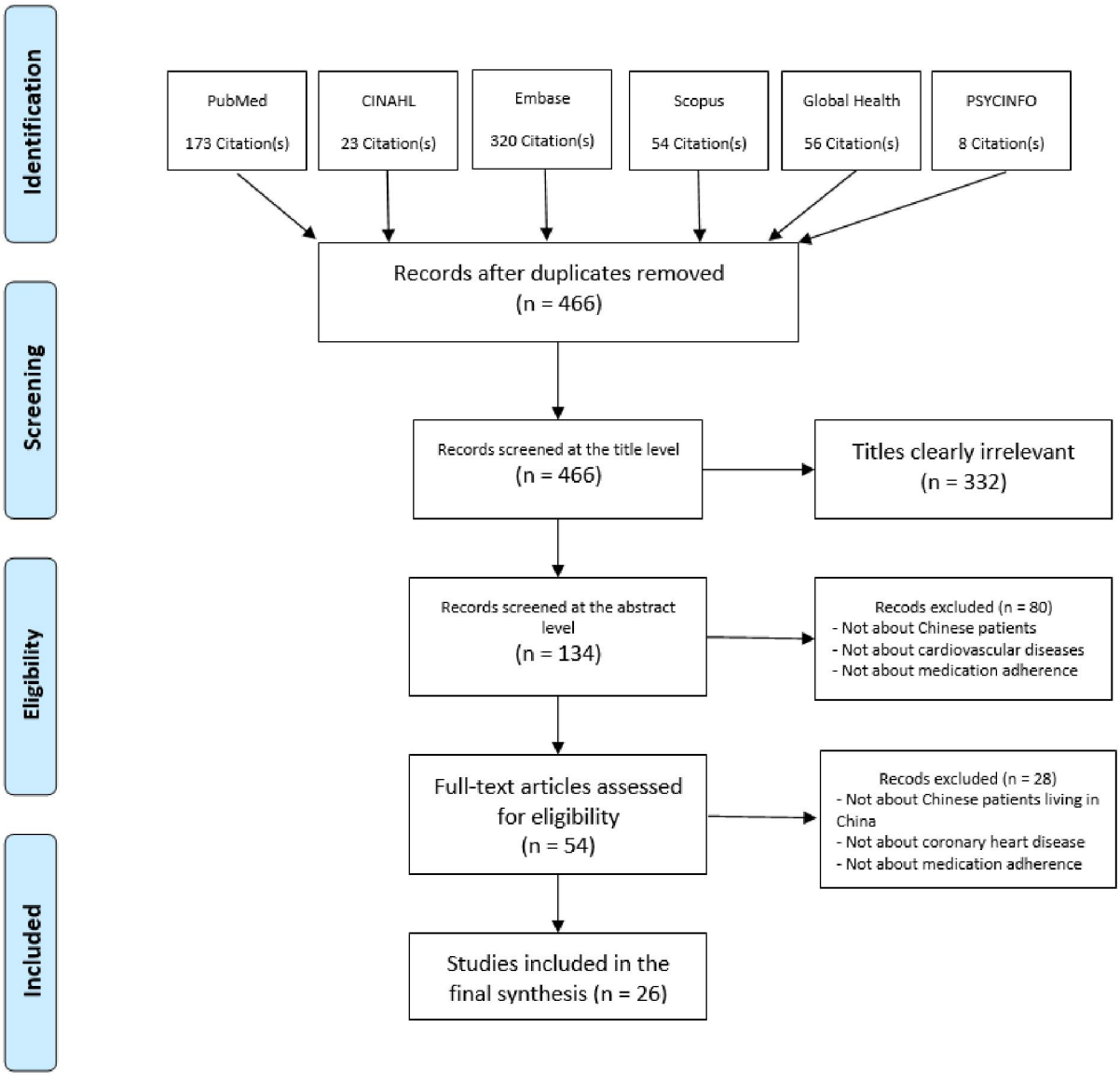

Figure 1: Literature review flow chart for English database
Source: Adapted from PRISMA 2009 Flow Diagram [48].

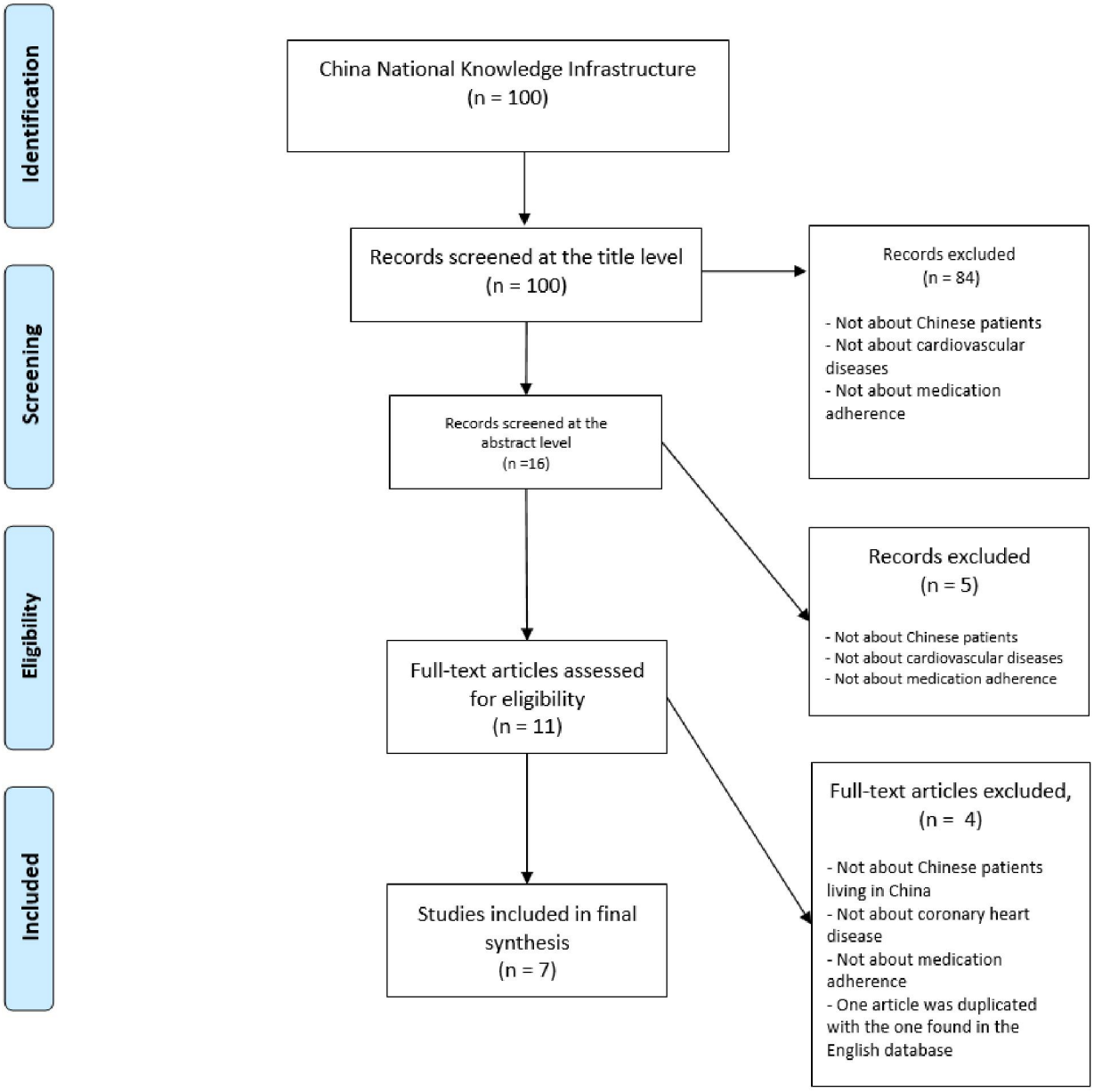

Figure 2: Literature review flow chart for Chinese database
Source: Adapted from PRISMA 2009 Flow Diagram [48].

Table 1: Search trial on PubMed, CINAHL, Embase, Scopus, Global Health, and PSYCINFO

Database	Search #	MeSH Terms and Key Words	Articles Revealed
PubMed	#1	("coronary disease"[MeSH Terms] OR ("coronary"[All Fields] AND "disease"[All Fields]) OR "coronary disease"[All Fields] OR ("coronary"[All Fields] AND "heart"[All Fields] AND "disease"[All Fields]) OR "coronary heart disease"[All Fields]) OR ("coronary artery disease"[MeSH Terms] OR ("coronary"[All Fields] AND "artery"[All Fields] AND "disease"[All Fields]) OR "coronary artery disease"[All Fields])	294,895
	#2	china"[MeSH Terms] OR "china"[All Fields]) OR ("asian continental ancestry group"[MeSH Terms] OR ("asian"[All Fields] AND "continental"[All Fields] AND "ancestry"[All Fields] AND "group"[All Fields]) OR "asian continental ancestry group"[All Fields] OR "chinese"[All Fields])	1357,102
	#3	adherence [All Fields] OR ("patient compliance"[MeSH Terms] OR ("patient"[All Fields] AND "compliance"[All Fields]) OR "patient compliance"[All Fields] OR "compliance"[All Fields] OR "compliance"[MeSH Terms]) OR persistence [All Fields] OR discontinue [All Fields] OR underuse [All Fields] OR non-adherence [All Fields] OR non-compliance [All Fields] OR comply [All Fields] OR ("patient compliance"[MeSH Terms] OR ("patient"[All Fields] AND "compliance"[All Fields]) OR "patient compliance"[All Fields] OR "compliant"[All Fields]) OR adhere [All Fields]	353,524
	#4	#1 AND #2 AND #3	**173**
CINAHL	#1	(coronary heart disease OR coronary artery disease)	33,626
	#2	(China OR Chinese)	59,960
	#3	(adherence OR compliance OR persistence OR discontinue OR underuse OR non-adherence OR non-compliance OR comply OR compliant OR adhere)	105,750
	#4	#1 AND #2 AND #3	**23**
Embase	#1	(coronary AND ('heart'/exp OR heart) AND ('disease'/exp OR disease) OR coronary) AND ('artery'/exp OR artery) AND ('disease'/exp OR disease)	433,989
	#2	china OR chinese	1,695,781
	#3	adherence OR compliance OR persistence OR discontinue OR underuse OR 'non adherence' OR 'non-compliance' OR comply OR compliant OR adhere	524,776
	#4	#1 AND #2 AND #3	**320**
Scopus	#1	(coronary heart disease OR coronary artery disease)	201,258
	#2	(China OR Chinese)	1,096,428
	#3	(adherence OR compliance OR persistence OR discontinue OR underuse OR non-adherence OR non-compliance OR comply OR compliant OR adhere)	696,604
	#4	#1 AND #2 AND #3	**54**
Global Health	#1	(coronary heart disease OR coronary artery disease)	39,659
	#2	(China OR Chinese)	315,129
	#3	(adherence OR compliance OR persistence OR discontinue OR underuse OR non-adherence OR non-compliance OR comply OR compliant OR adhere)	58,414
	#4	#1 AND #2 AND #3	**56**
PSYCINFO	#1	(coronary heart disease OR coronary artery disease)	6,844
	#2	(China OR Chinese)	99,722
	#3	(adherence OR compliance OR persistence OR discontinue OR underuse OR non-adherence OR non-compliance OR comply OR compliant OR adhere)	80,844
	#4	#1 AND #2 AND #3	**8**

Table 2. Details of the thirty-three articles included in this systematic review.

First author / year	Research design	Sample	Location	Measuring medication adherence	Findings	Theme topic
Bi 2009 [2]	A multicenter prospective study	N=2901, average age: 64.5 ± 12, female 948	51 hospitals (41 tertiary and 10 non-tertiary urban hospitals) in China	Standardized paper case report forms were used to document if participants were adherent to their medication	Medications adherence was high at the time of hospital discharge, but decreased during follow-up. Patients discharged on more drugs had even lower adherence	Healthcare providers' lack of knowledge
Jin 2014 [3]	Two-groups comparison study	N=469, female 142 (30.3%)	Nanjing, Jiangsu province, China	Did not use instrument	Older patients had a significantly decreased medication adherence than younger patients	Age; Income; Comorbidity; Adverse effects; Education; Discharge; Medication cost/insurance
Zhang 2015 [12]	Three-group comparison study	N=5926, female 1095 (18%)	Beijing, China	Participants' medication adherence was measured by their patterns of β-blocker use at hospital discharge and during the first year after discharge: (1) always users, (2) never users, and (3) inconsistent users	Consistent β-blocker use after hospital discharge was noted in 2922 patients (49.3%), whereas 1323 patients (22.3%) never used β-blockers	Healthcare providers' lack of knowledge
Jiang 2012 [13]	Cross-sectional study	864 physicians participated in the survey, representing 86% of all attending physicians and residents in cardiology departments in the 35 hospitals	35 tertiary hospitals located in urban areas of China	Did not measure medication adherence	Medication adherence is related to physicians. Knowledge of physicians was not precise or up-to-date	Healthcare providers' lack of knowledge
Wang 2014 [16]	Retrospective analysis study	N=1368, age range: 80 to 101, age average age: 86.4 ± 6.6, female 528	Beijing, China	Morisky-Green (MG) questionnaire	Chinese people with CHD older than 80 years had poor adherence to statin. 22% of them did not adhere to their statins	Age; Education; Patients' lack of knowledge; Income
Li 2015 [17]	Retrospective analysis study	N=138, age range: from 54 to 76, average age: 62.12 ± 10.11, 68 female	Enshi City, Hubei province, China	Used a self-made scale. Very much like Morisky Medication Adherence Scale (MMSA-4), but one question is different. Validity and reliability were not reported	Adherence to statins is poor among Chinese people with CHD. 36.23% of them had poor adherence	Number of discharge medications; Adverse effects; Income; Patients' lack of knowledge; Age; Education; Medication cost/insurance
Ding 2013 [18]	Cross-sectional study	N=903, average age: 64.9±10.7, female 257 (29.3%)	Beijing, China	Self-made questionnaire	LDL-C control rate is very low in people with CHD living in Beijing. Only 36.9% reached the standard of LDL-C control	Patients' lack of knowledge; Healthcare providers' lack of knowledge

Zhao 2015 [19]	Cross-sectional study	N=159, average age: 61.7 y, female 58 (36.5%)	Zhengzhou, Hennan province, China	The Morisky Medication Adherence Scale (MMSA-8)	Among Chinese people with CHD, who lack knowledge about their medications were more likely to divert from the instructions for their medication	Patients' lack of knowledge
Dai 2013 [20]	Cross-sectional study	N=200, age range: from 28 to 67, 88 female	Donggu village, Pinggu District, Beijing, China	Used a self-made survey, which was tested in a pilot study	Medication adherence is poor in Chinese rural areas. 61.7% participants had poor adherence	Number of discharge medications; Adverse effects; Patients' lack of knowledge; Education
Hu 2008 [21]	Cross-sectional study	N=4,778, female 1,719 (36.0%)	52 medical centers in 6 Chinese cities: Shanghai, Beijing, Guangzhou, Zhejiang, Tianjin and Xinjiang	Did not use instrument. Adherence to Statins was measured as the rate of achieving the target LDL-C level	18.6% of CHD patients at high risk of cardiac event were not taking statins as lipid-lowering therapy; 17.5% of CHD patients at very high risk of cardiac event were not taking statins	Healthcare providers' lack of knowledge
Jiang 2015 [22]	Cross-sectional study	N=5407, average age: 67.6, female 2152 (42.9%)	298 hospitals in 15 Chinese provinces	Did not use instrument. Participants who were adherent were defined as those who were still on their medications at the third month after baseline survey	Medication non-adherence is common in Chinese people with CHD. Several factors were identified	Education; Healthcare providers' lack of knowledge
Xu 2012 [23]	A retrospective cross-sectional study	N=200, female 62	Hangzhou, Zhejiang province, China	Medication use was calculated by percentage of CHD participants who were prescribed cardio-protective medication	Patients discharged from the Chinese medical hospital were less likely to receive ACE inhibitors/ARBs and beta-blockers than those discharged from the general hospital	Healthcare providers' lack of knowledge
Li 2016 [24]	A sequential cross-sectional study	N=2463, female 673	Hospitals were chosen from both economic-geographical regions (eastern, central, and western) and rural/urban regions	Did not use instrument. Used the 2010 Chinese Guideline for Diagnosis and Treatment of Patients with ST-elevation Myocardial Infarction to determine whether patients received the appropriate fibrinolytic dosage. Appropriate dosage was defined as between 80% and 120% of the recommendation. Underdosing was defined as less than 80% and overdosing was defined as more than 120% of the recommended dose	Many CHD patients were not treated with fibrinolytic therapy: only 49.5% ideal candidates for fibrinolytic therapy received it	Healthcare providers' lack of knowledge
Wang 2015 [25]	Retrospective analysis study	N=2128, 724 female (34.02%)	20 tertiary hospitals in Heilongjiang province of China	Did not use instrument. Medication adherence rate was calculated as the number of eligible patients who actually received the recommended	The adherence rates to aspirin, beta-blocker, clopidogrel, ACEI, statin were much less than the target level recommended by the	Healthcare providers' lack of knowledge

				medication divided by all patients eligible for it	ACC/AHA as first-line treatments for practice guidelines	
Li 2008 [26]	Cross-sectional study	N=4778, female 1719	52 centers in 6 cities in China: Shanghai, Beijing, Guangzhou, Xinjiang, Zhejiang, Tianjin	Did not use instrument	The number of CHD patients achieved the recommended LDL-C level was suboptimal. 18.6% of CHD patients at high risk did not receive statin therapy; 17.5% at very high risk did not receive statin therapy	Healthcare providers' lack of knowledge
Li 2012 [27]	Randomized controlled trial	N=16860, average age: 63, female 4384 (26%)	72 study sites in 14 Chinese cities	Did not use instrument. Medication adherence was assessed by the rate of medication usage among participants	Among Chinese people with CHD, antiplatelet therapy was commonly used but the use of statins, beta-blockers and ACEIs was still not optimal	Age; Comorbidity; Discharge; Adverse effects
Zhuang 2016 [28]	Cross-sectional study	N=348, age range: from 45 to 75, average age: 60 ± 6, female 166	Shanghai, China	Did not use instrument. Medication adherence was identified as following physician's prescriptions to take antiplatelets. Non-adherence was identified as changing dosage/frequency of prescribed antipletelets or stopping prescribed antipletelets	The percentage of participants who adhered to their antipletelets were 98.3%, 92.8% and 81.9% respectively in 3 months, 6 months, 12 months after being discharged from hospital	Discharge; Age; Education
Yang 2012 [29]	Two-groups comparison study	N=403, age range: 48-84, average age: 66.98± 7.98, female 161 (40%)	Guiyang, Guizhou province, China	Morisky Medication Adherence Questionnaire	Medication adherence can be different among male and female. Female participants had better medication adherence in aspirin, beta-blockers, and angiotensin-converting enzyme inhibitors / angiotensin II receptor blockers; There was no significant difference between female and male participants in adherence to Statins	Gender
Huang 2014 [30]	Longitudinal study	N=262, 51 female (19.5%)	Nanning city, Guangxi province, China	Morisky Green Levine Test	Six months after the PCI, 48.9% participants did not adhere to their antipletelets. 12 months after the PCI, 62.9% participants did not adhered to their antipletelets	Income; Education; Discharge; Medication cost/insurance
Zhang 2011 [31]	Retrospective analysis study	N=500, average age: 72±8.82, female 228 (45.6%)	Chongqing, China	Did not use instrument. Participants were interviewed within 12 months after percutaneous coronary intervention (PCI). If a participant told	All participants adhered to their medications at baseline. After being discharged from hospital, the adherence	Comorbidity; Discharge; Medication cost/insurance; Education

				s/he the same medication as s/he was at the time of discharge, the participant was regarded as adherent	rate started to decrease. 185 (37%) participants did not adhere to their medications. Among the 185 participants, nearly 97% stopped their medications 6 months later after being discharged or even earlier	
Li 2013 [32]	Cross-sectional study	N=272, age range: from 39 to 71, 100 female	Wuding county, Yunnan province, China	Did not use instrument. Participants were identified as nonadherent as long as they missed one dose, changed the dosage/frequency, or made self-decision to stop medication	87.82% participants did not adhere to prescribed medications. Of these participants, 22.9% changed their medications' dosage or frequency, 30.6% missed at least one dose of medication, 34.3% stop physician-prescribed medications and replaced them by other medications	Income
Liu 2017 [33]	An observational cohort study	N=404, average age: 58 ± 10, female 99 (24.5%)	Beijing, China	Did not use instrument. Medication adherence was assessed by whether participants stopped taking prescribed medication--ticagrelor	39.1% participants did not adhere to their medications. Economic reasons and hemorrhagic event were the main causes of the non-adherence to ticagrelor.	Adverse effects; Income
Chen. 2015 [35]	Longitudinal study	N=512, female 302	Jiangsu province, China	Did not use measurement. Medication adherence was defined as taking the same category of drugs at discharge during the follow-up period	Compared with those with preserved LVEF, patients with reduced LVEF have lower medication adherence	Comorbidity
Atkins 2017 [36]	A cohort analysis	N=15,140, female 3651 (24.11%)	70 hospitals from 17 provinces of China	Did not use instrument. Medication adherence was assessed by the rate of medication usage among participants	Use of cardio-protective medications declines over time after discharge	Discharge
Du 2015 [38]	Randomized controlled trial	N=964, female 264	Zhengzhou, Hennan province, China	did not mention	Intervention group had better medication adherence than control group	Follow-up phone call
Li 2012 [39]	Randomized controlled trial	N=100, female 43	Xi'an, Shaanxi province, China	Proportion of days covered (PDC) was used to measure medication adherence. PDC=Number of days when medications were taken / Number of days being interviewed	Intervention group had significantly better medication adherence than control group	Follow-up phone call; Medication memo card; Educational session/ individual face-to-face education
Cao 2017 [40]	Randomized controlled trial	N=236, average age: 68.10, female 64 (27.12%)	Chengdu, Sichuan province, China	The Morisky Medication Adherence Scale (MMSA-8)	Intervention group had significantly higher medication adherence scores than control group at 30 days and	Educational session/ individual face-to-face education;

					90 days after discharge	Follow-up phone call
Jiang 2007 [41]	Randomized controlled trial	N=167, female 48	Chengdu, Sichuan province, China	The self-reported drug compliance scale, a five-point Likert scale ranging from 1 (totally drug refusal) to 5 (100% drug compliance). This instrument is reliable and valid.	Medication adherence was decreased over time, but to a significantly lesser extent in intervention group	Educational session/ individual face-to-face education; Follow-up phone call; Booklet
Zhao 2009 [42]	Randomized controlled trial	N=200, female 53 (53%)	Tianjin, China.	Did no mention the name of the survey, but the authors explained the content validity of the instrument was confirmed by experts in the study team	Medication adherence was not significantly different between control group and intervention group at baseline, but intervention group participants' adherence was better became significant in weeks 4 and 12	Follow-up phone call
Zhao 2015 [43]	Randomized controlled trial	N=90, didn't mention female	Zhengzhou, Hennan province, China	Questionnaire, did not mention the name of the questionnaire, and did not mention its reliability and validity	Medication adherence was significantly better in intervention group than in control group	Educational session/ individual face-to-face education; Follow-up phone call
Wu 2012 [44]	Two-groups comparison study	N=110, female 22 (20%)	Chengdu, Sichuan province, China	Did not use measurement. Interviewed participants to see if they were still taking their medication	Medication adherence of the intensive group was much better than the control group	Booklet
Zhao 2015 [45]	Randomized controlled trial	N=120, female 48	Zhengzhou, Henan province, China	Did not use instrument	Intervention group had better medication adherence than control group	Booklet; Educational session/ individual face-to-face education; Follow-up phone call
Fang 2016 [46]	Randomized controlled trial	N= 280, age range: 38-69, female 80 (28.58%)	Chengdu, Sichuan province, China	Morisky Medication Adherence Scale (MMAS-4)	Participants in the intervention group of using WeChat had better Medication adherence	Short message service; Mobile app

2/25/2019