Review Article

Effect of Pharmacist-Led Interventions on Blood Pressure Among Adult Asian Patients with Hypertension: A Systematic Review and Meta-Analysis

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ABSTRACT

The expanding role of pharmacists in patient-centered care prompted investigation of its effectiveness in hypertension management; however, data are inconsistent and less generalizable to the Asian population. This study aimed to determine the effect of pharmacist-led interventions on the blood pressure (BP) of adult Asian patients with hypertension, compared to no pharmacist-led intervention. Five databases, grey literature, and hand search were used to locate articles from inception to September 2023. We included randomized controlled trials among adult Asian patients with hypertension receiving pharmacist-led intervention versus no pharmacist-led intervention, reporting changes in systolic and diastolic BP (SBP & DBP) from all languages. Study quality was assessed with Cochrane Risk of Bias tool, results analyzed qualitatively and quantitatively per PRISMA guidelines, meta-analysis conducted with random-effects model, heterogeneity explored through subgroup analysis, and publication bias assessed through funnel plots. From 11,914 studies, 14 studies were analyzed. Results show the most common pharmacist-led intervention was educational intervention (n=13, 92.86%); pharmacist-led interventions significantly decreased SBP by -5.15 mmHg (95% CI: -8.43, -1.88) and DBP by -2.59 mmHg (95% CI: -4.85, -0.32). Subgroup analysis revealed healthcare setting, number of interventions investigated, non-use of technology, predominant sex, country income status, and prevailing level of education affect SBP and DBP lowering. Findings should be used with caution due to various sources of heterogeneity, moderate- to high-risk of bias, and potential publication bias. The findings support optimization of hypertension management via pharmacist-led interventions.

Keywords: Hypertension; Blood pressure; Pharmacist-led intervention; Asia; Systematic review and meta-analysis

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1.0 Introduction

More than one billion individuals worldwide suffer from hypertension, which is the primary cause of cardiovascular (CV) mortality and morbidity. Asia is home to around 60% of the total global population and accounts for more than half of the worldwide population with hypertension, making hypertension a crucial issue (1, 2).

Pharmacists, as highly accessible healthcare professionals (HCPs) with extensive medication expertise, are well-positioned to optimize drug therapy and fill the gaps of the healthcare system. As they transition to a more patient-focused approach, pharmacists can conduct interventions in a variety of settings to improve the medication taking behavior and disease management of patients with chronic diseases, particularly hypertension (3).

Most published trials, systematic reviews, and meta-analyses on pharmacist-led interventions in the management of hypertension reported significant improvement in blood pressure (BP) for the intervention groups. However, there are also some that show little to no significant change. These inconsistencies may be due to differences in study populations, types and intensities of interventions, healthcare settings, and follow-up durations. Additionally, most research has focused on Western populations, so these results cannot be generalized to the Asian population which has notable differences in their culture and characteristics, such as higher salt intake, a high incidence of physical inactivity, and obesity (1,4).

Evidence specific to Asian populations living in Asia remains limited. Moreover, many of the existing reviews restricted their search strategy to English-language publications, excluded grey literature, inconsistently discussed risk of bias analyses, and rarely integrated these biases into their interpretation of results (5-9). These methodological gaps limit the applicability of prior findings to Asian contexts and highlight the need to collate all existing evidence on this topic through a systematic review and meta-analysis.

The objective of this review was to determine the effect of pharmacist-led interventions to the blood pressure of adult Asian patients with hypertension by describing these interventions, qualitatively and quantitatively synthesize the effect of these interventions on systolic blood pressure (SBP) and diastolic blood pressure (DBP), and determine both pharmacist-led and patient factors that can change SBP and DBP. The results of this review can be used in the implementation and pilot testing of pharmacist-led interventions across different healthcare settings. The general research question of this review is: Among adult Asian patients with hypertension, how do pharmacist-led interventions, as compared to no pharmacist intervention, affect blood pressure?

This review only included studies with an outcome of interest that considered change in BP as noted by increase, decrease, or mean differences (MDs) of SBP and DBP. Results were based on available data from existing literature, because no primary data collection was conducted. Articles were limited to databases that were utilized for screening and databases accessible to the college and university library.

2.0 Materials and Methods

2.1 Study design

A systematic review with meta-analysis adhering to the “Preferred Reporting Items for Systematic Review and Meta-Analyses” (PRISMA) standardized reporting guidelines was conducted (10). The protocol was registered prospectively on PROSPERO (Registration No.: CRD42024500886).

2.2 Search strategy

An electronic search was conducted through five databases, PubMed, Scopus, EBSCO, Web of Science, and Wiley Online Library from inception to September 30, 2023. Articles of all languages were included in the search. References of relevant trials and systematic reviews with or without meta-analysis were hand searched. Clinical trial registries such as ClinicalTrials.gov (https://clinicaltrials.gov/), International Clinical Trials Registry Platform (ICTRP) (https://trialsearch.who.int/), EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/), and other appropriate registries were explored. Review of unpublished, local, and grey literature through national repositories likely to contain relevant research, such as the College of Pharmacy Library, University of the Philippines Manila Library through the TUKLAS website, and Philippine National Library was conducted. These sources were selected because they provide access to local theses, dissertations, and government-funded studies that are not indexed in international databases. Review of reference lists of included and selected publications was also done. Choices of databases and sourcing of unpublished studies and grey literature were consulted with an expert (MAJG). The main keywords used were "pharmacist led intervention", "blood pressure", and "hypertension" which were combined using Boolean Operators (AND, OR), with no language or year restrictions applied. The search strings, and the databases/sources where they were used, are listed in Table 1.

2.3. Inclusion and exclusion criteria

The inclusion and exclusion criteria applied in this review are summarized in Table 2. The classification of pharmacist interventions was adapted and modified from Morgado *et al*. (2011) (12).

2.4 Study selection

Articles captured from databases using the search strings were imported into EndNote 21. The three reviewers with the following initials: S.B.D., M.G.G., and A.A.H. independently screened the titles and/or abstracts of identified studies and eliminated those deemed irrelevant through EndNote 21. This screening form was encoded in Google Sheets.

Studies with inconclusive suitability for inclusion were read in full via a screening form created for this study. Duplicates were automatically removed upon compilation of screening results through EndNote. Non-English articles were to be translated through the Google Translate website, or other appropriate applications if Google Translate was inadequate. However, since all studies included were in English, translation was not needed. Studies excluded were documented and reported with the reason for exclusion. Disagreements were managed through discussion and consensus.

2.5 Data extraction

Data extraction was conducted independently by the three reviewers. Data extracted included publication details, study design characteristics, participant characteristics, methodological characteristics, intervention and comparator characteristics, the outcome measures, and data for pooling if available.

2.6 Risk of bias assessment

Three reviewers independently assessed the risk of bias using the Cochrane RoB 2 tool. This tool evaluates bias from: (a) randomization process, (b) deviations from intended interventions, (c) missing outcome

Table 1: Search strings used for specific databases.

Database	Search String
PubMed **Scopus** **EBSCO** **Web of Science** **Clinical Trial Registries such as:** ● **ClinicalTrials.gov** ● **International Clinical Trials Registry Platform (ICTRP)** **EU Clinical Trials Register**	(pharmac* OR pharmacist) AND (led OR intervention OR service OR care OR counsel) AND (hypertens* OR HTN OR "High Blood Pressure" OR "Elevated Blood Pressure") AND (RCT OR "randomized controlled trial")
Wiley Online Library	"((pharmac* OR pharmacist) AND (led AND (intervention OR service OR care OR counsel))) AND (hypertens* OR HTN OR "High Blood Pressure" OR "Elevated Blood Pressure") AND (asia) AND (RCT OR "randomized controlled trial")" anywhere and "pharmac* OR hypertens*" in Keywords
University of the Philippines Manila Library through the TUKLAS website	(pharmac* OR pharmacist) AND (led OR intervention OR service OR care OR counsel) AND (hypertens* OR HTN OR "High Blood Pressure" OR "Elevated Blood Pressure")
College of Pharmacy Library	(pharmac* OR pharmacist) AND (led OR intervention OR service OR care OR counsel) AND (hypertens* OR HTN OR "High Blood Pressure" OR "Elevated Blood Pressure")
National Library of the Philippines through eLib website	(title) pharmacist OR (any field) hypertension OR (subject) pharma

Table 2: Inclusion and exclusion criteria.

Criteria	Inclusion	Exclusion
Study Design	Randomized controlled trials (RCTs)	Not original studies; duplicate data from other articles
Population	Adult Asians (≥18 years) diagnosed with hypertension, on antihypertensive medications, with/without comorbidities	Pregnant, comatose in ICU, cancer, hypertensive emergency/urgency, psychological conditions
Location	Studies conducted in Asia	Studies conducted outside Asia
Intervention	Led or conducted solely by a pharmacist for hypertension management	Pharmacist collaboration with other healthcare professionals
Comparator	No pharmacist intervention	Not applicable
Timeframe	≥1 month duration	<1 month
Outcomes	Change in BP (SBP, DBP) at baseline and follow-up, or reported mean difference (MD)	Insufficient data for analysis, data not extractable, or untranslatable
Setting	Change in BP (SBP, DBP) at baseline and follow-up, or reported mean difference (MD)	Not applicable
Date	Published from inception to September 30, 2023	Not applicable

data, (d) measurement of outcome, and (e) selection of the reported result. Domains were rated as 'Low risk,' 'Some concerns,' or 'High risk' of bias (18). Inconsistencies were resolved through consultation with an expert (MAJG).

Studies with high risk of bias were not excluded if they met all other eligibility criteria, as exclusion could introduce selection bias and limit the comprehensiveness of evidence synthesis. Instead, their inclusion was accompanied by explicit risk-of-bias reporting and sensitivity analyses where applicable. A risk-of-bias summary graph was generated using the robvis online tool, which visually displays the proportion of studies rated at each risk level across domains, allowing quick appraisal of the overall quality of evidence in the review (19).

Publication bias

Publication bias was assessed using funnel plot asymmetry, where treatment effect size is plotted on the x-axis and its standard error (variance) on the y-axis. A symmetrical funnel indicates low likelihood of bias, while asymmetry may indicate potential small-study effects or selective publication. This visual assessment aids in determining whether results may be skewed by under-reporting of negative or non-significant findings. Funnel plot was generated using Review Manager v5.4.

2.7 Statistical analysis

Qualitative analysis

The characteristics of included studies were analyzed with frequency statistics. A narrative synthesis of evidence was created based on the data extracted.

Quantitative analysis

Data of interest for the outcome measures were evaluated as continuous variables: sample size, mean, and standard deviation (SD). Baseline and follow-up mean values were extracted; if such values were unavailable, these were calculated based on reported data. If SDs were not provided, they were imputed using available data to obtain the MD or the change of SBP and DBP from baseline to last follow-up. The Cochrane Handbook guidelines were observed in undertaking imputation of SDs through use of a correlation coefficient (*r*). Since reported r values varied widely across studies, a conservative value of 0.7 was used, in line with the meta-analysis conducted by Yagiz *et al*. (2022) (20). Figure 1 shows the equations for calculating the SD of change for (a) the experimental group and (b) the control group up.

Once data were ready for pooling, meta-analysis was conducted using a random-effects model. Forest plots were visually inspected, and heterogeneity was quantified using Higgins' I^2 statistic, interpreted as low (<25%), moderate (25–74%), or high (≥75%). Potential sources of heterogeneity were explored via a meta-regression model. A co-variable was considered a source of heterogeneity if the regression coefficient was statistically significant or if the Tau^2 value decreased by at least 50%. Subgroup analyses were then performed.

Results from aggregate data on individual RCTs were used have an estimate MD of BP change based on the stratification between intervention characteristics (i.e., type and frequency of intervention), patient factors (i.e., age, sex, and comorbidities), and the setting (i.e., hospital outpatient clinic, community pharmacy, and primary healthcare setting).

Google sheets were utilized for data input and cleaning. All statistical analyses were conducted through Review Manager 5.4 and with 95% CI ($\alpha = 0.05$).

3.0 Results

The search conducted from the databases, registries, and hand search yielded 11,914 potential eligible articles. Upon removing duplicates (n = 1,144), the remaining articles were screened for title and abstract through EndNote 21; 33 RCTs met the inclusion criteria and were then screened in full-text. Overall, fourteen studies with 2,945 participants were included in the review (21-34). All studies were published in English and no translations were required. Overview of the conducted search and selection of studies is presented in the PRISMA diagram (see Figure 2).

(a) $$SD_{E,change} = \sqrt{SD^2_{E,baseline} + SD^2_{E,final} - (2 \times Corr \times SD_{E,baseline} \times SD_{E,final})}$$

(b) $$SD_{C,change} = \sqrt{SD^2_{C,baseline} + SD^2_{C,final} - (2 \times Corr \times SD_{C,baseline} \times SD_{C,final})}$$

Figure 1: Equation for calculating SD change of the (a) experimental group and (b) control group.

3.1 Quality assessment

Data from included studies were extracted using a pre-established data extraction form. As shown in Figure 3, the risk of bias summary shows that most articles were with high risk (n=8, 57.14%) of bias and with some concern (n=5, 35.71%) and only one had low risk of bias. The assessment of risk of bias shows that the studies mostly had difficulties in blinding their participants, intervention providers, and the assessors. This may be due to the nature of pharmacist-led interventions, as patients who interact with pharmacists will be aware they are part of the intervention group. Included studies were published in the years 2004 to 2023, with countries from the East Asian (n=5, 35.71%), South Asian (n=5, 35.71%), Southeast Asian (n=2, 14.28%) and West Asian regions (n=2, 14.28%), further categorized as belonging to low-middle (n=8, 57.14%), upper-middle (n=4, 28.57%) or high income (n=2, 14.28%) status in accordance with the latest World Bank data (35). Different settings were utilized in the trials, namely the hospital (n=9, 64.29%), primary health (n=3, 21.43%), and community (n=2, 14.28%) healthcare setting.

3.2 Participant characteristics

Within-study mean age of participants ranged from 39 to 65 years old. Nine studies reported being predominantly male while five reported being predominantly female. The smallest sample size comprised 56 participants (26) and the largest among the studies is 385 (27). Only nine studies reported the levels of education attained by their participants, with most having the highest attained level of primary (n=4, 28.57%) and high school (n=4, 28.57%). There were eight studies which included patients with comorbidities and the rest (n=6, 42.86%) did not report such information. A summary of the participant characteristics can be found in Table 3.

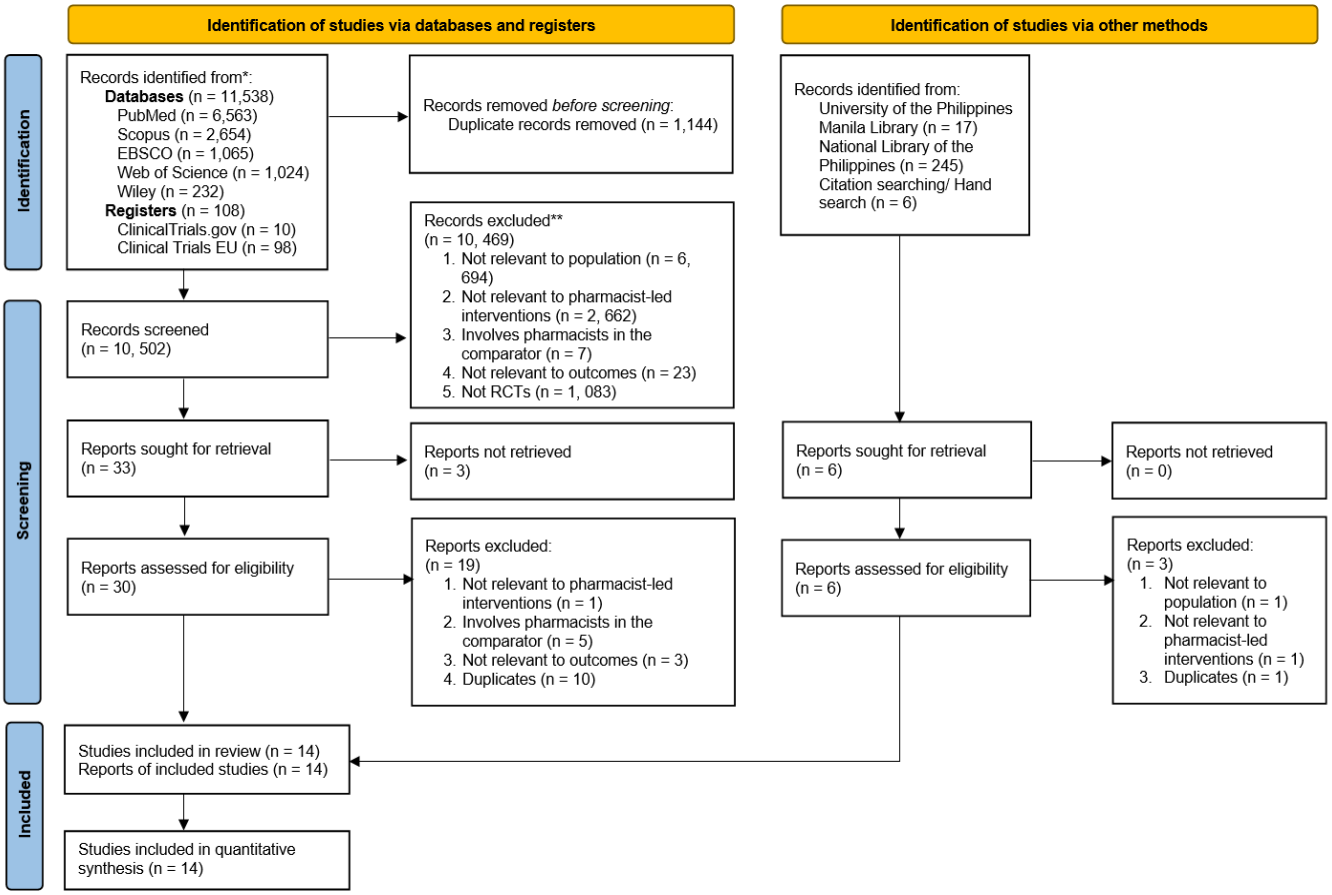

Figure 2: PRISMA Diagram.

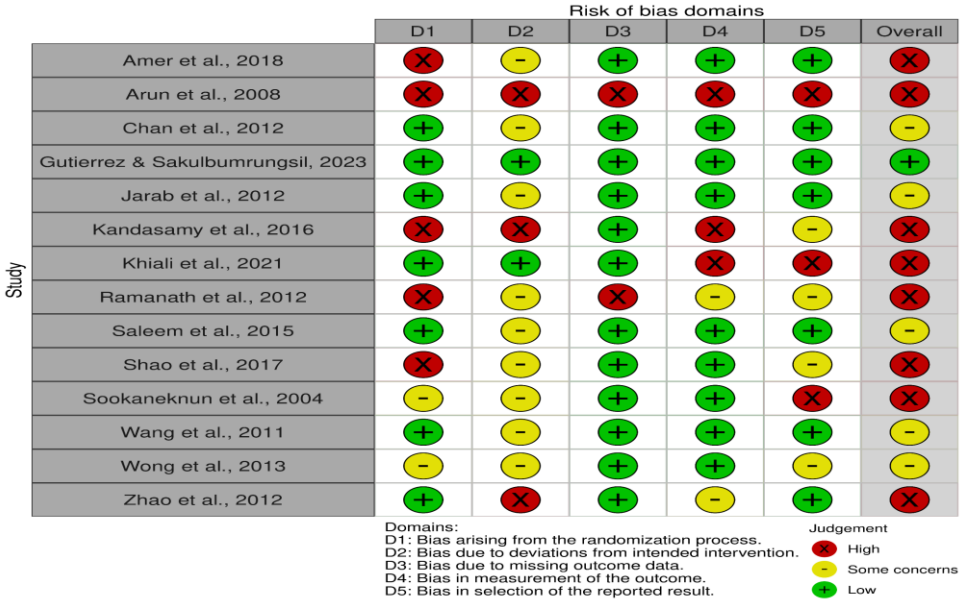

Figure 3: Risk of bias summary.

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Table 3: Patient Characteristics in the Pharmacist-led Interventions.

Study ID & Country	Measure of outcomes	Sex Ratio (Male: Female) [Intervention]	Sex Ratio (Male: Female) [Control]	Reported Age of Participants	With Comorbidities? (Yes (Y)/ No (N))	Country's Income Status	Level of Education
Amer *et al*., 2018 Pakistan	Mean SBP (mmHg); Mean DBP (mmHg)	117:75	98:94	**30-40 y/o** Intervention: 31 Control: 30 **41-50 y/o** Intervention: 64 Control: 74 **51-60 y/o** Intervention: 63 Control: 62 **61-70 y/o** Intervention: 34 Control: 26	N	Lower- Middle	**Illiterate** IG: 14 CG: 73 **Primary** IG: 15 CG: 22 **Middle** IG: 30 CG: 28 **Matriculation** IG: 60 CG: 41 **Intermediate** IG: 20 CG: 9 **Graduate** IG: 36 CG: 11 **Post graduate** IG: 17 CG: 8
Arun *et al*., 2008 India	Change in SBP and DBP from baseline to endpoint	46:58	24:26	**Intervention group:** 57.5 ± 8.63 **Control group:** 58.8 ± 9.95	Y	Lower- Middle	Unreported
Chan *et al*., 2012 Hong Kong	Change in SBP and	30:21	28:26	**Control group**: 61.7 +/- 11.2	Y	High	Unreported

	DBP from baseline to endpoint			**Intervention group**: 63.2 +/- 9.5			
Gutierrez & Sakulbumrungsil, 2023 Philippines	Mean SBP (mmHg); Mean DBP (mmHg)	78:137	53:148	**Mean of all**: 57.36 SD of all: 11.11	Y	Lower- Middle	: **Upper Secondary Education** (Senior High School, NC I and NC II): Majority (25.42%) **Primary Education** (Elementary): 22.30% **Bachelor Level Education** (Baccalaureate degree): 22.06%
Jarab *et al*., 2012 Jordan	Mean SBP (mmHg); Mean DBP (mmHg)	49:36	51:38	**Intervention Group**: 63.4 **Control Group**: 65.3	Y	Lower- Middle	**University** Intervention: 21 Control: 23 **Secondary/ High School** Intervention: 64 Control: 63

Kandasamy *et al*., 2016 India	Mean SBP (mmHg); Mean DBP (mmHg)			**21-30 years:** 1 (1.67%) **31-40 years:** 3 (5.00%) **41-50 years:** 14 (23.33%) **51-60 years:** 17 (28.33%) **61-70 years:** 15 (25.00%) **71-80 years:** 10 (16.66%)	Unreported	Lower- Middle	**Illiterate:** 27 **Primary:** 12 **Secondary:** 17 **Graduate:** 4
Khiali *et al*., 2021 Iran	Mean SBP (mmHg); Mean DBP (mmHg)	34:27	37:24	**Intervention Group**: 51.9±13.3 **Control Group**: 49.4±12.9	Y	Lower- Middle	Unreported
Ramanath *et al*., 2012 India	Mean SBP (mmHg); Mean DBP (mmHg)	16:10	21:5	Age in years **31–40:** Control = 3 **41–50:** Control = 3 Intervention = 8 **51–60:** Control = 9 Intervention = 7 **61–70:** Control = 7 Intervention = 10	Y	Lower- Middle	**Illiterate:** IG: 18 CG: 16 **Primary:** IG: 6 CG: 3 **High school:** IG: 1 CG: 3 **Pre-university:** CG: 1 **Degree+:** IG: 1 CG: 3

				>70: Control = 4 Intervention = 1			
Saleem *et al*., 2015 Pakistan	Mean SBP (mmHg); Mean DBP (mmHg)	125:68	140:52	Age 18-27: 48 participants Age 28-37: 186 participants Age 38-47: 128 participants Age >48: 23 participants **MEAN OVERALL**: 39 ± 6.5	Y	Lower- Middle	**Illiterate**: 9 **Religious**: 62 **Primary:** 7 **Secondary**: 51 **High secondary**: 51 **Bachelors**: 154 **Masters**: 51
Shao *et al*., 2017 China	Mean SBP (mmHg); Mean DBP (mmHg)	51:49	52:47	**Intervention Group** 58.86±10.59 **Control Group**: 59.20±10.34	Y	Upper- Middle	**None** IG: 4 CG: 5 **Primary** IG: 2 CG: 3 **Secondary** IG: 63 CG: 58 **Bachelor and Above** IG: 31 CG: 30
Sookaneknun *et al.*, 2004 Thailand	Mean SBP (mmHg); Mean DBP (mmHg)	42:76	33:84	**Intervention Group:** 63.20 ± 9.33 **Control Group:** 63.23 ± 9.25	Y	Upper- Middle	Unreported

Wang *et al*., 2011 China	Mean SBP (mmHg); Mean DBP (mmHg)	15:14	14:16	**Intervention group:** 47.23±7.69 **Control group:** 48.30±9.06	Unreported	Upper- Middle	Unreported
Wong *et al*., 2013 Hong Kong	Mean SBP (mmHg); Mean DBP (mmHg)	28:64	58:81	**Intervention group:** 62.3±8.11 **Control:** 62.5±10.1 **All:** 62.4±9.35	Unreported	High	**Primary or below:** 117 (42 in intervention, 75 in control) **Secondary:** 101 (41 in intervention, 60 in control) **Tertiary or above:** 13 (9 in intervention, 4 in control)
Zhao *et al*., 2012 China	Mean SBP (mmHg); Mean DBP (mmHg)	80:59	82:57	**Intervention Group**: 62.4 ± 19.1 **Control Group**: 65.6 ± 18.8	Y	Upper- Middle	**Illiterate**: 164 **Elementary**: 62 **High schooling**: 43 **University education**: 9

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Table 4: Characteristics of the Pharmacist-led Interventions.

Study ID & Country	Type of Intervention+ (Number of Interventions)	Intervention Description	Setting	Use of technology (Yes (Y)/ No (N))	Frequency of Follow-ups	Timeframe of the Study	Other Hypertension-Related Outcomes
Amer *et al*., 2018 Pakistan	B (1)	Identification of issues related to poor adherence, provision of disease related education to the patient (hypertension-related information, lifestyle education, medication counseling tips to increase knowledge about hypertension, adherence to medication and HRQoL), and printed booklet (in Urdu language) of hypertension related educational material was provided.	Hospital	N	3	4.5	Hypertension Knowledge: use of self-administered and pre-validated knowledge questionnaire (Self-designed) Medication Adherence: use of Morisky Medication Adherence Scale (MMAS-U) Health Related Quality of Life: use of EuroQol (ED-5D)
Arun *et al*., 2008 India	B (1)	Provision of counseling about diabetes and health care.	Community	N	1	5	Health-related quality of life: use of a questionnaire with reference to Ferrans and Powers Quality of Life Index-Diabetes version III, translated into Tamil
Chan *et al*., 2012 Hong Kong	B (1)	Complete medication history recording, medication adherence evaluation, drug adherence education, CVD education, and lifestyle modifications were provided.	Hospital	N	1	Unreported	Compliance score: calculated by dividing the number of tablets taken by the correct number and

							expressed as a percentage. Patients were considered compliant to medication regimen if their compliance score was greater than 80%.
Gutierrez & Sakulbumrungsil, 2023 Philippines	B, F (2)	Use of an expert system to produce outputs: 1.) a personalized patient information material; 2.) a medication reminder function in the patient's smartphone; 3.) a tailored guide for pharmacists that can be used during patient counseling; and 4.) a formal communication channel between the patient and the pharmacist.	Primary care	Y	3	6	Medication Adherence: use of medication possession ratio
Jarab *et al*., 2012 Jordan	B, C, G (3)	Provision of a structured patient education and discussion about type 2 diabetes, risks for and types of complications from diabetes, prescribed drug therapy, proper dosage, possible side effects, and the importance of medication adherence. Reinforcement of lifestyle management. Provision of 8 weekly telephone calls to assess adherence, review meds, reminders of follow up visit and address any patient queries.	Hospital	Y	9	6	Medication Adherence: Use of Morisky Medication Adherence Scale (MMAS-4)

Kandasamy *et al*., 2016 India	B (1)	Before 1st follow-up: Audiovisual session on hypertension on the cause, diagnosis, normal BP values, complications on the first half, and counseling on lifestyle modifications (salt intake moderation, dietary changes, weight reduction, exercise, and smoking and alcohol cessation) on the latter half of the month. Before 2nd follow up: Discussion on drug compliance, proper intake of drugs, and common side effects on the first half, and provision of leaflets on the latter half of the month.	Community	N	4	6	QoL Score: use of WHOQOL-BREF questionnaire KAP Score: use of Knowledge, Attitude, Practice Questionnaire
Khiali *et al*., 2021 Iran	E, G (2)	Training of patients by student pharmacists under the supervision of a clinical pharmacist on proper BP measurements on initial visit. Weekly phone calls with patients and advice on adjustment of medications.	Hospital	Y	3	6	Medication compliance: measured through pill counting

Ramanath *et al*., 2012 India	B (1)	Provision of diary cards for medication adherence. Provision of counseling on drugs, lifestyle changes, side effects, and disease management as well as giving leaflets.	Hospital	N	1	Unclear	Medication adherence: use of Morisky Medication Adherence Scale (4 items) and Medication Adherence Report Scale (5 items) QOL: use of SF-12v2 Quality of life Questionnaire Patient satisfaction questionnaire: use of self-made questionnaire from the validated osteoporosis patient satisfaction questionnaire (OPSQ) to know the impact of clinical pharmacy services and types of counseling services
Saleem *et al*., 2015 Pakistan	B (1)	Identification of problems on adherence by the pharmacists and provision of patient education, leaflets, and adherence cards (all in Urdu language) at each visit through a thorough interview with patients.	Hospital	N	2	7	Disease (HTN) knowledge: use of Hypertension Fact Questionnaire (Self-made based on literature) Medication adherence: use of Drug Attitude Inventory (DAI-10) by Voruganti and Awad

							HRQoL: use of European Quality of Life scale (EQ-5D)
Shao *et al*., 2017 China	B, G (2)	Education on diabetes, risk of complications, proper use of diabetes medications and/or insulin, identification of hypoglycemia, blood glucose monitoring, and healthy lifestyle. Conduct of telephone follow up once a month on adherence, exercise, monitoring of blood glucose, side effects of drugs, possible drug interactions, and reminder of next follow ups.	Hospital	Y	11	6	Medication adherence: use of Morisky Green Levine Scale
Sookaneknun *et al.*, 2004 Thailand	A, B (2)	Conducted BP measurement, evaluation of pharmacy records, patient consultations, identification of drug-related problems, provided pharmacist's recommendations for medication regimen changes after detecting drug-related problems to physicians, provided nonpharmacologic approaches and distributed educational leaflets and diaries	Primary	N	1	6	Medication adherence rate: calculated by the number of medicines taken divided by the number supplied, multiplied by 100. A rate ≥80 was considered good adherence; <80 represented poor adherence.
Wang *et al*., 2011 China	A, B, E (3)	Clinical consultations with pharmacists every 2 months providing education regarding drug names, indications, strengths, adverse effects, and usage instructions, how to get accurate BP measurements, medication compliance, and healthy lifestyle behaviors. Actual effect of treatment and identified drug therapy problems were recorded and drug-related problems were relayed to the doctors immediately, so that patients could get proper treatment in time.	Hospital	N	6	13	Medication adherence: use of MMAS 16 [Morisky Medication Adherence Scale]

Wong *et al*., 2013 Hong Kong	A, B, D, G (4)	The intervention group received: (1) addressing of concern and uncertainties in taking medications; (2) reinforcing relevant knowledge on the chronic diseases they are suffering from; (3) education on the proper methods to take their medications; and (4) provision of medication knives and pill boxes as necessary. Interventions were tailored-made to the specific needs of each patient with participant goals designed to enhance antihypertensive medication adherence referred to the measurement of the Morisky self-reported adherence questionnaire scores. Comprehensive pamphlets summarizing the content of medication counseling were distributed with motivation to enhance compliance to antihypertensive agents.	Primary care	N	3	3	Medication adherence: use of a Validated Chinese translation of the Morisky Medication Adherence Scale (MMAS-8)
Zhao *et al*., 2012 China	B, E, F, G (4)	Communicated knowledge about hypertension to patients and their family members, educated patients need long-term antihypertensive medication to maintain stable blood pressure and other announcements, supervise patients with adverse drug reactions, get in touch with a clinical pharmacist and physician in time to find a solution, conduct follow-up survey through telephone calls and messages to advice on medication compliance and note the registration table monthly, provision of basic medication treatment principles and, individualization of patients	Hospital	Y	2	6	Medication adherence: measured through self-designed questionnaire

PIL: Patient information leaflet; IG: Intervention group; CG: control group; BP: blood pressure; HRQoL: health-related quality of life; CVD: Cardiovascular Diseases; DOH: Department of Health; SMBG: self-monitoring of blood glucose; HBPM: home BP monitoring; NGO: non-government organization

[+]Type of Interventions:

A = medication management such as drug therapy monitoring and adjustments, simplification of antihypertensive regimen, and optimization of drug regimen to address adverse drug reactions and drug interactions,
B = educational interventions directed to the patient such as conduct of hypertension education, lifestyle education, and counseling,
C = arrangement of schedules for extra follow-up appointments or contacts,
D = provision of improved administration systems such as conducting a medication event monitoring system, giving in blister packs,
E = establishment of patient practice of self-monitoring and recording of BP through education, encouragement, and validating BP monitor,
F = provision of medication reminders, including education and counseling tips, with or without adherence aid tools, and appointment reminders through telephone- or computer-based means,
G = telepharmacy

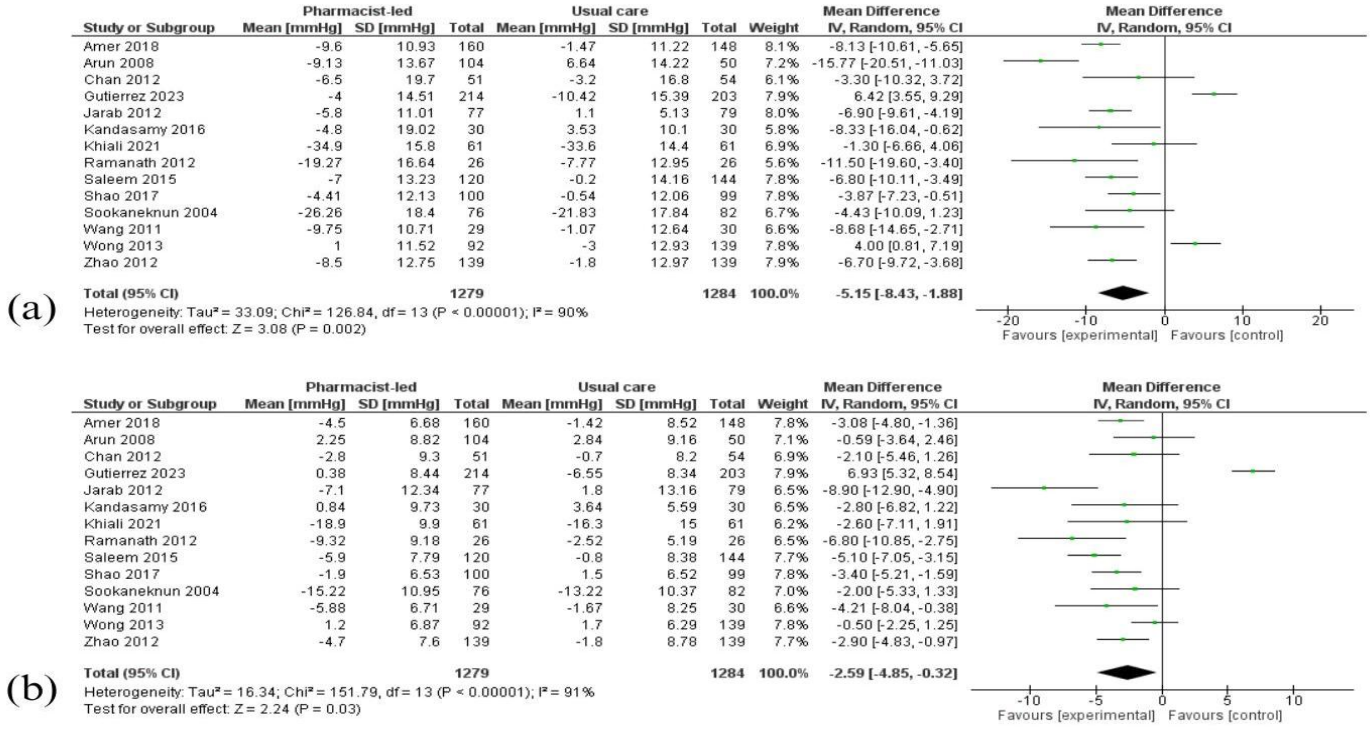

Figure 4: Forest plot for (a) systolic and (b) diastolic blood pressure lowering.

Table 5: Mean differences of systolic blood pressure with the pharmacist-led intervention and no pharmacist-led intervention.

Change In Systolic Blood Pressure						
First Author, Year	**Sample Size**	**Intervention Group**		**Sample Size**	**Comparator Group**	
	n	**Mean Difference**	**SD**	**n**	**Mean Difference**	**SD**
Amer *et al*., 2018	160	-9.6	10.93	148	-1.47	11.22
Arun *et al*., 2008	104	-9.13	13.67	50	6.64	14.22
Chan *et al*., 2012	51	-6.5	19.7	54	-3.2	16.8
Gutierrez & Sakulbumrungsil, 2023	214	-4	14.51	203	-10.42	15.39
Jarab *et al*., 2012	77	-5.8	11.01	79	1.1	5.13
Kandasamy *et al*., 2016	30	-4.8	19.02	30	3.53	10.1
Khiali *et al*., 2021	61	34.9	15.8	61	33.6	14.4
Ramanath *et al*., 2012	26	-19.27	16.64	26	-7.77	12.95
Saleem *et al*., 2015	120	-7	13.23	144	-0.2	14.16
Shao *et al*., 2017	100	-4.41	12.13	99	-0.54	12.06
Sookaneknun *et al*., 2004	76	26.26	18.4	82	21.83	17.84
Wang *et al*., 2011	29	-9.75	10.71	30	-1.07	12.64
Wong *et al*., 2013	92	1	11.52	139	-3	12.93
Zhao *et al*., 2012	139	-8.5	12.75	139	-1.8	12.97

Table 6: Mean differences of diastolic blood pressure with the pharmacist-led intervention and no pharmacist-led intervention.

Change In Diastolic Blood Pressure						
First Author, Year	**Sample Size**	**Intervention Group**		**Sample Size**	**Comparator Group**	
	n	**Mean Difference**	**SD**	**n**	**Mean Difference**	**SD**
Amer *et al*., 2018	160	-4.5	6.68	148	-1.42	8.52
Arun *et al*., 2008	104	2.25	8.82	50	2.84	9.16
Chan *et al*., 2012	51	-2.8	9.3	54	-0.7	8.2
Gutierrez & Sakulbumrungsil, 2023	214	0.38	8.44	203	-6.55	8.34
Jarab *et al*., 2012	77	-7.1	12.34	79	1.8	13.16
Kandasamy *et al*., 2016	30	0.84	9.73	30	3.64	5.59
Khiali *et al*., 2021	61	18.9	9.9	61	16.3	15
Ramanath *et al*., 2012	26	-9.32	9.18	26	-2.52	5.19
Saleem *et al*., 2015	120	-5.9	7.79	144	-0.8	8.38
Shao *et al*., 2017	100	-1.9	6.53	99	1.5	6.52
Sookaneknun *et al*., 2004	76	15.22	10.95	82	13.22	10.37
Wang *et al*., 2011	29	-5.88	6.71	30	-1.67	8.25
Wong *et al*., 2013	92	1.2	6.87	139	1.7	6.29
Zhao *et al*., 2012	139	-4.7	7.6	139	-1.8	8.78

3.3 Pharmacist-led interventions

The following pharmacist-led interventions were seen: (a) medication management (n=3, 21.43%); (b) educational interventions or counseling (n=13, 92.86%); (c) arrangement of schedules for extra follow-up appointments or contacts (n=1, 7.14%); (d) provision of improved administration systems (n=1, 7.14%); (e) establishment of patient practice of self-monitoring and recording of blood pressure (n=3, 21.43%); (f) provision of medication reminders (n=2, 14.29%); and (g) telepharmacy (n=5, 35.71%). A summary is presented in Table 4. Majority of the studies integrated multiple types of interventions as part of a larger intervention provided by pharmacists in the management of hypertension, with or without comorbidities. The pharmacist-led interventions were further categorized with the use (n=5, 35.71%) and non-use (n=9, 64.29%) of technology in the provision of interventions.

The frequency of the follow-up session for each study ranged from one to eleven follow-ups, with a median of three follow-ups. This consists of face-to-face follow-ups in the clinics or office, and contact through phone-based means. There were eight studies (57.14%) that did not report the average duration for the interventions done by the pharmacists (21, 23-26, 29, 31, 33). Studies that did report the duration of each session ranged from ten to fifty minutes. Only one trial averaged more than thirty minutes in providing pharmacist intervention to the participants (31)

3.4 Outcome measures

The main outcomes of this systematic review are the change in SBP and DBP of the participants. Studies report the following in regards to the values and endpoints measured: (a) Mean SBP/DBP at baseline and at follow-up/s (21, 24, 26, 28-30, 32-34); (b) Average change in SBP/DBP from baseline to endpoint (22, 23, 25); or (c) Both mean SBP/DBP at baseline and at follow-up/s and average change in SBP/DBP from baseline to endpoint (27, 31). These are summarized in Table 5 and Table 6. Other outcomes aside from change in BP noted in the studies that are related to hypertension include medication adherence or medication compliance (n=12, 85.71%), disease-related knowledge or knowledge, attitudes, and practice (KAP) (n=3; 21.43%), health related quality of life (n=5, 35.71%), and patient satisfaction (n=1, 7.14%).

3.5 Meta-analysis

Upon analysis of the BP lowering measures, it was found that pharmacist-led interventions are able to reduce SBP by 5.15 mmHg (95% CI: -8.43, -1.88) and DBP by 2.59 mmHg (95% CI: -4.85, -0.32) as shown in Figure 4, respectively. There was high heterogeneity for both SBP (I^2=90%, p<0.01) and DBP (I^2=91%, p<0.01), thus a random-effects model was used.

3.6 Subgroup analysis

To explore sources of heterogeneity, pre-determined patient and pharmacist-led intervention factors underwent subgroup analysis. The intervention factors considered were healthcare setting, number of interventions investigated, use or non-use of technology, timeframe of intervention, and frequency of follow-up. The patient factors considered were the presence and absence of comorbidities, predominant age group, predominant sex, income status of the country where the study was conducted and the predominant highest level of education obtained by the participants. Results of the subgroup analyses are summarized in Table 7. Analysis showed that for the healthcare setting, the effect of pharmacist-led

interventions showed significant effects when conducted in the community and hospital outpatient setting for SBP lowering (-12.70 [95% CI: -19.88, -5.52] and (-6.43 [95% CI: -7.88, -4.97], respectively), but only hospital outpatient for DBP (-3.99 [95% CI: -5.11, -2.87]). Having only one type of intervention also showed better lowering for SBP (-8.98 [95% CI: -12.12, -5.85]) and DBP (-3.40 [95% CI: -4.98, -1.83]).

Table 7: Summary of the results of subgroup analyses for the difference in systolic and diastolic blood pressure with pharmacist care compared with no pharmacist-led intervention group according to intervention and patient characteristics.

Intervention/ Patient Characteristics	SBP Mean Difference (mmHg)		Between Subgroup Differences	DBP Mean Difference (mmHg)		Between Subgroup Differences
	n	95% CI	p-value	n	95% CI	p-value
Health Care Setting						
Community	2	-12.70 (-19.88 to -5.52)	< 0.01	2	-1.40 (-3.83 to 1.03)	0.26
Hospital	9	-6.43 (-7.88 to -4.97)	< 0.01	9	-3.99 (-5.11 to -2.87)	< 0.01
Primary health care	3	2.50 (-2.49 to 7.65)	0.32	3	1.58 (-4.20 to 7.35)	0.59
Number of Interventions Investigated						
Single type of intervention	6	-8.98 (-12.12 to -5.85)	< 0.01	6	-3.40 (-4.98 to -1.83)	< 0.01
Multiple types of intervention	8	-2.54 (-6.76 to 1.67)	0.24	8	-2.04 (-5.53 to 1.44)	0.25
Incorporated Technology in the Interventions						
With technology	5	-2.49 (-7.93 to 2.94)	0.37	5	-2.04 (-7.53 to 3.45)	0.47
Without technology	6	-6.81 (-11.01 to -2.62)	< 0.01	6	-2.87 (-4.26 to -1.47)	< 0.01
Frequency of Follow Up						
Once	4	-8.88 (-15.36 to -2.41)	< 0.01	4	-2.63 (-5.04 to -0.22)	0.03
Multiple	10	-3.86 (-7.52 to -0.20)	0.04	10	-2.53 (-5.39 to 0.33)	0.08
Time Frame of Study						
≤ 6 months	10	-4.36 (-8.46 to -0.27)	0.04	10	-1.85 (-4.61 to 0.92)	0.19
> 6 months	4	-7.14 (-9.69 to -4.60)	< 0.01	4	-4.59 (-6.23 to -2.94)	0.03
Predominant Age Group						
Adults (<65 years old)	9	-3.61 (-8.35 to 1.14)	0.14	9	-1.42 (-4.53 to 1.69)	0.37
Geriatrics (≥ 65 years old)	2	-6.81 (-8.83 to -4.79)	< 0.01	2	-5.63 (-11.49 to 0.22)	0.06
Presence of Comorbidities						
With Comorbidities	9	-4.48 (-8.27 to -0.70)	0.02	9	-2.95 (-6.55 to 0.64)	0.11
Without Comorbidities	1	-8.13 (-10.61 to -5.65)	< 0.01	1	-3.08 (-4.80 to -1.36)	< 0.01
Predominant Sex						
Male-dominated	9	-7.06 (-9.28 to -4.83)	< 0.01	9	-3.70 (-4.97 to -2.44)	< 0.01
Female-dominated	5	-1.6 (-7.35 to 4.33)	0.60	5	-0.34 (-4.91 to 4.22)	0.88
Income Status of Country						
High-Income	2	1.05 (-5.97 to 8.07)	0.77	2	-0.84 (-2.39 to 0.71)	0.29
Upper-Middle Income	4	-5.67 (-7.64 to -3.69)	< 0.01	4	-3.12 (-4.29 to -1.95)	< 0.01
Lower-Middle Income	8	-6.31 (-11.26 to -1.35)	0.01	8	-2.75 (-6.87 to 1.37)	0.19
Prevailing Level of Education						
Primary and below	4	-5.12 (-12.50 to 2.26)	0.17	4	-2.80 (-5.12 to -0.49)	0.02
High School	4	-3.14 (-9.73 to 3.45)	0.35	4	-1.97 (-8.18 to 4.25)	0.53
University and above	1	-6.80 (-10.11 to -3.49)	< 0.01	1	-5.10 (-7.05 to -3.15)	< 0.01

Risk of Bias						
Low Risk of Bias	1	6.42 (3.55 to 9.29)	< 0.01	1	6.93 (5.32 to 8.54)	< 0.01
Some Concerns	5	-4.24 (-9.32 to 0.85)	0.10	5	-3.94 (-6.74 to -1.14)	< 0.01
High Risk of Bias	8	-7.28 (-10.14 to -4.42)	< 0.01	8	-2.98 (-3.86 to -2.09)	< 0.01

Non-use of technology in providing the interventions showed better lowering for both SBP (-6.81 [95% CI: -11.01, -2.62]) and DBP (-2.87 [95% CI: -4.26, -1.47]) and in patients of the male sex (SBP: -7.06 [95% CI: -9.28, -4.83]; DBP: -3.70 [95% CI: -4.97, -2.44]).

The upper-middle income countries showed significant lowering for both SBP (-5.67 [95% CI: -7.64, -3.69]) and DBP (-3.12 [95% CI: -4.29, -1.95]), while lower-middle income countries only significantly lowered SBP (6.31 [95% CI: -11.26, -1.35]).

A single follow-up, longer duration of intervention, and patients without comorbidities showed significant DBP lowering (-2.63 [95% CI: -5.04, -0.22]; -4.59 [95% CI: -6.23, -2.94]; -3.08 [95% CI: -4.80, -1.36], respectively). Patients of geriatric age showed significant lowering of SBP (-6.81 [95% CI: -8.83, -4.79]).

Lastly, patients that attained university and above level of education significantly lowered both SBP (-6.80 [95% CI: -10.11, -3.49]) and DBP (-5.10 [95% CI: -7.05, -3.15]) while those with at least primary and below level of education had significant lowering of DBP (-2.80 [95% CI: -5.12, -0.49]).

The effect of the risk of bias was also analyzed; it was found that the only study with low risk of bias did not favor the intervention for both SBP and DBP, while the studies with high risk favored the intervention for both SBP (-7.28 [95% CI: -10.14, -4.42]) and DBP (-2.98 [95% CI: -3.86, -2.09]) and some concern for DBP (-4.24 [95% CI: -9.32, -0.85]).

3.7 Publication bias and sensitivity analysis

Visual inspection of generated funnel plots for both SBP and DBP measures was conducted as shown in Figure 5. The plot of the studies in the SBP measures were spread out, showing asymmetry indicating a high risk of publication bias. However, for DBP, studies are concentrated in one area, with some observably clustered upon each other indicating more symmetry compared to SBP and a lower risk of publication bias.

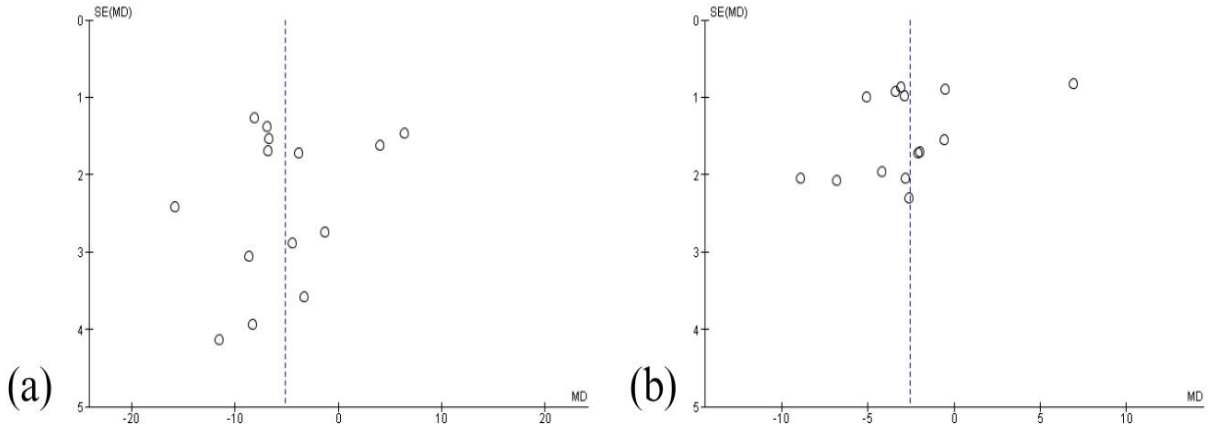

Figure 5: Funnel plot on (a) systolic and (b) diastolic blood pressure.

Sensitivity analysis between studies with standard deviation imputed and non-imputed was conducted. Based on the values obtained, there are no significant differences between non-imputed and imputed SD both in the SBP and DBP mean differences. Values calculated are I^2=0% (p=0.51) and I^2=0% (p=0.70) for SBP and DBP, respectively. The same can be said upon visual inspection of the generated forest plots as shown in Figure 6.

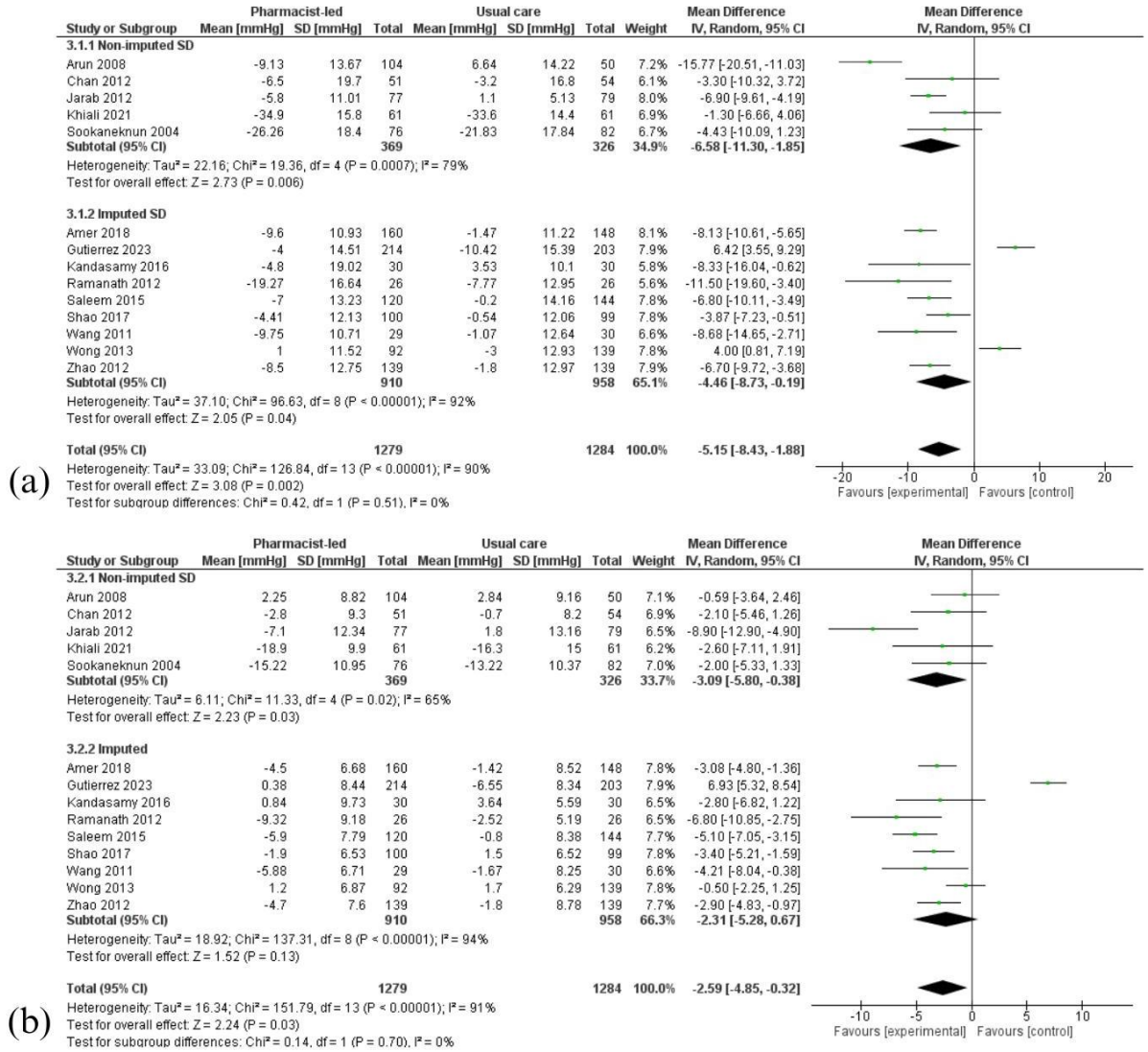

Figure 6: Subgroup analysis on (a) SBP and (b) DPB lowering based on the imputation of SD of mean differences.

4.0 Discussion

To the authors' best knowledge, this is the first SRMA to focus on investigating the effect of pharmacist-led interventions to blood pressure of patients with hypertension specifically from countries within the Asian region. Present SRMAs published majorly investigates the Western population, which limits the generalizability of their results to the Asian population. Furthermore, in the conducted appraisal of existing SRMAs (5, 6, 8, 9), using AMSTAR2 tool, all studies assessed possess critically low quality, and identified reasons are the following: (a) no explicit statement of methods established prior to conduct and justification of deviations from protocol, (b) not explaining the study design of included studies, (c) not performing data extraction in duplicate, (d) not providing list with justification of excluded studies, (e) not reporting sources of funding, (f) not interpreting the RoB in the study's discussion of results, and (g) not investigating the risk of publication bias and its impact to the study's results. All identified issues were addressed in this study. Additionally, the literature search conducted was not limited by language, and grey literature was explored for more thorough identification of studies. Moreover, this study conducted a comprehensive meta-analysis and subgroup analysis to assess heterogeneity and effect of different factors originating from pharmacist-led interventions and those from the patients' characteristics. Lastly, this study provides up-to-date information.

Meta-analysis of 14 included studies showed that pharmacist-led interventions can reduce both SBP and DBP of adult Asian patients with hypertension. For SBP, the estimated lowering is 5.15 mmHg (95% CI: -8.43, -1.88) and 2.59 mmHg (95% CI: -4.85, -0.32) for DBP. While the researchers recognize that the results are subject to many confounders, it still validates the effect of implementing pharmacist-led interventions to blood pressure as such findings are consistent with existing literature which reported significant decreases in blood pressure from implementation of pharmacist-led interventions to patients with hypertension (9, 36).

Patient characteristics and conduct of interventions were highly varied. Among the healthcare settings, the primary care setting did not show significant effects on both BP measures. This is in contrast to the results of another study which reported positive outcomes for BP measures in this setting (37). Such findings show that the primary healthcare setting should be focused on for its potential in clinical outcome improvement in diseases.

The findings also suggest that interventions conducted singly were effective in lowering the BP measures, while studies that conducted a combination of types of interventions failed to provide significant effects. Because there is evidence that reports the number of interventions provided was not a factor affecting BP control, the researchers hypothesize that for this study, having multiple components in the interventions which make programs more complex affected the quality of the provision of interventions by the pharmacist/s or the patient adherence to the program (36).

Additionally, because there was difficulty pooling for analysis of efficacy of each intervention since most conducted these in combination, the researchers were unable to create a pooled estimate of the mean SBP and DBP lowering; thus, the individual effects were not quantitatively estimated. Such is the same with that of Santschi *et al.* (2014) (36). where they failed to identify the pooled effect of each type of intervention. Therefore, only educational intervention, which was the only one investigated singly among the studies, had its effect estimate analyzed. Results showed that educational interventions such as patient counseling that provided disease- and

drug-related information to patients to improve their understanding of their diseases can provide a significant lowering of SBP and DBP. Future studies may consider investigating the other pharmacist-led interventions singly as well in order further investigate which of these methods are more effective in reducing BP of participants.

The non-use of technology in conducting the interventions appeared to have better effects on BP measures than those who incorporated technology, providing an opportunity to improve its use in healthcare. Notably, eight (57.14%) studies were conducted in lower-middle income countries resulting in such findings. One of the studies highlighted challenges such as limited availability of smartphones and internet connectivity as well as barriers in digital literacy, which likely affected the effectiveness of the interventions (24). Regardless, only countries from the lower- and upper-middle income countries have shown significant lowering in BP measures. Effects from high-income countries were less evident, suggesting they provide similar benefits with that of the interventions due to the resources to support their healthcare system (1).

The findings also suggest that males show more significant response for both SBP and DBP to the intervention, consistent with reports that HTN is more common in males, while females tend to have higher rates of treatment and controlled BP (38, 39). Single follow-up, longer duration of treatment and having no comorbidities only significantly lowered DBP; however, there is a lack of supporting evidence to justify this finding. Meanwhile, the geriatric population only showing significant lowering of SBP is aligned to existing evidence, wherein it is stated that SBP is relevant for prognosis of patients > 60 years old (40).

Lastly, it was found that patients with at least university level of education appeared to respond more for both BP measures possibly due to a higher health literacy resulting in better health seeking behavior. Moreover, higher educational attainment may offer numerous job opportunities to help patients adhere to the treatment (24) and lower educational attainment may have additional barriers in getting their medications resulting in poor SBP outcomes (26). However, primary and below level of education also showed significant DBP lowering, to which evidence to support such finding is still lacking.

Evaluation of the impact of the risk of bias to the effect of the interventions to BP measures showed that the studies with some concerns and high risk of bias favored the interventions, while the low risk favored the control. Nonetheless, these studies were retained in the analysis to ensure comprehensiveness, consistent with PRISMA recommendations, as excluding them could have introduced additional selection bias. Additionally, the potential publication bias in the SBP lowering results also pose concern, as there is a possibility that included studies only published favorable outcomes, which may have exaggerated the effects of the intervention (41). As such, it is recommended for the results to be interpreted with caution.

Thus, in summary, the study is limited to having included only eight countries in Asia and hinders the generalizability of the results to the Asian continent. Furthermore, risk of bias assessments done on included studies revealed that only one study was of low risk (23) and majority (n=8) have high risk of bias. Nine studies needed their SD imputed due to it being unreported, which may affect the precision of the pooled estimates. Upon the conduct of the meta-analysis, the researchers found statistically significant and high heterogeneity for both SBP lowering (I^2=90%, p<0.01) and DBP lowering (I^2=91%, p<0.01). A subgroup analysis was

undertaken for the effect of SD imputation and address heterogeneity. While the analysis proved imputed values did not differ from non-imputed SD values, the heterogeneity remains unexplained, which reduces confidence in the precision of pooled estimates. Lastly, the majority of the trials performed multiple types of interventions and cannot be differentiated in terms of subgroup analysis.

5.0 Conclusion

This systematic review and meta-analysis showed that pharmacist-led interventions appeared to significantly reduce blood pressure in adult Asian patients with hypertension compared to no pharmacist-led intervention. The findings support the use of pharmacist-led interventions and align with previous systematic reviews and meta-analyses.

However, the overall certainty of evidence is low to moderate and results should be interpreted with caution due to various sources of heterogeneity, as the benefit from interventions may differ across populations, healthcare settings, and differences in implementation. The moderate to high risk of bias stemming from the lack of blinding and incomplete reporting affecting the outcomes assessment also reduces the confidence in the effect estimate. There is also a potential presence of publication bias across these studies. Another limitation is the limited geographic representation in the Asian region included in the review, which restricts generalizability of the findings across the region.

Notably, this review is the first to focus on the Asian region since the majority of studies included in existing reviews are conducted in Western countries. Appraisal of such reviews also revealed they are of critically low quality with contributing factors that this review then tried to address. Additionally, this review also provides updated information through a rigorous search strategy. Detailed subgroup analyses were also conducted which identified factors influencing blood pressure lowering, such as healthcare setting, number of interventions, technology use, sex, country income status, education level, age group, frequency of follow-up, and timeframe. These insights contribute to a nuanced understanding of pharmacist intervention effectiveness.

For future research, it is recommended that more comprehensive randomized controlled trials be conducted across more countries in Asia, with improved blinding (e.g., blinding of outcome assessors) and full reporting of findings to ensure robust data. Future studies should explore the long-term impact of interventions on blood pressure, particularly in primary care settings and low-income countries. Additionally, reviewers should consider including other outcomes such as quality of life, medication adherence, and patient satisfaction, and explore the use of network meta-analyses for direct and indirect comparison of multiple interventions. Policymakers and relevant institutions are encouraged to use these findings to optimize pharmacy services in their respective countries and explore the feasibility of integrating pharmacist interventions in hypertension management across healthcare settings. Integration of these interventions should be guided by local culture and context, resources, and supporting data from domestic or regional studies.

Authorship contribution statement

SBD, AAH, MMG: Data analysis, Methodology, Formal analysis, Writing–original draft, Visualization, Resources, Draft corrections. **SBD, AAH, MMG:** Writing – review & editing. **MAJG:** Technical review and editing, Draft corrections.

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Conflict of Interest

The authors declared that they have no conflicts of interest to disclose.

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