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Mahmood, Sajid ; Jalal, Zahraa; Hadi, Muhammad Abdul; Khan, Tahir Mehmood; Haque, Sayeed; Ullah Shah, Kifayat

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Author and Affiliation

Sajid Mahmood[1], Zahraa Jalal[2], Muhammad Abdul Hadi[2], Tahir Mehmood Khan[4], M. Sayeed Haque[3], Kifayat Ullah Shah[1]

[1]Department of Pharmacy, Quaid-e-Azam University, Islamabad 45320, Pakistan
[2]School of Pharmacy, Institute of Clinical Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK
[3]Institute of Applied Health Research, University of Birmingham, B15 2TT, UK
[4]Institute of Pharmaceutical Sciences, University of Veterinary and Animal Science (UVAS), Lahore, Pakistan

Mr. Sajid Mahmood (M. Phil)
Department of Pharmacy, Quaid-e-Azam University, Islamabad, 45320, Pakistan
Email address: sajidmahmood@bs.qau.edu.pk
Telephone number: +92-3364478696

Dr. Zahraa Jalal (PhD)
School of Pharmacy, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK
Email address: z.jalal@bham.ac.uk
Telephone number: +44 (0)121 414 4042

Dr. Muhammad Abdul Hadi (PhD)
School of Pharmacy, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK
Email address: m.a.hadi@bham.ac.uk

Dr. Tahir Mehmood Khan (PhD)
Institute of Pharmaceutical Sciences, University of Veterinary and Animal Science (UVAS), Lahore, Pakistan
Email address: tahir.khan@uvas.edu.pk
Telephone number: +923235568664

Dr. M. Sayeed Haque (PhD)
Institute of Applied Health Research, University of Birmingham, B15 2TT, UK
Email address: m.s.haque@bham.ac.uk

Corresponding Author:

Dr. Kifayat Ullah Shah (PhD)
Department of Pharmacy, Quaid-e-Azam University, Islamabad, 45320, Pakistan
Email address: kushah@qau.edu.pk
Telephone number: +92-3325542722

Prevalence of non-adherence to antihypertensive medication in Asia: A Systematic Review and Meta-Analysis.

Abstract

Background: Hypertension and its associated complications are one of the leading causes of morbidity and mortality in Asia. Racial disparities in terms of treatment outcomes among hypertension patients have been reported in literature with Asian patients resulting in poorer treatment outcomes. Non-adherence to antihypertensive therapy is frequently associated with poor treatment outcomes.

Aim of the Review: The aim of this review was to estimate the prevalence of non-adherence to antihypertensive medications among patients with hypertension residing in Asia.

Method: PubMed, Google Scholar, MEDLINE, Embase, Scopus, CINHAL and Cochrane library were searched for studies published between 2000 and 2019 involving hypertensive patients. Studies investigating the prevalence of medication non-adherence in Asian countries, rated either good or fair on National Institute of Health quality assessment tool and published in English language were included in our review. Data were extracted by one author and checked by another using a structured and pilot-tested data extraction sheet. A random-effects meta-analysis was performed using STATA version 14.3®.

Results: Sixty-Seven studies from 22 Asian countries including 2,532,582 hypertensive patients were included. Mean (±SD) age of participants was 58(±6) years. Overall, the estimated prevalence of non-adherence to antihypertensive medication in Asia was 48% (95% CI: 41-54, P=0.001). The rate of non-adherence was higher among females 49% (95% CI: 41-56, P=0.001) compared to males 47% (95% CI: 40-53, P=0.001). As per the region, the highest prevalence of non-adherence was found in South Asia 48% (95% 44-51, P=0.877) followed by East Asia 45% (31-59, P=0.001) and the Middle East 41 (95% 30-52, P=0.001). Similarly, higher rate of non-adherence was observed in low and lower middle-income countries i.e. 50% (95% CI: 47-54, P=0.220) as compare to upper-middle and high-income countries i.e. 37% (95% CI: 25-49, P=0.001) and 44% (29-59, P=0.001) respectively.

Conclusion:

The prevalence of non-adherence to antihypertensive medication is high in Asia. This may partly explain poor treatment outcomes and incidence of higher mortality rate in Asia frequently reported in the literature. There is a need to implement appropriate policies and clinical practices to improve medication adherence.

Impact on Practice:

- Non-adherence to antihypertensive therapy and barriers to medication adherence should be frequently discussed and during routine clinical consultation.
- Health policy makers should design and implement policies and promote good clinical practices to improve medication adherence taking into consideration local socioeconomic and cultural factors.
- More research is required to establish the effectiveness of interventions to improve medication adherence in low-and-middle-income countries.

Keywords: Compliance; Hypertension; Drug therapy; Asia, Systematic review,

Introduction:

Hypertension is a significant public health challenge globally especially in Asia, which is home to two-thirds of the world's population. Uncontrolled blood pressure may lead to stroke, coronary artery disease CAD, heart failure, renal insufficiency and blindness [1]. The prevalence of hypertension varies from 15% to 35% in different parts of Asia. In addition, hypertension control rate is poorer in Asia with China and India having hypertension control rates of only 8% and 6% respectively [2].

Adherence is the extent to which a patient takes his/her medicines as prescribed by a healthcare practitioner [3]. A meta-analysis found that adherence to prescribed antihypertensive therapy may reduce the risk for poor treatment outcomes by 26% and the odds of good treatment outcomes in adherent patients are three times higher than odds of good treatment outcomes in non-adherent patients [4]. For measurement of non-adherence both direct and indirect methods have been used in the literature to assess medication adherence. Direct methods (e.g. direct observation, assays to measure drug concentration in urine and blood) are considered as gold standard but are rarely used due to their high cost. Indirect methods (e.g. pill counting, questionnaires) are easier and more cost effective to apply for assessment of non-adherence [5].

Asia differs from other regions in the world in terms of ethnicity, culture, economy and systems of governance. The existing literature has reported that racial disparities exist in Asia with respect to prevalence, treatment and control of hypertension. The rate of blood pressure control in different parts of Asia varies between 10.6% to 41.4% [6]. Medication non-adherence is the main reason behind uncontrolled hypertension [7]. Low availability of electronic medical records, low health literacy, un-availability, unaffordability and lastly the scarcity of pharmacy refill records in Asian countries are the main factors that precludes the accurate measurement of medication adherence in these countries [8]. Hence it is important to estimate the 'burden' of non-adherence so that necessary policies and interventions to support clinical practice can be developed and implemented to improve medication adherence among hypertension patients in

Asia. Previous systematic reviews have evaluated factors associated with medication non-adherence and barriers to medication non-adherence among patients with hypertension and other cardiovascular disease conditions in different parts of the world [9, 10]. One systematic review estimated the overall global prevalence of non-adherence to antihypertensive medication to be 45.2% among hypertensive patients [9]. However, this systematic review only included studies using Morisky Medication Adherence Scale (MMAS-8) for assessing medication adherence and studies published between January 2009 and March 2016. Furthermore, authors did not perform any regional analysis to explore regional differences in medication adherence, if any. Therefore, these findings do not provide any exclusive information regarding the prevalence of non-adherence in the different regions of the world particularly in Asia. Given limitations of existing literature, a more comprehensive and up-to-date systematic review and meta-analysis was required to estimate the prevalence of non-adherence among hypertension patients. We focused this review to studies originated from Asia as hypertension and its associated morbidities are one of the leading causes of premature deaths in Asia. Furthermore, to the best of our knowledge, no such systematic review exists in the literature.

Aim of the review: The aim of this review was to estimate the prevalence of non-adherence to antihypertensive medications among hypertensive patients residing in Asia. This systematic review was designed to answer the following research questions:

Question#01: What is the overall prevalence of medication non-adherence to prescribed antihypertensive medication in Asia?

Question#02: Does the prevalence of non-adherence to prescribed antihypertensive medication differ across gender groups, geography, and income levels?

Method:

Preferred Reporting Item for Systematic Review and Meta-analysis (PRISMA) and Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed in undertaking and reporting this systematic review [11, 12]. The review was registered with PROSPERO, an international database of prospectively registered systematic reviews (ID number: CRD42018117403).

Inclusion and Exclusion Criteria: All cross-sectional studies conducted among patients with hypertension between 2000 and 2019 estimating the prevalence of non-adherence to medication therapy were included in this review. We did not include studies published prior to 2000 as including older studies would not truly represent the current status of non-adherence to anti-hypertensive therapy in Asia. Studies published in English language only were included in our review. Studies on Asian population residing outside Asia were not included in our review.

Only those studies that were rated either good or fair on National Institute of Health quality assessment tool [13] were included in our review. Quality assessment was done by one author and counterchecked by another author. In case of any disagreement, a third review author was consulted.

Study Search: A systematic search was carried out in PubMed, Google Scholar, MEDLINE, Embase, Scopus, CINHAL and Cochrane library. Some of the keywords used were: compliance, adherence, medication non-compliance, medication non-adherence, and antihypertensive therapy. These keywords were combined using Boolean operators as appropriate. Detailed search strategy has been provided in online supplementary file. Additionally, some relevant research papers were also retrieved through searching of reference lists, author contact and studies sent by colleagues through email.

Study selection and data extraction:

A reference management software Endnote® (version X5) was used for compilation of retrieved articles. The titles and abstracts were screened by one author for inclusion and when unsure, another author was consulted. Full-texts of relevant articles were downloaded and assessed for inclusion against the inclusion and exclusion criteria by one author and checked by another author. Disagreements were resolved through consensus. In instances where consensus had not reached between the two review authors, third review author was consulted. The data extraction sheet was created using Microsoft Excel©. The structured data extraction sheet was pilot-tested and changes were made, where necessary. The data extracted included: name of investigator, year of study, country of study, adherence scale used, population of study, gender percentage, mean age of participants, percentage of non-compliance to the prescribed antihypertensive therapy. The extracted data were grouped into different variables such as by country, geographic region and income level. Asian countries were categorised in different income level categories as defined by World Bank [14].

Data Quality Assessment:

National Institute of Health quality assessment tool [13] was used for quality assessment of all included studies. This tool consists of a fourteen-question standard quality checklist and is suitable for both observational cohort and cross-sectional studies. For each question, the

reviewer can choose from the three options, “Yes”, “No” and “Not applicable”, as appropriate. Based on these questions, the studies were categorized as of good, fair or poor quality by two reviewers independently. Differences in quality assessment were resolved through discussion among review authors. A third reviewer was consulted if differences were not resolved through discussion.

Statistical Analysis:

Meta-analysis was performed using STATA version 14.3®. Only clinical and statistical homogenous studies were combined using meta-analysis. Clinical homogeneity was assessed by review authors in terms of study population and methods used to assess medication adherence. I^2 with 95% confidence interval test was used to evaluate statistical heterogeneity of studies. I^2 value of less than 50% was used to indicate statistical homogeneity [15]. Analysis of proportions were carried out using random effect model to account for statistical heterogeneity. Furthermore, subgroup analyses were performed to address heterogeneity. Gender, income level and regional geography were used as grouping variables. In order to rule out the effect of different methods used for measuring the medication adherence on overall results of this study, sensitivity analyses were performed by separately analysing: the studies that used similar method/tool for measurement of medication adherence e.g. MMAS-8, MMAS-4; after removing the outlier values and studies that have either too large (sample size greater than 5,000) or too small sample size (sample size < 100); the studies with less frequently used adherence measurement tool/method i.e. less than two studies.

PRISMA 2009 Flow Diagram [11]

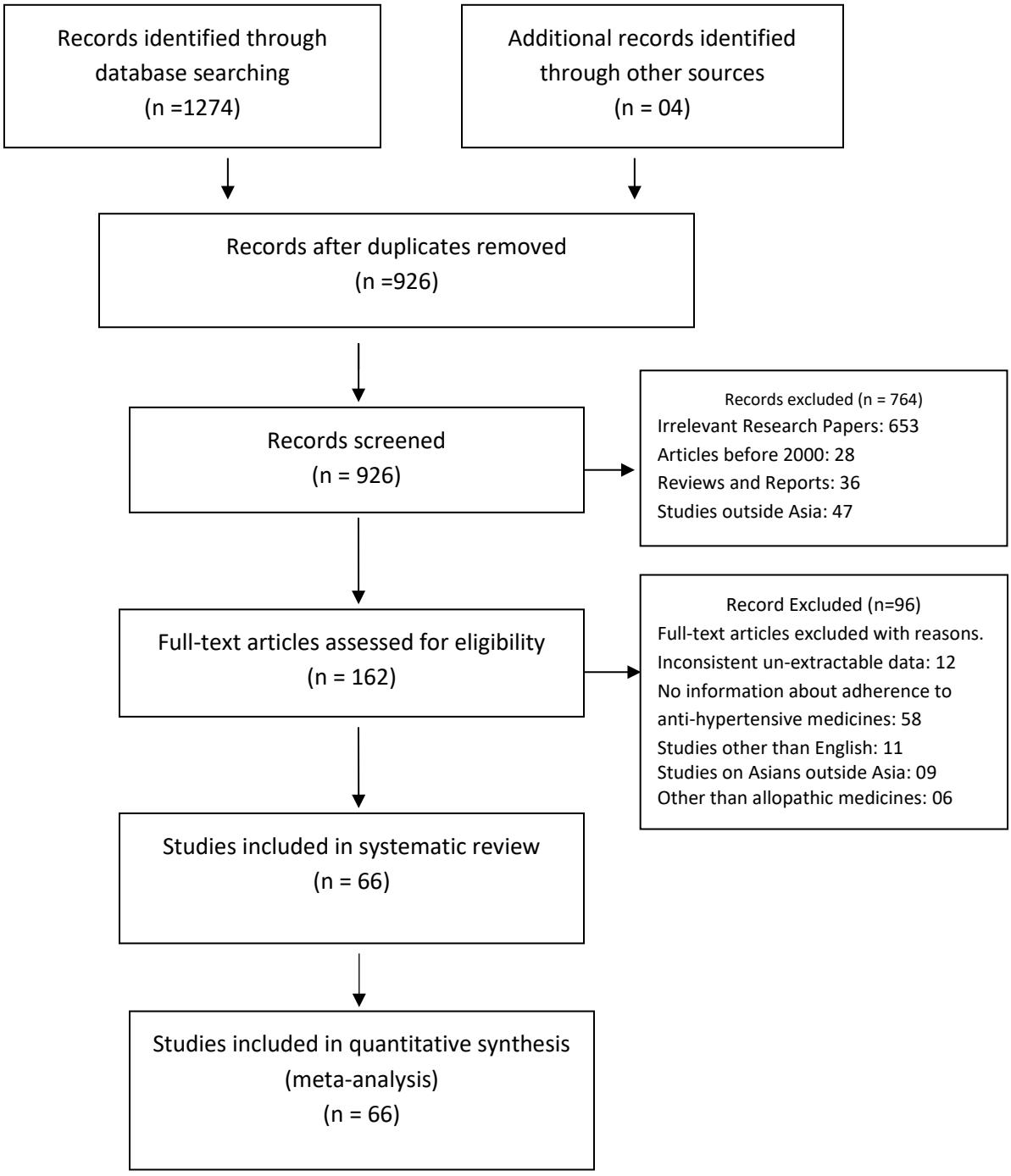

Figure 1. PRISMA flow diagram

Results:

Search results: A total 1274 articles were identified from searching databases and additional four articles were retrieved from searching websites and reference lists. After deduplication, titles and abstracts of 926 studies were screened by one author (SM). Full-text of remaining one hundred and sixty-two were downloaded and reviewed for inclusion by one author and checked by another author. Finally, 66 articles met inclusion criteria. Reasons for exclusion of full-texts are given in PRISMA 2009 Flow Diagram (Figure 1).

Quality assessment of included studies: Over half of the studies 44/66 (66%) included in this review were rated good on the NIH Quality Assessment Tool and showed high internal validity. The remaining 22/66 (34%) studies rated good/fair.

Tools to Assess Medication Adherence: Morisky Medication Adherence Scale was the most commonly used instrument (34 studies) to assess medication adherence to anti-hypertensive drugs. Out of above referred 34 studies, 21 studies used "8-item Morisky Medication Adherence scale" (MMAS-8) [16-36], 11 studies used "4-item Morisky Medication Adherence scale" (MMAS-4) [37-47] and one study used "Morisky Green scale" (MGS) [48], for measurement of adherence. Twenty-four studies used "validated self-structured questionnaires" [49-72]. Pill count method [73, 74] and Hill-Bone Compliance Scale [75, 76] were used in two studies each. Brief Medication Questionnaire (BMQ) [77], "Therapeutic Adherence Scale for Hypertensive Patients" (TASHP) [78], "Cumulative Medication Adherence" (CMA) [79], Proportion of days covered PDC (≥80%) [80] and Hypertensive Adherence to Therapeutic Regimen Scale (HARTS) were used in one study each [81].

Characteristics of Studies Included: A total of 2,532,582 Asian subjects were included in 66 selected studies. Eight studies each from India [21, 52, 77, 45, 65, 34, 66, 48] and Saudi Arabia [24, 41, 59, 31, 68-71], six each from Bangladesh [53-57, 76] and China [16, 17, 38, 39, 63, 78], four each from Iran [26, 27, 43, 35], Pakistan [37, 58, 46, 22] and Japan [51, 64, 80, 72], three studies were from Jordan [44, 82, 75] and Indonesia[20, 32, 33] and Hong Kong [18, 19, 47], two studies each from United Arab Emirates [25, 42], South Korea [79, 73] Nepal [40, 67] Thailand [81, 74] and Iraq [61, 36] and one each from Malaysia [49], Oman [28], Myanmar [23], Turkey [62], Vietnam [50], Lebanon [30] and Palestine [29]. All included studies were cross sectional observational studies with sample size ranging from 45 to 2,455,193 subjects. Sixty-three studies collected their data through self-administered questionnaires, two studies used pill count method and one study each used proportion of days covered (PDC) and cumulative medication adherence (CMA) method for the measurement of medication adherence. Of 66 studies included in the review, 41 studies separately investigated non-adherence in males and females while remaining 25 studies only mentioned overall compliance in both male and female.

Key characteristics of the 2,532,582 subjects in the included 66 studies are given in Table-1. Majority of subjects were female (n= 1,462,746, 58% of total subjects included in the meta-analysis). The mean age (±S.D) of participants was 58 (±6) years.

Non-adherence to antihypertensive medication: Overall, the meta-analysis estimated prevalence of medication non-adherence in Asia to be 48% (95%CI: 41-54, P=0.001) (Figure 2). A high statistical heterogeneity was observed in the analysis (I^2 = 99.6%). The rate of non-adherence was marginally higher in females 49% (95%CI: 41-56, P=0.001) compared to males 47% (CI: 40-53, P=0.001) (see Supplementary Fig-1 and 2). As per the region, the highest prevalence of non-adherence to antihypertensive medication was found in South Asia 48% (95% CI:44-51, P=0.877) followed by East Asia 45% (95%CI:31-59, P=0.001) and the Middle East 41% (95% CI:30-52, P=0.001) (Supplementary Table-1) (Figure-3). However, a high statistical heterogeneity was observed in the analysis (I^2 = 97.3%) Similarly, as per income level of the countries, comparatively higher prevalence of non-adherence was observed in low and lower middle-income countries i.e. 50% (95%CI:47-54, P=0.22) as compared to upper-middle and high-income countries i.e. 37% (95% CI:25-49, P=0.001) and 44% (95% CI: 29-59, P=0.001) respectively (Supplementary Table-2) (Figure-4). Similarly, a high statistical heterogeneity was observed in the analysis (I^2=99.6). The sensitivity analysis was undertaken on forty-five studies further stratified on the basis of research tool/method used. Among these forty-five studies, eighteen studies used MMAS-8, eight studies used MMAS-4 and remaining nineteen studies used validated structured questionnaires. The sensitivity analysis shown that no significant difference in level of non-adherence was observed from the overall pooled percentage when the studies using different methods/tools for measuring medication adherence were analysed separately after removing the outliers (Supplementary Fig-3-5). One study was automatically removed from meta-analysis by the software, treating it as an outlier because it had too large sample size i.e. 2,455,193 [79]. Adding a study with such a big sample size would have skewed the results and introduced bias in over-all results.

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Sr#	Investigator	Year	Place of Study	Study Design	Scale Used	Sample Size	Gender Distribution		Gender Ratio Male: Female	Mean Age	Non-Adherence in Male % (CI 95%)	Non-Adherence in Female % (CI 95%)	Overall Non-Adherence % (CI 95%)
							Male	Female					
1.	Lee et al.	2012	China	Cross Sectional	MMAS-8	1114	465	649	41.7 :58.3	65.7 ± 11.1	38 (33-43)	32 (27-37)	35 (32-38)
2.	Ma et al.	2015	China	Cross Sectional	MMAS-4	1159	673	486	58.1 : 41.9	59.9 ± 10.06	N/A	N/A	79 (76-81)
3.	Yang et al.	2014	China	Cross Sectional	MMAS-4	745	345	400	46.3 : 53.7	56.4 ± 10.8	53 (48-58)	60 (55-65)	56 (53-60)
4.	Yue et al.	2014	China	Cross Sectional	MMAS-8	232	110	122	47.4 : 52.6	64.1 ± 11	N/A	N/A	26 (21-32)
5.	Pan et al.	2019	China	Cross Sectional	TASHP	488	242	246	49.59 : 50.41	N/A	79 (74-84)	66 (60-72)	73 (69-77)
6.	Zhang et al.	2018	China	Cross Sectional	Structured Questionnaire Form	1916	762	1154	39.8 : 60.2	72.2 ± 7.7	17 (14-19)	14 (12-16)	15 (13-16)
7.	Kang et al.	2014	Hong Kong	Cross Sectional.	MMAS-8	2445	1371	1074	43.9 : 56.1	65.5 ± 10.95	19 (17-21)	26 (23-29)	45 (43-47)
8.	Li et al.	2015	Hong Kong	Cross Sectional.	MMAS-8	2445	1120	1325	45.8 : 54.2	65.3 ± 11	N/A	N/A	46 (44-48)
9.	Suzanne et al.	2016	Hong Kong	Cross Sectional.	MMAS-4	195	40	151	20.5 : 79.5	76 ± 6.6	55 (40-70)	56 (48-64)	56 (49-63)
10.	Chui et al.	2017	South Korea	Cross Sectional.	Pill Count	1523	907	616	59.6 : 40.4	N/A	19 (17-22)	17 (14-19)	18 (16-20)
11.	Park et al.	2007	South Korea	Cross Sectional.	CMA (Cumulative Medication Adherence)	2,455,193	1,028,724	1,426,469	42 : 58	N/A	N/A	N/A	45 (45-45)
12.	Ramli et al.	2012	Malaysia	Cross Sectional	Structured Questionnaire Form	653	243	410	37.2 : 62.8	58 ± 9.8	44 (38-50)	51 (46-57)	47 (43-50)
13.	Athiyah et al.	2015	Indonesia	Cross Sectional	MMAS-8	204	55	149	27 : 73	N/A	N/A	N/A	66 (59-73)
14.	Rahmawati et al.	2017	Indonesia	Cross Sectional	MMAS-8	384	96	288	25 : 75	65.7 ± 10.3	N/A	N/A	89 (86-92)
15.	Violita et al.	2018	Indonesia	Cross Sectional	MMAS-8	134	41	93	30.6 : 69.4	57.6 ± N/A	N/A	N/A	58 (50-67)

16.	Pinprapapan et al.	2013	Thailand	Cross Sectional	Hypertensive Adherence to Therapeutic Regimen Scale (HARTS)	321	110	211	34.27 : 65.73	49 ± 5.79	N/A	N/A	51 (45-56)
17.	Woodham et al.	2018	Thailand	Cross Sectional	Pill Count	408	143	265	35 : 65	68 ± 5.92	82 (75-88)	89 (85-93)	87 (83-90)
18.	Nguyen et al.	2016-17	Vietnam	Cross Sectional	Structured Questionnaire Form	315	171	144	54.3 : 45.7	53.7 ± 6.95	55 (47-63)	44 (36-52)	50 (44-56)
19.	Saito et al.	2008	Japan	Cross Sectional	Structured Questionnaire Form	292	157	135	53.7 : 46.3	50.2 ± 6.6	43 (36-50)	N/A	64 (58-69)
20.	Suzuki et al.	2018	Japan	Cross Sectional	Structured Questionnaire Form	1372	953	419	69 : 31	67 ± 12	N/A	25 (21-29)	17 (15-19)
21.	Matsumura et al.	2018	Japan	Cross Sectional	Structured Questionnaire Form	687	342	323	51 : 49	65 ± 10.2	N/A	N/A	25 (22-28)
22.	Ishida et al.	2019	Japan	Cross Sectional	PDC-Proportion of days covered (≥80%)	47,891	27,293	20,598	57 : 43	70 ± 11.5	N/A	N/A	8.5 (8-9)
23.	Thomas et al.	2008-09	India	Cross Sectional	BMQ	608	310	298	51 : 49	58.40 ± N/A	N/A	N/A	50 (46-54)
24.	David et al.	2015	India	Cross Sectional	Morisky Green Scale	214	71	143	33 : 67	N/A	42 (32-51)	60 (51-69)	53 (46-60)
25.	Sutar et al.	2015-16	India (Goa)	Cross Sectional	MMAS-8	213	96	117	45 : 55	60.52 ± 5.4	N/A	N/A	5 (2-8)
26.	Bhandari et al.	2009	India	Cross Sectional	Structured Questionnaire Form	348	111	237	32 : 68	55.13 ± 12.4	N/A	N/A	27 (22-32)
27.	Balasubramanian et al.	2018	India	Cross Sectional	MMAS-4	189	93	96	49.2 : 50.8	65.12± 11.7	46 (36-56)	61 (51-71)	54 (47-61)
28.	Jayesh Shah et al.	2018	India	Cross Sectional	Structured Questionnaire Form	330	141	189	42.7 : 57.3	55.2 ± 12.6	62 (54-70)	60 (53-67)	61 (55-66)
29.	Jhag et al.	2018	India	Cross Sectional	MMAS-8	200	90	110	45 : 55	57.1 ± 12	29 (20-38)	28 (20-36)	29 (22-35)
30.	Gupta et al.	2019	India	Cross Sectional	Structured Questionnaire Form	100	33	67	33 : 67	55.6 ± 12.03	61 (44-77)	72 (61-82)	68 (59-77)
31.	Hossain et al.	2015	Bangladesh	Cross Sectional	Structured Questionnaire Form	146	103	43	70.5 : 29.5	N/A	49 (37-62)	35 (23-47)	45 (36-53)

32.	Karmokar et al.	2014	Bangladesh	Cross Sectional	Structured Questionnaire Form	350	251	99	71.6 : 28.4	50.49 ± 8.44	N/A	N/A	49 (44-54)
33.	Khanam et al.	2014	Bangladesh	Cross Sectional	Structured Questionnaire Form	1068	417	651	39 : 61	44.6 ± 15.8	29 (24-35)	24 (19-30)	26 (24-29)
34.	Hussain et al.	2006	Bangladesh	Cross Sectional	Structured Questionnaire Form	120	83	37	69.2 : 30.8	57 ± 11	N/A	N/A	85 (77-91)
35.	Ekram et al.	2006-07	Bangladesh	Cross Sectional	Structured Questionnaire Form	300	177	123	59 : 41	52 ± 11	N/A	N/A	87 (83-91)
36.	Ullah et al.	2019	Bangladesh	Cross Sectional	Hill-Bone Scale	144	66	78	46 : 54	56.1 ± N/A	58 (46-69)	51 (40-62)	55 (47-63)
37.	Ahmed et al.	2007	Pakistan	Cross Sectional	Structured Questionnaire Form	89	22	67	25 : 75	56 .1± 12.5	N/A	N/A	52 (41-62)
38.	Hashmi et al.	2005-06	Pakistan	Cross Sectional	MMAS-4	438	199	239	45.4 :54.6	54 ± 10	23 (15-32)	24 (16-33)	23 (19-28)
39.	Ali et al.	2012	Pakistan	Cross Sectional	MMAS-8	32	18	14	56 : 44	56 ± N/A	77 (56-91)	86 (75-96)	81 (64-93)
40.	Arshad et al.	2015	Pakistan	Cross Sectional	MMAS-4	106	53	53	50 : 50	58.8 ± 12.26	49 (36-63)	51 (37-64)	29 (21-38)
41.	Bhandari et al.	2009-10	Nepal	Cross Sectional	MMAS-4	154	N/A	N/A	N/A	N/A	31 (21-41)	54 (41-66)	44 (36-52)
42.	Shreshta et al.	2018	Nepal	Cross Sectional	Structured Questionnaire Form	260	132	128	51 : 49	N/A	53 (45-62)	43 (34-52)	48 (42-54)
43.	Han et al.	2015	Myanmar	Cross Sectional	MMAS-8	216	89	127	41.2 : 58.8	52.8 ± 12.5	46 (36-56)	54 (44-64)	49 (42-56)
44.	Elbur et al.	2013	Saudi Arabia	Cross Sectional	MMAS-4	144	N/A	N/A	N/A	N/A	N/A	N/A	65 (57-63)
45.	Al-Sowielem et al.	2001	Saudi Arabia.	Cross Sectional	Structured Questionnaire Form	190	51	139	27 : 73	50 ± 11.7	69 (61-77)	65 (57-73)	66 (59-73)
46.	Shaik et al.	2013-14	Saudi Arabia	Cross Sectional	MMAS-8	282	111	171	39.4 : 60.6	52 ± 12.05	56 (48-64)	54 (46-62)	55 (49-61)
47.	Khayyat et al.	2016	Saudi Arabia	Cross Sectional	MMAS-8	204	58	146	28.4 : 71.6	59 ± 12.2	40 (27-53)	59 (51-66)	54 (46-62)
48.	Alkhamis et al.	2019	Saudi Arabia	Cross Sectional	Structured Questionnaire Form	372	231	141	62 : 38	53 ± 12.4	52 (46-58)	42 (34-50)	49 (44-54)

49.	Alotayfi et al.	2018	Saudi Arabia	Cross Sectional	Structured Questionnaire Form	267	116	160	42 : 58	N/A	71 (62-79)	65 (58-72)	67 (62-73)
50.	Abdelhalim et al.	2019	Saudi Arabia	Cross Sectional	Structured Questionnaire Form	402	198	204	49 : 51	54.09 ± 10.7	80 (75-86)	41 (34-47)	60 (56-65)
51.	Alqarni et al.	2018	Saudi Arabia	Cross Sectional	Structured Questionnaire Form	108	30	78	27.8 : 72.2	N/A	58 (47-69)	90 (79-101)	67 (58-76)
52.	Bader et al.	2012-13	UAE	Cross Sectional	MMAS-4	250	134	116	53.6 : 46.4	44 ± 5.6	53 (43-62)	37 (28-46)	46 (39-52)
53.	Fahey et al.	2005-06	UAE	Cross Sectional	MMAS-8	203	102	101	50 : 50	52 ± N/A	N/A	N/A	48 (41-55)
54.	Sadat et al.	2014	Iran	Cross Sectional	MMAS-8	280	118	162	42.1 : 57.9	60.3 ± 10	N/A	N/A	51 (45-57)
55.	Behnood-Rod et al.	2014	Iran	Cross Sectional	MMAS-8	280	118	162	42.1 : 57.9	60 ± 10	50 (42-59)	50 (41-59)	50 (44-56)
56.	Kamran et al.	2013	Iran	Cross Sectional	MMAS-4	671	169	501	25.18 : 74.8	N/A	77 (74-81)	75 (71-79)	76 (72-79)
57.	Sadeghi et al.	2018	Iran	Cross Sectional	MMAS-8	600	181	419	30 : 70	56.44 ± 12.3	N/A	N/A	51 (47-55)
58.	Laila et al.	2016	Jordan	Cross Sectional	Hill-Bone	192	65	127	34 : 66	52.8 ± N/A	N/A	N/A	8 (4-12)
59.	Al-Jbour et al.	2013	Jordan	Cross Sectional	MMAS-4	273	84	189	30.8 : 69.2	69 ± 2.3	N/A	N/A	13 (9-17)
60.	Goussouset et al.	2015	Jordan	Cross Sectional	Structured Questionnaire Form	471	216	255	45.9 : 54.1	59 ± 11.18	26 (19-35)	23 (15-31)	24 (20-28)
61.	Al-banna et al.	2008	Iraq	Cross Sectional	Structured Questionnaire Form	418	127	291	30.4 : 69.6	N/A	14 (8-20)	12 (5-19)	12 (9-15)
62.	Ismael et al.	2018	Iraq	Cross Sectional	MMAS-8	335	145	190	43.3 : 56.7	58.69 ± 11.9	39 (31-47)	62 (55-79)	46 (41-51)
63.	Al-Noumani et al.	2015	Oman	Cross Sectional	MMAS-8	45	16	29	35.6 : 64.4	52 ± 14.6	N/A	N/A	51 (36-66)
64.	Al-Ramahi et al.	2011	Palestine	Cross Sectional	MMAS-8	450	197	253	43.8 : 56.2	59 ± 12.2	54 (48-60)	54 (48-60)	54 (49-59)
65.	Mohammad et al.	2015	Lebanon	Cross Sectional	Structured Questionnaire Form	210	85	125	40.5 : 59.5	59.3 ± 12.2	N/A	N/A	22 (17-29)
66.	Cingil et al.	2005	Turkey	Cross Sectional	Structured Questionnaire Form	194	50	144	26 : 74	N/A	13 (3-21)	35 (27-42)	29 (23-36)

293 Abbreviations: MMAS-8: 8-items Morisky Medication Adherence Scale, MMAS-4: 4-items Morisky Medication Adherence Scale, TASHP: Therapeutic Adherence Scale for Hypertensive Patients, CMA:
294 Cumulative Medication Adherence, HARTS: Hypertensive Adherence to Therapeutic Regimen Scale, PDC: Proportion of days covered (≥80%), BMQ: Brief Medication Questionnaire, N/A: Not Available.

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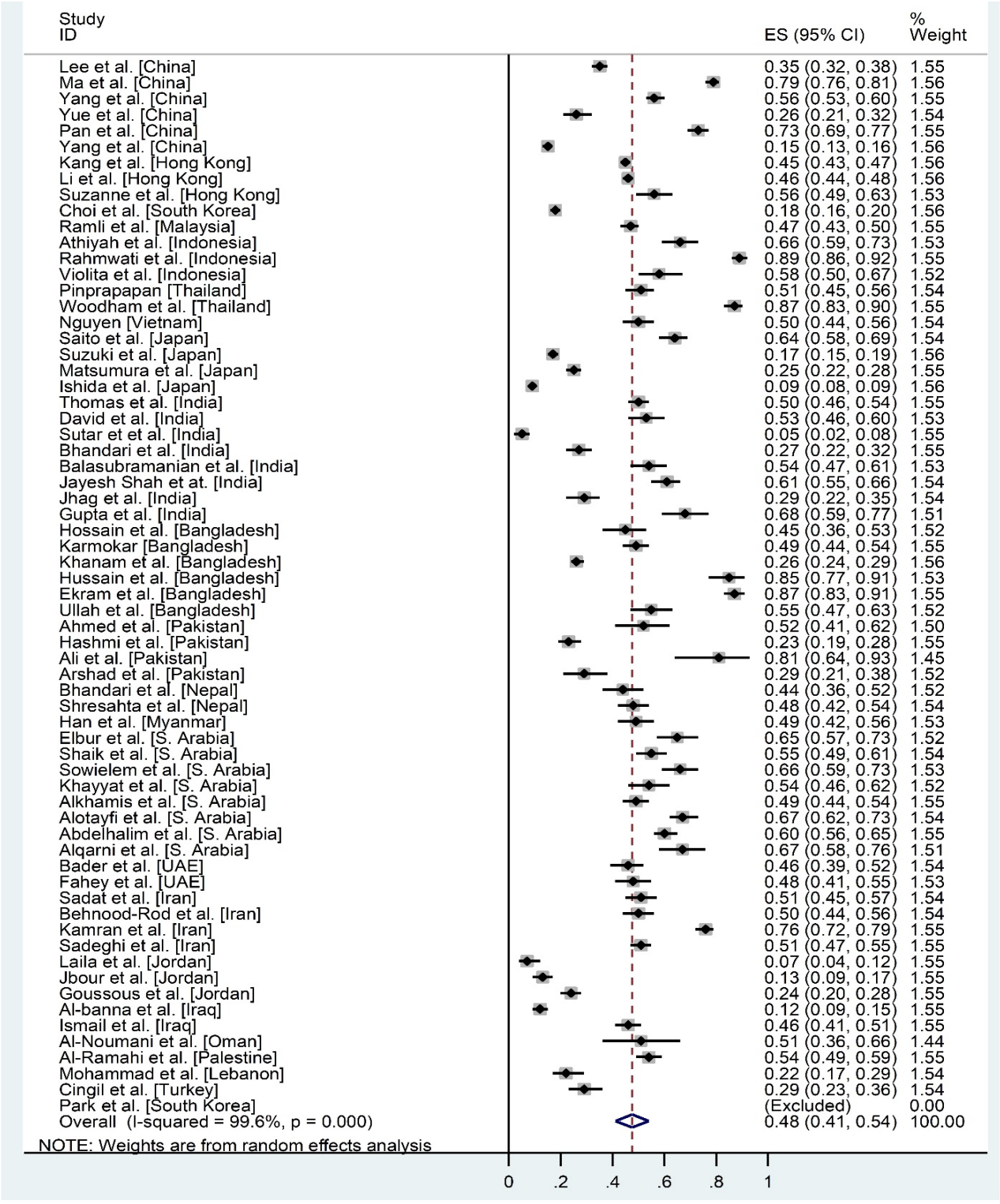

Figure 2: Meta-analysis of non-adherence among hypertensive patients (66 studies)

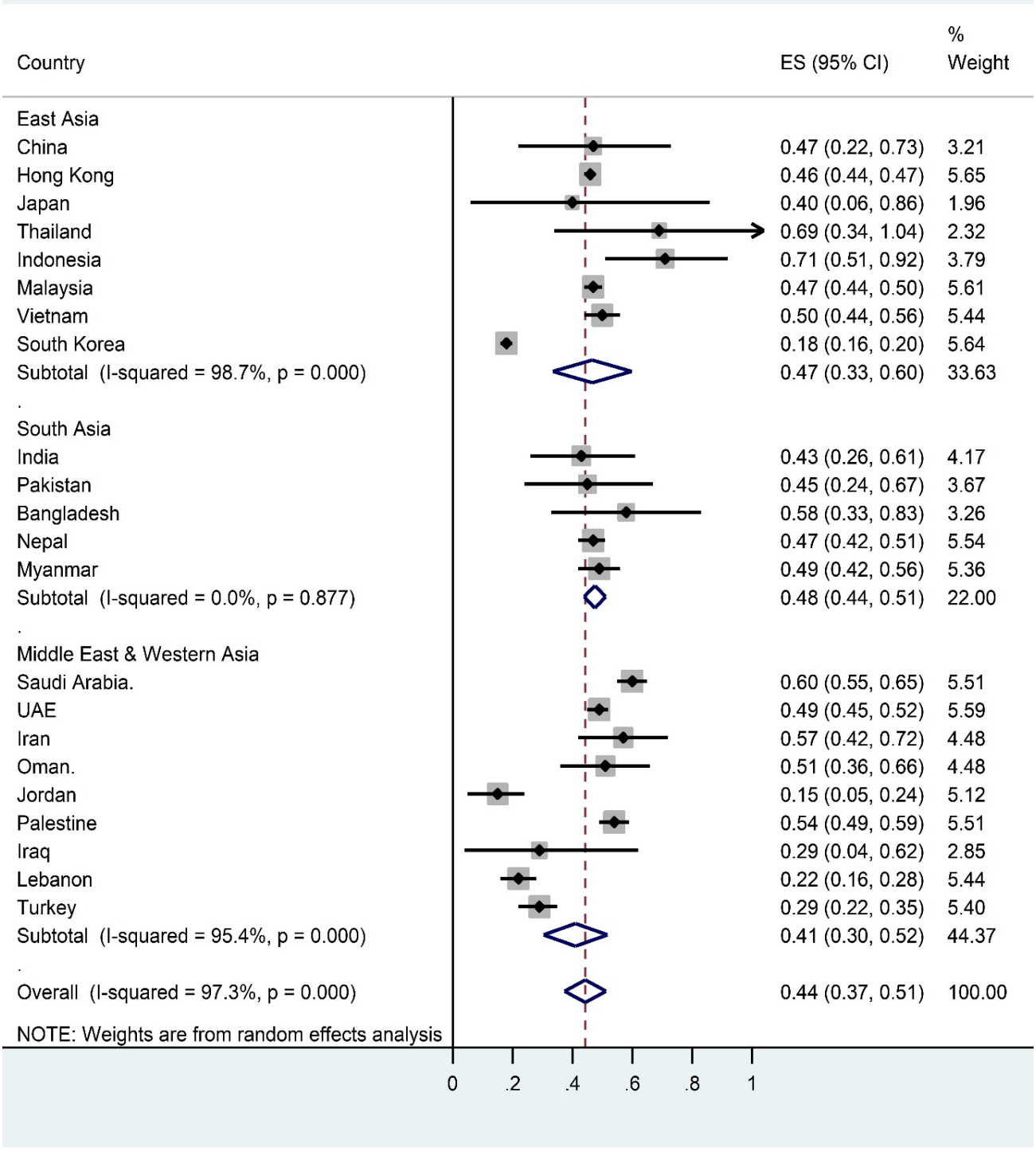

Figure 3: Meta-analysis of non-adherence in different regions of Asia (22 countries)

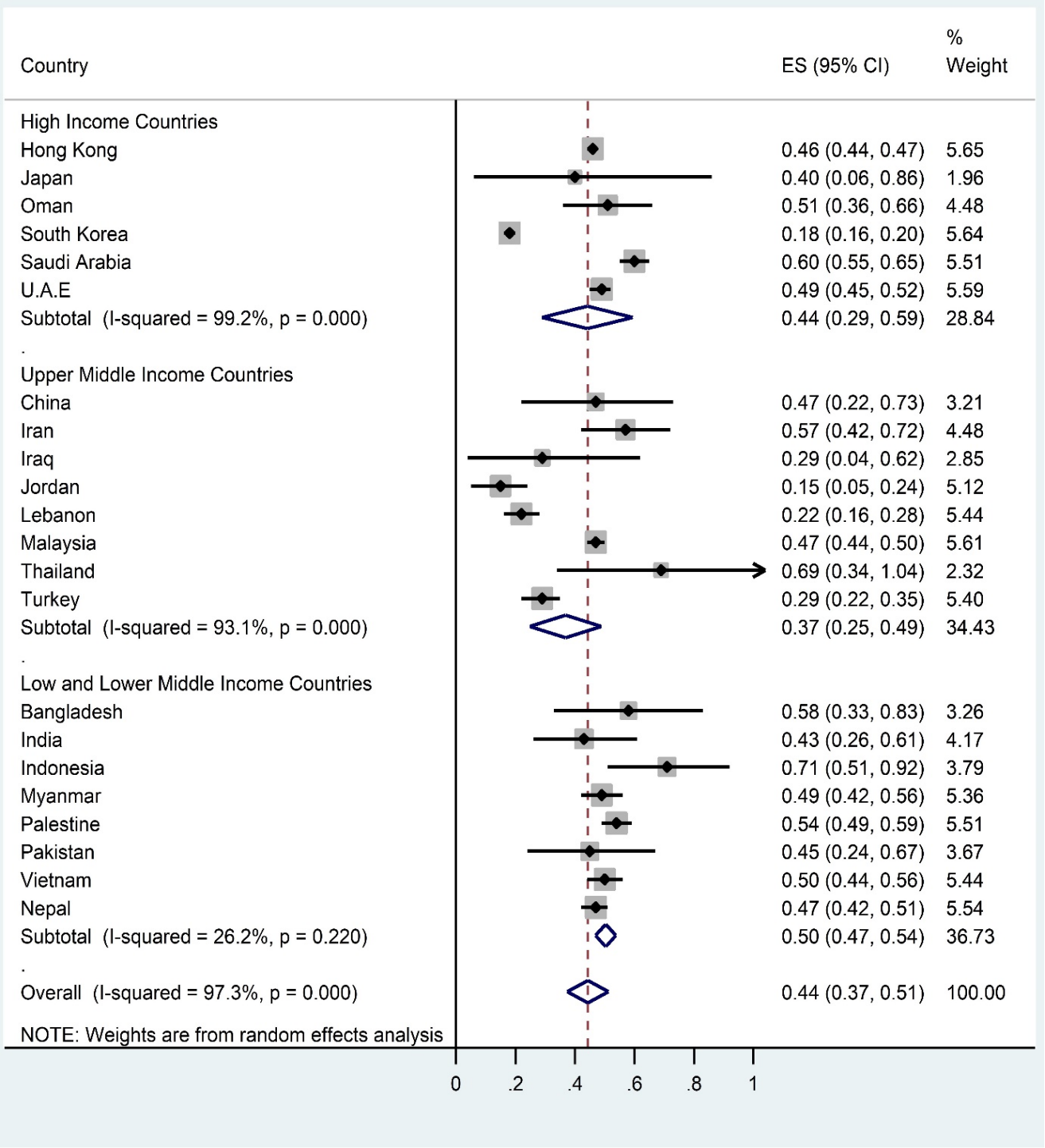

Figure 4: Meta-analysis of non-adherence in different income countries of Asia (22 countries)

Discussion:

The purpose of this review was to estimate the prevalence of non-adherence to antihypertensive medications in Asia. The findings of our review found that almost half of the studied participants across 22 countries in Asia were non-adherent to antihypertensive medications. This may explain poor treatment outcomes and increased financial burden on healthcare systems due to the complications associated with hypertension [83].

The prevalence of non-adherence to antihypertensives reported in our review [48% (41-54 P=0.001)] is higher than that reported in Asia in an earlier meta-analysis by Abegaz et al. [43.5% (35-53, P>0.001)]. However, this study included only seven Asian countries mostly from East Asia [9]. The sensitivity analysis found no significant difference in the rate of non-adherence among studies that used different methods/tools to measure non-adherence. Similarly, the outliers and sample size also had very little effect on overall results.

We stratified results based on gender and found a statistically non-significant higher prevalence of non-adherence among females compared to male hypertensive patients. Mixed results have been reported in the literature terms of gender differences related to medication adherence. Some studies from Asia found female patients to be more adherent to antihypertensive treatment than their male counterparts [84, 85, 16]. On the contrary, there are Asian studies that found male patients more adherent to their prescribed anti-hypertensive medication than female patients [31, 24].

A number of studies conducted in Asia have explored the barriers associated with medication adherence in hypertensive patients. These identified barriers can be categorized into patient related factors, socioeconomic factors, Therapy related factors and disease related factors [86, 87]. The patient related factors cited in different studies include forgetfulness, language barriers and patient preferences, patient knowledge, disruption of patient routine and family support. The socioeconomic factors identified by different studies include unaffordability, unemployment, low-income. The therapy related factors include side effects and dosage regimen frequency. Healthcare system related factors include lack of insurance, longer wait times to get hospital appointment, poor communication between healthcare provider and patient and lack of automatic prescription renewal. Similarly, condition related barriers cited in different Asian studies include absence of symptoms, presence of disease related complication and previous hospitalization due to the disease [8, 7, 38]. However, among women, dissatisfaction with communication with healthcare providers and depressive symptoms are the most important causes of medication non-adherence [63]. Clinicians should take into consideration gender differences and be aware that reasons may vary between patients [88]. Therefore, interventions to improve adherence should be tailored to the needs of patients in order to have a positive effect [89].

We found a higher rate of non-adherence to antihypertensive medications in low and lower middle-income countries i.e. 50% (47-54, P=0.220) as compared to upper-middle and high-income countries i.e. 37% (25-49, P=0.001) and 44% (29-59, P=0.001) respectively. This difference may be due to higher level of disease awareness and better healthcare system across higher-middle and high- income countries compared to lower-middle and low-income countries. Furthermore, factors such as lack of suitable healthcare resources, inequality in terms of access to healthcare facilities and lack of affordability all play a role in augmenting the problem [90, 10] in low- and middle-income counties. Subsequently, the burden and incidence of hypertension associated complications is higher in low- and middle-income countries compared with developed countries [61, 65].

The regional factors such as ethnicity, culture, economic conditions and healthcare systems should be kept in mind while designing any intervention aiming at improving medication adherence among patients with hypertension. A number of countries in Asia have limited healthcare resources, hence there is a need to develop interventions that are cost effective and easily implementable. Any interventions targeting at improving health awareness could be useful in improving medication adherence. The healthcare providers such as physicians, pharmacists and community health workers could play their role in educating the patients regarding the benefits of taking their medications regularly [8, 91, 92]. Better communication between patient and healthcare providers has shown a positive effect on medication adherence. Several regions in Asia have high cell phone density, hence using the communication technologies such as SMS reminders, mobile applications and electronic medication reconciliation could help improving medication adherence [93-95]. Motivational interviewing has also shown positive results in improving medication adherence [96]. Behavioural interventions such as memory aids and synchronizing therapeutic activities with daily routine for example taking medication after prayer or before shower could be useful in improving medication adherence [97, 98]. Lastly the Unaffordability and unavailability of anti-hypertensive medications also contributes to the medication non-adherence, hence any intervention targeting these issues could be helpful in improving medication adherence [7].

Limitations:

A high level of heterogeneity was observed in the studies included in the meta-analysis. This high proportion of heterogeneity may be due to differences in patient characteristics, cultural variations, demographic variations and study methodologies. Furthermore, a questionnaire that is successfully used to measure non-adherence in one country does not always mean that it can measure adherence in another country with the same degree of accuracy. This could be due to cultural and linguistic differences in different parts of the world. We only included studies published in English language only which might have resulted in missing some valuable articles

published in languages other than English. Furthermore, we only searched for peer-reviewed articles but not grey literature and conference abstracts and used minimum quality threshold for studies to be included which might have introduced publication bias. Despite our best efforts to include each and every country in our study we could not find any study from Afghanistan, Maldives, Uzbekistan, Tajikistan and Turkmenistan. However, the countries included in our review represent more than 90% of the population of Asia.

Conclusion:

Overall non-adherence to antihypertensive medications is high in Asian countries. Non-adherence to prescribed antihypertensive therapy is slightly higher in South Asia when compared to East Asia and the Middle East. Similarly, the rate of non-adherence to prescribed antihypertensive medications was higher in low- and lower middle-income countries as compared to upper-middle and high-income countries. Interventions aimed at improving adherence in Asian countries should consider gender differences. Prevention policies need to be in place for Asian countries to raise awareness of hypertension and reduce its burden.

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