

Meta-Analysis: Drug Side Effects, Smoking, Alcohol Consumptions and Their Relationships with Drug-Taking Adherence in Tuberculosis Patients

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ABSTRACT

Background: Inappropriate tuberculosis treatment is a major determinant of multidrug-resistant tuberculosis (MDR) TB, which is related to patient adherence to treatment. There are several factors that affect MDR-TB such as drug side effects, smoking and alcohol consumption. The aim is to estimate the magnitude of the effect of drug side effects on tuberculosis treatment adherence, based on the results of a number of similar primary studies.

Subjects and Method: This study is a systematic review and meta-analysis research. Article search was carried out based on the eligibility criteria of the PICO model including: P= Tuberculosis patient; I= drug side effects, smoking and alcohol consumption; C= no drug side effects, no smoking and no alcohol consumption; O= Tuberculosis treatment adherence. Articles were collected from Google scholar, PubMed, Science Direct, and Springerlink. Keywords using “drug side effects” OR “tobacco smoking” OR “alcohol consumption” OR “tuberculosis” AND “medication adherence” AND “cross sectional” AND “adjusted odds ratio”. Inclusion criteria in this study included articles with a cross-sectional study design, the relationship size used was the adjusted Odds Ratio (aOR), articles published in the 2009 to 2022 range. Selected articles were tested for eligibility using CEBM and analyzed using the PRISMA diagram and the Review Manager 5.3 application.

Results: 14 Cross-sectional studies were selected for the meta-analysis of 8 studies with 2,045 TB patients showed that drug side effects reduced TB treatment adherence by 0.26 times than no drug side effects (aOR= 0.26; 95% CI= 0.14 to 0.49; p< 0.001). 7 studies with 2,966 TB patients showed that alcohol consumption decreased TB treatment adherence by 0.61 times than not consuming alcohol (aOR= 0.61; 95% CI= 0.32 to 1.16; p= 0.130). Study 6 with 1,748 TB patients showed that smoking decreased TB treatment adherence by 0.86 times than non-smokers (aOR= 0.86; 95% CI= 0.17 to 4.37; p= 0.850).

Conclusion: Side effects of drugs, alcohol, and smoking reduce treatment adherence in tuberculosis patients.

Keywords: drug side effects, alcohol consumption, smoking, treatment adherence

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BACKGROUND

Tuberculosis is still the main cause of disease in the world. In addition, its presence is one of the top ten causes of death worldwide and remains the most common cause of death from a single infectious agent (WHO, 2021). Tuberculosis in Indonesia is the 13th cause of death and the second deadliest infectious disease after COVID-19 (WHO, 2020). Tuberculosis is a disease that can be cured with various kinds of treatment, but often tuberculosis treatment is not given properly and completely (Muna and Soleha, 2018).

In general, the main factor affecting the cure rate of tuberculosis patients is the adherence of tuberculosis patients in taking anti-tuberculosis drugs (OAT). From 2009 to 2011 the world tuberculosis cure rate was 80%. Asia's recovery rate is the second highest at 85%, after the Western Pacific at 91%. Followed by 74% in the Eastern Mediterranean, 72% in Africa, 54% in the Americas, and 51% in Europe. The cure rate for tuberculosis in Indonesia in 2015-2017 decreased by 85.8% in 2015, 86.0% in 2016 and 85.1% in 2017 (RI Ministry of Health, 2018).

Non-adherence to TB treatment is an important barrier and one of the most important barriers to global TB control. Non-adherence to TB treatment has emerged as a major factor in treatment failure (Gebreweld et al., 2018). Previous studies have shown that people experience side effects from heavy class drugs, and it is known that tuberculosis patients decide to stop treatment as one of the side effects experienced after taking anti-tuberculosis drugs. Non-adherence in undergoing treatment often triggers resistance to OAT (Bello and Itiola, 2010). The results of this study indicate that there is a relationship between the phase of treatment and adherence to treatment of tuberculosis patients.

This study used a systematic review and meta-analytic approach to analyze the effect of side effects of drugs, smoking and alcohol consumption on adherence to treatment of tuberculosis patients. Systematic review includes quantitative techniques (meta analysis) which are carried out by combining several previous research results, statistically on the same test so as to obtain quantitative results. The findings of this study can assist health care providers in taking preventive and treatment measures for tuberculosis treatment. The aimed to estimate the effect of drug side effects on tuberculosis treatment adherence, based on the results of a number of similar primary studies.

SUBJECTS AND METHOD

1. Study Design

This research is a systematic review and meta-analysis. Article search was carried out based on the eligibility criteria of the PICO model including: P= Tuberculosis patient; I= Drug side effects, smoking and alcohol consumption; C= no drug side effects, no smoking and no alcohol consumption; O= Tuberculosis treatment adherence. The articles used came from 4 databases, namely Google scholar, PubMed, Science Direct and Springerlink. The keywords used included "drug side effects" OR "tobacco smoking" OR "alcohol consumption" OR "tuberculosis" AND "medication adherence" AND "cross sectional" AND "adjusted odds ratio".

2. Steps of Meta-Analysis

The meta-analysis was carried out through 5 steps as follows:

- 1) Formulate PICO format research questions (Population, Intervention, Comparison, and Outcome).
- 2) Searching for primary study articles from various databases.
- 3) Assessing research quality.

4) Combining primary study data and synthesizing effect estimates using the Revman application.

5) Interpreting results and conclusions.

3. Inclusion Criteria

The inclusion criteria in this study were adult TB patients aged >15 years old, articles must be full text with observational studies (cross-sectional), articles in English or Indonesian, the article uses a cross-sectional study design, the size of the relationship used is the aOR value, and articles published from 2009 to 2022.

4. Exclusion Criteria

Study articles were articles that do not use multivariate analysis, primary studies that have been meta-analyzed or review articles.

5. Operational Definition of Variables

treatment adherence: is the action of a patient with tuberculosis who can fulfill the treatment according to the doctor's direction and agreement. Treatment adherence can be interpreted as a description of the patient's behavior in following the treatment program for certain diseases correctly and complete.

Drugs side effects: is an adverse and unwanted response to drug that occurs at doses normally used in humans for the prevention, diagnosis, or treatment of disease or for the modification of physiological functions.

Alcohol consumption: is a drink containing ethanol, a psychoactive substance which when consumed will result in loss of consciousness, and also beverages containing ethyl alcohol or ethanol (C₂H₅OH), processed from agricultural products containing carbohydrates by means of fermentation and distillation or without distillation.

Smoking: is the act of inhaling smoke, the result of burning tobacco in the form of cigarettes, pipes and cigars, and is a roll of tobacco (approximately the size of a little finger) wrapped in nipa leaf or paper.

6. Study Instruments

Quality assessment in this study used a critical assessment checklist from the Cross-sectional study checklist published by CEBM.

7. Data Analysis

The articles in this study were collected according to the PRISMA flowchart and analyzed using the Review Manager 5.3 application. The analysis was carried out by calculating the effect size and heterogeneity consistency value (I²) of the results.

RESULTS

The process of selecting articles systematically is described in PRISMA Flow chart figure 1.

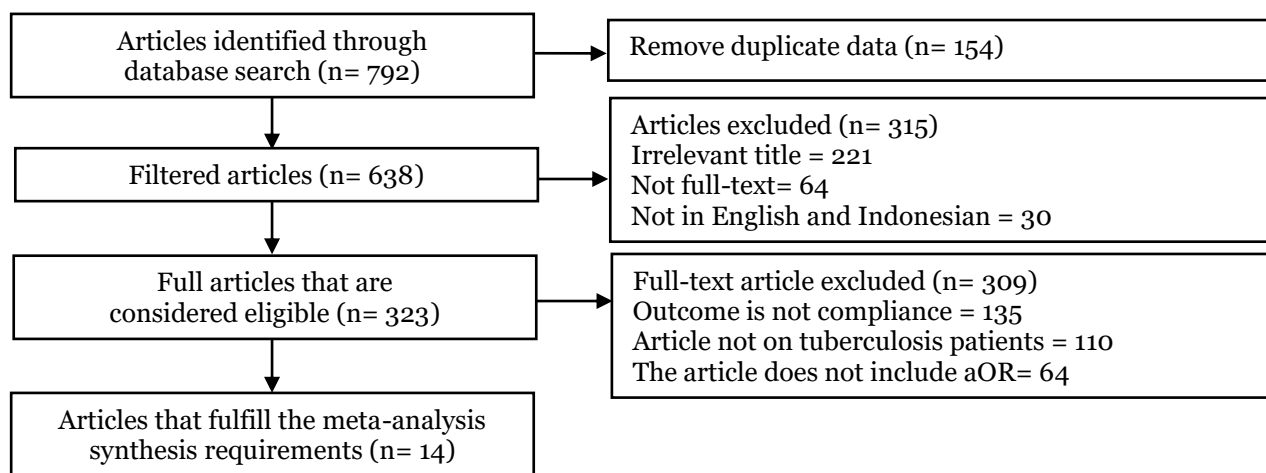


Figure1. PRISMA Flow Diagram research on the effect of side effects of drugs, smoking and alcohol on tuberculosis treatment adherence

Related research on the effect of side effects of drugs, smoking and alcohol consumption on medication adherence consisted of 14 articles from the initial search process resulting 792 articles, after the deletion process of published articles, 638 articles were obtained and 328 of them fulfilled the requirements for further full text review by 14 articles

that met the quality assessment were included in the quantitative synthesis using meta-analysis.

It can be seen in Figure 2 that research articles come from 2 continents, namely Africa and Asia. 11 were from Africa (Ethiopia, Nigeria, Uganda, Burkina Faso) and 3 were from Asia (China, India and Indonesia).



Figure 2. Map of research areas on the effect of side effects of drugs, smoking and alcohol on tuberculosis treatment adherence

Table 1. Results of cross-sectional study quality assessment of the influence of drugs side effects, smoking and alcohol on tuberculosis treatment adherence

Primary Study	Criteria of Questions												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
Ajema et al. (2020)	2	2	2	2	2	2	2	2	2	2	2	2	24
Amuha et al. (2009)	2	2	2	2	2	2	2	2	2	2	2	2	24
Bagchi et al. (2010)	2	2	2	2	2	2	2	2	2	2	2	2	24
Bereda et al. (2021)	2	2	2	2	2	2	2	2	2	2	2	2	24
Chen et al. (2020)	2	2	2	2	2	2	2	2	2	2	2	2	24
Eticha et al. (2014)	2	2	2	2	2	2	2	2	2	2	1	2	23
Gube et al. (2018)	2	2	2	2	2	2	2	2	2	2	2	2	24
Iweama et al. (2021)	2	2	2	2	2	2	2	2	2	2	2	2	24
Kiros et al. (2014)	2	2	2	2	2	2	2	2	2	2	2	2	24
Kisambu et al. (2014)	2	2	2	2	2	2	2	2	2	2	2	2	24
Meda et al. (2013)	2	2	2	2	2	2	2	2	2	2	2	2	24
Mekonnen et al. (2018)	2	2	2	2	2	2	2	2	2	2	2	2	24
Woimo et al. (2017)	2	2	2	2	2	2	2	2	2	2	1	2	23
Wulandari (2015)	2	2	2	2	2	2	2	2	2	2	2	2	24

Description of the question criteria:

- 1 = Does this objective clearly address the research focus/problem?
- 2 = Is the cross-sectional research method suitable for answering the research question?
- 3 = Is the research subject selection method clearly written?
- 4 = Does the sampling method not cause bias (selection)?
- 5 = Does the research sample taken represent the designated population?
- 6 = Is the sample size based on pre-study considerations?
- 7 = Is a satisfactory response achieved?
- 8 = Is the research instrument valid and reliable?
- 9 = Is statistical significance assessed?
- 10 = Are confidence intervals given for the main results?
- 11 = Have confounding factors (gender and age) been taken into account?
- 12 = Can the results be applied to your study?

Description of the answer score:

- 0 = No
- 1 = Uncertain
- 2 = Yess

Table 2. Description of the primary study of the effect of drug, smoking and alcohol side effects on treatment adherence in a meta-analysis

Author (year)	Country	Sample size	P	I	C	O
Bereda et al. (2021)	Ethiopia	168	Tuberculosis patient, age 25-34 years, male 82, female 86	There are drug side effects	No drugs side effect	Obediently take medication
Chen et al. (2020)	China	481	Tuberculosis patients, age ≥18 years, 298 male, 183 female	There are drug side effects	No drugs side effect	Obediently take medication
Gube et al. (2018)	Ethiopia	271	Tuberculosis patients, age ≥15 years, 158 male, 113 female	There are drug side effects, Alcohol, Smoking	No drug side effects, No alcohol, No smoking	Obediently take medication
Iweama et al. (2021)	Nigeria	390	Tuberculosis patients, age ≥18 years, 124 male, 266 female	There are drug side effects, Alcohol, Smoking	No drug side effects, No alcohol, No smoking	Obediently take medication
Kiros et al. (2014)	Ethiopia	278	Tuberculosis patient, age 15 years, male 171, female 106	There are drug side effects	No drug side effects	Obediently take medication
Kisambu et al. (2014)	Ethiopia	126	Tuberculosis patient, age ≥18 years, male 55, female 71	There are drug side effects	No drug side effects	Obediently take medication
Woimo et al. (2017)	Ethiopia	261	Tuberculosis patients, age 15-24 years, 140 male, 121 female	There are drug side effects	No drug side effects	Obediently take medication
Wulandari (2015)	Indonesia	70	Tuberculosis patient, age 22-60 years, male 45, female 25	There are drug side effects	No drug side effects	Obediently take medication
Ajema et al. (2020)	Ethiopia	289	Tuberculosis patients, age >15 years, 148 male, 101 female	Alcohol, Smoking	No alcohol, not smoking	Obediently take medication

Author (year)	Country	Sample size	P	I	C	O
Amuha et al. (2009)	Uganda	140	Tuberculosis patient, age 25-75 years, male 80, female 60	Alcohol, Smoking	No alcohol, not smoking	Obediently take medication
Eticha et al. (2014)	Ethiopia	120	Tuberculosis patients, age >18 years, 66 male, 54 female	Alcohol, Smoking	No alcohol, not smoking	Obediently take medication
Meda et al. (2013)	Burkina Faso	1,043	Tuberculosis patients, age ≥36 years, 453 male, 590 female	Alcohol	No alcohol	Obediently take medication
Mekonnen et al. (2018)	Ethiopia	713	Tuberculosis patients, age ≥18 years, 166 male, 140 female	Alcohol	No alcohol	Obediently take medication
Bagchi et al. (2010)	India	538	Tuberculosis patients, age >19 years, 344 male, 194 female	Smoking	Not smoking	Obediently take medication

Table 3. Adjusted Odd Ratio (aOR) of the drug side effects on treatment adherence in a meta-analysis

Author (Year)	aOR	95%CI	
		Lower Limit	Upper Limit
Alemayehu (2019)	0.40	0.24	0.66
Bereda (2021)	0.33	0.19	0.57
Chen (2020)	0.68	0.46	0.98
Eticha (2014)	0.48	0.14	1.64
Gube (2018)	0.07	0.01	1.00
Iweama (2021)	0.10	0.00	3.24
Kisambu (2014)	0.19	0.07	0.51
Kiros (2014)	0.30	0.08	1.12
Woimo (2017)	0.58	0.14	2.40
Wulandari (2015)	0.04	0.01	0.16

The forest plot in Figure 3 showed that patients who had drug side effects were 0.26 times more likely to comply with treatment than patients without drug side effects and these results were statistically significant (aOR= 0.26; 95% CI= 0.14 to 0.49; p<0.001).

The heterogeneity of the study data showed high heterogeneity in effect estimates (I²= 69%; p= 0.001). The calculation of average effect estimate was carried out using the random effect model approach because the spread of the data was heterogeneous.

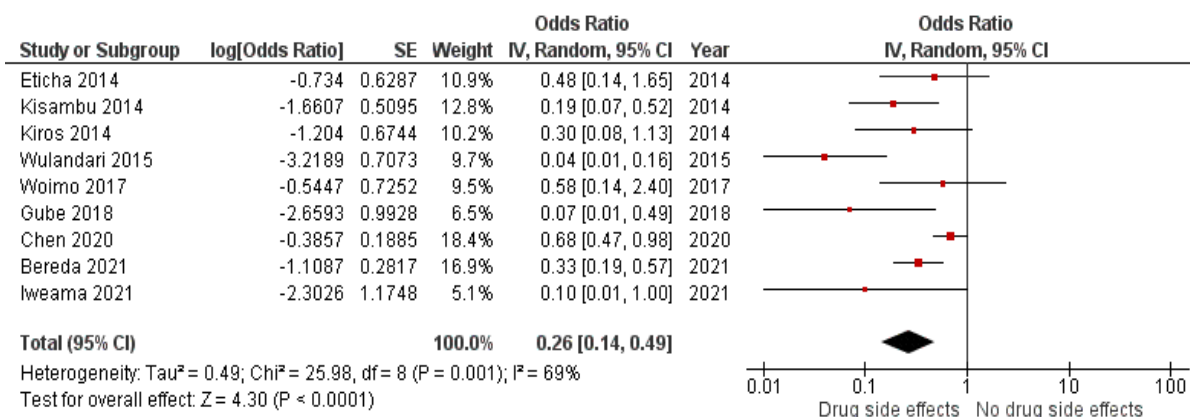


Figure 3. Forest plot of the effect of drug side effects on treatment adherence in tuberculosis patients

The funnel plot in Figure 4 from a small sample primary study distribution of effect estimates was more to the left than to the right of the average vertical line, so the funnel plot indicated publication bias. Because the distribution of the estimated

effects on the funnel plot was mostly located on the left, which was the same as the Diamond location of the forest plot in Figure 3, which was located on the left, the publication bias tends to overestimate the true effect.

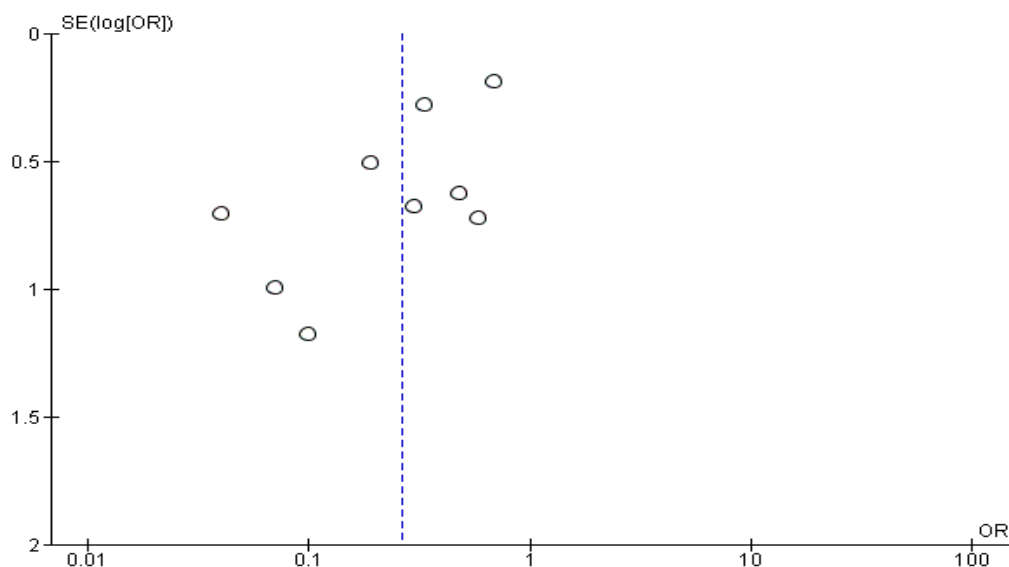


Figure 4. Funnel plot of drug side effects on treatment adherence in tuberculosis patients

Table 5. Adjusted Odd Ratio (aOR) of the effect of alcohol consumption on treatment adherence of tuberculosis patients

Author (Year)	aOR	95 % CI	
		Lower limit	Upper limit
Ajema (2020)	1.66	0.25	11.02
Amuha (2009)	0.25	0.06	1.04
Eticha (2014)	1.00	1.31	3.23
Gube (2018)	0.30	0.10	1.36
Iweama (2021)	0.54	0.26	1.12
Mekonnen (2018)	0.19	0.06	0.60
Woimo (2017)	0.83	0.08	8.61
Meda (2013)	1.31	1.25	1.37

Forest plot in Figure 5 showed that consuming alcohol can reduce treatment adherence in tuberculosis patients. Patients who consume alcohol were 0.61 times more likely to comply with treatment than those who do not consume alcohol and these results were not statistically significant (me . (aOR= 0.61; 95% CI= 0.32 to 1.16; $p < 0.001$).

Heterogeneity of research data showed ($I^2 = 72\%$; $p < 0.001$). So that the calcu-

lation of the average effect estimate was carried out using a random effect model approach or the distribution of data was declared heterogeneous.

The funnel plot in Figure 6. Shows asymmetry between the right and left plots, this shows that the distribution of estimates between studies was symmetrical to the right and left of the mean line, thus the funnel plot did not indicate publication bias.

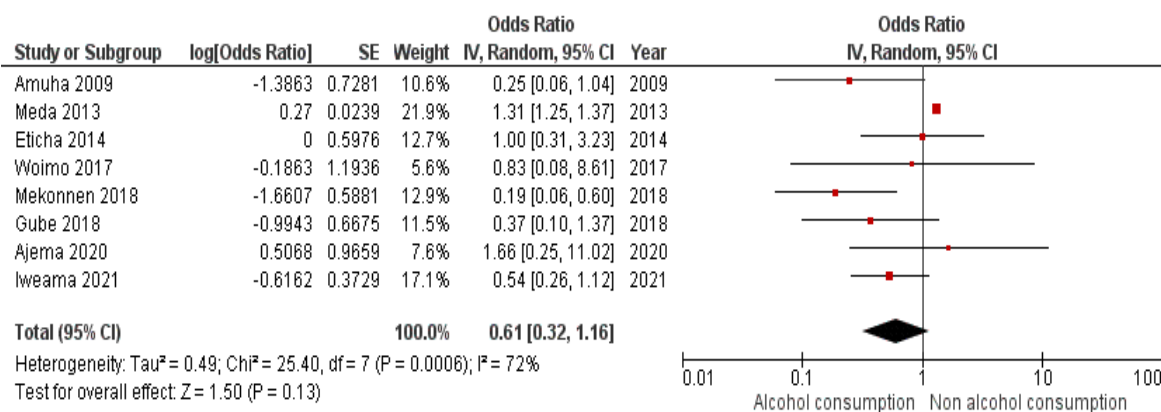


Figure 5. Forest plot of the effect of alcohol consumption on treatment adherence of tuberculosis patients

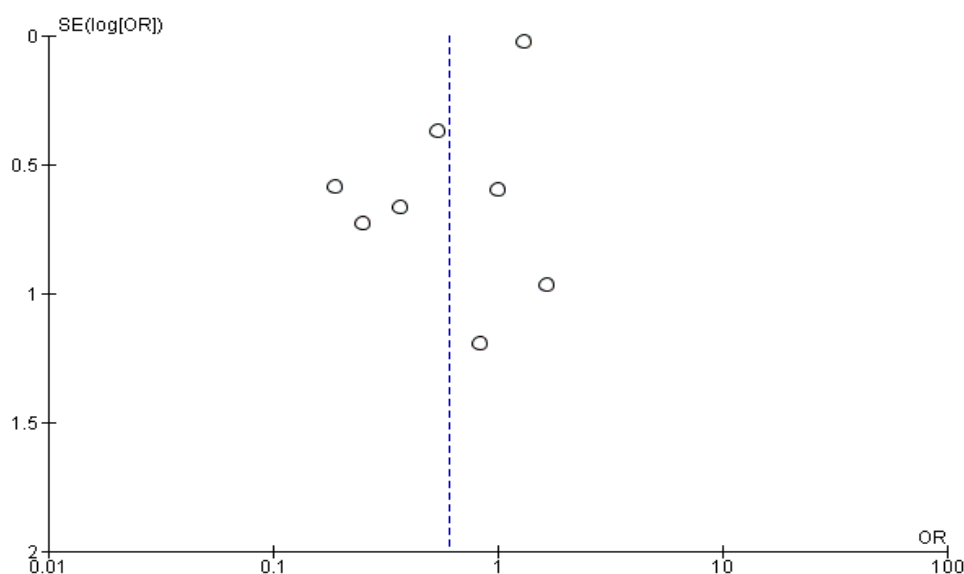


Figure 6. Funnel plot of the effect of alcohol consumption on treatment adherence of tuberculosis patients

Table 6. Adjusted Odd Ratio (aOR) of the effect of smoking on treatment adherence of tuberculosis patients

Author (Year)	aOR	95 % CI	
		Lower limit	Upper limit
Ajema (2020)	0.08	0.02	0.32
Amuha (2009)	5.80	5.00	6.72
Bagchi (2010)	0.52	0.22	1.22
Eticha (2014)	0.73	0.20	2.66
Gube (2018)	1.10	0.09	23.4
Iweama (2021)	2.24	0.12	41.8

Forest plot in Figure 7 showed that patients who smoke are 0.86 times more likely to comply with medication than non-smokers and these results were not

statistically significant (aOR= 0.86; 95% CI= 0.17 to 4.37; p= 0.850).

The heterogeneity of the research data showed high heterogeneity (I²=

93%; $p < 0.001$) therefore, the calculation of the average estimate was carried out using a random effect model approach.

Funnel plot Figure 8. Shows that the distribution of effect estimates among

small sample primary studies was not symmetrical. The distribution of effect estimates was more on the right than on the left, the average vertical line of estimates thus indicating publication bias.

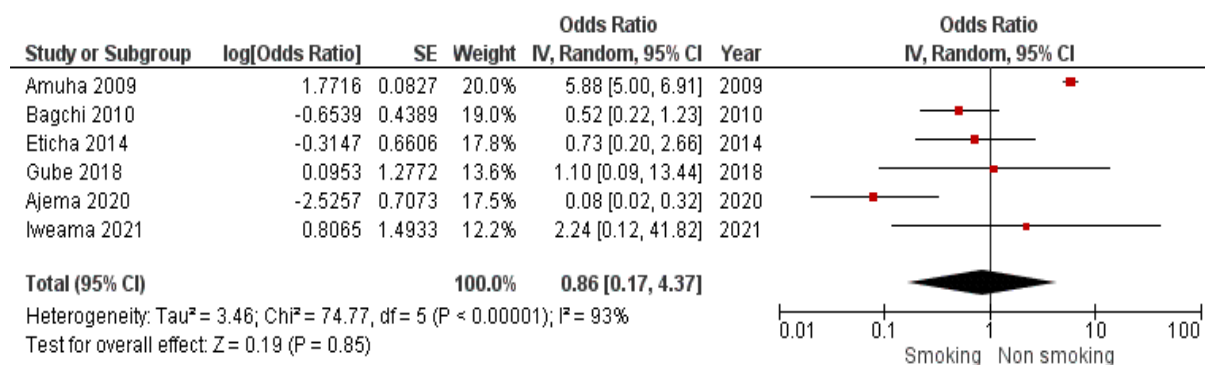


Figure 7. Forest plot of the effect of smoking on treatment adherence of tuberculosis patients

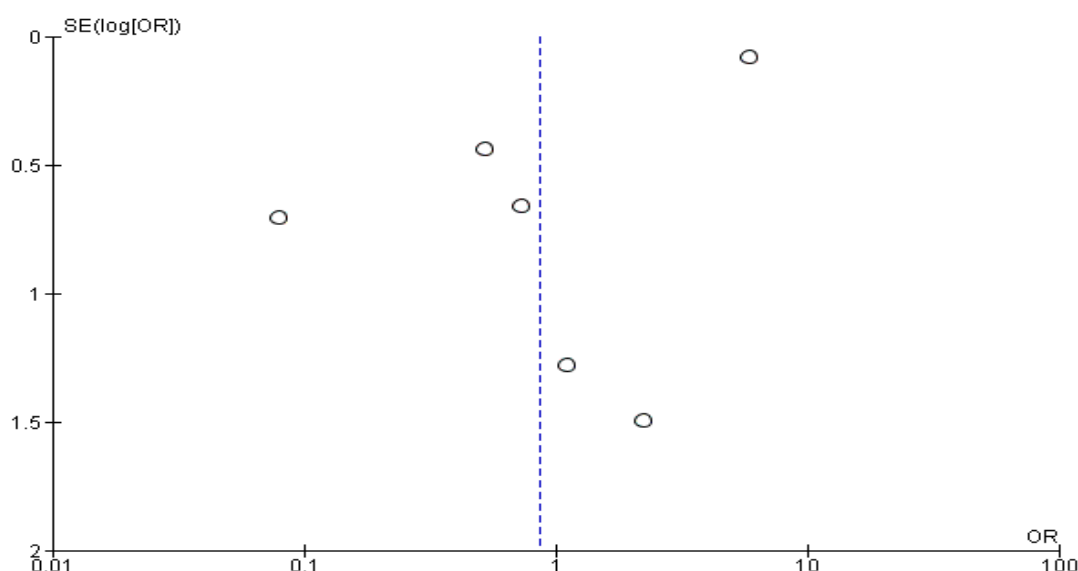


Figure 8. Funnel plot of the effect of smoking on treatment adherence of tuberculosis patients

DISCUSSION

Based on the results of the analysis of 14 primary studies which conducted systematic review and meta-analysis showed that drug side effects can reduce treatment adherence in tuberculosis patients by 0.26 times compared to no drug side effects and these results are statistically significant (aOR = 0.26; CI 95 % = 0.14 to 0.49 $p < 0.001$). This is in line with re-

search by Rahmi et al. (2017) which showed that respondent who experienced drug side effects caused non-adherence to treatment, because some respondents did not know that anti-tuberculosis drugs could cause complaints or side effects. Side effects are a risk factor for compliance in patients with advanced pulmonary tuberculosis, based on a study by Wulandari (2015) showing that pulmo-

nary TB patients with severe side effects have a risk of non-adherence by 6.1 times greater than mild side effects. Statistically, there is a significant relationship between side effects and adherence to taking medication in patients with pulmonary TB ($p= 0.007$).

According to Cahyaningtyas et al. (2018), side effects of anti-tuberculosis drugs are one of the causes of failure in tuberculosis treatment, and this research is in line with his research at Panti Waluya Malang Hospital showing that there is relationship between side effects of anti-tuberculosis drugs on tuberculosis patient adherence to treatment. Based on the results of systematic review analysis and meta-analysis, it was shown that alcohol consumption can reduce medication adherence in tuberculosis patients by 0.61 times compared to not consuming alcohol and these results were not statistically significant ($aOR= 0.61$; 95% $CI= 0.32$ to 1.16 ; $p= 0.130$), this results are in line with studies in Southern Ethiopia and Plateau State, Nigeria, which said that alcohol use was not statistically significant $p=0.07$ on non-compliance with tuberculosis treatment (Woimo et al., 2017).

Although the variable of alcohol consumption and treatment adherence of tuberculosis patients was not statistically significant, but alcohol consumption has a significant relationship with the incidence of tuberculosis, such as toxic effects caused either directly or indirectly through macronutrient and micro-nutrient deficiencies as a result of alcohol consumption which weakens the immune system (Olys and Ardiyansah, 2018). Unhealthy habits are another important aspect in predicting treatment adherence, alcohol consumption habits are associated with low treatment adherence, alcohol consumption can paralyze nerves

and cause unconsciousness which can result in forgetting to take anti-TB treatment (Gloria et al., 2019). In addition, both alcohol consumption and taking anti-TB drugs can cause liver damage, which can decrease a patient's motivation to take medication (Nortajulu et al., 2022). The results of the systematic review analysis and meta-analysis showed that smoking can reduce tuberculosis patient treatment adherence by 0.86 times compared to not smoking and these results were not statistically significant ($aOR= 0.86$; 95% $CI= 0.17$ to 4.37 ; $p= 0.850$). Statistically, it was not significant caused the characteristics of the respondents were mostly female (68.2%) than male (31.8%).

In fact, smoking behavior was mostly occurred among male than female, and the number of respondents who smoked was less (21.8%) compared to non-smokers (70.8%). This is because the respondents who have been studied smoked and after being exposed to tuberculosis, these respondents stopped smoking and did not smoke anymore (Iweama et al., 2021). This is in line with the study of Ibrahim et al. (2011) which suggested that smoking had no effect on non-compliance with tuberculosis treatment.

AUTHOR CONTRIBUTION

Aem Ismail as the researcher who selected topics, searched for and collected study data. Hanung Prasetya and Burhannudin Ichsan analyzed the data and reviewed research documents.

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CONFLICT OF INTEREST

There is no conflict of interest.

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