ASSOCIATION BETWEEN SMOKINGBEHAVIOR AND TUBERCULOSIS IN INDONESIA : A META-ANALYSIS

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Abstrak

According to WHO, Pulmonary TB is still one of the most deadly diseases and the death rate has reached millions of lives throughout the world including Indonesia. Smoking is one of the main causes of someone contracting pulmonary TB. The goal of this study is to find association between Pulmonary TB and smoking habits in Indonesia using published study. Published studies that reproting Pulmonary TB and smoking habits was complemented by manual searching. Thirty-six studies were selected that covering 12 province in Indonesia. Meta-analysis was conducted using Random effect model. 46641 patients were included in the analysis, and there were 1698 patients that suffering from Pulmonary TB and 44943 patients that not suffering. The association between Pulmonary TB and smoking habits is statistically significant with <0.0001 in p-value and 4.94 in z-score. The pooled odds ratio estimate for smokersvsnon smokers was of 1.8697dan 95% -CI [1.4583; 2.3972] or patients who smoked 1.86 times at risk of pulmonary TB than non-smoking patients. Smoking habits is significantly associated with the risk of Pulmonary TB in Indonesia.

Key Word: *Smoking Behavior ; Tuberculosis; A Meta-Analysis*

1. INTRODUCTION

Smoking is known as one of the causes of death which is quite large in the world. 600 million people worldwide including 600,000 people who die from smoking. WHO also releases that 80% of smokers in the world while living in poor and developing countries. In 2015, 1 in 4 men and 1 in 20 women were active smokers. Now, the number of Indonesian smokers ranks third in the world after China and India. Indonesia has contributed for 35% of the world's smokers. Meanwhile for the state of Indonesian smokers, West Java is province with the highest number of smokers of 32.7% received by Gorontalo province with a percentage of 32.3%(WHO, 2015; Kemenkes 2014).

Tuberculosis or pulmonary TB is one of the effects of smoking. Based on data collected by WHO, it is known that pulmonary TB is one of the top 10 diseases that causing death in the world. In 2017, 10 million people were affected by pulmonary TB and 1.6 million died from pulmonary TB. More than 95% of cases of pulmonary TB occur in developing countries such as countries in Southeast Asia and the western Pacific region which are the biggest contributors to the number of cases of pulmonary TB in the world. Eight countries accounted for 2/3 of the largest cases of pulmonary TB, including India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh and South Africa(WHO, 2018).

Indonesia is one of the highest countries in terms of disease with pulmonary TB with high smoking rates. In 2016, 351,893 cases of pulmonary TB in Indonesia increased from 330,729 cases in 2015. The highest percentage of patients with pulmonary TB were in men, which is as much as 60% of the total sufferers of pulmonary TB in Indonesia. According to the General Chair of the Indonesian Lung Doctors Association (PDPI), Dr. M. Arifin Nawas, SpP (K), MARS, there are 8 deaths per hour due to pulmonary TB and around 140,000 deaths occur annually. In 2016, of a total of 123,453 cases of pulmonary TB in Indonesia (Kemenkes , 2016 dan 2017; Riskesdas, 2013).

To educate the public regarding the risks given by smoking habits in pulmonary TB disease, especially Indonesia itself, it would be more informative if comprehensive information about related research was carried out. So it is expected that by summarizing various studies on pulmonary TB and smoking the community will be more vigilant. For this reason, a summary of various studies is needed regarding TB & smoking cases in Indonesia.

One of statistics method that can be used in this case is Meta-Analysis, analysis of several studies using a systematic approach and statistical techniques to identify, assess, and combine the results of relevant research to reach a stronger conclusion. Interesting Meta-Analysis and an advantage to be used in a review study is because Meta-Analysis is closely related to effect size, where the effect size can avoid wrong conclusions such as Type I or Type II errors.

Another interesting thing to see is the characteristics of different patients in each study, the variations in each study allow for differences in the effect or value of the effect size so that to overcome these differences and to determine the effect size in a whole can be obtained using Random Effect Model.

2. METHOD

a. Meta-Analysis

This study uses Meta-Analysis. Meta-Analysis is a statistical technique for combining results from some original, systematic, planned literature or research and has the same topic of discussion so that the combined data in the form of quantitative data is obtained, as well as a technique aimed at re-analyzing research results that are processed statistically based on primary data collection (Card, 2012).

Meta-Analysis is closely related to effect size. According to Hunter, Schimdt and Jakson, the effect size calculation is done to determine the size of the population effect or it can be interpreted as an effect size reflecting the magnitude of the relationship between variables in each study.

In this case the effect size is formed from the category data, namely the odds ratio. The odds will be obtained by calculating cross between the number of smokers affected by pulmonary TB with people who do not smoke and not affected by pulmonary TB.

b. EM-Algorithm

After choosing the characteristic of study and deduce the result of each of them, it's really possible to find that there is a uncomplete data. So, to cover that problem, we can use EM Algorithm to estimate the uncompleted data.

In this case, algorithm for Multinomial distribution is used for EM-algorithm in contingency table 2×2. Log likelihood model for Multinomial distribution is

$$\mathrm{L}(p|y) = \ln k + y_{11} \ln p_{11} + y_{12} \ln p_{12} + y_{21} \ln p_{21} + y_{22} \ln p_{22} \quad (2.1)$$

With Constrain

$$\sum_{m=1}^{2} \sum_{n=1}^{2} p_{mn} = 1 \quad (2.2)$$

Where y_{mn} is observed value for each cell, p_{mn} is probability of each cell and MLE with Langrange Multiplier to maximize ln L(p) ,

$$L(p_{11}, p_{12}, p_{21}, p_{22}, \lambda) = \mathrm{L}(p|y) + \lambda \left(1 - \sum_{m=1}^{2} \sum_{n=1}^{2} p_{mn} \right) \quad (2.3)$$

λ = lagrange multiplier

Making all the derivatives becomes 0, so that the maximum likelihood estimate is obtained for p_{mn}

$$\hat{p}_{mn} = \frac{y_{mn}}{n} \quad (2.4)$$

where n is total of observed value.

To start the step in EM-Algorithm, set $\hat{\gamma}^{(0)}$ which will be the initial guess for γ. E-step requires the following calculation (Geoffrey ,dkk., 2008)

E-step :

$$Q\left(\gamma \middle| \hat{\gamma}^{(0)}\right) = E_{\theta^{(0)}}[logL(p|y)|y] \quad (2.5)$$

M-step:

Based on the log likelihood function obtained, an estimation is used using MLE to obtain $\hat{\gamma}^{(l)}$ and substitute the results at stage E of the MLE results obtained at $\hat{\gamma}^{(l)}$..

Steps E and M are alternately repeated

$$\left| \hat{\gamma}_{mn}^{(l+1)} - \hat{\gamma}_{mn}^{(l)} \right| \leq \varepsilon \quad (2.6)$$

Because of that, when $\rightarrow \infty$, $\lim_{l \to \infty} \left| \hat{\gamma}_{mn}^{(l+1)} - \hat{\gamma}_{mn}^{(l)} \right| = 0$; $\lim_{l \to \infty} \left| \hat{\gamma}_{mn}^{(l+1)} - \hat{\gamma}_{mn}^{(l)} \right| = 0$

c. Effect Size Odds Ratio (OR)

Odds ratio is a comparison of the frequency or likelihood of an event with a frequency or likelihood of the opponent of the event.

$$T = \frac{y_{11}y_{22}}{y_{12}y_{21}} \tag{2.7}$$

With reference to Formula (2.1), then if there is j = 1,2, ..., J research, the T value for the jth research is (Agresti, 2007)

$$T_j = \frac{y_{11j}y_{22j}}{y_{12j}y_{21j}} \tag{2.8}$$

which:

T_j :estimated odds ratios in the j-th research / study

y_{mnj}:observation value in each cell in the j-th research

OR equals 1 occurs when the proportion is the same in both groups or there is no relationship at all between the 2 groups. Smaller OR 1 means a lower risk than the experimental group compared to the control group and vice versa. OR the occurrence of an event A is inversely proportional to OR not occurring A (Agresti, 2007).

The approximate standard error for the OR estimator is :

$$\sigma\widehat{(lnT_j)} = \sqrt{\frac{1}{y_{11j}} + \frac{1}{y_{12j}} + \frac{1}{y_{21j}} + \frac{1}{y_{22j}}} \tag{2.9}$$

While the confidence interval for the odds ratio is based on the superiority and nature of the distribution of estimated MLE on large data sizes, namely asymptotic normality and efficiency (Watkins, 2011)

Asymptotic normality: $\sqrt{n}\left(\hat{\theta}_n(X) - \theta_0\right)$

Asymptotic efficiency: $Var_{\theta_0}\left(\hat{\theta}_n(X)\right) \approx \frac{1}{nI(\theta_0)}$

So based on these traits, it can be written in the form of z-score, where the z-score value converges with normal standard distribution. In addition, exponential use is due to the invariant nature of MLE estimates. Therefore, it can be obtained the confidence interval (1-α) as follows:

$$\left\{exp\left(lnT_j \pm Z_{\frac{a}{2}}\sigma\widehat{(lnT_j)}\right)\right\} \tag{2.10}$$

d. *Random* Effect Model

Random Effect Model is used when the studies to be examined are random variables. there is Random Effect Model variance between research and variance in research involved in the formation of the model (Borenstein, dkk., 2009)

$$T_{lk} = \theta_{lk} + \varepsilon_{lk} \tag{2.11}$$

$$T_{lk} = \mu + u_{lk} + \varepsilon_{lk} \tag{2.12}$$

Which :

T_{lk} = estimator ofθ_{lk} , $T_k \sim N(\mu, {\sigma_k}^2 + \tau^2)$

${\sigma_k}^2$ = within-study variance for eachk-th study

τ^2 = between-study variance

μ = mean
θ_{lk} = true effect size of Random Effect Model
u_{lk} = error fromθ_{lk}

Where μ is the true effect value, u_{ij} is an error that distributes N (0,τ^2) with$\tau^2$is between-study variance.

Effect of the k-size research for random effect models can be defined according to Equation (2.11) and (2.12)(Borenstein et al., 2009)

With asumption :

1) $E(\varepsilon_{ij}) = 0$
2) $E(u_{ij}) = 0$
3) $E(\varepsilon_{ij}, u_{ij}) = 0$
4) $E(\varepsilon_{ij})^2 = \sigma^2$
5) $E(u_{ij})^2 = \tau^2$

The DerSimonian Laird (2009) method can be used in obtaining a between-study variance estimate.

$$\tau^2 = \begin{cases} \dfrac{Q - df}{c} & jika\ Q \geq df \\ 0 & jika\ Q < df \end{cases} \tag{2.13}$$

with:

τ^2 = component of between-study variance
df = degree $of\ freedom,\ (i-1)$
i = total of sub-grup
j = the amount of research
Q = statistics's test of homogenity
$= \sum_{j=1}^{J} w_j {T_j}^2 - \dfrac{\left(\sum_{j=1}^{J} w_j T_j\right)^2}{\sum_{j=1}^{J} w_j}$
w_j = weighting factor for the j-th research $= \dfrac{1}{\left(\widehat{\sigma^2(T_j)}\right)}$
c $= \sum_{j=1}^{J} w_j - \dfrac{\sum_{j=1}^{J} {w_j}^2}{\sum_{j=1}^{J} w_j}$

Weighting factors for the jth research in the Random Effect Model are defined by (Borenstianet al, 2009).

$$w_j{}^* = \frac{1}{\left(\sigma^2(T_j) + \tau^2\right)} \tag{2.14}$$

Estimated composite effect size for the Random Effect Model is defined as (Borenstianet al, 2009)

$$\bar{T} = \frac{\sum_{j=1}^{J} w_j{}^* T_j}{\sum_{j=1}^{J} w_j{}^*} \tag{2.15}$$

The estimated variance of the effect size odds ratio can be obtained by

$$\widehat{\sigma^2(ln\bar{T})} = \frac{1}{\sum_{j=1}^{J} w_j{}^*} \quad (2.16)$$

Confidence Interval *(1-*α*)* 100%for$\bar{T}$ is

$$\left\{exp\left(ln\bar{T} \pm z_{\frac{\alpha}{2}}\hat{\sigma}(ln\bar{T})\right)\right\} \quad (2.17)$$

e. *Effect* Size Hypotesis Test

This test was conducted to see whether there was a effect of the treatment on the study.

1) Hypotesis
   H_0 : $\mu = 0$, there is a significant influence or relationship between smoking habits and pulmonary TB.
   H_1 : $\mu \neq 0$, there is not a significant influence or relationship between smoking habits and pulmonary TB

2) Test statistic

$$Z_{value} = \frac{\bar{T}}{\hat{\sigma}(\bar{T})} \quad (2.18)$$

   Which :
   $\bar{T}$: estimated of pooled *effect size* (*odds ratio)*
   $\widehat{\sigma(\bar{T})}$: estimated standard error of$\bar{T}$
3) Alpha : α
4) Reject H_0 if $Z_{value} \leq$ - $Z_{\frac{\alpha}{2}}$ and $Z_{value} \geq Z_{\frac{\alpha}{2}}$or $p - value \leq \alpha$

3. RESULTS

The number of patients affected by pulmonary TB in this meta-analysis was as many as 1698 temporary people who were not affected by pulmonary TB as much as 44943 so that the total patients included in this meta-analysis were 46641 patients.

a. EM-Algorithm

1) Ryan AF's Study

Table 1. EM-Algorithm'result for Ryan AF's Study

Iteration	Value ofγ
1	0.119675
2	0.134722
3	0.146729
4	0.156584
.	.
.	.

Iteration	Value ofγ
.	.
59	0.221414
60	0.221424

Iteration stop if the conditions is done as $\left|\hat{\gamma}_{mn}^{(l+1)} - \hat{\gamma}_{mn}^{(l)}\right| \leq \varepsilon$, with ε =1-e5 .

Based on Formula (2.6), it is gotten result as :

$\left|\hat{\gamma}_{mn}^{(60)} - \hat{\gamma}_{mn}^{(59)}\right| \leq \varepsilon$
$|0.2214239 - 0.2214143| \leq \varepsilon$
$|9.6337 \times 10^{-6}| \leq \varepsilon$

$y_{12} = \hat{\gamma} \times n$
$= 0.2214239 \times 70$
$= 15$

$y_{21} = n - y_{11} - y_{22} - y_{12}$
$= 70 - 18 - 21 - 15$
$= 16$

2) AgustinaAyu, et.al's Study

Table 2. EM-Algorithm's result for AgustinaAyu, et.al's Study.

Iteration	Value of γ
1	0.184798
2	0.215573
3	0.225756
4	0.229021
5	0.230057
6	0.230385
7	0.230488
8	0.230521
9	0.230531
10	0.230535

Iteration stop if the conditions is done as $\left|\hat{\gamma}_{mn}^{(l+1)} - \hat{\gamma}_{mn}^{(l)}\right| \leq \varepsilon$, with ε =1-e5 .

Based on Formula (2.6), it is gotten result as :

$\left|\hat{Y}_{mn}^{(10)} - \hat{Y}_{mn}^{(9)}\right| \leq \varepsilon$

$|0.2305346 - 0.2305313| \leq \varepsilon$

$|3.3 \times 10^{-6}| \leq \varepsilon$

$y_{12} = \hat{Y} \times n$

$= 0.2305346 \times 130$

$= 29$

$y_{22} = n - y_{11} - y_{21} - y_{12}$

$= 130 - 24 - 41 - 29$

$= 36$

b. Odds Ratio for each study

Table 3. Odds Ratio for each study

Study	OR	95%-CI	%W(fixed)	%W(random)
Fariz Muaz 2010	1.3823	[0.7900; 2.4187]	5.7	3.6
NN 2015	1.6682	[0.7421; 3.7497]	2.7	3
Ardhitya Sejati, et al 2015	1	[0.3400; 2.9415]	1.5	2.4
Dudeng D, et al 2006	0.6505	[0.3752; 1.1281]	5.9	3.6
Mada TS 2015	4.9381	[2.9126; 8.3722]	6.5	3.7
Rahmanu 2013	0.9	[0.2508; 3.2297]	1.1	2
Budi Riantoet al 2014	0.7109	[0.2785; 1.8151]	2	2.7
Ira K 2010	0.4687	[0.2311; 0.9505]	3.6	3.2
Jeaneria,et al 2014	7.5281	[3.2267; 17.5635]	2.5	2.9
Fitria Agustina et al 2015	2.2963	[1.1245; 4.6891]	3.5	3.2
Aruisza Ryan 2014	3.4364	[1.1871; 9.9472]	1.6	2.4
Ryan A F 2014	1.575	[0.6123; 4.0511]	2	2.7
Nurwanti 2015	1.6531	[0.4089; 6.6825]	0.9	1.8
Agustina Ayu, et al 2015	0.7267	[0.3601; 1.4664]	3.6	3.3
Ageng Brahmadhi, et al 2016	4.7802	[1.9217; 11.8906]	2.2	2.8
Halim, et al 2017	1.9688	[0.8608; 4.5029]	2.6	3
Gita Sekar, et al 2014	6.9231	[2.2431; 21.3669]	1.4	2.3
Diah A 2010	0.2125	[0.0508; 0.8898]	0.9	1.8
Sari Anugrah 2012	2.7337	[1.1864; 6.2993]	2.6	2.9
Feni W 2013	3.5185	[1.2698; 9.7497]	1.7	2.5
Jumriana 2012	0.4667	[0.1594; 1.3664]	1.6	2.4
Yusran Mohammad 2018	2.7755	[1.0442; 7.3773]	1.9	2.6

Study	OR	95%-CI	%W(fixed)	%W(random)
Rosdiana 2018	4.9875	[1.6309; 15.2521]	1.4	2.3
Nurhanah 2010	1.8288	[1.2527; 2.6699]	12.6	4
NN 2012	4.125	[1.3867; 12.2702]	1.5	2.4
Indri Surentudkk 2013	1.1797	[0.3818; 3.6456]	1.4	2.3
Kholis Ernawati, et al 2017	1.1188	[0.5889; 2.1256]	4.4	3.4
Franki 2010	1.9259	[0.6974; 5.3187]	1.7	2.5
Engelina 2017	3.0952	[1.1467; 8.3550]	1.8	2.6
Cantika Dinita, et al 2017	2.0057	[0.6135; 6.5577]	1.3	2.2
M. Jamil 2013	4.2926	[1.7633; 10.4500]	2.3	2.8
Setia Agung 2016	1.8173	[0.6921; 4.7718]	1.9	2.6
Surakhmi, et al 2016	2.2515	[0.9417; 5.3831]	2.4	2.9
Sebayang Yan 2017	1.75	[0.9045; 3.3859]	4.1	3.4
Yustika H 2018	2.9	[1.2114; 6.9425]	2.4	2.8
NN 2010	2.1675	[0.9417; 4.9891]	2.6	2.9

Based on the table above, in the study conducted by Sari Anugrah, Feni W, Indri Surentu, the dds ratios were 2.7337, 3.5185, 1.1797 which were greater than 1. This means the risk of pulmonary TB disease in someone who smoke is higher than someone who doesn't smoke. In the research of Jumriana, Budi Rianto, et al., Agustina Ayu, et al., respectively obtained odds ratios 0.4667, 0.7109, 0.7267 which were smaller than one and could mean that the risk of pulmonary TB disease in someone who smoked was lower than with someone who doesn't smoke. Whereas in the study conducted by Ardhitya Sejati, et al., It was found that the odds ratio was 1 and it could be interpreted that there was no difference in risk between someone who smoked and did not smoke with the occurrence of pulmonary TB.

Table 4. Odds Ratio for each province

Province	Study	T_{ij}	T_i
North Sumatera	Sebayang Yan	1.7500	2.1211
	Yustika H	2.900	
	NN	2.1675	
West Sumatera	CantikaDinitaet al	2.0057	3.2572
	M.Jamil	4.2926	
South Sumatera	Surakhmi, dkk	2.2515	1.8501
	SetiaAgung	1.8173	
Banten	NN	1.6682	1.6682
	FarizMuaz	1.3800	
West Java	Budi Riantoet al	0.7109	2.6576

Province	Study	T_{ij}	T_i
	FitriaAgustinaet al	2.2963	
	Jaenariaet al	7.5281	
	Ira Kartika	0.46869	
Central Java	Aruisza R	3.4364	1.92018
	Ryan A F	1.575	
	Nurwanti	1.6531	
	AgustinaAyuet al	0.7267	
	AgengBrahmadhiet al	4.7802	
	Halimet al	1.9688	
East Java	Gita Sekar, et al	6.9231	1.2488
	Diah A	0.2125	
DIY	ArdhityaSejati et al	1	0.7110
	Dudeng, et al	1.5152	
West Kalimantam	Sari Anugrah	2.7337	3.0252
	Feni W	3.5185	
North Sulawesi	NN	4.125	1.8645
	Indri Surentuet al	1.1797	
	KholisErnawatiet al	1.1188	
	Engelina W, et al	1.9259	
	Franki M, et al	3.09524	
South Sulawesi	Jumriana	0.4667	1.8500
	Yusran Mohammad	2.7755	
	Rosdiana	4.9875	
	Nurhanah, et al	1.8288	
DKI	Mada TS	4.9381	3.8526
	Rahmanu	0.900	

For each province there were also different odd ratio values. Seen from Table 4, in a study conducted in the province of Banten, South Sulawesi in succession, odds ratios 1.6682 and 1.85 were found which were greater than 1. This means that the risk of developing pulmonary TB in someone who smokes is higher than someone who does not smoke. In a study conducted in North Sumatra, West Java province, odds ratios of 2.1211 and 2.6576 were obtained, which means that the risk of developing pulmonary TB disease in someone who smoked in these provinces was twice as high as someone non-smokers.

c. Pooled Odds Ratio

Table 5. Pooled *Effect Size Odds Ratio*

	Odds Ratio	95% - Confidence Interval	z	p-value
Random Effect Model	1.8697	[1.4583; 2.3972]	4.94	< 0.0001

Based on Table 5 above, the estimated combined odds ratio of 1.8697 and 95% - Confidence Intervals between 1.4583 and 2.3972 and does not contain 1, it can be concluded that true odds of pulmonary TB disease are different for each group. We estimate that the likelihood of pulmonary TB occurring is at least 45% higher for patients who smoke placebo than non-smoking patients. Because the Odds ratio is greater than 1, it can be interpreted that overall patients who smoke 1.87 times or almost twice the risk of developing pulmonary TB compared with non-smoking patients.

This hypothesis test was conducted to determine whether there was or no effect of treatment on the study.

Z_{score} dan *p-value* can be used to test the effect size for each study and in this case Z_{score} dan p-value are calculated based on Formula (2.18).

Based on Table 5,obtained Z_{score} =4.94 and *p-value* = <0.0001. So that it can be concluded that H_0 is rejected, it can be concluded that there is a significant relationship between smoking habits and the risk of pulmonary TB.

d. Identification of Heterogenity

This analysis was conducted to determine whether there was heterogeneity in the studies studied or whether the effect size of each study studied in the meta-analysis was the same or not.

Table 6. Identification of Heterogenity

Inverse Variance			df	$\chi^2_{(0.05,24)}$	τ^2
Q	I^2	*p-value*			
109.79	68.1%	<0.0001	35	49.80	0.3664

Based on Table 6 above, the p-value obtained is equal to 0.0016 and Q = 109.79. So that it can be concluded that H_0 is rejected, which means there is a heterogeneity of effect size in the studies studied and with this, the level of heterogeneity will be tested.

Based on Table6, it is known that the I2 value is 68.1% so it can be concluded that the heterogeneity that occurs includes heterogeneity which falls into the fairly high category

4. CONCLUSION

The results of the application of the meta-analysis in several studies indicate that there is a significant relationship between smoking habits and the risk of developing pulmonary TB disease in Indonesia with a combined odds ratio of 1.8697 or this can be interpreted that the risks that occur in Indonesia today are almost 2 times risky. From this study, it is seen that province which have big risk are West Sumatra, West Java and DKI.

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