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Meta-Analysis Study Of The Effect Of Cigarette Smoke Exposure On The Incidence Of Pulmonary Tuberculosis In Children

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ABSTRACT
The child population has a higher risk of being exposed to tuberculosis compared to the adult population. Children who are exposed to cigarette smoke from adults in the home environment, both children and adults have a high risk of being infected with tuberculosis. This study aims to determine the effect of exposure to cigarette smoke on the incidence of pulmonary tuberculosis in children. This research uses the Meta-analysis method using RevMan 5.4.1 software. Data estimation using the Random Effect Model from 7 pieces of literature with the number of samples and controls being 518 and 1,294 individuals. It was found that the RR of exposure to cigarette smoke on pulmonary tuberculosis was 1.67 (CI95% 1.18 – 2.36). So children who are exposed to cigarette smoke have a 1.67 times higher risk of developing pulmonary tuberculosis compared to those who are not. Exposure to cigarette smoke increases the risk of pulmonary tuberculosis in children, this can be observed in the greater number of cases of pulmonary tuberculosis in children in groups exposed to cigarette smoke compared to those who are not. Almost half of pulmonary tuberculosis in children can be prevented if exposure to cigarette smoke can be avoided in children.

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INTRODUCTION

Based on data from the World Health Organization (WHO), in 2018, around a quarter of the world's population was at risk of being infected with Mycobacterium tuberculosis (TB), with 70 million of them being children aged 0 - 14 years. It is estimated that around 7.5 million children aged 0 – 14 years are infected with Mycobacterium tuberculosis every year. Tuberculosis is one of 10 diseases with high morbidity and mortality rates in children. The child population has a higher risk of being exposed to tuberculosis bacteria compared to the adult population. The presentation of pulmonary tuberculosis in children is also quite different compared to pulmonary tuberculosis in adults. Based on the level of risk of developing pulmonary tuberculosis, it is influenced by exogenous and endogenous factors. Exogenous factors are risk factors related to the process of exposure to tuberculosis bacteria until infection occurs, while endogenous factors play a role in the infection process

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and the process of activating tuberculosis bacteria in a person.

Exposure to cigarette smoke is an exogenous factor that can increase the risk of tuberculosis infection and the progression of pulmonary tuberculosis in populations with active tuberculosis. Populations with active pulmonary tuberculosis are also at risk of causing families at home to become infected with tuberculosis bacteria. 6 Intermittent and continuous exposure exposure to cigarette smoke can cause changes in the morphology of the epithelium in the respiratory tract. Then it can cause several changes in immunity which result in inflammation. Cigarette components will be deposited in the lungs and activate many inflammatory factors, causing damage to the lung structure.

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis. In recent years, attention to tuberculosis (TB) in children has increased with increasing awareness that more children are suffering from tuberculosis than ever before.7–9 The risk of Mycobacterium tuberculosis infection in children depends on the probability, duration, and proximity to an active case of infection. . Children aged <15 years account for approximately 1.1 million cases and 205,000 deaths each year. An increase of 535,000 cases per year is estimated to occur in adolescents aged 15 to 19 years. Symptoms and signs of tuberculosis in children are often non-specific and include fever (sometimes accompanied by night sweats), failure to thrive or weight loss, and fatigue or lethargy. Typical tuberculosis symptoms, such as coughing for more than 2 weeks, are less sensitive in young children or children who are immunocompromised. For example, young children may exhibit wheezing that does not respond to bronchodilator administration due to airway compression from enlarged intrathoracic lymph nodes. In addition, the discrepancy between relatively mild clinical symptoms and severe radiological symptoms often suggests tuberculosis. Tuberculous lymphadenitis, which is the most common extrapulmonary manifestation of tuberculosis in children, often presents as a unilateral, painless, tender lymph node mass in the cervical or supraclavicular area.9 With limited mobility, very young children Young people (< 3 years old) usually contract tuberculosis from people living in the same household. Because children's social interactions outside the household increase with age and independence, their risk of contracting tuberculosis from the community also increases, depending on the level of tuberculosis transmission in the community.

Children who are exposed to cigarette smoke and indoor air pollution have twice the risk of developing tuberculosis compared to children who are not exposed. Passive smoking can increase the risk of active pulmonary tuberculosis in children by more than three times. Smoking is common in most developing countries. Therefore, exposure to tobacco smoke may be of great concern because smoking causes downregulation of macrophage TNF-α in the lungs. Toxic particulate matter produced from burning biomass induces inflammation in the lungs leading to respiratory tract infections and asthma.

METHOD

This study uses a meta-analysis approach, namely a statistical model used to combine more than one existing study to obtain new quantitative data. This meta-analysis study was created based on professional reporting for systematic reviews and meta-analysis

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(PRISMA).

Search Strategy

Searches were carried out from electronic databases such as PubMed, Google Scholar, Cochrane Liberary and Google search engine. The search strategy used the keywords second hand smoke, involuntary smoking, passive smoking, pediatric tuberculosis, child tuberculosis, neonatal tuberculosis, adolescent tuberculosis by including synonyms and Boolean operators in each database. In the PubMed database, the following search strategy is used:

Search: (((((second hand smoke[MeSH Terms]) OR (involuntary smoking[MeSH Terms])) OR (passive smoking[MeSH Terms])) OR (second hand smoke[Title/Abstract])) OR (involuntary smoking[Title/Abstract])) OR (passive smoking[Title/Abstract])

Search: (((((((pediatric tuberculosis[MeSH Terms]) OR (child tuberculosis[MeSH Terms])) OR (neonatal tuberculosis[MeSH Terms])) OR (adolescence tuberculosis[MeSH Terms])) OR (pediatric tuberculosis [Title/Abstract])) OR (child* tuberculosis[Title/Abstract])) OR (neonatal tuberculosis[Title/Abstract])) OR (adolescence tuberculosis[Title/Abstract])

Search: (#1) AND (#2)

Strategi pencarian yang sama dilakukan pada database *Cochrane Library*, dan menggunakan Boolean operator pada database *Google Schoolar* dan *search engine Google*.

Inclusion and Exclusion Criteria

The inclusion criteria used:

1) Journals are published with full text
2) The age of the sample used is pediatrics (< 18 years)
3) Epidemiological based (case-control, cohort and cross-sectional)
4) Speak English or Indonesian
5) Has treatment variables and control variables

Exclusion criteria:

1) The journal is not full access
2) Published within the last 10 years.

Data Synthesis and Extraction

Data is extracted based on author, year of publication, population and sample size for each treatment variable and control variable.

Statistic analysis

The software used for statistical data analysis is Review Manager 5.4. Effect size analysis using a random effect model because the heterogeneity of the sample is I2 > 50% and p-value > 0.05 which can be seen directly in the software. The results of the analysis are in the form of a Risk Ratio (RR) which is presented in the form of a forest plot. To assess the impact of research results when applied to society, the Population Attributable Risk (PAR) value will be calculated using the formula: PAR= $\frac{p\,(r-1)}{p\,(r-1)+1}$

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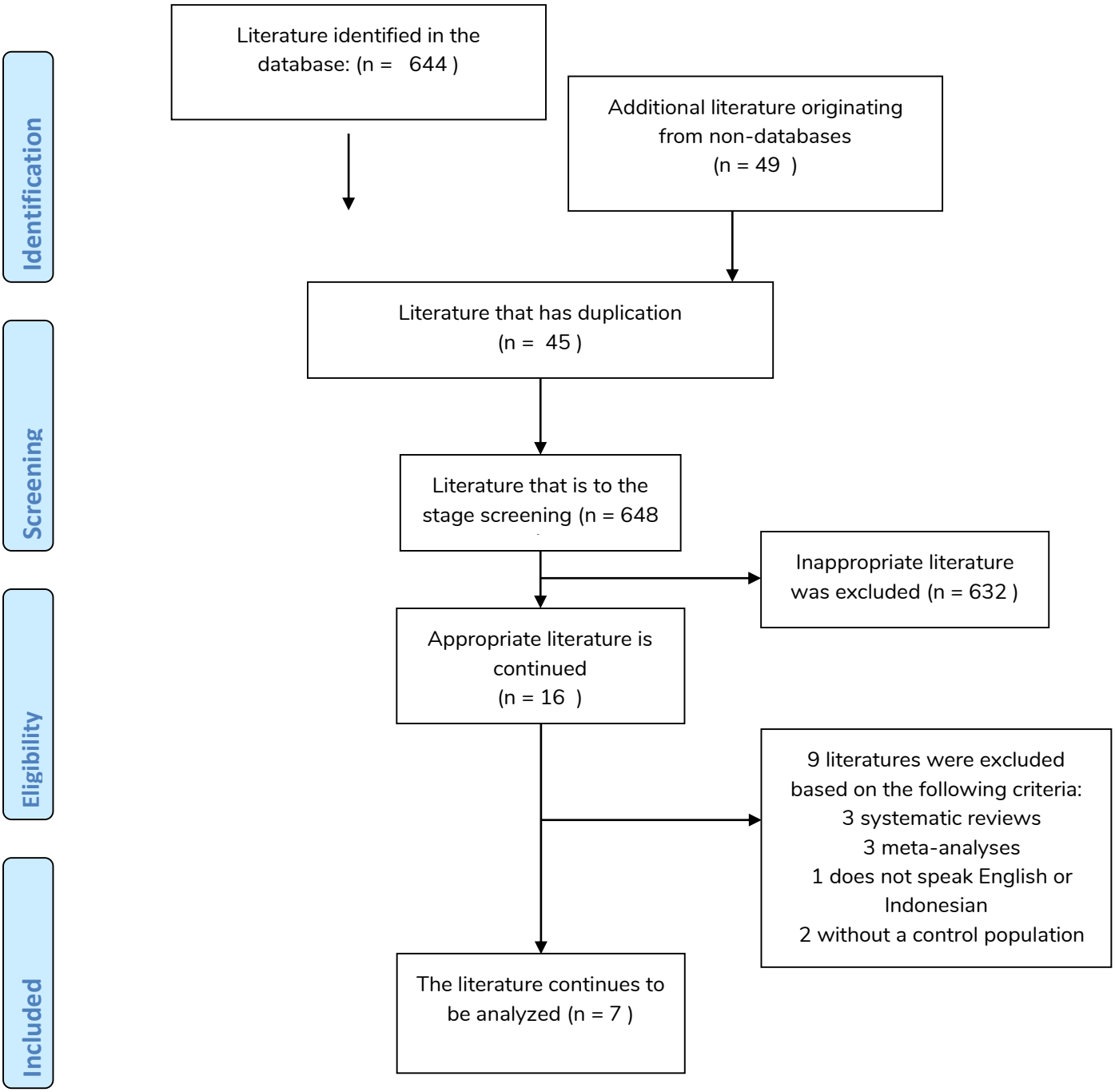
p : proporsi subjek yang terpapar pada populasi
r : radio odd (dapat dilihat pada hasil di *software*).



Picture 1. PRISMA Flow Chart

RESULT AND DISCUSSIONS

In a literature study search, 693 pieces of literature were found. Of the 693 pieces of literature, 45 are duplicates of the same research. Then 648 pieces of literature were

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screened for titles and abstracts, which resulted in 632 pieces of literature with inappropriate titles or abstracts. In the next stage, 9 pieces of literature were excluded because they did not meet the inclusion criteria or met the exclusion criteria, so there were 7 pieces of literature that could be continued to the data extraction and synthesis stage. The estimated total sample in this meta-analysis study is 814 individuals and the population is 1812 individuals as follows:

Table 1. Characteristics of literature data

Nomor	Individuals with TB		Control	
	SHS*	N	SHS	N
Study 1[13]	27	67	44	233
Study 2[14]	120	172	92	172
Study 3[15]	51	107	45	127
Study 4[16]	43	50	32	150
Study 5[17]	24	46	36	46
Study 6[18]	36	46	229	536
Study 7[19]	23	30	12	30
Total	324	518	490	1294

* : *second hand smoke*, number exposed to cigarette smoke

Analysis of the risk of tuberculosis in the population of children exposed to cigarette smoke obtained an estimated RR of 1.67 with a 95% CI of 1.18 - 2.36 so it can be concluded that the population of children exposed to cigarette smoke has a 1.67 times higher risk. high rates of tuberculosis compared to the population of children who are not exposed to cigarette smoke. Obtained p value <0.004 and I2 91% which illustrates that the heterogeneity of the study sample is high.

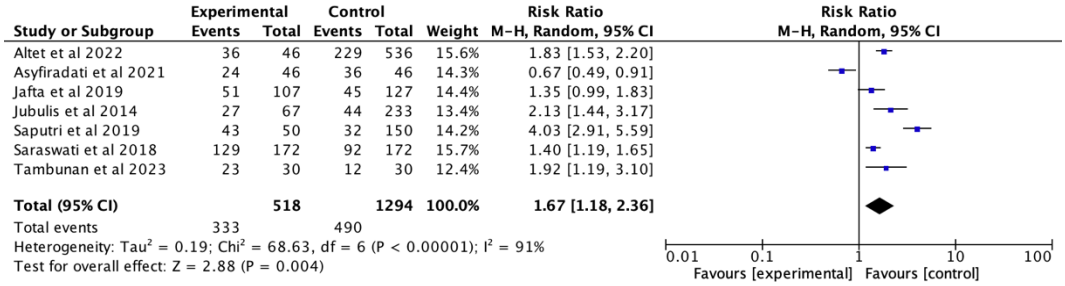

Figure 2. Forest plot of cigarette smoke exposure on the incidence of tuberculosis

Table 2. Accumulated data on exposure to cigarette smoke on tuberculosis

	Case	Control	Amount
Exposed	324	490	814
Not exposed	194	804	998
Amount	518	1294	1812

p = 814 / 1812 = 0,44

r = 2,93 (*odd ratio* from the calculation results in the software *RevMan*)

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$$PAR = \frac{0,44\ (2,93-1)}{0,44\ (2,93-1)+1} = \frac{0,8492}{1,8492} = 0,45$$

From the calculations above, it can be concluded that almost 45% of cases of pulmonary tuberculosis in children can be prevented by avoiding exposure to cigarette smoke which acts as a risk factor for pulmonary tuberculosis in children. Like active smokers, exposure to cigarette smoke in the home environment is also a predisposing factor in the development of tuberculosis. 5,20 Children who are exposed to cigarette smoke from adults in the home environment both have a risk of contracting tuberculosis infection.

In a previous meta-analysis study on the same topic conducted by Siddalingaiah, et al (2023), it was found that the risk factor of exposure to cigarette smoke increased the risk of developing pulmonary tuberculosis in children by up to 2.61 times. 12 Meanwhile, in research conducted by Patra et al al (2015) obtained a lower risk increase of 1.67 times. 22 In adults, smoking habits can increase the risk of tuberculosis by 1.5 – 2.7 times in a systematic review conducted by Melsew, et al (2018). 11 Meanwhile, in adults exposure to cigarette smoke (passive smoking) can also increase the incidence of tuberculosis by up to 1.49 times according to research by Leung, et al (2010).

The results of this study have an RR figure that is almost the same as the pRR by Patra, et al (2015) who also used meta-analysis to assess the effect of exposure to cigarette smoke on the incidence of pulmonary tuberculosis in children, namely 1.67 times and 1.61 times, however in the literature used by Patra, et al 2015, is limited only to 2014. In this meta-analysis study using new literature from the last 10 years, it was found that a total of 4 out of 7 (57.1%) literature samples came from Indonesia and 1 out of 7 (14 .2%) from India where these two countries are the 2 countries with the highest incidence of tuberculosis in the world. This literature study has limitations when collecting references which are limited to literature that has free access without payment so it has limitations in the number of databases that can be accessed and the number of literature that can be sampled.

CONCLUSSION

Exposure to cigarette smoke can increase the risk of pulmonary tuberculosis in children. This can be seen from the higher incidence of pulmonary tuberculosis in populations exposed to cigarette smoke compared to control populations. Therefore, preventing pulmonary tuberculosis in children can be done by avoiding exposure to cigarette smoke. Almost half of pulmonary tuberculosis patients in children can be prevented, if exposure to cigarette smoke can be eliminated.

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