Sytematic Review: The Effect of Plumbum and Zinc on Attention-Deficit/Hyperactivity Disorder (ADHD)

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Abstract

Attention-Deficit/Hyperactivity Disorder (ADHD) is a mental disorder characterized by a lack of attention, and/or hyperactivity-impulsivity and is related to the growth and development of one's functions in carrying out social life at home and school. Attention-Deficit/Hyperactivity Disorder (ADHD) can be diagnosed in patients aged 6-18 years. The cause of ADHD is still not known for certain, but there are several factors that are considered to be the cause of ADHD, namely genetic factors, biological factors such as brain development, active neurotransmitter factors, psychosocial factors, trauma factors, family factors, emotional factors or children's temperament, and environmental factors Environmental factors can include exposure to chemicals, exposure to heavy metals, exposure to toxins, nutrition, and childbirth complications. Pb is a heavy metal and toxin can cause ADHD symptoms. Zn is a compound that when levels in the body are reduced, it can cause ADHD symptoms. Pb and Zn substances are predisposing factors for ADHD. The aim from this study is to determine the effect of Pb and Zn on Attention-Deficit/Hyperactivity Disorder. Studies was conducted through 4 e-databases, namely PubMed, ScienceDirect, Scopus, and SpringerLink. The literature quality assessment was carried out using the NOS (Newcastle-Ottawa Scale). From 1124 citations, we identified 20 relevant articles consisting of 4 cohort studies, 12 case-control studies, and 4 cross sectional studies. There are 14 studies discussing Pb exposure, 4 studies discussing Zn deficiency, and 2 studies discussing both on ADHD symptoms. Exposure to Lead (Pb) has been shown to have an effect on ADHD symptoms especially the type of hyperactivity and impulsivity and zinc (Zn) deficiency has been shown to affect ADHD symptoms especially the inattention type.

Keywords: Lead; Plumbum; Zinc; ADHD

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a disorder associated with young children characterized by inattention and/or hyperactivity-impulsivity (American Psychiatric Association, 2013;

Barkley, 1998; Maslim, 2013). Attention-Deficit/Hyperactivity Disorder (ADHD) can be diagnosed in patients aged 6-18 years (Subcommittee on Attention-Deficit/Hyperactivity Disorder, 2011). The diagnosis of ADHD is carried out using the Diagnostic and Statistical Manual of Mental Disorder (DSM) – 5 which classifies into 3 types, namely hyperactivity – impulsivity (<15%), inattention / neglect (20% - 30%), and combined (50% - 70%) (Aprilia, 2017). The cause of ADHD is still not known for certain, but there are several factors that are considered to be the cause of ADHD, namely genetic factors, biological factors such as brain development, active neurotransmitter factors, psychosocial factors, trauma factors, family factors, emotional factors or children's temperament, and environmental factors (cigarettes, alcohol and Plumbum) (American Psychiatric Association, 2013; Permenkes, 2011; Rohmatin, 2018). Environmental factors can be in the form of exposure to chemicals, exposure to heavy metals, exposure to toxic substances, nutrition, and childbirth complications (NH, 2017). Plumbum (Pb) and Zinc (Zn) substances are predisposing factors for ADHD (Donzelli, 2019; Villagomez, 2014).

Plumbum is known as a heavy metal that is toxic. In children, the potential for toxicity symptoms due to lead exposure is higher than in adults due to high intakes per body mass, frequent insertion of foreign objects into the mouth, higher uptake, and immature body system development (Tong et al. al, 2000). Plumbum works to suppress the release of acetylcholine, dopamine, and amino acids related to calcium activity in the presynaptic section and can reduce dopamine levels by inhibiting tyrosine synthesis (Lidsky and Schneider, 2003; Setiawati, 2020). This can affect the dopamine system in the body. This substance can be found in various places such as medicine, food, water, soil, fuel, and the surrounding environment (Needleman, 1991). The reference for normal blood levels according to the Centers for Disease Control and Prevention (CDC) is 3.5 g/dL.

Zinc is known for its role in various kinds of metabolism in the body related to the performance of enzymes and proteins (Hambidge, 2000). Its role in the immune system is very important because in people with severe zinc deficiency, it can cause symptoms of recurrent infections, diarrhea, alopecia, and bullous pustular dermatitis and mental disorders (Shankar and Prasad, 1998). Decreased levels of zinc can affect the ability of cell proliferation and neuronal survival by interfering with every signaling pathway that can trigger cell apoptosis (Adamo and Oteiza, 2010). According to a reference from the Centers for Disease Control and Prevention (CDC) that normal levels of zinc in serum are 70-120 g/dL.

The levels of Pb and Zn in the body affect the function of the frontal cortex of the brain through disruption of the mechanism of action of dopamine which can cause ADHD symptoms (Barkley, 1998). Dopamine is a neurotransmitter that regulates motor skills, understanding and learning functions (Berke, 2018). Zinc plays a role in the formation of the central nervous system, the synthesis of dopamine, serotonin and norepinephrine (Setiawati, 2020). Zinc deficiency can interfere with these processes. It is suspected that low serotonin levels also can cause hyperactivity and impulsivity (Setiawati, 2020). Exposure to heavy toxic metals such as Pb can reduce dopamine levels by inhibiting tyrosine synthesis (Setiawati, 2020). Therefore, this study aims to examine previous research on the effect of Pb and Zn substances on ADHD.

This research is expected to provide knowledge, especially to workers who are involved with hazardous substances such as Pb to always use Personal Protective Equipment (PPE). The importance of giving Zn supplementation in children with low body and children with ADHD for clinicians. The importance of managing factory waste and other waste containing heavy metals before being disposed of to a final disposal site so as not to pollute the environment and society.

2. Methode

This type of research is a qualitative systematic review. The population of this study were all published studies that discussed Pb and Zn on ADHD. The sample in this study was taken by total sampling, namely the technique of taking all samples that met the inclusion and exclusion criteria. The inclusion criteria are Contains the keywords “ADHD”, “GPPH”, “Lead”, “Plumbum”, “Pb”, “Plumbum”, “Zinc” and “Zn”; Research studies using English or Indonesian; Research studies describe ADHD symptoms according to the Diagnostic and Statustical Manual of Mental Disorder (DSM) – IV or DSM – 5 and the Guidelines for Classifying the Diagnosis of Mental Disorders in Indonesia III (PPDGJ III); The research design was case control, cohort and cross sectional; The age limit of subjects in the study was one to thirteen years. The exclusion criteria are The study did not use humans as research subjects; There is duplication of research studies; Research studies published over five years.

The sampling technique in this study is to collect studies available on e-databases: PubMed, ScienceDirect, Scopus, and SpringerLink. The instrument used in this research is a computer or laptop hardware device to process data. The application of the PRISMA method to avoid duplication and to process the research studies obtained to fit the inclusion criteria. The tool for assessing research studies obtained is the NOS (Newcastle-Ottawa Scale). After assessing the study to be reviewed, we summarize the research studies by creating a summary table containing data extraction regarding the title, author, research method, research area, research subject, and research results. At the end we analyze the result and come to a conclusion.

3. Result

The summary of the article screening process is presented in figure 1. There are 20 relevant articels that consist of 4 cohort studies, 12 case-control studies, and 4 cross sectional studies. The results of the assessment of articles using NOS in each study category can be seen in tables 1, 2, and 3. The characteristics of each article can be seen in table 4.

Table 1. Newcastle-Ottawa Scale (NOS) result for cohort study

Study	Selection				Comparability	Outcome			Total Score
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Ji, Y., et. al (2018)	-	*	*	*	**	*	*	*	8
Choi, W. J., et. al (2016)	*	*	*	*	**	*	*	*	9

Xu, J., et. al (2015)	*	*	*	-	**	*	*	-	7
Neugebauer, J., et. al (2015)	*	*	*	*	**	*	*	*	9

Table 2. Newcastle-Ottawa Scale (NOS) result for case-control study

Study	Selection				Comparability	Outcome			Total Score
	Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Elbaz, F., et. al (2019)	*	*	-	*	**	*	*	*	8
Park, J. H., et. al (2016)	*	*	-	*	**	*	*	*	8
Lin, Y., et. al (2019)	*	*	-	*	*	*	*	*	7
Viktorinova, A., et. al (2016)	*	*	-	*	**	*	*	*	8
Kim, J. I., et. al (2018)	*	*	-	*	**	*	*	*	8
Choi, J. W., et. al (2020)	*	*	-	*	*	*	*	*	7
Elbaz, F., et. al (2017)	*	*	*	*	**	*	*	*	9
Joo, H., et. al (2017)	*	*	*	*	*	*	*	*	8
Skalny, A. V., et. al (2020)	*	*	*	*	**	*	*	*	9
Setiawati, Y., et. Al	*	*	-	*	**	*	*	*	8

(2019) Hawari, I., et. al (2020)	*	*		-	*	*	*	*	7
Nigg, J. T., et. al (2016)	*	*		*	*	*	*	*	8

Table 3. Newcastle-Ottawa Scale (NOS) result for cross sectional study

Study	Selection				Comparability	Outcome		Total Score
	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure (risk factor)	The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.	Assessment of the outcome	Statistical test	
Huang, S., et. al (2016)	*	*	*	**	**	***	-	10
K. Pereira, et. al (2016)	-	*	-	**	**	***	*	9
Hong, S. B., et. al (2015)	*	*	*	**	*	***	*	10
Lee, M. J., et. al (2018)	-	*	*	**	**	***	*	10

Table 4. Charateristic of the articles

No.	Author (Year)	Title	Method	Country	Subject	Research time	Data Collection	Result
1	Ji, Y., et. Al (2018)	A Prospective Birth Cohort Study on Early Childhood Lead Levels and	Cohort study	Boston – United States	1479 participants (mean age 9.6 years)	3 years	• Non-fasting blood sample to measure lead levels • MLR	131 children had blood lead levels of 5 – 10 g/dL.

		Attention Deficit Hyperactivity Disorder: New Insight on Sex Differences					(Multivariate Logistic Regression) to evaluate the relationship between lead levels and the risk of ADHD in children	
2	Elbaz, F., et. al (2019)	Association Between Circulating Zinc/Ferritin Levels and Parent Conner's Scores in Children with Attention Deficit Hyperactivity Disorder	Case-control study	Cairo - Egypt	50 participants (43 males, 7 females; mean age 9 ± 2.2 years)	-	• Checking blood samples 6 months before and after treatment • Colorimetric Test to measure zinc concentration in serum	In the group of zinc-deficient children with ADHD, data were found to improve inattention ($p > 0.05$) and hyperactivity-impulsivity scale ($p > 0.001$) after taking zinc supplementation at 55 mg/kg for 6 months.
3	Park, J. H., et. al (2016)	Blood Lead Concentrations and Attention Deficit Hyperactivity Disorder in Korean Children: A Hospital-Based Case Control Study	Case-control study	Busan - Korea	228 participants (114 ADHD and 114 healthy controls; mean age 8.7 years)	-	Measurement of lead levels in blood samples was carried out using the graphite furnace atomic absorption spectrometry method featuring Zeeman background correction	The geometric mean of blood lead levels in the ADHD and control groups were 1.90 ± 0.86 g/dL and 1.59 ± 0.68 g/dL.
4	K. Pereira,	Blood Lead Level	Cross	Venezue	47	-	Measurement	• Based on

	et. al (2016)	and Presence of Attention Deficit Hyperactivity Disorder (ADHD) in School Children	sectional study	la	participants (21 males, 26 females; ages 6 – 9 years)		of lead levels in blood samples was carried out using atomic absorption spectrophotometry to the flame, Perkin Elmer model 3110 and NIOSH 8003 methods.	ADHD according to parents, lead levels in the blood were found in the type of hyperactivity, combination and non-specific, namely 11.8 g/dL, 11 g/dL, and 9.5 g/dL • Based on ADHD according to the teacher, the lead levels in the blood were found in the types of hyperactivity, inattention, combination, and non-specific, namely 9.5 g/dL, 12.2 g/dL, 10 g/dL, and 9.5 g/dL.
5	Lin, Y., et. al (2019)	Blood Lead, Bone Lead and Child Attention-Deficit-Hyperactivity-Disorder-Like Behavior	Case-control study	Xinhua - China	164 participants (ages 3 – 15 years)	-	• Measurement of lead levels in blood samples was carried out using atomic absorption spectroscopy	It was found that the incidence of children with ADHD was more in the group with the

							• In vivo measurement of lead levels in the tibia bone using KXFR (K-shell X-ray Fluorescence)	geometric mean of high blood and bone lead levels, namely 19.6 g/dL and 12.8 g/dL.
6	Choi, W. J., et. al (2016)	Blood Lead, Parental Marital Status and The Risk of Attention-Deficit/Hyperactivity Disorder in Elementary	Cohort study	Korea	2195 participants (age 7 – 9 years)	2 years	Measurement of lead levels in blood samples was carried out using atomic absorption spectroscopy	The risk of ADHD increases in children with blood lead levels > 2.17 g/dL
7	Viktorinova, A., et. al (2016)	Changed Plasma Levels of Zinc and Copper to Zinc Ratio and Their Possible Associations with Parent- and Teacher-Rated Symptoms in Children with Attention-Deficit Hyperactivity Disorder	Case-control study	Bratislava – Slovakia	108 participants (58 ADHD and 50 healthy controls; 45 boys and 13 girls; mean age 9.4 ± 2.1 years)	-	Measurement of zinc levels in plasma samples was carried out using the flame technique of atomic absorption spectroscopy	The mean plasma zinc level in the ADHD group was lower than the control group (p = 0.0005), namely 10.63 g/dL and 11.32 g/dL
8	Huang, S., et. al (2016)	Childhood Blood Lead Levels and Symptoms of Attention Deficit Hyperactivity Disorder (ADHD): A Cross-Sectional Study of Mexican Children	Cross sectional study	Mexico	578 participants (mean age 9.1 ± 1.3 years)	-	Measurement of lead levels in blood samples was carried out with ICP MS (Inductively Coupled Plasma Mass Spectrometry)	The average blood lead level in children with ADHD is 3.4 ± 2.9 g/dL
9	Hong, S. B., et. al (2015)	Environmental Lead Exposure and Attention Defcit/Hyperactivity Disorder Symptom Domains in A Community	Cross sectional study	South Korea	1001 participants (mean age 9.05 ± 0.7 years)	-	Measurement of lead levels in blood samples was carried out using an atomic absorption	It was found that high blood lead levels are associated with ADHD in children (ADHD

		Sample of South Korean School-Age Children					spectrometer-graphite furnace	Rating Scale, 1.99; 95% CI: 0.17, 3.81 and 3.66; 95% CI: 1.18, 6.13, respectively)
10	Lee, M. J., et. al (2018)	Heavy Metals' Effect on Susceptibility to Attention-Deficit/Hyperactivity Disorder: Implication of Lead, Cadnium and Antimony	Cross sectional study	Taiwan	122 participants (age 6 – 10 years)	-	Measurement of lead levels in urine samples was carried out using ICP/MASS (Inductively Coupled Plasma Mass Spectrometry) and mass spectrometry.	The data found that lead was positively associated with ADHD symptoms in children ($p < 0.05$)
11	Kim, J. I., et. al (2018)	Interaction Between DRD2 and Lead Exposure on The Cortical Thickness of The Frontal Lobe in Youth With Attention-Deficit/Hyperactivity Disorder	Case-control study	Seoul - South Korea	150 participants (75 ADHD and 75 healthy controls; mean age 9.8 years)	-	Measurement of lead levels in blood samples was carried out using an atomic absorption spectrometer-graphite furnace	The mean levels of lead in blood samples of children with ADHD were higher than controls, namely 1.5 g/dL compared to 1.3 g/dL
12	Choi, J. W., et. al (2020)	Interaction Between Lead and Noradrenergic Genotypes Affects Neurocognitive Functions in Attention-Deficit/	Case-control study	South Korea	355 participants (259 ADHD and 96 healthy controls; mean age of ADHD children and controls	-	Measurement of lead levels in blood samples was carried out using an atomic absorption spectrometer-graphite furnace	The mean levels of lead in blood samples of children with ADHD were higher than controls, namely 1.4 g/dL

					were 8.8 and 10.5 years)			compared to 1.3 g/dL
13	Elbaz, F., et. al (2017)	Magnesium, Zinc and Copper Estimation in Children with Attention Deficit Hyperactivity Disorder (ADHD)	Case-control study	Cairo – Egypt	40 participants (20 ADHD and 20 healthy controls; mean age of children with ADHD and controls were 7.74 ± 1.48 and 7.40 ± 1.35 years)	-	• Measurement of zinc levels in serum samples was carried out with an auto analyzer • Measurement of zinc levels in hair samples was carried out with IC-MS (Inductively Coupled Mass Spectroscopy) and compared with the magnesium cut off value.	• The mean zinc level in the serum sample in the ADHD group was smaller than the control group, namely 69.68 g/dL compared to 159.54 g/dL • The number of participants with zinc levels below the cut off value in children with ADHD was more than controls, namely 14 compared to 2 children
14	Xu, J., et. al (2015)	Prenatal Lead Exposure Modifies the Impact of Maternal Self-Esteem on Children's Inattention Behavior	Cohort study	Mexico	192 participants (109 males and 83 females; mean age 11.1 ± 3.4 years)	10 years	Measurement of lead levels in blood samples was carried out using ICP/MASS (Inductively Coupled Plasma Mass Spectrometry)	The geometric mean of blood lead levels in children with ADHD is 2.8 g/dL

15	Joo, H., et. al (2017)	Secondhand Smoke Exposure and Low Blood Lead Levels in Association With Attention-Deficit Hyperactivity Disorder and Its Symptom Domain in Children: A Community-Based Case-Control Study	Case-control study	Cheonan – South Korea	428 participants (214 ADHD and 214 healthy controls; ages 6 – 10 years)	-	Measurement of lead levels in blood samples was carried out by atomic absorption spectrophotometry	The mean blood lead levels in children with ADHD were higher than controls, namely 1.65 g/dL compared to 1.49 g/dL
16	Skalny, A. V., et. al (2020)	Serum Zinc, Copper, Zinc-to-Copper Ratio, and Other Essential Elements And Minerals in Children with Attention Deficit/Hyperactivity Disorder (ADHD)	Case-control study	Russia	136 participants (68 ADHD and 68 neurotypical controls; ages 4 – 9 years)	-	Measurement of zinc levels in serum samples was carried out by inductively-coupled plasma mass spectrometry at NexION 300D plus an ESI SC-2 DX4 autosampler.	The mean serum zinc level in children with ADHD was lower than in neurotypical controls at 0.93 ± 0.101 g/mL compared to 1.007 ± 0.166 g/mL
17	Setiawati, Y., et. Al (2019)	The Influence Of Lead (Pb), Zinc (Zn), Ratio Lead (Pb) to Zinc (Zn) in Attention Deficit Hyperactivity Disorder (ADHD)	Case-control study	Surabaya - Indonesia	44 participants (23 ADHD and 21 non-ADHD; ages 6 – 9 years)	-	Measurement of lead and zinc levels in hair samples was carried out by atomic absorption spectrophotometry	• The results showed that there was no significant difference in lead levels in hair samples between the ADHD and non-ADHD groups with median values of 10.74 and 11.39.

								• The median of zinc levels in children with ADHD and non-ADHD had a significant difference, namely 307.84 and 177.55
18	Neugebauer, J., et. al (2015)	The Influence of Low Level Pre- and Perinatal Exposure To PCDD/Fs, Pcbs, and Lead on Attention Performance and Attention-Related Behavior Among German School-Aged Children: Results From The Duisburg Birth Cohort Study	Cohort study	Duisburg – Germany	117 participants (63 males and 54 females; mean age 8.5 ± 0.3 years)	2 years	Measurement of the level of lead in blood samples in prenatal mothers was carried out by atomic absorption spectroscopy	The results obtained mean levels of lead in maternal blood samples during prenatal period of 22.16 g/L
19	Hawari, I., et. al (2020)	The Role of Lead, Manganese, and Zinc in Autism Spectrum Disorders (ASDs) and Attention-Deficient Hyperactivity Disorder (ADHD): a Case-Control Study on Syrian Children Affected by the Syrian Crisis	Case-control study	Syria	101 participants (31 ASD, 29 ADHD, 11 ADHD comorbid ASD, and 30 healthy controls; ages 3 – 12 years)	-	• Measurement of lead levels in blood samples was carried out with an atomic absorption spectrometer • Measurement of zinc levels in serum samples was carried out with an Olympus AU400 auto analyzer coupled with	• The mean levels of lead in blood samples in children with ADHD were higher than controls, namely 3.243 ± 0.855 g/dL compared to 2.84 ± 0.7 g/dL • The mean zinc level

							multi-wavelength diffraction grating spectrophotometry.	in serum samples in children with ADHD was higher than controls, namely 83.45 ± 13.42 g/dL compared to 79.97 ± 13.72 g/dL
20	Nigg, J. T., et. al (2016)	Variation in an Iron Metabolism Gene Moderates the Association Between Blood Lead Levels and Attention-Deficit/Hyperactivity Disorder in Children	Case-control study	Michigan - America	269 participants (122 ADHD and 147 non-ADHD; mean age group for ADHD and non-ADHD were 12.5 and 11.5 years)	-	Measurement of lead levels in blood samples was carried out using inductively coupled plasma mass spectrometry	The mean levels of lead in blood samples in children with ADHD were higher than non-ADHD, namely 0.94 g/dL compared to 0.74 g/dL

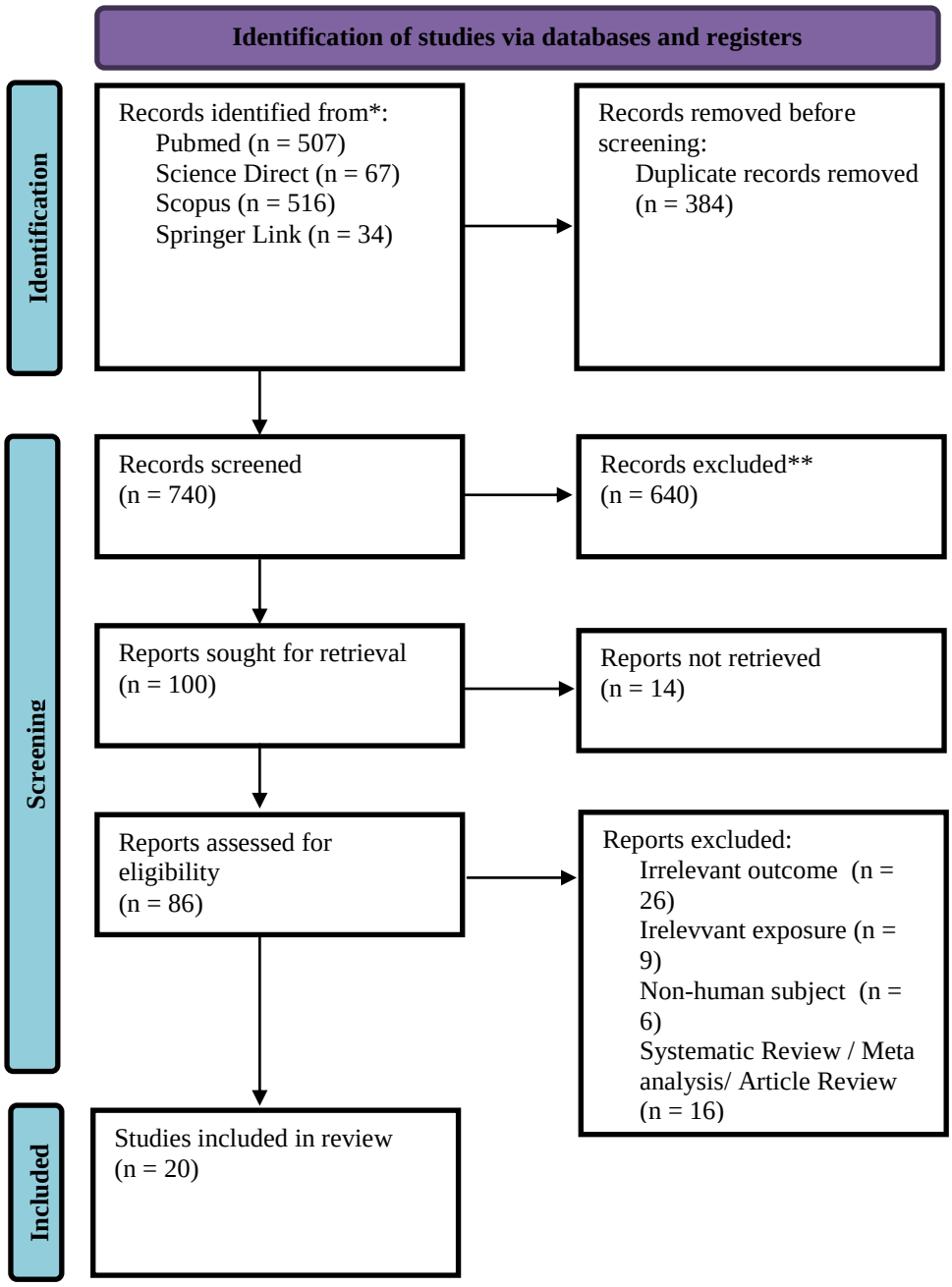

Figure 1. PRISMA flow chart articles processing

4. Discussion

The results of the studies involved in this study showed evidence that Plumbum exposure was positively associated with the risk of developing ADHD, especially the types of hyperactivity and impulsivity. There is no reference to the minimum level of lead in the blood that can cause ADHD symptoms in children. The zinc category provides evidence that people with ADHD have lower zinc levels in the studies involved. As is well known, Attention-Deficit/Hyperactivity Disorder (ADHD) or Attention Deficit Disorder and Hyperactivity (GPPH) is a persistent neurodevelopmental disorder with a prevalence of 5% in children and 2.5% in adults in worldwide (Faraone, et. al, 2015). This systematic review expands knowledge about the influence of Pb and Zn on ADHD because it includes the most recent studies published in 2015-2020. The results of this study support the previous review regarding Plumbum exposure to ADHD which was limited to articles with the year published until 2018. There are very few systematic review articles on Zinc, so this research can add insight on the role of Zinc on ADHD symptoms.

Of the 20 studies discussed, there are 15 studies that support the theory of Pb exposure to ADHD symptoms and 5 studies that support the theory of lack of Zn levels on ADHD symptoms. These studies consisted of 4 cohort studies, 12 case-control studies, and 4 cross-sectional studies which broadens the scope of the topic of this research. In this study, it was shown that Pb levels in ADHD sufferers increased and exposure to small amounts could lead to an increased risk of ADHD. In the Zn category, there is evidence that levels are low in ADHD sufferers and are correlated with inattention subtypes that will improve with supplementation. The studies that have been reviewed are strong enough because the studies presented are published studies from good, official literature, and have been peer reviewed before publication.

Plumbum (Pb) has been widely known to be a neurotoxic substance for the nervous system with mechanisms related to the release of neurotransmitters and dopamine at the presynaptic (Bressler and Goldstein, 1991; Lidsky and Schneider, 2003). The Centers for Disease Control and Prevention (CDC) states that normal levels of lead in the blood are around 3.5 g/dL. Based on this systematic review, there were no significant results that levels that exceeded the new normal reference would cause ADHD symptoms in children. Other results show that there is a positive relationship between lead exposure from the environment with low levels that can affect levels in the body and increase ADHD symptoms in children. Exposure to lead which is neurotoxic from the environment can be mixed in the form of air, food and water (Dórea, J.G., 2019). Several studies in this study did not include whether the subjects who were part of the study received lead exposure in a certain period of time or in a certain form of exposure.

The role of Zinc (Zn) in the human body has an important role in protein synthesis, DNA synthesis, the body's immune system, growth - development, synaptic transmission, signaling cascades, and regulates the production of neuronal oxidant cells in the nervous system (Adamo and Oteiza, 2010; Villagomez and Ramtekkar, 2014). Zinc plays an important role in the production and regulation of melatonin whose job it is to modulate the dopamine system, which is impaired in children with ADHD (Villagomez and Ramtekkar, 2014). In addition, zinc can help regulate and bind to the dopamine transporter for distribution. In this systematic review, the results were not significant. All studies in this study were case-control studies, most of which showed that serum zinc levels in children with ADHD were lower than normal controls. The Centers for Disease Control and Prevention (CDC) states that the normal level of zinc in serum is 70-120 g/dL. One study showed that zinc levels in children with ADHD exceeded the normal reference set by the CDC. It is proven in one study that zinc supplementation can improve ADHD symptoms in children, especially the

inattentive type. This systematic review supports previously published research that decreased or increased zinc levels can influence ADHD symptoms (Colquhoun and Bunday, 1981).

The quality and evidence presented by the studies is strong enough and is based on the Diagnostic and Statistical Manual of Mental Disorders edition 4 or 5, but because the country of origin of each study is different and the respondents are different, the ADHD diagnostic tools used are different in each study. Several studies have not considered separating the subtypes of ADHD symptoms into inattention and hyperactivity-impulsivity. The limitation of the language used in this study, namely English, causes the possibility of not covering research that is relevant to other languages. The existence of confounding variables that differ in each study such as age, gender, parental marital status, maternal stress level, maternal lipoprotein levels, and others cause possible bias in this review.

5. Conclusion and Sugesstions

Of all the studies that have been reviewed in this study, Plumbum (Pb) exposure has been shown to have an effect on ADHD symptoms, especially the type of hyperactivity and impulsivity, although in small levels and zinc (Zn) deficiency has been shown to affect ADHD symptoms, especially the inattention type. Future research is expected to consider the separation of ADHD symptoms in each of its subtypes. It is hoped that in the future further research will be carried out regarding the minimum reference for lead and zinc levels in relation to increasing ADHD symptoms in children and more research that will reveal the effects of Pb exposure and Zn deficiency on ADHD symptoms, especially in Indonesia.

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