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HIGH BLOOD LEAD LEVELS AS A RISK FACTOR OF STUNTING: A STUDY OF CHILDREN IN AGRICULTURAL AREAS

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Abstract

Introduction: *The prevalence of stunting among student aged children in Indonesia is relatively high (24.5%). Stunting can threaten the quality of human resources one day. Lead exposure, particularly from pesticides, is thought to disrupt children's development and growth. This study aims to demonstrate that high blood lead levels (BLL) is a risk factor of stunting for children who lives in agricultural areas through the intermediate variable, namely interference with growth hormone (IGF-1).* ***Methods:*** *This study used a case-control design, involving 35 cases (children with HAZ scores of less than -2 SD) and 40 controls (children with HAZ scores of more than -1.5 SD). BLL were measured using the atomic absorption spectrophotometer (AAS) method. Meanwhile, insulin-like growth factor-1 (IGF-1) levels using an ELISA kit (R&D Systems). BLL variables and IGF-1 levels were determined using the receiver operating characteristic (ROC) curve.* ***Results and Discussion:*** *High BLL (>20.44 µg/dL) and low IGF-1 levels (<100 ng/ml) were identified risk factors for stunting in children in agricultural areas with odd ratios (OR) od 2.8 (1.1-7.1) and 3.3 (1.3-8.5) respectively. Meanwhile, a negative correlation was discovered between BLL and IGF-1 levels (p = 0.002, r = -0.356).* ***Conclusion:*** *High lead exposure has been proven to be a risk factor for stunting in children in agricultural areas through the process of interference with the growth hormone, namely IGF-1. Efforts to prevent stunting, especially in agricultural areas, need to take into account exposure to environmental toxicants, including lead from pesticides.*

INTRODUCTION

Stunting is defined as impaired growth and development in children resulting from recurrent infections, poor nutrition and inadequate psychosocial stimulation. Stunting is classified by a height-for-age measurement that is more than two standart diviations below the median of the World Health Organization (WHO) child growth standarts (1). Stunting has an impact on child morbidity and mortality (2). Children who have undergone stunted growth will experience delays in their both physical growth and intellectual development (3). As such, there will be a great impact on the human resources' quality in the future (4). The WHO data show that the prevalence of stunting in children under five in the world has reached 22.3%, with Asia reporting a prevalence of 27.4% (5). Indonesia stunting prevalence in 2020 was the second highest in Southeast Asia, reaching 31.8%. This figure is only better than Timor Leste at 48.8%(6).

Data in 2022 show a significant reduction in the incidence of stunting in Indonesia, namely 21.6%, but this figure is still far from the national target of 14% in 2024 (7). Data from the Central Java Provincial Health Service in 2021 show that child stunting prevalence between the ages of five and 12 years was 24.5%, with the Brebes Regency ranking the third highest at 23.7% (8). Stunting on children can happen during the first 1.000 days after

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conception and is associated with many factors, including dietary intake, environmental conditions, maternal nutritional status, infections, micronutrient deficiencies, and socioeconomic status (9).

The primary causes of stunting are low nutritional intake, recurrent infections, and insufficient psychosocial stimulation (10). These factors are closely related to the socio-economic conditions of the family. Environmental factors, particularly poor sanitation, including poor air quality, water, and waste management at the household level, also play a crucial role in the occurrence of stunting. Such conditions often lead to recurrent infections, such as pneumonia and diarrhea, and respiratory tract infections (ARI) (11-12). Repeated infections result in the inefficient use of energy from nutritional intake, partly due to oxidative stress, impairing the optimal use of nutrients for growth and development (13).

In addition to the main hygiene issues, the effects of toxic substances in the environment have been shown to increase the risk of stunting children. Research in Brebes Regency, an agricultural area with a high level of pesticide use, identified pesticide exposure as an independent risk factor for stunting in children (14). It is also found in another study in the same regency that pregnant woman exposed to pesticides is a determinant for low birth weight (15). One of the toxic ingredients contained in pesticides, which is thought to cause growth and development disorders, especially in the first 1.000 days of life, is the heavy metal lead (plumbum/ Pb) (16). Lead and pesticides are endocrine-disrupting chemicals (EDCs) (17). Lead exposure has been demonstrated to interfere with the function of growth hormones, including one of the most significant hormones involved in the growth process, insulin-like growth factor-1 (IGF-1). In the body, the presence of lead causes the suppression of IGF-1 secretion in exposed individuals, resulting in a delay in the growth process (18). Research in Brebes Regency has shown that IGF-1 hormone (the insulin-like growth factor-1) is greatly affected by exposure to pesticides (14-15). In addition to IGF-1, the thyroid hormone, which is essential for metabolic processes in cells or tissues, are also critical for child growth and development (19). Several studies have demonstrated that lead exposure has a negative effect on thyroid function (20-21). Studies conducted in Brebes Regency confirmed a great influence of lead exposure among the communities, with BLL in almost all pregnant women and elementary school children exceeding the safe limit, namely 5.0 µg/dL (22).

Previous research has explain the relationship between lead exposure and the incidence of stunting in several countries. For example, a study in the mining area of Bangka Island found, that 'high' BLL (≥5.0 µg/dL) are a risk factor for the incidence of stunting in children (adjustedOR = 9.8; 95% CI (3.1-30.7)) (23). However, there is limited research that measures and analyzes IGF-1 levels as an intermediate variable. This study aims to demonstrate that high BLL is a risk factor for stunting children who live in the agricultural area of Brebes Regency through disruption of the IGF-1 hormone.

METHODS

A case-control study design was used at four elementary schools situated within the catchment area of the Kluwut Health Center in Bulakamba subdistrict, Brebes Regency, where the prevalence of stunting is notably high. The minimum sample size was calculated using the sample size formula for case-control studies, with a significance level of 5%, a study power of 80%, a proportion of lead exposure of 45% in non-stunted children, and an odds ratio (OR) of 3.58. This calculation yielded a minimum sample size of 35 participants for both the case and control groups.

The study included children between the ages of nine and 12. The study excluded the individuals who refused to fill in the complete data had no blood sample as well. The minimum sample size required for this study was 35 people, calculated using the sample size formula for case-control studies (24).

$$\frac{\left\{Z1-\alpha_{/2}\sqrt{[2.P(1-P)]}+Z\,1-\beta\sqrt{[P1(1-P1)+P2(1-P2)]}^{2}\right\}}{(P1-P2)^{2}}$$

The value of Zα: 1,96 (CI 95%), Zβ: 0,84 (power 80%), and the odd ratio from previous research is 3.5. The study measured the height of 349 elementary school children (119 boys and 119 girls) in order to identify individuals who were stunted. In accordance with the WHO Child Growth Standards, 80 students were identified as stunted. From this cohort, 40 students were selected through simple random sampling. Of the aforementioned students, three declined to provide blood samples, and one exhibited a low hemoglobin value. This resulted in a total of 35 students comprising the case group, which was subjected to further analysis. Meanwhile, 40 students who were not stunted were selected using simple random sampling and included in the control group (Figure 1), resulting in a 1:1 sample size ratio for the case and control groups in accordance with case-control study standards.

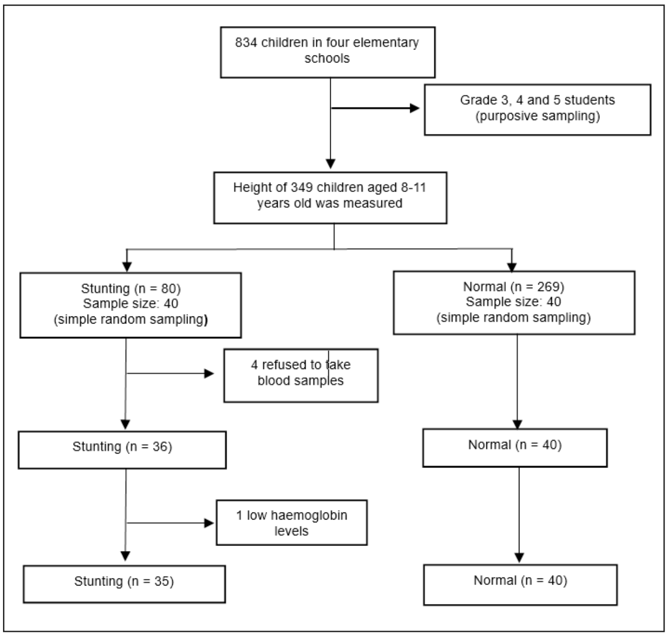

Figure 1. Flow of Sample Selection

A survey was employed to gather data on fundamental characteristics, including sex, age, parental educational attainment, parental occupation, history of lead exposure, and history of infectious diseases (e.g., worms, acute respiratory infections, diarrhea, and tuberculosis) in the previous month. The students' age data were obtained from secondary sources, namely school records. Height was measured by four trained individuals with graduate degrees in nutrition, in accordance with standard procedures. The children's heights were measured using a Seca 213 stadiometer. Each child was instructed to stand barefoot, upright, and looking forward, with their feet together on a flat surface. Stunting was defined in accordance with the WHO Child Growth Standards as a height-for-age z-score (HAZ) of less than -2 SD, while a normal HAZ was defined as a score between -2 SD and +2 SD. A total of 75 students provided peripheral venous blood samples for analysis.

BLL were quantified using the atomic absorption spectrophotometer (AAS) method. Concurrently, the concentrations of IGF-1 were quantified through the use of an enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems). Both variables were assessed by the IDD laboratory, Medical Faculty, Diponegoro University. The measurement of hemoglobin levels was conducted using the cyanide-free hemoglobin method, in accordance with the standards set by accredited laboratories. The definition of anemia was based on the threshold of 12 g/dL (25).

The data on total dietary intake, including the daily energy intake (in kilocalories) and protein intake (in grams), were assessed using a 2 x 24-hour food recall questionnaire. The levels of energy and protein adequacy were classified as "low" if they fell below 90% of the respective adequacy standards. In the absence of these data, the levels were considered sufficient (26).

The data were analyzed using the statistical software package SPSS (version 26). The statistical methods employed included the independent t-test, chi-squared test, Mann-Whitney test, and odds ratio (OR) with 95% confidence interval (CI). The cut-off values for BLL and IGF-1 levels were determined using the receiver operating characteristic (ROC) curve method, with consideration given to the area under the curve (AUC), specificity, and sensitivity values. The optimal cut-off value for BLL was determined to be 20.4 μg/dL, with a specificity and sensitivity of 0.65 and 0.60, respectively (Figure 2).

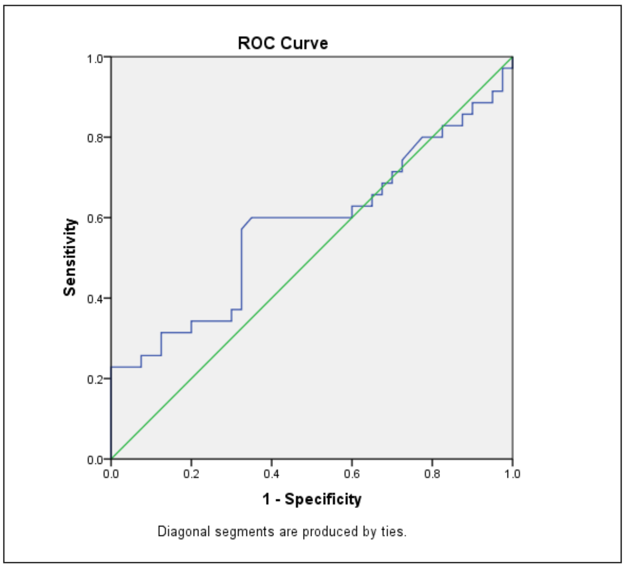

Figure 2. ROC Curve for Various Cut-off Values of BLL

Accordingly, BLL were classified as elevated if they exceeded 20.4 μg/dL. With regard to IGF-1 levels, the cut-off value was established at 100.5 ng/mL, with specificity and sensitivity of 0.60 and 0.69, respectively (Figure 3).

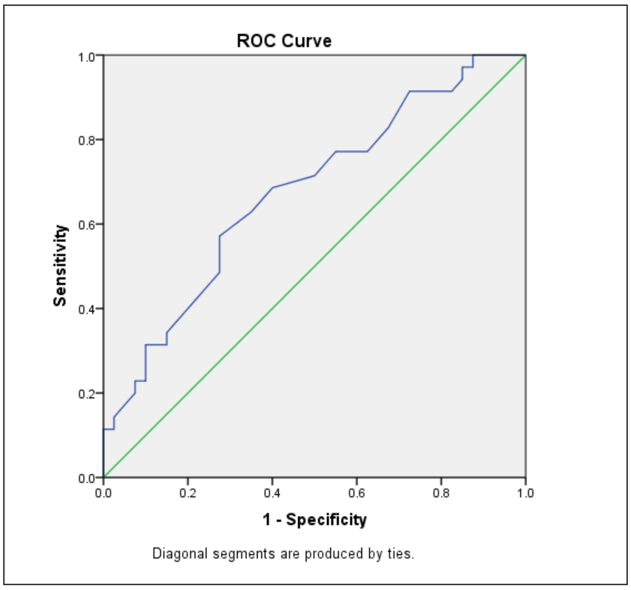

Figure 3. ROC Curve for Various Cut-off Values of IGF-1

Accordingly, IGF-1 levels were classified as "low" if they were below 100.5 ng/mL. A multivariate test logistic regression the backward Wald method to identify the primary risk factors for stunting from three candidate variables namely sex, water source, and BLL. This study was approved by the Medical Research Ethics Committee, Faculty of Public Health, Diponegoro University (No. 444/EA/KEPK-FKM/2022). The parents, students, and teachers were well-informed about the purpose and benefits of the study. Parents signed a written informed consent form.

RESULTS

The results demonstrated most participants were 10 years old. Socio-economic factors showed that most parents had a low level of education and many of the parents were farmers (Table 1). The environmental factor observed in this study was the source of water used in the family, which showed that there was no correlation between groundwater and tap water (p = 0.095). The dietary intake also showed that the average energy and protein intake was higher in the case group than in the control group (p = 0.629). The prevalence of anemia was similar in cases and controls (p = 1.000). The majority of subjects in both groups had no history of infectious diseases (p = 1.000) (Table 1).

Table 1. Characteristics of the Participants

Variable	Case (n = 35)	Control (n = 40)	p-value
Age (year)	10 ± 1	10 ± 1	0.224[a]
Energy intake (kcal)	1705 ±199.015	1692 ± 228.392	0.326[a]
Protein intake (g)	50.21 ± 11.650	48.12 ±10.882	0.629[a]
Sex			
Male	26 (74.3%)	20 (50.0%)	0.055[a]
Female	9 (25.7%)	20 (50.0%)	
Hemoglobin level			
Anemia	8 (22.9%)	9 (22.5%)	1.000[b]
Normal	27 (77.1%)	31 (77.5%)	
Parental education			
Low	29 (82.4%)	29 (72.5%)	
Middle	5 (14.3%)	10 (25.0%)	0.534[b]
High	1 (2.8%)	1 (2.5%)	
Parental occupation			
None	8 (22.9 %)	14 (35.0 %)	
Farmer	18 (51.4 %)	18 (45.0 %)	0.50[b]
Trader	9 (25.7%)	8 (20.0%)	
History of Infectious Disease			
Yes	14 (40.0%)	16 (40.0%)	1.000[b]
No	21 (60.0%)	24 (60.0%)	
Water sources			
Groundwater	19 (54.3%)	13 (32.5%)	0.095 [b]
Tap water	16 (45.7%)	27 (67.5%)	

The results demonstrated no statistically significant difference in age, sex, hemoglobin level, dietary intake, socioeconomic status, history of infectious diseases, and environmental factors between the case and control groups. It also shows that the potential of these variables as confounders can be controlled. The mean BLL in the case group (21.81 µg/dL) was higher than in the control group (18.46 µg/dL), although the difference was not statistically significant (p = 0.249). Contrarily, it was found that the IGF-1 level in the case group (96.46 ng/mL) was observed to be lower than in the control group (105.03 ng/mL), and the difference was found to be statistically significant (p = 0.009) (Table 2).

Table 2. Comparison of BLL and IGF-1 in Case and Control Groups

Variable	Case (n = 35)	Control (n = 40)	p-value
BLL (mg/dL)	21.81 ±11.464	18.47 ±7.487	0.249[a]
IGF-1 (ng/mL)	96.46 ±10.004	105.03 ±17.6 85	0.009[a]

The present study did not identify any significant differences in BLL between the two groups. However, the mean blood lead level observed in the case group was higher than that observed in the control group (Table 2). When the lead levels were categorized into high (>20.4 µg/dL) and low (≤20.4 µg/dL), a correlation was identified between the level of lead exposure and the incidence of stunting, with a p-value of 0.053 and an OR of 2.8 (95% CI 1.1-7.1) (Table 3).

Table 3. The Relationship between Lead Exposure and IGF-1 Level with the Incidence of Stunting

Variable	Case (n = 35)	Control (n = 40)	p-value	OR (95% CI)
Categories of blood lead levels				
High (>20.4 µg/dL)	21 (60.0%)	14 (35.0%)	0.053	2.8 (1.1-7.1)
Low (≤20.4 µg/dL)	14 (40.0%)	36 (65.0%)		
Categories of IGF-1 levels				
Low (< 100.5 ng/ml)	24 (68.6%)	16 (40.0%)	0.025	3.3 (1.3-8.5)
Not low (≥ 100.5 ng/ml)	11 (31.4%)	24 (60.0%)		

Furthermore, a difference was found in the average IGF-1 levels between the case and control groups. The results of the bivariate tests indicated that children with low IGF-1 levels exhibited a 3.3-fold increased risk of stunting in comparison to those with high IGF-1 levels (Table 3). Meanwhile, logistic regression analysist of lead levels, sex, and water source in the family revealed that children with high lead levels had a 2.8 times higher risk of stunting than children with low lead levels (Table 4).

Table 4. Logistic Regression Results

Variable	B	p	Adj-OR (95% CI)
Sex	0.868	0.101	2.3 (0.8-6.7)
Water sources	0.789	0.126	2.2 (0.8-6.0)
Blood lead levels	1.048	0.038	2.8 (1.1-7.6)

Additionally, this study identified a correlation between BLL and IGF-1 levels. Correlation analysis revealed a negative correlation between BLL and IGF-1, with a p-value of 0.002 and a correlation coefficient (r) of -0.356, indicating a moderate correlation (Figure 4).

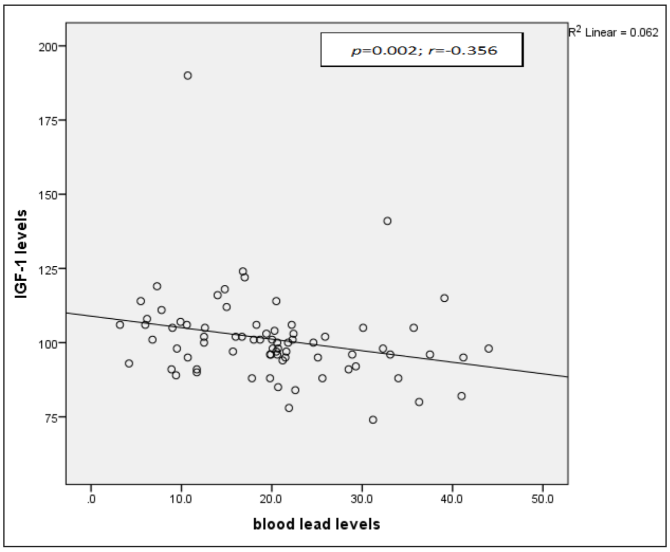

Figure 4. Scatter Plot of the Correlation Between Blood Lead and IGF-1 Levels

DISCUSSION

BLL is a measure of human exposure to lead. The results showed that in both case and control groups, the mean BLL of school children was 20.7 µg/dL and 97% were still above the WHO lead limit. The measurements in this study are higher than in previous studies. A study by Brown, et.al. in India found a mean BLL in primary school children of 11.6 µg/dL and 87% of the children had a BLL greater than 5 µg/dL (27). Meanwhile, another study by Kumar et al. showed that the median BLL in primary school children in 10 cities in India was 8.8 µg/dL (28). High exposure to lead can lead to childhood disorders such as poisoning and long-term health effects. One of the programmes that can be done to reduce lead exposure is to increase calcium consumption, because high calcium can inhibit the absorption of lead in the digestive tract (29).

In this study, the source of risk of lead exposure to the subjects was exposure to pesticides used in agriculture. In the study area, pesticides are used in agricultural activities because they can support good agricultural yields. However, sometimes the correct use of pesticides is not followed. The effects can cause pollution and leave residues on soil, water, seeds or fruits, and plants, even in water bodies and public waters. Lead is one of the heavy metals found in pesticides. Ingredients mixed with solvents in pesticide formulations are kerosene, which is the result of crude oil refining, and carriers such as kaolin, lime, sand and clay, which contain lead (30).

The mechanism of pesticide exposure to children in the study area includes through agricultural activities such as helping to harvest onions, helping to clean agricultural equipment, picking onions, and also simply playing in the agricultural area. Apart from agricultural activities, the risk of exposure to pesticides through contamination of agricultural products is known. It is known that as many as (54.2%) respondents have the habit of storing seeds and shallots in the house. This activity is actually a source of contamination for people living in the house, including children.

Apart from agricultural activities, the findings of the analysis of the source of lead exposure in the study subjects was through food consumed from marine products. The results of a previous study showed that food derived from marine products in the Kluwut area of Bulakamba sub-district, Brebes District, had a high lead content (31). Another study in the same area showed that pregnant women who had a history of consuming seafood such as fish, cuttlefish and kerrang had higher BLL compared to those who did not like to consume seafood (32).

The results showed that the study site, Bulakamba District, is a coastal area in addition to being a shallot farming area. Geographically, Bulakamba sub-district, which is close to the sea area and the center of seafood trade, makes marine fishery products a popular type of food for the community, which is evident from the food recall results where 75% of the research subjects were categorized as frequent consumers of marine products such as fish, squid, and sea shrimp. However, the level of lead in seafood consumed by the subjects needs to be further substantiated.

The mechanism of lead exposure in the body can be through several entry portals including 50%-70% through inhalation and about 40% through digestion (33). Further, lead that is adsorbed in the body will be distributed through the blood, soft tissues, bones, teeth and hair. In the body, the presence of lead will affect the working function of organs in the body and interfere with enzyme activity and provide toxic effects on hematopoiesis, reproduction, endocrine system, neurology, kidney and cardiovascular organs (34).

Lead is one of the heavy metals grouped as EDCs (endocrine disrupting chemicals), which are toxic substances that can interfere with the synthesis, transport, secretion, binding, or elimination of thyroid hormones in the body (35). In this study, lead exposure in children was shown to negatively affect IGF-1 hormone, one of the important hormones in child growth. The mechanism by which lead affects endocrine hormones is in response to the kinetics of growth hormone (GH). Lead exposure can cause GH levels to decrease within 24 hours, thereby reducing plasma IGF-I levels and decreasing the GH response to challenge with L-dopa cells. Impaired GH release may occur due to a reduction in GHRH synthesis, which would further uncouple or reduce the somatotrophic response. Low serum IGF-1 may also be due to the effect of lead exposure in the liver, which impedes the secretion or translation or secretion of the peptide. Thus, lead exposure has been seen to affect longitudinal bone growth, somatic growth and bone strength during the pubertal period. Thus, by suppressing GH and IGF-I secretion in exposed individuals, resulting in a delay in the growth process (36).

Stunting, a condition characterized by impaired linear growth, is commonly associated with poor nutritional intake (3). The causes of stunting in children include prolonged periods of insufficient food intake and postnatal inflammation that inhibits the production of IGF-1, a crucial hormone for early childhood development (1). Several nutrients and microorganisms play a role in stunting. Micronutrients are very important for physical growth, sexual maturity, brain development, and immune function (37). For instance, deficiencies in calcium and vitamin D can cause rickets in children (38). Additionally, inadequate intake of vitamin A and zinc indirectly affects the immune system and exacerbate infections in stunted children (39). Moreover, insufficient consumption of macronutrients such as energy and protein, as well as micronutrients such as zinc and iron, especially during the growth period, disrupts child growth and development, resulting in stunting (40). Therefore, various factors contribute to stunting, such as prolonged nutritional deficiencies.

Nutritional intake influences linear growth along various mechanisms. Experimental studies have shown that dietary protein and energy restrictions reduce plasma levels of IGF-1, a hormone important for linear growth (41). Since IGF-1 binds proteins in the body, inadequate energy and protein intake results in decreased IGF1 concentrations.

This study found no correlation between protein intake and energy and the incidence of stunting. The food recall method was used to measure the daily energy intake, where the average energy intake was 1,713 kcal in the case group and 1,710 kcal in the control group. The average energy and protein intake was higher in the case group than in the control group, indicating that these variables did not influence stunting. The use a 2 x 24-hour food recall may have introduced information bias in this study. In addition, the existence of environmental enteric dysfunction (EED) in the small intestines as a subclinical disorder characterized by physiological, in the form of raising permeability impaired nutrient absorption, and stunted growth, could affect nutrient absorption and contribute to stunting even with adequate energy and protein intake both in the case and control groups (42-43). The independent t-test also revealed no difference in energy and protein intake between the case and control groups.

Lead exposure affects growth through several mechanisms, including hypothyroidism which interferes with the thyroid-stimulating hormone (TSH) receptor in the thyroid gland (44). Several studies have shown that lead exposure is a risk factor for hypothyroidism (45). Thyroid hormone deficiency known as (hypothyroidism) causes metabolic disorders, thereby disrupting development and growth (46).

Furthermore, lead exposure interferes with the function of IGF-1 as a growth hormone (47). Research in China showed that lead exposure can induce the expression of MAPK signaling molecules, which can then influence the binding of IGF-1 in short children (18). The findings of this study revealed that children who have low levels of IGF-1 are at 3.1 times higher risk of stunting compared to those with normal IGF-1 levels. Taking part in growth, IGF-1 acts as a mitogen and stimulator of cell proliferation, as well as in tissue repair/regeneration (48). IGF-1 also mediates the processes of protein anabolic and improving GH activity. GH and IGF-1 are critical for growth and development because growth delays occur when these hormones are impaired (49). This study also revealed a correlation between BLL and IGF-1 levels. The correlation test results indicated that lead exposure decreased IGF-1 levels in the body, as seen in Figure 4.

Figure 4 shows that high BLL decreases IGF-1 levels, with a moderate negative correlation ($r = -0.356$). Decreased IGF-1 levels in the body due to lead exposure may lead to memory impairments through the IGF-1 mediated signaling pathway (50). Meanwhile, impaired GH release can occur due to reduced GHRH synthesis, inhibition of GHRH release, or diminished somatotroph response (51). This is similar to other studies that concluded that lead exposure causes a decrease in the hormone IGF-1 (18, 50-52). In this study we found a negative dose-response relationship between blood lead levels in children aged nine-12 years old and their serum IGF-1 concentrations.

However, this study could not account for all potential confounders, such as exposure to other EDC (e.g., arsenic, phthalates, and PCBs). Nevertheless, it addressed several known risk factors, including IGF-1 levels, hemoglobin, and nutritional intake. In conclusion, this study identified an correlation between lead exposure and stunting in children residing in agricultural areas. The long-term effects of lead exposure on child development such as intelligence level and neurodevelopment disorders need to be studied. In this study, the number of samples used was small but in selecting samples using random sampling. The findings of this study can make a strong contribution to efforts to prevent stunting by reducing the risk of lead exposure in pregnant women and children and limiting involvement in agricultural activities.

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AUTHORS' CONTRIBUTIONS

The authors contributed to the paper as follows: AA: conceptualization, data collection, original draft preparation; SS: methodology, writing, original draft preparation; BB: analysis and interpretation of results; AM: writing; AK: data analysis, editing and reviewing. The final version of the manuscript and the results were being approved and reviewed by All authors.

CONCLUSION

BLL were higher in stunted children compared to normal children. BLL in the high in the high category (>20.4 μg/dL) are an independent risk factor for stunting. Related to the findings of high BLL in children in agricultural areas, it is necessary to conduct health education (counselling) to the community to reduce the use of pesticides containing lead, reduce the involvement of mothers and children in agricultural activities. Intervention efforts that can be made to reduce the level of lead exposure in mothers and children is to provide high doses of calcium supplementation (1000 mg/day), because calcium can inhibit the absorption of lead in the gastrointestinal tract. Future research needs to study the effects of lead on the long-term effects of child growth and measure confounding variables such as parenting. Furthermore, it is incumbent upon the subsequent researcher to augment the number of samples utilised.

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