

ORIGINAL ARTICLE

Lipid profile, TNF- α , IL-18, hsCRP, and carotid intima-media thickness (CIMT) diameter in relation to insulin resistance of Indonesian adolescents with overweight and severe obesity

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Abstract. *Background and Aim:* There is an obvious correlation between insulin resistance (IR) in children and adolescents, obesity, and the elements of metabolic syndrome (MetS), which contributes to an increased risk of cardiovascular issues via pro-inflammatory response (TNF- α , IL-18, hsCRP), leading to early atherosclerosis development, marked with carotid intima-media thickness (CIMT). This study aimed to explore the relationships between IR and various factors, including lipid profiles, TNF- α , IL-18, hsCRP, and CIMT in adolescents. *Methods:* A cross-sectional study was performed between August - December 2023 involving 94 healthy adolescents with obesity. Anthropometric measures and blood biochemistry were done by professional laboratory staff; CIMT diameters were also assessed. IR was established using the HOMA-IR with the parameters of > 5.22 for boys and >3.82 for girls. *Results:* IR in adolescents with overweight and severe obesity was detected in 26.60% subjects, that much lower than other findings in Southeast Asia and Indonesia and not related to sex. IR subjects had moderate correlation with anthropometric values, including body weight, body mass index (BMI), BMI-for-age Z-score, waist circumference, and hip circumference. In lipid profile, IR had a positive correlation with triglycerides (TG), but a weak negative correlation with HDL. IR had a significant weak correlation with hsCRP and CIMT diameter. *Conclusion:* IR was positively associated with higher triglycerides (TG), TNF- α , hsCRP levels, and CIMT diameter, while it showed a negative relationship with HDL cholesterol (HDL-c). No significant correlation or difference was observed between IR and serum levels of IL-18. (www.actabiomedica.it)

Key words: obesity, HOMA-IR, adolescents, lipid profile, TNF- α , IL-18, hsCRP, CIMT diameter-

Introduction

The incidence of insulin resistance (IR) in children is rising due to a surge in obesity among adolescents, coupled with lifestyle changes (reduced physical activity, increased caloric intake, excessive reliance on technology, and sedentary behaviors) (1,2). IR is indicated when the insulin can't effectively prompt the

peripheral tissues (skeletal muscle and fat) to absorb glucose in plasma, reduce gluconeogenesis by the liver, or control the release of glucose into the bloodstream. Additionally, it may involve inadequate suppression of very-low-density lipoprotein production (VLDL) (3). IR is also characterized as a condition with a broad range of severity and is commonly associated with obesity (4). Tanner stage and sex as proven that girls are

more prone to have IR compared to boys due to their earlier onset of puberty. The prevalence of IR is higher among girls during prepuberty and early puberty but decreases in later stages of puberty. Meanwhile, boys continue to develop a higher metabolic risk. Therefore, boys at 16 years old were found to exhibit a greater incidence of IR compared to girls, despite appearing leaner and more physically active (5,6). IR, obesity, and the elements of metabolic syndrome (MetS) have been known to be correlated, which contributes to an increased risk of cardiovascular issues (7). IR leads to several metabolic changes, including lipid metabolism, leading on the elevated of atherogenic lipid (triglyceride and low-density lipoprotein (LDL) cholesterol), while reducing the anti-atherogenic lipid, high-density lipoprotein (HDL) cholesterol, and sex hormone-binding globulin, that contribute to atherogenic dyslipidemia and increased the risk of developing early atherosclerosis (8), the major causes of cardiovascular disease, including myocardial infarction (MI), stroke, and other heart conditions (9). An elevation in CIMT may serve as an early indicator of subclinical atherosclerosis and has been recognized as a reliable, non-invasive tool for detecting the initial stages of atherosclerosis (10–12). The onset of IR associated with obesity is influenced by a low-grade tissue-specific inflammatory response, that are activated by various pro-inflammatory and oxidative stress factors. Key pro-inflammatory cytokines involved include IL-1 β , IL-6, IL-8, tumor necrosis factor- α (TNF- α), as well as chemokines and adipocytokines (13,14), epigenetic factors, glucolipotoxicity (15), and different transcriptional and metabolic pathways (16). Persistent exposure to pro-inflammatory agents activates cytokine signaling proteins, which can inhibit the function of insulin receptors in β -cells within the pancreatic islets. Previous research has also indicated that individuals with IR often have elevated levels of pro-inflammatory cytokines and/or experience glucolipotoxicity. Regarding the rising global prevalence of IR among children and adolescents, this study aimed to explore the relationships between IR and various factors, including lipid profiles, TNF- α , IL-18, hsCRP, and CIMT in adolescents with obesity.

Methods

Study design

This cross-sectional study was performed between August - December 2023, involving 94 healthy pubertal adolescents who were studying in local schools in Surabaya and Sidoarjo, East Java, Indonesia. This study focused on examining the relationships between IR with lipid profiles, TNF- α , IL-18, hsCRP, and CIMT diameter in adolescents. IR was determined using the HOMA IR with cut-off values of >5.22 for boys and >3.82 for girls (17). The chosen cut-off to determine IR was considered: the subject's age and condition were similar in this study. If we determine IR using other cut-offs, such as >2.77 (18), all subjects had IR.

Samples

The study population was selected through simple random sampling, including healthy adolescents aged 13 to 18 years. Subjects were excluded if they had used corticosteroids in the six months before the study, undergone hormone therapy, taken dyslipidemia medications in the three months before the study, used antibiotics, smoked, consumed alcohol, experienced infections, or had any endocrine or immune system disorders.

Measurements

ANTHROPOMETRIC MEASUREMENTS

Anthropometric data were collected by qualified medical staff. Participants were instructed to remove their socks and shoes, wearing only the minimum of the school uniform. Body weight was measured using calibrated electronic scales (SECA[®], Germany), with precision to the nearest 0.1 kg. Participants were then positioned with their heels, calves, buttocks, scapulae, and the back of their heads touching the stadiometer's vertical surface. Body height was assessed using a stadiometer (SECA 213 Stadiometer[®], Germany), with accuracy to the nearest 0.1 cm. According to CDC guidelines, obesity is defined as a BMI above the 95th percentile for age and gender, while overweight is classified as a BMI between the 85th and 95th percentiles

(19). Waist circumference (WC) and hip circumference (HC) were measured with a constant-tension tape measure (SECA 201®, Germany). WC was recorded by placing the tape measure horizontally at the mid-point between the lower edge of the last palpable rib and the top of the iliac crest, while HC is measured at the widest point around the buttocks, with both measurements taken to the nearest 0.1 cm. Blood pressure was measured in a sitting position as recommended by ISH Global Hypertension Practice Guidelines using an Omron automatic blood pressure monitor HEM-8712 (20). The cutoff to determine hypertension based on the IDF guideline: Systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg (21).

BLOOD CHEMICAL MEASUREMENTS

Participants were instructed to fast for eight to twelve hours before taking blood samples for LDL, HDL, and total cholesterol level measurements using Cholestest®LDL, Cholestest®N HDL, and Pureauto®S CHO-N assays (Sekisui Medical Co., Ltd., Japan). Triglycerides were assessed with the TG-N Kit Autosera S (Sekisui Medical Co., Ltd., Japan). TNF- α , hsCRP, and IL-18 were quantified using the ELISA (Enzyme-Linked Immunosorbent Assay) method, reported in ng/L. IR was measured by fasting plasma glucose and fasting insulin using the Enzyme-linked Immunosorbent Assay (ELISA) method and calculated for HOMA-IR by the formula: $\text{HOMA-IR} = \frac{\text{glucose (mg/dL)} \times \text{Insulin } (\mu\text{IU/L})}{405}$. Blood samples were collected and analyzed by trained local laboratory technicians.

CIMT MEASUREMENTS

CIMT diameter was assessed on the posterior wall of the left carotid artery using a carotid ultrasound machine (Toshiba®, Japan) by a cardiologist. Atherosclerotic plaques were characterized as areas where the blood vessel walls extended into the vessel lumen by more than 50% of the intima-media thickness.

STATISTICAL ANALYSIS

Data analysis was performed using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA). Descriptive

statistics were presented according to the data type. Continuous data were assessed for homogeneity of variance and normality. The comparison between two groups was assessed using the Independent T-test (for normally distributed populations) or the Mann-Whitney U test (for non-normally distributed populations). Comparisons involving more than two groups were conducted using One-Way ANOVA (for normally distributed populations) and the Kruskal-Wallis test (for non-normally distributed populations). Categorical data were analyzed using either the Pearson chi-squared test or Fisher's exact test. Statistical significance was considered with a *P*-value less than 0.05.

Results

This study involved 94 participants, of whom 26.60% (25 out of 94) were found to have IR. The prevalence of IR did not differ significantly between sexes ($P=0.164$); 29.57% of male adolescents had IR compared to 33.33% of female adolescents. Subjects with IR had significantly higher anthropometric measurements: body weight, BMI, BMI-for-age *z*-score, and waist circumference compared to subjects without IR. In lipid profile, IR subjects had significantly higher triglycerides and lower HDL-c levels. No significant difference was found in total cholesterol ($P=0.579$) and LDL-c ($P=0.240$) serum between groups. In the pro-inflammatory cytokines profile, IR subjects had significantly higher hsCRP levels than non-IR subjects as well as TNF- α levels, but no significant difference in IL-18 levels ($P=0.145$). There was no significant difference in CIMT diameter between IR and non-IR subjects ($P=0.123$) (Table 1).

Subjects were also categorized according to their nutritional status: normal BMI (14 subjects), overweight (40 subjects), and obese (40 subjects). Table 2 depicts the characteristics of the subjects based on their nutritional status. The gender distribution was 46 males and 48 females, with no significant difference in nutritional status across sexes ($P=0.449$). IR was more common in the obese group compared to those who were overweight or had a normal BMI, with the prevalence of 18.09%, 7.45%, and 1.06% respectively ($P=0.008$). HOMA-IR values were notably elevated in obese subjects compared to those with normal or overweight status, as well as higher insulin levels. Regarding the lipid

Table 1. Clinical and laboratory characteristics of adolescents included in the study

Variables	IR (n=25) Mean + SD	Non-IR (n=69) Mean + SD	P value
Demography			
Gender (n. and %)			
Boys	9 (29.57)	37 (80.43)	0.164 ^c
Girls	16 (33.33)	32 (66.67)	
Age (years/months)	15.44 + 1.47	15.10 + 1.48	0.338 ^a
Anthropometry			
Weight (Kg)	93.18 + 16.01	80.76 + 18.99	0.004 ^{a*}
Stading height (cm)	160.33 + 7.99	163.21 + 8.21	0.104 ^b
BMI (Kg/m ²)	35.63 + 6.32	31.34 + 5.83	0.003 ^{a*}
Range:	16.80 – 42.70	16.80 – 56.90	0.003 ^{a*}
BMI-for-age (Z-score)	3.09 + 0.56	2.43 + 1.16	0.002 ^{b*}
Waist circumference (cm)	106.62 + 12.13	95.43 + 17.34	0.004 ^{a*}
Hip circumference (cm)	113.26 + 12.54	104.36 + 12.36	0.005 ^{b*}
Laboratory findings			
FBG (mg/dL)	87.16 + 10.26	80.04 + 6.36	0.003 ^{a*}
HOMA -IR index	9.26 + 5.86	2.71 + 1.06	<0.0001 ^{b*}
Range:	4.24 – 26.40	0.86 + 4.99	
Total cholesterol (mg/dL)	177.76 + 28.98	173.22 + 36.78	0.579 ^a
LDL-c (mg/dL)	121.40 + 23.81	113.87 + 28.42	0.240 ^a
Triglycerides (mg/dL)	137.12 + 53.19	99.67 + 59.52	<0.001 ^{b*}
HDL-c (mg/dL)	41.64 + 7.43	46.65 + 9.65	0.026 ^{b*}
IL-18 (ng/dL)	6.33 + 2.68	7.83 + 6.80	0.145 ^b
TNF- α (ng/dL)	127.38 + 90.73	104.30 + 55.43	0.044 ^{b*}
hsCRP (ng/dL)	5,570.92 + 2,582.29	4,301.38 + 2,573.98	0.012 ^{b*}
CIMT (mm)	0.60 + 0.16	0.54 + 0.12	0.123 ^b

^aIndependent T test; ^bMann Whitney-U test; ^cFisher's Exact Test, *significantly different if $p < 0.05$; *Abbreviation:* BMI: Body Mass Index; FBG: Fasting Blood Glucose; LDL: Low Density Lipid; HDL: High Density Lipid; TNF- α : Tumor Necrosis Factor- α ; IL-18: Interleukin-18; hsCRP: High Sensitivity C-Reactive Protein; CIMT: Carotid Intima Media Thickness.

profiles, obese subjects had significantly higher LDL-c levels compared to both overweight and normal subjects, as well as higher triglyceride levels. Conversely, obese individuals had lower HDL cholesterol levels compared to those who were overweight or had a normal BMI. TNF- α levels were significantly lower in the normal weight group compared to both the overweight and obese groups. On the other hand, IL-8 levels were elevated in the overweight group compared to both the obese and normal weight groups. Additionally, hsCRP levels were also higher in obese adolescents. Carotid intima-media thickness (CIMT) was greater in the

obese group than in both the normal weight (0.61 ± 0.16 vs. 0.49 ± 0.06 mm, $P=0.003$) and overweight groups (0.61 ± 0.16 vs. 0.52 ± 0.11 mm, $P=0.002$).

Table 3 illustrates the correlation analysis between HOMA-IR, as a predictor of IR, with anthropometric, pro-inflammatory markers, and CIMT.

Discussion

Recently, there has been a notable global increase in the prevalence of IR among children and

Table 2. Subject's characteristics based on nutritional status

	Mean Mean + SD			P value
Variables	Normal (n=14)	Overweight (n=40)	Severe obesity (n=40)	
Gender (n. and %)				
Boy	9 (64.29)	19 (47.50)	18 (45)	0.449 ^c
Girl	5 (35.71)	21 (52.50)	22 (55)	
IR (n. and %)				
Yes	1 (7.14)	7 (17.50)	17 (42.50)	0.008 ^c
No	13 (92.86)	33 (82.50)	23 (57.50)	
Age (years/months)	16.06 + 1.02	14.19 + 0.92	15.90 + 1.48	<0.001 ^{a*}
Anthropometry				
Weight (Kg)	58.57 + 8.26	75.66 + 9.36	101.38 + 11.63	<0.001 ^{a*}
Stading height (cm)	160.73 + 7.62	157.89 + 7.63	164.43 + 7.55	0.001 ^{b*}
BMI (Kg/m ²)	22.85 + 3.27	30.38 + 1.98	37.95 + 4.08	<0.001 ^{a*}
BMI-for-age (Z- score)	0.51 + 1.09	2.57 + 0.23	3.37 + 0.32	<0.001 ^{b*}
Waist circumference (cm)	70.46 + 14.05	96.39 + 7.84	110.21 + 10.90	<0.001 ^{b*}
Hip circumference (cm)	87.31 + 5.85	102.39 + 5.94	117.85 + 8.49	<0.001 ^{a*}
Laboratory findings				
FBG (mg/dL)	80.79 + 7.30	80.58 + 7.75	83.70 + 8.70	0.198 ^a
Insulin (mU/ml)	12.51 + 5.81	18.89 + 16.32	26.66 + 20.13	0.018 ^{b*}
HOMA-IR index	2.48 + 1.17	3.94 + 4.09	5.64 + 4.79	0.033 ^{b*}
Total cholesterol (mg/dL)	169.98 + 31.25	170.43 + 45.57	180.28 + 33.98	0.377 ^a
LDL-c (mg/dL)	102.57 + 26.15	115.93 + 26.54	120.48 + 27.67	0.001 ^{a*}
HDL-c (mg/dL)	56.64 + 12.54	45.85 + 7.99	41.53 + 6.76	<0.001 ^{b*}
TG (mg/dL)	72.29 + 29.37	113.75 + 52.81	118.58 + 70.00	0.037 ^{b*}
TNF-α (ng/dL)	81.16 + 36.51	149.45 + 42.05	154.49 + 26.20	<0.001 ^{a*}
hsCRP (ng/dL)	1,530 + 348.63	2,314 + 380,49	5,422+ 2,414	<0.001 ^{b*}
IL-18 (ng/dL)	3.74 + 1.65	7.80 + 0.64	6.38 + 26.15	<0.001 ^{b*}
CIMT (mm)	0.49 + 0.06	0.52 + 0.11	5.64 + 4.79	0.001 ^{b*}

^aOne way Anova; ^bKruskal Wallis, ; ^cPearson Chi-Square, *P-values in bold represent significant results. *Abbreviation:* BMI: Body Mass Index; FBG: Fasting Blood Glucose; LDL: Low Density Lipid; HDL: High Density Lipid; TNF- α : Tumor Necrosis Factor- α ; IL-18: Interleukin-18; hsCRP: High Sensitivity C-Reactive Protein; CIMT: Carotid Intima Media Thickness.

adolescents (23). Our study has documented that IR (> 5.22 for boys and > 3.82 for girls) was present in 26.60% (25 out of 94) of adolescents with obesity. This finding is consistent with a study that found a global prevalence of IR in children and adolescents, ranging from 3.1% to 44% (23). Meanwhile, a meta-analysis focusing on adolescents in Southeast Asia found the overall rate of IR was 44.3%. Within this region, Malaysia had the highest prevalence at 50.4%, while Indonesia followed closely with a rate of 44.2% (24). Our

results indicated a lower prevalence of IR compared to Southeast Asia. In contrast, a study examining Slovakian adolescents, aged 14-18 years, found a prevalence of 18.6%, which is lower than the rate observed in our study (2). Variations in IR prevalence among children and adolescents across different countries can be attributed to a range of factors, including genetic, racial, and environmental influences. Additionally, differences in data collection methods and the thresholds used to diagnose IR can contribute to these

Table 3. Correlation of HOMA-IR with anthropometric, pro-inflammatory markers, and MetS components

Variables	Association with IR ^a	
	<i>r</i>	<i>P</i>
Weight (Kg)	0.444	<0.001*
Stading height (cm)	0.252	0.014*
BMI (Kg/m ²)	0.411	<0.001*
BMI-for-age (Z- score)	0.439	<0.001*
Waist circumference (cm)	0.472	<0.001*
Hip circumference (cm)	0.478	<0.001*
Total cholesterol, (mg/dL)	0.073	0.484
LDL-c (mg/dL)	0.138	0.183
HDL-c (mg/dL)	-0.299	0.003*
TG (mg/dL)	0.476	<0.001*
TNF- α (ng/dL)	0.183	0.077
hsCRP (ng/dL)	0.362	<0.001*
IL-18 (ng/dL)	0.075	0.475
CIMT (mm)	0.242	0.019*

^aSpearman rho, *P -values in bold represent significant results; Abbreviation: BMI: Body Mass Index; FBG: Fasting Blood Glucose; LDL: Low Density Lipid; HDL: High Density Lipid; TNF- α : Tumor Necrosis Factor- α ; IL-18: Interleukin-18; hsCRP: High Sensitivity C-Reactive Protein; CIMT: Carotid Intima Media Thickness.

discrepancies. A study found that South Asian adolescents exhibited significantly higher levels of insulin and body fat compared to their White European counterparts, potentially increasing their risk of developing type 2 diabetes (25). Others also found that East Asian and South Asian adolescents exhibited higher levels of IR compared to non-Hispanic White and African American adolescents (26). Currently, there appears to be a lack of epidemiological research comparing the prevalence of IR among Southeast Asian adolescents with that of other racial or ethnic groups. As we noted above, girls were more likely to have IR than boys (5), which differs from our results that indicated no significant sex differences in the prevalence of IR. This discrepancy might be attributed to the age range of our study participants, with an average age of 15.20 ± 1.48 years. At this stage, our subject population was primarily in late puberty, a period when IR in girls may decrease, while boys may not yet have reached the age

where they start to show a higher prevalence of IR (6). Based on the nutritional status, IR was detected more frequently in obese subjects. We found that 42.56% (40 out of 94) of our study population were obese, and 42.5% (17 out of 40) of the obese subjects were found to have IR. These results showed a higher prevalence compared to a study by Das *et al*, which involved urban Indian school-children that reported 28.2% of the total subjects were overweight or obese, and roughly 21.8% of them had IR (26). Previous research has detailed the link between IR and obesity (4,23,27–31). There are multiple reasons behind the connection between IR and obesity. Primarily, excess weight and obesity can worsen insulin sensitivity, which contributes to the onset of IR (32). Obesity contributes to the onset of IR through various intricate mechanisms, including adipokines and cytokines, inflammatory responses, mitochondrial dysfunction, generation of reactive oxygen species (ROS), endoplasmic reticulum stress, imbalances in gut microbiota, and remodeling of the adipose extracellular matrix (ECM). From this perspective, IR acts as a crucial junction that connects weight gain and obesity (33). IR linked to obesity has been shown to adversely affect lipid metabolism. This condition can disrupt systemic lipid metabolism, leading to dyslipidemia and lipoprotein abnormalities (34). This abnormality may arise from a combination of factors, including heightened transport of free fatty acids to the liver due to increased visceral fat, IR, and a pro-inflammatory environment triggered by macrophage infiltration into adipose tissue (34–37). This phenomenon may clarify why lipoprotein abnormalities are evident across all stages of glucose intolerance, including prediabetes (38). Changes in lipid metabolism manifest as dyslipidemia, characterized by a typical proatherogenic lipid profile. This includes low plasma levels of high-density lipoproteins, elevated levels of small and dense low-density lipoproteins, and increased plasma triglycerides (39). These observations align with our findings, which indicate that adolescents with IR exhibit higher triglyceride levels and lower HDL-c levels. The persistence of elevated insulin levels starting in childhood can initiate the atherothrombotic changes, disrupt fibrinolytic balance, and damage endothelial function, which collectively

contribute to an increased future risk of cardiovascular events in the future (40,41). CIMT is an essential early indicator of atherosclerotic cardiovascular disease (CVD) (42,43) and represents the endothelial structure before the development of atheromatous plaque (43,44). In our study, there was a weak positive correlation between HOMA-IR. In addition, our study showed that CIMT had a stronger correlation with BMI and BMI-for-age Z-score. No significant difference in CIMT diameter between male and female subjects. CIMT as a subclinical atherosclerosis marker is of special interest for investigating the complex link between cardiovascular risk factors in childhood and cardiovascular disease in adults. This may indicate that in obese adolescents, an increase in CIMT diameter has already developed, as well as an increase in insulin, although still not yet been indicated as IR. Prior study explained that compared to metabolically healthy normal weight, children and adolescents with metabolically healthy obese and metabolically healthy overweight had increased CIMT (45). That study corroborates our hypothesis that CIMT is already elevated in obese and overweight adolescents, even if they were metabolically normal. Meanwhile, a study by Asghari et al. (46), which was conducted in 378 children aged 6 to 13 years old, reported that insulin metabolism markers were the independent predictors of CIMT, even only in overweight and obese boys, not in girls. In addition, the lack of a significant difference in CIMT diameter value between the IR and non-IR groups may be attributed to the IR cut-off values that we adapted. Obesity is characterized by elevated levels of pro-inflammatory cytokines (47). Numerous studies have connected the pro-inflammatory cytokines to IR, highlighting their presence in both adipose tissue and the bloodstream (48–50). This connection may be caused by the IR disrupts glucose metabolism, leading to persistent high blood sugar levels, oxidative stress, and inflammation, resulting in results to cellular damage (51,52). IL-18 levels were reported to effectively detect chronic inflammation linked to IR (53,54). However, our findings do not document a correlation between IL-18 levels and TNF- α versus IR in adolescents with obesity, supporting the study of Smart et. al (55) that the effects of IL-18 are only linked with

increasing age. Therefore, further research is necessary to assess the elevation of serum levels of IL-18 and TNF- α in children with IR, as well as to pinpoint the age at which these mildly inflammatory cytokines start to increase in adolescents with IR (56). Nonetheless, our findings indicate a significant correlation between high-sensitivity C-reactive protein (hsCRP) and IR in adolescents, which diverges from previous studies that found no such link (53,57,58). High-sensitivity C-reactive protein (hsCRP) has been identified as a significant marker of inflammation, particularly in individuals with obesity and IR. This indicator is commonly found in those with both conditions (59–62). Our study has several limitations. Firstly, the sample size was limited. Secondly, there were no non-obese subjects with normal BMI included as a comparison group about gender and pubertal status. Thirdly, further research are needed to explore more complete independent variables that have not been covered in this study (such as information on nutrition, physical activity, lifestyle, blood pressure, and IR about gender and pubertal stage). Lastly, we used as criteria for IR that no sex difference was noted in CIMT diameter ($0.57 + 0.16$ vs. $0.53 + 0.09$ mm, $P=0.534$). In conclusion, IR was positively associated with higher triglycerides (TG), TNF- α , hsCRP levels, and CIMT diameter, while it showed a negative relationship with HDL cholesterol (HDL-c). Obese children were more likely to have IR. No significant correlation or difference was observed between IR and serum levels of IL-18.

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Ethics Committee: This study was approved as ethically appropriate by the Research and Ethics Scientific (282/EC/KEPK/FKUA/2023) released on 2nd October, 2023, by the Faculty of Medicine, Airlangga University, Surabaya, Indonesia, and also registered in ClinicalTrial.gov (NCT06152068). Subjects were screened and measured with the approval of their parents and the head of school.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity

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Authors Contribution: N.A.W. (conceptualization, methodology, investigation, critical review, and writing original draft), M.A. (methodology, investigation and critical review), M.H.H. (investigation, data curation, writing original draft), E.A. (investigation, data curation, writing original draft, supervision project administration), F.M.S. (data curation, writing original draft, visualization and supervision).

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