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## Overlapping patterns and unique differences: a study into immunological variation within and between populations

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# Chapter 2

## **The relationship between malnutrition and T<sub>H</sub>2 immune markers: a study in school-aged children of different socio-economic backgrounds in Makassar, Indonesia**

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## ABSTRACT

**Background.** The burden of underweight remains a major problem in Indonesia and at the same time the prevalence of overweight is increasing. Malnutrition is a major determinant of health and has been linked to allergic disorders in children.

**Objective.** Here we examine the relationship between malnutrition and T<sub>H</sub>2 immune markers in school-aged children in Makassar, Indonesia.

**Methods.** A cross-sectional study was performed in five schools where socio-demographic characteristics were recorded. The child's standardized z-scores of body mass index (z-BMI) and age-standardized z-scores of height (z-HA) were assessed using WHO's child growth standards. Skin prick test (SPT) reactivity was determined to house dust mite allergens. Helminth infection status, (growth) hormones including insulin-like growth factor (IGF-1), and T<sub>H</sub>2 immune markers were measured.

**Results.** In total, 954 children were included of which 21.6% were underweight and 14.8% overweight. After controlling for confounders, overweight was positively associated with leptin (GMR 3.55, 95% CI: 2.99 - 4.23) and IGF-1 (GMR 1.45, 95% CI: 1.15 - 1.82) while for underweight a negative association was found (respectively GMR 0.57, 95% CI: 0.49 - 0.66 and GMR 0.78, 95% CI: 0.63 - 0.97). Underweight was associated with a lower eosinophil count (GMR 0.79, 95% CI: 0.64 - 0.97) but not with total IgE levels or SPT reactivity. Overweight was positively associated with SPT reactivity (Adjusted OR 2.68, 95% CI: 1.50-4.78) but no relationship was found with the other T<sub>H</sub>2 immune markers.

**Conclusion.** Malnutrition is prominent in school-aged children in Makassar, with overweight associating with increased SPT reactivity. Therefore, interventions should focus on undernutrition, but also on overweight to prevent the increase of allergic disorders in Indonesia.

## INTRODUCTION

Despite great efforts to reduce undernutrition, underweight remains a major problem in Indonesia and almost 10% of school-aged children is still underweight. Meanwhile, the nutritional transition in Indonesia has triggered a rapid increase in the prevalence of overweight and obesity, as illustrated by the increase in frequency of overweight in children aged 6-13 years from 5.1% in 1993 to 15.6% in 2014 (1). Both overweight and underweight are forms of malnutrition, a condition that can negatively affect health and cause a great health burden (2). In parallel to the nutritional transition, allergic disorders are also on the rise in Indonesia, leading to an increase in the prevalence of allergic rhinitis from 5% to 23% percent in Indonesia (3).

An association between overweight/obesity and the prevalence of allergic disorders has been documented in children (4-7). Children with an elevated body mass index (BMI) were shown to have an increased risk for wheeze and asthma and a positive association was seen between BMI and the prevalence of allergic rhinitis and atopic dermatitis (4-7).

Allergic disorders are mediated by T<sub>H</sub>2 response characterized by elevated IgE and eosinophils. The T<sub>H</sub>2 response is thought to have evolved to eliminate extracellular parasites like helminths, but can also be misdirected towards harmless allergens in atopic individuals (8). Malnutrition influences the functioning of the immune response, including total IgE levels, and might thereby affect existing allergic predispositions and the development allergic disorders (9,10).

An important factor that affects both nutritional status and allergic disorders is socioeconomic status (SES) (11,12). In Indonesian low SES urban and rural populations, infections with helminths are still prevalent (11,13). These infections can interfere with child growth and affect the nutritional status (14). Although helminths are known to skew immune responses towards the T<sub>H</sub>2 response, they are also able induce strong immunoregulatory responses and thereby suppress allergic disorders (15). As a result, helminth infections were shown to be associated with reduced skin reactivity (16). In the present study, we aimed to assess the degree of malnutrition in schoolchildren from different socioeconomic backgrounds in Makassar, Indonesia and explore the relationship between malnutrition and T<sub>H</sub>2 mediated responses.

## METHODS

### Study population and design

This cross sectional study comprised of children attending five primary schools in the urban centre of Makassar, the capital city of South Sulawesi, Indonesia. The data was obtained from three different studies with similar study design and research aim, namely exploring differences in allergy, helminths and  $T_H2$ -related parameters between high and low SES (See flow chart in **Figure S1**). These studies were conducted from September 2017 until October 2019 upon receipt of approval from the Health Research Ethical Committee, Faculty of Medicine, Hasanuddin University (No: 1504/H04.8.4.5.31/PP36-KOMETIK/2016, No: 613/H4.8.4.5.31/PP36-KOMETIK/2017 and No: 703 / H4.6.4.5.31 / PP36 / 2019). Schools were selected on the basis of the socioeconomic background of its pupils. The primary school SD Mangkura is a public school that is mostly attended by children of high SES background due to its great reputation and will henceforth be referred to as 'High SES A'. The private school SD Athirah has extensive facilities and is only attended by children from high SES families and will therefore be referred to as 'High SES B'. The three other primary schools are public schools with limited facilities, that are solely attended by children of low SES. Based on alphabetical order, those are referred as 'Low SES A' (SD Baraya), 'Low SES B' (SD Cambaya) and 'Low SES C' (SD Maccini Sombala). Within every school the grades were selected that could participate. This selection was based on the age of the children. Within these selected grades all children were invited to participate in the study. Parents were informed about the study and written consent was obtained for their child to participate in the study prior to sample collection. All children with parental/ guardian consent were included in the study. Children who had taken antihistamines or corticosteroids in the week before the start of the study were excluded.

### Questionnaire and measurements

Information regarding demographics and indicators of socioeconomic status were obtained using a questionnaire. Parental educational level was categorized as 'high' if a parent attended academy or university and 'low' if the parent was illiterate or only completed elementary school or high school. Body weight and height were measured using a Seca scale and stadiometer (Seca GmbH & Co KG, Hamburg, Germany). These were used to calculate the age-standardized z-scores of body mass index (z-BMI) and age-standardized z-scores of height (z-HA), according to WHO guidelines (17). A high z-BMI score indicates overweight or obesity and a low z-BMI score reflects wasting, thinness and underweight (17,18). For the purpose of this study, the categorization of BMI-for-age was simplified by classifying

all children with a z-score above 1 as 'overweight', all children with a z-score between 1 and -2 as 'normal weight' and all children with z-scores lower than -2 as 'underweight'. In this study, a z-HA score below -2 reflects a stunted growth and below -3 a severely stunted growth, according to the recommendations of the WHO (17).

### Skin prick testing

To determine skin reactivity to common aeroallergens, a skin prick test (SPT) was performed. SPT reactivity to house dust mite (HDM) was tested by using two extracts; *Dermatopagoides pteronyssinus* and *D. farinae* (ALK-Abello BV, Almere, the Netherlands). Saline was used as a negative control and histamine chloride (10 mg/mL) was the positive control. The SPT was performed on the volar side of the child's lower arm using skin prick lancets. Fifteen minutes after application, the wheal sizes were measured. Skin test reactivity was considered positive if the longest diameter plus the diameter perpendicular of wheal size divided by two was 3 mm or larger. Only subjects with skin reactivity positive to histamine were included in the analysis.

### Leptin, IGF-1 and total IgE levels and eosinophil count

Blood samples were collected from children's fingertips using Microvette® CB 300 tubes (Sarstedt Inc, Nümbrecht, Germany) or by venipuncture using BD vacutainer® blood collection tubes (Becton Dickinson and Company, New Jersey, US). Total IgE and leptin levels were measured by ELISA as previously described (19). The levels of IGF-1 were quantified using Human IGF-1 Duo Set (R&D System, Abingdon, UK), according to the manufacturer's guidelines. The results were expressed in International Units (IU/mL), ng/mL and pg/mL for total IgE, leptin and IGF-1, respectively. A Giemsa-stained peripheral thin blood smear was read in the Department of Clinical Pathology, Hasanuddin University, Makassar to assess differential white blood cell counts, resulting in a relative percentage of eosinophils.

### Parasitological examination

All the children were asked to fill the stool container (Sarstedt Inc, Nümbrecht, Germany), by using the enclosed plastic spatula without contamination with water or urine. Eggs of intestinal helminths such as *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm were quantified using Kato-Katz methods.

### Statistical analysis and conceptual framework

**Figure 1** shows the conceptual framework for this study. We hypothesised that socioeconomic status and helminth infection status may be important confounding factors for the relationship between nutritional status and  $T_H2$  immune markers. In addition, age and sex were considered as *a priori*

confounders. Descriptive statistics were used to examine the characteristics of the whole study population and stratified based on zBMI. To obtain approximately normally distributed data, leptin, IGF-1, total IgE and eosinophil count were log10-transformed. To examine the association between under- and overweight and continuous outcome variables linear regression models were fitted. The association between zBMI and SPT was examined using logistic regression models. Confounding by helminth infection and socioeconomic status were examined and the models were adjusted accordingly. Statistical testing was performed using F-tests for the linear regression models and likelihood ratio tests for the logistic regression models. All data were analysed using IBM Statistical Package for the Social Sciences Statistics version 24 (IBM-SPSS Inc., Chicago, IL, USA) and the visualization was performed using RStudio.

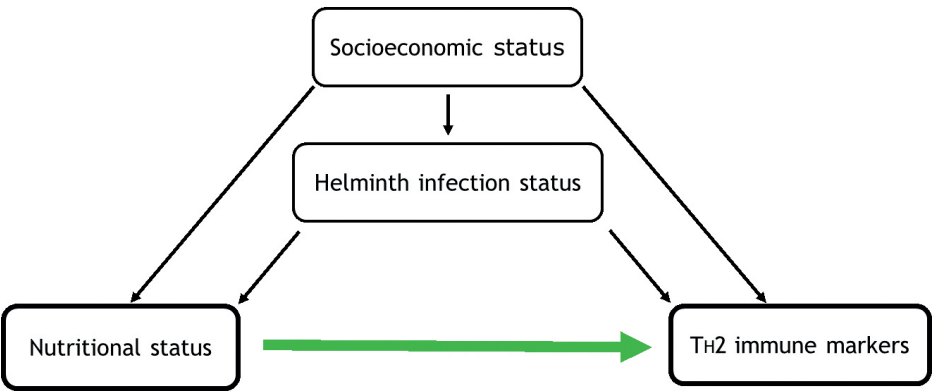


**Figure 1.** Conceptual framework of the study. Relationship between nutritional status and Th2 immune markers, confounded by an individual’s socioeconomic status (SES) and helminth infection status.

RESULTS

Characteristics of study participants

A total of 996 school-aged children were included from 5 different schools (Table 1). Of these, 260 children attended high SES schools (High SES A: n = 160, High SES B: n = 100) and 736 children attended low SES schools (Low SES A: n = 260, Low SES B: n = 165 and Low SES C= 311). The overall helminth infection prevalence was 25.2 and 12.5% of the children were SPT positive for HDM allergens.

**Table 1. Characteristics of children attending primary school in Makassar, Indonesia (N = 996)**

|                                                                     | Total population<br>N = 996 |
|---------------------------------------------------------------------|-----------------------------|
| Age (in years, mean, SD)                                            | 9.34 ± 1.51                 |
| Sex (female %, n/N)                                                 | 52.5 (521/ 993)             |
| School (low SES %, n/ N)                                            |                             |
| Low SES A                                                           | 26.1 (260/996)              |
| Low SES B                                                           | 31.2 (165/ 996)             |
| Low SES C                                                           | 16.6 (311/ 996)             |
| High SES A                                                          | 16.1 (160/996)              |
| High SES B                                                          | 10.0 (100/996)              |
| Helminth infection by microscope (%, n/N)                           |                             |
| Any helminth infection                                              | 25.2 (196/ 773)             |
| Only <i>A. lumbricoides</i>                                         | 10.6 (82/773)               |
| Only <i>T. trichiura</i>                                            | 7.2 (56/ 773)               |
| Hookworm                                                            | 1.0 (0/ 773)                |
| Both <i>A. lumbricoides</i> and <i>T. trichiura</i>                 | 7.6 (59/773)                |
| Education father (high %, n/N)                                      | 23.6 (172/730)              |
| Maternal education (high %, n/N)                                    | 20.2 (150/742)              |
| Floor material (ceramics %, n /N)                                   | 50.8 (397/782)              |
| Wall material (brick or concrete %, n/N)                            | 57.0 (441/774)              |
| Toilet (private inside %, n/N)                                      | 90.1 (702/779)              |
| Leptin (ng/m) [geometric mean (95% CI)]                             | 2.77 (2.58; 2.97)           |
| IGF-1 (pg/ml) [geometric mean (95% CI)]                             | 0.67 (0.61; 0.74)           |
| Eosinophil count (% of total) [geometric mean (95% CI)]             | 3.09 (3.78; 4.44)           |
| Total IgE (IU/ml) [geometric mean (95% CI)]                         | 324.0 (297.0; 353.5)        |
| Atopy by skin prick reactivity (%, n/N)                             |                             |
| Any skin prick reactivity                                           | 12.5 (112/895)              |
| Only <i>D. pteronyssinus</i>                                        | 2.2 (20/895)                |
| Only <i>D. farinae</i>                                              | 3.8 (34/ 895)               |
| SPT reactive for both <i>D. pteronyssinus</i> and <i>D. farinae</i> | 6.3 (56/895)                |

The number of positives (n) of the total number (N). SD: standard deviation. SES: socio-economic status. CI: confidence interval

### Distribution of z-BMI and z-HA

Information regarding the z-BMI was available for 954 children. Although the majority of the children had a normal weight (63.6%), a wide range of z-BMI scores was observed (-7.88 to +4.50). When z-BMI is plotted based on school, a distinct distribution is shown. The pattern of z-BMI in children from high SES schools was more towards overweight while the distribution towards underweight was shown in children of low SES schools. With regards to low SES schools, wider pattern towards underweight is observed in children of Low SES A compared to the other 2 low SES schools which presented quite a similar pattern (**Figure 2A**).

The distribution of z-HA ranged from -5.02 to +1.81. While the majority of children were of an age-appropriate length (70.0%), 23.0% of the children were stunted and 7.0% were severely stunted. When type of school is considered, we observed most children of high SES schools had an age-appropriate length (88.8% high SES A and 95.5% high SES B). Contrarily, the z-HA pattern in low SES schools was more towards (severely) stunted with a proportion of 37.1%, 28.4% and 45.2% of the children attending low SES school A, B and C respectively (**Figure 2B**).

Next, the 954 children were categorized based on their z-BMI, creating three categories; underweight, normal weight and overweight. Children were slightly older in the overweight group, whereas the sex distribution was similar (**Table 2**). Almost all children with underweight were in low SES schools (93.2%) while more than half of the children with overweight were in high SES schools (61.7%). Fewer helminth infections were detected in children with overweight (12.5%) than in those with underweight (22.6%) or normal weight (28.8%). Children in the overweight group appeared to have more highly-educated parents and better housing conditions than children with normal or underweight.

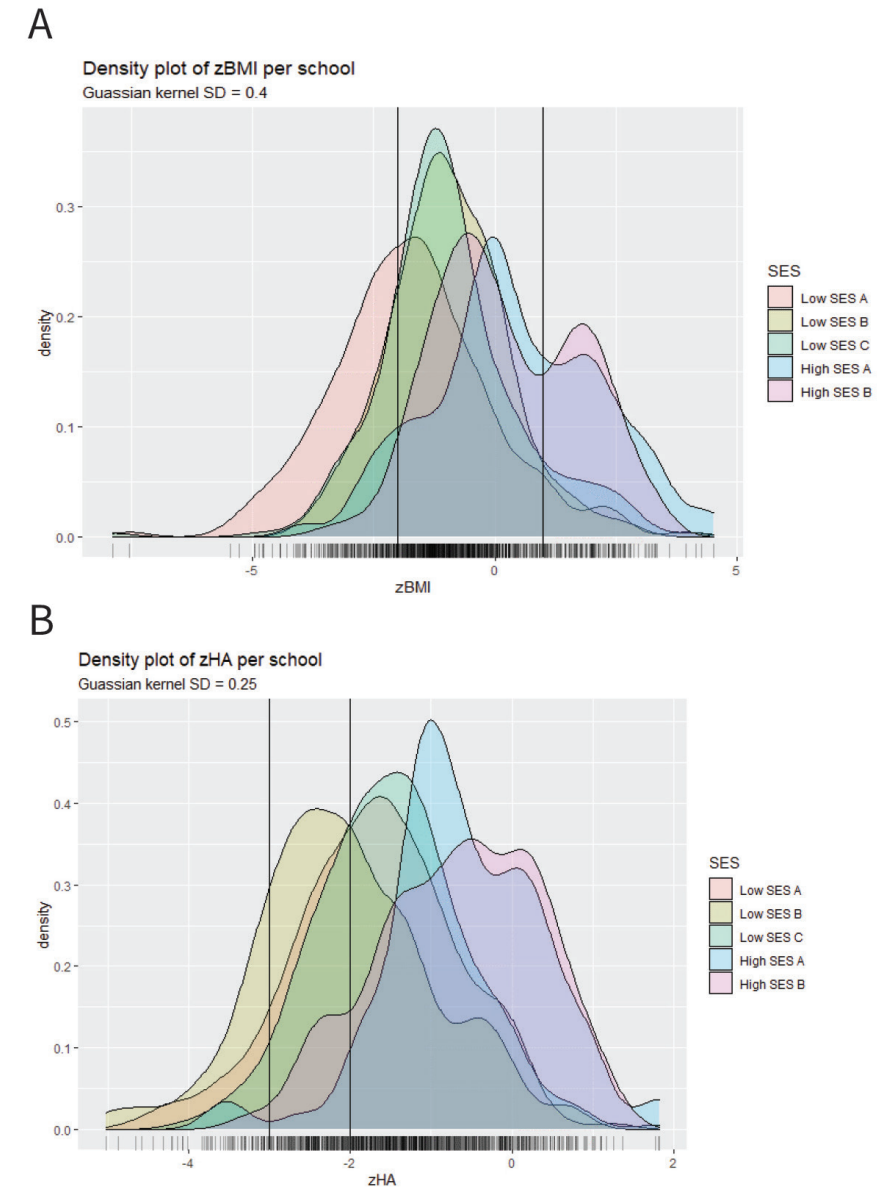


**Figure 2.** Distribution of zBMI (A) and zHA (B) depicted in a density plot per school. A. The leftmost vertical line is at a z-BMI score of -2, indicating cut-off between underweight and normal weight and the rightmost vertical line is at a score of +1, indicating the cut-off between normal weight and overweight. Gaussian Kernel SD = 0.4. B. The leftmost vertical line is at a z-HA score of -3, indicating the cut-off between severely stunted and stunted. The rightmost vertical line is at a z-score of -2, indicating the cut-off between stunted and normal height. Gaussian Kernel SD = 0.25. SD: standard deviation. z-BMI: z score of Body Mass Index-for-age. z-HA: z score of Height-for-age

**Table 2. Sociodemographic characteristics by z-BMI category of children attending primary school in Makassar, Indonesia (N = 954)**

|                                          | Underweight<br>N = 206 | Normal weight<br>N = 607 | Overweight<br>N = 141 |
|------------------------------------------|------------------------|--------------------------|-----------------------|
| Age (in years, mean, SD)                 | 9.19 (1.60)            | 9.34 (1.51)              | 9.68 (1.36)           |
| Sex (female %, n/N)                      | 46.6 (96/206)          | 55.7 (338/269)           | 49.6 (70/141)         |
| School (High SES %, n/N)                 |                        |                          |                       |
| Low SES A                                | 51.0 (105/206)         | 19.3 (117/607)           | 9.2 (13/141)          |
| Low SES B                                | 14.6 (30/206)          | 20.8 (126/ 607)          | 6.4 (9/141)           |
| Low SES C                                | 27.7 (57/206)          | 35.7 (217/ 607)          | 22.7 (32/141)         |
| High SES A                               | 3.9 (8/206)            | 7.7 (47/ 607)            | 23.4 (33/141)         |
| High SES B                               | 2.9 (6/206)            | 16.5 (100/607)           | 38.3 (54/141)         |
| Helminths (infected %, n/N)              | 22.6 (36/159)          | 28.8 (144/500)           | 12.5 (13/104)         |
| Education father (high %, n/N)           | 13.0 (21/162)          | 22.8 (104/ 457)          | 42.0 (42/100)         |
| Maternal education (high %, n/N)         | 11.0 (18/164)          | 18.6 (87/ 467)           | 40.4 (40/99)          |
| Floor material (ceramics %, n/N)         | 44.7 (76/170)          | 47.5 (231/486)           | 72.2 (78/108)         |
| Wall material (brick or concrete %, n/N) | 51.8 (87/168)          | 55.5 (267/481)           | 70.1 (75/107)         |
| Toilet (private inside %, n/N)           | 87.8 (151/172)         | 89.6 (432/ 482)          | 97.2 (105/108)        |

Underweight is a z-BMI score < -2, normal weight is a z-BMI > 1 and > -2 and overweight/obesity is a z-BMI > 1. The number of positives (n) of the total number within that z-BMI category (N). SD : standard deviation. z-BMI: z score of Body Mass Index-for-age.

**Association between z-BMI and IGF-1 and leptin**

A strong association was observed between leptin and IGF-1 levels with the z-BMI (**Table 3**). Leptin levels showed an increasing gradient across the z-BMI with the highest detected levels in the overweight group (GM 11.49, 95% CI: 10.27 - 12.84). After adjustment for confounders, overweight remained positively associated with leptin (adjusted GMR 3.55, 95% CI: 2.99 - 4.23), while for underweight a negative association was found (adjusted GMR 0.57, 95% CI: 0.49 – 0.66).

A similar pattern was seen for IGF-1 levels, with lowest IGF-1 levels in the underweight (GM 0.38, 95% CI: 0.31-0.46) and highest in the overweight group (GM 1.42, 95% CI: 1.10 – 1.48). Upon considering confounders, overweight was still positively associated (adjusted GMR 1.45, 95% CI: 1.15 - 1.82) and underweight negatively associated with IGF-1 (adjusted GMR 0.78, 95% CI: 0.63 – 0.97).

| Table 3. Association between underweight or overweight and the level of (growth) hormones and T <sub>H</sub> 2 immune markers |                  |                         |                               |                                            |         |
|-------------------------------------------------------------------------------------------------------------------------------|------------------|-------------------------|-------------------------------|--------------------------------------------|---------|
| (Growth) hormones                                                                                                             |                  | Crude <sup>1</sup>      |                               | Adjusted for SES and helminth <sup>2</sup> |         |
|                                                                                                                               | n/N <sup>a</sup> | Geometric mean (95% CI) | Geometric mean ratio (95% CI) | Overall p-value                            | p-value |
| <b>Leptin</b>                                                                                                                 |                  |                         |                               |                                            |         |
| Underweight                                                                                                                   | 180/877          | 1.29 (1.14; 1.45)       | 0.54 (0.47 - 0.61)            | <0.001                                     | <0.001  |
| Normal weight                                                                                                                 | 571/877          | 2.56 (2.37; 2.76)       | Reference                     |                                            |         |
| Overweight                                                                                                                    | 126/877          | 11.49 (10.27; 12.84)    | 4.38 (3.76 - 5.11)            |                                            |         |
| <b>IGF-1<sup>3</sup></b>                                                                                                      |                  |                         |                               |                                            |         |
| Underweight                                                                                                                   | 91/620           | 0.38 (0.31; 0.46)       | 0.57 (0.45 - 0.73)            | <0.001                                     | <0.001  |
| Normal weight                                                                                                                 | 437/620          | 0.65 (0.58; 0.72)       | Reference                     |                                            |         |
| Overweight                                                                                                                    | 92/ 620          | 1.42 (1.10; 1.84)       | 1.91 (1.50 - 2.44)            |                                            |         |
| <b>T<sub>H</sub>2 immune markers</b>                                                                                          |                  |                         |                               |                                            |         |
|                                                                                                                               | n/N <sup>a</sup> | Geometric mean (95% CI) | Geometric mean ratio (95% CI) | p-value                                    | p-value |
| <b>Eosinophil count<sup>4</sup></b>                                                                                           |                  |                         |                               |                                            |         |
| Underweight                                                                                                                   | 143/532          | 2.20 (1.73-2.76)        | 0.71 (0.59; 0.86)             | <0.001                                     | 0.04    |
| Normal weight                                                                                                                 | 327/ 532         | 3.41 (2.97-3.91)        | Reference                     |                                            |         |
| Overweight                                                                                                                    | 62/ 532          | 4.13 (3.06-5.58)        | 1.16 (0.89; 1.50)             |                                            |         |
| <b>Total IgE</b>                                                                                                              |                  |                         |                               |                                            |         |
| Underweight                                                                                                                   | 180/878          | 383.4 (314.6; 467.1)    | 1.12 (0.90; 1.40)             | 0.02                                       | 0.86    |
| Normal weight                                                                                                                 | 572/878          | 334.0 (299.3;372.6)     | Reference                     |                                            |         |
| Overweight                                                                                                                    | 126/ 878         | 237.2 (189.5;296.9)     | 0.73 (0.56; 0.94)             |                                            |         |

Table 3. Association between underweight or overweight and the level of (growth) hormones and T<sub>H</sub>2 immune markers - continued.

| (Growth) hormones          |                      | Crude <sup>1</sup>     |                    | Adjusted for SES and helminth <sup>2</sup> |                    |       |
|----------------------------|----------------------|------------------------|--------------------|--------------------------------------------|--------------------|-------|
| n/N <sup>a</sup>           | % (n/N) <sup>b</sup> | Odds Ratio<br>(95% CI) | p-value            | Odds Ratio<br>(95% CI)                     | p-value            |       |
| Skin prick test (positive) |                      |                        |                    |                                            |                    |       |
| Underweight                | 180/ 884             | 10.0 (18/ 180)         | 0.94 (0.54-1.65)   | <0.001                                     | 1.57 (0.81 – 3.07) | 0.004 |
| Normal weight              | 575/884              | 10.1 (58/575)          | Reference          |                                            | Reference          |       |
| Overweight                 | 129/884              | 27.1 (35/129)          | 3.33 (2.06 – 5.38) |                                            | 2.68 (1.50 - 4.78) |       |

1. Adjusted for sex and age (in years). 2. Adjusted for sex, age (in years) and SES as categorical variable and helminth infection status. 3. Data only available for Low SES B, C and High SES A. 4. Data only available for Low SES A, C and High SES B. Leptin is in ng/mL IGF-1 in pg/mL, eosinophil count in percentage of the white blood cell count and total IgE levels in IU/mL. <sup>a</sup>The number of children in each z-BMI category (n) of the total children measured (N). <sup>b</sup>The number of children with SPT positivity (n) of the number of children within each z-BMI category. CI: confidence interval

Association between z-BMI and T<sub>H</sub>2 immune markers

Children with underweight exhibited a lower eosinophil count (GM 2.20, 95% CI: 1.73-2.76) than normal weight and overweight children (respectively GM 3.41, 95% CI: 2.79 - 3.91 and GM 4.13, 95% CI: 3.06 - 5.58). Even in the adjusted model, there was still a significant inverse association between underweight and eosinophil count (adjusted GMR 0.79, 95% CI: 0.64 - 0.97, overall p-value = 0.04).

Lowest total IgE levels were seen in overweight children (GM 237.2, 95% CI: 189.5 - 296.9), which were lower than in the normal weight group and overweight group (respectively GM 334.0, 95% CI: 299.3 - 372.6 and GM 383.4, 95% CI: 314.6 - 467.1). After controlling for confounding, total IgE levels were not associated with overweight (adjusted GMR 0.98, 95% CI: 0.73 - 1.32) or underweight (adjusted GMR 0.94, 95% CI: 0.73 - 1.20).

The proportion SPT reactivity was equal in the underweight and normal weight group (respectively 10.0% and 10.1%), but higher in the overweight group (27.1%). After adjustment for SES and helminth infection status, evidence was found that overweight children had higher odds of SPT reactivity compared to normal weight children (adjusted OR 2.68, 95% CI: 1.50 - 4.78), whereas underweight children did not (adjusted OR 1.57, 95% CI: 0.81 - 3.07).

DISCUSSION

This study aimed to assess the degree of malnutrition and to delineate the effect of z-BMI on T<sub>H</sub>2 immune markers in Indonesian children attending high and low SES schools in an urban area. The results show that both underweight and overweight were highly prevalent in these children, with the majority of underweight children attending low SES schools and the majority of overweight children high SES schools. Underweight and overweight were respectively associated with lower and higher leptin and IGF-1 levels. In addition, underweight was associated with lower eosinophil count but no association was found with total IgE levels or SPT reactivity. Overweight was positively associated with SPT reactivity, but no relationship was found with other T<sub>H</sub>2 immune markers.

The high proportion of children with either underweight or overweight in our study illustrates the double burden of malnutrition (DBM) on the population level that Indonesia is currently facing. The double burden of over- and undernutrition on a population level can be found in almost all low- and middle income countries, including many in South-East Asia (19).

Despite the rapid increase in the prevalence of overweight and obesity, especially in urban populations, reducing underweight is still prioritized by many countries, including Indonesia. Traditionally, Indonesian health policies solely focused on undernutrition, but to tackle the DBM in Indonesia, interventions are needed that address both underweight and overweight as a nutritional problem (20).

The differences between the distribution of the z-BMI and z-HA in this study highlight the dissimilarity between malnutrition and stunted growth. In the current study, the lowest z-scores for both z-BMI and the z-HA were seen in low SES schools and highest in the high SES schools. However, most children with underweight were observed in Low SES A, whereas the stuntedness was most prevalent in Low SES B. The differences between the malnutrition and stuntedness in children has also been reported before (17,21,22). As described by the WHO, a low height-for-age indicates impaired growth (stunting), likely resulting from long-term nutritional deprivation that can already start *in utero*, whereas a low weight-for-age or BMI-for-age implies underweight or wasting, which often due to a recent and severe process of weight loss due to acute undernutrition or severe pathology (17,22). A recent study by Scheffler *et al.* in Indonesian school-aged children supports the findings of the current study, by showing that malnutrition and growth indicators did not correlate (22). Although, stunting and malnutrition are often used as synonyms, the results of our study suggest that these might be different concepts.

In the current study, a strong association between z-BMI and (growth) hormones was found, which is in line with previous literature (23–25). Leptin is secreted in response to increasing levels of adiposity and elevated leptin levels are seen in overweight and obese children compared to normal weight children (25). The levels of IGF-1 are also related to an individual's nutritional status, since the levels are regulated within the GH/IGF-1 axis that is highly sensitive to alternations in the nutritional state. Caloric restriction for six days already resulted in significantly lower IGF-1 levels in children and a positive association was found between a child's weight and overall IGF-1 levels (23,24). Therefore, our results are in line with the notion that these (growth) hormones might serve as markers for nutritional status in children.

A low z-BMI was associated with a reduced eosinophil count, but underweight did not appear to affect the odds of SPT reactivity or the total IgE levels. These results are not in line with the study of Mutius *et al.*, which found no association between eosinophil count and BMI (6), probably due to the limited number of children with underweight in this study. The absence of

an association between underweight and other SPT reactivity in the current study, might be related to the severity of underweight. An earlier study by Tanaka *et al.* showed that the association of asthma prevalence and BMI follows a U-shaped curve, indicating increased risk of asthma in children with either severe overweight or severe underweight (26). Only few children with very low z-BMI values were seen in our study population. Therefore, the results of this study suggest that moderate/light underweight has a limited effect on allergic sensitization.

Overweight in school-aged children was positively associated with SPT reactivity, but no association was found with other T<sub>H</sub>2 immune marker such as total IgE and eosinophilia. Visness *et al.* showed that obese and overweight children had elevated total and allergen-specific IgE levels compared to normal weight children, but these associations were only observed in response to food allergens and were solely found in (severely) obese children (27). In addition, the results of Cibella *et al.* show that overweight and obesity are associated with asthma and allergic sensitization, but that eosinophilic airway inflammation is not involved (7). Finally, the T<sub>H</sub>2 immune markers measured in this study, eosinophil count and total IgE levels, are general markers of this response, meaning that involvement of specific elements of the T<sub>H</sub>2 response cannot be ruled out.

Possible limitations of these studies include the inability to assign causality to the associations and the introduction of bias by missing data due to the self-administration of questionnaires and limited quantity of samples. Another concern is that the SES was not measured objectively by using standard tools, however this study includes children with diverse socioeconomic backgrounds within one urban centre making these results generalisable to the urban school-aged children in Indonesia at large. Finally, we were not able to assess the nutritional status, since only anthropometric measurements were made. Future studies into the correlation between nutritional status and T<sub>H</sub>2 immune markers, should therefore make use of biochemical/biophysical, clinical and dietary methods in addition to anthropometry measurements to properly assess the nutritional status and study its effect on T<sub>H</sub>2 immune markers.

To conclude, in this study we found that both underweight and overweight are prominent in school-aged children in Makassar, Indonesia and overweight is positively associated with allergic sensitization. These findings highlight the need of interventions to tackle not only underweight, but also the problem of overweight to prevent the increase of allergic disorders in Indonesia.

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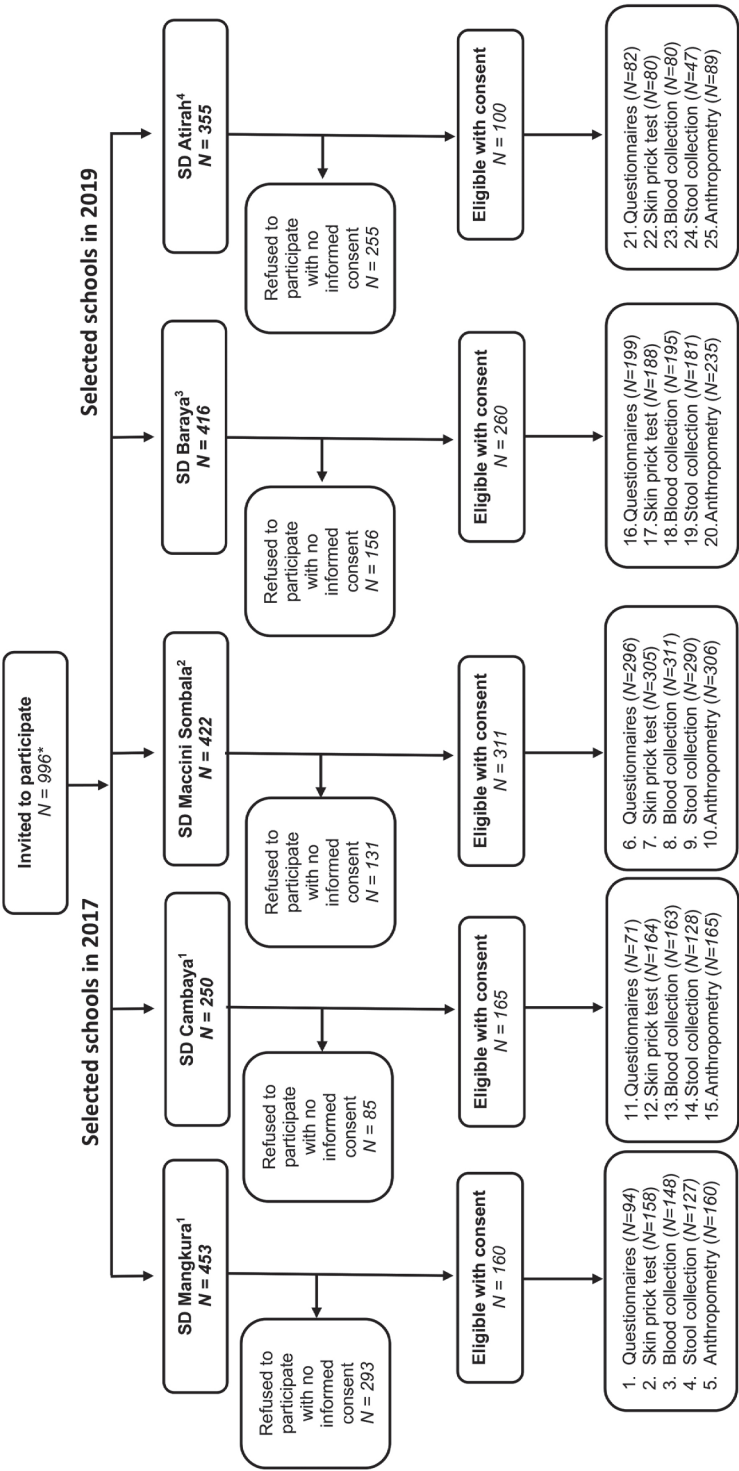
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Supplementary material

Figure S1. Flow chart of the study. The flow chart showing participation at each school and the measurements collected.



¹ children from third to fifth grades of elementary school ² children from first to sixth grades of elementary school ³ Children from first to fourth grades of elementary school. N, number. SES, socioeconomic status