Mal J Nutr 24(2): 153-161, 2018

Insulin resistance, inflammation and metabolic syndrome in normal weight and overweight/obese primary school children in Kuala Lumpur

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ABSTRACT

Introduction: Studies on metabolic syndrome (MetS) of children are important in view of rising prevalence of childhood obesity worldwide. This study compares the risks of insulin resistance, inflammation and metabolic syndrome between overweight/obese (OW/OB) and normal weight (NW) children in Kuala Lumpur. **Methods:** A cross-sectional study was conducted in 12 primary schools selected using multi-stage stratified random sampling. Height and weight were taken of a total of 1971 children aged 10-11 years. Based on BMI-for-age, 235 OW/OB children matched for age, sex and ethnicity with 226 NW children were selected for the study. Overnight fasting blood samples were collected to determine insulin, high-sensitivity C-reactive protein (hsCRP), glucose and lipid profiles. Logistic regression analysis was conducted to estimate associations between weight status and metabolic risk factors. **Results:** Prevalence of MetS among OW/OB children was 3.8% compared to 0% in the NW. Prevalence of insulin resistance among OW/OB was 45.5% compared to 18.6% among NW children. High risk of inflammation was found in 28.1% of the OW/OB children compared to 12.4% in the NW. The odds ratio of having insulin resistance, inflammation and metabolic risk factors among OW/OB were 3.66 (95% CI: 2.40-5.59), 2.76 (95% CI: 1.69-4.50), 4.93 (95% CI: 3.42-7.10), respectively compared to the NW. **Conclusion:** The OW/OB children in this study showed higher risks of developing insulin resistance, inflammation and MetS compared to the NW counterparts. Further studies are suggested to better understand the relationships between insulin resistance, inflammation and MetS in children.

Keywords: Children, insulin resistance, hsCRP, metabolic syndrome, obesity

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INTRODUCTION

Childhood obesity is a serious public health condition due to its alarming increase in both developed and developing countries. In 2011, the South-East Asia Nutrition Survey (SEANUTS) revealed that the prevalence of overweight and obesity among children aged 6 months to 12 years was 21.6% (Poh *et al.*, 2013). The National Health and Morbidity Survey (NHMS) 2015 reported that the prevalence of obesity among children aged 10-14 years in Malaysia was 14.4% (IPH, 2015). Similarly, the MyBreakfast study revealed that the prevalence of overweight and obesity among Malaysian children age 6-12 years was 14.7% (Mohd Nasir *et al.*, 2017).

Metabolic syndrome (MetS) is defined as a clustering of risk factors of dyslipidaemia, hyperglycaemia and high blood pressure, which directly increases the chances of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) (Agirbasli, Tanrikulu & Berenson, 2016). MetS in children is receiving attention due to the rise in the prevalence of childhood obesity worldwide. In Malaysia, the prevalence of metabolic syndrome among overweight and obese children was reported to range from 1.3% to 5.3% based on the International Diabetes Federation's paediatric definition (IDF) (Quah, Poh & Ismail, 2010; Wee *et al.*, 2011). Another metabolic complication observed among the overweight/obese children is insulin resistance (van der Aa *et al.*, 2015). Insulin resistance is defined as a decrease in the ability of insulin to stimulate glucose uptake by muscles and adipose tissues and to suppress hepatic glucose production (Matthaei *et al.*, 2000). Obesity is known to be a state of low-grade inflammation due to the rise in inflammatory factors (DeBoer, 2013).

Despite the increasing prevalence of childhood obesity in Malaysia, studies pertaining to the state of insulin resistance and levels of high-sensitivity C-reactive protein in Malaysian children are limited. As early detection of the risk of cardiovascular disease is important for early prevention strategies, this study aimed to determine the risk of insulin resistance, inflammation and MetS in overweight/obese (OW/OB) children compared to normal weight (NW) children in Kuala Lumpur.

MATERIALS AND METHODS

Study setting and subjects

A comparative cross-sectional study was conducted among primary school children aged 10-11 years. A multistage stratified random sampling was used whereby stratification was conducted according to the school type, namely National Type, National Type Cina and National Type Tamil primary schools in the Federal Territory of Kuala Lumpur. Out of the three education zones in the Kuala Lumpur, namely Bangsa-Pudu, Keramat and Sentul, Bangsar-Pudu Zone was randomly selected for the study. A total of 85 schools fulfilled the inclusion criteria of co-educational in composition.

The sample size for the study was calculated using the formula by Aday & Cornelius (2014). With the power of the study set at 80% and confidence level set at 95%, the estimated sample size was a minimum of 157 respondents for each group of NW and OW/OB children. The sample size was increased by approximately 30% to compensate for missing data. Hence a total of 205 children for each of the NW and OW/OB group.

A total of 1971 students from all Year 4 and Year 5 classes in the selected schools were screened for body mass index (BMI) based on height and weight measurements. The WHO growth reference 2007 (BMI-for-age) (de Onis *et al.*, 2012) was used to classify the nutritional status of the children. There were 10% thinness (*n*=197); 57.5% normal weight (*n*=1136); 16.5% overweight (*n*=326); and 15.8% obesity (*n*=312). All the 638 OW/OB children were invited to participate. An equal number of NW children matched for age, sex and ethnicity with the OW/OB children was randomly selected. However, only 285 OW/OB and 299 NW children agreed to participate in the blood draw (response rate 46.9% OW/OB, 44.7% NW). During data collection, a total of 64 OW/OB and 59 NW children were excluded as they were unwell, afraid to have their blood drawn, did not fast for 10 hours or were absent. The final number of respondents were 235 OW/OB and 226 NW children, matched for age, sex and ethnicity.

The research protocol of this study was approved by the Ethics Committee for Research Involving Human Subjects, Universiti Putra Malaysia (FPSK(FR14) P017) and the Ministry of Education Malaysia (KP(BPPDP)603/5/JLD.10(17)) and Department of Education Federal Territory of Kuala Lumpur (JPNWP.900-6/1/7 Jld. 10(92)). Signed informed consent was obtained from the respondents and their parents prior to data collection between July 2014 and October 2015.

Anthropometric measurements

(i) Height and weight

Body weight was measured using OMRON Body Fat Analyzer model HBF-356 (Omron Matsusaka Co. Ltd, Matsusaka, Japan) to the nearest 0.1 kg. Height was measured using a SECA Body Tape Measure SE206 (SECA, Germany) to the nearest 0.1 cm. Both height and weight were measured twice, and the mean values were used for the calculation of BMI. The AnthroPlus software version 10.4 (WHO, Geneva, Switzerland) was used to assess the BMI-for-age of the respondents, which classified the nutritional status of the children based on BMI-for-age *z*-scores, according to the WHO Growth Reference 2007 (de Onis *et al.*, 2012).

(ii) Waist circumference

Waist circumference (WC) was measured over the skin midway between the tenth rib and the iliac crest at the end of a normal expiration, using a SECA Ergonomic Circumference Measuring Tape SE203 (SECA, Germany) to the nearest 0.1 cm. The 90th percentile was used as the cut-off point to define abdominal obesity for use among Malaysian children and adolescents (Poh *et al.*, 2011). Waist-to-height ratio was calculated by dividing waist circumference (cm) measurements with height (cm).

Blood pressure measurements

Arterial blood pressure was measured automatically using an OMRON Digital Automatic Blood Pressure Monitor HEM-907 (OMRON, Japan) with a suitable cuff size for each participant after a 5-minute rest. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded three times after an interval of 30 seconds each and the mean was calculated.

Biochemical measurements

A total of 5 ml venous blood sample was collected after 10-hour fast using standard venepuncture by a trained phlebotomist with an attendant nurse or physician. Fasting lipid profiles: triglycerides, total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C); high-sensitivity C-reactive protein (hsCRP) and fasting blood glucose were assessed using Roche Cobas E311 (Germany) whereas fasting blood insulin was assessed using Roche Cobas E411 Immunoassay Analyzer (Germany). All biochemical analyses were outsourced to a certified laboratory for analysis.

Metabolic syndrome criteria

Metabolic syndrome was defined based on the International Diabetes Federation's paediatric definition (Zimmet *et al.*, 2007). According to the definition, metabolic syndrome is defined as waist circumference ≥90th percentile plus two or more of the following indices for all boys and girls: triglycerides: ≥150mg/dL (1.7mmol/L); blood pressure: systolic ≥130 mmHg or diastolic ≥85 mmHg; fasting blood glucose: ≥100mg/dL (5.6mmol/L); high-density lipoprotein cholesterol: ≤40mg/dL (1.03mmol/L). Insulin resistance was determined according to the following formula fasting blood insulin (mU/L) x fasting blood glucose (nmol/L)/ 22.5, (Khoury, Manlhiot & McCrindle, 2013). A cut-off value of >2.8 as an indication of insulin resistance (Wee *et al.*, 2015). As for inflammation profile, hsCRP levels were categorised into low (<1.0mg/L), moderate (1.0-3.0 mg/L) and high (>3.0 mg/L) risk of inflammation or acute infection (Pearson *et al.*, 2003).

Statistical analysis

Data were analysed using IBM SPSS Statistics (Version 22.0). Pearson Chi-square test was used to estimate associations between categorical variables. Independent samples *t*-test and Mann Whitney U-test (where assumptions for the *t*-test could not be met) was used to analyse the differences in a continuous variable between two groups. Binary logistic regression analysis was performed to estimate the association between weight status (normal weight vs overweight/obese) and metabolic risk parameters. Observed associations were expressed as odds ratios (OR) with 95% confidence intervals (CI). Statistical significance level was set at p<0.05.

RESULTS

Socio-demographic factors, anthropometric characteristics, biochemical profiles and blood pressure of the children are shown in Table 1. Overweight/obese (OW/OB) children had significantly higher anthropometric measurements [height, weight, BMI and WC] compared to their normal weight (NW) counterparts (p<0.001). In terms of biochemical profiles, OW/OB children had significantly higher biochemical profiles [TG, LDL-C, glucose, insulin, HOMA-IR, hsCRP, SBP, DBP] compared to the NW (p<0.05). A significantly higher proportion of OW/OB children (45.5%) had insulin resistance compared to NW children (18.6%) (χ^2=38.246; p<0.001). Similarly, a significantly higher proportion of OW/OB children had high (28.1%) level of hsCRP compared to the NW (12.4%) (χ^2=74.640; p<0.001).

More than half of the OW/OB children (60.4%) had waist circumference ≥90th percentile compared to only 3.1% of the NW (χ^2=173.090; p=0.001) (Table 2). High blood pressure was present in 5.1% of the OW/OB children compared to 0.9% of the NW (χ^2=6.972; p=0.008). Prevalence of MetS was 3.8% among the OW/OB children while none of the NW had MetS (χ^2=9.830; p=0.002).

Table 3 shows the binary logistic regression analysis assessing the relationship between body weight status with metabolic risk components such as fasting blood glucose, triglycerides, high-density lipoprotein, blood pressure, insulin resistance (HOMA-IR) and inflammation (hsCRP). OW/OB children had significantly higher odds of hypertension (OR: 6.01; 95% CI: 1.33-27.24; p=0.020), insulin resistance (OR: 3.66; 95% CI: 2.40-5.59; p<0.001), inflammation (OR: 2.76; 95% CI: 1.69-4.50; p<0.001) and metabolic risk factors (OR: 4.93; 95% CI: 3.42-7.10; p<0.001) compared to the NW.

Table 1. Mean values and distribution of sociodemographic factors, anthropometric measurements, biochemical indicators and blood pressure between OW/OB and NW children

Description	*Normal Weight (n=226)*	*Overweight/ Obese (n=235)*	*t/z/χ²*	*p-value*
Age (years)§			0.433	0.510
10	106 (46.9)	117 (49.8)		
11	120 (53.1)	118 (50.2)		
Sex§			2.292	0.130
Male	112 (49.6)	133 (56.6)		
Female	114 (50.4)	102 (43.4)		
Ethnicity§			0.188	0.910
Malay	69 (30.5)	76 (32.3)		
Chinese	77 (34.1)	79 (33.6)		
Indian	80 (35.4)	80 (34.1)		
Anthropometric measurements				
Height (cm)†	138.89 ± 7.91	143.61±7.88	-6.408	<0.001**
Weight (kg)‡	31.65 ± 5.36	48.55±10.25	-16.492	<0.001**
BMI (kg/m²)‡	16.32±1.54	23.32±3.19	-18.409	<0.001**
BMI-for-age z-score‡	-0.38±0.83	2.10±0.71	-18.571	<0.001**
Body fat percentage (BF %)†	19.71±6.16	30.41±3.59	-22.777	<0.001**
Waist circumference†	59.99±5.48	76.52±9.36	-15.885	<0.001**
Lipid				
Triglycerides (mmol/L)†	1.07 ± 0.35	1.22 ± 0.41	-4.251	<0.001**
HDL-cholesterol (mmol/L)†	1.60 ± 0.36	1.44 ± 0.37	4.718	<0.001**
LDL-cholesterol (mmol/L)†	2.66 ± 0.78	2.85 ± 0.79	-2.512	0.012*
Total cholesterol (mmol/L)†	4.47 ± 0.97	4.54 ± 0.93	-0.752	0.453
Total cholesterol/ HDL ratio†	2.86 ± 0.56	3.28 ± 0.83	-6.349	<0.001**
Insulin resistance				
Fasting blood glucose (mmol/L)†	5.01 ± 0.55	4.93 ± 0.52	1.657	0.098
Fasting blood Insulin (μmol/L)‡	8.27 ± 5.30	14.25 ± 9.74	-7.714	<0.001**
HOMA-IR‡	1.86 ± 1.24	3.15 ± 2.23	-7.153	<0.001**
No insulin resistance (<2.8)§	184 (81.4)	128 (54.5)	38.246	<0.001**
Insulin resistance (≥2.8)	42 (18.6)	107 (45.5)		
Inflammation				
HsCRP (mg/L)‡	1.04 ± 1.74	2.60 ± 3.15	-9.144	<0.001**
Low (<1.0 mg/L)§	170 (75.2)	83 (35.3)	74.640	<0.001**
Moderate (1.0-3.0 mg/L)	28 (12.4)	86 (36.6)		
High (>3.0 mg/L)	28 (12.4)	66 (28.1)		
Blood pressure				
Systolic blood pressure (mmHg)†	99.66 ± 8.94	109.43 ± 11.51	-10.181	0.001**
Diastolic blood pressure (mmHg)†	57.77 ± 7.67	65.23 ± 8.25	-10.053	0.001**

†Independent *t*-test; ‡Mann Whitney U-test; §Chi-square-test
*significant at $p<0.05$; **significant at $p<0.001$

Table 2. Comparison of metabolic syndrome indicators between OW/Ob and NW children

Biochemical indicators	*Normal Weight (n=226)*	*Overweight/ Obese (n=235)*	χ^2	*p-value*
Waist circumference ≥90th percentile†			173.090	<0.001**
No	219 (96.9)	93 (39.6)		
Yes	7 (3.1)	142 (60.4)		
Fasting blood glucose ≥5.6 mmol/L†			2.283	0.131
No	204 (90.3)	221 (94.0)		
Yes	22 (9.7)	14 (6.0)		
Triglycerides ≥1.7 mmol/L†			2.280	0.131
No	214 (94.7)	214 (91.1)		
Yes	12 (5.3)	21 (8.9)		
HDL-cholesterol ≤1.03 mmol/L†			3.161	0.075
No	216 (95.6)	215 (91.5)		
Yes	10 (4.4)	20 (8.5)		
Blood pressure (Systolic ≥130 mmHg or Diastolic ≥85 mmHg)†			6.972	0.008*
No	224 (99.1)	223 (94.9)		
Yes	2 (0.9)	12 (5.1)		
Metabolic syndrome†			9.830	0.002*
No	226 (100.0)	225 (96.2)		
Yes	0 (0.0)	10 (3.8)		

†Chi-square test
*significant at p<0.05; **significant at p<0.001

Table 3. Odds ratios for metabolic risk factors in overweight/obese children

Metabolic risk factors‡	*Odds ratio (95% CI)*	*p-value*
	Overweight/obese†	
Fasting blood glucose ≥5.6 mmol/L	0.59 (0.29-1.18)	0.134
Triglycerides ≥1.7mmol/L	1.75 (0.84-3.65)	0.135
HDL-cholesterol ≤1.03mmol/L	2.01 (0.92-4.40)	0.080
SBP/DBP (≥130/85mmHg)	6.01 (1.33-27.24)	0.020*
HOMA-IR (>2.8)	3.66 (2.40-5.59)	<0.001**
hsCRP (>3.0mg/L)	2.76 (1.69-4.50)	<0.001**
Metabolic risk factors	4.93 (3.42-7.10)	<0.001**

†Reference is normal weight children
‡Logistic Regression
*significant at p<0.05; **significant at p<0.001

DISCUSSION

Consistent with a previous study among Malaysian children (Wee *et al.*, 2011), significantly poorer anthropometric and biochemical parameters were observed among the OW/OB than in the NW except for fasting blood glucose. It was suggested that abnormal levels of blood glucose might be manifested only when other metabolic complications were present, as it takes years for blood glucose levels to be high in children (Misra *et al.*, 2007). In this study, despite the lack of difference observed in fasting blood glucose levels, the mean values and prevalence of insulin resistance measured through HOMA-IR were observed to be higher among the OW/OB compared to the NW.

The prevalence of insulin resistance of 45.5% among the OW/OB in this study is consistent with the findings among Japanese (46.8%) (Fujii & Sakakibara, 2012), Korean (47.1%) (Yi *et al.*, 2014) and Chinese children (44.3%) (Yin *et al.*, 2013). Insulin sensitivity in children has been attributed by the production of metabolites, hormones and adipocytokines, which in turn, is related to the pathogenesis of insulin resistance (Fujii & Sakakibara, 2012). As insulin resistance is more commonly observed among the OW/OB children, the measurement of HOMA-IR may be useful to assess undetected insulin resistance conditions in children (Barseem & Helwa, 2015).

The use of HOMA-IR index requires consideration of gender, ethnicity and pubertal stage (Andrade *et al.*, 2016). Although the HOMA-IR cut-offs used in this study provided high sensitivity and specificity, it is noteworthy that the cut-off was specifically developed for Malay children in Malaysia (Wee *et al.*, 2015). There could be a need to develop reference cut-offs for Chinese and Indian children in Malaysia.

The OW/OB had higher levels of hsCRP values and higher odds of developing inflammation compared to NW children. This is consistent with other findings whereby obesity was associated with elevated levels of hsCRP in various populations including children (Choi, Joseph & Pilote, 2013; El-shorbagy, 2010). The state of low-grade inflammation among the OW/OB is attributed by total adiposity through the production of inflammatory factors such as tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which in turn stimulate the production of high sensitivity C-reactive protein (hsCRP) (Calder *et al.*, 2011).

As inflammation is understood to be a key pathogenic mechanism in the initiation and progression of cardiovascular diseases (Bisoendial *et al.*, 2010; Calder et al., 2011), assessing levels of hsCRP may be an alternative for the screening of risk of MetS and cardiovascular diseases (DeBoer, 2013). Other benefits of hsCRP are that it is an easy tool to differentiate between the "healthy obese" children and those with higher risks of cardiovascular diseases without consideration of ethnicity (DeBoer *et al.*, 2013). Despite the benefits of the use of hsCRP as a screening tool, there is a lack of prospective studies that linked increased hsCRP levels to cardiovascular diseases specifically in children.

The prevalence of 3.8% among the OW/OB with MetS in the present study is much lower than that reported previously in Malaysia (5.3%) (Wee *et al.*, 2011) and Korea (7.3%) (Kang *et al.*, 2010). However, different definitions of MetS were owing to a lack of consensus on the definition for children. Hence, there is a need for a harmonized definition of MetS for children in the same way as has been agreed for adults.

In this current study, the International Diabetes Federation's (IDF) paediatrics definition (Zimmet *et al.*, 2007) was used as it is age specific and the cut-offs for each risk factor was fixed for blood pressure, lipid profiles, glucose and waist circumference compared to the National Cholesterol Education Program for Children (NCEP/ATP III) and the World Health Organization (WHO) paediatrics definition. Also, the IDF definition was easier to apply as it does not use multiple tables to assess the metabolic criteria as proposed by other definitions (Mancini, 2009).

Although the overall prevalence of insulin resistance, inflammation and metabolic syndrome in the studied children is relatively low when compared to the prevalence in adult population (Lim & Cheah, 2016), it could pose a public health problem with the rising childhood obesity in Malaysia.

A major limitation of this study is that the association between insulin resistance, inflammation and metabolic syndrome was not examined due to the small percentage of children diagnosed with MetS. It is suggested that future studies include a larger sample size with a wider age range of children.

CONCLUSION

Overweight/obese children aged 10-11 years showed higher risks of insulin resistance, inflammation and metabolic risk factors than their normal weight counterparts. These findings suggest a need for further research and interventions to address obesity and associated metabolic problems among Malaysian children.

Acknowledgement

This project was funded by the UCSI University Research Grant Scheme (RGS) Proj-In-FAS-016). The authors would like to thank all the children involved for their participation and cooperation and also their parents for permission and support during the course of this study. We are also grateful to the school principals, teachers, administrators and the Ministry of Education for their cooperation and assistance.

Authors' contributions

All authors contributed to conception, design and interpretation of data. SEHT, MNMT, YSC, ZMS, ZJ, HSY contributed to the study concept and design. TSEH contributed to the data collection, data analysis and drafted the manuscript. MNMT, YSC, ZMS contributed to critical revisions of the manuscript. SEHT, SHY contributed by obtaining funding.

Conflict of interest

The authors declare no conflict of interest.

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