Clinical Nutrition ESPEN xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Original article

The association between fat mass and subclinical atherosclerosis in healthy schoolchildren

Alaa Al-Shorman*, Buthaina AlKhatib, Baha'a Abusalma, Hayder Al-Domi

Department of Nutrition and Food Science, School of Agriculture, The University of Jordan, Amman 11942, Jordan

ARTICLE INFO

Article history:
Received 12 May 2019
Accepted 16 March 2020

Keywords:
Children and adolescents
Subclinical atherosclerosis
Inflammation
Endothelial dysfunction
Obesity
Fat mass

SUMMARY

Background and aims: Childhood obesity is associated with increased risk of cardiovascular disease (CVD) later in life. The aims of this study were to investigate the change of atherosclerosis risk factors in three fat mass percentiles and to examine the association between fat mass and atherosclerosis risk factors among a group of schoolchildren.

Methods: A total of 125 schoolchildren (64 boys) aged 10–15 years were distributed into three groups: (i) the lower fat mass (LFM) group, for participants who reported fat mass ≤50th percentile; (ii) the middle fat mass (MFM) group, for participants who reported fat mass >50th percentile and <75th percentile; and (iii) the higher fat mass (HFM) group for participants who reported ≥ 75th percentiles. Measurements of carotid intima-media thickness (cIMT) using high-resolution B-mode ultrasound, lipemic profile, blood pressure, serum proinflammatory cytokines and soluble adhesion molecules were performed.

Results: Significant differences ($p \leq 0.05$) were shown between the three groups in total cholesterol (TC), triglycerides (TG), LDL, interlukien-6 (IL-6), and interlukien-1 beta (IL-1β). Using multiple linear regression analysis of fat mass as the dependent variable with the studied subclinical atherosclerosis risk, fat mass was significantly ($p \leq 0.05$) associated with the variation expressed in systolic blood pressure ($\beta = 0.490$), diastolic blood pressure ($\beta = 0.470$), TC ($\beta = 0.399$), TG ($\beta = 0.306$), HDL ($\beta = -0.281$), LDL ($\beta = 0.446$), E-selectin ($\beta = 0.314$), and cIMT ($\beta = 0.257$).

Conclusion: Higher fat mass is associated with increased risk of atherosclerosis in schoolchildren. Atherosclerosis risk factors including biomarkers of inflammation, endothelial dysfunction, a state of dyslipidemia, increased cIMT, and high blood pressure were associated with fat mass. Studies evaluating the appropriate fat mass cut-off points in children and adolescents are needed.

1. Introduction

The prevalence of childhood obesity, which is defined as excess fat mass accumulation that presents health risk, has risen dramatically. Today, childhood obesity is considered one of the major global health concerns [1]. Reports showed that childhood obesity is associated with developing serious cardiometabolic health problems later in life, including but not limited to insulin resistance, type 2 diabetes, different types of cancer, and cardiovascular disease (CVD) [2,3].

Cardiovascular disease is the leading cause of death worldwide [4], and is expected to become more critical public health burden, since obesity is considered the most significant CVD risk factor [5], and yet that the prevalence of obesity is increasing steadily in both developed and developing countries [6] and has tripled over the last decades. Atherosclerosis process starts at childhood as subclinical atherosclerosis stage, which is an indicator for early atherosclerotic burden [7] and progresses through life [8]. And if atherosclerosis is recognized at the subclinical stage, the occurrence of atherosclerosis can be slowed or prevented [7].The modifiable risk factors of atherosclerosis are observed in adults and children alike [9], childhood obesity is one of the strongest risk factors that is associated with developing CVD during adulthood [10]. The measurement of carotid intima-media thickness (cIMT) of the common carotid artery is a noninvasive and quick measure of

* Corresponding author.
E-mail addresses: alaa.a.shorman@hotmail.com (A. Al-Shorman), buthaynamk85@yahoo.com (B. AlKhatib), bahaabusalma@gmail.com (B. Abusalma), h.aldomi@ju.edu.jo (H. Al-Domi).

https://doi.org/10.1016/j.clnesp.2020.03.014

Abbreviations

CVD	cardiovascular disease
cIMT	carotid intima-media thickness
IL-6	interleukin-6
TNF-α	tumor necrosis factor-alpha
IL-1β	interleukin-1beta
ICAM-1	intercellular adhesion molecule-1
VCAM-1	vascular cell adhesion molecule −1
BMI	body mass index
WHO	World Health Organization
WC	waist circumference
HC	hip circumference
SBP	systolic blood pressure
DBP	diastolic blood pressure
WHR	waist-to-hip ratio
CV	coefficient of variation
TC	total cholesterol
HDL	high density lipoprotein cholesterol
LDL	low density lipoprotein cholesterol
TG	triglycerides
ELISA	enzyme-linked immunosorbent assay
BIA	bioelectrical impedance
LFM	lower fat mass
MFM	middle fat mass
HFM	higher fat mass
CHD	coronary heart diseases

subclinical atherosclerosis. Increased cIMT has been associated with a higher risk of atherosclerosis and other CVD [11], which has been used to detect subclinical atherosclerosis in children and adolescents [11], and has been associated with obesity [12].

Obesity is a low-grade inflammatory state [13]. The pathophysiological process that links obesity with atherosclerosis involves chronic inflammatory markers induced by white adipose tissue. Increased circuiting levels of leptin, interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α) and interleukin-1beta (IL-1β) are associated with initiation, acceleration and progression of atherosclerotic lesions [14]. Soluble adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule −1 (VCAM-1), and E-selection are early molecular markers of endothelial dysfunction and atherosclerosis [14,15]. Additionally, Reports demonstrated that soluble adhesion molecules could play a more essential role in the initiation of the atherosclerosis process than the traditional risk factors [15,16]. This inflammatory state had been reported among children and adolescents with obesity [12,17].

The majority of investigations have used anthropometric measurements; mainly body mass index (BMI) to identify obesity and to investigate the association between obesity and subclinical atherosclerosis among children, such index is considered a measure of excess body weight rather than body fatness, since it cannot distinguish between fat mass, muscle mass, and skeletal mass, resulting in major errors in body fat mass estimation [18]. Whereas Few studies have investigated the role of body composition, particularly fat mass [19], studies evaluating the association of fat mass *per se* on subclinical state of atherosclerosis in healthy schoolchildren is not thoroughly investigated, no data about which was reported in Jordanian in schoolchildren as well as children of the Middle East. Therefore, the objectives of this study were to study the change of atherosclerosis risk factors in three fat mass percentiles and to examine the association between fat mass and atherosclerosis risk factors among a group of schoolchildren.

2. Materials and methods

2.1. Study population

The study recruitment was conducted in four public schools, which enrolled pupils from the 5th to the 9th grades. Schools were selected from a list of 20 public schools in four districts of Amman, as provided by the Jordanian Ministry of Education. A total of 125 normal bodyweight and obese schoolchildren, aged 10–15 years were selected to participate in the study. Data was collected from 64 boys (35 obese and 29 normal bodyweight), and 61 girls (30 obese and 31 normal bodyweight).

Inclusion criteria was for apparently healthy of normal bodyweight or obese schoolchildren according to the criteria of the World Health Organization (WHO) BMI-z score adjusted for age and gender [20]. Exclusion criteria were for schoolchildren who reported chronic use of medications, having chronic diseases (e.g. renal, cardiac or hepatic diseases) or schoolchildren with a history of first-hand smoking. Parents of the participating children gave written consent before inclusion and were provided with brief guidance to explain the objective and the procedures of the study to their children. Upon examination, verbal assent was obtained from children after explaining the study objective and procedures.

The protocol of this study was approved by the Deanship of Academic Research at the University of Jordan, The Jordanian Ministry of Education and Abdul Hameed Shoman Foundation Research Committee, Jordan.

2.2. Anthropometric measurements and blood pressure

Weight, height, waist circumference (WC), hip circumference (HC), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using standard procedure [21]. BMI and waist-to-hip ratio (WHR) were calculated [21].

2.3. Carotid intima-media thickness measurement

Intima-media thickness of the common carotid artery was measured using B-mode ultrasound, linear probe at 7.5 MHz frequency. Longitudinal ultrasonographic scan of the right common carotid artery were taken 1 cm below the carotid bulb. Images were taken at the lateral angle while participants were laying in supine position, head turned 45–50°' rotation of the neck to the contralateral side. Mean cIMT values were taken for the far wall, after participants were in the supine position for at least 5 min before starting the examination [22]. Measurements were performed by a single-blinded sonographer at the King Hussein Medical City, Jordan. The intra-observer reliability analyzed with coefficient of variation (CV) in 20 participants was 5.3% [23].

2.4. Biochemical analysis

In a follow-up visit, blood samples were drawn after 10–12 h overnight fasting, serum aliquots were stored at −20 °C until analyzed. Lipid profile of total cholesterol (TC), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL) and triglycerides (TG) were determined by a colorimetric direct

Please cite this article as: Al-Shorman A et al., The association between fat mass and subclinical atherosclerosis in healthy schoolchildren, Clinical Nutrition ESPEN, https://doi.org/10.1016/j.clnesp.2020.03.014

method using the CHOD-PAP method (BIOLABO SAS, Maizy, France), and the GPO method (BIOLABO SAS, Maizy, France). The reproducibility of the intra- and inter-assay CV were <9% and <13%, respectively, for all lipid profile measurements. Serum biomarkers of IL-6, IL-1β, TNF-α, sVCAM-1, sICAM-1 and E-selectin were measured by high-sensitivity sandwich enzyme-linked immunosorbent assay (ELISA) kits (®RayBio, USA), using plate reader at $\lambda = 450$ nm. The reproducibility of the intra- and inter-assay CV were <10% and <14%, respectively, for all ELISA measurements.

2.5. Body composition analysis

Body composition measurements were estimated using bioelectrical impedance (BIA). Fat mass, fat mass percentage, fat free mass, dry fat free mass, water volume and basal metabolic rate were determined. Students were asked to fast overnight except for water, refrain from exercise for at least 12 h before the test and to urinate within 30 min before starting the examination. At the time of the test, participants were placed in supine position, with legs and arms abducted around 45°. Two sets of electrodes were attached to the dorsal surface of the wrist and the dorsal surface of the ankle on the right side of the body [23].

2.6. Study population categorization

In order to meet our objectives, and based on [24], which indicates that the odds of having higher inflammatory markers at levels of body fat ≥70th percentile, we used FM to categorize our population into 3 groups as follows: (i) the lower fat mass (LFM) group, for schoolchildren who reported fat mass ≤50th percentile (≤15 kg of fat mass); (ii) the middle fat mass (MFM) group, for schoolchildren who reported fat mass >50th percentile and <75th percentile (>15 kg of fat mass and ≤23 kg of fat mass); and (iii) the higher fat mass (HFM) group for schoolchildren who reported ≥ 75th percentiles (>23 kg of fat mass).

2.7. Statistical analysis

Statistical analysis was performed using SPSS software (SPSS Inc. Released 2008. SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc.). Data are expressed as mean ± standard deviation. Mean difference of continuous variables were examined using one-way ANOVA. Correlation analysis was performed using partial Spearman correlation analysis. Multiple linear regression analysis was performed using FM as dependent variable, and cIMT, SBP, DBP, TC, TG, LDL, HDL, IL-6, TNF-α, IL-1β, VCAM-1, ICAM-1 and E-selectin as the independent variables. *p*-value less than or equal 0.05 was considered statistically significant.

3. Results

Table 1 represents the clinical, anthropometrics, and body composition characteristics of the study group divided by three fat mass groups. Except for cIMT, there were significant differences ($p \leq 0.001$) in all the studied variables between the LFM group, MFM group and HFM group.

Table 2 shows that TC, TG, LDL, IL-6, and IL-1 β were significantly ($p \leq 0.05$) different between the three groups. Nonetheless, no statistical difference ($p > 0.05$) was found in HDL, TNF-α, VCAM-1, ICAM-1, and E-selectin.

Significant correlations were found between FM and SBP ($r = 0.490$, $p = 0.001$); DBP ($r = 0.479$, $p = 0.001$); TC ($r = 0.399$, $p = 0.009$); TG's ($r = 0.306$, $p = 0.002$); HDL ($r = -0.281$, $p = 0.018$); LDL ($r = 0.446$, $p = 0.005$); E-selectin ($r = 0.314$, $p = 0.048$); and cIMT ($r = 0.253$, $p = 0.036$) among all the study population using Spearman correlation analysis (Table 3).

Linear regression analysis revealed associations between mean fat mass and SBP ($\beta = 0.490$, $p = 0.001$); DBP ($\beta = 0.470$, $p = 0.001$); TC ($\beta = 0.399$, $p = 0.001$); TG's ($\beta = 0.306$, $p = 0.009$); HDL ($\beta = -0.281$, $p = 0.018$); LDL ($\beta = 0.446$, $p = 0.005$); E-selectin ($\beta = 0.314$, $p = 0.045$); and cIMT ($\beta = 0.257$, $p = 0.036$) among the study population (Table 4).

4. Discussion

Obesity among children and adolescent is associated with manifestations of the cardiovascular system [25]. Obesity and obesity etiopathiogenetic risk factors are major predictors for CVD. Reports evaluating the role of obesity among healthy schoolchildren in developing atherosclerosis are scare. Hence, the current

Table 1
Clinical, anthropometrics, and body composition characteristics of study groups according to fat mass percentile.

Parameter	LFM (n = 58)	MFM (n = 38)	HFM (n = 29)	*p*-value
Boys, n (%)	27 (46.6%)	18 (47.4%)	19 (65.5%)	
Age (years)	11.98 ± 1.28	12.96 ± 1.04	12.84 ± 1.22	0.001
Weight (kg)	42.88 ± 12.24	61.67 ± 8.24	78.80 ± 14.96	0.001
Height (m)	1.50 ± 0.12	1.60 ± 0.09	1.60 ± 0.08	0.001
BMI (kg/m^2)	18.60 ± 3.07	24.02 ± 2.47	30.44 ± 3.88	0.001
WC (cm)	65.33 ± 8.88	79.08 ± 7.94	94.47 ± 12.72	0.001
HC (cm)	81.23 ± 9.57	96.18 ± 5.83	107.54 ± 7.12	0.001
WHR	0.81 ± 0.10	0.82 ± 0.08	0.88 ± 0.10	0.01
SBP	111.19 ± 13.24	121.88 ± 11.48	125.07 ± 12.56	0.001
DBP	62.67 ± 8.14	70.71 ± 14.31	74.97 ± 8.82	0.001
fat %	18.43 ± 5.43	29.15 ± 3.64	34.89 ± 3.77	0.001
FM (kg)	7.94 ± 3.48	17.78 ± 2.05	27.55 ± 6.06	0.001
FFM %	78.02 ± 13.61	69.81 ± 5.72	63.25 ± 8.43	0.001
FFM (kg)	34.07 ± 10.41	43.74 ± 7.57	51.04 ± 11.66	0.001
Dry FFM (kg)	8.54 ± 2.95	10.77 ± 1.91	12.89 ± 2.86	0.001
water %	61.41 ± 4.22	54.08 ± 5.11	48.74 ± 2.76	0.001
water (L)	26.34 ± 7.23	32.90 ± 5.59	38.51 ± 7.59	0.001
BMR (kcal/day)	1332.93 ± 235.82	1616.67 ± 193.01	1945.26 ± 324.67	0.001
cIMT (mm)	0.41 ± 0.12	0.38 ± 0.05	0.45 ± 0.09	0.08

Data are means ± SD or number (%).
LFM, lower fat mass group; MFM, middle fat mass group; HFM, higher fat mass group; BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist-to-hip ratio; WHR, waist-to-hip ratio; SPB, systolic blood pressure; DPB, diastolic blood pressure; FM, fat mass; FFM, fat-free mass; BMR, basal metabolic rate; cIMT, carotid intima-media thickness.
†P value is significant for values equal or less than 0.05, which represents the difference between the three groups.

Please cite this article as: Al-Shorman A et al., The association between fat mass and subclinical atherosclerosis in healthy schoolchildren, Clinical Nutrition ESPEN, https://doi.org/10.1016/j.clnesp.2020.03.014

Table 2
Biochemical markers of the study population.

Biomarker	LFM (n = 58)	MFM (n = 38)	HFM (n = 29)	*p*-value
TC (mg/dL)	133.39 ± 34.27	133.61 ± 41.38	176.96 ± 17.25	0.001
TG (mg/dL)	115.07 ± 34.38	129.45 ± 30.58	140.79 ± 40.68	0.01
HDL (mg/dL)	52.87 ± 14.68	46.18 ± 12.08	46.81 ± 8.71	0.11
LDL (mg/dL)	75.19 ± 11.63	79.88 ± 12.12	92.23 ± 13.28	0.001
IL-6 (pg/ml)	1.58 ± 0.57	2.10 ± 0.78	2.20 ± 1.09	0.05
TNF-α (pg/ml)	3.01 ± 0.60	3.47 ± 1.44	3.25 ± 1.06	0.45
IL-1 β (pg/ml)	2.71 ± 1.73	2.57 ± 1.34	4.19 ± 2.53	0.05
VCAM-1 (ng/ml)	238.50 ± 46.58	234.79 ± 69.48	259.71 ± 78.80	0.55
ICAM-1 (ng/ml)	157.75 ± 31.96	168.95 ± 33.44	167.47 ± 36.61	0.52
E-selectin (ng/ml)	25.19 ± 8.97	34.08 ± 13.32	34.76 ± 11.98	0.06

Data are means ± SD.
p-value is significant for values equal or less than 0.05, which represents the difference between the three groups.
LFM, lower fat mass group; MFM, middle fat mass group; HFM, higher fat mass group; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; IL-6, Interleukin 6; TNF-α, Tumor necrosis factor −alpha; IL-1β, Interleukin-1 beta; VCAM-1, vascular cell adhesion molecule −1; ICAM-1; intercellular adhesion molecule-1.

study aimed at investigating the attribution of fat mass in subclinical atherosclerosis in a group of healthy schoolchildren.

Obesity during childhood and adolescents is associated with adverse CVD risk factors, including elevated blood pressure, TC, LDL, and TG as well as reduced HDL [12], and is correlated with obesity and CVD in adulthood [26]. The findings of the current study demonstrated that TC, TG and LDL serum levels were significantly ($p \leq 0.05$) higher in HFM group than that in both LFM and MFM groups. Furthermore, we demonstrated that fat mass was significantly ($p \leq 0.05$) correlated with TC, TG, LDL, and HDL serum levels. These findings are consistent with other reports, which indicated that obesity in children can increase the risk of atherosclerosis among children and adolescents [27,28]. The Bogalusa Heart Study demonstrated that high BMI at the ages of 5–17 years was associated with abnormal concentrations of TG, LDL, HDL, and insulin [29]. Llewellyn and colleagues [30] reported in their systematic review and meta-analysis of 37 studies that obesity during childhood was associated with increased risk of CVD and type 2 diabetes mellitus in adulthood, which could be attributed, at least in part, with abnormal lipid profile and fasting blood glucose levels resulted from excess fat mass [8]. Furthermore, Stefan and his colleagues showed that excess body fat, mainly central obesity might be more related to CVD and type 2 diabetes in adulthood [31]. As well as several other investigations that supported the association between childhood and adolescence obesity and abnormal lipid profile [13,15,32,33]. In addition, our findings showed that as fat mass was increased, significant systolic and diastolic blood pressure increased concurrently. In line with these findings, most researches confirmed the association between obesity and increased blood pressure [34,35]. Likewise, fat mass was significantly ($p \leq 0.05$) correlated to SBP and DBP.

The findings of the current study are in agreement with various reports that examined the association between obesity and inflammatory biomarkers, in which we reported that there was significant ($p \leq 0.05$) elevation in IL-6 levels in MFM and HFM groups as compared to that in LFM group. Moreover, IL-1β levels were significantly ($p \leq 0.05$) increased in HFM group as compared to that in MFM and LFM groups. Given that IL-1β has been shown to be a key contributor to the pathogenesis of atherosclerosis [36][]. Notably, higher white adipose tissue increases the concentration of the inflammatory cytokines [13], chemokines in turn promote the migration of macrophages to the white adipose tissue [37]. Plasma levels of pro-inflammatory factors such as TNF-α, IL-6 and IL-1β were all increased in obese children and adolescents; all of which have been suggested as CVD risk factors [12,23,36,38]. Also, inflammation is thought to play a central role in the pathogenesis of atherosclerosis and consequently coronary heart diseases [14]. Obese children and adolescents have been shown to develop many pro-inflammatory and pro-atherogenic changes associated with vascular diseases [39]. Beauloye and colleagues [40] concluded that the subclinical inflammatory state in obese children could lead to early atherosclerosis. Studies on the relationship between the degree of childhood obesity and surrogate markers of future cardiovascular disease revealed that inflammatory biomarkers such as IL-6 levels increased with the degree of obesity. However, in a large-sample study that was conducted on 2846 boys and girls, inflammatory levels, particularly C-reactive protein did not correlate significantly with insulin resistance or with the metabolic syndrome; which are well-known cardiovascular risk factors, suggesting an underlying inflammation may be an additional factor contributing to adverse long-term cardiovascular outcomes [41]. It has been reported that the enhancement of endothelial adhesion molecules plays a pivotal role in the earliest phases of atherosclerosis [42]. Also, concentrations of soluble adhesion molecules have been found to be higher in obese children as compared to non-obese [12,23]. Given that in Huang and colleagues study [43] the endothelial injury and cIMT level were increased in obese children, also it might be useful for identify for the degree of damage. However, few studies have considered the type of obesity as a contributing risk factor in atherosclerosis; children with abdominal obesity are at increased risk for atherosclerosis, and WC could be useful for measuring the risk of atherosclerosis in children [19,23,44]. Therefore, the findings of the present study are in agreement with previous reports that showed significant correlations between fat mass and endothelial-leukocyte adhesion molecule, and cIMT.

Notwithstanding of our results, the relationship between cIMT and obesity have not always has been found. Tounian and colleagues [45] investigated the increase in arterial wall rigidity of cIMT in 48 obese children as compared to controls, and concluded that there were no significant differences in cIMT between both groups [45]. Furthermore, Beauloye and colleagues [40] did not report correlations between cIMT and the classical cardiovascular risk factors such as positive familial history of type 2 diabetes or precocious CVD, visceral obesity, or dyslipidemia. Also, adhesion molecule levels were not associated with cIMT in obese children and adolescents [40]. In a large group of normal children and young adults, aged 10–25 years, Sass et al. [46] found that cIMT was not

Table 3
Spearman correlation analysis between fat mass and selected atherosclerosis markers.

Variable	SBP	DBP	TC	TG's	HDL	LDL	IL-6	TNF-α	IL-1β	VCAM-1	ICAM-1	E-selectin	cIMT
R	0.490	0.479	0.339	0.306	−0.281	0.446	0.154	0.145	0.262	0.111	0.171	0.314	0.253
p-value	0.001	0.001	0.009	0.002	0.018	0.005	0.229	0.268	0.064	0.428	0.221	0.048	0.036

p-value is significant for values equal or less than 0.05.
SPB, systolic blood pressure; DPB, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; IL-6, Interleukin 6; TNF-α, Tumor necrosis factor −alpha; IL-1β, Interleukin-1 beta; VCAM-1, vascular cell adhesion molecule −1; ICAM-1; intercellular adhesion molecule-1; cIMT, carotid intima-media thickness.

Please cite this article as: Al-Shorman A et al., The association between fat mass and subclinical atherosclerosis in healthy schoolchildren, Clinical Nutrition ESPEN, https://doi.org/10.1016/j.clnesp.2020.03.014

Table 4
Linear regression analysis, with fat mass as the dependent variable with selected atherosclerosis markers.

	Standardized coefficients β	T	*p*-value
SBP	0.490	5.788	0.001
DBP	0.470	5.295	0.001
TC	0.399	2.7	0.009
TG"s	0.306	3.127	0.002
HDL	−0.281	−2.428	0.018
LDL	0.446	2.988	0.005
IL-6	0.154	1.216	0.299
TNF-α	0.145	1.118	0.268
IL-1 β	0.262	1.897	0.064
VCAM-1	0.111	0.798	0.428
ICAM-1	0.171	1.24	0.221
E-selectin	0.314	2.041	0.048
cIMT	0.253	2.14	0.036

p-value is significant for values equal or less than 0.05.
SPB, systolic blood pressure; DPB, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; IL-6, Interleukin-6; TNF-α, Tumor necrosis factor −alpha; IL-1β, Interleukin-1 beta; VCAM-1, vascular cell adhesion molecule −1; ICAM-1; intercellular adhesion molecule-1; cIMT, carotid intima-media thickness.

affected by age and sex until 18 years of age. After 18 year, cIMT had increased sharply in men, leading to significantly greater cIMT in men than in women. In line with this lack of correlation, Whincup et al. [47] showed that inflammation levels made only a modest contribution to the reduced arterial distensibility observed in obese adolescents and that this weak contribution was almost completely abolished after adjustment for adiposity.

This study has both strengths and limitations. Far to our knowledge, this is the first study investigating atherosclerosis risk factors in different fat mass percentile groups in children and adolescents, and investigating the role of fat mass *per se* in low income counties. The participants of this study were healthy, non-smokers and do not consume any medication which might strengthen the findings; furthermore, the study has investigated higher number of variables compared to other studies. A few limitations are worth mentioning: due to the cross-sectional nature of the study, it is not possible for the conformation of the speculation or making cause−effect relations. The study sample size may also reduce the statistical power of our findings. There were no commonly accepted cutoff point reference for fat mass among schoolchildren from different ethnicity; hence, the interpretation of the findings was not possible.

Conclusion

The results of the current study suggested that higher fat mass in schoolchildren is associated with increased atherosclerosis risk, by increasing its risk factors such higher blood pressure, a state of dyslipidemia, increased pro-inflammatory biomarkers and endothelial dysfunction. Therefore, more attention is required to obesity of children in both epidemiological studies and in clinical practices. This study highlighted the need for future studies evaluating the appropriate fat mass cut-off points in children and adolescents.

Funding sources

This work was supported Abdul Hameed Shoman foundation (Grant number 1/2015) and The Deanship of Academic Research, University of Jordan (Grant number 657), The University of Jordan, Jordan.

Author Contribution

Alaa Al-Shorman: Conceptualization, data collection, formal analysis, investigation, methodology, writing- original draft, review & editing. **Buthaina AlKhatib:** Writing - original draft, writing − review & editing. **Baha'a Abusalma:** Writing - original draft, writing − review & editing. **Hayder Al-Domi:** Conceptualization, investigation, methodology, supervision, approving the final draft.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

Acknowledgment

We would like to thank the students who participated in the study and we appreciate with gratitude the consent of their parents.

References

[1] World Health Organization (WHO). Obesity and overweight fact sheet. at, https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. [Accessed 4 March 2019].
[2] Geng T, Smith CE, Li C, Huang T. Childhood BMI and adult type 2 diabetes, coronary artery diseases, chronic kidney disease, and cardiometabolic traits: a mendelian randomization analysis. Diabetes Care 2018;41(5):1089−96.
[3] Weihrauch-Blüher S, Schwarz P, Klusmann JH. Childhood obesity: increased risk for cardiometabolic disease and cancer in adulthood. Metabolism 2019;92:147−52.
[4] Rao GH. Number one killer: vascular disease. Ann Clin Diabetes Endocrinol 2018;1(1):1008.
[5] Yusuf S, Reddy S, Ôunpuu S, Anand S. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. Circulation 2001;104(22):2746−53.
[6] Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980−2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014;384(9945):766−81.
[7] SingS, Pilkerton CS, Shrader CD, Frisbee SJ. Subclinical atherosclerosis, cardiovascular health, and disease risk: is there a case for the Cardiovascular Health Index in the primary prevention population? BMC Publ Health 2018;18(1):429.
[8] Koskinen J, Juonala M, Dwyer T, Venn A, Thomson R, Bazzano L, et al. Impact of lipid measurements in youth in addition to conventional clinic-based risk factors on predicting preclinical atherosclerosis in adulthood: international Childhood Cardiovascular Cohort Consortium. Circulation 2018;137(12):1246−55.
[9] Pollock BD, Stuchlik P, Harville EW, Mills KT, Tang W, Chen W, et al. Life course trajectories of cardiovascular risk: impact on atherosclerotic and metabolic indicators. Atherosclerosis 2019;280:21−7.
[10] Shah AS, Urbina EM. Childhood obesity, atherogenesis, and adult cardiovascular disease. Pediatr Obes 2018:527−38 [Humana Press, Cham].
[11] Groner JA, Joshi M, Bauer JA. Pediatric precursors of adult cardiovascular disease: noninvasive assessment of early vascular changes in children and adolescents. Pediatrics 2006;118(4):1683−91.
[12] Al-Shorman A, Al-Domi H, Faqih A. Markers of subclinical atherosclerosis in schoolchildren with obesity and metabolic syndrome. Swiss Med Wkly 2017;147(2122).
[13] Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. Annu Rev Immunol 2011;29:415−45.
[14] Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002;105(9):1135−43.
[15] Desideri G, De Simone M, Iughetti L, Rosato T, Iezzi ML, Marinucci MC, et al. Early activation of vascular endothelial cells and platelets in obese children. J Clin Endocrinol Metab 2005;90(6):3145−52.
[16] Caballero AE, Bousquet-Santos K, Robles-Osorio L, Montagnani V, Soodini G, Porramatikul S, et al. Overweight Latino children and adolescents have marked endothelial dysfunction and subclinical vascular inflammation in association with excess body fat and insulin resistance. Diabetes Care 2008;31(3):576−82.
[17] Montero D, Walther G, Perez-Martin A, Roche E, Vinet A. Endothelial dysfunction, inflammation, and oxidative stress in obese children and adolescents: markers and effect of lifestyle intervention. Obes Rev 2012;13(5):441−55.
[18] Freedman DS, Sherry B. The validity of BMI as an indicator of body fatness and risk among children. Pediatrics 2009;124(Supplement 1):S23−34.

Please cite this article as: Al-Shorman A et al., The association between fat mass and subclinical atherosclerosis in healthy schoolchildren, Clinical Nutrition ESPEN, https://doi.org/10.1016/j.clnesp.2020.03.014

[19] Al-Shorman A, Al-Domi H, Al-Atoum M. The associations of body composition and anthropometric measures with carotid intima-media thickness in obese and non-obese schoolchildren: a possible predictor for cardiovascular diseases. Vascular 2018;26(3):285–90.
[20] World health organization (WHO). Growth reference 5-19 years. http://www.who.int/growthref/who2007_bmi_for_age/en/. [Accessed 26 August 2015].
[21] Center for disease control and prevention (CDC). National health and nutrition examination Survey (NHANES): anthropometry procedures manual. http://www.cdc.gov/nchs/data/nhanes/nhanes_07_08/manual_an.pdf. [Accessed 30 January 2013].
[22] Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr 2008;21(2):93–111.
[23] Al-Domi H, Al-Shorman A. Increased waist circumference is associated with subclinical atherosclerosis in schoolchildren. Diabetes & Metabolic Syndrome. Clin Res Rev 2019;13(1):264–9.
[24] Singer K, Eng DS, Lumeng CN, Gebremariam A, Lee JM. The relationship between body fat mass percentiles and inflammation in children. Obesity 2014;22(5):1332–6.
[25] Park MH, Skow Á, De Matteis S, Kessel AS, Saxena S, Viner RM, et al. Adiposity and carotid-intima media thickness in children and adolescents: a systematic review. BMC Pediatr 2015;15(1):161.
[26] Umer A, Kelley GA, Cottrell LE, Giacobbi P, Innes KE, Lilly CL. Childhood obesity and adult cardiovascular disease risk factors: a systematic review with meta-analysis. BMC Publ Health 2017;17(1):683.
[27] Kelishadi R, Mirmoghtadaee P, Najafi H, Keikha M. Systematic review on the association of abdominal obesity in children and adolescents with cardiometabolic risk factors. J Res Med Sci 2015;20(3):294.
[28] Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. The relation of menarcheal age to obesity in childhood and adulthood: the Bogalusa heart study. BMC Pediatr 2003;3(1):3.
[29] Freedman DS, Kahn HS, Mei Z, Grummer-Strawn LM, Dietz WH, Srinivasan SR, et al. Relation of body mass index and waist-to-height ratio to cardiovascular disease risk factors in children and adolescents: the Bogalusa Heart Study. Am J Clin Nutr 2007;86(1):33–40.
[30] Llewellyn A, Simmonds M, Owen CG, Woolacott N. Childhood obesity as a predictor of morbidity in adulthood: a systematic review and meta-analysis. Obes Rev 2016;17(1):56–67.
[31] Stefan N, Kantartzis K, Machann J, Schick F, Thamer C, Rittig K, et al. Identification and characterization of metabolically benign obesity in humans. Arch Intern Med 2008;168:1609–16.
[32] Hu YH, Reilly KH, Liang YJ, Xi B, Liu JT, Xu DJ, et al. Increase in body mass index, waist circumference and waist-to-height ratio is associated with high blood pressure in children and adolescents in China. J Int Med Res 2011;39:23–32.
[33] Adegboye AR, Andersen LB, Froberg K, Sardinha LB, Heitmann BL. Linking definition of childhood and adolescent obesity to current health outcomes. Int J Pediatr Obes 2010;5:130–42.
[34] Vohr BR, Heyne R, Bann C, Das A, Higgins RD, Hintz SR, Eunice Kennedy Shriver National Institute of Child Health. High blood pressure at early school age among extreme preterms. Pediatrics 2018;142(2).
[35] Rodrigues PRM, Pereira RA, Gama A, Carvalhal IM, Nogueira H, Rosado-Marques V, et al. Body adiposity is associated with risk of high blood pressure in Portuguese schoolchildren. Rev Port Cardiol 2018;37(4):285–92.
[36] Masters SL, Latz E, O'Neill LA. The inflammasome in atherosclerosis and type 2 diabetes. Sci Transl Med 2011;3(81). 81ps17-81ps17.
[37] Lee S, Bacha F, Gungor N, Arslanian SA. Racial differences in adiponectin in youth: relationship to visceral fat and insulin sensitivityv. Diabetes Care 2006;29(1):51–6.
[38] Olza J, Aguilera CM, Gil-Campos M, Leis R, Bueno G, Martínez-Jiménez MD, et al. Myeloperoxidase is an early biomarker of inflammation and cardiovascular risk in prepubertal obese children. Diabetes Care 2012;35(11):2373–6.
[39] Ghomari-Boukhatem H, Bouchouicha A, Mekki K, Chenni K, Belhadj M, Bouchenak M. Blood pressure, dyslipidemia and inflammatory factors are related to body mass index in scholar adolescents. Arch Med Sci 2017;13(1):46.
[40] Beauloye V, Zech F, Tran Thi Mong H, Clapuyt P, Maes M, Brichard SM. Determinants of early atherosclerosis in obese children and adolescents. J Clin Endocrinol Metab 2007;92(8):3025–32.
[41] Ford ES. C-reactive protein concentration and cardiovascular disease risk factors in children: findings from the National Health and Nutrition Examination Survey 1999-2000. Circulation 2003;108:1053–8.
[42] Gimbrone Jr MA, García-Cardeña G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. Circ Res 2016;118(4):620–36.
[43] Huang K, Zou CC, Yang XZ, Chen XQ, Liang L. Carotid intima-media thickness and serum endothelial marker levels in obese children with metabolic syndrome. Arch Pediatr Adolesc Med 2010;164(9):846–51.
[44] Hacihamdioglu B, Okutan V, Yozgat Y, Yildirim D, Kocaoglu M, Lenk MK, et al. Abdominal obesity is an independent risk factor for increased carotid intima-media thickness in obese children. Turk J Pediatr 2011;53(1):48.
[45] Tounian P, Aggoun Y, Dubern B, Varille V, Guy-Grand B, Sidi D, et al. Presence of increased stiffness of the common carotid artery and endotelial dysfunction in severely obese children: a prospective study. Lancet 2001;358:1400–4.
[46] Sass C, Herbeth B, Chapet O, Siest G, Visvikis S, Zannad F. Intima-media thickness and diameter of carotid and femoral arteries in children, adolescents and adults from the Stanislas cohort: effect of age, sex, anthropometry and blood pressure. J Hypertens 1998;16:1593–602.
[47] Whincup PH, Gilg JA, Donald AE, Katterhorn M, Oliver C, Cook DG, et al. Arterial distensibility in adolescents: the influence of adiposity, the metabolic syndrome, and classic risk factors. Circulation 2005;112:1789–97.

Please cite this article as: Al-Shorman A et al., The association between fat mass and subclinical atherosclerosis in healthy schoolchildren, Clinical Nutrition ESPEN, https://doi.org/10.1016/j.clnesp.2020.03.014