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Comparison of plasma adipocytokines & C-reactive protein levels in healthy schoolgoing adolescents from private & government-funded schools of Delhi, India

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***Background & objectives*: Obesity-mediated chronic inflammatory state is primarily governed by lifestyle and food habits in adolescents and marked by alterations in the level of various inflammatory markers. This cross-sectional study was aimed to compare the inflammatory status of healthy Indian adolescents *vis-à-vis* their obesity profile. The inflammatory state of urban adolescents attending private and government-funded schools, and the relationship between inflammatory marker levels and anthropometric indices in the study participants from both groups were examined.**

***Methods*: A total of 4438 study participants (10-17 yr) were chosen from various schools of Delhi, India, and their anthropometric parameters were measured. Plasma adipocytokines (adiponectin, leptin and resistin) of the study participants were measured by enzyme-linked immunosorbent assay, and plasma C-reactive protein (CRP) levels were assayed by a biochemical analyzer. Metabolic syndrome-related risk factors such as waist circumference, hip circumference (HC), fasting glucose, fasting insulin, Homeostatic Model Assessment of Insulin Resistance, total cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol and triglycerides of normal-weight adolescents were also evaluated.**

***Results*: The level of leptin and CRP increased with increasing adiposity, whereas adiponectin levels were found to be negatively related to obesity. All plasma cytokine levels (adiponectin, leptin and resistin) were significantly elevated in female than male adolescents. Age-based classification revealed a distinct trend of variability in the levels of all the inflammatory markers among adolescents of varying age groups. Significant differences were observed between private and government schoolgoing adolescents in terms of anthropometric and inflammatory parameters, with higher adiposity indices in the former group. The relationship of plasma adipokine and CRP levels with various adiposity indices was found to be distinctly different between private and government schoolgoing students.**

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***Interpretation & conclusions*: Inflammatory markers were significantly elevated in overweight/obese adolescents. The socio-economic condition of urban Indian schoolgoing adolescents reflecting lifestyle transition has profound effects on their adiposity indices and inflammatory states. Longitudinal studies in different regions of the country need to be done to further confirm the findings.**

Key words Adipocytokines - CRP - Indian adolescents - inflammatory markers - juvenile health - lifestyle changes - obesity - socio-economic status

Increasing evidence of obesity in children and adolescents has grown into an alarming public health concern worldwide[1]. In 2015, India was second highest globally in the number of obese children and adolescents[1]. The severity of being overweight or obese early in life poses future risk for adverse life-threatening conditions such as metabolic syndrome, cardiovascular diseases, type 2 diabetes mellitus (T2DM) and certain malignancies[1].

Obesity is a condition which includes excess adiposity, concomitant by a mild chronic inflammatory state that is not a resultant of infection or autoimmunity[2]. This subclinical inflammatory state is characterized by abnormal levels of adipocytokines and acute-phase reactants [such as C-reactive protein (CRP)] and activation of pro-inflammatory signalling pathways[2,3]. Some key adipocytokines such as leptin, resistin (pro-inflammatory hormones) and adiponectin (anti-inflammatory hormone) serve as important link between obesity and related metabolic disorders[2,3]. Socio-economic status (SES) has a significant influence on dietary habit and physical activity in adolescents and therefore, may be a contributing factor for growing obesity gaps among different socio-economic strata[4]. The socio-economic condition of Indian adolescents has been shown to influence the dietary intake of essential nutrients[5]. School type based on locality can be used as a proxy indicator for SES in India, wherein government and private schoolgoing students may represent lower and upper socio-economic groups, respectively[6-8].

Previous school-based surveys have shown higher prevalence of overweight and abdominal obesity in adolescents from private schools than government schools in India[7,8]. However, rapid urbanization in large metropolitan cities and peri-urban areas, overconsumption of affordable energy-dense food of poor nutritional benefit and sedentary lifestyle may play a potential role in the steady rise of obesogenic frequency among government schoolchildren as well[8].

Earlier, the association between adiposity, adipocytokines and inflammatory markers has been explored in adults from western and southern parts of India[9-12]. These studies have revealed an altered adipokine and inflammatory profile of metabolically obese phenotype that may confer risk of insulin resistance, T2DM and cardiovascular disease[9-12]. The perturbations in inflammatory marker levels of obese Indian adolescents have been documented mostly in small study groups (n~100), lacking comparison based on socio-economic conditions of the study participants[13,14]. Furthermore, a large number of Indian studies compared adiposity in adolescents among two different socio-economic groups based on general anthropometry-based adiposity parameters such as body mass index (BMI), waist circumference (WC), hip circumference (HC), neck circumference and waist-hip ratio (WHR)[7,8]. However, none of these analyzed the levels of major classical inflammatory molecules (adiponectin, leptin, resistin and CRP) collectively in terms of obesity and SES featured by a larger adolescent section of urban India. Majority of the global studies linking adolescent adiposity with inflammation consisted of comparatively small sample groups, with no comparison of these inflammatory mediators based on differing socio-economic conditions[15,16]. A study conducted on a large population of Chinese children and adolescents (n=3505) of 6-18 yr age group evaluated several parameters of the study participants and found leptin, adiponectin and leptin/adiponectin ratio as useful biomarkers for obesity, central obesity, metabolic syndrome and abnormal metabolic profiles even within normal-weight children/adolescents[17]. The Beijing Child and Adolescent Metabolic Syndrome (BCAMS) study on 2119 children from Beijing, PR China, measured several adipokines and observed two categories of obese children - metabolically healthy obese (MHO) and metabolically unhealthy obese, with the later displaying increased leptin and resistin and reduced adiponectin concentrations than normal-weight healthy controls[18].

The present study was aimed to assess the combined classical inflammatory mediators in urban Indian adolescents of private and government-funded schools in New Delhi, India, belonging to two different socio-economic strata, with differing obesity status, gender and age. Plasma levels of four major inflammatory molecules (adiponectin, leptin, resistin and CRP) were determined. The role of the studied inflammatory molecules as plausible biomarkers of metabolic syndrome risk factors in urban adolescents was evaluated.

Material & Methods

The cross-sectional study was conducted during January 2012 to November 2014 after obtaining approval from the Human Research Ethics Committees of All India Institute of Medical Sciences (AIIMS) and CSIR-Institute of Genomics and Integrative Biology, New Delhi, India. Prior permission from school authorities, written informed consent from parents/guardians and verbal assent from the participants were obtained.

Study participants: A total of 4438 adolescents (1871 boys and 2567 girls) of age group 10-17 yr were selected from 28 private and four government-funded schools situated in the urban localities of Delhi-National Capital Region, as part of pursuing genome-wide association study of childhood obesity and related traits in Indians. Participants were selected through an ongoing health survey of Delhi schoolchildren in four different geographical zones of Delhi-NCR (north, south, east and west). From the listed private and government schools located in these four regions, at least one government and one private school from each zone were selected. In case the selected school refused to participate, the next school from the randomly generated list was approached in each zone.

Following permission, 28 private schools were selected [6 school samples from North Delhi, 8 from South Delhi, 2 from East Delhi, 5 from West Delhi and 7 from NCR (National Capital Region) near Delhi]. Among the four government schools, one school each from North, South, East and West Delhi was allowed by the school authorities for sample collection. In each school, once the age range was decided, the relevant classes were identified, *e.g.,* classes 6-12. From these, one section was randomly selected, and all children from that section were approached and studied.

The study participants were assessed with a detailed clinical and hormonal profiling (thyroid function test) and were found to be free of any systemic ailments as declared by a specialist through medical examinations. All participants spoke Indo-European language and were settled in North India. The following criteria were used to define 'North-Indian' ethnicity: (*i*) study participants should have either their State of birth or parents' and grandparents' State of origin from the northern part of India, (*ii*) participants who resided in Delhi and nearby areas of NCR surrounding Delhi during sample collection, (*iii*) surnames of participants were also carefully considered to belong to north Indian part, and (*iv*) participants with languages spoken in the northern part of India. The participants were evaluated through a pre-designed questionnaire reviewing their age, dietary habits, physical activity, state of birth, parent's state of origin and past and current medical history. The following criteria for sample selection were followed: urban, apparently healthy, schoolgoing children of 10-17 yr age group, North-Indian ethnicity speaking Indo-European language, not under any medication, not suffering from any chronic infection or disease and have not undergone surgery or hospitalized in the last six months.

As a proxy indicator to SES, the students enrolled in private schools were categorized into upper socio-economic strata, whereas those in government schools were considered into lower socio-economic strata[6-8]. Several other important parameters of school going adolescents were evaluated to assess their economic condition. Through the detailed questionnaire-based survey, information on their total family income was collected. Parameters such as presence of television, air conditioner, refrigerator and vehicle type were carefully considered. Based on the availability of these amenities, government schoolgoing adolescents were considered in the less privileged group in comparison to those attending private schools. Overall, based on school type, 3643 adolescents belonged to private schools and 795 adolescents belonged to government schools of Delhi. Anthropometric measurements including height, weight, waist and hip circumference were measured using standard methods[7,19]. Obesity status of the study participants was determined using age- and sex-specific BMI cut-offs[20].

Cytokine and biochemical measurements: Blood samples (2.5-3 ml) were collected from the participants by venipuncture after overnight fast. The plasma levels of adiponectin, leptin and resistin were measured with the help of commercially available enzyme-linked

immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN, USA).

Plasma CRP levels were measured using a Cobas Integra 400 Plus biochemical analyzer (Roche Diagnostics, Mannheim, Germany). Herein, anti-CRP antibodies coupled with latex microparticles react with CRP antigen in the biological sample to form an antigen-antibody complex that undergoes an agglutination process. Subsequently, this complex is measured turbidimetrically. Participants with CRP above 10 mg/l were excluded from the analysis because such an elevation of CRP might occur from a possible systemic infection. Fasting levels of glucose (FG), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C) and triglycerides (TG) were measured enzymatically with the help of COBAS Integra 400 Plus biochemical analyzer. Fasting insulin (FI) was measured using COBAS e411 biochemical analyser (Roche Diagnostics, Mannheim, Germany). Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was calculated according to the following formula: FI (μU/l)×FG (nmol/l)/22.5[21].

Statistical analysis: Data were represented as median (interquartile range) for continuous variables and as percentage for categorical variables. Comparison of anthropometric indices and plasma inflammatory markers between participants from private and government-funded schools and between severely lean and obese study participants was done by Wilcoxon-Mann-Whitney test. Comparison of cytokine levels according to varying age and obesity status was done by Kruskal-Wallis test. The association of different plasma cytokines with each other and with age, gender and anthropometric variables (BMI, WC, HC and WHR) was determined by multiple linear regression analysis.

Results

Table I represents the distribution of anthropometric variables and plasma levels of various cytokines in students from private and government-funded schools. Significant differences were observed for all variables, with private schoolgoing adolescents having higher level of adiposity indices as compared to government-funded school students (P<0.001). Adolescents from private schools were found to have lower levels of anti-inflammatory marker (*i.e.*, adiponectin) and higher levels of CRP, in comparison to their contemporaries from government-funded schools (P<0.001). Plasma concentrations of leptin and resistin were found to be lower in private schoolgoing adolescents (P<0.05 and P<0.001, respectively) compared to government schoolchildren.

Table I. Comparison of anthropometric indices and plasma cytokine levels among adolescents from private and government schools

Parameters	School type			
	Private		Government	
	Median or n	P25, P75 or %	Median or n	P25, P75 or %
Total samples (n)	3643		795	
Male (n and %)	1600	43.9	271	34.1
Age (yr)	13***	12, 15	14	13,15
BMI (kg/m^2)	19.3***	16.8, 22.9	17.5	15.9,19.3
Overweight (n and %)	704	19.3	37	4.7
Obese (n and %)	284	7.8	7	0.9
Waist circumference (cm)	71.5***	64.5, 80.0	64.0	60.0,69.0
Hip circumference (cm)	85.0***	78.5, 93.0	79.0	73.0,83.5
WHR	0.84***	0.80, 0.89	0.82	0.78,0.86
Plasma adiponectin (μg/ml)	3.9***	2.8, 7.9	10.3	6.7,15.1
Plasma leptin (ng/ml)	3.2*	1.8, 9.1	3.6	1.3,8.2
Plasma resistin (ng/ml)	4.5***	3.0, 6.2	6.7	5.4,8.8
Plasma CRP (mg/l)	0.5***	0.2, 1.4	0.3	0.1,0.8

*P<0.05, ***<0.001 compared to respective values in government schoolchildren. P25, 25th percentile; P75, 75th percentile; WHR, waist-to-hip ratio; CRP, C-reactive protein; BMI, body mass index

Distribution of inflammatory markers across various groups of the study population: The study participants were divided according to their obesity status, gender and age. Plasma concentrations of various inflammatory markers were analyzed across the groups (Table II). Significant increase in the plasma concentrations of leptin and CRP was observed with increased adiposity among adolescents, along with a concomitant decrease in plasma adiponectin levels (P<0.001). All plasma cytokine levels (adiponectin, leptin and resistin) were found to be higher in females in comparison to their male contemporaries (P<0.001). Upon age-wise stratification, a distinct trend of fluctuations

Table II. Comparison of plasma cytokine levels across different groups in the study population

Plasma cytokine levels[a]	n	Plasma adiponectin (µg/ml)			Plasma leptin (ng/ml)			Plasma resistin (ng/ml)			Plasma CRP (mg/l)		
		Median	P25, P75	P[a,b]	Median	P25, P75	P[a,b]	Median	P25, P75	P[a,b]	Median	P25, P75	P[a,b]
Total samples	4438	4.7	3.0, 9.5	-	3.3	1.7, 8.9	-	4.9	3.4, 6.7	-	0.5	0.2, 1.3	-
Obesity status													
Normal	3406	5.0	3.0, 10.1	<0.001	2.9	1.2, 5.8	<0.001	4.9	3.3, 6.7	0.420	0.4	0.2, 0.9	<0.001
Overweight	741	4.3	2.7, 8.3		8.7	3.3, 17.7		5.0	3.5, 6.9		1.2	0.5, 2.4	
Obese	291	3.7	2.5, 6.0		15.4	5.0, 27.2		5.3	3.6, 6.6		2.0	0.8, 3.9	
Gender													
Male	1871	3.8	2.8, 7.6	<0.001	2.3	0.7, 4.1	<0.001	4.5	3.0, 6.3	<0.001	0.5	0.2, 1.3	0.272
Female	2567	5.7	3.2, 11.0		4.6	2.8, 11.6		5.2	3.6, 6.9		0.5	0.2, 1.2	
Age (yr)													
10-<11	139	4.5	2.9, 8.6	<0.001	3.8	1.4, 8.9	<0.01	4.5	3.2, 6.3	<0.01	0.6	0.2, 1.6	<0.001
11-<12	507	4.4	2.9, 8.4		3.0	1.7, 6.4		4.5	2.9, 6.5		0.5	0.2, 1.5	
12-<13	726	5.6	3.3, 10.2		3.5	1.9, 9.0		4.8	3.7, 6.3		0.5	0.2, 1.2	
13-<14	851	4.9	3.1, 9.5		3.4	1.8, 8.8		4.8	3.5, 6.5		0.4	0.2, 1.1	
14-<15	854	4.3	2.9, 9.1		3.2	1.6, 8.4		5.0	3.2, 6.8		0.5	0.2, 1.1	
15-<16	595	4.3	2.8, 8.7		3.2	1.6, 9.1		5.1	3.3, 7.0		0.5	0.2, 1.3	
16-<17	477	4.7	2.8, 10.1		3.7	1.8, 10.5		5.3	3.5, 7.3		0.6	0.2, 1.4	
17-<18	289	5.3	3.0, 10.5		3.5	1.3, 10.8		5.3	3.0, 7.0		0.7	0.2, 1.6	

[a]Kruskal-Wallis test used to analyze differences in cytokine levels among the study participants of different obesity status and age; [b]Wilcoxon-Mann-Whitney test used to analyze differences in cytokine levels among male and female study participants

was observed in all the inflammatory marker levels (P<0.001, adiponectin and CRP; P<0.01, leptin and resistin).

The levels of plasma inflammatory mediators were assessed in severely lean (BMI <15 kg/m^2) and obese (BMI >30 kg/m^2) study participants. Majority of them were students of private schools (Table III). All the anthropometric adiposity indices and levels of pro-inflammatory markers such as leptin and CRP significantly increased in the study participants with BMI >30 kg/m^2. Adiponectin as an anti-inflammatory marker was significantly (P<0.001) lower in obese participants compared to lean. No significant difference in resistin levels was observed between severely lean and obese participants.

The plasma adipocytokine and CRP levels were compared among severely lean (BMI <15 kg/m^2) and obese (BMI >30 kg/m^2) study participants in different subgroups stratified by gender and age. On gender-wise analysis, obese males and females showed significantly reduced adiponectin and elevated leptin and CRP in comparison to their lean counterparts (Table IV), with no significant differences in resistin levels between lean versus obese males and lean versus obese females. On age-wise analysis, the participants were stratified into different age groups: 12-<13, 13-<14, 14-<15, 15-<16, 16-<17 and 17-<18 yr, respectively. Age groups 10-<11 and 11-<12 yr were not included in the analysis as the sample size for obese category under these age groups was low (n=1, for age group 10-<11 yr and n=2 for age group 11-<12 yr). Adiponectin was significantly reduced in obese participants than severely lean participants in 12-<13, 14-<15 and 17-<18 age group (Table V). Leptin and CRP were significantly elevated in obese participants in comparison to severely lean participants in all the age groups (Table V). Resistin was not significantly different between severely lean and obese participants across all age groups.

Relationship of plasma inflammatory markers with various adiposity indices: Table VI shows multiple linear regression analysis for private schoolgoing adolescents having inverse-normalized plasma cytokine levels as dependent variable and various anthropometric indices and other inverse-normalized inflammatory marker levels as independent variables. Among private school students, plasma adiponectin levels were found to be associated with BMI, HC, WHR, leptin, resistin and CRP levels. Plasma leptin levels were found associated

Table III. Comparison of anthropometric indices and plasma cytokine levels among severely lean and obese study participants

Parameters	Lean (BMI <15 kg/m^2)		Obese (BMI >30 kg/m^2)	
	Median or n	P25, P75 or %	Median or n	P25, P75 or %
Total samples (n)	398		123	
From private school (n and %)	301	75.6	122	99.2
Age (yr)	12***	11, 14	15	14, 16
BMI (kg/m^2)	14.3***	13.6, 14.7	31.5	30.7, 33.7
Waist circumference (cm)	58.5***	55.2, 62.0	96.0	88.0, 103.0
Hip circumference (cm)	71.0***	67.0, 75.0	110.0	106.0, 114.0
WHR	0.83***	0.79, 0.87	0.86	0.82, 0.94
Plasma adiponectin (µg/ml)	4.6***	3.1, 10.7	3.3	2.0, 5.6
Plasma leptin (ng/ml)	1.2***	0.4, 2.8	17.1	4.0, 36.1
Plasma resistin (ng/ml)	4.7	3.0, 6.5	5.3	3.7, 6.6
Plasma CRP (mg/l)	0.3***	0.1, 0.6	1.9	0.6, 4.3

Wilcoxon-Mann-Whitney test used to test for difference among participants, based on severely lean and obese category.
***P<0.001. P25, 25th percentile; P75, 75th percentile; WHR, waist-to-hip ratio; CRP, C-reactive protein; BMI, body mass index

Table IV. Comparison of plasma cytokine levels among severely lean and obese adolescents stratified by gender

Plasma cytokine levels	Males		Females	
	Lean (BMI <15 kg/m^2) (n=231)	Obese (BMI >30 kg/m^2) (n=47)	Lean (BMI <15 kg/m^2) (n=173)	Obese (BMI >30 kg/m^2) (n=82)
	Median (P25, P75)		Median (P25, P75)	
Plasma adiponectin (µg/ml)	4.42 (2.99, 9.53)***	2.73 (1.94, 4.43)	4.93 (3.3, 12.42)***	3.92 (2.34, 5.98)
Plasma leptin (ng/ml)	0.63 (0.28, 1.4)***	7.16 (3.4, 18.2)	2.1 (1.3, 3.7)***	25.02 (9.51, 41.14)
Plasma resistin (ng/ml)	4.32 (2.82, 5.83)	4.25 (3.57, 6.04)	5.33 (3.75, 7.39)	5.47 (3.77, 7.02)
Plasma CRP (mg/l)	0.35 (0.13, 0.6)***	2.16 (0.89, 5.1)	0.28 (0.12, 0.62)***	1.57 (0.56, 3.34)

***P<0.001 compared to obese group in the respective category

with age, gender, BMI, adiponectin, resistin and CRP concentrations. Associations of plasma resistin concentration were found with age, gender, BMI, WHR, adiponectin, leptin and CRP levels. Plasma CRP levels were associated with age, BMI, adiponectin, leptin and resistin concentration.

For the government schoolgoing adolescents (Table VII), plasma adiponectin levels were in association with gender and plasma resistin concentration. Associations for plasma leptin were found with age, gender and HC. Plasma resistin levels were associated with BMI and adiponectin levels. Finally, plasma CRP levels were in association with gender and BMI.

Adipocytokines and CRP levels as biomarkers for metabolic syndrome-related risk factors: The important metabolic syndrome-related risk factors were also measured in our normal-weight adolescent samples such as WC, HC, FG, FI, HOMA-IR, TC, HDL-C, LDL-C and TG. Detailed characteristics of normal-weight adolescents with respect to metabolic parameters are presented in Table VIII. The normal-weight adolescent samples (n=3406) were further categorized based on lower quartile (bottom 25% values) and upper quartile (upper 25% values), *i.e.*, values <25th percentile as low and values >75th percentile as high of adipocytokines and CRP and a significant variation was observed in the median levels of metabolic syndrome-related risk factors in low versus high strata (Table IX). Participants with low adiponectin levels had high median levels of WC, HC, FI, HOMA-IR and TC compared to participants with high adiponectin levels. Similarly,

Table V. Comparison of plasma cytokine levels among severely lean and obese adolescents stratified by age

Age (yr)	Category (BMI, kg/m^2)	Median (P25, P75)			
		Plasma adiponectin (µg/ml)	Plasma leptin (ng/ml)	Plasma resistin (ng/ml)	Plasma CRP (mg/l)
12-<13	Lean (<15), n=96	6.67 (3.55, 12.59)	1.39 (0.51, 2.45)	4.91 (3.35, 6.41)	0.27 (0.1, 0.48)
	Obese (>30), n=11	3.51 (2.56, 5.73)*	16.97 (6.23, 19.94)***	3.93 (2.81, 5.3)	0.61 (0.26, 4)*
13-<14	Lean (<15), n=64	4.1 (3.04, 7.95)	1.39 (0.62, 2.95)	4.79 (3, 6.16)	0.22 (0.11, 0.49)
	Obese (>30), n=17	5.27 (4.36, 6.59)	26.75 (16.25, 41.38)***	5.92 (4.22, 7.1)	1.45 (0.81, 3.79)***
14-<15	Lean (<15), n=54	4.85 (3.12, 10.770)	0.92 (0.31, 3)	4.95 (3.66, 8.99)	0.32 (0.11, 0.83)
	Obese (>30), n=27	3.57 (1.85, 5.56)**	25.69 (4, 38.59)***	5.49 (3.9, 8.1)	2.54 (1.14, 6.13)***
15-<16	Lean (<15), n=30	5.62 (2.76, 10.78)	1.1 (0.29, 2.02)	5.56 (3.81, 7.26)	0.36 (0.15, 0.96)
	Obese (>30), n=19	3.28 (2.37, 5.31)	18.19 (6.46, 26.98)***	4.62 (4.3, 5.73)	0.7 (0.37, 3.53)*
16-<17	Lean (<15), n=9	3.35 (2.97, 5.43)	0.75 (0.2, 2)	5.8 (3.53, 6.44)	0.46 (0.42, 0.61)
	Obese (>30), n=26	3.1 (2.38, 4.77)	9.94 (3.42, 34.88)***	4.6 (3.43, 6.4)	1.44 (1.09, 4.14)**
17-<18	Lean (<15), n=8	5.1 (3.6, 15.14)	4.38 (1.72, 5.83)	7.87 (4.77, 10.02)	0.35 (0.1, 0.58)
	Obese (>30), n=20	2.37 (1.84, 3.46)**	10.8 (4.35, 21.66)*	5.5 (3.56, 6.46)	2.27 (1.09, 2.94)**

*P**<0.05, ***<0.01, ****<0.001 compared to lean group in the respective category

Table VI. Linear regression analysis of plasma cytokine and C-reactive protein levels with various adiposity indices, for private schoolgoing adolescents

Parameters (n=3643)	Plasma adiponectin (µg/ml)			Plasma leptin (ng/ml)			Plasma resistin (ng/ml)			Plasma CRP (mg/l)		
	β[a]	95% CI[a]	*P*	β[a]	95% CI[a]	*P*	β[a]	95% CI[a]	*P*	β[a]	95% CI[a]	*P*
Age (yr)	−0.02	−0.18, 0.04	0.199	−0.13	−0.81, −0.53	<0.001	0.05	0.03, 0.22	<0.01	−0.11	−0.12, −0.06	<0.001
Gender	0.03	−0.02, 0.74	0.065	0.26	4.33, 5.29	<0.001	−0.05	−0.78, −0.11	<0.05	−0.02	−0.18,0.04	0.182
BMI (kg/m^2)	−0.32	−0.47, −0.31	<0.001	0.48	0.88, 1.08	<0.001	0.07	0.00, 0.14	<0.05	0.13	0.02,0.07	<0.001
Waist circumference (cm)	−0.30	−0.30, 0.01	0.071	0.07	−0.15, 0.27	0.598	0.24	−0.04, 0.24	0.171	0.28	−0.01,0.08	0.095
Hip circumference (cm)	0.29	0.01, 0.28	<0.05	−0.01	−0.19,0.17	0.941	−0.24	−0.22, 0.02	0.091	0.03	−0.03,0.04	0.828
WHR	0.17	0.26, 27.28	<0.05	−0.02	−20.46, 15.75	0.799	−0.19	−24.81, −0.84	<0.05	0.02	−3.48,4.19	0.856
Plasma adiponectin (µg/ml)	-	-	-	0.24	0.36, 0.44	<0.001	0.15	0.10, 0.15	<0.001	−0.05	−0.02, −0.01	<0.01
Plasma leptin (ng/ml)	0.38	0.20, 0.25	<0.001	-	-	-	0.20	0.08, 0.12	<0.001	0.06	0.00,0.02	<0.01
Plasma resistin (ng/ml)	0.14	0.12, 0.20	<0.001	0.12	0.18, 0.28	<0.001	-	-	-	−0.06	−0.03, −0.01	<0.001
Plasma CRP (mg/l)	−0.05	−0.29, −0.06	<0.01	0.04	0.08, 0.39	<0.01	−0.07	−0.31, −0.10	<0.001	-	-	-
Constant		−1.73			−16.53			13.81			−1.62	

[a]Values are coefficient regression β (95% CI) by multiple linear regression analysis. Categorical variable: Male as reference for gender; all the cytokine concentrations were inverse normalized

Table VII. Linear regression analysis of plasma cytokine and C-reactive protein levels with various adiposity indices, for government schoolgoing adolescents

Parameters (n=795)	Plasma adiponectin (µg/ml)			Plasma leptin (ng/ml)			Plasma resistin (ng/ml)			Plasma CRP (mg/l)		
	β[a]	95% CI[a]	*P*	β[a]	95% CI[a]	*P*	β[a]	95% CI[a]	*P*	β[a]	95% CI[a]	*P*
Age (yr)	0.07	−0.05, 0.38	0.123	−0.15	−0.98, −0.35	<0.001	−0.03	−0.20, 0.11	0.533	−0.03	−0.09, 0.04	0.538
Gender	0.18	0.95, 2.59	<0.001	0.28	3.71, 6.10	<0.001	0.05	−0.25, 0.95	0.254	−0.08	−0.51, −0.01	<0.05
BMI (kg/m^2)	−0.03	−0.24, 0.15	0.625	0.09	−0.03, 0.55	0.083	−0.12	−0.29, −0.00	<0.05	0.22	0.06, 0.18	<0.001
Waist circumference (cm)	−0.03	−0.52, 0.48	0.940	−0.32	−1.12, 0.38	0.336	0.28	−0.24, 0.50	0.484	0.44	−0.06, 0.24	0.242
Hip circumference (cm)	−0.16	−0.52, 0.33	0.663	0.65	0.05, 1.32	<0.05	−0.09	−0.35, 0.27	0.793	−0.29	−0.19, 0.08	0.405
WHR	0.01	−37.38, 39.20	0.963	0.27	−23.44, 91.14	0.246	−0.22	−39.37, 16.37	0.418	−0.20	−16.25, 7.06	0.439
Plasma adiponectin (µg/ml)	-	-	-	0.01	−0.09, 0.12	0.821	−0.08	−0.11, −0.01	<0.05	0.07	0.00, 0.04	0.057
Plasma leptin (ng/ml)	0.01	−0.04, 0.05	0.821	-	-	-	0.08	−0.00, 0.07	0.064	0.06	−0.00, 0.03	0.155
Plasma resistin (ng/ml)	−0.08	−0.21, −0.01	<0.05	0.06	−0.01, 0.28	0.064	-	-	-	−0.02	−0.04, 0.02	0.624
Plasma CRP (mg/l)	0.07	−0.01, 0.46	0.057	0.05	−0.10, 0.60	0.155	−0.02	−0.21, 0.13	0.624	-	-	-
Constant		16.08			−57.03			16.44			1.27	

[a]Values are coefficient regression β [95% confidence interval (CI)] by multiple linear regression analysis. Categorical variable: Male as reference for gender; all the cytokine concentrations were inverse normalized

participants with high leptin levels had significantly higher median WC, HC, FG, FI, HOMA-IR, TC, HDL, LDL and TG levels compared to their low leptin level counterparts. Participants with high resistin levels had significantly elevated median FG and TG levels in comparison to low resistin level participants. Further, participants with high CRP levels had significantly elevated median levels of WC, HC, FI and HOMA-IR than participants having low CRP levels. However, among the low versus high strata of adipocytokines and CRP levels, though medians differed significantly for majority of the metabolic parameters, data ranges were overlapping between the two groups (Table IX).

Discussion

Drastic lifestyle alterations during the past few decades have consequentially contributed to adolescent obesity and associated co-morbidities in both low- and middle-high-income countries, irrespective of age, sex or race[1]. The recent trends in the emergent cases of obesity are mainly attributed to harsh shift in our environment[22]. Age is a primary factor that contributes substantially to variations in blood biochemistry[23]. Amid multiple life stages, adolescence represents a significant step from childhood to adulthood characterized by fast growth and development[24]. Entry from childhood to adolescence is principally dominated by gender of an individual that dictates distinct hormonal levels among males and females during puberty, resulting in severe alterations in blood adipocytokine profile[25]. Evaluating imperative health-related parameters during adolescence can effectively delay the associated metabolic diseases in adulthood.

Adolescent obesity is paralleled by dysregulated release of acute-phase reactant (CRP) and inflammatory cytokines (leptin, resistin and adiponectin), leading to the manifestation of metabolic and hormonal anomalies[3]. There are no data on the relation of inflammatory biomarkers with adolescent obesity and SES in a large-scale urban Indian setting.

Table VIII. Metabolic profiles of normal-weight urban Indian adolescents

Trait	Normal-weight adolescents (n=3406), median (P25, P75)	
	Male (n=1455)	Female (n=1951)
Age (yr)	13 (12, 14.6)*	14 (12, 15)
BMI (kg/m^2)	16.98 (15.55, 18.78)***	18.31 (16.5, 20.1)
Waist circumference (cm)	68.5 (64, 74)	65 (60, 70)
Hip circumference (cm)	81 (76, 86)***	83 (78.3, 87)
Fasting glucose (mg/dl)	87 (79.3, 94)***	83.8 (76.2, 91)
Fasting Insulin (pmol/l)	45.1 (30.52, 65.2)***	56.26 (39.3, 78.4)
HOMA-IR	1.38 (0.93, 2.05)***	1.67 (1.2, 2.4)
Total cholesterol (mg/dl)	138 (122.6, 155.7)***	141.88 (127, 158.9)
High-density cholesterol (mg/dl)	44.85 (40.39, 50.32)***	46.72 (41.8, 54.2)
Low-density cholesterol (mg/dl)	81.9 (69, 92)	82 (69.2, 94)
Triglycerides (mg/dl)	86 (62.9, 108.2)	87.8 (62, 116)

P<0.05, ***<0.001 compared to females. HOMA-IR, Homeostatic Model Assessment of Insulin Resistance

The present study compared the distribution of inflammatory markers among urban Indian youth across differing obesity and socio-economic conditions of study groups. In consistence with prior findings[7,8], students from private schools had significantly higher adiposity indices such as BMI, WC, HC and WHR. Lower levels of adiponectin and higher levels of CRP were found in private schoolgoing adolescents as compared to those in government schools, probably as a result of increasing prevalence of obesity. In contrast, plasma levels of two other pro-inflammatory mediators, namely leptin and resistin, were higher in government school students than private schoolgoing group. This is because obesity is no longer a disease of affluence and is rapidly switching into groups with lower socio-economic strata[2,8]. As rapid urbanization has resulted in sedentary lifestyles coupled with unbalanced dietary habits[8], this may predispose urban adolescents to a chronic inflammatory cytokine load[22].

Inflammatory load in government schoolgoing adolescents may be attributed to limited residential playground availability, reduced focus on outdoor games and more indoor activities, availability of high calorie food of poor nutritional value, low fruit consumption, occasional alcohol consumption and smoking, *etc*[8].

Our study revealed the intrinsic load of inflammatory burden even in apparently healthy-looking normal-weight adolescents of private and government schools, who are generally perceived to be under low-risk for metabolic diseases. However, our data suggested that mere measurement of apparent visible anthropometric features as evaluated by earlier studies[7,8] might not uncover the potential disease risk population unless the key intermediary biomolecules are measured.

Leptin and CRP levels were positively associated with adiposity among the study participants, while adiponectin levels were found to be negatively associated with obesity status. Leptin and CRP levels were clearly distinguishable among normal-weight and obese adolescents, whereas resistin levels were only different between normal-weight and obese adolescents. A study conducted in Brazil found these adipokines to differ only between lean and overweight/obese adolescents and not among consecutive groups, albeit in a smaller sample size (n=104)[16].

Congruent to multiple evidences[25-28], gender-based analysis revealed higher levels of all the three cytokines among females, in comparison to their male contemporaries. The disparity in metabolic control observed between males and females may be attributed to different gender-specific hormones regulating body fat distribution[26]. Leptin levels are higher in females than males due to the stimulatory effects by oestrogen and inhibitory effects by androgen[26]. Further, leptin secretion is positively related to subcutaneous fat in comparison to visceral fat. As females have greater proportion of subcutaneous fat, leptin levels are in general elevated in females that positively correlate with female reproductive functions[26].

Elevated testosterone levels reduce plasma adiponectin levels in males[27]. In contrast to the stimulatory effect of oestrogen on leptin and adiponectin levels, a study conducted in mouse has suggested the suppressive effect of oestrogen on resistin expression. This finding indicates other gonadal factors or body fat content changes specific to females that may induce elevated resistin levels in females[28]. Furthermore, this

Table IX. Metabolic profiles of normal-weight adolescents based on lower and upper quartiles of plasma adpocytokines and C-reactive protein (n=3406)

Metabolic syndrome risk factors	Plasma cytokine categories							
	Low adiponectin (≤3.02 µg/ml) (n=822)	High adiponectin (≥10.11 µg/ml) (n=825)	Low leptin (≤1.25 ng/ml) (n=822)	High leptin (≥5.85 ng/ml) (n=824)	Low resistin (≤3.31 ng/ml) (n=812)	High resistin (≥6.73 ng/ml) (n=818)	Low CRP (≤0.16 mg/l) (n=822)	High CRP (≥0.86 mg/l) (n=842)
	Median (P25, P75)		Median (P25, P75)		Median (P25, P75)		Median (P25, P75)	
Waist circumference (cm)	68.5 (63, 74.5)***	65 (60, 70)	64.5 (60, 69)***	69 (63.5, 74)	68.5 (63, 74.5)***	65.5 (61, 71)	64 (59, 69)***	70 (64, 76)
Hip circumference (cm)	82 (76.5, 88)***	80 (74, 85)	78 (72, 83)***	84 (80, 89)	82 (76, 87.5)**	81 (75.5, 86)	79 (74, 84)***	83 (78, 89)
Fasting glucose (mg/dl)	82 (72.2, 90.8)***	87 (80.5, 93)	85 (76.3, 92)***	87 (81, 92.9)	77.8 (70.7, 87.4)***	87 (81, 93.9)	89 (83, 96)***	83 (73.8, 91)
Fasting insulin (pmol/l)	56.3 (38.1, 84.5)***	50.4 (33.4, 68.4)	41.8 (28.5, 59.4)***	55.8 (38.9, 76.3)	54.8 (39, 80.01)**	50.4 (35.3, 70.1)	47.7 (33.2, 65.3)***	55.6 (37.6, 80.1)
HOMA-IR	1.64 (1.12, 2.46)***	1.53 (1.02, 2.13)	1.23 (0.83, 1.8)***	1.71 (1.19, 2.41)	1.59 (1.12, 2.25)	1.55 (1.07, 2.25)	1.5 (1, 2.1)**	1.62 (1.12, 2.38)
Total cholesterol (mg/dl)	143.8 (125.9, 162.3)***	138 (125.2, 152.7)	136 (120.4, 152)***	145 (130, 163)	139.7 (123.2, 157.8)	140 (125.2, 154.6)	141 (126, 159.1)	141.2 (125, 160.5)
High-density cholesterol (mg/dl)	46 (39.8, 53.4)**	46 (43, 53.7)	45.2 (40.6, 52.4)*	46 (42, 52)	46.3 (40.9, 54.2)	46 (42, 52.8)	46 (41, 53.04)***	45 (40, 51)
Low-density cholesterol (mg/dl)	81.7 (69.7, 96.5)*	81.7 (69, 91.9)	79.6 (66.1, 91)***	84 (72, 95.2)	82.3 (69.2, 94.1)	82 (69, 93)	82 (71, 94)	82.6 (69.4, 94.1)
Triglycerides (mg/dl)	80.8 (60.8, 113)*	85 (58.5, 101)	81 (60.5, 103)***	92.7 (66.9, 120.3)	78 (57.9, 106.3)**	86 (62.6, 107)	92 (72.9, 123)***	87.4 (61.5, 116)

P<0.05, **<0.01, ***<0.001 compared to high level category in the respective groups

observation was concordant with a human study that found no correlation of resistin levels with estradiol, a female-specific hormone[29].

All the four inflammatory markers tested in our study were found to be significantly associated with BMI in case of private schoolgoing adolescents, whereas BMI was found to be associated with only resistin and CRP levels in adolescents from government schools. These data indicated that not only the percentage of obesity differed between our private and government schoolgoing groups, but obesity-driven inflammatory state was also differentially regulated as per the socio-economic condition of the study participants.

The aggregated clustering of metabolic syndrome risk factors with reduced adiponectin and elevated leptin, resistin and CRP levels were observed even in normal-weight adolescents. In line with earlier studies on Chinese children and adolescents[17], our study suggested that the studied inflammatory biomolecules might serve as valuable biomarkers for identifying even phenotypic healthy-looking adolescents at risk for later metabolic complications. As multiple studies have suggested that the maintenance of healthy lifestyle practices can cut the inflammatory burden and thereby may reduce obesity and related co-morbidities[30], children should be encouraged to follow healthy lifestyle.

In conclusion, our results indicated the significant role of obesity, socio-economic conditions and anthropometric indices in determining inflammatory health of schoolgoing adolescents from urban India. A major limitation of this study was to use school enrolment as a surrogate and not an absolute indicator for SES of urban adolescents. This study was also limited by its cross-sectional design restricted to a large urban adolescent population residing in the capital of India, thus might not be generalized for the other regions of the country. Longitudinal cohort studies are needed to assess the future evolution of metabolic perturbations even in those perceived as metabolically normal today, based on their BMI.

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