UNIVERSITA' DEGLI STUDI DI VERONA

MODELLING STUDIES FOR A 'WHOLE OF SOCIETY (WOS)' FRAMEWORK TO MONITOR CARDIO-METABOLIC RISK AMONG CHILDREN (6 TO 18 YEARS)

FOR THE AWARD OF THE DEGREE OF DOCTOR OF PHILOSOPHY (Ph.D)

BY

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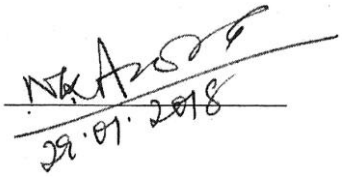
Signature 

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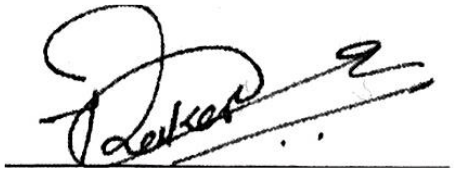

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ABSTRACT

In the World Health Assembly (WHA) 2013, India was among the first country to adapt global framework for monitoring non-communicable diseases (NCD) - Government of India (GOI) has set targets to halt the prevalence of diabetes and obesity by 2025. To halt the prevalence of major NCDs it is necessary to protect children from becoming obese or overweight. Childhood obesity is a precursor of adulthood obesity and attendant cardio-metabolic risk. In last 15 years the prevalence of overweight and obesity increased almost four times (4 to 15%). This translates in to approximately 58 million obese and 122 million overweight children in the country. Studies have reported at least one cardiovascular risk factor among 70 per cent of these children. It is frightening to know that, unit percentage rise in its prevalence in India shall add at least another five million children into the cardiovascular risk pool.

Body Mass Index (BMI) [Weight (kg)/Height (m^2)] is the most widely used definition for monitoring overweight and obesity; among children BMI-for-age based growth curves (centile values) are used. There are number of BMI-for age based guidelines with varying cut offs (like IOTF, WHO, CDC etc.) – in India, the growth curves published Indian Association of Pediatrics (IAP), 2015 is considered as the standard. Despite BMI's large scale application in clinical and public health programs it has many inherent problems. Firstly, BMI cannot distinguish between fat and fat free mass. Excess body fat is an independent risk factor for cardio vascular and metabolic diseases. In an individual with BMI of 20, body fat may range from 5%-40% whereas for body fat content of 20% BMI may vary from 15-30 points. Validity studies using BMI to identify children with excess adiposity have generally documented low to moderate sensitivities (6-46%). Secondly, BMI is not independent on height of the individuals. BMI may not be a sensitive measure in children at the extremes of the height due to unusual fat distribution or highly developed muscles. BMI preferentially classifies taller children and adolescents as overweight. Finally, the definition of childhood overweight and obesity is arbitrary as it is extrapolated from adult reference data and not based on its association with health outcomes. Considering these variations, there has been a growing concern about using single standard to define overweight and obesity which may be appropriate for many sub-populations in the world.

Methods: Overall aim of this study was to develop a monitoring mechanism that correlates with cardio-metabolic risk factors among Indian children aged 6-18 yrs. Primary objective of the study was to relate health outcomes, i.e. measures of cardio-metabolic risk, to body fatness and to

measure its distribution. Under this overarching goal specific objectives were finalized as mentioned in section 1.4 (Page no.40).

Quantitative data was collected from schools in 3 regions (New Delhi, Shillong and Hyderabad) from a representative sample of 3242 children between 6 to 18 years of age. Detailed assessments were done on; a) anthropometry; b) pubertal staging; c) blood biochemistry (fasting plasma insulin, fasting plasma glucose, lipid profile and sub-fractions uric acid) using semi-automated analyzer), d) body composition by bio impedance (BIA) (InBody 720, body composition analyzer, Biospace©), e) body composition using DEXA (Hologic QDR 4500A) on selected sub samples, f) socio-economic status (standard of living index), g) media and market exposures, h) food frequency and dietary recalls, and i) physical activity recalls. The results are presented as:

- Study 1: Assessment of whole-body composition using bioelectrical impedance analysis (BIA) among children 6 to 18 years: Validation with Dual X-Ray Absorptiometry (DEXA)
- Study 2: Reference values and Percentile curves for cardio-metabolic risk factors among Indian children (6 to 18 years)
- Study 3: Clustering of Bio-chemical Markers of Cardio-metabolic Risk among Indian Children: An Imperative for Continuous Monitoring of Risk Factors
- Study 4: A multi-level framework for monitoring cardio-metabolic risk: proximal & distal factors associated with clustering of bio-chemical markers

Results:

Around 3241 children (1611 boys and 1630 girls) between 6 to <19 years (13 age bands) were recruited from schools in rural and urban settings in three study locations. As per revised national standards (IAP Growth charts, 2015) there was 8.4% overweight and 4.9% obese boys as compared with 10.6% overweight and 3.9% obese girls (Table 6).

Body fat estimation: For estimating body fat DEXA measurements were considered as the criterion standard; which was done in a sub-sample of 206 children (105 boys and 101 girls). Body fat from DEXA were compared with direct outputs of bio-impedance (BIA) machine and have shown a mean bias of -18.9% fats among boys and -11.2% fats among girls; highlighting that the existing fat predictions does not represent Indian children and there is a need for new prediction equations for estimating fat. Linear prediction models were developed to predict lean mass and fat mass among girls and boys (developed in sub-sample and were predicted in full

sample). Absolute difference (bias) and percentage differences in predicted lean (BIA) from expected lean (DEXA lean) were tested among thin, normo-weight, overweight and obese children (Table 10). In our study, the new BIA prediction equation could precisely predict lean mass among 82.4% (n=84) boys, moderately in 15.7% (n=16) and imprecise in 2% (2) boys. Among girls, the BIA prediction could precisely predict lean mass among 77.6% (n=76) girls, moderately in 21.4% (n=21) and imprecise in 1% (1).

Growth curves: Lambda (L), Median (Mu) and Sigma (S) values were estimated for each age bands for boys and girls – templates were developed for manual calculation and compared with LMS chart maker (Pro version). Reference values for 5th, 10th, 25th, 50th, 75th, 85th and 95th centiles were estimated to prepare smoothened centile curves. Reference values and centile curves for various cardio-metabolic risk conditions are presented under two subheads; a) bio-chemical markers [Glucose monitoring (Fasting glucose & HbA1C (Glycated Hemoglobin)); Insulin Resistance (HOMA-IR); blood pressure monitoring (Systolic BP, Diastolic BP and Mean Arterial Pressure) lipid monitoring (Total cholesterol, Low HDL-C, Triglycerides, Apo-B representing non-HDL and Apo-A proteins representing HDL-C) and Uric acid levels] and b) clinical markers [Nutritional status (BMI for age, Weight for age & Height for age); Body Composition (Percentage body fat & Fat mass index) and abdominal obesity (Waist circumference).

Clustering of Cardio-metabolic risk: Standard definitions were used for seven different clinical conditions that shall indicate cardio-metabolic risk among children. Clustering of these risk factors were studied among children ≥ 10 years using two models. Overall, there was substantial level of agreement between two models (boys: kappa 0.64, P=0.001) and (girls: kappa 0.63, P=0.001). Clustering of 3+ risk factors are distributed among normo-weight, overweight and obese as per existing BMI-for-age categorization: among normal weights 2.2% boys (19/871) and 5.5% girls (45/818) were having clustering of 3 and more risk factors. Among overweight children, 11% boys (10/90) and 21.7% girls (20/92) were having clustering of 3 and more risk factors as compared to 34% obese boys (14/41) and 37.8% obese girls (14/37) having clustering of risk factors. Moreover existing classification system based on BMI-for-age (at 23rd adult equivalent centile for overweight and 27th adult equivalent centile for obese) could not capture all children with cardio-metabolic risk (less sensitive more false negatives).

The current public health system, across the globe, emphasis on obesity (above 27th adult equivalent BMI-for-age in South-east Asia and 30th adult equivalent in other countries); however

it shall be too late to intervene as changes in cardio-metabolic profile starts much earlier – at the level of overweight or even lesser. Distribution of fat mass index (FMI) and percentage body fat (PBF) along with waist circumference (indicator of abdominal obesity) were compared in children having risk factors. Average BMI, FMI, PBF and WC was significantly higher among children with 3 and more risk factors (Figure 16 to 19).

Thus, on the existing BMI-for-age classification system (IAP growth charts), we propose to include the new definition based on cardio-metabolic risk. New growth charts (modified existing growth standards) has been developed and presented in figure 21 (Page no.151). It can classify children (dotted lines) as;

- High risk: Those children with more than 3 risk factor clustering across age groups
- Intermediate risk: Those children having 1 or 2 risk factors across age groups and
- Low risk: Those children with less than 0 risk factors

In addition, we propose to use FMI based growth charts with CMR categorization for monitoring overweight and obesity. ROC curves were plotted against clustered risk factors and anthropometric variables (BMI, FMI, PBF and WC). Area under ROC curves were higher among children with 3 and more risk factors as compared to children with no risk factors (Table 24a and 24b) – indicating strong association. Table 25 depicts the sensitivity and specificity of identifying children with clustered risk factors by BMI-for age categorization.

Environmental correlates: Study were done to understand: a) list of variables in a child's environment (individual practices, home, school and neighbourhoods) that are significantly associated with clustering of cardio-metabolic risk; and b) to estimate the strength of their direct and indirect associations.

a. **Standard of Living (SLI):** Distribution of cardio-metabolic risk across social strata's (SLI) highlights that cardio-metabolic risk as well as obesity is not only a problem of affluence and the risk is distributed across social strata, urban-rural settings and gender.
b. **Consumption pattern:** Overall, around 36.5% boys (537/1473) and 34.8% girls (517/1485) were consuming inadequate energy per day (less than 80% of recommended dietary intake). At the same time, 29% (429/1473) boys and 26.2% girls (389/1485) consume more than 120% of RDA. Mean Adequacy Ratio (MAR) for 11 micro nutrients were estimated. Among those children with 3 and more cardio-metabolic risk clustering mean nutrient adequacy ratio (MAR) was higher among boys (P=0.004) while this was not different in girls.

c. **Food groups:** Among those children with 3+ risk factors, snacking was higher among boys (P=0.01) (diff: +52.2 g/day) while no difference was observed among girls (P=0.54) (diff: +6.5 g/day). Overall, cereal consumption was higher among boys (P=0.03) (diff: +93.6gm/day) and girls (P=0.005) (diff: +69 g/day) who had clustering of 3 and more cardio-metabolic risk factors. No difference in consumption of fruits among girls with 3+ CMR clustering. In multivariate analysis inadequacy of micro-nutrients were significantly predicting clustering of CMR (OR=3.2; P=0.03) while among girls inadequacy of proteins (P=0.000) and micro-nutrients (OR=7.9; P=0.001) were significantly predicting the clustering of cardio-metabolic risk. After adjusting for age-groups and settings, snack eating behaviour (P=0.006) and sugar sweetened beverages (SSB) consumption (P=0.019) were found to be positively associated with increase in BMI among boys. However there was no such association among girls. Similarly, per-capita cereal consumption was the only food group that was associated with 3+ clustering of cardio-metabolic risk among girls.

d. **Physical activity:** Duration of sedentary activities (in minutes and % time of all activities) and their MET minutes during week days and weekends were not significantly different among children with 3+ clustering of risk factors; both in rural and urban settings. After adjusting for age groups (6 to <10 years, 10 to <15 years and 15 to <19 years), gender and rural-urban settings the multivariate analysis could not discriminate children with 3+ clustering of risk factors on the basis of type of physical activities reported. However among overweight/obese boys, percentage time spent on sedentary physical activities during week days (P=0.014) and light physical activities during week end's (P=0.011) were positively associated with increase in BMI. Percentage time spent on moderate physical activities during week days (P=0.025) were negatively associated with increase in BMI. Similarly, among overweight/obese girls, percentage time spent on sedentary activities during week days (P=0.008), week end's (P=0.02) and percentage time on vigorous physical activities during week days (P=0.026) were positively associated with increase in BMI.

e. **Sleep:** Among boys and girls, duration of sleep was found as a protective factor against clustering of cardio-metabolic risk.

f. **Mode of transport to school:** Boys commuting to schools in motorized scooter/bike were having 5 times increased risk of clustering of cardio-metabolic risk as compared to those walking to schools – however this relationship were not significantly different among girls.

g. **Distance of school from home:** Another factor which was found significantly associated with clustering of risk factors among boys is the distance of school from home however this was not significant among girls.
h. **Access to gadgets:** Increased access to video games, DVD, Radio/FM, Computer/laptops, separate video games and personal mobile phones were all significantly associated with clustering of risk factors.
i. Parental control and duration of watching TV were also found to be significantly associated.

Whole of Society Monitoring framework: Entire thesis was conceived as an effort to identify a whole of society monitoring framework that shall help in identifying and monitoring children with cardio-metabolic risk factors without actually collecting individual level data. That means by looking at specific indicators at aggregate levels in a society, WoS framework should help to predict the number of children at risk of cardio-metabolic risk. For example, sales of sugar-sweetened beverages, snacks, standard of living index, distance to schools, parental controls etc., shall help to predict CMR clustering in a WoS monitoring framework. Unfortunately, the current data collected have not shown such predictive properties directly and this require 'Structural Equation Models' to identify and control variables that are mutually interacting. Further, continuing studies are required in this direction.

Acknowledgements

Indian Council of Medical Research (ICMR) in 2012-13 have constituted an obesity task force including partners from AIIMS New Delhi, NIN Hyderabad, NEIGRHMS Shillong, GMC Srinagar, and MP Shah Medical College, Jamnagar with INCLEN Institute of Global Health (IIGH) as the coordination agency. Members of the task force felt the urgent need to critically look at the issues pertaining to childhood obesity in India. Task force has conceptualized and executed this study entitled *"Childhood Obesity in India: A multi-center study on its measurements and determinants with reference to cardio-metabolic risk factors"*. Entire effort was a team work and had multiple stakeholders and investigators involved at various levels who have played critical roles as defined in the protocol. The topic was conceptualized by investigators in the team. I am deeply indebted to all those who have directly and indirectly contributed in the study.

During this thesis analysis, I was extensively exposed to various aspects of Quantitative and Qualitative data (392 interviews) which has helped me to understand the subject in-depth. I sincerely thank Prof. Narendra Kumar Arora, Executive Director, INCLEN for providing guidance, opportunity, mentorship and support through-out the time-period. I also acknowledge the team members and colleagues at INCLEN who have directly and indirectly enhanced my understanding on the subject.

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Major Activities Accomplished during this Thesis

In addition to the thesis following activities were accomplished:

	Title	**Agency**	**Timeline**	**Comment**
Compendium of research on childhood obesity in India	Status Report of Childhood Obesity Research in India.	Indian Council of Medical Research (ICMR) - Peer review process completed	2017-18	11 chapter on different aspects of childhood obesity research. Contributed in 4 chapters & coordinated with different authors in preparing compendium
Multi-sectoral Policy Analysis	Scoping study for Addressing Obesity among Children and Adolescents in India	World Health Organization (WHO), India	May 2016 to Mar 2017	9 ministries and 40 public policies reviewed. 19 interviews conducted with stakeholders and policy briefs submitted to ministries for policy level action
Path for convergence	Pulse Innovation Platform (PIP)	McGill University, Canada	Since Apr 2016	Facilitating a model for bringing multiple sectors together for increasing pulses availability and consumption in market.

Teaching/Training Programs

	Title	**Agency**	**Timeline**	**Comment**
Invited Faculty (Strategic Planning & Management)	International Public Health Management Development Program (IPHMDP)	School of Public Health, PGIMER, Chandigarh	Since Mar 2016	So far, 4 training sessions on strategic planning have been conducted
Coordination & organizing	Leadership & Management Program (LAMP)	The INCLEN Trust International	Nov 2015 & Jan 2017	15 days residential training program for medical faculties
Invited faculty	Data management & statistical analysis	Jamia Hamdard University, New Delhi	May 2017	Post-graduate trainees on clinical trials
Speaker	Pharmacovigilance & Pharmacoepidemiology	Kerala State Pharmacy Council	Nov 2017	More than 100 participants across the state
Speaker	Determinants of Childhood Obesity	NIN, Hyderabad	Dec 2017	Centenary Celebrations

- 4 manuscripts in relation to thesis topic has been submitted to investigators of task force for their inputs.

- Johnson, Claire; Praveen, Devarsetty; Pope, Alun; Raj, Thout S.; **Pillai, Rakesh N**.; Land, Mary Anne; Neal, Bruce. Mean population salt consumption in India: a systematic review. Journal of Hypertension, 2016 [doi: 10.1097/HJH.0000000000001141]

- **Pillai R**, Dasgupta R, Mathur P, Arora NK. Can competitive advantages of markets be leveraged for addressing childhood obesity in India?. Indian J Community Med 2015;40(3):145-8

- Dasgupta R, **Pillai R**, Kumar R, Arora NK. Sugar, Salt, Fat, and Chronic Disease Epidemic in India: Is There Need for Policy Interventions?. Indian J Community Med 2015;40(2):71-4

- Arora, N. K., **Pillai, R**., Dasgupta, R. and Garg, P. R. Whole-of-society monitoring framework for sugar, salt, and fat consumption and noncommunicable diseases in India. Annals of the New York Academy of Sciences. 2014. doi: 10.1111/nyas.12555.

CHAPTERS IN BOOKS

- **Rakesh N Pillai,** Narendra K Arora, Abha Mishra. Concepts and Applications of Planning in Health: An imperative for Coping with Uncertainties. Essentials of Health Management. Oxford University Press, India. 2017 (Under process)

- Narendra K Arora, **Rakesh Pillai**. Research in Office Practices: Translating Clinical Information to Evidence based Research, (Chapter 1.6). IAP Textbook of Pediatrics, Sixth Edition. Indian Association of Pediatrics. Jaypee Publications. 2016. P:22

- Narendra K Arora, **Rakesh Pillai,** Sanjiv Kumar. Introductory Research Methodology. Frontiers in Social Pediatrics, (Section 6: Chapter 29). Second Edition, Jaypee Publications. 2016, P:282

- Narendra K Arora, Priyankarani Garg, **Rakesh Pillai**. Childhood Obesity and its determinants. Textbook of chronic non-communicable diseases: The health challenge of 21st century. Jaypee Publications. 2016: P:142-165

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ABBREVIATIONS (ALPHABETICAL)

AACE	American Association of Clinical Endocrinology	IDF	International Diabetes Federation
AAP	American Academy of Pediatrics	IFA	Iron Folic Acid Tablets
ADP	Air-Displacement Plethysmography	IGF-1	Insulin-like Growth Factor-1
AIIMS	All India Institute of Medical Sciences	IGT	Impaired Glucose Tolerance
AMA	American Medical Association	IIGH	INCLEN Institute of Global Health
APEDA	Agricultural And Processed Food Export Development Authority	IOTF	International Obesity Task Force
APO-A	Apolipo-protein A	IR	Insulin Resistance
ASSOCHAM	Associated Chambers of Commerce and Industry of India	ISPAD	International Society of Pediatric and Adolescent Diabetes
ATMs	Adipose Tissue Macrophages	IL-6	Inerlukin-6
ATP	Adenosine Tri-phosphate	INS	Insulin
BAT	Brown Adipose Tissue	IOTF	International Obesity Task Force
BIA	Bio-electrical Impedance Analysis	LDL	Low Density Lipoprotein
BIS	Bureau of Indian Standards	LPL	Lipoprotein Lipase
BCM	Body Cell Mass	MAP	Mitogen-Activated Protein Kinase
BMC	Body Mineral Contents	MAP	Mean Arterial Pressure
BMD	Bone Mineral Density	MeSH	Medical Subject Headings
BMI	Body Mass Index	MPI	Multi-Dimensional Poverty Indices
BPD	Bilio-Pancreatic Diversions	MUAC	Mid Upper Arm Circumference
BP	Blood Pressure	MUFAs	Mono-unsaturated Fatty Acids
CAGR	Compound Annual Growth Rate		
CCK	Cholecystokinin	NAFLD	Non Alcoholic Fatty Liver Diseases
CCO	Central Coordinating Office	NCD	Non-Communicable Disease
CHO	Carbohydrate	NEFA	Non-esterified fatty acids
CLA	Conjugated Linoleic Acid		
CMRF	Cardio-Metabolic Risk Factors	NF□ B	Nuclear Factor □ B
CPON	Chronic Postnatal Over Nutrition	NIN	National Institute of Nutrition
CRP	C Reactive Proteins		
CURES	Chennai Urban Rural Epidemiology Study	NMFP	National Mission on Food Processing
CV	Coefficient of Variation	NNMB	National Nutrition Monitoring Bureau
CVD	Cardiovascular Diseases	NSSO	National Sample Survey Organization
DBP	Diastolic Blood Pressure		
DEXA	Dual-energy X-ray Absorptiometry	OGTT	Oral Glucose Tolerance Testing

EAT	Epicardial Adipose Tissue	PBF	Percentage Body Fat
ECF	Extracellular Fluids	PCOS	Polycystic Ovarian Syndrome
BCPE	Box-Cox Power Exponential	PDS	Public Distribution System
ECW	Extracellular Water	PHVO	Partially Hydrogenated Vegetable Oils
ECS	Extracellular Solids	PPP	Purchasing Power Parity
EE	Energy Expenditure	PUFA	Polyunsaturated Fatty Acids
EI	Energy Intake	RDI	Recommended Dietary Intake
EPODE	Ensemble Prevenons l'Obesité Des Enfants	RMR	Resting Metabolic Rate
ES	Energy Storage	SAP	Statistical Analysis Plan
FFA	Free Fatty Acids	SBP	Systolic Blood Pressure
FFDM	Fat Free Dry Mass	SD	Standard Deviations
FFM	Fat Free Mass	SEM	Standard Error Of Means
FFQ	Food Frequency Questionnaire	SFT	Skinfold Thickness
FM	Fat Mass	T2D	Type 2 Diabetes
FMI	Fat Mass Index	TBW	Total Body Water
FPU	Food Processing Units	TBK	Total Body Potassium
FT4	Free Thyroxine	TEE	Total Energy Expenditure
FTO	Fat Mass and Obesity Associated Gene	TEI	Total Energy Intake
GDP	Gross Domestic Product	TFA	Trans Fatty Acids
GHRL	Ghrelin	TNF-α	Tumor Necrosis Factor-□
GI	Glycemic Index	TSH	Thyroid Stimulating Hormone
GL	Glycemic Load	UWW	Underwater Weighing
GOI	Government of India	VLDL	Very Low Density Lipoprotein
HC	Hip Circumference	VVOF	Vanaspati, Vegetable Oils and Fats
HDI	Human Development Index	WAT	White Adipose Tissue
HDL	High Density Lipoprotein	WC	Waist Circumference
HGIF	High Glycemic Index Foods	WHA	World Health Assembly
HOMA-IR	Homeostatic Model Assessment – Insulin Resistance	WHR	Waist-Hip Ratio
hsCRP	High sensitive C reactive protein	WHO	World Health Organization
IAP	Indian Association of Pediatrics	ZI	Impedance Index
ICMR	Indian Council of Medical Research		
ICW	Intracellular Water		

Rapid changes in societies and living conditions have generated exceptional changes in lifestyle especially to food habits leading to greater rates of chronic diseases like and a strain on any nation's healthcare budget. Cardio-metabolic risk factors (CMRF), majorly hypertension, overweight or obesity, Type 2 diabetes, dyslipidemias and metabolic syndrome, are prevalent in all age group in all geographic regions. These are related to birth characteristics as well as continuing effects of prenatal, maternal and fetal factors interacting with postnatal exposures. Often the metabolic changes to chronic diseases start earlier in childhood that predicts individual's overall risk of cardio-metabolic diseases in adulthood.[1] Over 70% of obese children were found to have at least one risk factor for cardio vascular diseases.[2] These children are prone for metabolic consequences such as insulin resistance, fatty liver, coronary artery diseases and poly-cystic ovarian syndromes (PCOS). Such effects may probably due to a combination of gene-environment interactions mediated through toxic metabolic effects of free fatty acids and adipose tissues.

Primarily, overweight and obesity is due to accumulation of fats in adipose tissues attributed to the imbalance between calories consumed and calories spent. Other energy stores like carbohydrate glycogens or proteins in liver and muscle do not have the potential to increase body weight that could exceed the limits. Variation in prevalence rates of childhood overweight and obesity from region to region and from time to time implies that changes in physical, built and social environment, especially those associated with economic and human development will have mutually interacting and influencing roles. Changes to behavioural and environmental lifestyle of individual and family as a whole are the primary driver of obesity epidemic, exacerbated with underlying biological causes – such forces are commonly referred to as 'obesogenic' environment. With rapidly transitioning societies and more disposable income among Indian families, children are consuming more and more processed foods with high calories and invisible salt, sugar and fat in it. Sugar consumption has direct associations with rising obesity/overweight prevalence while it is a rate determining step in cardio-metabolic risk factors like diabetes and hypertension. Econometric studies predict that every 150kcal/person/day increase in sugar availability could increase 1.1% of diabetes prevalence in the population.[3]

In addition to increased risk of cardio-metabolic consequences; children with excess weight could suffer from adverse conditions like: 1) physical and 2) psychological and social. In physical consequences child could suffer respiratory and sleep problems, complications of hormones

including insulin resistance, high blood pressure and abnormal cholesterol, high serum triglycerides and orthopedic morbidities. Morbidly obese children are prone for spectrum disorders like NAFLD, ranging from benign fatty liver (steatosis) to more serious inflammatory condition like steatohepatitis which can potentially progress to fibrosis, cirrhosis and end stage liver disease. In addition, excess adiposity could have detrimental effect on child's psychological and social functioning skills. Chances of discrimination and stereotyping are high among these children which leads to low self-esteem, increased depressive symptoms and unhealthy dietary practices.

1.1. Defining Cardio-Metabolic Risk and Childhood Obesity

Broadly, cardio-metabolic diseases refers to the combination of cardio-vascular and metabolic disorders - those factors that increases an individual's chance of damaging his/her heart and/or blood vessels are referred to as cardio-metabolic risk factors (CMRF).[4] This includes anthropometric, bio-chemical, behavioural and environmental drivers. There are several other mutually interacting factors that are associated in this disease continuum (from birth till death) and CMRFs are particularly prevalent among patients diagnosed with obesity/overweight, diabetes and hypertension patients; especially in a rapidly transitioning societies.[5]

World Health Organization (WHO) defines overweight and obesity as: 'abnormal or excessive fat accumulation in fatty tissues (adipose tissue mass) that may impair health'.[6] Measuring fat and estimating its level in the body, when it is likely to impair health, is a difficult task. With advancement of technologies, many techniques for measuring fat are available however for logistic reasons most of their use are limited to healthcare settings. At population level estimations using body height and weight are most widely used. Most common is Quetelet index, better known as body mass index (BMI), which is body weight (kg) divided by height squared (m^2) – an estimate found to have high correlation with body fatness among adults however this fails to distinguish between lean body mass and fat especially among children. For instance at same BMI, percentage body fat for males and females are different.[7] In addition, cut off's for defining overweight or obesity is different in ethnic regions – for Asian adults, BMI greater than or equal to 23 is defined as overweight and above 27 as obese while this is 25 and 27 for people from developed world. This is because; Asians are known to have more adiposity and higher cardio metabolic risk at lower BMI levels.[8]

In children and adolescents, ascertaining obesity using BMI is complicated due to fluctuating body weight, height and body composition with time (increasing age) and gender. Therefore growth charts (normogram) for age and genders are commonly used. There is no internationally acceptable index to assess childhood obesity nor there is any established cut offs to define overweight or obesity. Growth charts are available from CDC[9] and WHO[10] with different indicators like: height for age, weight for age, weight for length, weight for height and BMI for age. BMI for age, though not a perfect measure of adiposity as it co-varies with height, can be considered appropriate in the absence of another pragmatic measure to define body fat. Indian Association of Pediatrics (IAP) recommends specific growth charts for boys and girls prepared on Indian children between 5 to 18 years while for younger children it recommends the use of WHO growth charts.[11]

However a clear recommendation on which percentile to be used to define overweight and obesity is still not clear. Cutoffs for children (5-19 years) recommended by WHO is BMI > +1 SD (85th percentile) for overweight and for obesity this cut off is BMI > +2 SD (97th percentile).[12] In India, most commonly used cut-offs are: children above 95th percentile (adult equivalent) as obese and those over 85th percentile and below 95th percentile (adult equivalent) as overweight. Indian Association of Pediatrics, recommends to consider Indian children above 10 years of age as overweight if their BMI is > 85th percentile for age or if their weight is >120% of 50th percentile of weight for height as per national standards.[13] Marwaha et al., (2011) in one of the largest nationwide study, with over 100,000 children form 19 cities recommends of using 75th percentile in current BMI charts to categorize as overweight. These disparities in recommendations in India are highlighted to emphasize the need of more accurate strategies based on body fat for re-defining obesity and overweight. This report will discuss the utility of various growth charts in subsequent sections.

1.2. Trends in Childhood Obesity Epidemic in India

Childhood obesity has been interpreted as compulsive overeating under the influence of brain mediated through dopamine receptors.[14] Children consume significantly more calories and products having invisible salt, sugar and fat products, with taste thresholds adapted/changing with time – depending upon the exposure, accessibility, availability and affordability of products in the market.[15] In the past two to three decades: national prevalence of prevalence of overweight and obesity increased almost four times from 4% to 15%,[16] while type 2 diabetes among Indian adults

increased from 5.9% to 9.1% and hypertension prevalence increased from 17.2% to 29.2%, with significant urban-rural differences.[17]

It is pertinent to point out that, most Indian studies are not comparable as difference exists in methods, datasets, BMI cut offs, smoothening methods and using arbitrary assumptions;[18] therefore presently no reliable national level estimate in the prevalence of childhood obesity is available. However a systematic review conducted by Gupta et al., (2012)[19] reported that prevalence of overweight, among 5 to 19 years children, ranges between 6.1 and 25.2% while that of obesity ranges between 3.6 to 11.7%. Khadilkar et al., in 2010 have estimated the combined prevalence of overweight and obesity as 19.6% as per IOTF classification while this was 27% when using WHO standards.12 Among adolescence, between 10 to 17 years, the percentage was 22.3% (as per IOTF cut off) and 29.8% (as per WHO cut off) – this age groups should be considered as most vulnerable for adiposity.

Table 1: Prevalence of childhood obesity in India

Author	Year	Age group	Region	Overweight	Obesity
Ramachandran et al.	2002	13 to 18	Chennai	Boys 17.8 and Girls 15.8	Boys 3.6 and Girls 2.7
Kapil et al.	2002	10 to 16	Delhi	24.7%	7.4%
Mohan et al.	2004	11 to 17	Ludhiana	Urban 11.6 and Rural 4.7	Urban 2.3 and rural 3.6
Khadilkar et al.	2004	10 to 15	Pune	19.9%	5.7%
Rao et al.	2006	9 to 16	Pune	Boys 24.7 and Girls 21.1	
Sharma et al.	2007	4 to 17	Delhi	22%	6%
Laxmiah et al.	2007	12 to 17	Hyderabad	Boys 6.1 and Girls 8.2	Boys 1.6 and Girls 1
Kaur et al.	2008	5 to 18	Delhi	LIG 2.7, MIG 6.5 and HIG 15.3	LIG 0.1, MIG 0.6 and HIG 6.8
Bhardwaj et al.	2008	14 to 17	New Delhi		PS 29.0, GS 11.3 and total 24.3
Premnath et al.	2009	5 to 16	Mysore	8.5%	3.4%
Misra et al.	2010	8 to 18	North and west India	18.5%	5.3%
Gupta et al.	2009	14 to 17	New Delhi	25.2%	11.7%

Studies have reported high prevalence of overweight and obesity among children from higher socio-economic strata especially in private schools and in urban and semi urban environment: Kaur et.al, (2008) reported three times higher number of overweight children (15.3%) and 6.8% obese children in high income schools.[20] Alarmingly, among high income schools about 12% children were consuming energy dense fast foods more than four times in a week. Another study reported obesity prevalence (including overweight) as high as 29% in private schools while compared to 11.3% in government schools.[21]

Considering the wide base of Indian population; these rates would translate in to approximately 58 million obese and 122 million overweight children in the country, many of them likely to continue in adult ages contributing to cardio-metabolic risk pool of the country. Also, it is frightening to know that a unit percent rise in its prevalence in India shall add at least another 5 million obese and overweight children into the cardiovascular risk pool; demanding urgent need for population intervention to curb this epidemic. A close relationship with overall improvement of various dimensions of development, including economy can be assessed by the differences in the regional prevalence of overweight and obesity and HDI (human development index): 22.7% in high HDI states and 20.8% in low HDI states. With studies reporting at least one cardiovascular disease risk in 70% of obese children,[2] there is a need for immediate social, political and market based interventions to contain this 'public health catastrophe'.

1.3. Drivers of Childhood Obesity Epidemic in India

Unprecedented changes in lifestyle, especially individual's food preferences and food choices coupled with less physical activity, are the after-effects of rapid urbanization, mechanization and globalization. The process of acquisition of food preferences is a continuous learning process trigged by internal and external cues and mediated by rewarding and disgust. A confluence of these factors has led to escalating rates of obesity, dyslipidemia, subclinical inflammations, metabolic syndrome, T2D and coronary heart diseases. At same time, India is home to 40% of the world's malnourished children while becoming a victim of rising obesity rates, even in its urban slums, and taking on the dubious reputation of being the "diabetes capital of the world". In this context where deprivation and obesogenic conditions often coexist, we try to build a case for addressing various drivers of cardio-metabolic risk conditions. In this thesis, drivers of childhood obesity are discussed at micro (child), meso (family) and macro level (community

context); we followed the EPODE program ('Ensemble Prevenons l'Obesité Des Enfants') to address childhood obesity in France.[22]

Major drivers of childhood obesity epidemic can be clubbed under 3 broad headings: 1) Macro level perspectives (society and community level), 2) Meso level perspectives (household level) and 3) Micro level (individual level).

1.3.1. Societies in Transition (Macro level perspectives):

In the past two to three decades in India, there has been fairly rapid industrialization, urbanization and improvement in services in both the public and private sectors. India's gross domestic product (GDP) growth is among the top five in the global list and the per capita purchasing power parity (PPP) is increasing[23] while the GINI Index is among the lowest. Paradoxically, multi-dimensional poverty indices (MPI) are fairly high with India ranked at 74 out of 104 countries.[24] These indices for Indian states and social groups indicate wide variations and inequalities within India, signifying both economic and demographic transitions as well as vulnerability.

India's food processing industry is currently the fifth largest globally. The overall size of the industry was estimated around $200 billion by the end of 2016. Concomitantly, the number of food processing units (FPU) and their contribution to India's GDP, from registered and unregistered units, is increasing sharply.[25] The Agricultural and Processed Food Export Development Authority (APEDA) noted a significant expansion of India's agro and processed food exports while CII-McKinsey reports highlight a forecasted expansion of nine per cent every year.[26] The non-alcoholic ready-to-drink beverages segment has also grown at a compound annual growth rate (CAGR) of 13 percent since 2009.[27] Caloric beverages are emerging nationally as an additional and significant source of energy both among children and adults. In lower middle, middle and upper social classes the proportion of annual energy consumption attributed to beverages has increased substantially. In US this has gone up from 242 kcal per person per day in 1988-1994 to 270 kcal per person per day in 1999-2004.[28] Stern et al., (2014) reported similar trends from Mexico however at present such information is not available from India.[29]

The domestic demand for processed foods, sugar sweetened beverages and savory snacks are associated with disposable household incomes of the Indian middle class.[30] The consumption pattern of the middle class is non-homogenous, steadily increasing and the driving force for

household consumer goods in the market. Market research studies on the financial independence of middle class women highlighted that the purchasing power and income of urban women has doubled in the past decade. Brand experts from industries recognize that purchasing power in families is moving into the hands of women.[31] Around 26 per cent of the working force in rural areas and 13.8 per cent of urban workers are women.[32] A recent study on under nutrition, by The INCLEN Trust International, highlighted that women in both urban and rural India are spending less time on cooking. This along with the shift in purchasing power and disposable family incomes probably explains the rising demand for packet foods and semi cooked food items.

The Indian processed food market is boosted by a range of supply side factors including favorable agro-climatic conditions for a wide variety of crops, availability of water, enhancement in end-product manufacturing and packaging technologies, large livestock base (for dairy and meat processing units) and low cost of labor. So far, policy instruments that have facilitated setting up of food processing units include: 100 per cent tax exclusion for the initial five years; followed by 25 per cent tax-exemption for another five years; allowing 100 per cent export-oriented units to sell 50 per cent of their products in the domestic market; waiving off import duty on raw materials and capital goods for 100 per cent export-oriented units; exempting export from taxes and 100 per cent FDI.

The government has made several direct budgetary interventions to boost the food-processing sector. For example, financial assistance of $24.37 million was provided to 966 food-processing entities in 2012-13 under the up-gradation, launching and modernization scheme.[33] The government has already initiated plans for creating 30 more mega food parks. Growing at a compound annual growth rate (CAGR) of about 15 to 20 per cent, the Indian packaged food industry (including snack foods, ready-to-eat foods, and healthy and functional foods) is likely to touch $ 30 billion by 2015 from the current level of $15 billion.

Presently, the main categories of packed food sold in India are bakery products; canned/dried processed foods; frozen processed foods, meal replacement products and condiments (like sauces). Some emerging new categories in this segment are processed dairy products; frozen ready-to-eat foods; savory snacks; processed meat and probiotic drinks. Sale of packaged food in 2011 was the highest in northern India (38%), followed by the west (36%), south (28%) and east and north-east (21%). The growth of organized retail and refrigeration facilities is expected

to further boost the market. The Associated Chambers of Commerce and Industry of India (ASSOCHAM) forecast a 40-60 per cent growth in the food processing industry in the next five years.[34] The National Mission on Food Processing (NMFP) was launched in 2010 with the aim to increase food-processing levels from 10 per cent (in 2010) to 25 per cent by 2025.

Market researchers highlight that most of the growth is reported for confectionary, biscuits, savory snacks, chocolates and ice creams, all of which have a high content of sugar, salt and fats.[35] A market research organization (KPMG) reported that 65 per cent of the total sugar sold across India is consumed by bulk purchasers indicating that the use of added sugar in food processing, as a preservative as well as for improving texture, has increased.[36] The amount of salt being consumed by humans through savory foods in India is not known as yet.

1.3.2. Changing Food Consumption Patterns at households (Meso level factors):

Concomitant to the above mentioned changes in society and markets, the food preferences and food choices of individuals and households have also changed. In India, per capita consumption of sugar increased from 22 grams/day in 2000 to 55.3 grams/day in 2010 (Figure 1) while per capita consumption of table salt ranges between 9 to 12 grams/day.[37] The per capita consumption of total fat was 21.2 grams/day in 2000 and increased to 54 grams/day in 2010. A similar trend was observed in the per capita edible oil consumption which increased from 27.3 grams/day to 37 grams/day. The consumption of partially hydrogenated vegetable oils (PHVO) including palm oils increased from 1.67 grams/day to 2.8 grams/day.[18] Palm oil is abundantly available in the market, largely imported from Malaysia. Till 2005-06, it attracted an import duty of over 60 per cent; thereafter, the import duty has been reduced to almost zero for more than one reason. Palm oils are high in saturated fat and low in polyunsaturated fat, thus contributing to heart diseases and WHO advices reduced consumption of palm oils.[38] Basu et al., (2013) use an economic epidemiologic model to demonstrate that a 20 per cent tax on palm oil purchases would help to avert approximately 363,000 deaths from myocardial infarctions and strokes over 2014-23 in India (a 1.3% reduction in cardiovascular deaths) if people substituted other oils and reduced palm oil consumption.[39]

At the national level, the per capita consumption of sugar is now approximately 10 spoons, adding up to 18 kg/year (ICAR, 2011).[40] The current global average is about 23 kg per capita per year; ranging from a low of 8 kg/year in Bangladesh to 66kg/year in Israel. Cumulative domestic purchase of white sugar in India has also increased. India produces 17 per cent of the total global

sugar but its share in export is only four per cent, signifying high demand in the domestic market.[41] Around 30 million tons of sugar was released for domestic consumption in 2015-16 compared to 16.7 million tons in 2001-02. Increased use of sugar could be related to the relatively lower market price of sugar in India. Sugar is currently sold at a price of about Rs.35 per kg (approximately half a US dollar); among the lowest in the world.[37]

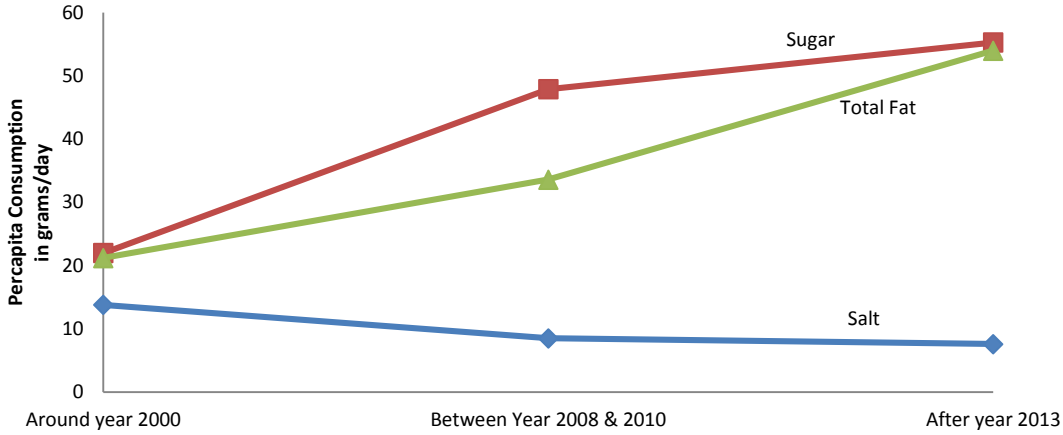
In 2012-13, around 26 million tons of sugar was consumed as per the Sugar Release Order, Food and Public Distribution Department. Market research companies (KPMG) reported that up to 55 per cent was procured by bulk purchasers and was majorly used in food processing and confectionery industry, and only 14.3 million tons was available for household consumption. (This works out to 11.46 kg/year i.e. 31.4 grams/day.) Further, 10 per cent of the total sugar produced was considered as levy sugar for the public distribution system (PDS). The National Sample Survey 2010 reported per capita consumption of 55.3 grams of sugar per day however this is based on self-reported data through household level questionnaires.

Population studies by the ICMR in 1988 in 13 Indian states reported salt consumption at 13.8 grams/day. Recent estimates by the ICMR-INDIAB study reports 7.6 ± 3.3 grams/day consumption in urban areas, significantly higher than that in rural areas (6.8 ± 3.5 grams/day). Salt consumption reported in the 66th Round of NSS in 2010 was 8.9 grams per person per day, which is above the National Institute of Nutrition (NIN) recommended RDI (Recommended Dietary Intake) of five grams per person per day.[42] The Chennai Urban Rural Epidemiology Study (CURES) also reported mean dietary salt intake as 8.5 grams/day; while higher salt intake was associated with older age and higher income.[43] The salt manufacturing industry puts the current daily consumption at about seven grams/ day on the basis of sales data. This has to be read in conjunction with rising annual production of edible salt, from 2.8 (million tons) in 1992-93 to 6.2 (million tons) in 2013.[31]

The per capita consumption of total fat was 54 grams/day while consumption of edible vegetable oils was 27.6 grams/person/day. The Directorate of Vegetable Oils, Vanaspati and Fats (VVOF), GoI reports that 19.8 million tons of edible oil was consumed in 2012-13 (including both domestic and imported sources), which was 11.8 million tons in 2004-05. The consumption of fat in 1983 was 25 grams/person/day in rural and 36 grams/day in urban areas (NSS, 38th round). Average consumption of hydrogenated vegetable oils was 2.8 grams/person/day while

trans-fat consumption was estimated at 1.64 grams/person/day. Trans fat consumption from edible oils was estimated at 0.28 grams/person/day.

Figure 1: Trends in per capita, per day consumption of salt, sugar and fat products



Around 19.8 million tons of edible oil (as reported by the Directorate of VVOF) was available in the market in 2012-13 (including import and export sources). No information is available on bulk purchasers of edible oils; it was assumed that 50 per cent was consumed by bulk purchasers (similar levels of salt and sugar are being procured by bulk producers). The annual percapita consumption works out to 8.0 kg/year i.e. 21.9 grams/day. The NSS 2010 round reported per capita consumption of 27.6 grams/day of vegetable oil; this is based on self-reported data through household level questionnaires. At present a recommendation has been made to the Government of India to regulate the amount of trans fats in partially hydrogenated vegetable oils (PHVO) to less than five per cent, however mandatory labeling of trans fats in oils is now being practiced. The current average dietary energy intake, through oils, per person per day was 2,147 kcal for rural India and 2,123 kcal for urban India.

1.3.3. Behavioural influencers among children (Micro level perspectives):

Behaviour is a result of complex and dynamic interactions of several internal (biological) and external environmental factors. Most studies in childhood obesity highlighted that foods particularly those high in refined sugars and fats are habit forming (addictive) and therefore some forms of obesity can be treated as behavioural issues. This perspective is supported by a growing body of neuroscience researchers who have demonstrated that the chronic consumption of energy-dense foods brings about changes in the brain's reward pathways that are central to the

development and maintenance of habits. While it is difficult to precisely define 'eating behaviour', such habits are associated with pleasure centers in the brain (neural reward circuitries) - characterized by symptoms such as loss of control while eating, over consumption and/or binge eating, continued consumption of high calorie foods despite the knowledge of its negative consequences and inability to cut down despite the desire to do so.[44] Binge eating may play a significant role in the development and maintenance of obesity. Overeating is an addiction marked by the compulsion to consume preferred food items that are influenced by lifestyle eventually resulting in unmanageable consequences. Agaras and Hamner[45] suggested that most eating disorders begin in adolescence, probably during puberty. Night eating syndrome is another disorder that can lead to significant weight gain among children.

Temple et al., 2008 reported that overweight children find foods more reinforcing than normal children.[46] In other words, among obese children, the reinforcing value of food is higher than that among children with normal weight. In general, bland foods are not eaten in excess whereas highly palatable foods are often consumed even after an individual's energy requirements have been covered. Evidence in rodents and humans supports the theory that the consumption of highly palatable foods and the use of habit-forming drugs have a common mechanism to mediate motivational behaviour.

Eating behaviour (healthy as well as unhealthy) among children is influenced by peer groups. In an in-depth interview, conducted by INCLEN, with over 392 stakeholders (including children, their mothers and fathers); half of the mothers and some fathers claimed that unhealthy eating among children increased due to peer group influence. Most of them reported an increased intake of high calorie foods (like beverages, sweets, chocolates, junk food and fast foods - chips, wafers, pizza, pasta, instant noodles, sandwiches, street foods and bakery products) and this perception is supported by majority of the children; contrary to this, some parents and approximately half of the children claimed that healthy eating habits were inculcated by peer groups and their dieting patterns (Table 2).

Table 2: Perception of parents and children on influence of peer groups on children's eating behaviour

Healthy food behaviour (Eating Healthy Foods/ Learn Healthy food habits/ Intake Decreased)	1+	1+	2+
Unhealthy food behaviour (Intake increased/ Overeating/ Unhealthy Eating)	1+	2+	3+
Influence (not specified)	2+	2+	<1+
No Influence	2+	2+	1+

Note: In table 2, <1+ means 'Very few', 1+ meaning 'Some', 2+ meaning 'Approximately half', 3+ means 'Majority', 4+ meaning 'Most' and 5+ means 'Almost all'.

Impulsive Eating: Several obese children overeat impulsively i.e., they continue eating even though they are not hungry. Highly impulsive children often do not think about the reactions or their consequences. Besides over eating, these children seem to be vulnerable to food triggers like the smell and taste of the food.[47] It has been suggested that poor control of neural centers related to impulsivity and/or addiction could foster impaired control of food intake leading to overeating and subsequent obesity.[48] Adaptive decision-making and the ability to delay gratification may positively influence eating behaviours, particularly in an energy rich food environment where conscious control of energy intake is essential for the maintenance of healthy body weight.[49]

For children, the drivers of food consumption in the family are largely dependent on the feeding practices and time spent by mothers (the act of eating has emotions attached to it),[50,51] availability of calorie dense foods,[52] preference for and increased consumption of sweet and fatty/fried foods and salty snacks,[53,54] skipping breakfasts and less physical activity.[3,8]

1.3.4. How positive-energy balance over time mediates overweight/obesity in children?

Core to obesity research is the understanding of ***energy balance system***; i.e., interplay among energy intake (EI), energy expenditure (EE) and energy storage (ES), often expressed in kcal/d – distortion in this system over a period of time will result in weight gains.

$$\boldsymbol{ES = EI - EE} \qquad \ldots\ldots \quad (1)$$

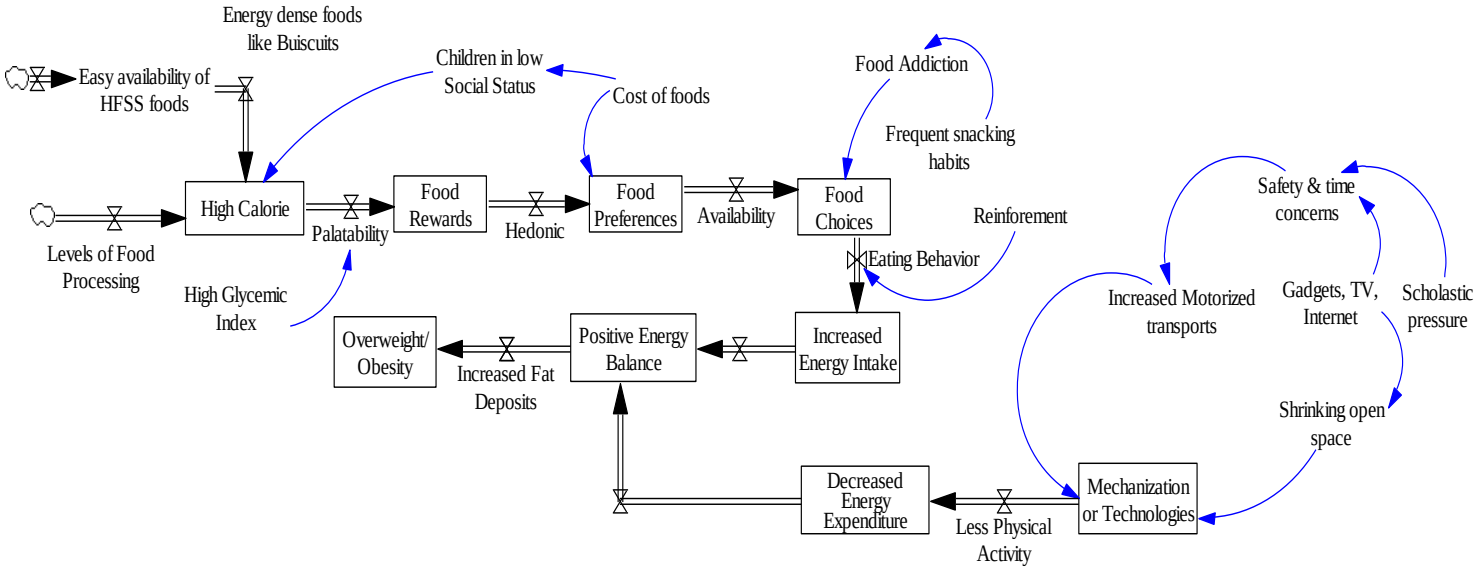
Energy intake in humans are majorly through proteins, carbohydrates (CHO), fat and alcohol while energy expenditure is through; a) resting metabolic rate (RMR) which is the amount of energy required for involuntary activities, b) thermogenesis effect of food which is energy spent on absorption and metabolism of foods and c) energy spent in physical activity which considers all voluntary movements.[55] Changing one component of energy balance system (for e.g.: energy intake) could produce compensatory changes in other components often exacerbated by genetic, environmental and psycho-social factors.[56] When energy intake equals energy expenditure then human body achieves energy balance. Human body is said to have acquired *'positive energy balance'* when energy intake exceeds energy expenditure resulting in increasing body mass. When energy expenditure exceeds energy intake, body is said to be in the state of *'negative energy balance'* resulting in body weight loss (Figure 2).[55] Thus, obesity is a result of positive energy balance over a period of time - during which excessive energy results in proliferation of adipocytes and/or its size by inducing hypertrophy of existing fat cells or may be stored in fat depots like pericardiac fat, perivascular fat and visceral fat.

Body weight and energy balance maintenance is subjected to several physiological controls and is not subjected to wide swings in behavioural mechanisms of controlling food intake and energy expenditure. These could be explained through first and second law of thermodynamics: first law state that change in stored energy in human body equals energy intake minus energy expenditure while second law state that conversion of excess energy into new tissue also requires energy.[57] At younger ages, there are strong anabolic drivers that will influence energy balance; through partitioning of energy between fat and lean tissues during growth, energy use during tissue synthesis, and have higher basal EE. However, as age advances these models need to be modified that reflects on ratio between fat and muscle (sarcopenia) which determines the energy balance.

Energy balance is achieved at different body weight and body composition at different levels of energy intake and expenditures. Studies highlight that humans tend to achieve energy balance at:

a) very low energy intake corresponding to very low energy expenditure, b) moderate intake corresponding to moderate energy expenditure or c) high energy intake corresponding to high energy expenditure. The changes in energy balance (positive or negative) will have meaningful effect on body composition only when it is distorted for a period.[58] Jean Mayer et al., (1956) postulated that, human body is best able to maintain energy balance at a relatively high energy throughput (high energy intake against high energy expenditure).[59] Thus with abundant food (availability), humans tend to have strong physiological drive to eat more and when it is combined with lower rates of energy expenditure, the risk for weight gain increases.[55] In case of body at positive energy balance (i.e., high energy intake and less physical activity), physiological stimulus would tend to increase the body weight as a measure of increasing energy expenditure through increased metabolism. Unlike previous eras, when there is a balance between positive and negative energy balances, substantial changes in lifestyles, behaviour and environment have resulted in humans facing more periods of positive energy imbalance. Thus, it is important to understand the body composition in detail.

Figure 2: Energy Balance Model

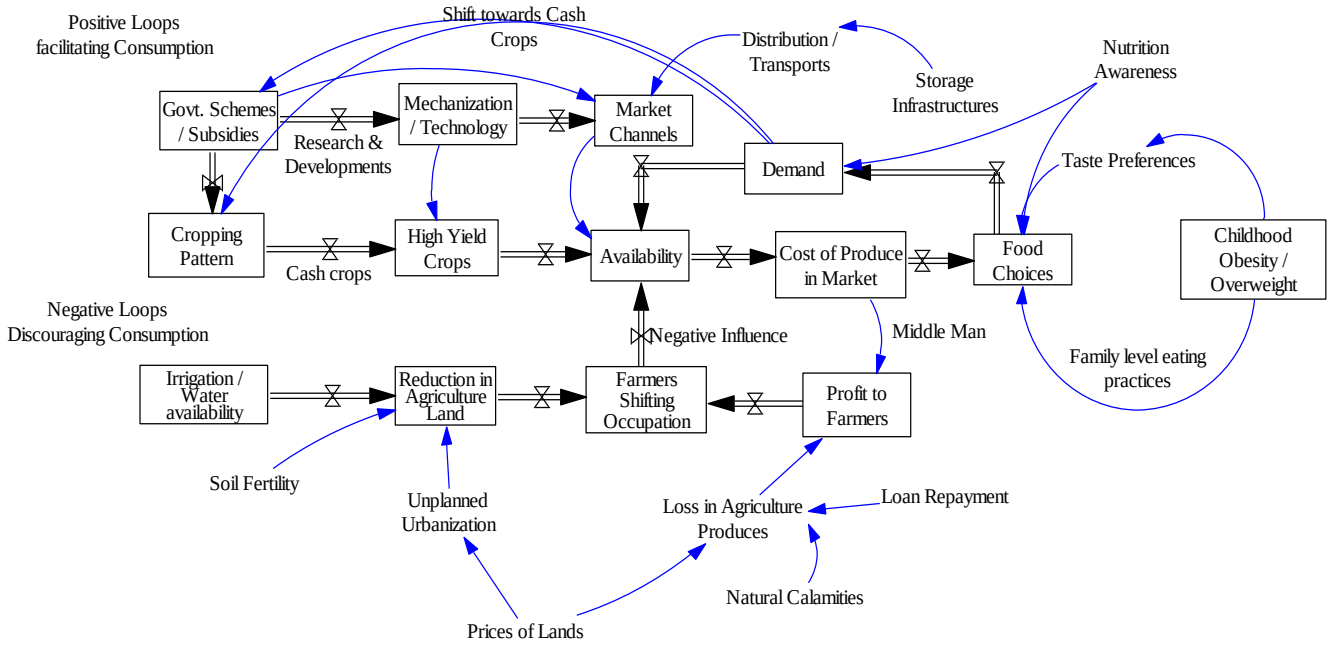


1.3.5. How changes in built environment influence diet and physical activity of children?

Infrastructure and environment play an important role in determining childhood obesity. Structural elements like road, transportation, structure of buildings, playgrounds, parks and public spaces influence childhood obesity and the overall health of people, directly as well as indirectly. Research conducted over the last decades provides increasing evidence that both a

better food retailing environment (e.g. more supermarkets and fewer convenience stores) **Error! Bookmark not defined.**,[14] and lower access to fast-food restaurants have associations with healthier diets and lower rates of obesity (Figure 3).[15] Other studies have failed to provide evidence for these associations. Variations in features of built environments (e.g. food outlets, buildings, roadways, physical activity resources, social institutions for education or training, infrastructure and health care), the physical (e.g. weather including heat, rainfall and wind) and social environments (e.g. crime, enforcement of law and order, or culture), and collective socioeconomic attributes of local residents (e.g., employment, education and income) are all related to obesity.

Figure 3: Drivers of diets and physical activity interacting with Energy Balance Model



Interviews with 392+ stakeholders revealed that the key drivers which include development of infrastructure, industrialization, diminishing open spaces and the presence of malls and shopping centers are likely to have a negative effect on physical activity behaviour.

1.3.6. Media and Market Environment – Changes in Accessibility, Availability and Affordability

The National Council of Applied Economic Research (2014) collated evidence on shifting dietary habits: between 1980 and 2014, sources of carbohydrates and proteins have shifted to high glycemic index (GI) foods, fruits and vegetables, and the animal based food share in the diet has increased exponentially.[60] Consumers moved away from 'coarse' grains like *jowar* and *bajra* to 'superior' grains such as rice and wheat, and diversified to high value food items like

milk, egg, meat and fruits and vegetables; the trends are similar in both urban and rural areas. The per capita consumption of coarse grains and pulses has decreased despite large imports of pulses, making them less available.[60] In 2011-12, pulse consumption was around 26 grams/person/day in rural and 27.5 grams/person/day in urban areas (NSSO).[61]This is significantly less than the recommended RDI of 40 grams/person/day by Indian Council of Medical Research (ICMR). Globally, India accounts for about 25 per cent of global pulse production but the share of pulses among total food grains, in Indian diets, decreased from 17 per cent in 1961 to 7 per cent in 2000.[62] The annual growth rate of coarse grains and pulse production lagged behind the population growth rate, resulting in a further adverse effect on the per capita availability. Thus, availability of pulses has come down from 66 grams/person/day in 1965 to 33 grams/ person/day in 2005 – with simultaneous increase in the availability and consumption of rice and wheat during the same period.[63]

An increase in household incomes, worldwide changes in food production, retailing, marketing and distribution systems have led to shifts in the quality of people's diet and consumption patterns. Increased access to energy-dense foods and beverages over time has influenced the health of individuals.[64]Processed and packaged foods are increasingly being consumed by every household across the social strata, both in rural and urban areas. These foods and beverages have become easily available and relatively affordable, particularly with rural marketing strategies. The relative cost of healthy eatables like fruits and vegetables has increased as compared to prices of refined grains. The domestic demand for processed foods, sugar sweetened beverages and savory snacks are linked to the disposable household income of the middle class population. Though income levels are non-homogenous in India, they are a driving force and determine spending patterns.[30] The consumption of value added foods like pickles, bread products, savory snacks, ketchup, mayonnaise and breakfast cereals has also increased.[65] The sale of packaged food was highest in northern India (38%), followed by west (36%), south (28%) and east and north-east (21%).[66] The market of packaged, processed and ready-to-eat food products is increasing at an annual growth rate of about 15 to 20 percent.[33]

Convenience and aspirations in families are the key factors driving the food markets. The geographic, demographic and socio-economic factors are over-arching but there are some specific factors that influence food purchase and choices including media (impacts marketing and choices), food availability and accessibility, religion, culture and consumer attitudes. Children are exposed to ultra-processed, energy-dense, poor-nutrient foods which are cheaper and readily

available. Studies show a positive association between such foods and higher body weight. The easy availability of fast foods is also a reason for increased consumption. Students who are overweight or obese are the most frequent consumers of fast foods due to irregular meals and frequent snacking. The consumption of sweetened carbonated drinks, sugar, and artificial sweeteners has also increased.[67]

The quality of grains consumed in Indian households has changed in the past three to four decades. The use of refined grains (polished rice and wheat) has replaced whole grains.[68] The refining process leads to the removal of outer bran and the germ resulting in the loss of many nutrients; the remaining portion is only the starchy endosperm, which increases its glycemic index; this in turn elevates plasma glucose, insulin, triglycerides and fatty acids – adversely affecting the cardio-metabolic risk factors.[69] In contrast, whole grains are rich in dietary fibers with micro and phytonutrients. Median intake of refined grains among Indians is 333 grams/day.[70] Important reasons for this shift include better shelf life, consumer appeal and other supply side factors; viz. altering availability, accessibility and affordability of food materials in India.

Staple foods consumed in India now have a higher glycemic index compared to what was consumed three decades ago. The average rice intake among south Indians is around 8.5 servings per day, which translates to around 255 grams/day. The quality and glycemic index of the same amount consumed varies with a change in the place of residence. This problem is further exacerbated with the portion size.[71] Consumption of value added foods like pickles, bread products, savory snacks, ketchup and mayonnaise have increased.[65] All these foods are usually processed and packaged with a high glycemic index and are increasingly being consumed by every household across social strata.

Individual factors that promote poor diet are: 1) cost of healthy eating, 2) portion sizes, 3) family support and lifestyle, 4) psycho-social stress mediated through peer influence, 5) lack of knowledge regarding healthy diet, 6) perceived benefits of healthy diet and 7) helplessness and/or frustration.[72] All these factors vary with gender and demography. As individuals, food behaviour may be moderated by negative emotions, resisting temptations, eating out, feeling deprived, time pressures, temptation to relapse to unhealthy eating, meal planning, competing priorities, social events, family supports and friends' support.

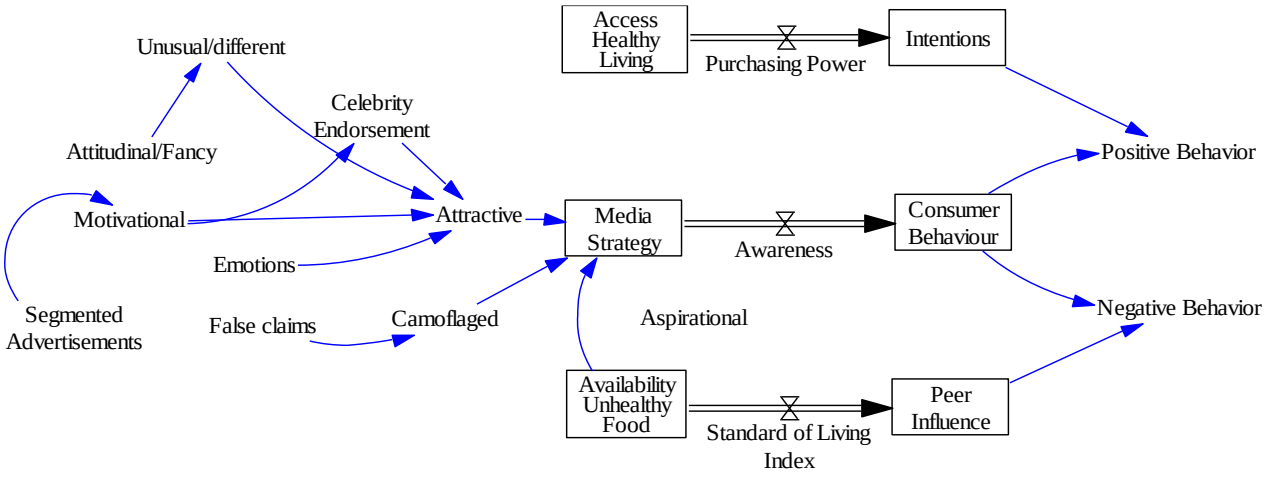
Markets exploit technologies and techniques to promote brands and new products. Children are particularly vulnerable to this influence through the media. Companies strategize to get the maximum customers and take advantage of the impulsive behaviour of children and communities. Traditionally, competition in the market was believed to improve the productivity of firms and increase social welfare; however, evidence shows that competition depends on the instruments the firm uses to compete.[73] Unethical use of tools to gain competitive advantage has led to undesirable societal outcomes. Lobbying by large industries may modify laws thereby providing an institutional support for business and entrepreneurial activities.[74] These result in unhealthy diet preferences, purchase behaviour and lifestyle choices.

Changes in media landscape have blurred the boundaries between commerce, content and information. In India, the television network revolution has penetrated the remotest parts of the country and advertisements through this medium have become an important brand building tool. Most Indian children and parents watch between two to four hours of television on weekdays and during vacations this increases beyond eight hours per day for 10 per cent of children and 3 per cent of parents. In India, advertisements to program ratio was of 1:3 - that means 15 minutes per hour is spent on advertisements. Thus, 10 per cent of Indian children who are watching over eight hours of television per day during vacations would be exposed to two hours of advertisements. Forty to fifty percent of these advertisements, during children's programs pertain to food and diet. These advertisements target children and are in contrast with national recommendations or local cultural diets. Sixty two percent of Indian children in a survey stated that they love to watch advertisements and considered them necessary. Advertisers recognize children and their influence on household purchases and consider them future shoppers - hence their messages attempt to instill brand loyalty from an early age.

Advertisements are made attractive, tempting, aspirational and use emotions, fancies and fantasies linked to unhealthy foods. False claims and camouflaged messages are common. Celebrity endorsements and expert opinions are incorporated, either as individuals or combined in ways that influence the consumers to change their purchase behaviour. Repeated advertisements, wide exposure through multiple mediums and sponsored events reinforce messages that influence food and physical activity behaviours. Different channels like the print media, electronic media, social media, hoardings, posters and signboards are effectively utilized by entrepreneurs to promote and reinforce messages regarding their products.

Modern living, dynamics of the home environment and peer influence maximize the effect of the media (Figure 4). The business environment and media along with evolving market trends have modernized traditional markets. Companies and marketing agencies adopt different strategies to produce a substantial impact on consumer behaviour among different segments, including children.

Figure 4: Common strategies by media to influence consumer behaviours



1.3.7. How socio-economic status of individuals influence obesity rates?

There is considerable heterogeneity in the patterns and trends of obesity across societies. Obesity rates have a strong and complicated relationship with income and social status. The prevalence of obesity in United States is higher among low socio-economic groups including among those who are less educated and among certain ethnic groups,[75, 76, 77] while obverse trends are reported from developing countries. The apparent paradox shall be explained through access to relatively lower cost of energy dense foods,[78,79] that have high sugar and fat content and are highly palatable. In developing countries, children from upper socio-economic strata are more likely to be obese as compared to children from low socio-economic strata.[80]

1.3.8. Influence of culture and peers on obesity epidemic?

Recent studies focus largely on community-level determinants of environmental exposure being nested within city/village/country/global health and non-health systems that singly and/or jointly contribute to childhood obesity. There may be adverse effects of economic and social inequalities as well as cultural differences and social distinctions. Studies have shown that eating and physical activity of children and adolescents is greatly influenced by their peers, families,

media and markets and various other sections of society. The culture within which a person lives is likely to be the most powerful influence. Culture is the learned system of categories, rules and plans that people use to guide their behaviour. Various socio-cultural beliefs, customs and practices affect the food intake and physical activity behaviours among children and adolescents. There are some beliefs and practices that are regionalized and culture specific and/or gender specific while some beliefs are not specific but people have obeyed and followed them for decades. In India festivals are not only related to customs but also to several kinds of tasty foods and sweets; most of these are high calorie foods. A child's primary exposure to healthy and/or unhealthy habits is usually through families, extended families, peers and schools. In urban areas especially where both parents are working and have time constraints children have access to their own money and have less guidance or control, thus influencing their lifestyle. Businesses and markets specifically target children after recognizing their influence on household purchases.

Competition and aspiration among children has escalated to new heights. Less leisure time with children is a contributing factor that leads to improper meals and snacks. Verma et al., reported that examination systems, burden of homework and attitudes of parents and teachers contribute to psycho-social stress among school children in Chandigarh.[81] Most children spend a significant amount of time with their peers and in schools. In India, schools in specific and society at large do not consider physical activity or sports a part of academic performance. Deb et al., reported that high expectation for academic success leads to stress and anxiety among school children.[82] Teachers and parents focus on scholastic performance and achievements and foster comparison. Therefore a healthy school and social environment is very important.

1.4. Aims and Specific Objectives for this thesis

Overall aim of this study was to develop and validate a **'Whole of Society'** monitoring mechanism for obesity and percentage body fats that correlates with cardio-metabolic risk factors among children aged 6-18 yrs.

With this broad aim there was four independent studies planned with following specific objectives:

Study 1:

- **a.** Develop predictive equations for estimating whole body fat mass (FM) and fat free mass (FFM) by using total fat estimated from DEXA in a subsample of 208 children and
- **b.** Study the distribution of body fat and lean mass among children in different BMI categories (thin, normo-weight, overweight and obese children) as per Indian Association of Pediatrics (IAP), Growth charts, 2015

Study 2:

- **c.** Age and sex specific reference values and smoothened centile curves (monitoring tools) for 20 bio-chemical and clinical markers of cardio-metabolic risk and
  Distribution of these markers in different BMI categories (thin, normoweight, overweight and obese) as per different guidelines

Study 3:

- **d.** Determine the burden of clustering of cardio-metabolic risk factors among boys and girls;
- **e.** Determine the relationships between clustering of cardio-metabolic risk factors and body mass index (BMI), percentage body fat (PBF), fat mass index (FMI) and waist circumference (WC); and
- **f.** Using an unifying approach to derive a new definition for childhood obesity based on clustering of cardio-metabolic risk factors among children

Study 4:

- **g.** To develop a multi-level framework for monitoring cardio-metabolic risk - Proximal & Distal factors associated with Clustering of bio-chemical Markers

Chapter 2: Literature Review

Section 1 - Biology and body composition analysis:

उपक्रम्यस्य हि द्वित्वाद् द्विधैषोपक्रमो मतः एकः संतर्पणस्तत्र द्वितीयाश्चापतर्पणाः १ बृंहणो लङ्घनश्चेति तत्पर्यायावुदाहृतौ बृंहणं यद्बृहत्वाय लङ्घनं लाघवाय यत् २ देहस्य	'The human body is of two types – obese and lean and therefore the treatments are also of two kinds' – Astanga Hridaya (Vagbhat), Chapter 14, Dvividha Upakarma, 5th to 7th century, AD

Mention on human body types (obese and lean) can be found in ancient treatise of Indian knowledge's, like Athrva Veda (800 BC) and Astanga Hridaya (5 to 7 AD), in which the body constituents are presented as a combination of 7 dhatus (blood, muscle, fat, bone, marrow, chyle and semen).[83] These are produced by the actions of three microcosmic elements air, phlegm and bile on which major therapies of Ayurveda are conceptualized and practiced; for so many centuries. Different therapies for different body constituents (obese and lean body types) are cited in these documents.[84] Dietetic treatments, daily routines (dina charya) and seasonal routines (ritu charya) were stated explicitly for different body types. Hygiene, two time meals, nature of diets, amount of water to be consumed, use of condiments etc., were all mentioned differently for different body types.83 These were closely tied with cultural beliefs among Indians and were practiced for generations.

Morgagni in 18th century in his famous book ('The seats and causes of diseases investigated by anatomy') has described the clinical history of an obese patient and reported large amount of fats in android areas – this was almost 200 years before John Vague's clinical definition of abdominal obesity.[85] More scientific evidences on different body constituents especially water, fat, nitrogen and minerals, under the realm of modern medicine are available since early 19th century. Lawes and Gilbert (1859) was the first to document the inverse relationship between total body water and fat content and Ludwig Pfeiffer (1887) have presented the concept of fat-free mass instead of total body water.[86] Since then, this concept of estimating fat mass (FM) and fat-free mass (FFM) forms the basis of all body tissue analysis - the constituents are clubbed under different compartments and studied in detail. Broadly, studies on human body constituents are called as body composition analysis which can be organized under three broad themes: 1) body composition models, 2) body composition methods and 3) body composition responses.

2.1. Theories in body composition analysis

2.1.1. Body Composition Models:

Models on body compartments have gained more importance due to increasing evidence on association of excess body fat with the risk of cardio-vascular diseases - models are generally our beliefs on how a system functions. In body composition analysis most commonly used models are two, three, four and recently whole body multi-compartmental models. Direct estimation of fat mass in human body is extremely difficult as each fat depot will have unique characteristics. There are numerous small and specific fat depots like pericardial and buccal fats to large depots of deep abdominal subcutaneous fats including omental / visceral fat depots.[87] Thus, body fat depots can be broadly classified as lower body fat, upper body sub-cutaneous fat and intra-abdominal/visceral fats. The influence of body fat (visceral fat and sub-cutaneous fat) on metabolism and obesity is discussed in the following chapters.

The premier and most widely used classical model on body composition is two compartmental models based on FM and FFM. It is hypothesized that, if the amount of FFM is determined then the FM can be estimated as the difference between body weight and FFM. More precise estimation of FFM can be obtained through hydro-densitometry and isotopic dilution techniques using radio-active water and 40K counting.[88] The body density is estimated for FM (0.9007 gm/cm3) which is anhydrous and for FFM (1.1000 gm/cm3) which have a water content of 73.72% (i.e., FFM = TBW / 0.732).[89] Body volumes are measured using Archimedean principles; either through underwater weighing or through water/air displacements.[90] However, each individual shall be at different levels of hydration and this shall influence the validity of two compartmental models. In addition, there are several practical difficulties in using displacement techniques at field level.

To control for inter-individual variations in FFM hydration status, Siri WE (1961), have proposed the three compartment model in which in addition to FM the FFM was further divided in to total body water (TBW) and fat free dry mass (FFDM), with a constant of 0.35 assumed against mineral-to-protein ratio. Here the density of water, fat and body solids was used in the estimations. One limitation was; in case of people having altered body proteins or mineral masses this model and FM estimation shall be incorrect. With advancement of technologies like dual-energy X-ray absorptiometry (DEXA), which can be used to more accurately measure bone mineral contents (BMC) and TBW, a four compartment (4C) model were suggested. In this 4C model in addition

to FM the FFM was divided in to body cell mass, extracellular fluids (ECF) and extracellular solids (ECS). ECS reflects to the bone mineral contents (BMC). Thus, FFM in DEXA reflects to the sum of body water, body protein, carbohydrate, non-fat lipids and soft tissue minerals – that is everything except bone mineral content.[91] One advantage in this model is, it does not require under water weighing or air plethysmography however the measurement errors will cumulate and influences the FM estimations. With each addition of measurements in the body composition analysis it is possible to increase the number of compartments. Wang Z M et al., (1992) have collated information on almost 40 body components systematically in to five levels of increasing complexity which includes 1) atomic, 2) molecular, 3) cellular, 4) tissue-system and 5) whole body (Figure 5).[92] In the whole body multi-compartmental model there are over 10 dimensions of human body components are included: 1) stature, 2) segmental lengths, 3) body breadths, 4) circumferences, 5) skinfold thickness, 6) body surface area, 7) body volume, 8) body weight, 9) body mass index and 10) body density.

Figure 5: Five level multi-compartment model with different levels of complexity

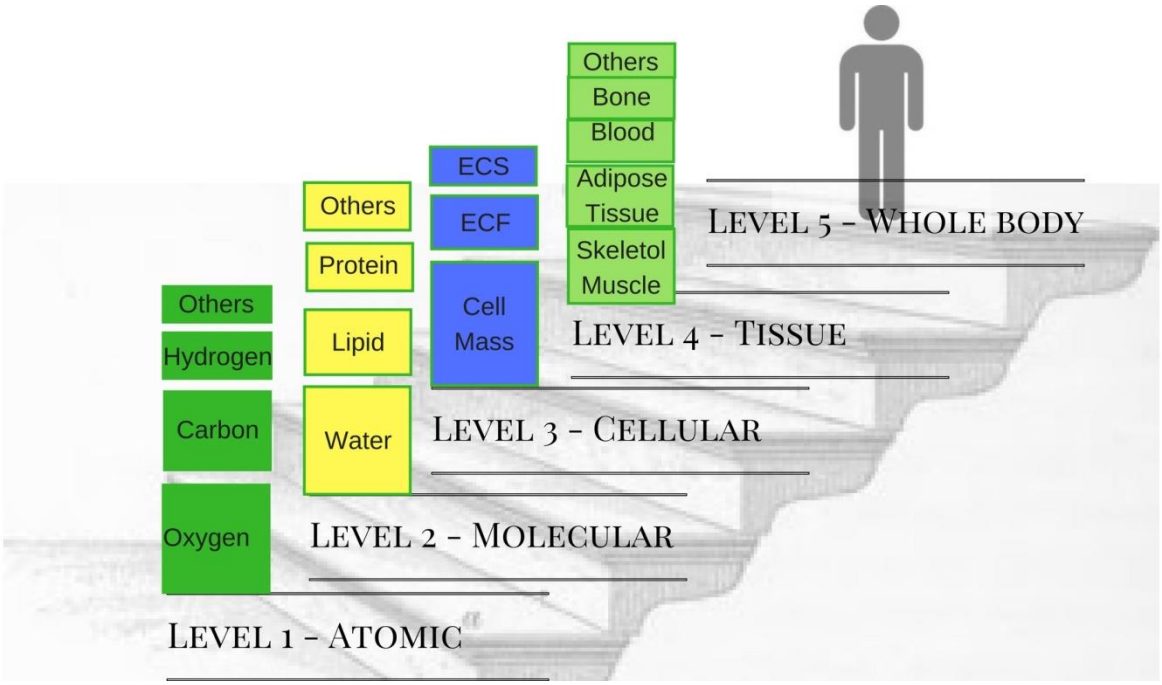


Figure 5: Multi-compartmental model on body composition adapted from Wang ZM et al., (1992). ECF = extracellular fluid, ECS = Extra cellular solids.

In most cases, FFM and LBM are used synonymously however they are not the same. Fat free mass is all residual chemicals and tissues including water, muscle, bone, connective tissue and internal organs.[93] Lean body mass is comprised of FFM plus essential lipids. Mineral-free lean tissue is FFM minus BMC. FM is the varying compartment that accounts for anywhere between 6-60% of an individual's total body weight.94 FM is essential lipids and stored adipose tissue which is present in almost all areas of the body. For e.g.: subcutaneous fat under the skin of human body is the type of FM that individuals can see and feel at the same time visceral fat is not measurable without using imaging techniques. FFM are found in the yellow bone marrow as well as within the muscle (intramuscular).

The human body is made with approximately 62% water and TBW is the sum of extracellular water (ECW) and intracellular water (ICW).[95] However the aqueous fraction of FFM of a reference man is 73%.[96] BMC is the amount of minerals per centimeter of bone (gm/cm) while BMD is the ratio of BMC to bone size (g/cm^2) and is commonly used as a marker for determining osteoporosis.[97]

2.1.2. Modifiable and non-modifiable components:

Among those body composition discussed, there are modifiable and non-modifiable factors. For example variations in age, sex, stature and race are non-modifiable. Often FM increases up to age 74 while adults above 30 to 40 years will experience a loss of bone mineral and skeletal muscle mass (sarcopenia). Rate of sarcopenia is higher after age 60 and in males. In addition, age related sarcopenia is associated with atrophy of muscle fibers. Studies have shown increasing waist circumference, in both genders, without increase in weight which is probably due to overall sarcopenia and abdominal adiposity. Abdominal adiposity increases the risk of chronic disease leading to premature deaths.[98]

Body composition is different in males and females - men have more FFM and less FM as compared to women.[99] It is estimated that men will have 36% more skeletal muscle than women. In contrary, the rate of decrease in skeletal muscle in older age is greater among men than women. Higher levels of subcutaneous fat are reported in women.100 Men tend to carry more FM in the android region and women tend to carry more FM in the gynoid region.[101] Women are likely to have low bone density than men.[102, 103] In addition, women would have decrease in BMC and BMD during menopausal and early postmenopausal years - due to the decrease in endogenous estrogens.[104] On the other hand, men tend to have higher BMD because of testosterone – with

age levels of testosterone decrease and BMD declines.105 Rate of BMD decrease is high in women after menopause, but the rate in men and women is same among adults in 65-70 years of age.106 In addition, body composition differs in races.

There are modifiable factors that can affect body composition like: lifestyle and disease status.[107,108] These could be acute or chronic. Acute could be due to hydration status and/or the use of diet or weight loss medications. Chronic factors include physical activity, diet and weight loss surgery etc. Increased physical activity will increase FFM and decrease FM.[109, 110] In contrast, decreases in physical activity can lead to decreased FFM and increased FM.111 Diet could alter FFM and FM. High protein diets potentially increase the amount of skeletal muscle mass or FFM.112 Decrease in calorie consumption leads to a decrease in FM.

2.2. Body Composition Methodologies

Body composition analysis are conducted primarily to estimate the size of individual compartments (FM or FFM) that cannot be measured directly – these are calculated based on several relationships assumed and are reproducible. BIA estimates:

1. Total Body Water: Bio-impedance analysis could help us to exactly estimate water / electrolyte in the human body. Amount of body water is estimated through body cell mass and therefore through muscle mass. It works with an assumption that, over 73% of lean body mass has water content in it.
2. Lean Body Mass: LBM is the tissue mass that contains no fat. For a healthy hydrated subject: LBM=TBW/0.73
3. Body fat: BF acts as an insulator to AC in human body. Fat mass is often calculated as the difference between lean body mass and body weight.
4. Body cell mass: BCM is the sum of all cells in metabolic process which includes skeletal muscles, cardiac muscles, smooth muscles, inner organs, GI tract, blood, glands, and nervous system.
5. Extra cellular mass: It is the remaining portion of LBM except body cell mass (BCM). It contains the connective tissue structures: collagen, eslatin, skin, tendons, fasciae and bones.

Often such analysis assumes a steady state and do not addresses the robustness of such methods in a non-steady state, especially in an obeso-diabetogenic environment. Steady states are

conditions when the body weight and mass of different body compartments are relatively constant in a given time period – for e.g., the total body water to fat free mass is relatively constant among healthy individuals, then TBW/FFM=0.732. The underlying philosophy is to estimate the unknown components from directly measurable components such as body weight, circumference and skin fold thickness. It has to be noted that there is no direct method for estimating fat compartments. For example, fat mass = 2.057 X body volume – 0.786 X total body water – 1.286 X body weight; especially in a steady state. Common methods in body composition analysis are mentioned below.

2.2.1. Underwater weighing (UWW) or hydro-densitometry:

This is one of the earliest techniques based on 2C model developed to estimate body density and volume based on hydrostatic displacements, Archimedean principle.[89] It assumes that the volume of human body shall be equal to the loss of body weight while immersed in water which is adjusted for the density of water (i.e.; body volume= weight in air – weight in water adjusted to lung volumes). There are several practical limitations in this technique including that on determining residual lung volumes, estimating intra-abdomen gas volumes, time consuming and tedious implementation process. Density of fat mass is assumed to be homogenous however density of fat free mass is heterogeneous within population. Later, 3C and 4C models for underwater weighing were developed which requires additional techniques like D2O dilution to estimate the density of fat free mass. However, such technical adjustments often introduce an error of 1% in percentage fat estimation but if such corrections are not done then an error of 3 to 4% were commonly observed.

2.2.2. Air-displacement plethysmography (ADP):

Plethysmographic techniques, based on air displacement in a sealed chamber which is equivalent to the volume of the subject introduced, were suggested as an alternative to hydrodensitiometry.[113] Body density is estimated from variation in pressure and volume of individual in the sealed chamber. This technique is affected by the changes in temperature, pressure, humidity of air in the chamber, isothermal properties of air, lung air volume and was tedious to patients in the chamber. Recently, BOD POD© chambers are available which have one reference chamber and one testing chamber and the changes in volume and pressure in the test chambers is compared with reference chambers, based on Poisson's law ($P1/P2 = (V2/V1)^{\gamma}$) – where P1, P2 and V1,

V2 are difference in pressure and volumes before and after estimation and ϒ is the specific heat of gas at constant pressure and volume.[114] However this method requires highly trained technicians and is highly impractical for clinical or field studies. In addition, as composition of FFM changes among children, ageing and in disease conditions the accuracy of using a common fixed density for FFM (which is common in all 2C based models) introduces larger errors in estimation and is not suitable for children, elders and patients.

2.2.3. Isotope dilution techniques for total body water estimation:

As the proportion of water, protein and minerals are changing with age the 2C models are considered less accurate in body composition analysis. In this context the TBW is estimated in the FFM which forms the basis of 3C model. Radioactive isotopes like deuterated (2D2O), tritiated (3D2O) and oxygen labelled (18O) water (commonly called as tracer elements) can be used to estimate the total body water through dilution principles.[115] Total body water is estimated from the ratio of quantity of tracers administered in to the body fluid (blood, saliva or urine) before and after an equilibrium time (2 to 3 hours) from administration orally or intravenously. It is assumed that the tracer elements will be distributed evenly in the body fluids and is not metabolized rapidly during the equilibrium time and these can be corrected mathematically. Another assumption is that, ratio of total body water and FFM are stable irrespective of minor changes in hydration status in intra-cellular and extracellular fluids (i.e., TBW/FFM=0.73). With different tracers used in dilution there can be a minimal estimated error in the final estimation of TBW. Tracers NaBr are used to estimate extra-cellular water (ECW) and the body fluid sampled are plasma while total body potassium (TBK) is used for estimating intra-cellular water (ICW).

2.2.4. Dual-Energy X-ray Absorptiometry (DEXA):

With advent of new technologies, several new methods have evolved over time for estimating body composition however none of them can be considered as error free. DEXA is one such method based on 4C model that provides bone mineral, bone free FFM and fat mass.[115] The principles of DEXA is based on photon attenuation of tissues – i.e., when an X-ray beam of known intensity is passed through a human body then the intensity of such beams passing through the bone, muscles and/or fat tissues will be different which depends on the densities and chemical composition of those tissues.[88] By determining the relative intensities of these transmitted beams and by calculating mass attenuation coefficients the approximate estimation of bone mass and soft tissue masses are possible. By scanning the body in supine position, DEXA divides the body

in to several pixels (using slice editor programs) and within each slices number of pixels and pixel surface area was estimated through photon attenuation; measured at two different energies and their ratio (R values) were used to estimate different body constituents.[116] R value for fat is assumed as constant (R=1.21).[115] Primarily, two components are differentiated: 1) soft-tissues containing water and organic compounds that reduces photon fluxes to much lesser extent than bone mineral and 2) the pixels with bones which are easily distinguished from no bone fractions. It helps to estimate BMD which is the ratio of bone mineral contents to total bone area. Then algorithms are used (different for each commercial instruments) to estimate the total bone fractions, total body fat and soft lean tissues. Some researchers have gone to the extent to recommend DEXA as a criterion method especially in the absence of a gold standard for body composition analysis. However DEXA is also based on approximations and there are certain studies reporting that DEXA underestimates the percent body fat among lean individuals and physically active individuals.117 DEXA does not differentiate the effect of hydration on lean tissue and does not specifically measure proteins.

2.2.5. Bioelectrical Impedance Analysis (BIA):

This is presently one of the cheapest and most widely used low-cost techniques to predict body composition. Bio-impedance is different from bio-electricity as later refers to the ability of tissues to generate electricity which is mostly endogenic. Bio-impedance is generally exogenic which refers to the externally applied electricity supplied through two, three or four electrode systems.

a. Theoretical overview of BIA:

The charge carriers in metals are mostly electrons while these within living tissues (in-vivo) are mostly ions present in electrolytes – soft tissues are electrolytic conductors as compared to poor conductors like bones and fat cells.[118] Bio-impedance is the ability of tissues to oppose (impede) electric current flow represented as the ratio between voltage (E) and current (I). Resistance (R) = E/I, as per Ohm's Law, which is measured by a Bio-impedance Analyzer (BIA) for AC currents. Electricity (not detectable to the subject) at different frequencies are passed through the human body and the amount of electricity conducted would be proportional to the total volume of electrolytes and components with high water concentration like FFM. The conductivity is directly proportional to the number of ions in the volume of electrolytes.[119] BIA measures the voltage drop in the flow of electricity (AC current) which will be primarily due to the resistance offered

by hydrophobic tissue compartments like fat and bone mass – thus it is the opposite of conductance.

Amount of resistance measured will be inversely proportional to the volume of electrolytic fluid in the compartment which can be expressed as R (or Z) α L/A (where L is length and A is area). That means, volume V = ϱL2/R, where ϱ is the specific resistivity which is the electrical resistance offered by unit length of the cylinder in a unit cross-sectional area.[120] This formula is valid for cylindrical conductors with uniform cross sectional areas. In BIA, human body is considered as 5 rough cylinders (left arm, right arm, trunk, left leg and right leg) with variable cross-sectional areas but it is highly heterogeneous with highly structured compositions. Therefore the value of ϱ is influenced and cannot be detected directly however an empirical relationship can be drawn between impedance quotient (Length2/R) and the volume of electrolytes.[95]

Technically impedance has two vectors; resistance (R) and reactance (Xc). Within tissues capacitive current flows are introduced by cell membranes posing barriers to the continuity of electrolytic flows – this is termed as reactance (Xc). In short, the reactance arises from cell membranes and resistance from intra and extra cellular fluids. This causes the administered current (I) to lag behind the voltage and creates a phase shift which is geometrically expressed as phase angle (φ) or arc tangent of Xc/R.[120] These are measured at different frequencies; at zero frequency (f_0) the current do not penetrate the cell membranes (that is the current passes through ECF) and therefore Z represents only for ECF but at infinite frequencies ($f\alpha$) (very high frequency) the cells become transparent to current and Z reflects for both ICF and ECF. Practically, it is not possible to have zero and infinite frequencies and therefore the Z0 and Zα are derived mathematically by fitting reactance with resistance curve – technically for an individual the total body water is proportional to 1/Rα and extracellular water is proportional to 1/R0.[121] Since exact functional relationships between conductivity and FFM cannot be determined directly the indirect estimations can be made through statistical calibrations against criterion measures like DEXA in a sample of subjects. Thus, equations for predicting body composition (fat mass and fat free mass) are developed on independent measures of resistance, stature and other anthropometric variables. By subtraction from the actual weight an estimate of fat mass can be calculated. These prediction equations are population specific and carry an error of $\pm$ 8% of body fat in healthy individuals.[122]

b. Prediction equations for fat and fat free mass:

Often in BIA human body is considered as 5 cylinders (right arm, left arm, trunk, right leg and left leg). The prediction equations (linear regression models) shall be developed for each compartment shall follow:

$$Y = \alpha + \beta 1x1 + \beta 2x2 + \varepsilon$$

Where, α is the intercept, β is the slope and ε is error/residual.

Due to the heterogeneity (composition) in the cylinders generally it is not possible to bring intercept (α) and residual error (ε) to zero. The measured impedance (Z) is used in the prediction models as Impedance index (ZI) = $Ht^2/Z(\Omega)$ - for relating resistance with cylinder volumes. If anthropometric variables (like WC, SFT) are added to these equations it will certainly reduce the residual errors however addition of these variables reduces the main benefits of BIA relative to anthropometric prediction equations. It is known that the predictions equations tends to lose accuracy when applied to subjects not in the sample in which equations were developed and therefore all BIA equations should be cross-validated in a random sample with accepted criterion methods like DEXA.[123]

c. Normalization of body composition data:

For meaningful comparisons of body composition within or between individuals, especially among children, it is important to normalize the data. Often fat mass estimated are normalized with body weight and is expressed as percentage body fat however there are some cautions. For e.g.: a child may have high percentage body fat due to low lean mass in the denominator or in other words children with low FFM and/or FM can have high percentage body fats and vice versa. Alternative to percentage body fat is the normalization with height of children as fat and lean mass varies with height of the child. However there is no commonly accepted method to adjust it for height, often fat mass index (fat mass/height2) and fat free mass index (fat free mass/height2) are used in several literatures for normalization. By normalizing with height the variability in lean mass will also be given same emphasis as fat mass and once height is taken in to account individuals can vary in their relative fat mass and relative lean mass. However, the

decisions on normalization of data for fat mass and fat free mass are dependent on the research questions asked.

Section 2 - Reference values and Percentile curves for Cardio-metabolic Risk Factors:

Metabolic disorders like insulin resistance, diabetes, hypertension, fatty liver diseases and dyslipidemia, all of them driven by obesity and overweight, are considered as the drivers of atherosclerotic cardio-vascular diseases. Broadly, cardio-metabolic diseases refers to the combination of cardio-vascular and metabolic disorders - those factors that increases an individual's chance of damaging his/her heart and/or blood vessels are referred to as cardio-metabolic risk factors (CMRF).[4] This includes anthropometric, bio-chemical, behavioural and environmental drivers. There are several other mutually interacting factors that are associated in this disease continuum (from birth till death) and CMRFs are particularly prevalent among patients diagnosed with metabolic syndrome, especially in a rapidly transitioning societies.[5] A good idea will be to look at the history of such diseases, step by step, that shall facilitate discoveries that impacts the future.

Broadly, cardio-vascular disease refers to progressive blockades in 4 major arteries supplying heart (narrowing of arteries). It is really difficult to track to the first reference on cardio-vascular disease however proofs of narrowed arteries through atherosclerotic plaques were reported in 9 out of 16 Egyptian Mummies, around 3500 year old.[124] Leonardo da Vinci (1507) has produced the first known documented description of coronary artery disease and degeneration of vessels.[125] Andreas Vesalius (1514-1564) and William Harvey (1628) have demonstrated the theories on circulation of blood and blood vessels.[126] Narrowing of coronary arteries as the reason for coronary artery diseases was first presented by Friedrich Hoffman (1660 – 1742).[127] Presence of cholesterol in human body from bile acids (cholesterine) was reported by Antonio Francois in 1755, Poulletier de Salle in 1769 and Chevreul in 1815. In 1856, Rudolf Virchow has noted that cholesterol blocks the blood vessels of cadavers who died with cardiac diseases. For the first time he have explained atheromatous plaque formation which was characterized by proliferated smooth muscles, accumulated connective tissues, masses of lipids, cholesterol clefts, cell debris, fibrin and other plasma proteins. Since then, several works was done on different aspects of atherosclerotic plaques and cardiac diseases.

History: James B Herrick (1861-1954) was the first to coin the term 'heart-attack' and described the electrocardiographic changes in coronary vessels. The experiments on coronary artery catheterization started in 1929 and selective coronary angiography became a routine procedure in clinics since 1959. Till 1950s the general perception was that, narrowing of arteries is a routine natural process attributed to ageing process and it was the famous 'Framingham Cohort Study' (1948) that has provided deep understanding on risk factors and prevention of such diseases.[128] Linkages of cardio-vascular diseases with behavioural and environmental factors were outputs of Framingham cohort. Concomitantly, John William Goffman (1949) has used ultra-centrifugal methods to isolate LDL and HDL as primary carriers of cholesterol in human blood and linked its role with atherosclerosis. Since then different lipoproteins were identified with different grades of cardio-metabolic risks.

Increasingly, there is another school of thought that emphasizes on autonomic nervous dysfunction particularly sympathetic hyper-stimulation as the cause for cardiac problems.[129,130] Sympathetic stimulations are accompanied by reduced parasympathetic tones and shifts the cell metabolism from mitochondria to cytoplasm – i.e.; glycolytic pathways are activated in myocardium resulting in lactic acid accumulation.[131] Excess of lactic acids causes metabolic acidosis and destroys cardiac tissues – this is also the reason for angina. Thus strengthening of para-sympathetic system is recommended however that means staying away from industrial civilizations, doing more physical activity and life style modifications.[132]

2.3. Role of cholesterols in cardio-metabolic risk:

Post world war-2; it was Ancel Keys who has related the dietary fats with levels of cholesterol in blood and facilitated the formation of famous "the lipid hypothesis" – that is high cholesterol levels in blood have causal association with atherosclerosis and coronary heart diseases.[133,134] By establishing that high levels of dietary cholesterols are responsible for cardiac diseases the physicians and scientific communities have started recommending for maintenance of low levels of serum cholesterols. However there were fewer consensuses in the role of cholesterol as a cause for CVDs. Steinberg D (2004-06) have presented 5 papers on the history of cholesterol and claimed that "the lipid hypothesis" is a much exaggerated skepticism.[135] Thus, it is important to understand the role of lipids briefly.

Primarily there are two types of lipids in human body: cholesterols and triglycerides. While cholesterols are used as building blocks triglycerides are broken down in the body for energy.

Broadly cholesterols are indispensable to human body – these are lipids (not actual fats) absorbed from diets and also synthesized in the liver primarily for producing bile that helps digestion. Cholesterols are essential for maintenance of cell membrane structures and serves as a scavenger of superoxide radicals for mediating immunity. It is important in the synthesis of cortisones and sex hormones and about 20% of brain functions require cholesterol. Bloch K and Lynen F have studied the synthesis of cholesterol in the human body which passes through very complex processes involving over 30 enzymes – the precursor molecule was identified as HMG CoA.

Cholesterols are shuttled in the blood primarily with help of three classes of lipo-proteins (LDL, HDL and VLDL). Cholesterol-LDL combinations are very sticky and adheres to the blood vessels to contribute to atherosclerotic plaques however there is no evidence that hyper-cholesterolemia plays a causative role, more than a contributing role.[136] To be more precise, when LDL is oxidized by super-oxide radicals it becomes more dangerous and therefore it is important for individuals to maintain low free radical burden. HDL is a scavenger of free radicals and protects human body from oxidative attacks. Generally, unhealthy levels of cholesterols are not desired and are judged harmful.

Triglycerides are tri-esters of fatty acids and glycerols found in blood and produced by liver (endogenously) or often absorbed from foods (dietary fats). These are absolute fats in the food and excess amounts are stored in adipose tissues. Thus it is the primary form in which calories are stored in body. About 95% of fats consumed are first converted into triglycerides and is transported in blood by two lipoproteins: very low density lipoprotein (VLDL) and chylomicrons. They are hydrolyzed in to free fatty acids by and enzyme lipoprotein lipase (LPL) in capillaries of muscles and fat tissues.[137] Some forms of VLDL, like partially degraded VLDL (or VLDL remnants), promotes atherosclerosis.[138] Often high levels of triglycerides are associated with elevated LDL and reduced HDL levels along with other risk factors like obesity and type-2 diabetes. Meta-analysis of several studies have suggested independent role for triglycerides in mediating cardio-vascular diseases.[139] Apo-lipoproteins are referred to proteins present on the surface of these lipoproteins; Apo-A (A1 & A2) are part of HDL cholesterol while Apo-B is part of LDL cholesterols.[140] Apo-B levels are considered as a superior predictor of cardiac risk especially in hyper-triglyceridemia.[141] Apo-B counts each LDL independently irrespective of their cholesterol concentration and is not affected by diet.

In short, these markers are not independent and are associated physiologically which requires much deeper understanding of lipid pathways. Since this is not under the scope of this chapter we limit our discussion for basic brief understanding.

2.4. Intra-abdominal adiposity (waist circumference) and cardio-metabolic risk:

Intra-abdominal adiposity, especially visceral fats, are known as an independent risk factor for all intermediary CVD risk factors like hypercholesterolemia, hypertension and type 2 diabetes and mediates atherogenic and diabetogenic abnormalities. However, an important unanswered question is whether it is just a marker of adverse metabolic conditions or plays causative roles. Intra-abdominal obesity can be estimated through imaging techniques like DEXA and MRI however often waist circumference and waist-to-hip ratios are used as a surrogate marker that reflects high abdominal obesity.

Broadly, abdominal obesity refers to two types of fats: subcutaneous and visceral fat depots. Often cardio-vascular diseases are common in people having higher visceral fat depots that are filled with excess triglycerides and release Non-esterified fatty acids (NEFA) to portal circulations. This leads to increased hepatic glucose production, decreased Apo-B degradation and increased production of triglyceride rich lipoproteins.[142] LDL particles are rapidly lipolysed by hepatic lipase enzymes and leaves smaller and denser LDL particles which is easily taken up by macrophage scavenger receptors that contributes to atherogenesis.[143] These free fatty acids released in to circulation will get accumulated in pancreas, heart and other organs. In addition, visceral adipose tissues releases cytokines and pro-inflammatory molecules like interleukin-6 (IL) and tumor necrosis factor-α (TNF) in to blood. Inflammatory markers like C-reactive proteins (CRP), that can more accurately predict the risk of CVDs, are higher among people with visceral adiposity. Further, adipose tissues are known to release hormones like adipokines (adiponectin and leptin) - hence considered as an endocrine organ. In visceral obesity, due to the influence of increased pro-inflammatory adipokines the concentration of adiponectin gets reduced - adiponectin is known to have several protective effects from atherogenic and diabetogenic metabolic risk.

2.5. Insulin and cardio-metabolic risk:

Key molecular mechanisms that mediate atherogenesis among hyperglycemic individuals are through increased super-oxide formation associated with 1) polyol pathways, 2) end products of gyration pathways, 3) protein-kinase activations 4) hexosamine pathways and 5) lipoxygenase pathways.144 In addition insulin resistance and hyperinsulinemia are common among overweight

and obese people, especially those with visceral adiposity, which also increases their risk for diabetes and coronary heart diseases. Increased exposure free fatty acids to skeletal muscles also induce insulin resistance while this exposure to pancreas impairs β-cell functioning. Changes in adipokines, especially cytokines, will also leads to reduced insulin signaling and results in insulin resistance and hyper-insulinemia. This situation is further exacerbated by inflammatory pathways associated with visceral fats.

Thus at individual levels overweight and obesity are primarily due to the mis-alignments in biology, however at the societal level they are influenced by several drivers attributed to human developments and unplanned industrialization. Presently, Government of India (GOI) has set targets to halt the prevalence of diabetes and obesity by 2025; which necessitates protecting our children from becoming obese or overweight.

2.6. Monitoring of key cardio-metabolic risk factors among children:

Several guidelines recommends for monitoring the children and adolescents for number of cardio-metabolic risk factors and growth curves or centile curves are one such useful tool.[145,146]

Growth Charts:

First growth chart was prepared in late 18th century by Philibert De Montbeillard who plotted his son's height every six month up to 18 years.[147] Collecting anthropometric data for monitoring human physical growth were first used by Adolphe Quetelet (1796-1874). He was a Belgian mathematician and a statistician who used probability calculus to conclude that the body weight increases with the square of height (Quetelet Index later termed as Body Mass Index (BMI) by Ancel Keys in 1972).[148] Quetelet in 1869 was the first to apply the concept of normal distribution to human characteristics using mean and probable errors. Later, Galton F (1875) has developed anthropometric cards for use in children and recognized the need for normal distribution in such data. However he realized that this often did not apply in real life situation and have applied the concept of percentiles based on the cumulative distribution functions (ogive curves); with mean and probable errors of distribution estimated from median and quartiles.[149] Ogive curves were cut into 100 sections or grades called as percentiles with median corresponding to 50th percentile and upper quartile to 75th percentile. In a normally distributed data the mean would equal median and probable error would be the distance from 50th to 75th percentile. Later Bowditch (1891) has applied the method of percentile grades, invented by Galton, and provided the first practical

standard of growth. Modern anthropometry on growth began to take shape when Tanner JM (1976) conducted 'Harpenden Growth Study' on pubertal development of children and since then many birth cohorts have been set up where anthropometric data has been collected and followed longitudinally.

Difference between centile charts and growth charts:

Centile charts are graphical representation of relationships (position) of a parameter in a cross-sectional data may be linear, exponential or cubic distributions. In contrary, growth charts are statistical summary of the reference sample measured over a period of time (obtained from a longitudinal data). Slope is meaningful in growth charts and not in centile charts. Generally both of them are constructed in healthy population from a normally distributed sample. They are smoothened curves depicting how a measurement changes (Y axis) when plotted against the time covariate (X axis). There are growth standard charts and growth reference charts. Growth standard charts suggest how a population of children should grow with optimal nutrition while growth reference charts are descriptive suggesting how children are growing rather than how children should grow12. Centile lines in the charts shows the estimated proportion of children in the population expected to fall below a particular line (i.e.; 50% below 50th centile, 90% below 90th centile etc.).[150] Biggest limitation in centile curve is: 1) it is not comparable across different measurements; 2) extreme values are lumped to the highest and lowest percentiles and 3) are not suitable for assessing longitudinal growth.[151]

What do centile curves communicate?

Often the perception is that centile curves are designed to monitor growth over time (hence the name 'growth chart') however readers should mind that centile charts created from cross-sectional data only communicate distance (position) and does not indicate rate of change (velocity or growth).[152] It shows the position of child's rank (observation) within a statistical distribution relative to other children of same sex and similar age. It does not interpret whether the subject is normal or abnormal. Serial measurements in same child (longitudinal data) are needed to provide information on child's growth where direction of curve is more important than growth. In addition, many users are not aware of the difference between growth standards and growth references.151 When a child's weight falls in 95th percentile of a reference chart it communicate that only 5 of 100 children in same age and sex in reference population have higher weight for

age.[153] If a parameter such as height is on the 3rd centile it means that for every 100 children of that age 3% would be expected to be shorter and 97% taller.

Centile spaces are the distance between two centile lines - any points within 1/4th of the line are counted within the same centiles. Choices for number of centile lines in a chart are not limited.[154] In Europe 3rd, 10th, 25th, 50th, 75th, 90th and 97th centiles are used while in America 5th and 95th centiles are used instead of 3rd and 97th centiles. WHO's international reference standards do not use percentiles at all – instead it uses standard deviation scores (SDS) also known as Z scores at -3, -2 and -1 SD score below the median and 1, 2 and 3 SD score above the median.[155] This corresponds to 0.14th, 2.3rd, 16th 84th, 97.7th and 99.86th centiles respectively. Z-scores represent the number of standard deviations (SD) away from the mean/median when the distribution is normal.

Section 3: Clustering of Bio-chemical Markers of Cardio-metabolic Risk among Indian Children

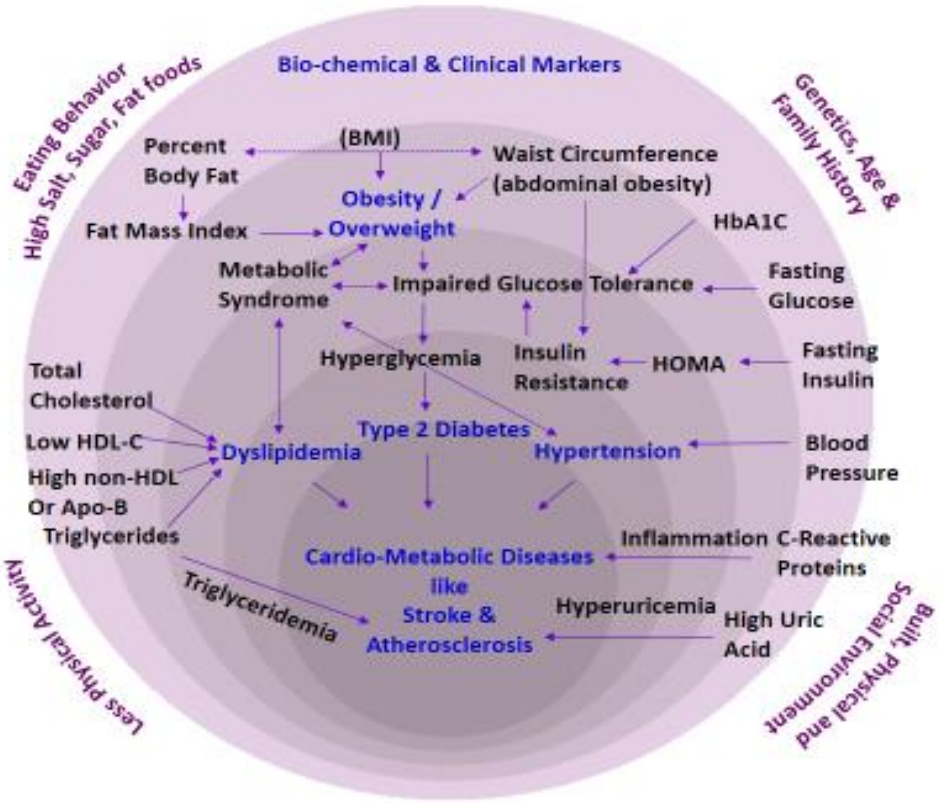
Post world war-II, the world has witnessed the evolution of a new branch of science called 'risk factor epidemiology' which was based on the quantitative and probabilistic approaches to address numerous chronic and multi-factorial diseases.[156] A risk factor is defined as 'any attribute, characteristic or exposure of an individual that increases his/her likelihood of developing a disease or injury' (World Health Organization).[157] Framingham cohort, started in 1947, was the first to use the concept of risk factors, instead of causation, and played a critical role in the development of this approach and methods. This field of epidemiology, especially in this chronic disease era, presumes privileged position to study multi-level factors and interactions associated with diseases.

Having said so, over the time, scholars in this field have started simply listing antecedent factors (exposures) that may have linkages with specific outcomes without understanding on what happens inside (black box paradigm).[158] More and more factors are cited frequently by applying measures of associations (like regression coefficients, odds ratios etc.) without considering the contextual determinants of individual's health.[159] Such situations are further exacerbated by listing more than one risk factor from multiple risk classes (like behavioural, biological and environmental) that co-exist and mutually interact in the same individual. What is really needed is to link their relationships at molecular level to describe what happens at micro level (biology) and explain the social forces, behavioural and economic factors at macro level to establish dynamic relationships.

Evolution of cardio-metabolic risk factor epidemiology: Early literature on coexisting cardio-metabolic risk factors can be tracked from 18th century - an Italian anatomist Morgagni JB have reported the co-occurrence of anatomical-clinical correlates like large fat depots in the intra-abdominal space, raised diaphragm in thorax and atherosclerotic plaques among obese patients.[160] Almost 250 years later (in 1947), the coexistence of obesity with diabetes mellitus and cardiovascular diseases were reported by a French physician John Vague.[161] In 1960s, the co-occurrence of obesity with raised lipids, diabetes and hypertension was reported under pluri-metabolical syndrome. Later in 1977, Herman Haller was the first to use the term metabolic syndrome in reference to the combined presence of factors like obesity, diabetes mellitus, raised lipids and high uric acids - all of them that can lead to cardiovascular diseases.[162] Cardiologists then have connected CVD risk factors (like dyslipidemia, obesity, diabetes and hyperuricemia) with dietary habits, sedentary life-style, environmental and psychosocial factors.

Gerald Philips (in 1978) was the first to hypothesize that all such factors are interlinked and identification of one underlying factor can help in the detection of co-existing factors that can lead to the prevention of cardio-vascular diseases. In 1988, Gerald Reaven (endocrinologist) from Stanford University has used the word Syndrome-X to describe disorders associated with such conditions and explained its relationship with peripheral insulin-resistance.[163] This was later re-defined by United States, National Cholesterol Education Program (2001-03) as collection of associated conditions such as obesity, elevated blood pressure (BP), impaired glucose tolerance (IGT), insulin resistance (IR), elevated triglycerides and low HDL cholesterols.[164] Independently each of these conditions promote risk for cardiac disease however clustering of them in an individual shall further increase his/her risk for cardio-metabolic diseases. Later World Health Organization (WHO) and International Diabetes Federation (IDF) have developed consensus statement on diagnostic criteria's for metabolic syndromes. Gerald Reaven in 2006 have reviewed all three definitions of metabolic syndrome and observed that there shall be different clinical scenarios in which people without metabolic syndrome would also be having greater risk of cardio-vascular diseases.[165] Thus, the science behind cardio-metabolic risk factors and clustering is still evolving. Based on literature definitions we have plotted all traditional and emerging bio-chemical and clinical markers of cardio-metabolic risk in a continuum that mutually interacts at various levels (Figure 6).

Figure 6: Bio-chemical and clinical markers of cardio-metabolic risk at different levels



Note: Almost all the factors in figure 1 are inter-connected but have independent as well as common pathways for mediating CVD risks. Dyslipidemia, Type 2 Diabetes and hypertension are immediate factors that increases the risk of CVDs

Clustering of cardio-metabolic risk among children:

Co-existence of risk factors (clustering) are common today and it was perceived that children have lesser risk for cardio-vascular diseases. However with increasing rates of childhood obesity it is now widely accepted that such children have higher relative risks for long term CVD complications.

Clustering of risk factors can be theoretically conceptualised at two levels: 1) clinically it represents the existence of more than one risk factor in the same individual and 2) at societal level it refers to the co-existence of groups of people who share the similar characteristics.[166] Former strategy focuses on clinical, anthropometric and bio-chemical risk factor clustering at individual levels while later reflect to behavioural and environmental risk factor clustering at community level.

Complexity of risk continuum increases specifically with central obesity, insulin resistance or glucose intolerance, hypertension and altered lipid metabolism (dyslipidemia).[167] The changes in vascular structures (endothelial dysfunction) starts earlier in such children.[168]

Broadly, it is difficult to dichotomize cardio-metabolic risk factors because there is no evidence for a clear threshold for these markers above which cardio-metabolic risk increases; especially among children. Often this is derived from adult cut offs. Among children this situation is further exacerbated due to changes in adiposity, insulin sensitivity and plasma levels of lipids and lipoproteins at different stages of pubertal growth. Concept of Metabolic Syndrome (MetS) was aligned for identifying individuals with clustered risk factors and to monitor their progression (tracking). However, it is important to objectively measure and study clustering of risk factors rather than using it only for diagnosing metabolic syndrome.

Section 4: Proximal & Distal factors associated with Clustering of Bio-chemical markers in children

Over the last few decades, India has achieved tremendous progress on both economic as well as on human development fronts including but not limited to health. Transitioning economies, societies and its spillover effects has resulted in changing lifestyles having implications on food habits and overall reduction in physical activities – in addition, there are rising demands for quality of life, value-added modern foods (high in fat, salt and sugar), comfortable living, health care and other quality services.[23] Caloric beverages have emerged nationally as an additional and significant source of energy intake both among children and adults. Concomitantly, India is facing multiple burden of cardio-metabolic diseases (like diabetes, hypertension and heart disease) with several of its pathways starting much earlier in life (childhood).[169] Children in all age groups, across all geographic regions, are at higher risk however relative risk varies with individual habits, socio-economy and built and spatial environment. Such situations are further exacerbated by multiple heterogeneous and interdependent factors that are related to food systems, household and school environments, business, media and market environments and overall physical and cultural context in the neighborhoods - which enables or disables healthful behaviours among children.[170] So far, several prophets of modern science have looked at these components in parts whereas in reality all these factors are interconnected and functions *'as a whole';* not in isolations. Worldwide communities of system thinkers underlines that *'it takes a village to raise a child'*.[171]

It is worth mentioning that transition, whether it is economic, epidemiologic or nutrition, are a continuous process (i.e., not limited between a start and an end point);[172] which happens across generations or decades and people in each generations shall face subsequent changes in their living style and immediate environment as compared to their predecessors. For example, Pluciennik M (2008) explains how early humans in Paleolithic age lived as a small hunter-gatherer tribe and how, around 8 to 10 thousand years BC, they have started growing foods (agriculture) which has brought radical changes in the way they lived then.[173] Such radical changes has enhanced more and more social organizations, tool-making and specialization of occupations and slowly key elements of civilization has started emerging: like states, towns and monuments. Animals like dogs, sheep, goats, pigs and cattle were tamed and animal products have further improved the crop yields and quality of life then.[174] As agriculture was largely dependent on climate conditions the early science to understand weather and floods have emerged with time. More and more large and stable communities ascended along with better irrigation systems. Societies have developed with enough economic surpluses to form divisions of labors and social hierarchies introducing significant inequalities. With excess production of goods more and more trades, religions and political scenarios has surfaced. Systems to manage taxes, contracts, treaties and communications were developed as well as a practise of recording events, observations and ideas have started. Finally technologies have emerged as an important facilitator of human development. Thus with evolution and growing population demands humankind has always transformed according to their immediate environmental cues.

Presently, with unprecedented changes in economy and human development indexes in the society, what has changed largely is the child's neighbourhood environment that have profound impacts on child's eating behaviour and their biological needs. Anatomically human brains are wired in such a way that it requires large quantities of calories for which proteins and nutrients are picked-up from the diet. In about 2 million years of evolution of humankind we have developed skills to acquire better foods faster and efficiently (called as food foraging).[175] Agriculture and food distribution systems have evolved over time to facilitate such human needs. Concurrently, in ancient times there was always shorter and prolonged periods of food shortages even though man-kinds have survived in such adverse environments. There were frequent wars, droughts and other conditions that have made food acquisition more and more difficult. Probably this might be one reason why human body have adapted to store fats in different parts so that the brain's requirement of energy could be satisfied even in famine situations (as explained in the

course on System Sciences and Obesity, John Hopkins University). Over a period of time individuals got optimized to extract the most energy from their neighbourhoods whenever available with less efforts. Neuroscientists explains that human brains has evolved to control eating behaviours through strong chemical signals which are difficult to be overruled;[176] they are governed through allocated, ingestive and/or exploratory behaviours that operates without conscious controls. Thus, in modern societies with abundance of food in the neighbourhood, humans tend to consume more energy under the influence of our natural foraging instincts. Such situations are further exacerbated by sensory-specific satiety mechanisms that makes humans highly susceptible to environmental cues[177,178] – meaning humans tend to eat more as they are attracted to a variety of foods, novelty in foods, ambience, packaging etc.

In contrary, under the influence of food foraging instincts, humans in modern societies tend to spent less energy per day which is further exacerbated with advancements in technologies and mechanization. With the maintenance of positive energy balance (energy consumed overriding the energy spending), over time, there are overwhelming changes in the metabolic and endocrine functions that pre-disposes vulnerable individuals to many endocrine disorders like diabetes, hypertension and heart diseases. These are progressive conditions with several changes starting earlier in the childhood. Few studies have already reported such factors influencing BMI of children (obesogenic environment) however the collective influence of these factors (relationships) are lacking.

A multi-level framework for cardio-metabolic risk and obesity:

Research pertaining to obesity and cardio-metabolic risk should take a radical conceptual shift, especially in the context systems perspectives, as these conditions has to be viewed as relationship between individual components and focus on patterns that emerges within.[179] The traditional focus is to look for specific factors that influence individual components like eating habits etc. Conventional analysis points towards five major determinants: (i) energy in - food intake pattern (quantity, and quality), (ii) energy out - physical activity pattern and sedentariness, (iii) physical environment (built), (iv) socio-cultural norms and (v) policy regulations. These factors individually or in combination promotes or prohibit adopting and maintaining an obesogenic lifestyle. Some of the available evidences are abstracted below.

A. Relationships in Food Behaviour: There are three important components of food behaviour related to obesity, (a) what is eaten; (b) how much consumed (portion size) and (c)

sources of eating. Most of the available information addresses these issues partly without considering the variables that influence the inter-relationships. Data are restricted and mainly available from high income countries.

Shaping of eating habits in children are related to factors like: *exposure and accessibility of foods, parental modelling of eating behaviour, providing foods that leads to positive and negative psychological consequences and feeding practices.*[180] Food behaviour of child, even in under-five years, most closely resembles that of their parents than anyone else, including their siblings.[181] Satter (1990), emphasized that the central problem in feeding practice rest in the relationship between parents and children.[182] These relationships and their influence are likely to be more complex in traditional societies.

Hursiti M (1999) claims that most familiar and preferred food in childhood tend to have two principal ingredients; *sugar and fats*. Restricting children's access to certain foods also encourages intake of the restricted foods when they became available - even in the absence of hunger. Generally, children prefer to eat foods that are served most often and tend to eat foods that are readily available at home.[183] Lack of time with working parents also encourages use of convenient and ready to eat foods. Snacking also contribute significantly to positive energy balance and self-reported information may be misleading. Foods eaten away from home, an increasing trend observed in most developed societies, are usually calorie dense and are larger in portion size.[184] Availability of precooked and ready to eat items itself drives passive over consumption. A preliminary data from south India,[53] reflected that consumption of fried food items, more than 6 times/ week was associated with significantly higher odds of being overweight (OR: 3.1, P=0.014) compared to those who consumed less than 2.5 times/week. We need to determine whether these practices are linked to prevalent cultural practices or due to additional factors like achieving minimum purchasing power by the families to indulge in frequent dining away from home.

B. Relationships in Physical Activity Behaviour: Physical activity in children is a complex behaviour driven by personal, family, school, sociocultural and physical environmental attributes and these need to be unraveled.[185] Identifying predictors and determinants of physical activity behaviour in children is of public health significance because such information could inform efforts that seek to increase health related physical activity among children and adolescents.[186] Although large number of studies show that lower levels of physical activity and habitual exercise among children are associated with higher BMI,[187] greater skin fold thickness,[188] greater fat mass,[189] and obese status,[190,191] there are also studies which fail to show such associations.[192]

In a recent study among adolescents (12-17 years) from Hyderabad found that prevalence of overweight and obesity was significantly higher (10.4%) among those who watched TV > 3 hours/day, and lower among those engaged in outdoor play >6hrs./week (3.1%) and household activities >3 hrs./day (4.7%). The odds of being overweight was higher among adolescents watching TV (OR=1.92; CI: 1.16-3.18) and less involved in outdoor games (OR=2.75; CI: 1.56-4.72).[193] A study from West Bengal, India suggests that the children without regular physical exercise had higher BMI, skinfolds, percent body fat, fat mass and fat mass index compared to the children who undertake regular physical activity.[194] Covariate analysis revealed that physical exercise has a significant negative effect on all measures of body fat composition (percent body fat, fat mass and fat mass index) with age as covariate even after controlling for impact of age.

Similar to food behaviour, parents appear to be primary influence on the physical activity behaviour of their children, through either direct (by providing a supportive, nurturing environment) or indirect (through modeling) means or, more likely, as an interaction of the two.[195],[196] Compared to food related issues, effect of intra-familial dynamics on child's physical activity related behaviour is not studied. How these influences vary between cultures and within the same socio-cultural settings are also not apparent? Involving parents along with obese children in physical activity intervention program resulted in greater weight reduction and maintenance over longer duration compared to the child-only strategy.[197] These observations indicate that effectiveness as well as long term sustainability of weight loss is likely to be more when the interventions are family-based.

Some data from developed countries suggest that perceived barriers to physical activity in children and youth may be external; lack of support from friends and family members, low resources, lack of time due to school homework, internal or psychological barriers; lack of motivation, lack of confidence and ability, and fear of injury.[198],[199],[200] Enjoyment appears to be another factor that determines the activity levels among both children and adults.[201] Parent's perceived barriers and concerns about their children's physical activity vary from that of their children; this however needs to be studied in different cultures. With lack of facility, family, and social support for recreational physical activities and concern for safety and pollution, children are progressively confined to home adopting sedentary options in several high income societies. Sedentary behaviour compounds the problem by encouraging in between snacking and passive consumption of energy-dense foods.[202,203]

Sleep: Children who slept less than 8.5 hours a day had significantly higher odds (6.7; p=0.013) of being overweight, compared to the children sleeping more than 9.5 hours a day; as reported in study on apparently healthy children from Bangalore.[53] Similarly the children watching TV for more than 1.5 hours a day had higher odds of being overweight (19.6, p=0.001) compared to children watching TV for less than 45 minutes a day. The duration of sleep and TV viewing were significantly associated with the BMI of children.

C. Psychosocial and Socio-cultural Determinants: Each culture have different notions/ norms about the size, shape, and appearance of the body. It is difficult to precisely isolate the effects of beliefs, norms and expectations versus change in behaviour due to availability of unhealthy but cheap food and sedentary life styles.

According to the "cultural materialistic model" of obesity suggested by Harris (1964), there are three layers in the occurrence of obesity: economic mode of production, social organization and ideology.[204] (a) Economic mode of production: It includes the technology and population size that the productive economy allows and requires. (b) Social organization: In highly stratified and culturally heterogeneous societies, the distribution of obesity is associated with ethnicity, social class and education. (c) Ideology or belief systems: It encompasses cultural symbols, beliefs, and values.

In developed societies obesity is socially stigmatized, but in most developing countries fatness is symbolically linked to psychosocial dimensions like health, prosperity, self-worth and sexuality, though not in a constant manner. In developed nations poor are considered to be at greater risk for developing overweight and obesity due to lack of acceptable norms and social pressure to be thin.[205] But this argument may not be completely true as obesity growth has cut across lines of age, sex, race, and annual income indicating the need to look at the ethnographic view of obesity in these populations more closely. In many of the traditional cultures, food is more than a bundle of nutrients: it represents an expression of which the person is, where they belong and what they are worth, and is also a focus for social exchange. In low income and ethnic minority communities mothers consider fat baby a healthy baby and a thin baby may reflect neglectful parenting.[206] Very few (up to one third) of the parents with overweight / obese children identify their offspring as overweight.[207] Beliefs about obesogenic diets and physical activity are even less explored in different cultural systems. Consumer/ individual behaviour differs among the different societies (developed and developing) in making food selection.

D. Built Environment: Research into the link between the built environment and childhood obesity is still in its infancy. It is not clear whether changes in environment have increased rates of obesity or which modifications will reverse it. Another challenge is to measure the various aspects of built environment, especially from Indian context. Which components of the built environment are ideal targets for modifications?

Classically built environment encompasses all of the buildings, spaces and products created and/or modified by people including houses, schools, workplaces, zoning rules, land use, street connectivity, parks, aesthetic qualities, and walking paths and transportation system.[208] Although there is consensus that environmental factors are likely to be important in influencing children's physical activity, there is lack of definite evidence about aspects of the built environment that promote obesity.[209] Mix land use have been reported to have strong inverse association with BMI (BMI $\geq$ 30 kg/m2) among adults, with each quartile increase in mix-land use being associated with a 12.2% reduction in likelihood of obesity across sex and ethnicity.[210]

Reports about the relation between physical activity of children and adolescents and variables like environmental barriers, proximity and access to recreational facilities near their homes are not consistent; indicating the need to study other factors that affect activity level in this age group.[192,211] There were some inconsistency also between children's and parent's perceptions of their local neighborhood, with children reporting less concern as compared to their parents about heavy traffic, strangers, road safety, and lack of parks or sports grounds.[212] There is need to study whether in the traditional societies, parents are comfortable and feel safe to let their children play around due to social cohesion in the neighborhood.

Urbanization is reported to influence the food consumption pattern and physical activity by promoting use of motorized transport, labor saving service sector, and lack of time for physical activity; all are contributors of an obesogenic environment. The impact of this change will be felt more strongly in developing communities than in the developed ones due to the rapidity of expanding urban population and availability of inadequate support services.[213] It will be important to determine the bearing of newly urbanized areas on children's food and activity behaviour. Walking for utilitarian purpose is consistently found to be more prevalent in dense, mixed land use neighborhoods, when compared to lower density, residential neighborhoods (urban sprawls).[214] It is in-conclusive how built environment affects the nutritional choices of individuals. Similar to the adults, school going children in urban areas also spend considerable time in

travelling to school. This issue needs exploration how this contributes to the sedentariness behaviour and body fatness in children.

E. School Environment: Relatively little attention has been paid to study the influence of school policies, teachers and peers on food and physical activity behaviour of students.[215] Recess period, physical activity programs, facilities for sports activities, food facilities and psychological support from the authorities are important policy aspects that deserve systematic analysis for their impact on children's behaviour towards food and physical activity. Another lacuna in the current information is about the influence of SES of the students on the school physical activity and nutrition environment. Studies indicate that school-based programs can improve the physical activity and eating behaviour of young people. Apart from the behaviour modifying environment, schools can be important place for feasible, cost-effective screening modalities and identifying children at risk. In developed nations, parents also perceive value of school environment in shaping the behaviour of their children, and expect schools to take proactive role in setting example for students.[216] Peer influence increases with age and remains a strong predictor of behaviour in adolescence for food selection and involvement in physical activity.[217,218]

During school years the physical activity level in American children decline by about 50%.[219],[220] Lunch and recess breaks in many schools have been reduced due to demands and greater pressure for higher academic grades.[221] Students commuting to school by walking or cycling had decreased over time. With more stress on academic achievement, progressively children are forced to be bound to the study desk with little diversion of the time for structured and unstructured physical activities at both school and house.

Role of Media: Over last 1-2 decades there has been explosion in mass media targeted to children with progressive penetration to poor societies. Majority of the advertisement targeted to children are convenient food related.[222] There are conflicting reports about the association between TV viewing and obesity. Several studies suggest positive association of BMI and risk of being overweight with duration of TV viewing among children, while others did not support these findings.[223],[224] Some of these variations might be region specific or due to other factors. Is it really due to the TV viewing or associated sedentariness, increased awareness and consumption of the snacks advertised on TV are not known?

Chapter 3: Study Methodology

As mentioned earlier, overall aim of this study was to develop a 'Whole of Society' monitoring mechanism to measure body fat that correlates with cardio-metabolic risk factors among Indian children aged 6-18 yrs. Under this overarching goal specific objectives were finalized as mentioned in section 1.4.

3.1. Study Overview:

In the World Health Assembly (WHA) 2013, India was the first country to adopt the Global Framework for non-communicable disease (NCD) monitoring and the Government of India (GOI) has set targets to halt the prevalence of diabetes and obesity by 2025. To halt the prevalence of major NCDs in India it is necessary to protect our children from becoming obese or overweight. Childhood obesity is a precursor of adulthood obesity and attendant cardio-metabolic risks like diabetes and hypertension. In this context the Indian Council of Medical Research (ICMR) in 2012-13 constituted an Obesity Task Force including partners from All India Institute of Medical Sciences (AIIMS), New Delhi, NIN Hyderabad, NEIGRHMS Shillong, GMC Srinagar, and MP Shah Medical College, Jamnagar with INCLEN Institute of Global Health (IIGH) as the coordination agency.

Members of the task force, in 2012-13 have designed this school based cross-sectional study *'Childhood Obesity in India: A Multi-center Study on its Measurement and Determinants',* to describe the difference in body composition of Indian children in three distinct ethnic settings which represent diverse environment at the individual, family, school and community levels. The study was planned as two parts:

1. Quantitative Component (measurements in childhood obesity)
2. Qualitative Component (determinants of childhood obesity)

This part of the thesis have used the quantitative component of this larger study however qualitative study (determinants of childhood obesity) was also conducted in the same population, analyzed using standard qualitative analytical procedures and is presented separately. Three partner institutions have implemented the quantitative component of this study with site specific principal investigators from each institutions.

1. All India Institute of Medical Sciences, New Delhi
2. National Institute of Nutrition, Hyderabad

3. North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences, Shillong

The INCLEN Trust International was the Central Coordinating Office (CCO) responsible for planning, analysis and overall co-ordination of the project. Study was designed in such way that the outcomes would have implication on childhood obesity across similar settings, especially in developing world. Study has also contributed significantly to the much-needed capacity-development in the area of childhood obesity research in India.

3.2. Design and Geographical locations:

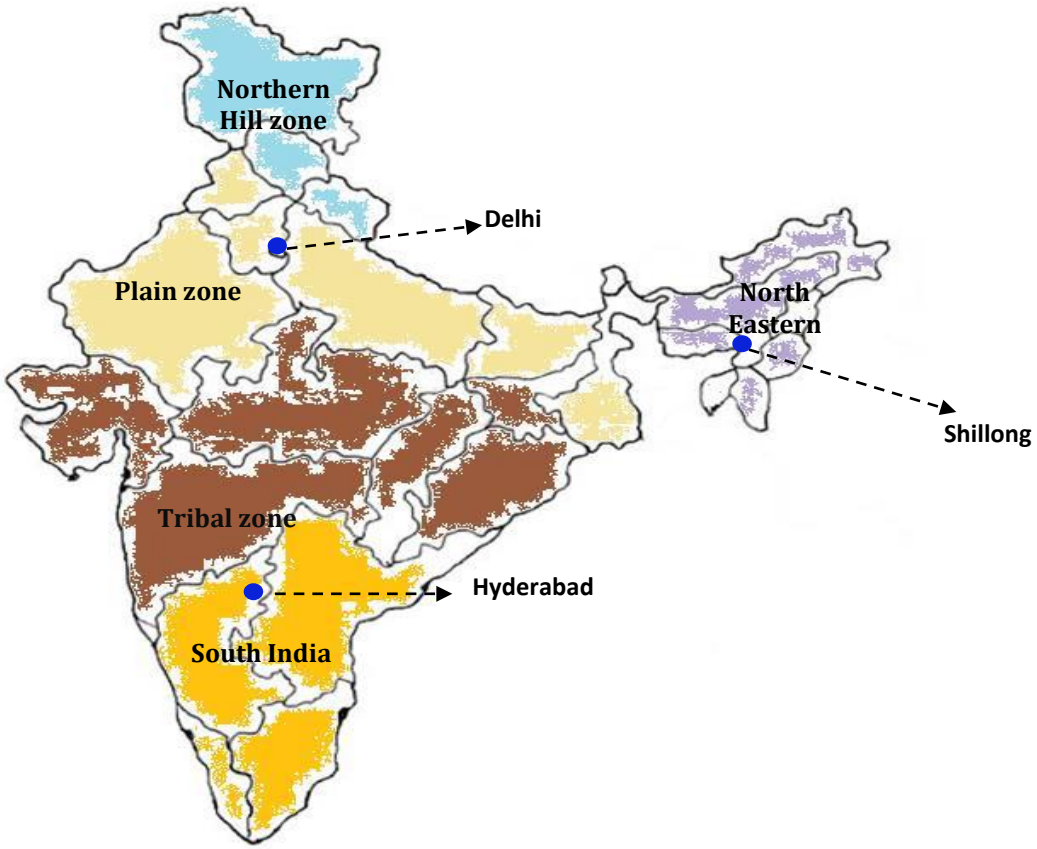
Study design: Cross Sectional design

Selection of locations: Based on the geographical zones (Figure 7) and socio-cultural variations, we categorized India into 5 zones. Three apex institutes, one each from plain zone, north-eastern zone and south India zone were selected as partner institutes. This step was considered important as childhood body composition would vary in each location and study has to capture variations related to ethnicity. Schools were selected from each study zones with reasonable representation after obtaining prior permission from Department of Education in each location. A team of experts from each partner institutes have visited the proposed schools and did initial screening of all children. This was done to ensure that all children have equal chance to participate in the study. As per the sample size, mentioned below, children were recruited randomly from the database generated during screening visits to schools.

The study locations selected were:

1. North India: The study team from AIIMS, New Delhi was responsible for conducting the study in Faridabad district, Delhi NCR region, both urban and rural areas, along with all data collection and transport of selected children and their parents to AIIMS, New Delhi for DEXA test.
2. North Eastern India: North Eastern Indira Gandhi Regional Institute of Medical Sciences, Shillong have selected Meghalaya location for this study, where Tibeto-Burman and Austro-Asiatic speaking population groups are dominant. In addition, East Khasi hill district, Shillong was also selected.
3. South India: National Institute of Nutrition, Hyderabad have selected Rangareddi district in Andhra Pradesh where Dravidian speaking groups are predominant.

Figure 7: Selection of study sites from different demographic zones



Biochemistry laboratory at NEIGRIHMS, Shillong and Cardiac Biochemistry Laboratory at AIIMS, New Delhi, were functioning as the Central Reference Laboratory and performed all bio-chemical evaluations.

3.3. Sample Size Calculations:

The primary objective of the study was to relate health outcomes, i.e. measures of cardio-metabolic risk to body fatness and to measure its distribution. Age groups under study was 6-18 years which will translate into 13 age bands with one-year interval.

Sample size was calculated for each objective's as mentioned below:

1. **Developing prediction equations using DEXA and BIA:** The reported correlations between DEXA and BIA techniques were ranging between 0.6-0.9. Considering that a correlation of 0.7 is likely, and for detecting this at 5% significance level and 90% power, with adjustment for at least two covariates (age and pubertal stages), around 80 children

was required per site (40 boys and 40 girls). Thus, we selected 100 children (50 boys and 50 girls) for each study site to perform DEXA scans. Thus, a total of 300 children were planned for DEXA scan at three study sites.

2. **Sample for developing CMRF growth curves:** In a previous study, the 5th to 95th centile curves for BMI values were done with 221 children. The results indicated that a sample of 150 (recruited @ 50 subjects at each study sites) in each age and sex band shall be robust enough to prepare CMRF centile curves.

Thus, in planning phase, a total sample of 3900 children (1950 boys and 1950 girls) were estimated. These subjects were recruited in equal numbers from three study sites; i.e. 1300 subjects (650 boys and 650 girls) from each of the three study sites. Blood bio-chemistry and BIA measurements was done in all of them. Thus, reference curves were developed for each of CMRF and body fat under study. The cutoffs for body fat measurements were identified through an Expert Group Consultation. The issues related to puberty and body fatness were also considered in this strategy.

3.4. Recruitment of Children:

Eligibility criteria: The eligibility criteria for sample recruitment were as follows:

A. Inclusion criteria:
   A. All eligible children from the school will be selected for initial screening, irrespective of the fact that they were residing in the area since past 1 day
   B. Child should have completed 6 years. It has to be 1 day less than 19 years, i.e.18 years 364 days
   C. Both boys and girls
B. Exclusion criteria:
   a. Absence of medical problems that may affect body fat status (e.g. clinical edema, visible thyroid)
   b. On any prolonged medication for more than a month
   c. Any known genetic disorders associated with obesity or cachexia, thyroid disorders, malignancy, etc.)
   d. Consent and assent
      1. Child aged <12 years- Consent form signed by parent and assent by child
      2. Child aged >12 years- Consent form signed by parent and child

All children satisfying the above criteria were selected through screening by a medical team in the formative phase of the study.

3.5. Steps in Implementation:

Step 1: Permission from the Education Department: Since the sample for the study were drawn from schools, it was imperative as the first step to take permission from the State and district Education department of the respective study sites. Permission from the respective education departments were taken by sending them a letter with the enclosed brief objectives of the study. After the permission from State Education Department, Principal Investigator have approached District Collector/District Officer for further permission.

Step 2: Selection of schools: List of private and government schools in urban and rural areas were obtained from the District Collector/District Officer. This helped us in the process of random selection of the schools for screening and recruitment of school children. Schools were listed based on the following considerations:

1.1 Strength of students in the particular school

1.2 Proportion of boys and girls in the School

1.3 Co-education school was given priority. If co-education schools were not available, to provide adequate sample, separate schools boys and girls schools were considered. In case after selection of schools, the desired sample of students cannot be recruited for unforeseen reasons from any particular school then another school of the same category was approached.

1.4 School were having classes at all the three levels i.e., primary, secondary and senior secondary. If the school does not have senior secondary class, another school were considered for inclusion.

1.5 In rural areas, if private school is not available, they were replaced by a government school

Step 3: Permission from School Authorities for study

1. After random selection of the schools in the urban and rural areas, the Principal investigator of the respective study site has approached concerned school authorities for approval to undertake the study in their school.

2. School authorities were initially approached with a telephonic or verbal conversation with the concerned authorities, followed by a letter and meeting in person

Step 4: Obtaining consent and assent from parents and children

1. After obtaining permission from the school authorities, consent were obtained before undertaking the screening process at school
2. Consent from any one parent of the child were obtained using the Informed Consent Form
3. Consent forms were distributed to parents through the children or as appropriate after discussion with the school authorities and were collected again through children. If desired, a discussion with the parents were done at an appropriate forum (parent-teacher meeting at school) as suggested with the school authorities
4. While distributing the Informed Consent Forms to children, they were explained in brief about the activities/procedures that would be undertaken in this phase of the study
    4.1. For, students less than 12 years of age: Consent from one parent of the child and assent of the child were mandatory
    4.2. Students above 12 years age: Consent from one parent or child

Step 5: Screening of children in schools

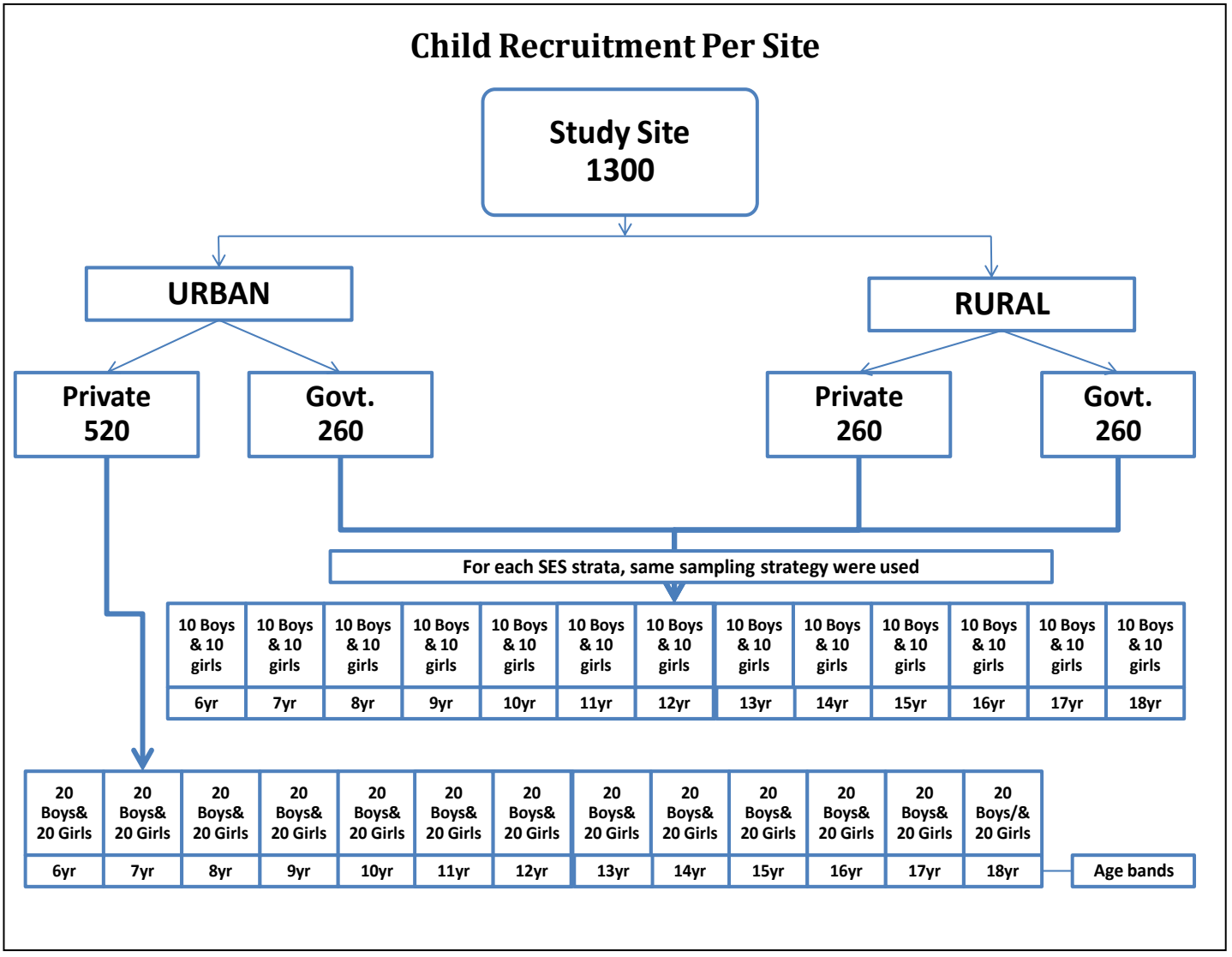
The purpose of screening the children was to ascertain the eligibility for the study. Information regarding age, ethnic origin, any medical problem that can affect body fatness (as mentioned earlier in the eligibility criteria) were documented. Screening was done for all the children in the age group of 6-18 years old (from all the classes and all sections) for whom consent and assent (as applicable) have been obtained. Screening camp/health clinic were organized by the respective sites for the screening purpose. Screening was be done by a doctor, nurse and research assistant recruited for the study at each site by using screening forms. Apart from the various information mentioned above, height and weight were also be measured for calculating Body Mass Index (BMI). Information on age (date of birth) was collected from the school register or records. In case any of the desired information was not available from the child or from school register, parents were contacted over phone for completing the form.

Step 6: Identifying eligible children

After screening, eligible children were selected for the study was selected randomly based on the eligibility criteria mentioned earlier. All children who satisfied the eligibility criteria per location were contacted for next step of evaluations – recruitment plan per site is depicted in figure 8.

- Assigned Unique ID to the recruited children: All the selected children were assigned with a unique ID for reference purpose. The unique ID considers the site at which the child is recruited, rural/urban, stakeholder code and the stakeholder number. All the quantitative tools were sequentially arranged in the form of a booklet and thus every booklet was assigned a unique ID. Unique ID for the stakeholders were generated by CCO, at INCLEN.

Figure 8: Flow diagram for sample selection per sites



3.6. Tools & Instruments:

Based on the above protocol, data collection was undertaken broadly in two phases: 1) screening phase and 2) after recruitment. During screening, only basic demography to assign origin/ethnicity and height and weight for BMI calculation were collected. After recruitment in the study, children were assessed for the following parameters: a) Anthropometry 2) Pubertal Stages 3) Bio-chemical markers of CMRF and 4) Bio-impedance (BIA). As mentioned, a selected sub-group of 206 children have undergone body fat estimation through Dual Energy X-Ray Absorptiometry (DEXA) technique. Additionally, 5) Socioeconomic status, 6) Dietary assessment, 7) household consumption and expenditure pattern 8) Media & market exposures and 8) physical activity patterns were also collected from each child.

Table 3: Data collected per child are summarized below

Phase	**Measurements**	**Methodology**	**Place**
Screening Phase	Height, Weight & Basic demography	Direct measurement Questionnaire	School
Post recruitment	Height, Weight, BMI (calculation) HC, WC, WHR (calculation) Skin fold thickness (triceps, biceps, subscapular, suprailiac) BP, BIA Pubertal assessment	Direct measurements using specific equipment's Caliper Digital BP equipment, BIA equipment, Observation and assessment	School
	Socioeconomic status Dietary intake Physical activity Home environment and expenditure pattern Media exposure and marketing behaviour School environment	Questionnaire	School and home
	Blood sample collection	Venipuncture	School or hospital
	DEXA (for selected subgroup)	DEXA machine	Hospital/ Institute

1. **Anthropometric Measurements**

Following anthropometric measurements were measured: Weight, Height, Waist and Hip circumference (WC and HC), Mid upper arm circumference (MUAC), skin fold thickness (triceps, biceps, sub-scapular and supra-iliac). All measurement were taken 3 times and an average was obtained.

- **Body Weight:** Weight was measured for each child using electronic weighing machine (Model: SECCA 813). The weighing machine had measurement precision of up to 100 grams.

- **Height:** Standing height of maximum vertical size of the participant was assessed using a portable stadiometer with a vertical backboard and a moveable head board using (Model: SECCA 213) with precision of 1mm.

- **BMI (Body Mass Index)** was calculated as: Weight (Kg) / Height in Meter^2

- **Body circumferences:** There were important measurements that recorded the size of cross-sectional and circumferential dimensions of the body. Circumferences used alone, or in combination with skin fold measurements, provides indices of nutritional status and level of fat patterning. All the body circumferences were measured using non-stretchable fiber glass tape (Model: SECCA 201)

- **Mid Upper Arm circumference (MUAC):** Arm circumference was measured with subject-standing upright, shoulders relaxed, and the right arm hanging loosely. It was important that the muscle of the arm was not flexed or tightened, which could yield a larger and inaccurate reading.

- **Waist (Abdominal) circumference / Hip circumference**

- WHR (Waist Hip Ratio) calculated from Waist Circumference / Hip Circumference

Skin fold thickness: sometimes called "fat fold" thicknesses, were taken to assess the thicknesses of double folds of skin and subcutaneous adipose tissue at specific sites of the body. They provided a relatively simple estimation of general fatness, and also information on the distribution of subcutaneous body fat. It was measured using Harpenden skin fold calipers. In addition triceps, biceps, subscapular and suprailiac skin fold thicknesses were also collected.

As part of clinical assessment, resting blood pressure and heart rate were also measured. Blood pressure (both the systolic and diastolic pressures) was recorded in the left arm using automated measuring instruments (Model: Omron HEM 7080). The systolic pressure is the maximum pressure in an artery at the moment when the heart is beating and pumping. The diastolic pressure is the lowest pressure in the artery in the moments between beats when the heart is resting. Pulse rate were also measured.

2. Pubertal Assessment

Pubertal assessment was undertaken along with clinical examination. Each child during pubertal assessment was supported by a research staff of same sex along with another person of same sex. Pubertal stages was categorized as pre-puberty, early puberty, late puberty and post-puberty were determined based on breast and pubic hair stages for girls and genital and pubic hair stages for boys according to Tanner criteria for pubertal staging. Pubertal staging were done for every recruited child. This assessment had two parts: self-assessment by the child and confirmation by the research team member.

A. **Pubertal assessment for females**: Each girl child was provided by photo tanner, which had different stages of the growth for breast and pubic hairs. After self-identification of present stage, for children below 12 years researchers/doctor of same sex have confirmed the stages in the questionnaire. For girls above 12 years age at menarche were also asked.

B. **Pubertal assessment for males:** For boy child photo tanner was provided to help them identify their stages of genital and pubic hair growth. Boys were also asked about their testicular volume by using "Orchidometer", by comparing with the beads of different sizes to the subject's testes size.

   - Orchidometer: consist of a string of twelve number wooden or plastic beads of increasing size from about 1 to 25 milli litres. The beads were compared with the testicles, and the volume is read from the bead, which matches most closely in size. Pre-pubertal sizes are 1–3 ml, pubertal sizes are considered 4 ml and up and adult sizes are 12–25 ml. This could accurately measure the size of testes. Discrepancy of testicular size with other parameters of maturation can be an important clue to various diseases. (Small testes can indicate either primary or secondary hypogonadism. Testicular size can help distinguish between different types of precocious puberty. Since testicular growth is typical the first physical sign of true puberty, it is used as a confirmation that puberty is beginning in a boy with delay. Large testes (macro orchidism) can be a clue to one of the most common causes of mental retardation, fragile X syndrome etc.

3. Bio-chemical Assessment

Biochemical assessment were done to estimate cardiometabolic risk factors like blood glucose, fasting insulin, serum lipids, apo-lipoproteins A and B and uric acid. For biochemical analysis total of 8 mL blood were collected (7mL in plain vacutainer and 1 mL in fluoride vacutainer) from each child in the morning, after at least 8 hours of last meal. After collection, samples were stored immediately in an ice-filled insulated containers at -20 degree centigrade refrigerator and were transferred to laboratory within 2 hours of collection. The samples were centrifuged and aliquoted as early as possible. Information were entered in the specified form in questionnaire.

4. Bio-Impedance Analysis

Impedance was done in all children (@ 1300 children per site X 3 sites) using BIA equipment (Model: Biospace Inbody 720). The machine will give outputs related to body composition, including percentage of body fat and lean body mass however since this study aimed at developing India specific fat prediction equations, the machine were customized for giving raw impedance (Z), reactance (X) and Phase angle (Xc) estimations. The machine passes a harmless, ultra-low level electrical current through the body through 8 electrodes. Assumption is that lean tissue, which is over 70% water, is a good conductor of electrical current while fat tissue low in water provides resistance to electric flow. Thus, the resistance to the flow of electrical current measured by the analyzer can be used to calculate body composition.

Assessment of specific gravity of urine: This was is an important step before conducting BIA, because it is affected by the hydration status of the body. Thus, the hydration status was assessed by doing urine specific gravity by using a hand held refractometer (Model: Hand Held-ACQ-1 Series). BIA test will be done if the urine specific gravity was 1.020 or less. Normal range of specific gravity in human urine was from 1.003 to 1.030. Values outside this range may be the result of specimen dilution, adulteration or may be indicative of a number of health related problem.

Accuracy of BIA was dependent on the condition of the subject and on the environment in which the test is conducted. Therefore, following precautionary steps were taken to assure accurate test results:

1. Test conducted in fasting state - the test were conducted in fasting condition immediately aft er the blood sample collection. This is primarily because the food could interfere with electri

c circulation and thus, may result in measurement errors.

2. Subject empties bladder before the test - Although not included in the body's compositional elements, the volume of urine can also interfere and can result in errors.

3. No moderate/severe physical activity immediately before the test - Exercise or sharp movem ents can cause temporary changes in body composition.

4. Child/subject was asked to stand still for 5 minutes before the test - Conducting the test im mediately after lying in bed or sitting for a long period of time might result in a slight change in the test results. This is because body water tends to move to the lower extremities of the b ody as soon as a person stands or gets up.

5. Not sweating excessively - Excessive sweating could cause temporary changes in the body co mposition. So conducted the test at normal temperatures (20℃~25℃). While the human bo dy is stable at normal temperatures, body composition is susceptible to change in hot or cold weather.

6. No measurements during menstrual cycle - Females experience increase in body water durin g menstrual cycle, so this was avoided. In such cases, child was called on another day under c onsistent conditions.

5. Dual Energy X-Ray Absorptiometry (DEXA) Assessment

In a randomly selected sub-sample (206 children), DEXA were done as a reference method for body fat estimation. The DEXA scan, works on the principle of two different energies of X-rays which are used to scan the body, one of which is absorbed more strongly by fat than the other. The machine will subtract one image from the other and the difference indicates the amount of fat relative to other tissues at each point. A sum over the entire image enables calculation of the overall body composition. DEXA test were conducted by Hologic DEXA machine in the study institutes. A standardized phantom was used for calibration of DEXA machines. In addition, routine periodic internal quality assurance measure was followed in the DEXA laboratory at each study site. It has been decided to take equal samples from rural and urban region.

6. Socio-Economic Status Assessment

Details pertaining to child's family were assessed for classifying their socio-economic status. The socio-economic status is an important determinant of health and nutritional status as well as

associated mortality and morbidity. Scores were given for each statement/question in the questionnaire and based on the scores and their aggregated child would be grouped under different social class.

7. Dietary Assessment

Diet and nutrition are important factors in the promotion and maintenance of good heath throughout the entire life course therefore assessing dietary patterns is an important step. There was type of diet assessment: 1) Food Frequency Questionnaire (FFQ) and 24-hour dietary recall.

- **24-hour dietary recall for 3 days**: In this method, the subject is asked to recall all the foods and drinks consumed over the previous 24 hours. This would be repeated for three days, two working days and one weekend days, however success of this method depends on subject's memory. A 3-days dietary recall was done in a sub-sample of 300 children (100 from each site).

- **Food Frequency Questionnaire:** FFQ is a list of food on which the subject is asked to indicate the typical frequency of consumption. It was designed to obtain qualitative, descriptive information about usual food consumption patterns. It was used as a cross validation technique along with 24-dietary recall to enhance the quality of dietary data. FFQ are good for describing groups but have serious limitations for making statements on individual habits. It is quick to administer, inexpensive, good at describing food intake pattern and foods can be ranked in relation to intakes of certain food items or groups. Though there is, a lot of disparity of food items in India within different states and different regions, FFQ designed for this study includes a comprehensive list of Indian foods.

8. Physical Activity Assessment

For children, physical activity and movement enhances fitness and fosters growth and development. Physical activity pattern of the child and adolescent were assessed through rapid physical activity measures and 3-day recall questionnaire.

9. Household consumption and Expenditure assessment

The expenditures incurred by household on domestic consumption during the reference period were mapped under household expenditure. However expenditure incurred towards productive enterprises of households were excluded. Thus, household consumption was assessed in terms of the consumption of food items in the household and the expenditure on non-food items in the

household. Household consumption assessment was done in a sub-sample in whom detailed dietary and physical activity assessment were done.

- Consumption was measured in terms of monetary expenditure and the quantity of various food-items consumed in a household every month. Lists of food items commonly consumed were listed. This was assessed on the basis of the amount of particular food item in a household and the monetary expenditure on the same.

- Household expenditure for various non-food items in the past 30 days and 1 year (365 days) were collected.

10. Media and Marketing Exposures

Purpose of this was to assess the impact of different media on dietary habits and physical activity behaviour of the children.

3.7. Quality Assurance Measures:

Validity and reliability of data was considered as most important component in this study therefore extensive quality assurance measures were incorporated at every stage of project. INCLEN has been following these quality assurance protocols for multisite studies in past which has evolved and proved to be robust. The quality assurance process had six levels:

- **Use of common protocol and processes:** All study sites were using common study protocol and study tools for data collection. All site investigators were consulted in the study tool preparation and protocol finalization process to ensure common understanding about the tools, procedures including quality assurance measures and consistency in data collection data recording and transmission. No flexibility was allowed after protocol and instruments were finalized.
- **Training of team members** for data collection: National & regional workshops were conducted using common operational manual in the presence of CCO investigators
- **Equipment and standardization:** All sites were using same make and model of equipment's to ensure comparable measurements and data. All equipment's in the anthropometric measurement were standardized as per the Bureau of Indian Standards (BIS) guidelines. For DEXA machines, the sites have used standardized phantoms for calibration.
- **Certification of researchers on measurement techniques:** The team members at each site were assessed by the CCT members for robustness and correctness of measurement

techniques and interpretation based on inter-observer agreement. The team members were then certified on achieving the acceptable level of competency during the training sessions.

- **Quality check at study site:** At each study sites, PIs were responsible for the quality of data collected. PIs have screened and supervised data collection by research team members. All study tools completed by team members were cross checked for completeness and consistency. Quantitative tools were checked for appropriate coding and summarization. Study site PIs have certified the data quality by signing every instrument. In case of any deficiency, study site PI have ensured collection of remaining information or repeating the data collection as required. Site investigators have also undertaken quality check measures for assessing the methodology, technique followed and the inter-observer and inter-observation agreement periodically.
- **Quality assurance field visit by CCO investigators:** Quality assurance field visits were done by CCO members to cross check the adherence to methodology and data collection procedures. Consistency in data collection at all study sites was prioritized. All CCO investigators have submitted their visit reports in confidential to CCO. All deviation or discrepancy in data collection or recording methodology, CCO have discussed the issue with the study site investigator and when necessary ICMR was contacted for appropriate action to resolve.
- **Monitoring and tracking project activities from the CCO**: Electronic and telephonic communications were used to ensure cohesive functioning of the entire research network. A regular bi-monthly teleconference were planned to monitor progress in project activity, problems encountered and future activities. In case of difficulties, study site PI and project coordinator have worked together to solve the problem.
- **Laboratory reference checks:** Random blood samples from all sites were retested at the CRL, AIIMS for checking the accuracy and agreements between site laboratories.
- **Data quality check at CCO:** The data at CCO were cross checked for completeness and correctness.

3.8. Customized software and double data entry processes:

Prior to data entry, all forms were physically verified for completeness in CCO. For error free and high quality data, INCLEN has designed SOMAARTH-1 software for entering and for assessing the quality of data. All data received at CCO were entered twice by two independent different data entry operators. There were two teams of data entry operators and each team have entered the

same booklets independently in to the software, as per UID (double data entry). Each team members were assigned a username and password and was not aware about the status of corresponding entry done by the other team. Software has automatically picked up each of mismatches between both teams which would be corrected by dedicated quality assessment team. In those forms, which had above 40% of errors (mis-matches) the entry was rejected and the teams has to re-enter the form completely.

3.9. Data cleaning and processing:

All data was retrieved from SOMAARTH-1 software and converted to STATA format for further data processing and preliminary analysis.

3.10. Ethical Issues:

The study was approved by independent ethical committee of IndiaCLEN (2012). Consents and assents were obtained from each child, parents and their teachers for each assessment. Presence of parents or teachers of same gender were entertained during the assessments at schools and for DEXA (sub-sample). All measures were taken to protect the rights and safety of participants during pubertal assessment. The identity of children and their parents were protected through unique identification numbers.

3.11. *Statistical Analysis Plan*

Data analysis for quantitative study was coordinated by CCO, INCLEN, New Delhi, in close consultation with study site PIs and coordination with ICMR Expert Group Members. All data, after quality checks, were compiled in to a master database and on to the server at INCLEN Executive Office. Working databases were backed-up on a daily basis for security purposes. A statistical analysis plan (SAP) was prepared and submitted to ICMR expert group for approval prior to the data analysis. Detailed plan of statistical analysis has been described in detail for each studies in following chapters.

Chapter 4: Results

As mentioned in the methods session; list of eligible schools, in government and private sector and in urban and rural areas, were obtained from respective education departments in each study locations (Delhi, Hyderabad and Shillong). After initial communications from concerned authority, site principal investigators have contacted the head of each schools. After prior approvals and consent from authorities, a health screening camp (medical screening) was conducted in each school. All children, their parents and school teachers were explained about the purpose of the study, methods and expected outcomes and a written consent were obtained for participation. An exhaustive list of eligible children, after inclusion and exclusion criteria, from both sex and age groups in rural and urban areas and in government and public schools, were prepared and shared with coordinating office in Delhi. This list served as the sampling frame for recruitment in study.

Appropriate number of children from each category was selected by the coordinating office and each child was assigned specific UIDs – initially a total of 3852 children has participated however during the analysis 611 children was removed due to various reasons. Thus final study sample analyzed were 3241 children. For each child a booklet with all 14 questionnaires were administered by site investigators. All data was collected in school in the presence of teachers and/or parents. For bio-impedance (BIA) and blood sample collection, each child was requested to fast for minimum 8 hours. A sub-sample of 206 children from both sex, along with their parents were requested to visit the site institutes for DEXA measurements. The site investigators have coordinated their travel and timely completion of protocols. An operational manual was prepared and shared with each sites to bring uniformity in the protocols. Blood sample were processed as per specific protocol prepared and shared with respective cardio-metabolic laboratories in each location. All blood samples from Delhi and Hyderabad location was transferred to cardio-metabolic lab under AIIMS, New Delhi while the results as per standard protocol were shared by Shillong location.

All filled booklets were checked and signed by site investigators and was couriered to central coordinating office – tracked and maintained through a log book at CCO. Research officers have physically verified each booklet for discrepancies and completeness and queries were communicated with site investigator. Simultaneously, questionnaires were designed in SOMAARTH-1 software for double data entry. Results are presented as 4 studies below.

Study 1 - Assessment of whole-body composition using bioelectrical impedance analysis (BIA) among children 6 to 18 years: Validation with Dual X-Ray Absorptiometry (DEXA)

1.1. Materials and methods specific for study 1:

a. **Specific Objectives**: We have used impedance (Z) values of 3241 school children, between 6 to 18 years (13 age bands) to develop:

1. Predictive equations for estimating whole body fat mass (FM) and fat free mass (FFM) by using total fat estimated from DEXA in a subsample of 208 children and
2. Study the distribution of body fat and lean mass among children in different BMI categories (thin, normo-weight, overweight and obese children) as per Indian Association of Pediatrics (IAP), Growth Standards, 2015.

b. **Pubertal Staging**: A photo card defined by Tanner's criteria for pubertal staging was used by children to do self-assessment under five physical stages of growth (Stage 1 to 5). Overall pubertal stages were estimated from physical development of breast and pubic hairs in girls and from physical development of genital and pubic hairs among boys. In addition, testicular volume was estimated in boys using 'orchidometer'. Over 93% boys (n=1504) and 87% girls (n=1425) have participated in this exercise.

c. **Definition of thinness, normo-weight, over-weight and obese children:** Indian Association of Pediatrics (IAP) has revised growth charts for Indian children between 5 to 18 years using pooled data from 33,991 children.[11] Data from fourteen cities were collated with approximately comparable number of children in each age bands and gender. Using LMS method, percentile curves were prepared for height for age, weight for age and BMI for age. As per new growth charts, based on International Obesity Task Force (IOTF) approach, for each age-bands and gender, the centile values corresponding to BMI 23 adult equivalent (71st centile for boys and 75th centile for girls) were considered as overweight cut-off and centile values corresponding to BMI 27 adult equivalent (90th centile for boys and 95th centile for girls) were considered as obese cut-off. Children below 3rd percentile were considered as thinness. In this study we have used centile values for BMI for age given in the tables of IAP growth charts to classify children as thin, normo-weight, over-weight and obese for each age-band and gender. Definition by WHO for BMI for age, based on z-scores, was used for verification purpose.[225]

d. **Bio-impedance**: For each child, prior to BIA measurements, specific gravity of urine was measured using a handheld refractometer (Model: Handheld ACQ-1 series). This was done to ensure that the body was not dehydrated. The BIA measurements were only done when the urine specific gravity was less than 1.020. In addition, the child was asked to rest for half an hour before the BIA tests were performed. The measurements were done in empty stomach (fasting) and ensured that child have not performed any physical activity immediately before the tests.

Multi-frequency, segmental bio-electrical impedance analyzer (Model: Biospace Inbody, 720) with 8 point tactile electrode system were used in all three study sites – two electrodes in contact with palms (2 on thumbs and 2 on thenar side) of both arms and two on foot platforms (toes and heels) of both foot. Ultra low level electrical AC current (I) was passed through source electrodes and recorded voltage difference (V) at different electrodes.[226] This was divided with I to obtain impedance (Z) for that compartment. The same procedure was repeated by switching source and detector electrodes to calculate Z of different segments at different frequencies. Impedance were measured at 1khz, 5khz, 50khz, 250khz, 500khz and 1mhz while reactance (Xc) and phase angle (φ or P) were measured at 5khz, 50khz and 250khz. Results of impedance, reactance and phase angle in each measured frequencies in Ω (Ohms) were obtained through algorithms as direct machine outputs. Impedance index (ZI) was then calculated for each segments and whole body Impedance Index (ZI) was then calculated, at different frequencies, using the following formula:

$$ZI_{frequency(f)} = \frac{Ht(cm)^2}{Z_{RA} + Z_{LA} + Z_{TR} + Z_{RL} + Z_{LL}}$$

BIA were done in 97% boys (1566/1611) and 96% (1568/1630) girl participants. Other than raw impedance, reactance and phase angle values no other outputs, from the Inbody machine, were used in this analysis. This section focuses only on the study of whole body lean and fat mass using BIA and this for each body segments will be discussed elsewhere.

e. **DEXA Scan**: For developing linear prediction equations for fat mass and lean mass, DEXA measurements were done in a subsample of 208 children. Considering that a 0.7 correlation is likely between DEXA and BIA body composition estimates and at 5% significance and 90% power a sample of 32 children were required. This for each sex and three sites adds up to 192 children and with 10% extra (n=18) the total sub-sample required was 210 children. Thus, from each age-band and for each sex, a minimum of 2 to 3 children (n=32/13) were planned. Measurements were done using Hologic DEXA machine among children in empty stomach (fasting) and in surgical

scrub uniforms. Bone mineral content (BMC), Lean Mass and Fat mass were obtained as direct DEXA machine outputs for each segments and for whole-body. The sum of lean mass and bone mineral content represents fat free mass while lean tissue mass is synonym with muscle mass.[227]

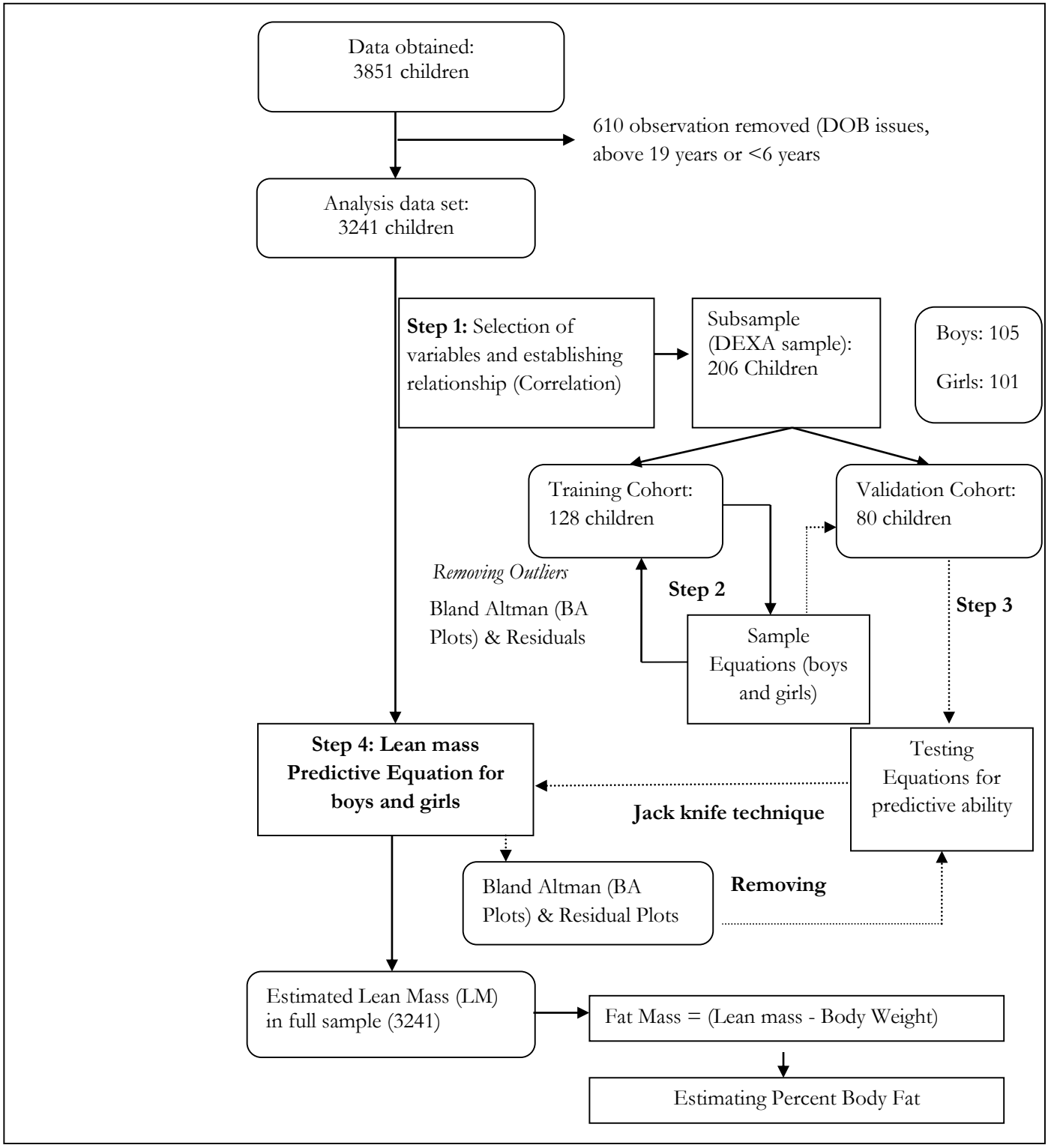
f. Statistical Analysis Plan – Study 1

The percentage body fat estimated from $BIA_{(Inbody)}$ and DEXA were significantly different in boys ($p=0.001$) and girls ($p=0.014$) and this forms the ground for developing new prediction equation for Indian children. Strengths of relationships between variables were established using Pearson's correlation coefficient. We constructed linear regression models for both sex using outputs from DEXA (lean, fat free mass (lean+BMC) and fat) as dependent variable to develop new prediction equations (using impedance Index) to predict whole body constituents. Primarily the equations were developed in the sub-sample of 208 children however this sample was further divided in to two: development cohort (n=128) and testing cohort (n=80) for validation purposes. The schema for developing prediction equation is depicted in Figure 9. Lean mass and fat free mass was then predicted in the full sample (n=3241) and fat mass was estimated by deducting it from body weight.

Jack-knife and bootstrap methods (commonly known re-sampling methods) are standard ways to estimating the standard error propagation – a systematic way for calculating 'standard deviation' of errors of measurements. The predicted lean were internally validated using Jack-knife by removing one observation at a time and estimating the changes in standard error of means – practically it suppress one observation at a time and helps to view the influence of other observation of SEM. Importantly, this method could detect overly influential observations in the datasets. Each jack-knifed block is close to final values and the distribution of jack-knifed data will be within the final error range. A jack-knifed block observation are said to be influential, if that observation will substantially change the estimates of coefficients – i.e., it is generally a product of outlier and leverage.

Model building using Jack-knife in STATA helps to store the difference in regression coefficients vs. dependent variable (df-beta); especially when each coefficients are changed by deleting one observation at a time. This can be explained with an example. Suppose, if df-beta of impedance index (ZI) is observed as -0.013 then it means the lean mass in DEXA shall decrease the coefficients of impedance index by 0.013 times of standard error (i.e., 0.013 times the standard error of zi50_wb in the regression model). Rule of thumb used to identify such influencers is to plot the regression coefficients against dependent variable and those values above 0.28 and below 0.28 can be considered for further investigations.

Figure 9: Schema for developing linear prediction equations



Note: Initially, prediction equations were developed in the subsample (n=206) and in training sample (n=128) using lean mass from DEXA. The residuals were plotted and outliers were removed through BA plots. Refined equation was then used in validation sample (n=80) and tested for predictive ability using jack-knife technique (Boot-strapping) to test changes in SEM (standard

error of means). The final equation was then used in full sample (n=3241) to predict lean mass and estimated fat mass and percent fat mass from these equations.

g. **Dealing with errors and uncertainties (Bias, Accuracy and Precision):** None of the measurements in epidemiology is said to be error free. Therefore in this study (among the sub-sample of 206 children) we have calculated bias, accuracy and precision for lean mass obtained from DEXA as criterion standard. Bias was defined as the absolute difference between predicted lean and expected lean (DEXA Lean).[228] Percentage difference can be calculated as (predicted lean – DEXA lean X 100 / DEXA Lean). Precision (for epidemiological use) were defined as the percentage difference <10% as precise, 10 to 20% as moderate and >20% as imprecise - this can be set at lower values for clinical use.[229] Accuracy can be defined as percentage children who were having the estimated lean mass within 10% of expected lean. Differences in bias and accuracy were compared using paired t-tests. The residual errors and agreement between estimated and measured lean were assessed through Bland-Altman plot (difference between estimated lean plotted against observed lean). A positive difference suggests over-estimation and negative difference suggest under-estimation. The limits of agreement were calculated as bias plus two times precision.

4.2. Results:

Subject characteristics: Body composition of 3241 children (1611 boys and 1630 girls) between 6 to <19 years (13 age bands) recruited from schools in rural and urban settings in three study sites were analyzed. Overall, boys and girls did not differ significantly in body weight (kg) (diff: 0.67; 95% CI: -0.23, 1.57) but boys were taller (diff: 2.78; 95% CI: 1.66, 3.91) and have higher waist circumference (diff: 1.19; 95% CI: 0.52, 1.85). In contrary, girls have higher BMI (diff: -0.54, 95% CI: -0.77, -0.31) and hip circumference (diff: -1.59; 95% CI: -2.41, -0.77). There were no significant difference in mid-upper arm circumference in both genders (diff: -0.06; 95% CI: -0.32, 0.20). As compared to rural settings, children in urban settings (boys and girls) have higher body weight (diff: -3.42; 95% CI: -4.32, -2.51), height (diff: -3.94; 95% CI: -5.07, -2.79) and waist circumference (diff: -2.87; 95% CI: -3.54, -2.20). Overall there was no difference (P=0.331) in mean arterial pressure (MAP) among boys and girls however MAP was significantly higher in rural settings for boys (diff: 1.23; 95% CI: 0.33, 2.15) and girls (diff: 1.86; 95% CI: 0.91, 2.81).

Mean ± SD of key anthropometric variables and whole-body impedance index (at different frequencies) across age bands in boys and girls are presented in Table 4. Almost all descriptive variables were different across 13 age-bands studied (P=0.001) and the difference increases significantly from 9 years; indicating that body composition of children (boys and girls) are

comparable at younger age bands (<9 years). Each variables were compared between boys and girls and significant difference ($P < 0.05$) are presented as (*). In addition, for each age band and gender the distribution of each descriptive variable were tested for rural and urban influence and significant difference ($P < 0.05$) are presented as (#). Broadly, except in few age-bands there were not much influence of rural and urban settings and therefore same prediction equation can be used in both settings. The preliminary analysis indicates that body compositions are different in boys and girls and age is a significant predictor.

Proportion of boys and girls in five stages of growth are reported in Table 5 (1504 boys and 1425 girls). Mean age of 1) pre-adolescents (stage 1) were 9.2 years in boys (95% CI; 9.0, 9.4) and 8.9 years in girls (95% CI; 8.8, 9.1); 2) stage 2 was 10.5 years in boys (95% CI; 10.3, 10.6) and 11.5 years in girls (95% CI; 11.2, 11.7); 3) stage 3 was 13.6 years in boys (95% CI; 13.4, 13.9) and 13.9 years in girls (95% CI; 13.7, 14.2); 4) stage 4 was 15.5 years in boys (95% CI; 15.3, 15.7) and 15.7 years in girls (95% CI; 15.5, 15.9); and stage 5 (full maturation) were 16.9 years in boys (95% CI; 16.7, 17.2) and 17.0 years in girls (95% CI; 16.7, 17.3). Boys and girls in different stages of growth in rural and urban settings are significantly different (boys, $p=0.001$ and girls, $p=0.004$).

Table 4: Characteristics of key descriptive variables in different age groups and gender

Boys (N=1611)								Impedance Index (Whole Body), Ω				
Age band	**n**	**Weight (kg)**	**Height (cm)**	**BMI (kg/m2)**	**WC (cm)**	**MUAC (cm)**	**MAP (mmHg)**	**ZI-1 (khz)**	**ZI-5 (khz)**	**ZI-50 (khz)**	**ZI-250 (khz)**	**ZI-500 (khz**
6 to <7	54	20.27±3.95*	117.13±9.34*	14.66±1.21	52.80±4.61	16.46±1.93	77.75±8.07	7.78±1.70*	7.87±1.72*#	8.48±1.89*	9.39±2.07*	9.79±2.12*
7 to <8	142	21.50±4.78	119.34±7.61	14.92±1.84	54.21±6.61*	16.71±2.13#	78.14±8.80#	8.16±1.60*#	8.25±1.62*	8.92±1.79*#	9.90±1.98*#	10.29±2.04*#
8 to <9	137	22.71±4.96#	123.25±6.66#	14.84±2.16	54.41±6.27#	17.22±2.20#	78.47±8.62	8.77±1.44*#	8.86±1.46*#	9.60±1.61*#	10.63±1.79*#	11.04±1.86*#
9 to <10	142	25.16±5.58	128.39±7.0#	15.14±2.34	55.60±7.30	17.87±2.41	79.91±8.58	9.58±1.58	9.69±1.63	10.51±1.80	11.64±1.99	12.08±2.05
10 to <11	141	27.93±7.29#	132.53±8.95#	15.70±2.57#	58.26±7.31#	18.77±2.89#	79.34±8.53	10.45±1.92#	10.58±1.97#	11.51±2.19#	12.74±2.40#	13.23±2.47#
11 to <12	143	30.83±8.29*#	137.66±9.0*	16.07±2.86	60.07±8.58	19.58±2.78	80.26±7.91	11.53±2.22	11.70±2.39	12.74±2.60	14.05±2.82	14.56±2.91
12 to <13	150	35.06±9.43#	144.24±9.62#	16.64±3.06	63.13±9.69*#	20.58±3.19#	79.78±8.32	13.37±3.01*#	13.53±3.07*#	14.80±3.44*#	16.35±3.81*#	16.93±3.93*#
13 to <14	148	38.87±9.34*#	150.00±8.95#	17.12±2.95*#	64.13±8.63#	21.36±3.00#	83.24±9.34	15.01±3.30*	15.21±3.36*	16.71±3.79*	18.43±4.21*	19.09±4.37*
14 to <15	130	45.27±10.77	157.28±8.83*	18.16±3.30*	66.75±9.59	22.54±3.12	83.00±10.26	17.10±2.94*#	17.34±2.98*#	19.22±3.43*	21.31±3.85*	22.06±3.97*
15 to <16	133	48.12±9.62*	160.98±9.15*#	18.48±2.89*	68.03±7.47	23.18±2.93	84.69±8.22	18.46±3.13*	18.72±3.18*	20.94±3.67*	23.28±4.15*	24.14±4.30*
16 to <17	98	49.67±9.43*#	162.05±7.92*#	18.81±2.54	69.39±7.86*#	24.14±2.84*#	87.24±8.47*	18.45±2.62*#	18.74±2.68*#	21.08±3.11*#	23.52±3.49*#	24.38±3.65*#
17 to <18	111	52.18±10.83*	163.46±8.87*	19.39±3.07	68.85±7.63	24.30±3.04*	86.17±9.14#	18.97±3.33*	19.24±3.39*	21.70±3.90*	24.23±4.38*	25.09±4.53*
18 to <19	82	53.22±11.11*	163.62±8.07*	19.76±2.97	70.84±9.24*	24.76±3.25*	85.59±9.28#	19.00±2.90*	19.30±2.98*	21.82±3.38*	24.43±3.75*	25.34±3.88*
P-Value		0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Girls (N= 1630)												
6 to <7	52	18.83±2.77	113.71±5.76	14.52±1.41	52.84±6.25#	16.75±2.72#	78.63±9.35	6.81±1.05	6.90±1.06	7.42±1.16	8.22±1.31	8.52±1.34
7 to <8	145	20.94±4.81#	118.97±8.30#	14.65±1.84	52.28±5.98#	16.76±2.22#	78.91±9.42	7.61±1.32#	7.70±1.35#	8.30±1.46#	9.13±1.58#	9.47±1.64#
8 to <9	134	23.07±5.04	123.60±6.74	14.98±2.22	54.15±6.74	17.48±2.29	77.80±9.24	8.30±1.39#	8.38±1.42#	9.05±1.55#	9.96±1.70	10.33±1.79
9 to <10	137	26.02±7.28	129.30±8.51#	15.32±2.61	55.99±7.95#	18.37±2.95#	80.03±9.43#	9.30±1.90#	9.41±1.96#	10.23±2.17	11.24±2.38	11.66±2.45

10 to <11	145	29.31±7.02#	134.62±9.16#	16.01±2.69	57.40±6.52	19.06±2.25#	80.23±8.01	10.44±2.23#	10.57±2.27#	11.48±2.49#	12.62±2.73#	13.07±2.81
11 to <12	137	33.03±8.45	140.57±9.16	16.54±2.92	59.30±8.24	19.92±2.95	80.39±9.07	11.41±2.14#	11.55±2.18#	12.56±2.38#	13.78±2.61	14.27±2.68
12 to <13	150	35.82±7.98#	144.73±7.17#	16.96±2.91	60.01±7.61#	20.56±2.92	81.32±8.87	12.31±2.14#	12.44±2.18#	13.57±2.43#	14.90±2.71#	15.41±2.80#
13 to <14	131	41.17±9.52	149.32±7.31#	18.33±3.25	63.91±9.75#	21.78±3.12	84.63±10.28	12.96±2.00#	13.14±2.04#	14.39±2.25#	15.81±2.46#	16.36±2.51#
14 to <15	123	43.38±9.06	150.68±6.90#	19.07±3.56	64.85±8.43	22.51±3.10	83.28±10.81#	13.28±2.06	13.48±2.07#	14.81±2.31	16.29±2.57	16.83±2.65
15 to <16	133	45.61±9.22	151.68±6.58	19.74±3.30	67.18±8.93	23.27±2.85	84.61±8.90#	13.40±2.29#	13.60±2.34#	15.02±2.56	16.56±2.80	17.03±3.02
16 to <17	113	44.39±8.44#	151.12±6.33	19.41±3.27#	65.33±8.03	23.00±2.48	84.74±9.44#	13.19±2.04	13.38±2.09	14.79±2.29	16.33±2.52	16.91±2.59
17 to <18	131	45.66±7.92	151.07±5.65	20.02±3.31	67.15±7.79	23.52±2.87	85.90±9.22#	13.19±1.63	13.38±1.66	14.81±1.89	16.38±2.12	16.95±2.19
18 to <19	99	44.87±6.84#	150.84±6.10	19.76±3.09	67.63±7.95#	23.30±2.82#	84.97±8.11	12.95±1.52	13.15±1.55	14.52±1.73	16.03±1.93	16.59±2.01
P-Value		0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001

Abbreviations: n (Number), BMI (Body Mass Index), WC (Waist circumference), MUAC (Mid upper arm circumference), MAP (Mean arterial pressure), ZI (Impedance Index)

Reported values are Mean ± SD

* Significantly different between boys and girls in same age (t test)

Significantly different between children in urban and rural settings in same sex (t test)

P-Value = One-way ANOVA for difference between age groups

Table 5: Stages of growth among boys and girls (Tanner classifications)

	Boys (n=1504)						Girls (n=1425)					
Age band (years)	**Stage 1 % (n)**	**Stage 2 % (n)**	**Stage 3 % (n)**	**Stage 4 % (n)**	**Stage 5 % (n)**	*Total (N)*	**Stage 1 % (n)**	**Stage 2 % (n)**	**Stage 3 % (n)**	**Stage 4 % (n)**	**Stage 5 % (n)**	*Total (N)*
6 - <7	73.08 (19)	26.92 (7)	-	-	-	*26*	100 (27)	-	-	-	-	*27*
7 - <8	59.23(77)	40.00 (52)	-	0.77 (1)	-	*130*	95.87 (116)	4.13 (5)	-	-	-	*121*
8 - <9	48.48 (64)	46.97 (62)	3.79 (5)	0.76 (1)	-	*132*	87.50 (112)	10.94 (14)	-	1.56 (2)	-	*128*
9 - <10	30.66 (42)	63.50 (87)	4.38 (6)	1.46 (2)	-	*137*	71.54 (88)	25.20 (31)	3.25 (4)	-	-	*123*
10 - <11	25.55 (35)	64.23 (88)	5.84 (8)	3.65 (5)	0.73 (1)	*137*	47.62 (60)	42.06 (53)	10.32 (13)	-	-	*126*
11 - <12	26.24 (37)	58.16 (82)	9.93 (14)	5.67 (8)	-	*141*	20.61 (27)	48.85 (64)	25.19 (33)	3.05 (4)	2.29 (3)	*131*
12 - <13	9.52 (14)	51.70 (76)	27.89 (41)	7.48 (11)	3.40 (5)	*147*	9.35 (13)	37.41 (52)	47.48 (66)	5.04 (7)	0.72 (1)	*139*
13 - <14	6.94 (10)	26.39 (38)	45.83 (66)	17.36 (25)	3.47 (5)	*144*	3.28 (4)	21.31 (26)	49.18 (60)	25.41 (31)	0.82 (1)	*122*
14 - <15	-	5.74(7)	40.16 (49)	48.36 (59)	5.74 (7)	*122*	0.85 (1)	5.08 (6)	44.07 (52)	44.07 (52)	5.93 (7)	*118*
15 - <16	0.85 (1)	3.39 (4)	25.42 (30)	55.93 (66)	14.41 (17)	*118*	-	4.35 (5)	27.83 (32)	63.48 (73)	4.35 (5)	*115*
16 - <17	-	-	11.58 (11)	61.05 (58)	27.37 (26)	*95*	-	1.05 (1)	33.68 (32)	42.11 (40)	23.16 (22)	*95*
17 - <18	-	-	4.04 (4)	50.51 (50)	45.45 (45)	*99*	-	2.83 (3)	13.21 (14)	55.66 (59)	28.30 (30)	*106*
18 - <19	-	2.63 (2)	2.63 (2)	31.58 (24)	63.16 (48)	*76*	-	1.35 (1)	17.57 (13)	43.24 (32)	37.84 (28)	*74*

Note: Percentages were calculated for each age band and gender separately. Total (N) reflects to the number of children in each age band per gender who have participated in the pubertal assessment.

Menarche: About 21% (137/660) of girls reported their age at menarche as less than 12 years while 78% of them have reported it as between 12 years and less than 15 years. Average age at menarche was 12.4 (95% CI: 12.3, 12.5)

Testicular Volume: Alternatively, boys were divided in to 4 stages of growth based on testicular volumes (TV).[230] Around 21% (293/1422) of boys were in stage 1 (pre-puberty) with TV less than 4 ml, 39% (552/1422) at stage 2 (early puberty) with TV between 4 and ≤ 8 ml, 31% (435/1422) were at stage 3 (mid-puberty) with TV between 9 and ≤ 15 ml and 10% (142/1422) at stage 4 (full maturation) with TV above 15 ml. Stages as per tanner classification and TV classification were showing reasonable correlation (r=0.7426, P=0.001).

***Proportion of thin, overweight & obese children in the sample**:* Though this sample is not a true representation of prevalence estimates of thin, overweight and obese children in the population; this data can give the trend in the population. As per revised national standards (IAP Growth charts, 2015) there was 8.4% overweight and 4.9% obese boys as compared with 10.6% overweight and 3.9% obese girls (Table 6). Around 4.3% boys and 3.8% girls were thin and there was no significant difference in distribution rates in boys and girls (P=0.080).

Rural-urban difference: Boys (P=0.001) and girls (P=0.003) in rural and urban settings were different. Overall, thinness was higher among boys (5.4%) and girls (4.2%) in rural areas as compared to boys (3.4%) and girls (3.5%) in urban areas. In contrary, the proportion of overweight in boys (9.9%) and girls (12.1%) in urban areas was significantly higher to boys (6.4%) and girls (8.3%) in rural areas. Similarly, prevalence of obesity in boys (7.2%) and girls (4.9%) were significantly higher in urban areas as compared to boys (2%) and girls (2.3%) in rural areas (P=0.001).

Difference across study sites (Ethnic Regions): To understand the influence of ethnicity in body composition the schools were selected from: 1) Faridabad district (NCR region, Delhi) where urban and rural areas co-exist; 2) East Khasi hills of northern Shillong where the Tibeto-Burman and Austro-Asiatic population dominates and 3) Rangareddi district of Hyderabad where the Dravidian speaking population dominates. The distribution of thinness, overweight and obesity in these three locations (urban and rural) are presented in Table 7.

Among boys in Delhi, the proportion of overweight (15.5%) and obesity (13.2%) were higher in urban areas as compared to rural areas (8.8% and 3.4%); while thinness was higher in rural areas (5.4%) as compared to urban (0.6%), (P=0.001). Same trends were observed among girls in Delhi: overweight (14.7%) and obesity (7.9%) was higher in urban as compared to rural areas (9.6% and 3.5%). Thinness was more in rural (3.0%, 1.3%); (P=0.011) areas of Delhi. In Shillong, thinness, overweight and obesity was more among boys in urban areas (3.4%, 7.9% and 3.4%) as compared to rural (1.8%, 4.6% and 1.4%) (P=0.061) and in girls, thinness was more in rural (3.5%) than urban (1.8%) but overweight and obesity was higher in urban (11% and 3.4%) vs. rural (7.9% and 1.8%) (P=0.196). Among boys in Hyderabad, thinness was high in rural areas (10.8%) as compared to urban (7.9%) while overweight was slightly higher in rural (5.9% vs. 4.2%). Proportion of obese children was higher in urban boys (3.76%) (P=0.112). Among girls, thinness was higher in urban (10.7%) when compared to rural (6.4%) and overweight was 9.3% in urban vs. 7.4% in rural. Obesity was 1.8% and 1.6% in urban and rural respectively (P=0.363). The rural urban differences were statistically non-significant for boys and girls in Hyderabad and Shillong.

Table 6: Prevalence of overweight and obesity in boys and girls as per national standards

	BOYS				GIRLS				Chi-Square (Boys vs. Girls)
Age Bands	**Thin % (n)**	**Normal % (n)**	**Over wt. % (n)**	**Obese % (n)**	**Thin % (n)**	**Normal % (n)**	**Over wt. % (n)**	**Obese % (n)**	
6-7	1.85 (1)	79.63(43)	18.52 (10)	-	-	82.69 (43)	11.54 (6)	5.77 (3)	0.174
7-8	4.23 (6)	76.06(108)	14.08 (20)	5.63 (8)	3.45 (5)	82.76 (120)	10.34 (15)	3.45 (5)	0.552
8-9	4.38 (6)	83.94(115)	8.03 (11)	3.65 (5)	4.48 (6)	80.60 (108)	11.19 (15)	3.73 (5)	0.849
9-10	4.93 (7)	86.62(123)	2.82 (4)	5.63 (8)	3.65 (5)	82.48 (113)	9.49 (13)	4.38 (6)	0.126
10-11	4.96 (7)	82.98(117)	5.67 (8)	6.38 (9)	6.90 (10)	77.93 (113)	11.72 (17)	3.45 (5)	0.177
11-12	7.69 (11)	81.12(116)	5.59 (8)	5.59 (8)	2.92 (4)	83.21 (114)	10.95 (15)	2.92 (4)	0.085
12-13	4.67 (7)	83.33(125)	6.00 (9)	6.00 (9)	10.00 (15)	78.00 (117)	8.67 (13)	3.33 (5)	0.169
13-14	6.08 (9)	78.38(116)	12.16 (18)	3.38 (5)	2.29 (3)	80.92 (106)	13.74 (18)	3.05 (4)	0.469
14-15	3.85 (5)	79.23(103)	9.23 (12)	7.69(10)	3.25 (4)	81.30 (100)	9.76 (12)	5.69 (7)	0.921
15-16	0.75 (1)	87.22(116)	6.77 (9)	5.26 (7)	1.50 (2)	81.20 (108)	12.78 (17)	4.51 (6)	0.368
16-17	2.04 (2)	84.69(83)	12.24 (12)	1.02 (1)	2.65 (3)	84.96 (96)	9.73 (11)	2.65 (3)	0.771
17-18	2.70 (3)	83.78(93)	9.01 (10)	4.50 (5)	0.76 (1)	83.97 (110)	11.45 (15)	3.82 (5)	0.619
18 – 19	4.88 (4)	85.37(70)	4.88 (4)	4.88 (4)	4.04 (4)	84.85 (84)	6.06 (6)	5.05 (5)	0.979
Overall (6 to <19)	**4.3 (69)**	**82.4 (1328)**	**8.4 (135)**	**4.90 (79)**	**3.80 (62)**	**81.72(1332)**	**10.61 (173)**	**3.87(63)**	0.080

Note: Chi-square test to compare the proportions between boys and girls. Thinness was <3rd centile values of IAP growth charts, Over weight (over wt.) was BMI for age above 23rd adult equivalent and below 27th adult equivalent in IAP growth chart, 2015 and obese was BMI for age above 27th adult equivalent in IAP growth chart.

Table 7: Distribution of thinness, over-weight and obesity across study sites (ethnic regions) and in rural-urban settings

Boys	Ethnic Regions	Total % (95% CI)	Rural % (95% CI)	Urban % (95% CI)
Thin	Delhi	2.6(1.29,3.88)	5.44(2.55,8.33)	0.59(-0.23,1.40)
	Shillong	2.7(1.42,3.95)	1.79(0.23,3.34)	3.40(1.50,5.30)
	Hyderabad	9.3(6.43,12.16)	10.81(6.32,15.31)	7.98(4.33,11.63)
Over Wt	Delhi	12.8(10.03,15.48)	8.79(5.18,12.39)	15.54(11.69,19.40)
	Shillong	6.5(4.56,8.39)	4.64(2.17,7.12)	7.93(5.11,10.76)
	Hyderabad	5(2.87,7.18)	5.95(2.52,9.37)	4.23(1.51,6.94)
Obese	Delhi	9.3(6.94,11.68)	3.77(1.34,6.19)	13.20(9.59,16.80)
	Shillong	2.5(1.30,3.75)	1.43(0.03,2.82)	3.40(1.50,5.30)
	Hyderabad	2.3(0.79,3.72)	0.54(-0.52,1.60)	3.76(1.19,6.32)
Girls				
Thin	Delhi	1.94(0.85,3.03)	3.04(0.81,5.27)	1.29(0.16,2.41)
	Shillong	2.47(1.23,3.70)	3.49(1.11,5.88)	1.85(0.49,3.21)
	Hyderabad	8.66(5.91,11.41)	6.35(2.86,9.84)	10.70(6.55,14.84)
Over Wt	Delhi	12.78(10.15,15.42)	9.57(5.75,13.38)	14.69(11.16,18.22)
	Shillong	9.87(7.49,12.24)	7.86(4.36,11.36)	11.08(7.91,14.25)
	Hyderabad	8.42(5.70,11.13)	7.41(3.66,11.16)	9.30(5.41,13.20)
Obese	Delhi	6.31(4.39,8.23)	3.48(1.10,5.86)	7.99(5.29,10.69)
	Shillong	2.80(1.48,4.11)	1.75(0.04,3.45)	3.43(1.59,5.27)
	Hyderabad	1.73(0.46,3.01)	1.59(-0.20,3.38)	1.86(0.05,3.67)

Note: Distribution of thin, overweight and obese children in rural and urban settings of three sites are summarized in table 7. In Delhi the schools were from Faridabad district (NCR region / Haryana) where both rural and urban areas co-exist. In Shillong the schools were selected from east khasi hills where Tibeto-burman and Austro-Asiatic speaking population dominates and in Hyderabad the schools were selected from Rangareddi district where Dravidians dominates.

BIA manufacturers Fat predicted vs. Fat mass from DEXA: As mentioned earlier, DEXA measurements were considered as a criterion standard which was done in a sub-sample of 206 children (105 boys and 101 girls) and the fat from DEXA were compared with direct outputs of BIA machine. The absolute fat (kg) obtained from both methods were significantly different in boys (r=0.917, p=0.001) and girls (r=0.9727, p=0.001). Comparison of inbuilt equations supplied by the manufacturer and with DEXA values in this population has shown a mean bias of -18.9% fats among boys and -11.2% fats among girls. Among boys, mean fat (kg) predicted by BIA was 7.4 kg (95% CI: 6.1, 8.8) as compared to 8.4 kg (95% CI: 7.4, 9.5) in DEXA (Diff: -0.98, P=0.001); while percent fat predicted by BIA was 17.5% (95% CI: 15.5, 19.5) as compared to 20.8% (95% CI: 19.3, 22.4) in DEXA (Diff: -3.3%, P=0.001). Among girls the mean fat (kg) from BIA was 11.3kg (95% CI: 9.4, 13.2) which was closer to that in DEXA, 11.5kg (95% CI: 10.2, 12.9) (Diff: -0.26, P=0.400); while among girls the percentage fat from BIA was 25.7% (95% CI: 23.5, 27.9) as compared to 27.4% (95% CI: 26.3, 28.7) from DEXA (Diff: -1.8%, P=0.014). The median values were also significantly different in boys (p=0.001) and girls (p=0.0003) (through Wilcoxon signed-rank tests). These figures highlight the need for new prediction equations for Indian children (boys and girls).

Development of linear prediction models for boys and girls: Total lean mass (kg), fat-free mass (lean+BMC) and fat mass obtained from DEXA were used as the dependent variable to develop different sets of linear prediction equations. The independent variables were selected from a correlation matrix of different impedance and anthropometric variables vs. DEXA lean mass (kg). Though, height (cm) was highly correlated, it was not used as an independent variable. Linear models for boys and girls were built through step-wise addition of independent variables. Change in R^2 was used for monitoring. Since age of child was a significant predictor in preliminary analysis it was used in the model irrespective of its statistical contribution to the model.

Models were developed in 4 steps: 1) exploratory models in a) sub-sample (n=206), b) training sample (n=128) and c) validation sample (n=80); 2) fine-tuning of models based on the distribution of residuals across the samples; 3) internal validation using jack-knife boot-strapping technique and 4) prediction of lean mass in full samples (Figure 9). At each level, the prediction (kg) and residual values were plotted. Bland-Altman (BA) plots (difference between predicted mass and DEXA mass) were used to identify outliers and then equations were further refined. Total of two boys and five girls were excluded to force better prediction of the model. Model fitting were done through jack-knife technique by monitoring the changes in the standard error of mean (SEM) and predictive equations were then finalized. STATA helped to store the differences in regression

coefficients vs. dependent variable (df-beta) and the standard error in the models has significantly changed after model fitting. Though separate predictive equations for lean mass, fat-free mass (lean+BMC) and fat mass were explored, the final equation considered was based on lean mass. This is because electricity flows only through lean mass (soft tissues) and not through bone mineral contents (BMC) or fat inside the body. Though DEXA measures BMC more accurately it may not be good strategy to predict BMC using Impedance. Thus, lean mass was predicted in boys and girls and this was used to estimate fat mass from the body weight. One technical limitation here is that, the fat predicted through this method will also have BMC included in it. However, if fat-free mass (lean+BMC) from DEXA was used for prediction then it does not reflect to the actual measurements between two techniques (DEXA and BIA). The final prediction equation developed was:

$$\textbf{Lean Mass (Boys)} = \left[(0.02) + \left(0.96\ X\ \frac{Ht^2(cm)}{Z(\Omega)_{50khz}}\right) + (0.37\ X\ bodyweight(kg)) + (0.06\ X\ age)\right]$$

$$\textbf{Lean Mass (Girls)} = \left[(-0.19) + \left(0.99\ X\ \frac{Ht^2(cm)}{Z(\Omega)_{50khz}}\right) + (0.33\ X\ bodyweight(kg)) + (0.09\ X\ age)\right]$$

$$\textbf{Fat Mass} = (body\ weight\ (kg) - lean\ mass\ predicted)$$

$$\textbf{Percent fat} = \frac{(Fat\ mass\ (kg))}{(body\ weight\ (kg))} \text{X } 100$$

Details of the linear regression models (after adjusting for residual errors) for predicting lean mass using DEXA as dependent and impedance index (50 khz) and body weight (kg) as independent variable is presented below:

Dependent variables (with DEXA)	Independent variable	β (95% CI)	P value	Adj R^2
Boys				
Lean mass (kg) (from DXA)	Whole body impedance index, 50 khz (Ω)	0.96 (0.69, 1.22)	0.001	0.94
(α = 0.02)	Weight (Kg)	0.37 (0.29, 0.44)	0.001	
(n=100)	Age	0.06 (-0.19, 0.32)	0.632	
Girls				
Lean mass (kg) (from DXA)	Whole body impedance index, 50 khz (Ω)	0.99 (0.76, 1.23)	0.001	0.96
(α = -0.19)	Weight (Kg)	0.33 (0.27, 0.38)	0.001	
(n=97)	Age	0.09 (-0.04, 0.24)	0.178	

Note: With impedance index alone the model could predict 0.84 of variance in boys and 0.89 of variance in girls. No anthropometric variables were contributing much in the model and hence this was avoided especially to limit measurements to impedance and body weight. 2 boys and 1 girl were excluded as values were extreme in BA plots. Further, 3 girls with DEXA have not participated in BIA.

Description of body composition from models compared with DEXA: Post internal validations, the final equations were used to predict lean mass (kg) in full sample of 3241 children.

From predicted lean mass then percentage lean, fat mass (kg) and percentage fat were estimated and the distributions are presented in Table 8.

Boys: the lean mass (kg) in thin (19.9 ± 5.6), normo-weight (27.3 ± 9.7), over-weight (34.0 ± 12.5) and obese boys (38.7 ± 11.1) were significantly different across categories (F=62.34, P=0.001). That is, thin have 82.8 ± 4.1%, normo-weight have 80.1 ± 4.3% as compared to overweight 73.9 ± 3.9% and obese boys have 68.8 ± 3.8% of their body weight as lean (soft tissues). There was no significant difference in the distribution of lean observed from DEXA and through linear predictions (p=0.960). In contrary, fat (kg) among thin (4.0 ± 1.2), normo-weight (6.7 ± 2.8), overweight (12.2 ± 5.3) and obese boys (17.8 ± 6.3) were also significantly different across categories (F=388.42, P=0.001). In summary thin, normo-weight, overweight and obese boys have 17.2%±4.1, 19.9%±4.3, 26.0%±3.9 and 31.2%±3.8 respectively as fat in their body weight.

Girls: the lean mass (kg) in thin (19.7 ± 5.1), normo-weight (24.8 ± 6.9), overweight (30.1 ± 7.9) and obese girls (36.8 ± 8.7) were significantly different across categories (F=88.54, P=0.001). That is thin, normo-weight, overweight and obese girls have 81.9 ± 5.0%, 74.9 ± 5.1%, 69.2 ± 4.3% and 64.9 ± 4.3 % of their body weight as lean (soft tissues). A difference of 2.7% was observed in the distribution of lean mass observed form DEXA and through linear predictions (P=0.001). The fat (kg) among thin (4.4 ± 1.9), normo-weight (8.6 ± 3.8), overweight (13.7 ± 4.9) and obese (20.5 ± 7.4) girls were also significantly different across categories (P=0.001). In summary, thin, normo-weight, overweight and obese girls have 18 ± 5%, 25 ± 5.1%, 30.8 ± 4.3% and 35.1 ± 4.3% respectively as fat in their body weight.

Distribution of lean and fat mass among children in different stages of growth has been tested between predicted lean and fat mass and those observed in DEXA (Table 9). Among boys, there was no significant difference in the lean and fat mass from both methods however there was slight difference in observation in both methods among girls. Paired t-tests were done to estimate these differences.

Table 8: Distribution of body constituents predicted across age-bands and gender

	Lean (Kg)	Percent Lean	Fat (Kg)	Percent Fat
Boys	Mean(95% CI)n	Mean(95% CI)n	Mean(95% CI)n	Mean(95% CI)n
6 to 7	15.73(14.64,16.81)53	77.21(75.87,78.55)53	4.50(4.25,4.75)53	22.79(21.45,24.13)53
7 to 8	16.63(16.00,17.26)141	77.27(76.56,77.97)141	4.88(4.63,5.12)141	22.73(22.03,23.44)141
8 to 9	17.92(17.33,18.52)133	78.74(77.96,79.53)133	4.92(4.59,5.25)133	21.26(20.47,22.04)133
9 to 10	19.89(19.23,20.55)138	79.06(78.31,79.81)138	5.36(4.99,5.74)138	20.94(20.19,21.69)138
10 to 11	21.85(21.01,22.69)137	78.86(78.02,79.69)137	6.02(5.56,6.49)137	21.14(20.31,21.98)137
11 to 12	24.25(23.31,25.20)140	79.37(78.54,80.20)140	6.54(5.99,7.09)140	20.63(19.80,21.46)140
12 to 13	28.01(26.93,29.09)146	80.10(79.19,81.02)146	7.24(6.59,7.88)146	19.90(18.98,20.81)146
13 to 14	31.27(30.19,32.34)147	80.80(79.81,81.79)147	7.70(7.06,8.35)147	19.20(18.21,20.19)147
14 to 15	36.08(34.91,37.25)129	80.58(79.47,81.68)129	9.23(8.33,10.13)129	19.42(18.32,20.53)129
15 to 16	38.83(37.71,39.96)126	80.40(79.49,81.31)126	9.77(9.00,10.55)126	19.60(18.69,20.51)126
16 to 17	39.25(38.00,40.50)95	79.24(78.35,80.12)95	10.61(9.79,11.43)95	20.76(19.88,21.65)95
17 to 18	40.44(39.08,41.79)107	78.06(77.17,78.94)107	11.66(10.78,12.55)107	21.94(21.06,22.83)107
18 to 19	41.00(39.37,42.63)73	76.44(75.45,77.44)73	13.01(11.88,14.14)73	23.56(22.56,24.55)73
Girls				
6 to 7	13.99(13.32,14.66)53	74.13(72.78,75.49)53	4.84(4.53,5.15)53	25.87(24.51,27.22)53
7 to 8	15.88(15.28,16.48)141	75.85(75.05,76.64)141	5.06(4.79,5.33)141	24.15(23.36,24.95)141
8 to 9	17.65(17.05,18.26)133	76.59(75.75,77.44)133	5.50(5.13,5.87)133	23.41(22.56,24.25)133
9 to 10	20.27(19.37,21.16)138	77.09(76.22,77.97)138	6.20(5.69,6.70)138	22.91(22.03,23.78)138
10 to 11	22.70(21.85,23.55)137	77.36(76.39,78.33)137	6.78(6.31,7.25)137	22.64(21.67,23.61)137
11 to 12	25.36(24.45,26.28)140	77.37(76.36,78.37)140	7.67(7.06,8.27)140	22.63(21.63,23.64)140
12 to 13	27.36(26.52,28.20)146	77.01(76.23,77.80)146	8.44(7.88,9.01)146	22.99(22.20,23.77)146
13 to 14	30.37(29.43,31.31)147	74.07(73.22,74.92)147	11.04(10.27,11.82)147	25.93(25.08,26.78)147
14 to 15	31.27(30.38,32.16)129	72.81(71.86,73.75)129	12.11(11.27,12.96)129	27.19(26.25,28.14)129
15 to 16	32.18(31.23,33.14)126	70.74(69.99,71.48)126	13.62(12.86,14.38)126	29.26(28.52,30.01)126
16 to 17	31.27(30.36,32.18)95	70.57(69.75,71.40)95	13.33(12.51,14.15)95	29.43(28.60,30.25)95
17 to 18	31.55(30.80,32.29)107	69.32(68.53,70.12)107	14.28(13.49,15.06)107	30.68(29.88,31.47)107
18 to 19	30.76(29.97,31.56)73	68.92(68.06,69.79)73	14.11(13.32,14.89)73	31.08(30.21,31.94)73

Table 9: Body composition (lean and fat (kg)) predicted among children in different stages of growth (Tanner)

	Lean (kg)			Fat (kg)		
	DEXA (n=206)	**Predicted (n=206)**	**(Diff (n), (P value)**	**DEXA (n=206)**	**Predicted (n=206)**	**(Diff (n), (P value)**
Boys (Pubertal)						
Stage 1	22.16 (19.3, 25.1)	21.8 (19.0, 24.7)	(0.32) (20), (P=0.427)	7.6 (5.2, 9.9)	7.3 (5.3, 9.3)	(0.27) (20), (P=0.483)
Stage 2	22.12 (19.5, 24.7)	22.6 (20.1, 25.2)	(-0.52) (24), (P=0.125)	8.0 (6.1, 10.0)	7.1 (5.2, 9.0)	(0.90) (24), (P=0.060)
Stage 3	33.7 (30.5, 36.8)	32.9 (29.9, 36)	(0.72) (20), (P=0.374)	8.7 (6.5, 10.9)	8.9 (6.1, 11.9)	(-0.27) (20), (P=0.674)
Stage 4	36.1 (33.4, 38.9)	36.1 (33.4, 38.8)	(0.02) (19), (P=0.971)	8.6 (5.2, 11.9)	8.5 (6.1, 10.9)	(0.06) (19), (P=0.930)
Stage 5	42.6 (37.3, 48.1)	42.5 (37.9, 47.1)	(0.14) (11), (P=0.912)	11.0 (6.7, 15.3)	13.5 (9.6, 17.4)	(-2.5) (11), (P=0.064)
Girls (Pubertal)						
Stage 1	19.6 (17.1, 22.2)	20.4 (18.0, 22.7)	(-0.69) (26), (P=0.041)	8.0 (6.4, 9.7)	7.0 (5.7, 8.3)	(0.97) (26), (P=0.004)
Stage 2	24.8 (22.3, 27.4)	25.7 (22.9, 28.5)	(-0.88) (21), (P=0.039)	10.0 (7.6, 12.5)	9.2 (6.9, 11.4)	(0.86) (21), (P=0.021)
Stage 3	29.1 (26.7, 31.6)	30.4 (27.7, 33.1)	(-1.29) (22), (P=0.007)	10.8 (8.5, 13.2)	11.1 (8.4, 13.9)	(-0.27) (22), (P=0.698)
Stage 4	33.1 (29.2, 36.9)	34.6 (30.7, 38.5)	(-1.57) (15), (P=0.004)	16.9 (13.5, 20.5)	16.6 (13.2, 19.9)	(0.38) (15), (P=0.497)
Stage 5	37.7 (31.8, 43.5)	38 (31.9, 44)	(-0.32) (11), (P=0.562)	17.8 (11.7, 24.0)	18.1 (11.4, 24.8)	(-0.23) (11), (P=0.796)

Dealing with errors and uncertainties (Bias, Accuracy and Precision):

Absolute difference (bias) and percentage differences in predicted lean (BIA) from expected lean (DEXA lean) were tested against boys and girls among thin, normo-weight, overweight and obese children (Table 10). Predictive capacity of equations for boys and girls were significantly different. Overall, there was only marginal difference between predicted lean and DEXA lean among boys as compared to girls. Percentage difference in predicted lean from BIA was comparatively higher among girls as compared to boys. In boys, the overall mean difference was 0.5% as compared to 4.3% in girls. Among overweight boys the percentage difference was 3.4% as compared to 8.6% in overweight girls.

The percentage difference less than 10% were considered as precise, 10 to 20% as moderate and above 20% as imprecise – for epidemiological use.229 In our study, the BIA prediction could precisely predict lean mass among 82.4% (n=84) boys, moderately in 15.7% (n=16) and imprecise in 2% (2) boys. Among girls, the BIA prediction could precisely predict lean mass among 77.6% (n=76) girls, moderately in 21.4% (n=21) and imprecise in 1% (1). These cut-offs could be set at lower levels for clinical use: <5% for precise, 5 to 10% for moderate and > 10% for imprecise. At lower cut off (for clinical use) the BIA prediction equation was precise in 77.5% (n=79), 4.9% (n=5) and 17.6% (n=18) boys and 59.2% (n=58), 18.4% (n=18) and 22% (n=22) girls. Table 8 depicts the ability of BIA prediction equation to predict lean in different body composition categories.

Accuracy was defined as percentage children with less than 10% of expected lean. BIA prediction equation could accurately predict lean mass among 82% boys and 77.6% girls. Among accurately predicted boys, the percentage difference was - 2.3% (95% CI: -3.7, -1.1) (n=84); indicating slight under-estimation. Among accurately predicted girls, the percentage difference was 1.2 % (95% CI: 0.03, 2.3) (n=76). Limits of Agreement were calculated as bias plus two times precision. The accuracy of prediction equation is depicted in Table 11.

Variability between lean predicted and expected (DEXA) was studied through Bland-Altman Plots (Figure 10 and 11). In boys, limits of agreements were -5.303 to 5.328 with mean difference of 0.012 (95% CI: -0.510 to 0.534). There was no significant difference in variances (r=0.099, p=0.324). In girls, limits of agreement were -4.722 to 2.673 with mean difference of -1.024 (95% CI: -1.395 to -0.654). No significant difference in variances (r= -0.072, p=0.481).

Table 10: Bias and Percentage difference in BIA Prediction Vs DEXA measured Lean

	Bias (absolute difference) (Predicted – Expected)			Percentage difference (Predicted – Expected X 100 / Expected)		
	Boys	**Girls**	**P value**	**Boys (%)**	**Girls (%)**	**P value**
Thin children	-0.09 ± 1.77 (5)	1.68 (1)	--	1.5 ± 9.0 (5)	9.6 (1)	--
Normo-weight	-0.02 ± 2.6 (73)	0.91 ± 1.7 (66)	0.013	0.35 ± 8.5(73)	4.1 ± 7.2 (66)	0.006
Overweight	0.84 ± 2.5 (11)	2.13 ± 2.3 (15)	0.191	3.4 ± 6.9(11)	8.6 ± 8.9 (15)	0.127
Obese	-0.63 ± 3.5 (13)	0.41 ± 1.8 (16)	0.308	-0.95 ± 9.8(13)	0.65 ± 5.2 (16)	0.576
Overall	-0.01 ± 2.7 (102)	1.02 ± 1.8 (98)	0.001	0.57 ± 8.5(102)	4.2 ± 7.5 (98)	0.001

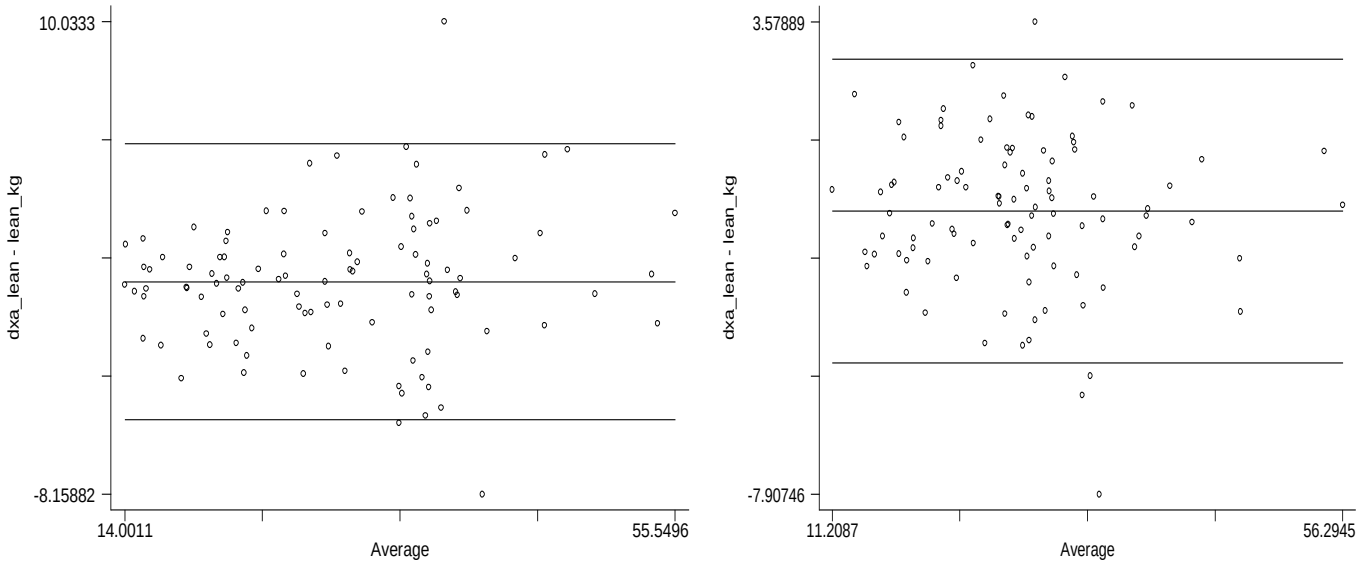
Note: Positive values represent over-estimation of lean mass by BIA method while negative values represent under-estimation of lean mass by BIA method.

Table 11: Precision and Accuracy among BIA prediction and DEXA measured lean mass

	Precision (Epidemiological use)		Precision (Clinical use)		Accuracy	
	Boys	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**
Thin children	80% (4)	-- (1)	80% (4)	--	80% (4)	--(1)
Normo-weight	82% (60)	75.8% (50)	78.1% (57)	54.6% (36)	82.2% (60)	75.7% (50)
Overweight	72.7% (8)	60% (9)	72.7% (8)	53.3% (8)	72.7% (72.7)	60% (9)
Obese	92.3% (12)	100% (16)	76.9% (10)	87.5% (14)	92.3% (12)	100% (16)
Overall	82.4% (84)	77.5% (76)	77.4% (79)	59.2% (58)	82.4% (84)	77.6% (76)

Note: Luque V et al (2014) have defined criteria for precision in BIA measurements as compared to DEXA for epidemiological use and clinical use. Accuracy was defined as a difference of less than <10% from DEXA measurement.

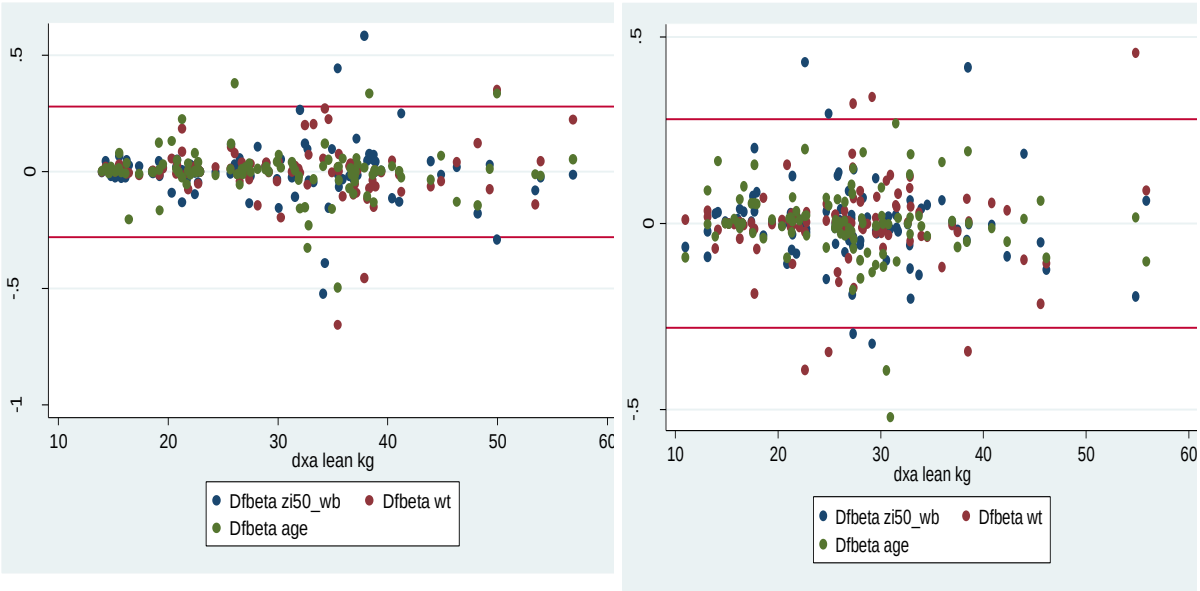
Figure 10: Bland - Altman plots of lean (kg), boys and girls, predicted from DEXA



Note: Bland Altman plot for difference in whole body lean mass (BIA – DEXA) (kg) for boys and girls

Figure 11: Regression coefficients plotted (jack-knife) against lean (kg) from DEXA

Boys (>0.28 and <-0.28 are influencers) **Girls** (>0.28 and <-0.28 are influencers)



Note: Rule of thumb to identify influencers is to plot the values against dependent variables and those values above 0.28 and below 0.28 needs to be considered for further investigation.

Study 2: Reference values and Percentile curves for cardio-metabolic risk factors among Indian children (6 to 18 years)

4.3. Materials and Methods specific for study 2:

Presently, centile curves for major anthropometric variables like BMI-for-age, height-for-age and weight-for-age are commonly used across the world however such curves for major cardio-metabolic risk factors (bio-chemical markers) are not available for routine clinical practices in many countries. In this context, we have developed centile curves for selected markers of cardio-metabolic risk factors among children (6 to 19 years).

a. Specific Objectives (Study 2): Blood samples and anthropometric data were collected from 3241 school children to develop:

1. Age and sex specific reference values and smoothened centile curves for 17 bio-chemical, anthropometric markers of cardio-metabolic risk and
2. Distribution of these markers in different BMI categories (thin, normoweight, overweight and obese) as per Indian Association of Pediatrics (IAP), Growth Charts, 2015.

b. Sample: This cross-sectional study was conducted among 3241 children (1611 boys and 1630 girls) healthy school going children (6 to 19 years) carefully selected from three geographical regions. A complex multi-staged, stratified sampling strategy was used as detailed in study 1.

c. Preparation of Centiles Curves (**LMS method)**: For each of the 17 markers of cardio-metabolic risk, centile values were estimated among healthy boys and girls between 6 to 19 years (13 age bands). LMS (lambda, mu and sigma) and Box-Cox Power Exponential (BCPE) are the most commonly used methods for fitting centile standards and smoothening of curves (removing of spikes).[231] Though both methods are popular both of these methods are based on the series of works published by Cole TJ et al., (in 1990,[232] 1994,[233] 1995,[234] 2000,[235] 2006,[236] and 2012[237]). We have used manual estimations based on Cole TJ et al., (1992) as well as used LMS chart maker (Pro) to calculate age and gender specific centile curves in two parts:

Part 1 – Estimation of centile values: The underlying assumption in this whole exercise is normally distributed data at specific age which could be approximated to Z-scores however most of the health data is non-normally distributed (skewed and kurtosis).[231] This was tested by applying tests for skewness and kurtosis along with QQ plots and box plots. For each marker of cardio-metabolic risk, outliers were spotted as values having ± 3 inter-quartile ranges (IQR) above or below the median values.

Since the distributions are not normal it is important to transform the distribution to Gaussian or it's approximate through LMS power transformation equations that treat the two tails of the distribution similarly.[238] Several studies have done Box-Cox Power Transformations (BCPE) to adjust for kurtosis. In addition, there are other methods like transforming to square-roots, squares or logs (natural logs) to adjust for skewness however each of them has their own disadvantages – often one tail are stretched relative to the other.232

Next step was to calculate the L (power), M (mean) and S (coefficient of variation) values as per standard protocol. LMS method calculates the best power; L (λ), mean (μ) and σl (coefficient of variation) using the equation:

$$(LMS)^{z} = \frac{1}{\sigma l \lambda}\left[\left(\frac{y}{\mu}\right)^{\lambda}\right] - 1$$

Where, Y, μ, σl and λ is $\neq 0$ and σl represents the measures of dispersion, that is σ/μ

Next step was to standardize the coefficient of variation (CV) for reducing the asymmetries. Maximum likelihoods were calculated using μ, σl *and* λ that could make the distribution closer to standard normal. Each step in LMS estimation were done as per Appendix-A of Cole TJ, 1992 as:

1. Mean and SD of natural logarithms of each measurement was calculated. The antilog of the mean is the geometric mean of the measurement (m_g) and its SD is called geometric CV (S_g)
2. Calculated the mean (arithmetic mean m_a) and SD of the original measurements and divided the SD with m_g to obtain arithmetic CV (s_a)
3. Reciprocal of mean was the harmonic mean (M_h) and multiplying the geometric mean (M_g) have given the harmonic CV (S_h)
4. Substituting these values into equations:
    a. $A=\log(S_a / S_h)$
    b. $B=\log(S_a S_h / S_g^2)$

- The power L is given by;
    - $L = -A/2(B)$ and its standard error as $1/\sqrt{(nB)}$
- Where n is the number of measurements in the age group

5. Generalized coefficient of variation S at L is calculated as

    $S=S_g \exp(AL/4)$

- to interpolate three CVs to find minimum values so that S is smaller than Sa, Sg and Sh. The approximated standard error of S is then
    - $S\sqrt{(S2 + 0.5)/n)}$

6. Then, generalized mean (M) for power L is obtained from interpolating M_a, M_g and M_h to give:
    a. $M=M_g+(M_a–M_h)L/2 +(M_a–2M_g + M_h)L2/2$

    With standard error $MS/\sqrt{(n)}$

Part 2 – Smoothening of centile curves: The next step after obtaining L, M and S was to plot these values and smoothening of the curves. Often it is assumed that the percentiles at different ages would follow some smooth trends but unfortunately this is not the case for health data. Most likely they follow irregular patterns and the challenge is to remove these splines and create a smooth curve. This was done in 2 steps:

A) **Age transformation:** Almost all markers in body increases rapidly at some age bands and therefore age was transformed by converting all values of λ at an interval of 0.25 and select those values that transforms the relationship to linear.

B) **Smoothing of L, M and S curves:** Best estimates of $\mu,\ \sigma l\ and\ \lambda$ was estimated and they were plotted for each age groups against the group means. Thus, there were one μ plot, σl plot and λ plot (or called as L plot, M plot and S plot). These smoothening involve statistical principles of cubic and polynomial equations and the relative precision at each age-band has to be considered while fitting a quadratic or polynomial curve. Then weights have to be assigned to each estimate after accounting for its reciprocal of the square of standard errors. Age groups with larger numbers or little variations are given higher weightage. If there is no specific trend then L and S curves can be summarized as the mean across all age groups.

Then, centile values (5, 10, 25, 50, 75, 85 and 95) for each age by gender were obtained by substituting the values of L, M and S in the equation: $C = M(1 + LSZ)^{1/L}$

LMS Chart Maker – Pro version: Simultaneously, along with the above mentioned manual methods we have used the software LMS chart maker (Pro) to estimate L, M and S values and centile values (at 5, 10, 25, 50, 75, 85 and 95). This software also follows the same principles mentioned above and the L, M and S values by both methods were comparable.

Both of these methods need to be accounted for effective degrees of freedom (edf). Each curve will have its own edf based on the number of twists that the curve has on different age groups.

The edf's also refers to smoothing parameters and are derived from penalized maximum likelihood functions. The key objective is to find out the least edf that provides good fit for L, M and S. After obtaining L, M and S values at appropriate edfs the centile values were obtained and plotted for smoothened centile curves. Basically, centile charts shows the position of the measured parameter within a statistical distribution while it does not communicate whether the parameter is normal or abnormal. They only express how the values would be in other age-groups. Children with their growth curves along the centile curves, over time, grow at average velocity while if they cross up or down the child is growing faster or slower – centile crossing is a measure of concern and often not calibrated.

St.John's Research Institute (SJRI), Bangalore has also used the above principles to estimate centile curves manually and have shared their methods with this study team.

4.4. Results:

Subject Characteristics: Among 3241 children (1611 boys and 1630 girls) who have participated in this study 98% children have provided blood samples (1566 boys and 1602 girls). Full description of anthropometric and stages of growth among the children are presented in study 1.

Broadly, between boys and girls the distribution of total cholesterol (p=0.001), LDL cholesterol (p=0.005), ApoB (p=0.001), Fasting Glucose (p=0.001) and HOMA (p=0.001) were significantly different while HDL (p=0.218), ApoA (p=0.184), Triglycerides (p=0.067), VLDL (p=0.068) and Mean Arterial Pressure (p=0.331) were comparable. Within age bands (6 to <19 years) there was no specific pattern in the distribution of bio-chemical markers between boys and girls. Among boys, triglycerides (p=0.044), uric acid (p=0.001), HOMA (p=0.001), fasting insulin (0.001) and mean arterial pressure (p=0.008) was significantly different in rural and urban settings while among girls triglycerides (p=0.016), uric acid (p=0.001), HDL (p=0.044), VLDL (p=0.016), HOMA (p=0.008), fasting insulin (0.002) and mean arterial pressure (p=0.001) were significantly different in rural and urban settings. No specific pattern within age groups among rural and urban boys and girls. Distribution of selected markers of cardio-metabolic risk (Mean ± SD) across age-groups among urban and rural boys and girls are presented in Table 12a and 12b.

In addition to serum markers, body mass index (BMI), percentage body fat, fat mass index (FMI) and waist circumference (WC) were also considered. In boys and girls, BMI, FMI and WC were significantly different in rural children as compared to urban children. Rural boys had less BMI (diff: -0.84; 95% CI: -1.15, -0.53), less FMI (diff: -0.20; 95% CI: -0.35, -0.05) and less WC (diff: -3.2; 95% CI: -4.18, -2.26) as compared to urban boys; while rural girls also had less BMI (diff: -

0.68; 95% CI:-1.03, -0.33), less FMI (diff: -0.22; 95% CI: -0.41, -0.03) and less WC (diff: -2.6; 95% CI: -3.6, -1.7). The percentage body fat was not different across rural and urban settings in both boys and girls.

Reference values and centile curves for monitoring cardio-metabolic risk conditions among children 6 to 18 years:

Following the steps mentioned in the methods, values for L, M and S were estimated for each age bands for boys and girls. Further reference values for 5th, 10th, 25th, 50th, 75th, 85th and 95th centiles were estimated to prepare smoothened centile curves. Reference values and centile curves for various cardio-metabolic risk conditions are presented under two subheads; a) bio-chemical markers and b) clinical markers.

I. Bio-chemical markers - (serum) for chronic disease monitoring		**II. Clinical markers - (anthropometric) for optimal nutrition monitoring**	
Conditions	**Indicators**	**Conditions**	**Indicators**
A. Glucose monitoring	1. Fasting glucose 2. HbA1C (Glycated Hemoglobin)	*A. Nutritional status*	14. Weight for age 15. BMI for age
B. Insulin Resistance monitoring	3. HOMA-IR	*B. Stunting*	16. Height for age
C. Blood Pressure monitoring	4. Systolic BP 5. Diastolic BP 6. Mean Arterial Pressure	*C. Body composition*	17. Percentage body fat 18. Fat mass index
D. Lipid monitoring	7. Total cholesterol 8. Low HDL-C 9. Triglycerides	*D. Abdominal Obesity*	19. Waist circumference
E. Atherogenic dyslipidemia	10. Apo-B representing non-HDL 11. Low Apo-A proteins representing HDL		
F. Hyperuricemia	12. Uric acid levels		

I. Bio-chemical markers – (serum) for chronic disease monitoring:

A. Glucose monitoring: India being the second largest country with number of type-2 diabetes cases it is important to monitor glucose levels among children. It can be either monitored through

fasting glucose levels or through HbA1C (glycated hemoglobin). For fasting glucose, reference values and percentile curves for boys and girls between 6 to 18 years are presented in table 13a. LMS curves and per centile categories highlights that glucose levels remains stable across age bands however it is important to track children shifting between centile categories. Among boys, across all centile categories, fasting glucose levels shall fluctuate slightly between 12 to 14 years and among girls this shall happen around 10 years and between 14 to 16 years. As per clinical practice consensus guidelines of international society of pediatric and adolescent diabetes (ISPAD); any child (both boys and girls) with fasting plasma glucose ≥ 126 mg/dl is considered as type 2 diabetes (hyperglycemic).[239] Children with fasting glucose above 100 mg/dl (pre-diabetes) should be closely monitored as per consensus definition of International Diabetes Federation (IDF, 2007).[240] Dotted lines in centile curves for fasting glucose level indicate pre-diabetes condition – which is ≥75th centile in boys and ≥85th centile in girls (table 13a).

Glycated hemoglobin (HbA1C) levels are also increasingly used to monitor glucose levels. Reference values and percentile curves for boys and girls between 6 to 18 years are presented in table 13b. LMS curves and per centile categories for HbA1C reaffirms that glucose levels remains stable across age bands. However boys and girls in lowest percentile centile (3rd, 10th and 25th percentiles) shall show reduction in glucose levels around 10 years. It is important to monitor children shifting between percentile curves. As per IDF consensus statement a value of HbA1C ≥ 6.5 is considered as type 2 diabetes while this above 5.8 to <6.5 is considered as pre-diabetes.

B. Insulin Resistance (IR) monitoring: Among Indians, one of the major risk factor for type-2 diabetes is insulin resistance which refers to the decreased physiological response to normal levels of insulin. IR shall increase the risk of type-2 diabetes over time. Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) is the commonly used indicator to monitor insulin resistance - calculated as fasting insulin (mIU/L) X fasting glucose (mg/dl) / 405 (for fasting glucose in mmol/L the constant used is 22.5). Reference values and percentile curves for HOMA-IR for boys and girls are presented in table 14. HOMA-IR ≥ 2.5 is generally considered for monitoring insulin resistance. Among boys the adult equivalent of HOMA-IR ≥ 2.5 passes through 85th percentile curve while among girls this passes through 75th percentile curve. All children above HOMA-IR 2.5 should be monitored for altered glucose metabolism (development of pre-diabetes & type 2 diabetes) over time. There was 14% (176/1245) boys and 25.3% (325/1285) girls with insulin resistance in this study.

C. Blood Pressure monitoring: Over 33% of urban and 25% of rural Indians are hypertensive and often indications start earlier in childhoods.[17] Thus it is important to monitor blood pressure

among boys and girls. Hypertension among children are defined as those having systolic blood pressure (SBP) ≥ 130 or diastolic blood pressure (DBP) ≥ 85 mmHG. It is also defined as SBP and DBP ≥95th percentile after adjusting for sex, age and for height of children. Reference values and percentile curves for SBP and DBP among boys and girls (aged 6 to 18 years) are presented in table 15a and 15b. Among boys adult equivalent of SBP ≥ 130 mmHG passes through 85th centiles while this among girl's passes through 95th centiles. Similarly among boys and girls adult equivalent of DBP ≥ 85 mmHG passes through 95th centiles. Among those children in higher centiles (i.e., above 85th centiles) there is an increase in systolic blood pressure between 12 to 14 years. In this study, there was 7.8% (125/1607) boys and 6.9% (112/1621) girls diagnosed as hypertensive as per above criteria.

In addition mean arterial pressure (MAP), which is the time-weighted average of cardiac outputs, is also suggested as an indicator for monitoring hypertension. However, at present there is no cut-offs suggested for MAP for diagnosing hypertension (table 15c). In this study, there was 4.9% (78/1607) boys and 4.3% (69/1621) girls with MAP above 95th centiles.

D. Lipid monitoring: Altered lipid metabolism is another risk factor for chronic diseases among Indians. This could be monitored through several lipoprotein levels in the body – most commonly used risk factors are total cholesterols, triglycerides and low levels of HDL. Reference values for total cholesterol, triglycerides and HDL-C are presented in table 16a, 16b and 16c.

Total Cholesterol: Age and gender specific centile values for total cholesterol are presented in Table 16a. Broadly total cholesterol levels remains constant across age bands however among boys a slight decrease can be observed between 12 and 16 years. Total cholesterol in our centile values were compared with Cook S et al., (2009).[145] Among boys, the mean difference were: at 10th centile -15.1 (95% CI: -15.8, -14.3), at 50th centile -17.2 (95% CI: -18.3, -16.2), at 75th centile -18.5 (95% CI: -19.7, -17.2) and at 90th centile was -19.5 (95% CI: -24.3, -14.8). The adult equivalent cut off for boys (200 mg/dl at 18 years) was 95th centile in our study. Among girls, the mean difference were: at 10th centile -14.7 (95% CI: -16.4, -12.9), at 50th centile was -15.3 (95% CI: -17.3, -13.3), at 75th centile -15.7 (95% CI: -18.2, -13.1) and at 90th centile was -16 (95% CI: -19.4, -12.5). The adult equivalent cut off for girls (200 mg/dl at 18 years) was closer to 90th centile in our study.

Triglycerides are fat molecules stored in adipocytes and are associated with atherogenic plaque formations. As per IDF consensus report triglycerides ≥ 150 mg/dl in above 6 year children (boys and girls) shall be considered as dyslipidemia. Percentile curves (table 16b) highlights that triglyceride levels also remain stable across age bands however it is important to monitor children

shifting between centile categories. In this study around 11.3% (176/1560) boys and 11.5% (182/1590) girls were having high triglyceride levels.

HDL cholesterol are good cholesterols which has protective effects against cardio-vascular diseases. Reference values and percentile curves for low HDL-C are presented in table 16c. Often low levels of HDL cholesterol are identified as high risk for cardiac events. Among boys ≤ 40 mg/dl in all age groups is considered as high risk while in girls below 16 years ≤ 40 mg/dl is considered as high risk. For girls above 16 years ≤ 50 mg/dl is considered as high risk. In this study there was 26.7% (415/1555) boys and 31.5% (502/1595) girls with HDL cholesterol below recommended limits.

E. Atherogenic dyslipidemia: Alternative to lipid monitoring is atherogenic dyslipidemia monitored through low Apo-A protein levels (representing HDL-C) and high Apo-B proteins (representing non-HDL-C). Reference values and percentile curves for low Apo-A proteins and high Apo-B proteins are presented in table 17a and 17b. Apo-A levels ≤ 115 mg/dl is suggested as a cut-off and Apo-B levels ≥ 110 mg/dl as cut-off for atherogenic dyslipidemia. Percentile curves across age bands were found as stable. There was 16.8% (263/1561) boys and 18.2% (290/1593) girls with low Apo-A levels and 6.7% (104/1561) boys and 8.2% (130/1595) girls with high Apo-B levels.

F. High uric acid: High levels of uric acid in serum is considered as an indicator of subclinical atherosclerosis – reference values presented in table 18. Presently there is no accepted thresholds for uric acid levels among Indian children. Therefore adult equivalent cut-offs (7.0 in boys and 5.7 in girls) at 18 years were extrapolated backwards to identify high uric acid levels. There was 5.5% (86/1561) boys and 9.9% (159/1596) girls with high serum uric acid levels.

II. Clinical markers – for nutrition monitoring:

A. Nutritional status :

Table 19a shows the age and sex specific BMI percentiles and curves which indicates linear growth pattern across age band. The reference values for BMI-for-age presented in Indian Association of Pediatrics (2015) growth charts were compared with this study results.**Error! Bookmark not defined.** Among boys, mean difference across age bands were: 1) at 3rd centile 0.12 (95% CI: -0.14, 0.26), 2) at 10th centile 0.44 (95% CI: 0.28, 0.59), 3) at 25th centile 0.81 (95% CI: 0.60, 1.01) and 4) at median 1.26 (95% CI: 1.02, 1.52). The adult equivalent cut off for BMI >23 in boys for overweight category (equivalent to 71st percentile in IAP growth charts) were closer to *85th centile* in this study (diff: 0.25; 95% CI: 0.13, 0.37) - limits of agreement for differences across age-groups (BA plots) was between

-0.13 to 0.64. The adult equivalent cut off for BMI > 27 in boys for obese category (equivalent to 90th percentile in IAP growth charts) were closer to *95th centile* in this study (diff: 0.73; 95% CI: 0.48, 0.97) – limits of agreement for difference across age-groups was between -0.08 to 1.5.

Among girls, mean difference in BMI across age bands were: 1) at 3rd centile 0.14 (95% CI: 0.01, 0.27), 2) at 10th centile 0.42 (95% CI: 0.27, 0.57), 3) at 25th centile 0.71 (95% CI: 0.54, 0.89) and 4) at median 1.0 (95% CI: 0.81, 1.2). The adult equivalent cut off for BMI > 23 among girls for overweight category (equivalent to 75th centile in IAP growth charts) were closer to *85th centile* in this study (diff: 0.01; 95% CI: -0.08, 0.11) – limits of agreement for difference across age-groups was between -0.31 to 0.34. The adult equivalent cut off for BMI > 27 in girls for obese category (equivalent to 95th centile in IAP growth charts) were closer to *97th centile* in this study (diff: -0.12; 95% CI: -0.43, 0.19) – limits of agreement for difference across age groups was between -1.15 to 0.91. The difference in centile values compared with IAP growth centiles for overweight and obese categories are plotted in figures.

Table 19b summarizes the age and gender specific reference values for percentage body fat across age bands. In boys, the percentage body fat especially in higher centiles (those above 75th centiles) almost remains constant across age bands – with some minor changes in body constitution between 11 years and 14 years. Among girls, in all centile categories the percentage body fat increases between 11 or 12 years and trend continues.

The reference values for percentage body fat, among 7 to 17 years, in this study were compared with the values presented by Marwaha RK et al., (2013).[241] Among boys, mean difference in percentage body fat were: at 3rd centile 4.2% (95% CI: 3.3 to 5.1), at 10th centile 2.9% (95% CI: 1.9 to 4.0), at 50th centile -2.1% (95%: -4.1, -0.09) and at 85th centile -9.3% (95% CI: -12.2, -6.4). Among girls, mean difference in percentage body fat were: at 3rd centile -0.96% (95% CI: -2.6, 0.66), at 10th centile -2.4% (95% CI: -4.2, -0.6), -6.4 (95% CI: -8.3, -4.5) and at 85th centile -10.2 (95% CI: -11.9, -8.4). In addition we have compared the percentage body fat with a Colombian study[242] and the mean difference were: at 3rd centile 4.2% (95% CI: 2.5, 6.1), at 10th centile 4.3% (95% CI: 2.7, 6.0), at 50th centile 5.1% (95% CI: 3.5, 6.6) and at 75th centiles 3.7% (95% CI: 2.4, 5.0). Similar trend was observed among girls also. Broadly, the percent difference is relatively more at higher centiles. This may be either due to the natural shifts in body composition with time or may be due to representativeness of sample in relation to selection process or geographic locations.

Table 12a: Age wise distribution of key markers of cardio-metabolic risk among boys in urban and rural locations

	URBAN boys Mean ± SD (n)								RURAL boys Mean ± SD (n)							
Age group	**TC**	**HDL**	**TG**	**FG**	**FI**	**Apo A1**	**Apo B**	**UA**	**TC**	**HDL**	**TG**	**FG**	**FI**	**Apo A1**	**Apo B**	**UA**
6-7	136.0± 26.7 (32)	41.7± 8.1(32)	83.4± 22.8(32)	91.4± 10.5(31)	3.6± 1.7(5)	112.5± 33.6(32)	71.2± 14.3(31)	4.3± 1.0(31)	150.4± 31.13(18)	47.9± 11.7(18)	104.3± 79.4(18)	96.2± 10.2(18)	7.67± 4.68(10)	125.1±3 6.1(18)	76.9± 18.3(18)	3.5± 0.9(18)
7-8	156.1± 29.0(65)	47.6± 9.5 (64)	88.7± 45.2 (65)	96.4± 12.5(65)	5.3± 3.5(51)	139.6± 30.8(65)	91.4± 19.3(65)	3.73± 0.9(65)	143.1± 26.9(70)	45.6± 9.7(69)	90.4± 40.6(69)	97.7± 11.9(70)	4.04± 2.89 (54)	129± 25.8(70)	74.5± 16.1(70)	3.52± 0.9(70)
8-9	151.7± 24.9(67)	49.4± 11.4(67)	84.8± 35.8(67)	97.1± 11.7(68)	5.79± 4.9(63)	148± 29.1(67)	85.9± 19.3(67)	4.22± 1.9(67)	149.7± 24.0(64)	46.2± 9.8(64)	92.9± 50.8(64)	98.3± 13.2(63)	3.8± 3.6(47)	136.5± 21.8(64)	79.4± 17.5(64)	3.6± 0.95(64)
9-10	152.3± 27.8(73)	48.2± 10.8(73)	86±33.4 (73)	96.3± 9.5(74)	6.3± 6.8(65)	143.4± 30.7(73)	84.7± 17.5(73)	4.19± 1.0(73)	144± 24.9(65)	44.6± 9.1(63)	95.4± 49.7(65)	97.3± 10.7(65)	4.9± 3.6(48)	130.7± 29.3(65)	73.3± 14.8(65)	3.6± 0.96(65)
10-11	151.5± 27.5(69)	47.7± 10.1(69)	94.5± 52.7(69)	96.4± 8.8(71)	6.15± 4.6(61)	142.2± 27.2(69)	86.2± 20.2(69)	4.26± 1.2(69)	152.7± 30.8(65)	47.9± 12.3(64)	93.8± 41.5(65)	97.2± 9.2(65)	4.84± 3.6(47)	136.4± 27.9(65)	77.7± 14.4(65)	3.9± 1.03(65)
11-12	148.7± 22.5(77)	46.9± 9.3(77)	81.5± 38.1(77)	95.3± 9.9(77)	7.4± 5.5(70)	146± 26.5(77)	76.9± 15.9(77)	4.6± 1.2(77)	153.7± 29.1(60)	45.8± 10.5(60)	87.6± 30.8(60)	98.7± 12.0(62)	6.4± 4.3(51)	140.6± 32.9(60)	83.1± 17.7(60)	3.9± 1.15(60)
12-13	147.8± 26.8(97)	46.6± 10.3(97)	90.8± 46.7(97)	97.0± 10.4(97)	7.4± 4.6(86)	139.8± 25.7(97)	82.2± 18.6(97)	4.7± 1.2(97)	150.4± 25.3(52)	45.4± 12.7(52)	92.2± 50.6(52)	95.7± 11.6(52)	5.4± 5.9(43)	140.4± 25.3(52)	80.0± 16.9(52)	4.45± 1.2(52)
13-14	147.6± 29.3(80)	46.1± 10.1(80)	90.3± 42.4(79)	97.1± 9.4(80)	7.8± 5.4(71)	137.8± 29.5(80)	80.1± 17.5(80)	5.34± 1.3(80)	147.0± 24.6(65)	45.3± 10.3(63)	90.3± 37.3(65)	100.8± 9.9(65)	6.64± 5.25(50)	137.5± 23.3(65)	76.3± 16.6(65)	4.6± 1.17(65)
14-15	133.6± 25.5(83)	42.9± 9.0(83)	89.3± 39.6(83)	97.6± 9.4(84)	8.4± 5.8(79)	126.9± 27.1(83)	74.1± 17.2(83)	5.6± 1.2(83)	150.6± 27.1(46)	46.3± 12.1(46)	96.3± 31.8(46)	97.9± 12.4(46)	5.6± 3.1(32)	143.3± 29.1(46)	77.4± 20.7(46)	5.5± 1.15(46)
15-16	132.9± 29.4(82)	42.0± 8.37(82)	88.6± 39.0(82)	96.8± 7.7(82)	7.6± 4.1(64)	125.4± 25.6(82)	73.4± 15.7(82)	5.5± 1.1(82)	141.1± 29.1(50)	45.5± 13.1(50)	93.1± 43.1(50)	98.5± 10.4(50)	5.9± 4.20(38)	123.1± 27.5(50)	80.5± 18.7(50)	5.6± 1.3 (50)
16-17	132.6± 27.8(49)	40.8± 8.3(49)	90.4± 35.8(49)	96.1± 10.8(48)	8.5± 6.4(39)	118.2± 21.7(49)	73.7± 17.0(49)	5.3± 1.1(49)	133.8± 29.2(48)	42.1± 11.3(48)	99.6± 55.2(48)	95.4± 11.2(48)	6.7± 6.9(33)	129.8± 29.8(47)	77.8± 18.17(48)	5.3± 1.5(48)
17-18	140.5± 31.8(66)	42.7± 10.1(66)	102.5± 45.5(66)	98.5± 9.1(66)	7.2± 4.7(56)	122.0± 23.0(66)	78.3± 16.9(66)	5.36± 1.1(66)	151.6± 31.9(42)	42.7± 7.9(42)	109.2± 64.4(42)	95.3± 11.8(42)	4.25± 1.93(21)	135.0± 28.7(42)	81.4± 21.2(42)	5.7±1.3 (42)
18-19	142.8± 31.2(50)	42.2± 7.6(50)	107.7± 53.2(50)	97.3± 10.8(50)	7.74± 6.3(43)	118.0± 19.8(50)	79.4± 14.7(50)	5.6± 1.1(50)	150.8± 31.9(26)	41.6± 10.4(27)	111.6± 53.8(27)	93.1± 8.3(27)	5.2± 2.6(19)	138.5± 35 (27)	93.2± 21.7(27)	5.9± 1.3(27)

Note: TC - Total Cholesterol, HDL - High Density Lipoprotein, TG - Triglycerides, FG - Fasting Glucose, FI - Fasting Insulin, Apo –Apolipoprotein and UA - Uric Acid

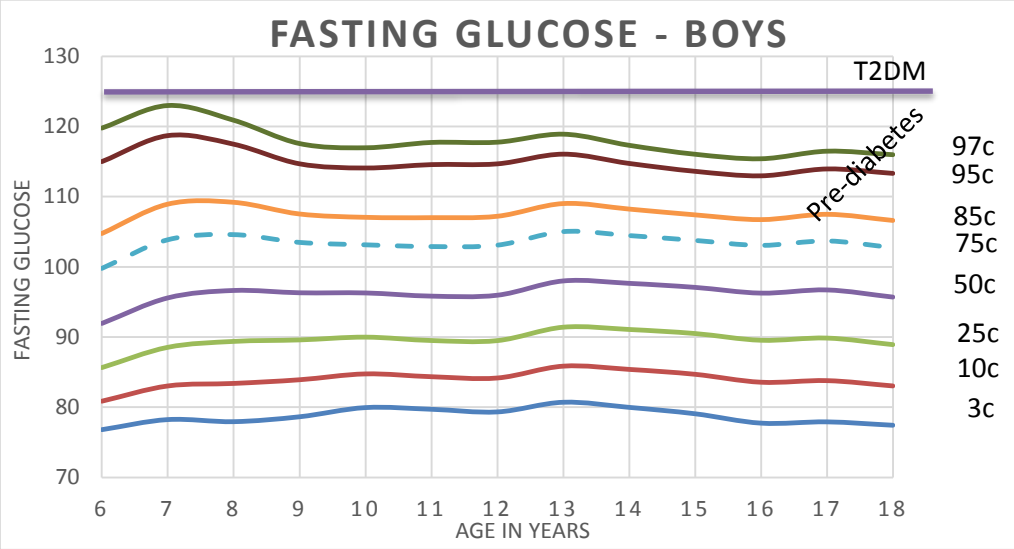
Table 12b: Age wise distribution of key markers of cardio-metabolic risk among girls in urban and rural locations

	URBAN GIRLS - Mean ± SD (n)								RURAL GIRLS - Mean ± SD (n)							
Age group	**TC**	**HDL**	**TG**	**FG**	**FI**	**Apo A1**	**Apo B**	**UA**	**TC**	**HDL**	**TG**	**FG**	**FI**	**Apo A1**	**Apo B**	**UA**
6-7	153.5± 26.4(32)	40.9± 9.2(31)	98.9± 32.1(31)	90.6± 10.9(32)	7.3± 4.6(20)	123.9± 22.7(32)	86.5± 17.0(32)	3.9± 0.9(32)	149.2± 17.9(17)	48.9± 12.0(17)	84.4± 34.9(17)	91.6± 7.8(17)	4.2± 2.5 (12)	127.7± 15.6(17)	76.5± 9.8(17)	3.5± 1.1(17)
7-8	156.8± 29.9(76)	46.6± 10.2(76)	84.1± 30.4(76)	92.9± 8.5(76)	7.6± 7.6(60)	139.2± 31.8(76)	86.6± 18.1(76)	4.0± 1.1(76)	148.4± 27.8(65)	43.9± 8.0(65)	97.9± 41.2(65)	93.6± 9.8(66)	4.8± 4.4(42)	134.1± 31.4(65)	80.5± 16.1(65)	3.8± 1.1(65)
8-9	152.0± 23.6(78)	47.7± 7.5(79)	86.8± 33.5(79)	93.1± 8.5(80)	5.4± 5.2(69)	140.8± 17.0(79)	85.0± 19.7(79)	4.0± 1.1(79)	148.7± 33.8(52)	45.7± 8.8(52)	95.5± 39.8(52)	94.9± 10.0(52)	5.7± 4.2(38)	124.0± 29.3(52)	76.5± 15.1(52)	3.6± 0.8(52)
9-10	150.2± 33.6(77)	46.8± 10.5(77)	88.4 ± 39.8(76)	95.3± 9.8(76)	5.8± 2.7(66)	140.6± 27.4(77)	86.3± 27.6(77)	4.1± 1.3(77)	148.8± 28.0(57)	45.3± 8.5(57)	101.5± 48.5(57)	95.4± 10.9(58)	6.5± 4.3(45)	133.7± 28.9(57)	80.2± 16.2(57)	3.9± 1.1(57)
10-11	145.7± 25.1(90)	46.5± 9.3(90)	92.5± 37.2(90)	98.3± 10.3(90)	7.8± 4.8(82)	136.9± 31.6(89)	79.1± 18.9(90)	4.4± 1.1(90)	145.6± 25.8(54)	45.1± 10.8(54)	100.6± 44.1(54)	97.7± 12.7(55)	6.8± 5.8(41)	134.0± 27.9(53)	79.4± 17.7(54)	3.7± 0.9(54)
11-12	148.8± 26.3(83)	46.7± 9.4(83)	92.9± 30.9(83)	95.9± 10.7(82)	7.5± 3.7(72)	138.6± 26.7(83)	78.7± 16.7(83)	4.2± 1.2(83)	152.8± 30.7(53)	44.8± 10.6(53)	89.7± 29.6(51)	95.4± 10.1(52)	8.03± 5.4(30)	130.8± 26.8(53)	81.2± 21.2(53)	4.25± 1.1(53)
12-13	145.1± 26.2(96)	47.4± 9.9(96)	91.9± 38.0(96)	95.4± 10.2(96)	7.9± 3.7(86)	132.6± 24.5(95)	78.9± 16.4(95)	4.16± 1.1(95)	151.5± 30.8(52)	43.8± 10.7(52)	112.1± 41.9(52)	95.2± 7.4(52)	7.2± 3.3(34)	126.7± 26.8(51)	79.7± 19.9(52)	4.2± 1.1(52)
13-14	146.6± 29.0(73)	45.5± 8.2(74)	93.4± 36.8(74)	96.7± 9.9(74)	10.3± 6.8(66)	135.3± 28.4(74)	77.9± 17.4(74)	4.3± 0.9(74)	150.4± 29.9(55)	45.4± 9.7(55)	103.2± 43.5(55)	94.3± 9.5(56)	10.4± 8.5(40)	134.2± 27.8(55)	79.6± 21.1(54)	4.0± 1.1(55)
14-15	148.2± 30.0(74)	45.5± 8.3(74)	94.1± 37.3(74)	95.7± 9.5(75)	11.5± 6.6(61)	127.2± 27.2(74)	83.7± 22.6(74)	4.4± 1.2(74)	151.7± 34.0(47)	45.2± 9.8(47)	94.1± 35.2(47)	97.5± 11.8(47)	8.2± 3.8(38)	135.6± 25.7(47)	83.8± 20.2(47)	4.1± 1.2(47)
15-16	148.2± 27.8(74)	45.9± 8.8(74)	98.8± 44.0(74)	98.9± 11.7(74)	9.8± 4.9(61)	133.2± 23.9(74)	80.9± 22.7(74)	4.15± 1.0(74)	157.5± 40.8(54)	44.6± 11.2(54)	101.0± 36.7(54)	94.3± 11.4(54)	9.5± 4.9(40)	136.1± 27.6(54)	87.9± 27.2(54)	4.3± 1.4(54)
16-17	145.0± 26.0(71)	44.7± 9.0(71)	97.9± 40.9(71)	93.3± 9.8(71)	9.7± 5.3(57)	132.4± 32.9(71)	80.9± 18.6(71)	4.2± 1.1(71)	147.5± 32.3(40)	43.6± 9.5(40)	96.7± 42.1(40)	91.3± 11.6(41)	8.2± 5.7(33)	133.8± 23.9(40)	87.0± 24.1(40)	4.3± 1.1(40)
17-18	150.9± 31.4(81)	43.6± 8.9(81)	98.9± 42.3(79)	92.1± 13.0(82)	9.5± 5.1(70)	120.2± 22.4(81)	82.9± 18.1(81)	4.3± 1.2(81)	153.9± 33.3(47)	45.9± 9.1(47)	92.5± 46.6(46)	93.4± 10.0(47)	8.3± 5.0(36)	134.4± 30.1(47)	80.8± 25.1(47)	4.1± 1.0(47)
18-19	152.7± 35.7(64)	48.3± 11.3(63)	98.4± 42.5(64)	87.6± 13.1(64)	9.5± 5.1(56)	124.5± 27.8(64)	80.6± 15.0(64)	4.2± 1.4(64)	150.9± 29.2(33)	47.6± 13.0(33)	92.0± 43.9(33)	92.1± 7.7(33)	6.8± 3.3(32)	131.7± 30.8(33)	88.1± 22.4(33)	3.7± 0.8(33)

Note: TC - Total Cholesterol, HDL - High Density Lipoprotein, TG - Triglycerides, FG - Fasting Glucose, FI - Fasting Insulin, Apo –Apolipoprotein and UA - Uric Acid

Table 13a. Reference Values and Centile Curves of **Fasting Glucose**

Age, Y	3C	10C	25C	50C	75C	85C	90C	95C	97C
Boys									
6 to 7	76.8	80.9	85.6	92.0	99.8	104.8	108.6	115.0	119.8
7 to 8	78.2	83.0	88.5	95.6	103.9	108.9	112.7	118.7	123.0
8 to 9	77.9	83.4	89.4	96.6	104.6	109.2	112.5	117.5	120.9
9 to 10	78.6	83.9	89.6	96.3	103.5	107.5	110.4	114.7	117.6
10 to 11	79.9	84.7	90.0	96.3	103.1	107.1	109.8	114.1	117.0
11 to 12	79.7	84.3	89.5	95.8	102.9	107.0	110.0	114.6	117.7
12 to 13	79.3	84.2	89.5	96.0	103.1	107.2	110.1	114.7	117.8
13 to 14	80.7	85.9	91.4	98.0	105.0	109.0	111.8	116.1	118.9
14 to 15	80.0	85.4	91.1	97.6	104.5	108.2	110.8	114.7	117.3
15 to 16	79.1	84.7	90.5	97.1	103.8	107.4	109.9	113.6	116.1
16 to 17	77.7	83.6	89.5	96.3	103.1	106.7	109.3	113.0	115.4
17 to 18	77.9	83.8	89.9	96.7	103.7	107.5	110.1	114.0	116.5
18 to 19	77.4	83.0	88.9	95.7	102.7	106.6	109.3	113.3	116.0
Girls									
6 to 7	74.5	79.5	84.7	90.7	97.0	100.5	102.9	106.6	109.0
7 to 8	76.5	81.5	86.7	92.9	99.4	103.0	105.5	109.4	111.9
8 to 9	76.9	81.9	87.2	93.4	100.1	103.8	106.4	110.4	113.0
9 to 10	77.9	82.9	88.3	94.8	101.7	105.6	108.3	112.5	115.3
10 to 11	79.8	85.1	90.8	97.5	104.7	108.7	111.5	115.9	118.8
11 to 12	78.0	83.1	88.7	95.2	102.2	106.1	108.9	113.1	115.9
12 to 13	77.9	83.0	88.5	94.9	101.9	105.8	108.5	112.7	115.5
13 to 14	78.0	83.1	88.6	95.2	102.2	106.2	109.0	113.2	116.1
14 to 15	78.1	83.4	89.1	95.9	103.2	107.4	110.3	114.7	117.7
15 to 16	77.6	83.2	89.3	96.4	104.0	108.3	111.3	115.8	118.8
16 to 17	73.0	78.8	85.0	92.2	99.7	103.9	106.8	111.2	114.1
17 to 18	71.6	78.1	84.8	92.4	100.3	104.5	107.5	111.8	114.7
18 to 19	67.4	74.4	81.4	89.2	97.0	101.2	104.0	108.2	110.9



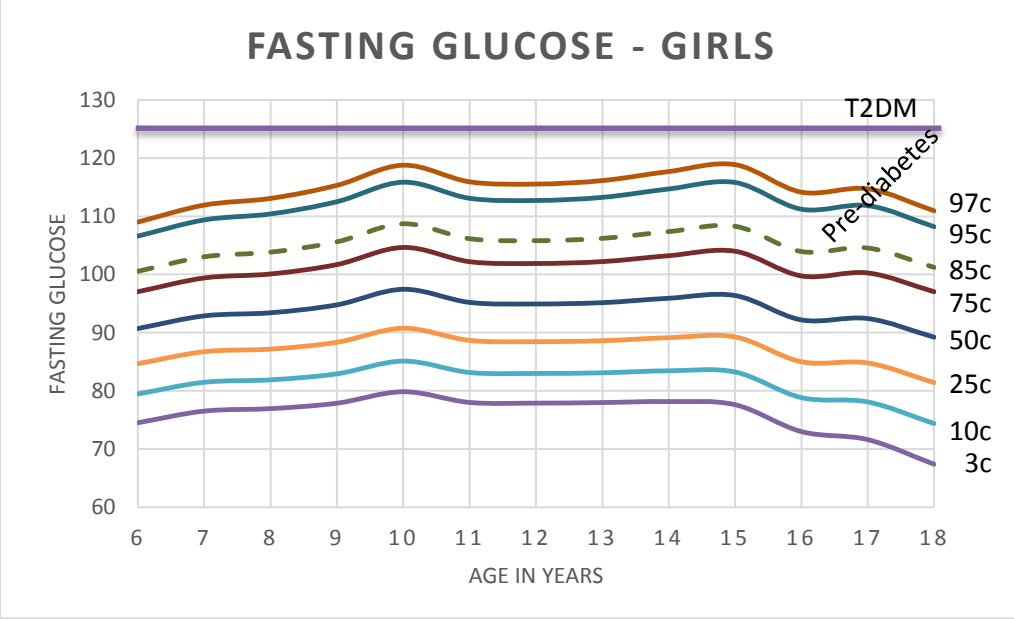
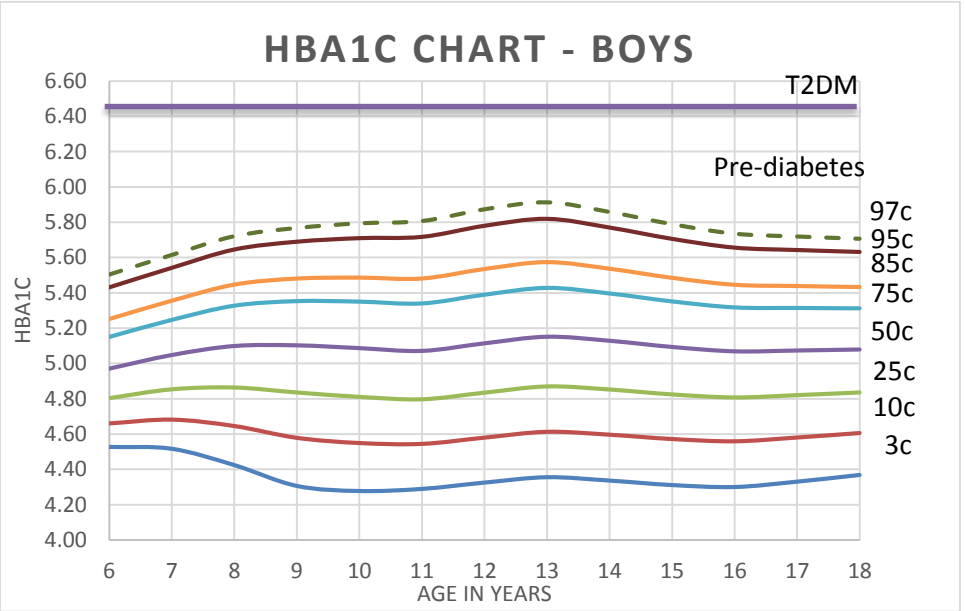


Table 13b. Reference Values and Centile Curves of **HbA1C levels**

Age, Y	3C	10C	25C	50C	75C	85C	90C	95C	97C
Boys									
6 to 7	4.53	4.66	4.80	4.97	5.15	5.25	5.32	5.43	5.50
7 to 8	4.52	4.68	4.85	5.05	5.25	5.36	5.43	5.54	5.61
8 to 9	4.42	4.65	4.86	5.10	5.33	5.45	5.53	5.65	5.72
9 to 10	4.31	4.58	4.84	5.10	5.35	5.48	5.57	5.69	5.77
10 to 11	4.28	4.55	4.81	5.09	5.35	5.49	5.58	5.71	5.79
11 to 12	4.29	4.54	4.80	5.07	5.34	5.48	5.58	5.72	5.81
12 to 13	4.32	4.58	4.83	5.11	5.39	5.54	5.63	5.78	5.87
13 to 14	4.36	4.61	4.87	5.15	5.43	5.57	5.67	5.82	5.91
14 to 15	4.34	4.60	4.85	5.13	5.40	5.54	5.63	5.77	5.86
15 to 16	4.31	4.57	4.82	5.09	5.35	5.49	5.58	5.71	5.79
16 to 17	4.30	4.56	4.81	5.07	5.32	5.45	5.53	5.66	5.74
17 to 18	4.33	4.58	4.82	5.07	5.31	5.44	5.52	5.64	5.72
18 to 19	4.37	4.61	4.84	5.08	5.31	5.43	5.51	5.63	5.71
Girls									
6 to 7	4.51	4.66	4.82	5.00	5.20	5.31	5.39	5.50	5.58
7 to 8	4.45	4.62	4.79	4.99	5.21	5.33	5.41	5.53	5.61
8 to 9	4.44	4.62	4.81	5.03	5.26	5.39	5.48	5.61	5.70
9 to 10	4.36	4.56	4.77	5.00	5.25	5.38	5.47	5.61	5.70
10 to 11	4.34	4.56	4.79	5.05	5.31	5.45	5.54	5.68	5.77
11 to 12	4.30	4.54	4.78	5.05	5.32	5.46	5.56	5.70	5.80
12 to 13	4.21	4.46	4.71	4.98	5.26	5.40	5.50	5.65	5.74
13 to 14	4.17	4.42	4.67	4.95	5.23	5.37	5.47	5.62	5.72
14 to 15	4.17	4.42	4.68	4.96	5.23	5.38	5.49	5.64	5.73
15 to 16	4.23	4.47	4.72	5.00	5.28	5.44	5.54	5.69	5.79
16 to 17	4.27	4.51	4.76	5.03	5.31	5.47	5.57	5.73	5.83
17 to 18	4.31	4.54	4.78	5.05	5.33	5.49	5.59	5.75	5.85
18 to 19	4.35	4.58	4.81	5.08	5.35	5.51	5.61	5.77	5.88



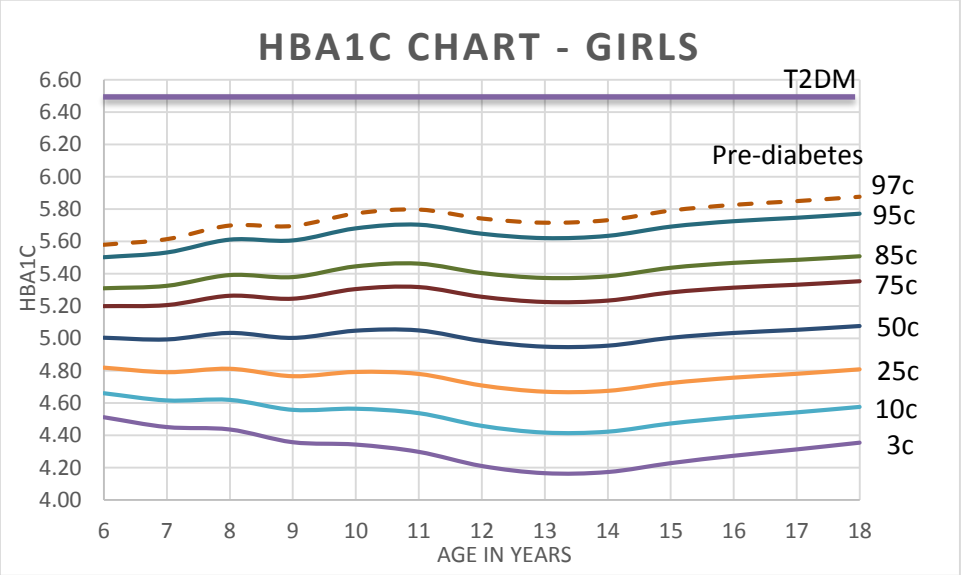
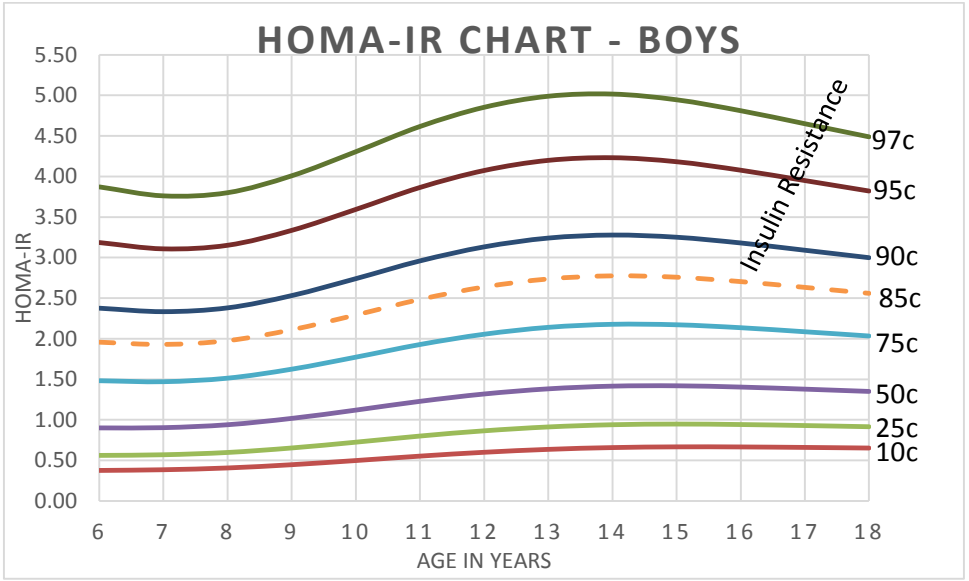


Table 14. Reference Values and Centile Curves of **HOMA-IR**

Age, Y	3C	10C	25C	50C	75C	85C	90C	95C	97C
Boys									
6 to 7	0.25	0.37	0.56	0.90	1.48	1.96	2.37	3.18	3.87
7 to 8	0.26	0.38	0.57	0.90	1.47	1.93	2.33	3.11	3.76
8 to 9	0.28	0.41	0.60	0.94	1.51	1.98	2.38	3.15	3.80
9 to 10	0.31	0.45	0.65	1.02	1.63	2.11	2.53	3.34	4.01
10 to 11	0.35	0.50	0.72	1.12	1.77	2.29	2.74	3.59	4.31
11 to 12	0.39	0.55	0.80	1.23	1.93	2.48	2.96	3.87	4.62
12 to 13	0.43	0.60	0.86	1.32	2.06	2.64	3.13	4.07	4.85
13 to 14	0.45	0.64	0.91	1.38	2.14	2.73	3.24	4.20	4.99
14 to 15	0.47	0.66	0.94	1.41	2.18	2.77	3.28	4.23	5.02
15 to 16	0.48	0.67	0.95	1.42	2.17	2.76	3.25	4.18	4.95
16 to 17	0.48	0.67	0.94	1.40	2.14	2.70	3.18	4.08	4.81
17 to 18	0.48	0.66	0.93	1.38	2.09	2.63	3.09	3.95	4.65
18 to 19	0.48	0.65	0.91	1.35	2.03	2.56	3.00	3.82	4.49
Girls									
6 to 7	0.31	0.44	0.64	1.01	1.70	2.31	2.88	4.10	5.25
7 to 8	0.32	0.45	0.64	1.00	1.61	2.14	2.62	3.58	4.45
8 to 9	0.34	0.47	0.66	1.01	1.58	2.05	2.45	3.25	3.94
9 to 10	0.42	0.58	0.81	1.20	1.84	2.33	2.76	3.56	4.23
10 to 11	0.51	0.70	0.98	1.43	2.14	2.67	3.12	3.95	4.62
11 to 12	0.57	0.78	1.08	1.56	2.29	2.84	3.28	4.10	4.75
12 to 13	0.64	0.87	1.20	1.72	2.50	3.07	3.53	4.36	5.01
13 to 14	0.74	1.00	1.37	1.96	2.83	3.45	3.95	4.85	5.55
14 to 15	0.78	1.06	1.46	2.08	2.99	3.63	4.15	5.06	5.76
15 to 16	0.76	1.04	1.43	2.04	2.92	3.54	4.03	4.90	5.56
16 to 17	0.70	0.97	1.34	1.92	2.74	3.32	3.77	4.56	5.16
17 to 18	0.64	0.89	1.25	1.79	2.56	3.09	3.50	4.22	4.76
18 to 19	0.57	0.81	1.14	1.65	2.35	2.83	3.21	3.85	4.33



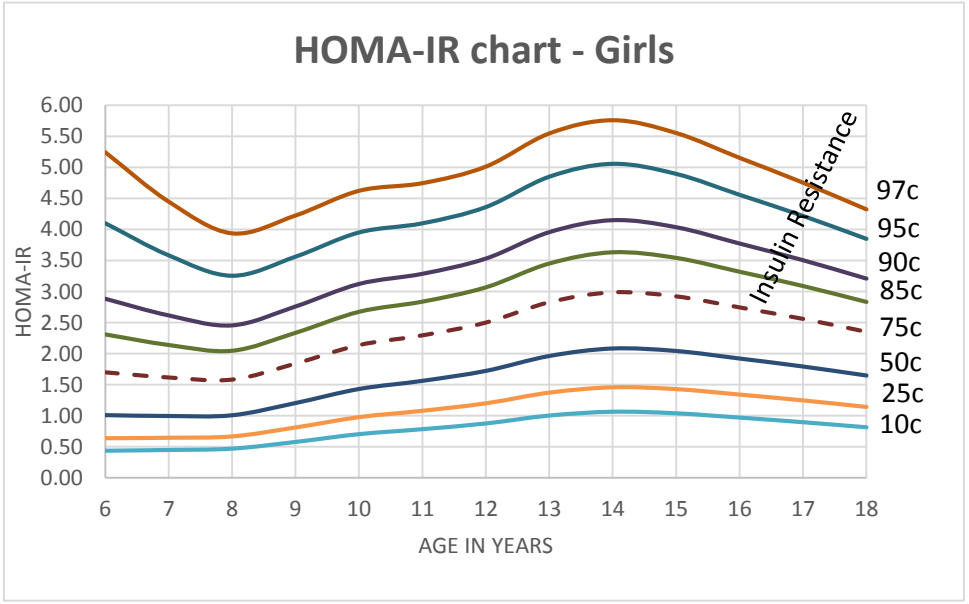
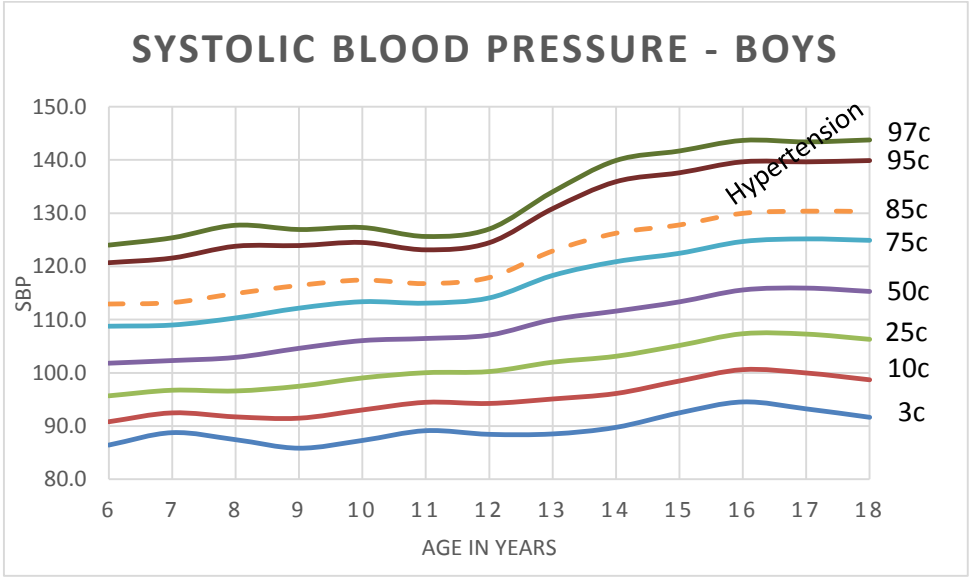


Table 15a. Reference Values and Centile Curves of **SBP**

Age, Y	3C	10C	25C	50C	75C	85C	90C	95C	97C
Boys									
6 to 7	86.4	90.8	95.7	101.8	108.8	112.9	115.9	120.7	124.0
7 to 8	88.8	92.5	96.7	102.3	109.0	113.2	116.4	121.6	125.4
8 to 9	87.4	91.7	96.6	102.9	110.3	114.9	118.3	123.8	127.7
9 to 10	85.8	91.5	97.5	104.6	112.2	116.4	119.4	123.9	126.9
10 to 11	87.3	93.0	99.1	106.1	113.4	117.4	120.3	124.5	127.3
11 to 12	89.1	94.5	100.0	106.5	113.1	116.8	119.3	123.1	125.6
12 to 13	88.4	94.2	100.3	107.1	114.1	117.9	120.5	124.4	127.0
13 to 14	88.5	95.1	102.0	110.0	118.3	122.9	126.1	130.8	134.0
14 to 15	89.8	96.1	103.1	111.6	120.9	126.3	130.0	135.9	139.9
15 to 16	92.5	98.5	105.1	113.3	122.5	127.8	131.6	137.6	141.7
16 to 17	94.5	100.6	107.3	115.6	124.7	130.0	133.8	139.6	143.7
17 to 18	93.2	100.0	107.3	115.9	125.2	130.4	134.0	139.6	143.4
18 to 19	91.7	98.7	106.3	115.3	124.9	130.3	134.1	139.9	143.7
Girls									
6 to 7	78.9	86.8	94.5	102.6	110.5	114.6	117.3	121.3	123.8
7 to 8	80.2	87.3	94.5	102.3	110.1	114.2	117.0	121.1	123.7
8 to 9	81.4	88.0	94.7	102.2	109.9	114.1	116.9	121.2	123.9
9 to 10	83.7	90.0	96.6	104.1	111.8	116.1	118.9	123.2	126.1
10 to 11	85.3	91.9	98.7	106.3	114.0	118.2	121.0	125.2	128.0
11 to 12	84.9	92.0	99.2	107.0	114.8	119.0	121.8	125.9	128.6
12 to 13	84.7	91.8	99.1	107.2	115.4	119.7	122.7	127.1	130.0
13 to 14	86.9	93.6	100.8	109.2	118.1	123.1	126.6	131.9	135.4
14 to 15	87.1	93.1	99.8	107.9	116.8	122.0	125.7	131.4	135.3
15 to 16	89.9	95.4	101.7	109.4	118.0	123.2	126.8	132.6	136.5
16 to 17	91.1	96.5	102.5	109.9	118.3	123.3	126.9	132.5	136.4
17 to 18	92.6	98.2	104.3	111.6	119.6	124.2	127.5	132.5	135.9
18 to 19	91.3	96.8	102.6	109.3	116.3	120.1	122.8	126.8	129.4



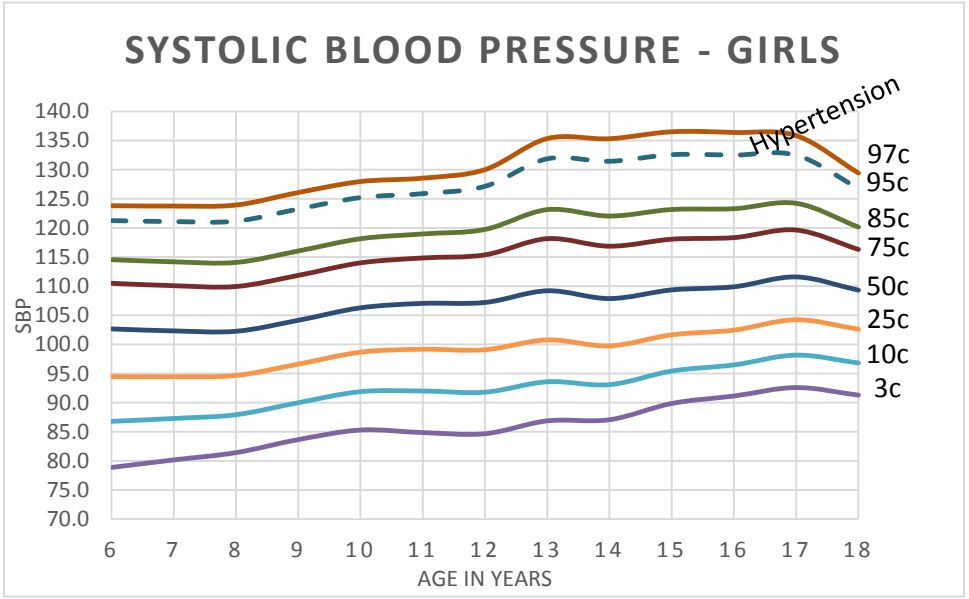
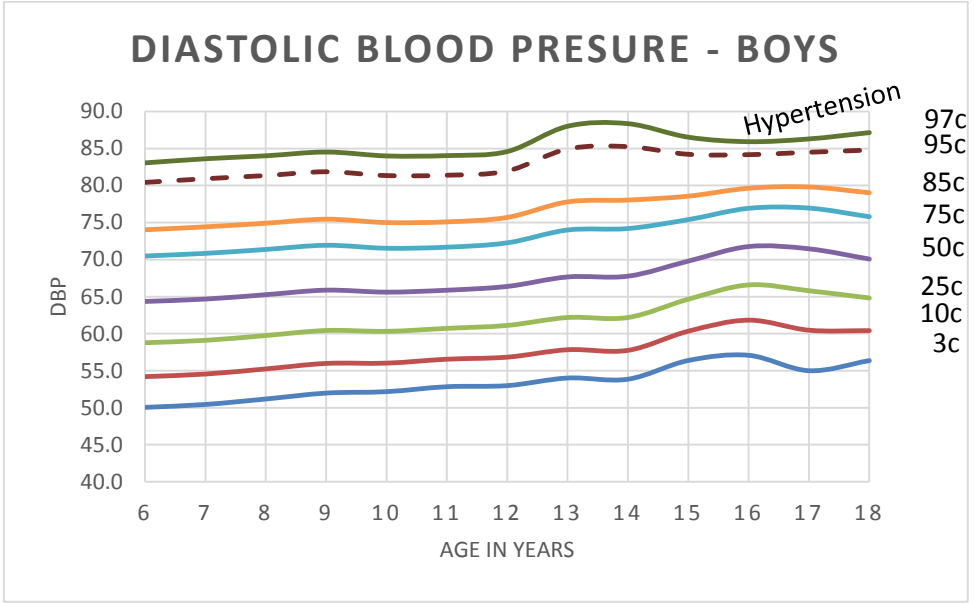


Table 15b. Reference Values and Centile Curves of **DBP**

Age, Y	3C	10C	25C	50C	75C	85C	90C	95C	97C
Boys									
6 to 7	50.1	54.2	58.8	64.4	70.5	74.0	76.6	80.4	83.1
7 to 8	50.5	54.6	59.1	64.7	70.9	74.4	77.0	80.9	83.6
8 to 9	51.2	55.3	59.8	65.3	71.4	74.9	77.5	81.4	84.0
9 to 10	52.0	56.0	60.4	65.9	71.9	75.5	78.0	81.9	84.5
10 to 11	52.2	56.0	60.3	65.6	71.5	75.0	77.5	81.4	84.0
11 to 12	52.8	56.6	60.7	65.9	71.7	75.1	77.6	81.4	84.1
12 to 13	53.0	56.8	61.1	66.4	72.3	75.7	78.2	82.0	84.6
13 to 14	54.0	57.8	62.2	67.7	74.0	77.8	80.6	85.0	88.0
14 to 15	53.9	57.8	62.2	67.8	74.2	78.1	80.8	85.3	88.4
15 to 16	56.4	60.3	64.7	69.8	75.4	78.6	80.8	84.2	86.6
16 to 17	57.1	61.8	66.6	71.8	76.9	79.6	81.5	84.2	85.9
17 to 18	55.0	60.5	65.8	71.5	76.9	79.8	81.7	84.5	86.3
18 to 19	56.4	60.4	64.8	70.1	75.8	79.0	81.3	84.8	87.2
Girls									
6 to 7	50.9	55.5	60.5	66.4	72.7	76.3	78.8	82.6	85.2
7 to 8	51.2	55.6	60.5	66.3	72.6	76.2	78.7	82.6	85.2
8 to 9	51.6	55.8	60.5	66.2	72.5	76.1	78.6	82.5	85.2
9 to 10	52.2	56.3	60.9	66.5	72.6	76.2	78.7	82.6	85.2
10 to 11	52.4	56.6	61.1	66.6	72.6	76.0	78.4	82.1	84.6
11 to 12	52.2	56.6	61.4	67.0	73.0	76.3	78.6	82.2	84.5
12 to 13	52.7	57.5	62.5	68.4	74.6	78.1	80.5	84.1	86.5
13 to 14	54.3	59.1	64.2	70.4	77.0	80.7	83.3	87.3	90.0
14 to 15	55.2	59.6	64.4	70.4	77.1	81.0	83.9	88.3	91.3
15 to 16	56.4	60.5	65.1	70.8	77.2	81.0	83.7	88.0	91.0
16 to 17	57.1	61.1	65.5	71.0	77.3	81.0	83.6	87.8	90.7
17 to 18	57.7	61.8	66.3	71.9	78.0	81.5	84.0	87.9	90.6
18 to 19	57.7	62.3	67.1	72.6	78.1	81.1	83.2	86.2	88.2



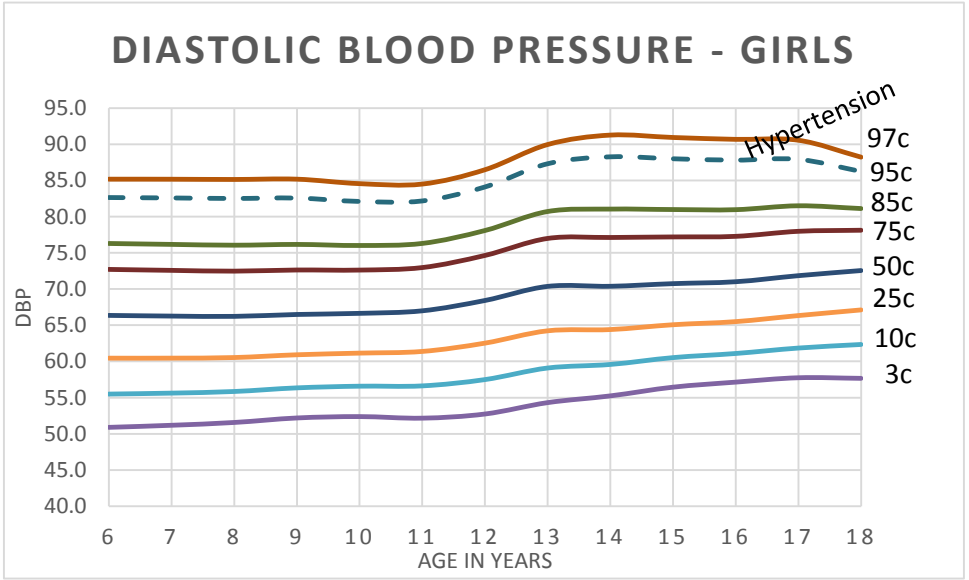
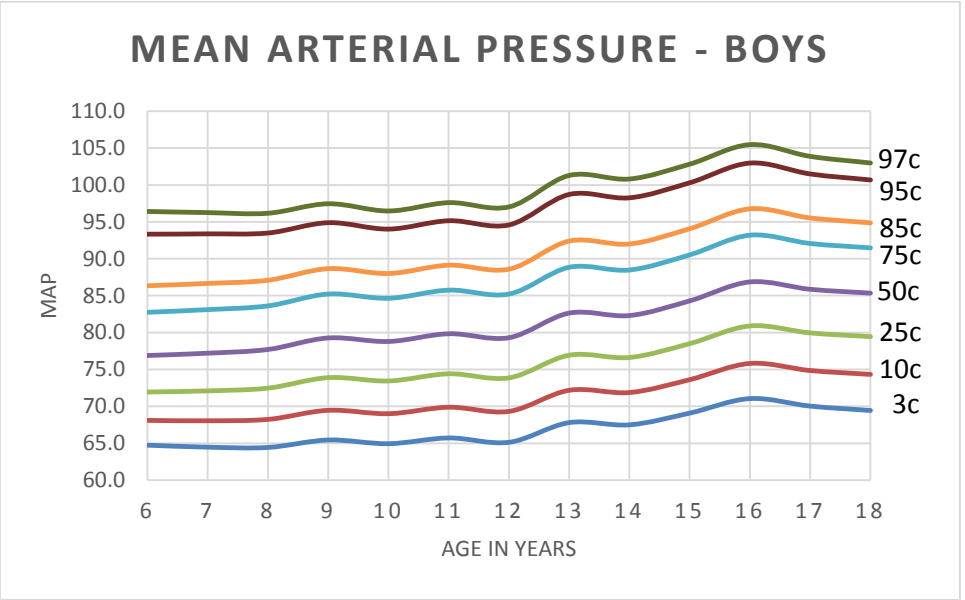


Table 15c. Reference Values and Centile Curves of **MAP**

Age, Y	3C	10C	25C	50C	75C	85C	90C	95C	97C
Boys									
6 to 7	64.7	68.1	71.9	76.9	82.7	86.3	89.0	93.3	96.4
7 to 8	64.5	68.0	72.1	77.2	83.1	86.6	89.2	93.4	96.3
8 to 9	64.4	68.2	72.5	77.7	83.6	87.1	89.6	93.5	96.2
9 to 10	65.4	69.5	73.9	79.3	85.2	88.7	91.1	94.9	97.5
10 to 11	64.9	69.0	73.4	78.8	84.6	88.0	90.4	94.0	96.5
11 to 12	65.7	69.9	74.4	79.8	85.7	89.1	91.5	95.2	97.6
12 to 13	65.1	69.3	73.9	79.3	85.2	88.6	90.9	94.6	97.0
13 to 14	67.8	72.2	76.9	82.6	88.8	92.4	94.9	98.7	101.3
14 to 15	67.5	71.9	76.6	82.3	88.5	92.0	94.5	98.3	100.8
15 to 16	69.1	73.6	78.5	84.3	90.5	94.1	96.5	100.3	102.8
16 to 17	71.0	75.8	80.9	86.9	93.2	96.8	99.2	103.0	105.5
17 to 18	70.0	74.8	79.9	85.9	92.1	95.5	97.9	101.5	103.9
18 to 19	69.4	74.3	79.4	85.4	91.5	94.9	97.2	100.7	103.0
Girls									
6 to 7	60.6	66.7	72.6	78.9	85.0	88.2	90.3	93.4	95.4
7 to 8	61.9	67.0	72.4	78.7	85.1	88.6	91.1	94.7	97.2
8 to 9	61.3	66.2	71.4	77.5	83.8	87.4	89.8	93.5	96.0
9 to 10	64.5	68.8	73.6	79.4	85.7	89.3	91.9	95.8	98.5
10 to 11	65.3	69.7	74.4	79.9	85.7	88.9	91.1	94.5	96.7
11 to 12	64.1	69.3	74.6	80.5	86.3	89.5	91.6	94.8	96.9
12 to 13	64.2	69.6	75.0	81.2	87.4	90.8	93.1	96.5	98.7
13 to 14	67.0	72.1	77.6	84.1	91.1	95.0	97.8	101.9	104.7
14 to 15	66.8	71.2	76.1	82.2	89.1	93.3	96.3	101.0	104.2
15 to 16	69.3	73.4	78.0	83.9	90.5	94.5	97.4	102.0	105.2
16 to 17	69.6	73.7	78.2	83.9	90.3	94.1	96.8	101.1	104.1
17 to 18	70.8	75.0	79.6	85.2	91.4	95.0	97.5	101.5	104.1
18 to 19	70.4	74.7	79.3	84.6	90.3	93.5	95.7	99.0	101.2



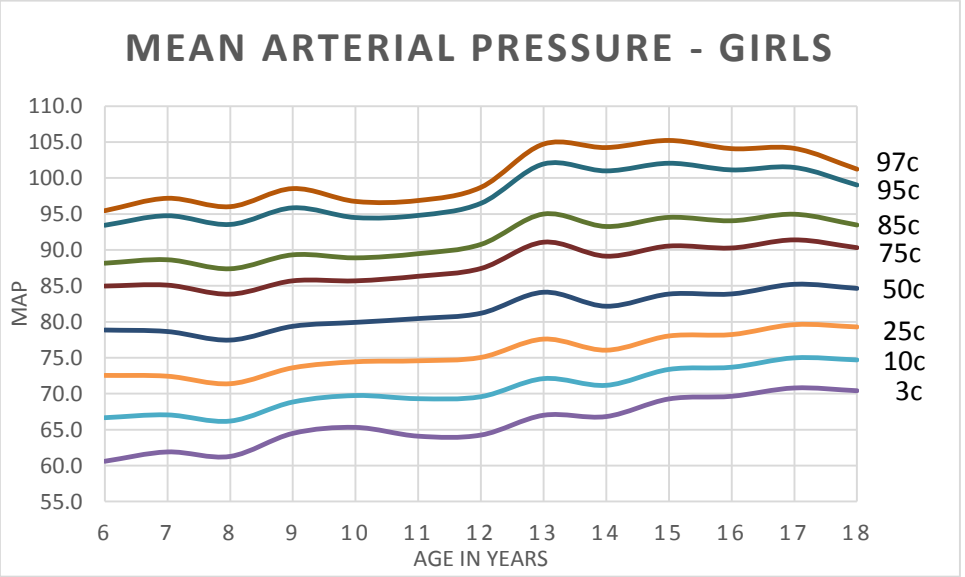
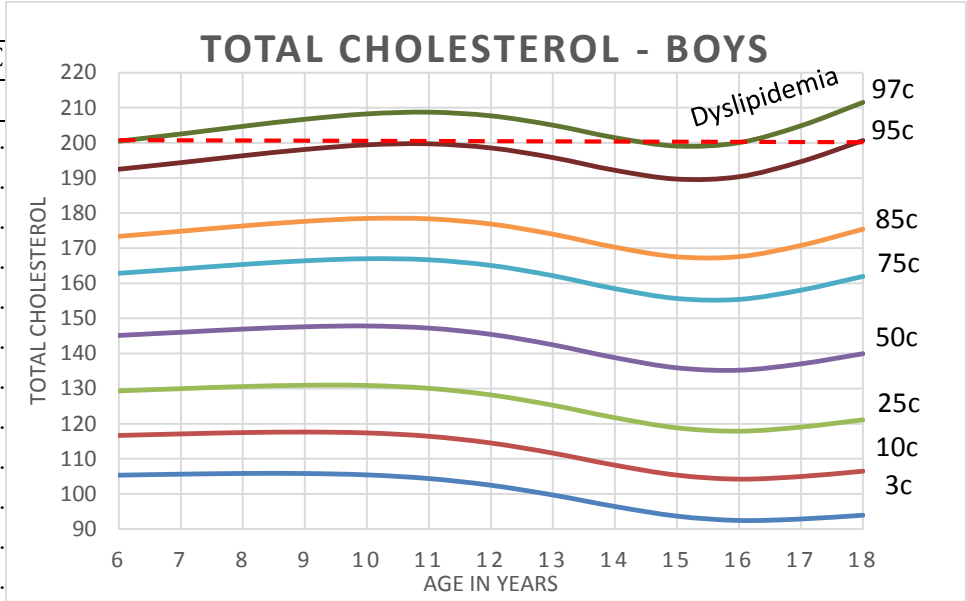


Table 16a. Reference Values and Centile Curves of Total Cholesterol

Age, Y	3C	10C	25C	50C	75C	85C	90C	95C	97C
Boys									
6 to 7	105.4	116.6	129.3	145.1	162.9	173.3	180.8	192.5	200.
7 to 8	105.6	117.1	129.9	146.0	164.1	174.8	182.4	194.4	202.
8 to 9	105.8	117.4	130.5	146.9	165.4	176.3	184.1	196.3	204.
9 to 10	105.8	117.6	130.9	147.6	166.4	177.6	185.6	198.1	206.
10 to 11	105.4	117.3	130.9	147.8	167.0	178.4	186.6	199.4	208.
11 to 12	104.4	116.4	130.0	147.2	166.7	178.3	186.6	199.7	208.
12 to 13	102.5	114.5	128.2	145.4	165.1	176.8	185.3	198.6	207.
13 to 14	99.7	111.6	125.2	142.4	162.2	173.9	182.4	195.8	205.
14 to 15	96.4	108.2	121.7	138.8	158.5	170.3	178.8	192.2	201.
15 to 16	93.7	105.4	118.8	135.9	155.7	167.5	176.1	189.7	199.
16 to 17	92.5	104.2	117.8	135.2	155.4	167.6	176.4	190.4	200.
17 to 18	92.9	105.0	119.0	137.0	158.1	170.8	180.0	194.7	204.
18 to 19	94.0	106.5	121.1	139.9	162.0	175.4	185.1	200.7	211.6
Girls									
6 to 7	116.3	132.3	147.8	164.4	180.4	188.8	194.4	202.5	207.
7 to 8	105.8	119.2	133.5	150.4	168.3	178.3	185.2	195.8	202.
8 to 9	104.9	117.1	131.1	148.7	168.8	180.8	189.5	203.1	212.
9 to 10	104.3	116.0	129.5	147.0	167.4	179.8	188.9	203.4	213.
10 to 11	102.9	115.0	128.6	145.6	164.8	176.2	184.3	197.0	205.
11 to 12	102.0	114.2	127.9	144.9	163.8	174.9	182.7	195.0	203.
12 to 13	102.9	115.3	129.3	146.8	166.5	178.1	186.5	199.5	208.
13 to 14	100.7	113.1	127.2	144.9	165.0	176.8	185.3	198.7	207.
14 to 15	99.9	112.3	126.5	144.7	165.7	178.3	187.5	202.0	212.
15 to 16	103.0	114.9	128.9	147.3	169.2	182.7	192.7	208.9	220.
16 to 17	102.5	114.0	127.5	145.2	166.5	179.8	189.6	205.6	217.
17 to 18	102.1	114.1	128.2	146.6	168.3	181.7	191.5	207.3	218.
18 to 19	99.5	113.0	128.4	148.0	170.5	183.9	193.6	208.9	219.



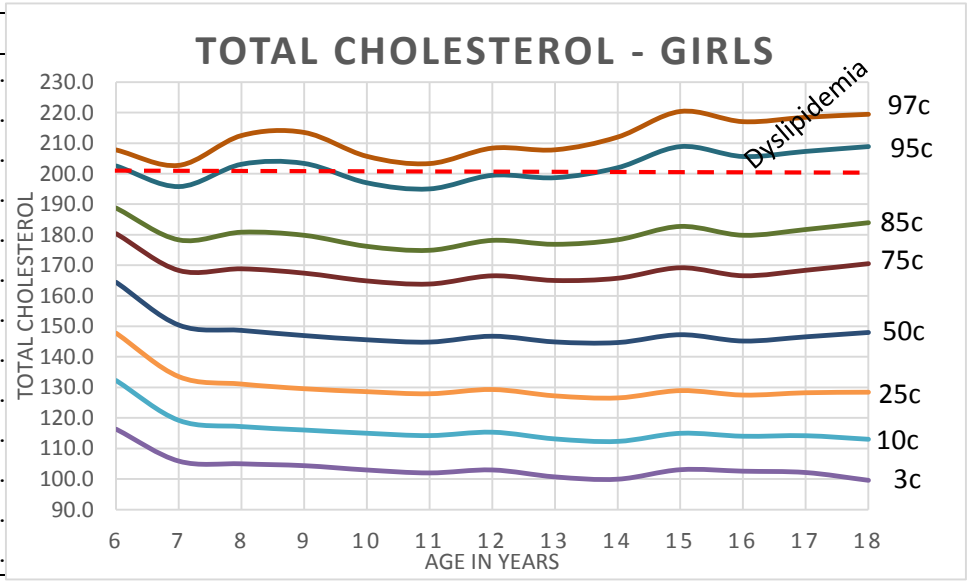
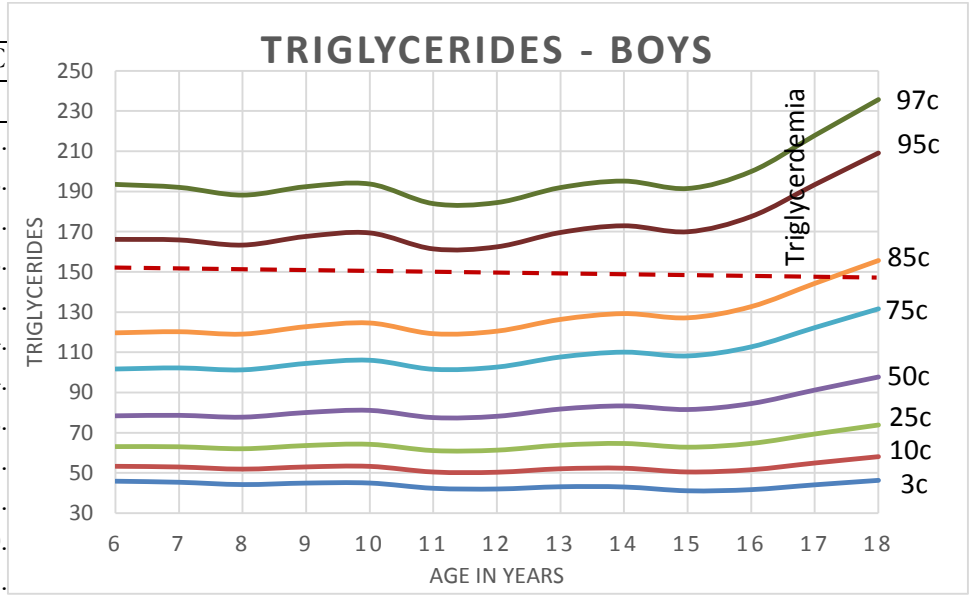


Table 16b. Reference Values and Centile Curves of **Triglycerides**

Age, Y	3C	10C	25C	50C	75C	85C	90C	95C	97C
Boys									
6 to 7	45.9	53.3	63.1	78.4	101.7	119.7	135.3	166.2	193.
7 to 8	45.4	52.9	63.0	78.7	102.2	120.2	135.7	165.9	192.
8 to 9	44.2	51.9	62.0	77.8	101.3	119.1	134.2	163.3	188.
9 to 10	45.0	53.0	63.6	80.1	104.4	122.8	138.3	167.6	192.
10 to 11	45.0	53.2	64.2	81.1	106.0	124.6	140.1	169.4	193.
11 to 12	42.4	50.4	61.1	77.5	101.5	119.2	134.0	161.4	184.
12 to 13	42.0	50.3	61.4	78.2	102.6	120.5	135.3	162.5	184.
13 to 14	43.1	52.0	63.8	81.8	107.7	126.4	141.7	169.6	192.
14 to 15	43.0	52.3	64.6	83.4	110.1	129.2	144.8	172.9	195.
15 to 16	41.1	50.4	62.8	81.6	108.2	127.2	142.5	170.0	191.
16 to 17	41.7	51.6	64.7	84.5	112.7	132.7	148.9	177.6	200.
17 to 18	44.1	54.9	69.3	91.2	122.3	144.3	162.0	193.5	217.
18 to 19	46.3	58.0	73.8	97.7	131.6	155.7	175.0	209.2	235.
Girls									
6 to 7	48.9	58.3	70.3	87.3	109.7	124.6	136.2	155.8	170.
7 to 8	46.8	55.3	66.3	82.7	105.4	121.5	134.4	157.4	175.
8 to 9	46.1	54.4	65.3	81.8	105.6	122.9	137.3	163.7	185.
9 to 10	46.1	54.6	65.8	82.8	107.6	125.8	141.0	169.0	192.
10 to 11	47.3	56.4	68.1	85.7	110.2	127.5	141.4	166.2	185.
11 to 12	48.2	57.6	69.6	87.2	110.9	127.2	139.9	162.0	178.
12 to 13	49.4	59.0	71.5	89.6	114.2	131.1	144.4	167.6	185.
13 to 14	48.7	58.3	70.8	89.1	114.2	131.5	145.2	169.2	187.
14 to 15	47.4	57.0	69.6	88.0	113.2	130.6	144.5	168.6	187.
15 to 16	48.2	57.7	70.1	88.7	114.8	133.2	148.0	174.5	195.
16 to 17	48.3	57.5	69.5	87.8	114.2	133.4	149.2	178.3	201.
17 to 18	47.8	56.5	68.1	86.0	112.4	132.1	148.7	180.1	206.
18 to 19	47.0	55.4	66.7	84.2	110.6	130.8	148.1	181.5	210.2



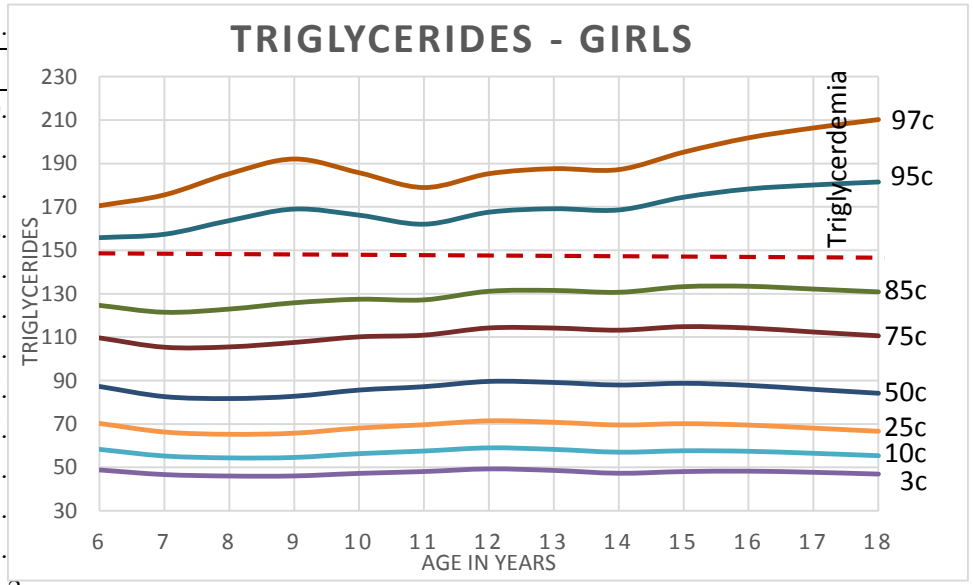
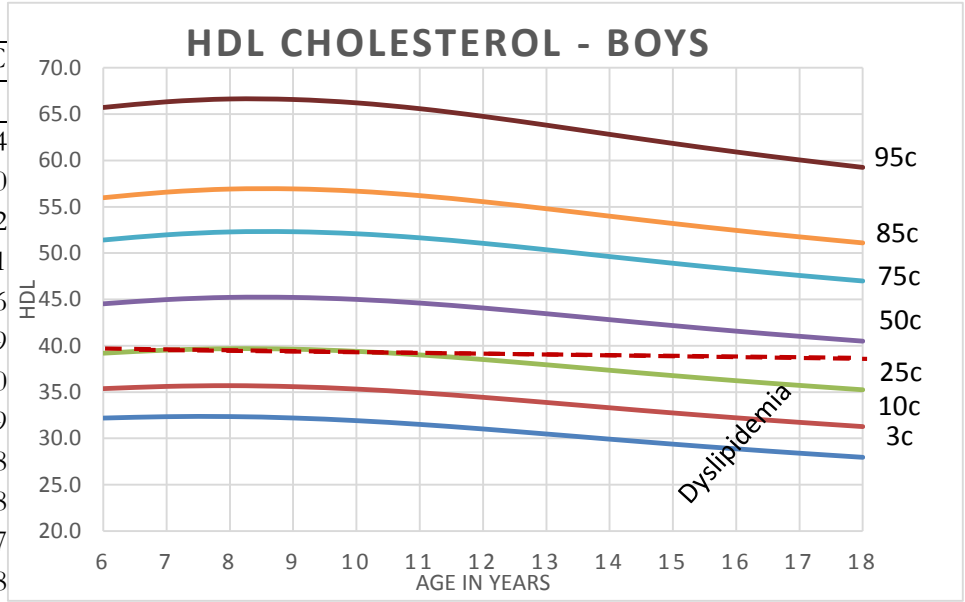


Table 16c. Reference Values and Centile Curves of **low HDL levels**

Age, Y	3C	10C	25C	50C	75C	85C	90C	95C	97C
Boys									
6 to 7	32.2	35.4	39.2	44.5	51.4	56.0	59.6	65.7	70.4
7 to 8	32.4	35.6	39.5	45.0	52.0	56.6	60.2	66.3	71.0
8 to 9	32.4	35.7	39.7	45.2	52.3	56.9	60.5	66.6	71.2
9 to 10	32.2	35.6	39.6	45.2	52.3	57.0	60.5	66.6	71.1
10 to 11	31.9	35.3	39.4	45.0	52.1	56.7	60.2	66.2	70.6
11 to 12	31.5	34.9	39.0	44.6	51.7	56.2	59.7	65.6	69.9
12 to 13	31.0	34.4	38.5	44.1	51.1	55.6	59.0	64.8	69.0
13 to 14	30.5	33.9	37.9	43.5	50.4	54.8	58.2	63.8	67.9
14 to 15	29.9	33.3	37.4	42.8	49.6	54.0	57.3	62.8	66.8
15 to 16	29.4	32.7	36.8	42.2	48.9	53.2	56.4	61.8	65.8
16 to 17	28.9	32.2	36.2	41.6	48.2	52.5	55.6	60.9	64.7
17 to 18	28.4	31.7	35.7	41.0	47.6	51.8	54.9	60.1	63.8
18 to 19	28.0	31.3	35.2	40.5	47.0	51.1	54.2	59.3	62.9
Girls									
6 to 7	29.7	32.7	36.4	41.5	48.3	52.8	56.4	62.6	67.3
7 to 8	31.5	34.9	38.9	44.2	50.6	54.6	57.6	62.5	66.0
8 to 9	32.5	36.2	40.4	45.8	52.1	56.0	58.8	63.3	66.5
9 to 10	31.8	35.4	39.7	45.2	51.7	55.7	58.6	63.3	66.6
10 to 11	31.4	34.9	39.1	44.6	51.3	55.5	58.6	63.7	67.4
11 to 12	31.5	34.9	39.0	44.4	51.2	55.5	58.8	64.2	68.1
12 to 13	31.7	35.0	39.0	44.4	51.1	55.3	58.6	64.0	67.9
13 to 14	31.8	35.1	39.0	44.3	50.8	55.0	58.1	63.3	67.0
14 to 15	31.7	35.0	38.9	44.1	50.5	54.6	57.6	62.7	66.4
15 to 16	31.2	34.5	38.4	43.6	50.0	54.1	57.2	62.3	65.9
16 to 17	30.7	34.0	38.0	43.3	49.9	54.0	57.1	62.3	66.1
17 to 18	30.7	34.1	38.3	43.8	50.7	55.1	58.4	63.9	67.9
18 to 19	31.2	34.8	39.2	45.2	52.6	57.4	61.0	67.1	71.5



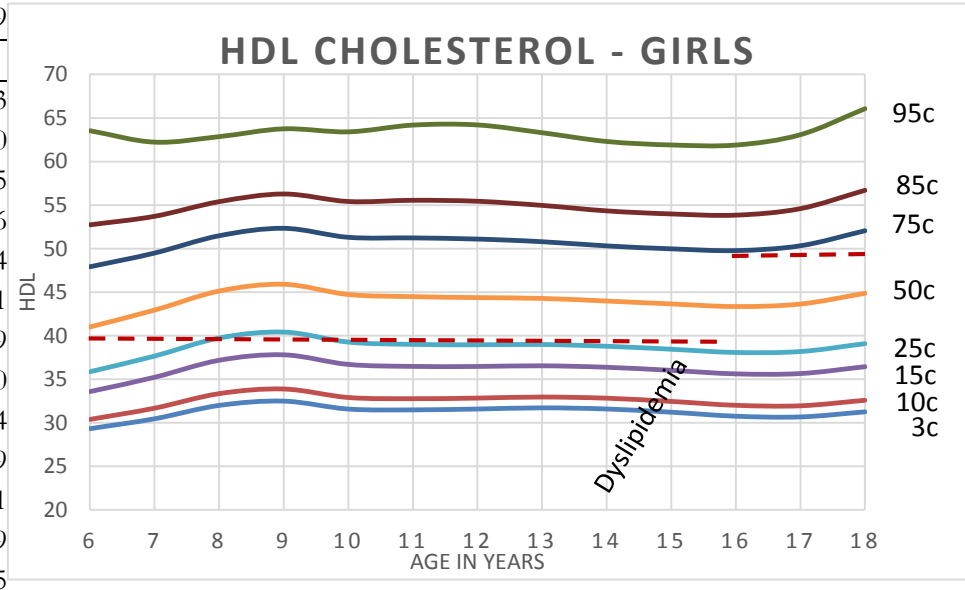
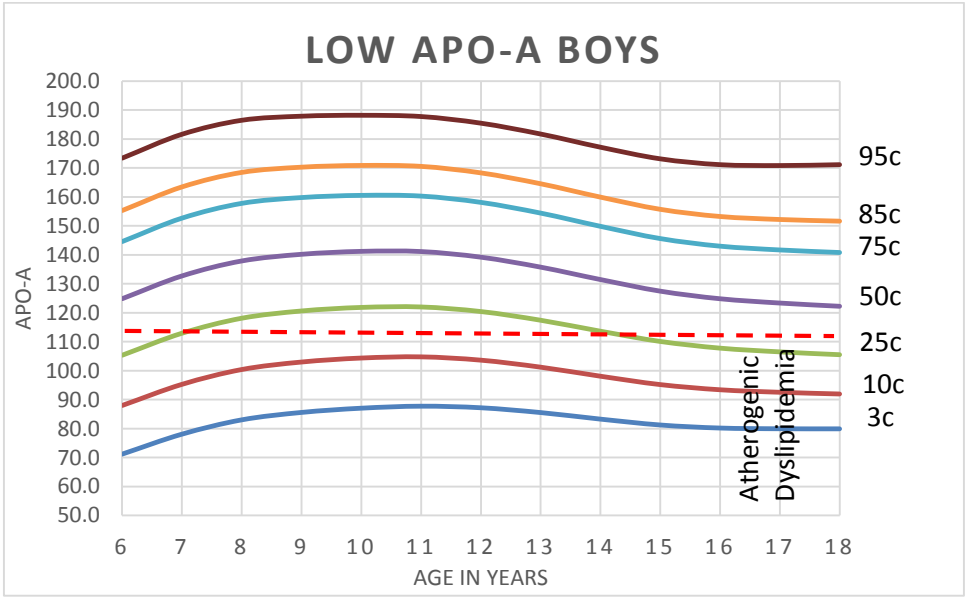


Table 17a. Reference Values and Centile Curves of **Apo-A proteins**

Age, Y	3C	10C	25C	50C	75C	85C	90C	95C	97C
Boys									
6 to 7	71.2	88.0	105.3	124.8	144.6	155.3	162.5	173.4	180.4
7 to 8	78.1	95.3	112.9	132.7	152.7	163.4	170.8	181.6	188.7
8 to 9	83.0	100.4	118.1	137.9	157.8	168.5	175.7	186.5	193.5
9 to 10	85.6	103.0	120.6	140.2	159.8	170.3	177.4	187.9	194.8
10 to 11	87.1	104.4	121.9	141.2	160.5	170.9	177.9	188.2	194.9
11 to 12	87.8	104.8	122.0	141.2	160.3	170.5	177.5	187.8	194.5
12 to 13	87.2	103.7	120.4	139.2	158.1	168.3	175.2	185.5	192.2
13 to 14	85.6	101.2	117.4	135.8	154.4	164.5	171.4	181.7	188.5
14 to 15	83.3	98.1	113.6	131.5	149.8	159.9	166.8	177.2	184.0
15 to 16	81.3	95.2	110.1	127.5	145.6	155.7	162.7	173.1	180.1
16 to 17	80.2	93.5	107.8	124.8	143.0	153.2	160.3	171.1	178.3
17 to 18	80.0	92.6	106.5	123.3	141.7	152.2	159.5	170.8	178.4
18 to 19	79.9	92.0	105.5	122.2	140.8	151.6	159.3	171.1	179.2
Girls									
6 to 7	79.3	92.7	107.0	123.6	140.9	150.4	157.0	166.9	173.4
7 to 8	87.6	102.6	118.4	136.8	156.0	166.6	173.8	184.8	192.1
8 to 9	85.0	99.5	114.9	132.8	151.5	161.8	168.9	179.6	186.6
9 to 10	87.4	102.4	118.3	136.8	156.1	166.7	174.1	185.1	192.4
10 to 11	86.4	101.3	117.1	135.5	154.6	165.2	172.5	183.5	190.7
11 to 12	85.6	100.5	116.3	134.6	153.6	164.2	171.5	182.4	189.6
12 to 13	82.3	96.6	111.8	129.5	148.0	158.1	165.2	175.7	182.7
13 to 14	84.9	99.8	115.6	134.0	153.1	163.7	171.0	182.0	189.2
14 to 15	81.9	96.3	111.7	129.5	148.1	158.4	165.5	176.1	183.2
15 to 16	83.9	98.8	114.6	133.0	152.2	162.8	170.2	181.2	188.4
16 to 17	83.2	98.1	113.9	132.4	151.6	162.2	169.5	180.5	187.8
17 to 18	78.0	92.1	107.1	124.5	142.7	152.7	159.6	170.1	176.9
18 to 19	79.1	93.5	108.7	126.5	145.1	155.4	162.5	173.1	180.2



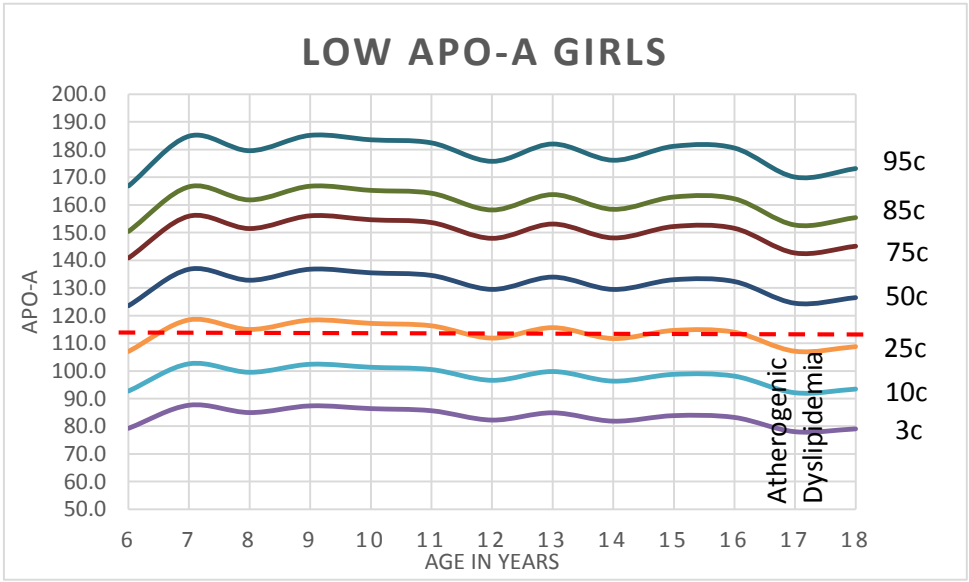
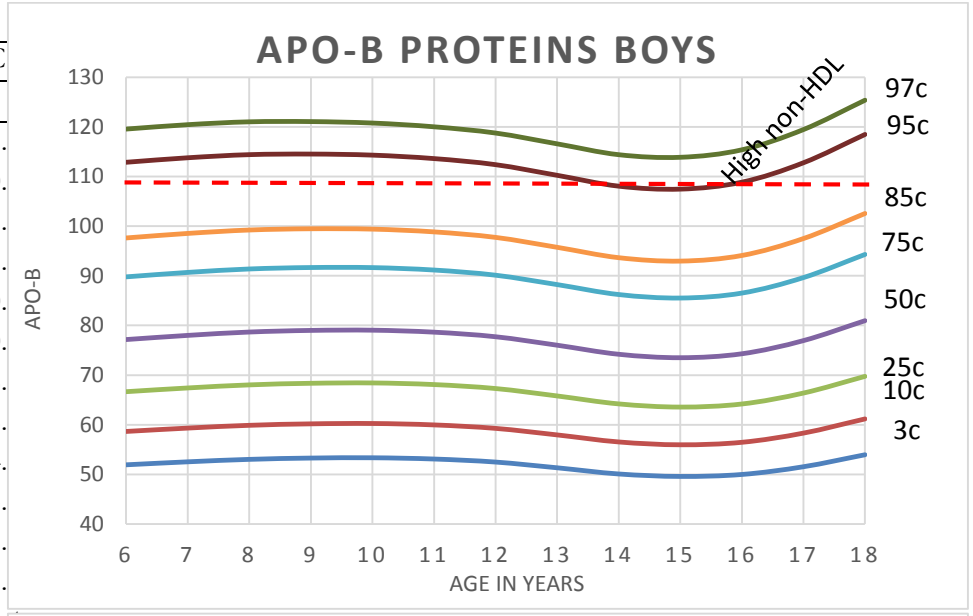


Table 17b. Reference Values and Centile Curves of **Apo-B proteins**

Age, Y	3C	10C	25C	50C	75C	85C	90C	95C	97C
Boys									
6 to 7	51.9	58.7	66.6	77.1	89.8	97.6	103.4	112.8	119.
7 to 8	52.5	59.3	67.4	78.0	90.7	98.5	104.4	113.8	120.
8 to 9	53.0	59.9	68.0	78.7	91.4	99.2	105.0	114.4	121.
9 to 10	53.3	60.2	68.3	79.0	91.7	99.5	105.2	114.5	121.
10 to 11	53.3	60.3	68.4	79.0	91.7	99.4	105.1	114.3	120.
11 to 12	53.1	60.0	68.1	78.6	91.2	98.9	104.5	113.6	120.
12 to 13	52.5	59.3	67.3	77.7	90.1	97.7	103.3	112.4	118.
13 to 14	51.3	58.0	65.8	76.0	88.2	95.7	101.3	110.2	116.
14 to 15	50.1	56.6	64.2	74.2	86.2	93.7	99.1	108.0	114.
15 to 16	49.6	56.0	63.5	73.5	85.5	93.0	98.5	107.5	113.
16 to 17	50.0	56.5	64.2	74.3	86.5	94.1	99.7	108.9	115.
17 to 18	51.5	58.3	66.4	76.9	89.6	97.5	103.3	112.8	119.
18 to 19	53.9	61.2	69.7	80.9	94.3	102.6	108.6	118.4	125.
Girls									
6 to 7	55.2	63.2	71.9	82.3	93.5	99.9	104.4	111.2	115.
7 to 8	54.5	62.3	71.1	82.1	94.5	101.7	106.9	114.9	120.
8 to 9	53.0	60.3	68.8	79.8	92.7	100.6	106.4	115.5	122.
9 to 10	53.3	60.3	68.6	79.6	93.0	101.5	107.8	118.0	125.
10 to 11	51.9	58.5	66.4	77.1	90.2	98.5	104.8	115.1	122.
11 to 12	51.8	58.3	66.2	76.8	89.9	98.2	104.5	114.9	122.
12 to 13	51.7	58.2	66.0	76.5	89.7	98.2	104.5	115.2	122.
13 to 14	51.7	58.2	66.0	76.6	90.1	98.8	105.4	116.5	124.
14 to 15	53.2	59.8	67.9	79.0	93.1	102.3	109.4	121.3	130.
15 to 16	53.4	60.1	68.3	79.5	93.8	103.2	110.4	122.6	131.
16 to 17	53.2	59.9	68.1	79.3	93.5	102.7	109.8	121.6	130.
17 to 18	52.9	59.7	67.9	79.1	93.0	102.0	108.7	120.0	128.
18 to 19	53.9	60.9	69.3	80.6	94.5	103.3	109.9	120.7	128.



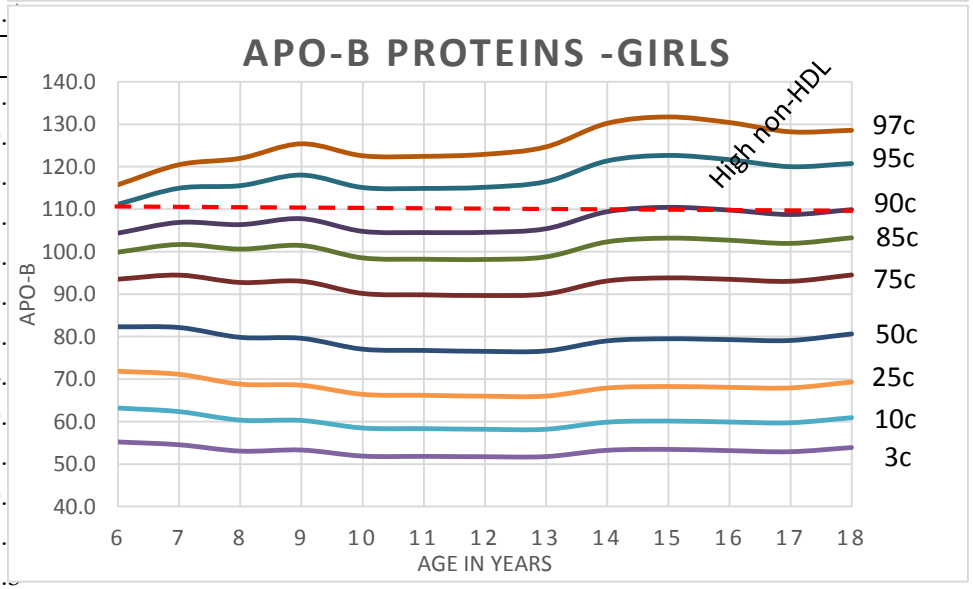
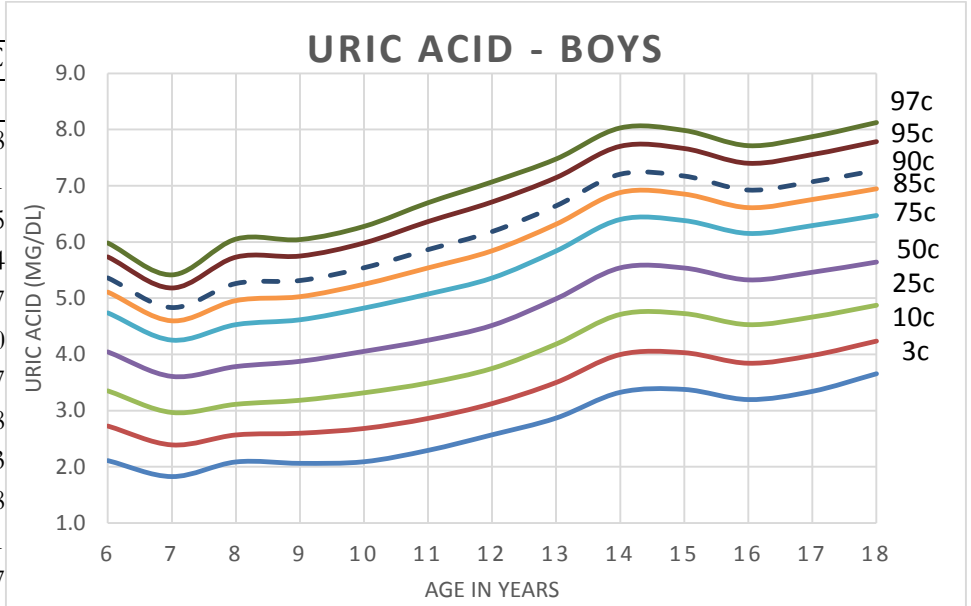


Table 18. Reference Values and Centile Curves of **Uric Acid levels**

Age, Y	3C	10C	25C	50C	75C	85C	90C	95C	97C
Boys									
6 to 7	2.11	2.73	3.35	4.04	4.74	5.11	5.36	5.74	5.98
7 to 8	1.83	2.39	2.96	3.61	4.25	4.60	4.83	5.18	5.41
8 to 9	2.09	2.57	3.11	3.78	4.53	4.96	5.26	5.73	6.05
9 to 10	2.06	2.60	3.18	3.88	4.61	5.03	5.32	5.75	6.04
10 to 11	2.09	2.68	3.32	4.05	4.82	5.25	5.54	5.98	6.27
11 to 12	2.29	2.86	3.49	4.25	5.07	5.54	5.87	6.36	6.70
12 to 13	2.57	3.13	3.75	4.51	5.36	5.84	6.19	6.71	7.07
13 to 14	2.87	3.50	4.18	4.99	5.84	6.32	6.65	7.14	7.48
14 to 15	3.33	4.00	4.71	5.54	6.40	6.88	7.21	7.70	8.03
15 to 16	3.38	4.03	4.73	5.53	6.38	6.85	7.17	7.66	7.98
16 to 17	3.20	3.84	4.53	5.32	6.15	6.61	6.93	7.40	7.71
17 to 18	3.34	3.98	4.66	5.46	6.29	6.75	7.07	7.56	7.87
18 to 19	3.66	4.24	4.87	5.64	6.47	6.94	7.28	7.78	8.12
Girls									
6 to 7	1.94	2.51	3.11	3.80	4.51	4.89	5.16	5.56	5.82
7 to 8	2.05	2.58	3.16	3.86	4.60	5.02	5.32	5.76	6.05
8 to 9	2.10	2.58	3.12	3.80	4.56	5.00	5.31	5.79	6.12
9 to 10	2.21	2.68	3.22	3.92	4.71	5.17	5.51	6.03	6.39
10 to 11	2.34	2.82	3.37	4.07	4.87	5.34	5.68	6.21	6.58
11 to 12	2.41	2.88	3.43	4.13	4.91	5.38	5.71	6.23	6.58
12 to 13	2.41	2.88	3.43	4.11	4.87	5.32	5.64	6.14	6.48
13 to 14	2.38	2.88	3.44	4.13	4.90	5.34	5.66	6.14	6.47
14 to 15	2.33	2.86	3.46	4.18	4.97	5.42	5.74	6.23	6.55
15 to 16	2.27	2.83	3.44	4.19	5.00	5.45	5.77	6.26	6.58
16 to 17	2.24	2.80	3.42	4.17	4.99	5.45	5.77	6.27	6.60
17 to 18	2.20	2.75	3.37	4.12	4.94	5.41	5.75	6.25	6.60
18 to 19	2.14	2.67	3.28	4.02	4.85	5.33	5.67	6.20	6.55



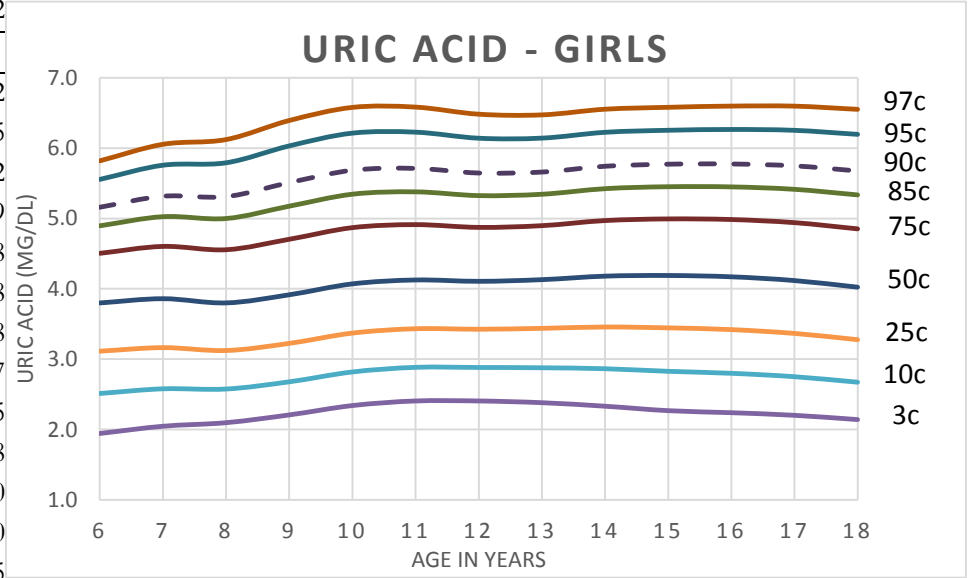
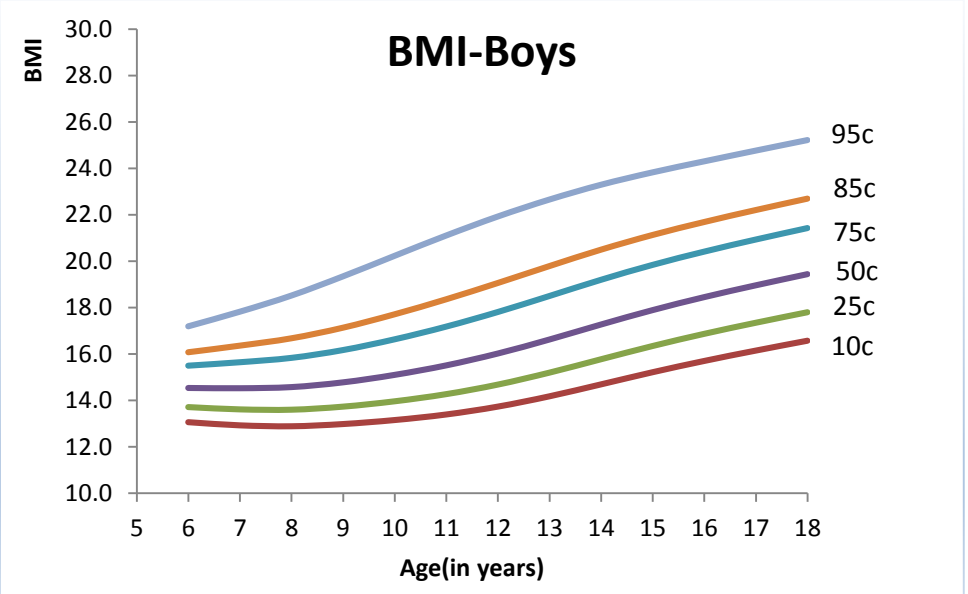


Table 19a: Reference values and centile curves for body mass index (BMI)

Age, Y	10C	25C	50C	75C	85C	90C	95C
Boys							
6 to 7	13.1	13.7	14.5	15.5	16.1	16.5	17.2
7 to 8	12.9	13.6	14.5	15.7	16.4	16.9	17.8
8 to 9	12.9	13.6	14.6	15.8	16.7	17.3	18.5
9 to 10	13.0	13.7	14.8	16.2	17.1	17.9	19.3
10 to 11	13.1	14.0	15.1	16.6	17.7	18.6	20.2
11 to 12	13.4	14.3	15.5	17.2	18.4	19.3	21.1
12 to 13	13.7	14.7	16.0	17.8	19.1	20.1	21.9
13 to 14	14.2	15.2	16.6	18.5	19.8	20.8	22.7
14 to 15	14.7	15.8	17.3	19.2	20.5	21.5	23.3
15 to 16	15.2	16.3	17.9	19.8	21.1	22.1	23.8
16 to 17	15.7	16.9	18.5	20.4	21.7	22.7	24.3
17 to 18	16.1	17.4	19.0	20.9	22.2	23.2	24.8
18 to 19	16.6	17.8	19.4	21.4	22.7	23.6	25.2
Girls							
6 to 7	12.9	13.5	14.3	15.3	16.0	16.5	17.3
7 to 8	12.7	13.4	14.4	15.6	16.4	17.0	18.1
8 to 9	12.7	13.5	14.6	15.9	16.9	17.6	18.9
9 to 10	12.9	13.7	14.9	16.4	17.5	18.3	19.7
10 to 11	13.1	14.1	15.4	17.1	18.2	19.1	20.6
11 to 12	13.6	14.6	16.0	17.9	19.1	20.0	21.6
12 to 13	14.1	15.2	16.8	18.7	20.0	21.0	22.7
13 to 14	14.7	15.9	17.5	19.6	20.9	22.0	23.8
14 to 15	15.3	16.5	18.2	20.4	21.8	22.9	24.7
15 to 16	15.7	17.0	18.8	21.0	22.4	23.5	25.4
16 to 17	16.1	17.4	19.2	21.4	22.8	23.9	25.8
17 to 18	16.3	17.7	19.4	21.7	23.1	24.2	26.1
18 to 19	16.6	17.9	19.7	21.9	23.4	24.5	26.4



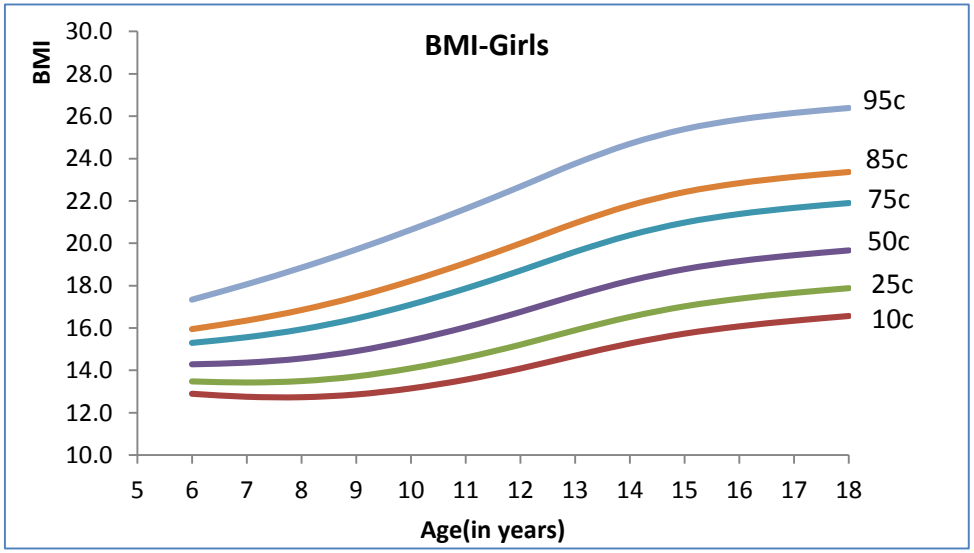
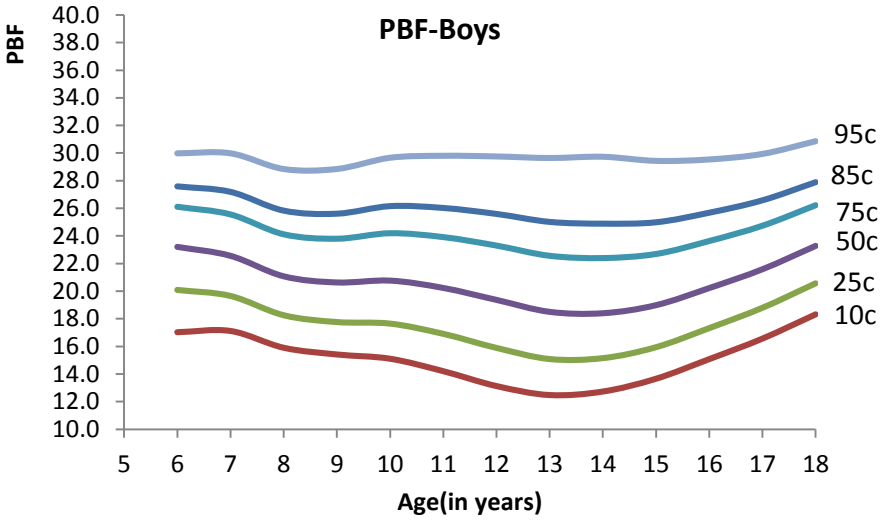


Table 19b: Reference values and centile curves of percent body fat

Age, Y	10C	25C	50C	75C	85C	90C	95C
Boys							
6 to 7	17.0	20.1	23.2	26.1	27.6	28.6	30.0
7 to 8	17.1	19.7	22.6	25.6	27.2	28.3	30.0
8 to 9	15.9	18.3	21.1	24.1	25.8	27.0	28.8
9 to 10	15.4	17.8	20.6	23.8	25.6	26.9	28.8
10 to 11	15.1	17.7	20.8	24.2	26.2	27.5	29.7
11 to 12	14.2	16.9	20.2	23.9	26.0	27.5	29.8
12 to 13	13.1	15.9	19.4	23.3	25.6	27.2	29.8
13 to 14	12.5	15.1	18.5	22.6	25.0	26.8	29.6
14 to 15	12.7	15.2	18.4	22.4	24.9	26.7	29.7
15 to 16	13.7	16.0	19.0	22.7	25.0	26.7	29.4
16 to 17	15.1	17.3	20.2	23.6	25.7	27.2	29.5
17 to 18	16.6	18.8	21.6	24.7	26.6	27.9	29.9
18 to 19	18.3	20.6	23.3	26.2	27.9	29.1	30.9
Girls							
6 to 7	19.5	22.4	25.6	28.8	30.6	31.7	33.5
7 to 8	18.0	20.9	24.1	27.5	29.3	30.6	32.5
8 to 9	16.9	19.8	23.2	26.7	28.6	29.9	31.9
9 to 10	16.2	19.2	22.6	26.2	28.2	29.6	31.6
10 to 11	16.0	19.0	22.5	26.1	28.0	29.4	31.4
11 to 12	16.3	19.3	22.7	26.3	28.2	29.6	31.6
12 to 13	17.4	20.3	23.7	27.2	29.1	30.4	32.3
13 to 14	19.1	22.0	25.4	28.8	30.7	32.0	33.9
14 to 15	20.9	23.8	27.2	30.5	32.3	33.5	35.3
15 to 16	22.5	25.4	28.6	31.8	33.5	34.7	36.4
16 to 17	23.9	26.7	29.8	32.8	34.4	35.4	37.0
17 to 18	25.0	27.7	30.7	33.5	35.0	36.0	37.5
18 to 19	26.0	28.6	31.4	34.1	35.5	36.4	37.8



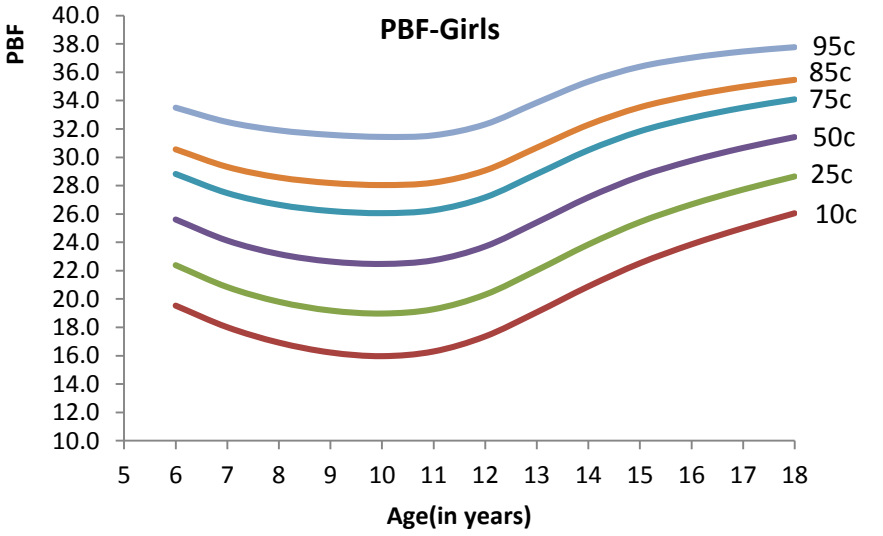
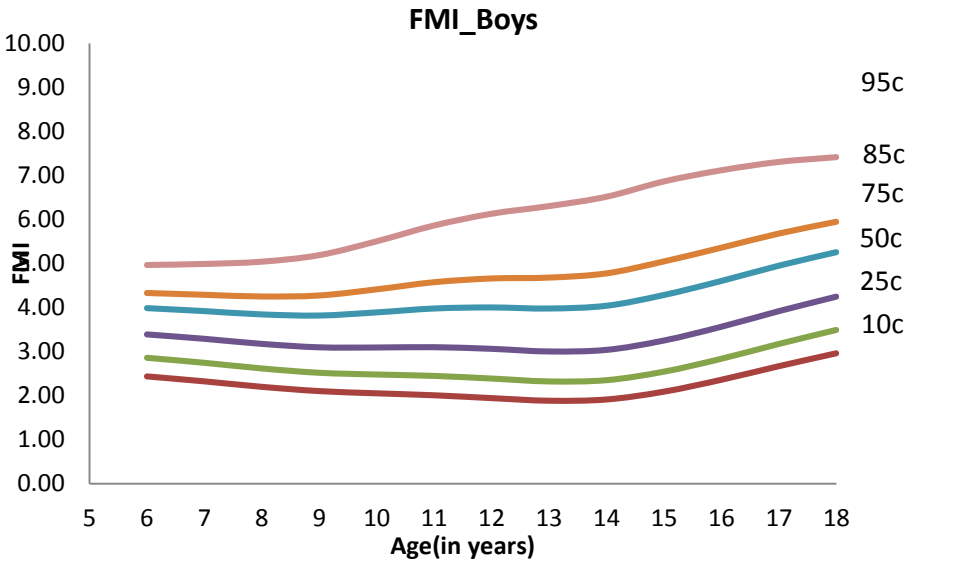
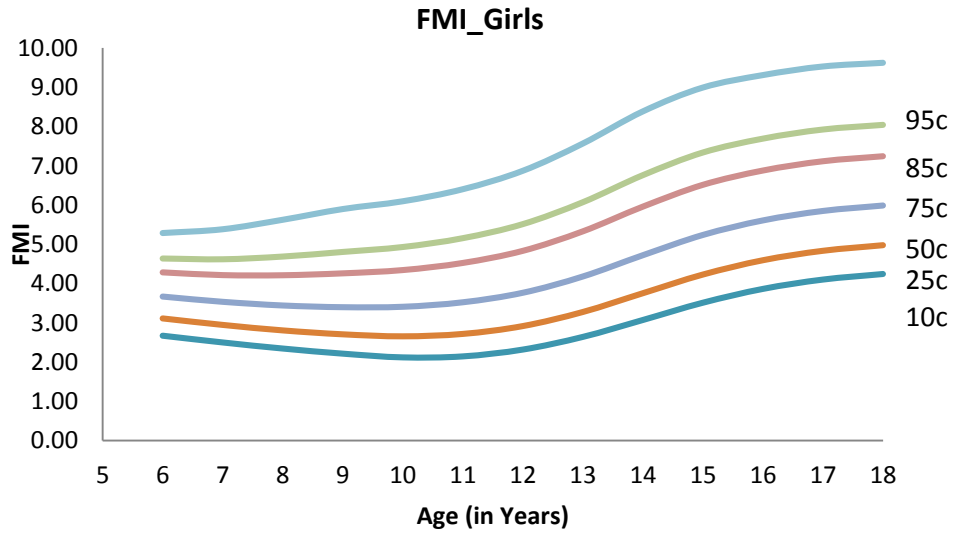


Table 19c. Reference values and centile curves of fat mass index

Age, Y	10C	25C	50C	75C	85C	90C	95C
Boys							
6 to 7	2.44	2.86	3.39	3.99	4.33	4.58	4.97
7 to 8	2.32	2.75	3.29	3.92	4.29	4.56	4.99
8 to 9	2.20	2.62	3.17	3.84	4.25	4.56	5.04
9 to 10	2.10	2.52	3.10	3.82	4.28	4.62	5.19
10 to 11	2.05	2.48	3.09	3.89	4.42	4.82	5.51
11 to 12	2.00	2.45	3.10	3.98	4.58	5.05	5.86
12 to 13	1.94	2.39	3.06	4.00	4.66	5.19	6.13
13 to 14	1.88	2.32	3.00	3.98	4.68	5.26	6.30
14 to 15	1.91	2.35	3.04	4.04	4.78	5.39	6.52
15 to 16	2.09	2.55	3.25	4.28	5.05	5.68	6.87
16 to 17	2.36	2.84	3.56	4.60	5.36	5.98	7.12
17 to 18	2.67	3.17	3.92	4.95	5.68	6.26	7.31
18 to 19	2.96	3.49	4.25	5.26	5.95	6.48	7.42
Girls							
6 to 7	2.67	3.11	3.67	4.28	4.64	4.90	5.29
7 to 8	2.50	2.95	3.53	4.21	4.62	4.92	5.39
8 to 9	2.34	2.81	3.44	4.21	4.69	5.05	5.63
9 to 10	2.21	2.71	3.39	4.26	4.81	5.22	5.90
10 to 11	2.12	2.66	3.41	4.34	4.93	5.38	6.10
11 to 12	2.14	2.72	3.52	4.52	5.16	5.63	6.41
12 to 13	2.32	2.92	3.76	4.83	5.52	6.03	6.88
13 to 14	2.64	3.28	4.18	5.33	6.07	6.64	7.57
14 to 15	3.07	3.76	4.72	5.96	6.76	7.37	8.39
15 to 16	3.51	4.23	5.24	6.51	7.34	7.96	9.00
16 to 17	3.86	4.60	5.61	6.88	7.69	8.30	9.31
17 to 18	4.10	4.84	5.85	7.11	7.92	8.53	9.53
18 to 19	4.24	4.98	5.99	7.24	8.04	8.64	9.63





Study 3 - Clustering of Bio-chemical Markers of Cardio-metabolic Risk among Indian Children: An Imperative for Continuous Monitoring of Risk Factor

4.5. Materials and Methods for study-3:

Metabolic syndrome has been studied among Indian children and most of them have looked independently at bio-chemical and clinical markers of dyslipidemia, hyperglycemia, hypertension and inflammation along with anthropological markers like high waist circumference, BMI etc. Very few of them have used a unifying approach to link CMR markers with measures of adiposity (fat depots). In this context, we have looked at clustering pattern of various clinical and bio-chemical markers of cardio-metabolic risk among children (6 to 19 years) and to link it with different body fat and fat mass index (FMI) categories.

b. **Specific Objectives (Study 3)**: This study among 3241 healthy school children (6 to <19 years) were developed to:
   1. Determine the burden of clustering of cardio-metabolic risk factors among boys and girls;
   2. Determine the relationships between clustering of cardio-metabolic risk factors and body mass index (BMI), percentage body fat (PBF), fat mass index (FMI) and waist circumference (WC); and
   3. Using an unifying approach to derive a new definition for childhood obesity based on clustering cardio-metabolic risk factors.

Detailed description of study participants, methods and sample sizes have been presented in study 1 and 2. Among 1608 boys and 1626 girls: 4.3% (69) boys and 3.8% (62) girls were thin, 82.4% (1328) boys and 81.7% (1332) girls were normo-weight, 8.4% (135) boys and 10.6% (173) girls were overweight and 4.9% (79) boys and 3.9% (63) girls were obese - as per IAP growth chart (2015).

Markers of cardio-metabolic risk studied were: *1) Fasting Glucose, 2) Fasting Insulin, 3) HOMA index (derived), 4) HbA1C, 5) Total Cholesterol, 6) LDL, 7) HDL, 8) VLDL, 9) Triglycerides, 10) Apo-A, 11) Apo-B, 13) Uric acid, 14) Systolic BP, 15) Diastolic BP, 16) Mean Arterial Pressure (MAP) (derived) and 17) Waist Circumference*. In addition, *percentage body fat (PBF), fat mass index (FMI) and body mass index (BMI)* were derived.

Definition for cardio-metabolic risk factors:

a. **Hyperglycemia**: As per International Society of Pediatric and Adolescent Diabetes (ISPAD), Clinical Practice Consensus Guideline (2014),[243,244] and American Diabetes Association criterion (2016),[245] a child (above 10 years age or after onset of puberty) having a fasting plasma glucose ≥126 mg/dl shall be considered as diabetic. Those children between ≥100-125 mg/dl shall be considered as pre-diabetes (Impaired Fasting Glucose). Therefore, in this study we define hyperglycemic as any child, above 10 years of age, having fasting glucose ≥126 mg/dl or HbA1C ≥ 6.5. Impaired fasting glucose are not considered in clustering of risk factors.

b. **Insulin Resistance**: refers to decreased physiological response to normal levels of insulin and is a major risk factor for type 2 diabetes. Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) is the most commonly used surrogate measure of Insulin resistance and its cut-offs are dependent on population. HOMA-IR is derived as Fasting Insulin (mIU/L) X Fasting Glucose (mg/dl) / 405 – where the constant is added to produce a reference value of 1.0. Most literatures, from India and abroad, have highlighted HOMA-IR ≥ 2.5 as having good sensitivity and specificity for predicting Insulin resistance.[246,247,248] This study considered HOMA-IR ≥ 2.5 among children in both gender, in all age-groups, as an indicator of Insulin Resistance.

c. **Hypertension:** As per International Diabetes Federation (IDF) consensus definition for metabolic syndrome; hypertension among children are defined as those having SBP ≥ 130 or DBP ≥ 85 mmHG.[249] Globally, as per fourth report on diagnosis, evaluation and treatment of high BP in children and adolescents, hypertension is defined as SBP or DBP that is greater than or equal to 95th percentile for sex, age and height, on at least three separate occasions.[250] Mean arterial pressure (MAP) is the time-weighted average of cardiac outputs and refer to the resistance of arterioles.[251] Some recent studies insist on including MAP in the definition of ambulatory hypertension for increasing detection rates;[252,253] however presently MAP is not a diagnostic criterion for hypertension. There was no cut off for MAP - one study suggest MAP ≥ 95th percentile as hypertensive.[254] In this study we have considered children as having elevated BP if SBP/DBP ≥ 130/85 mmHG.

d. **Altered Lipid Metabolism:** Disorders of lipoprotein metabolism in human body is manifested either as elevated total cholesterol or LDL cholesterol and triglycerides along with decrease in HDL cholesterol – collectively termed under dyslipidemia. Since LDL-C

are derived from Friedwald's equation, we have considered children having elevated total cholesterol ≥ 200 mg/dl, in all age group among boys and girls, as an indicator of elevated cholesterol for clustering of cardio-metabolic risk study.[255,256]

e. **High Triglycerides:** Triglycerides are either ingested through foods or synthesized by hepatocytes or adipocytes which circulates in blood and are stored in adipocytes. Excess triglycerides are directly associated with atherogenic plaque formation and therefore is a significant cardio-metabolic risk, especially among adolescents who are overweight or obese.[257] Children above 10 years with triglyceride levels ≥ 130 mg/dl (in both genders) are indicated as dyslipidemia and was considered in this study.[258,259]

f. **Low HDL cholesterol:** There are several mechanisms through which HDL-C protects against cardio-vascular diseases. This includes: 1) HDL-C enhances reversal of cholesterol transports, 2) it stimulates endothelial nitric oxide production (reduction in oxidative stress), 3) it inhibits endothelial adhesion of molecules (reversal of atherogenic plaques) and 4) it inhibits oxidation of LDL-C and other tissue factors.[260] Thus, low HDL cholesterols are considered as high risk for cardio-metabolic conditions. In this study we considered those children between 10 to 16 years (boys and girls) having HDL ≤ 40 mg/dl as high risk. Among children above 16 years, HDL-C ≤ 40 mg/dl in boys and HDL ≤ 50 mg/dl in girls was considered as high risk.

   Apolipoprotein-A is a primary protein constituent of HDL-C and therefore is increasingly used as a marker of dyslipidemia. In this clustering study, we considered children with Apo-A levels ≤ 115 mg/dl as having high risk.[261,262]

   Atherogenic dyslipidaemia: It is known that atherosclerosis are associated with non-HDL cholesterol levels, even in children as young as 6 years.[263] Non HDL-C is estimated as total cholesterol minus HDL cholesterol - among Indians the cut offs suggested for non-HDL cholesterol is ≥130 mg/dl as per the consensus statement for management of dyslipidemia. ApoB and non-HDL are highly correlated as Apo-B protein is present in almost all of the atherogenic particles (like LDL, IDL and VLDL).[264] Therefore in this study Apo-B ≥ 110 mg/dl was considered for studying clustering.[258]

   To overcome the issue of co-linearity we have replaced total cholesterol and HDL-C against Apo-A and Apo-B through a separate model (model 2).

g. **Hyperuricemia:** Uric acid is the final oxidative product of purine metabolism mediated by xanthine oxidase and releases reactive oxygen species (ROS);[265] which will induce endothelial dysfunctions by reducing the availability of nitric oxides. Therefore uric acid levels in serum has to be considered as a mechanism that is linked with sub-clinical atherosclerosis. Presently, there is no accepted thresholds for uric acid levels among children in India and in this study we used sex specific published upper limits (7.0 in boys[266] and 5.7 in girls[267]) as high uric acid levels.

Table 20: Age specific definition and cut-offs for bio-chemical markers for studying clustering

	Age group	**Gender**	**Model 1**	**Model 2**	**Reference**
Hyperglycemia	All child & Adolescents	Boys & Girls	Fasting glucose ≥126 mg/dl or HbA1C ≥6.5	-do-	ISPAD & ADA
Insulin Resistance	All child & Adolescents	Boys & Girls	HOMA-IR ≥ 2.5	-do-	
Hypertension	≥6 to ≤ 19y	Boys & Girls	SBP ≥ 130 or DBP ≥ 85 mmHG	-do-	
High Cholesterol	≥6 to ≤ 19y	Boys & Girls	Total cholesterol ≥ 200 mg/dl	-do-	
High Triglycerides	3 to 9y	Boys & Girls	≥ 150 mg/dl	-do-	Indian Study
	≥10y	Boys & Girls	≥ 150 mg/dl		IDF consensus
Low HDL cholesterol	≥6 to 16y	Boys & Girls	HDL ≤ 40 mg/dl	Low Apo-A ≤ 115 mg/dl	Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents
	≥16y	Boys	HDL ≤ 40 mg/dl		
		Girls	HDL ≤ 50 mg/dl		
High Non-HDL cholesterol	≥6 to ≤ 19 years	Boys & Girls		ApoB ≥ 110 mg/dl	
Hyperuricemia	≥6 to ≤ 19 years	Boys	7.0 mg/dl	-do-	
		Girls	5.7 mg/dl		

Note: Cut offs for risk factors were collated from different Indian studies, Consensus statements and apex body guidelines. The references for each cut offs are mentioned in the write up.

4. **Definition of high risk children:** Serum bio-chemical values were available for total 11 markers: 1) total cholesterol (n=3156), 2) LDL-C (n=3153), 3) HDL-C (n=3150), 4) VLDL-C (n=3155), 5) triglycerides (n=3150), 6) Apo-A (n=3154), 7) Apo-B (n=3156), 8) Uric Acid (n=3157), 9) Fasting Glucose (n=3168), 10) Fasting Insulin (n=2533) and 11) HBA1C (n=1837). In addition Mean Arterial Pressure (MAP) was calculated for 3228 children from Systolic and Diastolic blood pressure and HOMA-IR was estimated from fasting glucose and insulin for 2530 children. All the markers were used to study clustering of risk factors.

   As per the definition of individual risk factors in Table 20, we adopted two models to study clustering of risk factors:

   - **Model 1**: Clustering of 1) hyperglycemia (fasting glucose or HbA1C), 2) insulin resistance (HOMA-IR), 3) hypertension (SBP or DBP), 4) high cholesterol (total cholesterol or LDL cholesterol), 5) high triglycerides, 6) low HDL cholesterol and 7) high uric acid

   - **Model 2**: Clustering of 1) hyperglycemia (fasting glucose or HbA1C), 2) insulin resistance (HOMA-IR), 3) hypertension (SBP or DBP), 4) high Apo-B, 5) high triglycerides, 6) low Apo-A and 7) high uric acid levels

Since 3 out of 7 markers studied were applicable among children ≥10 years the study on clustering of risk factors were restricted to this age group only. Markers that independently predict each risk conditions were carefully selected for studying clustering effect. Distribution of BMI, percent body fat, fat mass index and waist circumference were studied among children with clustered risk factors as compared to no risk factors.

4.6. Results:

Subject Characteristics: Description of clinical and bio-chemical markers of 3241 children (boys and girls in urban and rural locations) are already presented in study 1 and 2. Among this, 3168 children (1566 boys and 1602 girls) have provided serum samples for bio-chemical assessment. Proportion of children with bio-chemical levels above age specific cut-offs, as per standard definitions in table 20, are summarized in table 21.

Among children ≥ 10 years, there was only 0.8% (9/1112) boys and 0.6% (7/1145) girls having fasting glucose levels higher than the absolute cut offs (hyperglycemic) – there was only one boy having HbA1C ≥ 6.5. However among all children (6 to 18 years), insulin resistance (HOMA-IR) was found in 13.3% boys and 23.3% girls: this was higher in children from urban areas 10.2%

(50/492) in rural boys vs. 15.3% (115/753) in urban boys (P= 0.009) and 20.5% (94/459) in rural girls vs. 24.8% (205/826) in urban girls (P= 0.078). In contrary hypertension (7.8% boys and 6.9% girls, 6 to 18 years) was significantly higher in rural areas: rural boy's 9.5% (67/703) vs. urban boys 6.4% (58/904) (P=0.021) and rural girls 9.5% (61/642) vs. urban girls 5.2% (51/979) (P=0.001).

Total cholesterol was higher in 4% boys (62/1561) and 5.3% girls (84/1595) however there was no statistically significant difference between rural and urban settings. Among ≥10 year children, elevated triglycerides was observed in about 15.9% boys and 16% girls: around 15% (98/652) of urban boys vs. 17% (78/455) of rural boys as compared to 14.5% (102/705) of urban girls vs. 18.5% (80/432) of rural girls. In children ≥ 10 years, 32% (18/56) of obese boys, 30% (27/89) of overweight boys, 13.6% (124/915) of normoweight boys and 14.9% (7/47) of thin boys were having elevated triglycerides as compared to 23.3% (10/43) of obese girls, 22.6% (28/124) of overweight girls, 14.9% (138/924) of normoweight girls and 13% (6/46) of thin girls were having elevated triglycerides.

Concomitantly among children ≥10 years, there was relatively higher proportion of children with low HDL levels (37.5% boys and 40% of girls): this include 38.9% (176/452) of rural vs. 36.6% (239/653) of urban boys and 48.1% (209/435) of rural vs. 41.5% (293/706) of urban girls. Apo-A markers which is technically highly correlated with HDL cholesterols were also lower in 24% of boys and 25.5% girls: this was lower in around 22% (100/454) of rural and 25% (163/653) of urban boys as compared to 23.8% (103/433) of rural and 26.5% (187/705) of urban girls. It is important to note that, around 41.1% (23/56) of obese, 42.7% (38/89) of overweight, 36.6% (334/913) of normoweight and 42.6% (20/47) of thin boys and 52.3% (23/44) of obese, 39.5% (49/124) of overweight, 44.0% (408/927) of normoweight and 47.8% (22/46) of thin girls were observed to have low levels of HDL cholesterols (in ≥10 years).

In addition, around 6% (25/415) of boys and 6.8% (34/502) of girls with low HDL levels were having high levels of non-HDL cholesterols (Apo-B) indicating higher risk of CMR (in ≥10 years). Overall high levels of non-HDL levels were found in 6.7% of boys and 8.2% of girls: among which 7.7% (35/455) was rural boys vs. 4.8% (31/653) was urban boys as compared to 11.1% (48/434) was rural girls vs. 6.7% (47/706) was urban girls. There was 5.5% of boys and 10% of girls with high uric acid levels: 5.2% (35/672) was rural boys and 5.7% (51/889) were urban boys as compared to 7.8% (49/626) was rural girls and 11.3% (110/976) was urban girls.

Table 21: Proportion of children with different risk conditions

Risk for	Marker	Boys % (n/N)	Girls % (n/N)
Hyperglycemia*	Fasting Plasma Glucose or HbA1C	0.81 (9/1122)	0.61 (7/1145)
Insulin Resistance	HOMA-IR	13.3 (165/1245)	23.3 (299/1285)
Hypertension	Systolic BP (SBP) or Diastolic BP (DBP)	7.8 (125/1607)	6.9 (112/1621)
High Cholesterols	Total Cholesterol	4.0 (62/1561)	5.3 (84/1595)
High Triglycerides*	Triglycerides	15.9 (176/1107)	16.0 (182/1137)
Low HDL Cholesterol*	HDL-C (low)	37.5 (415/1105)	44 (502/1141)
	Apo-A (low)	23.8 (263/1107)	25.5 (290/1138)
High Non-HDL cholesterol	Apo-B	6.7 (104/1561)	8.2 (130/1595)
Hyperuricemia	Uric Acid	5.5 (86/1561)	10 (159/1596)
Clustering in all age groups (≥ 10 years to 18 years)			
Clustering (Model-1)*	CMR = 0 risk factors	56.9 (646/1135)	48.3 (561/1162)
	CMR = 1 risk factors	27.3 (310/1135)	29.9 (347/1162)
	CMR = 2 risk factors	11.5 (130/1135)	14.4 (167/1162)
	CMR ≥ 3+ risk factors	4.3 (49/1135)	7.5 (87/1162)
Clustering (Model-2)*	CMR = 0 risk factors	60.9 (691/1135)	53.4 (620/1162)
	CMR = 1 risk factors	26.3 (298/1135)	27.8 (323/1162)
	CMR = 2 risk factors	9.2 (104/1135)	13.3 (154/1162)
	CMR ≥ 3+ risk factors	3.7 (42/1135)	5.6 (65/1162)

Note: (*) indicates that analysis was done only on children ≥10 years as per standard definition. Dichotomization was done as per absolute cut off in Table 21.

Clustering of serum markers of cardio-metabolic risk:

As mentioned earlier, clustering of cardio-metabolic risk factors were studied among children ≥ 10 years using two models (using 7 independent markers in each model) (Table 23). Cohen et al., (1968)[268] explains Kappa agreement as: values less than 0 indicating no agreement, 0.01 to 0.20 as none to slight, 0.21 to 0.40 as fair, 0.41 to 0.60 as moderate, 0.61 to 0.80 as substantial and 0.81 to 1.00 as almost perfect agreement. Overall, there was substantial level of agreement between two models (boys: kappa 0.64, P=0.001) and (girls: kappa 0.63, P=0.001); however this varies within

age bands. Therefore considering the feasibility of bio-chemical tests, model-1 has been emphasized in further analysis. As per model 1, there was 28% (278/994) boys and 31.6% (321/1017) girls with 1 risk factor; 11.6% (115/994) boys and 13.8% (140/1017) girls with 2 risk factors and 3.6% (36/994) boys and 6.9% (70/1162) girls with more than 3 risk factors.

1. **Urban-rural differences:** There was 69.4% (34/49) boys and 65.5% (57/87) girls having 3 and more risk factors from urban settings –there was no statistical significant difference in urban-rural settings on CMR (boys, p=0.111 and girls, p=0.417).
2. **Ethnicities:** Among boys above 10 years, around 5.9% (24/405) from Delhi, 3.7% (17/455) from Shillong and 2.9% (8/275) from Hyderabad were having 3 and more risk factors. In girls above 10 years, around 8% (35/436), 8.2% (37/449) and 5.4% (15/277) were having 3 and more risk factors. There was no statistical significant difference in study locations on CMR (boys, p=0.121 and girls, p=0.322). There was more boys (21/24) and girls (30/35) with 3 and more risk factors from urban settings in Delhi however no difference in Hyderabad and Shillong.

Presence of 3 and more risk factors were considered for defining clustering of risk factors as average distribution of clinical parameters (like BMI, FMI, Percent body fat and waist circumference) were significantly higher, across the age-groups, among children with 3 and more risk factors as compared to no risk factors (Fig 12 to 15). Sudden rise in the median values of these clinical parameters can be observed in figure 16 to 19 indicating that 3 and more risk factors can discriminate children in different anthropometric categories.

Why should Clustering of Cardio-metabolic risk to be monitored?

Clustering of 3+ risk factors are distributed among normo-weight, overweight and obese as per existing BMI-for-age categorization: among normal weights 2.2% boys (19/871) and 5.5% girls (45/818) were having clustering of 3 and more risk factors. Among overweight children, 11% boys (10/90) and 21.7% girls (20/92) were having clustering of 3 and more risk factors as compared to 34% obese boys (14/41) and 37.8% obese girls (14/37) having clustering of risk factors. Among children with normal BMI, body fat (kg) was 2.2 kg higher among boys and 4.5 kg higher among girls who had 3+ clustering of cardio-metabolic risk as compared to those with no clustering of risk factors (P=0.001 & P=0.0001). Similarly among children with normal BMI, waist circumference was 7.1 cm higher among boys and 8.4 cm higher among girls with 3+ clustering of cardio-metabolic risk (P=0.001 & P=0.001) indicating abdominal obesity. Thus, this study reaffirms the existence of ***thin-fat phenotypes*** among Indian children. In addition, height (in cm)

was significantly higher among boys (diff: +14.7, P=0.001) and girls (diff: +10.6 cm, P=0.001) among those having clustering of cardio-metabolic risk – the trend was similar among normal BMI and overweight categories; pointing towards the hypothesis that accelerated growth in childhood shall predispose children for cardio-metabolic diseases.

Also, it is important to note that, several overweight/obese children (as per current BMI-for age classification) does not have risk factors. Among boys, 7.9% (80) and 2.7% (27) boys who were overweight and obese, as per current classification system were not having any risk factors as compared to 8% (72) and 2.6% (23) girls who were overweight and obese and have no risk factors. However the percentage body fat was 3.5% higher (P=0.0004) in boys and 3.8% higher (P=0.0002) in girls who were having 3+ risk factors and were overweight/obese as compared to no risk factors and was overweight/obese. Moreover existing classification system based on BMI-for-age (at 23rd adult equivalent centile for overweight and 27th adult equivalent centile for obese) shall not be able to capture all children with cardio-metabolic risk (less sensitive and more false negatives).

Odds of clustering among children in different BMI-for-age categories

Overall, among boys there was 62.5% (1005) with no risk factors, 26.2% (421) with 1 risk factors, 8% (141) with 2 risk factors and 2.7% (43) with more than 3 risk factors. Among girls; there was 55.2% (899) with no risk factors, 28.7% (467) with 1 risk factor, 11.2% (182) with 2 risk factors and 5% (81) with 3 and more risk factors.

Odds ratio for clustering of risk factors among children in different BMI-for-age categories are summarized in table 23a – risk as per different guidelines are highlighted in table 23b. Maintaining normal body weights protect children from risk factors: among boys 34% decrease in any risk factors and 86% decreased risk for clustering of 3 and more risk factors; among girls 47% decrease in any risk factors and 80% decreased risk for clustering of 3 and more risk factors. However, being overweight/obese (BMI >23 adult eqvt.) shall increase the risk for clustering of 3 and more risk factors: among boys 43% increase in 1 or 2 risk factors, 78% increase for any risk factors and 10.6 times (906%) increase in clustering of 3 and more risk factors; among girls 70% increase in 1 or 2 risk factors, 200% increase for any risk factors and 6.1 times (500%) increase in clustering of 3 and more risk factors.

In addition, occurrence of clustering of risk factors were studied among stunted children also (based on height for age as per WHO classification system) however stunting was not significantly associated with clustering of cardio-metabolic risk (Table 23b).

Association of clustered risk factors with body fat (FMI, PBF & WC):

Distribution of fat mass index (FMI) and percentage body fat (PBF) along with waist circumference (indicator of abdominal obesity) were compared in children having risk factors. Average BMI, FMI, PBF and WC was significantly higher among children with 3 and more risk factors (Figure 16 to 19). Only marginal difference observed between children with no risk factors and those having 1 and 2 risk factors across age groups.

Thus based on the existing BMI-for-age classification system (IAP growth charts), we propose to include the new definition based on cardio-metabolic risk as;

- **High risk:** Those children with more than 3 risk factor clustering across age groups
- **Intermediate risk:** Those children having 1 or 2 risk factors across age groups and
- **Low risk:** Those children with less than 0 risk factors

Linking with existing definition of BMI-for-age (fig 16a and 16b) shall help to predict and monitor clustering of cardio-metabolic risk without undergoing the bio-chemical evaluation at fields and clinics. In addition, we propose to use risk categorization based on FMI (fat in kg adjusted for height of the child), for monitoring cardio-metabolic risk across age groups.

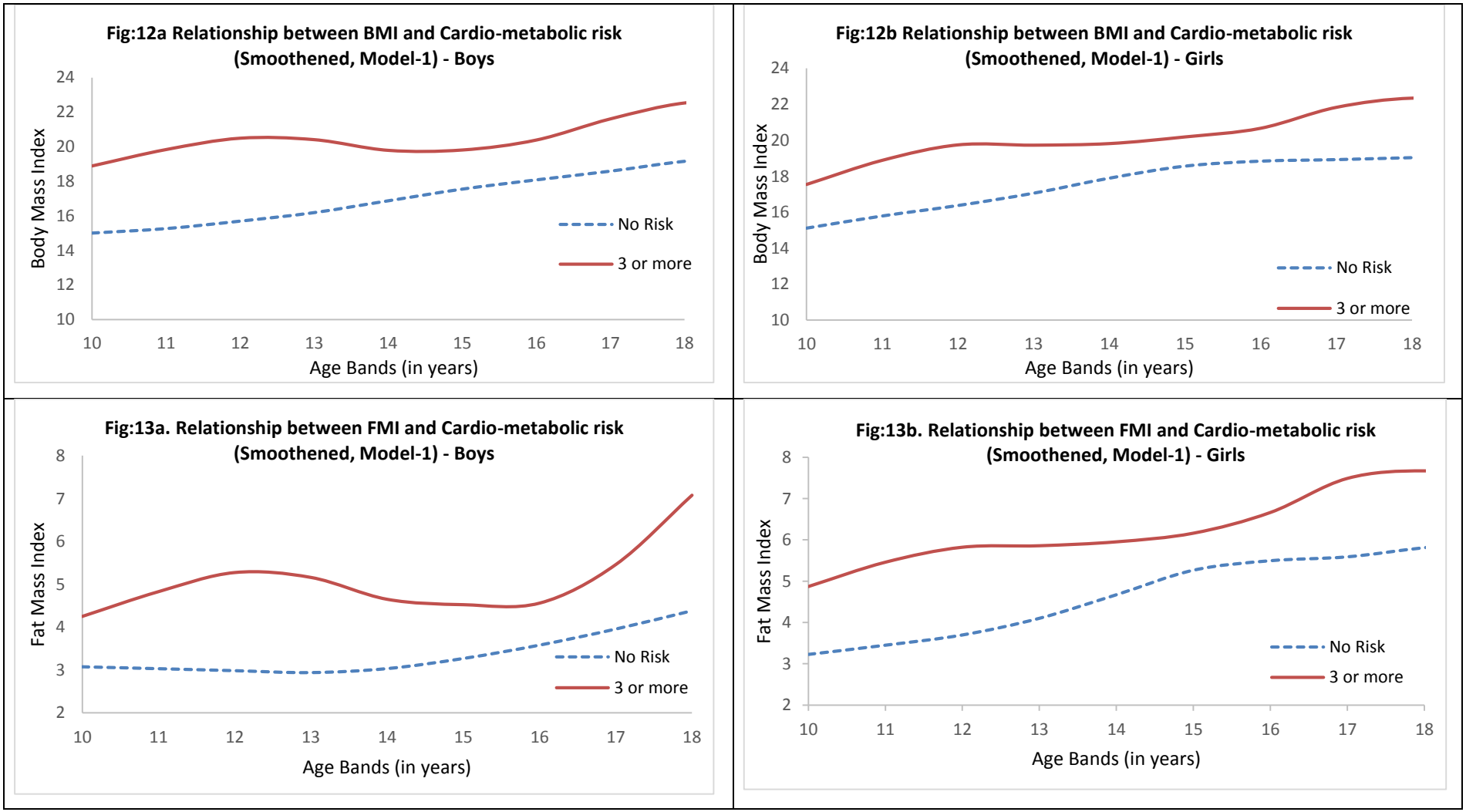
Sensitivity and Specificity of BMI-for-age to predict clustering of cardio-metabolic risk:

ROC curves were plotted against clustered risk factors and anthropometric variables (BMI, FMI, PBF and WC). Area under ROC curves were higher among children with 3 and more risk factors as compared to children with no risk factors (Table 24a and 24b) – indicating strong associations. Table 25 depicts the sensitivity and specificity of identifying children with clustered risk factors by BMI-for age categorization. As per current IAP guidelines, the 23rd adult equivalent (overweight categorization) can only identify 56% of boys and 42% of girls with clustering of risk factors while these have high specificity – indicating that there shall be more false negatives and is not a good screening tool in population. Therefore we proposes to further reduce the BMI-for-age cut-offs to 21 adult equivalent that shall have sensitivity of 65% in boys and 63% in girls.

New growth charts based on clustering of cardio-metabolic risk

This study proposes to modify existing growth charts based on BMI-for-age to diagnose and monitor cardio-metabolic risk among boys and girls (Figure 21a and 21b). The values are from existing growth charts which was superimposed with values above 2 CMR and 3+CMR from this study. Dotted lines indicate those children in high risk and intermediate zone. We also present fat mass index (FMI) based growth curves for boys and girls.

Figure 12 to 15: Relationship between clinical markers and 3+ cardio-metabolic risk factors among boys and girls



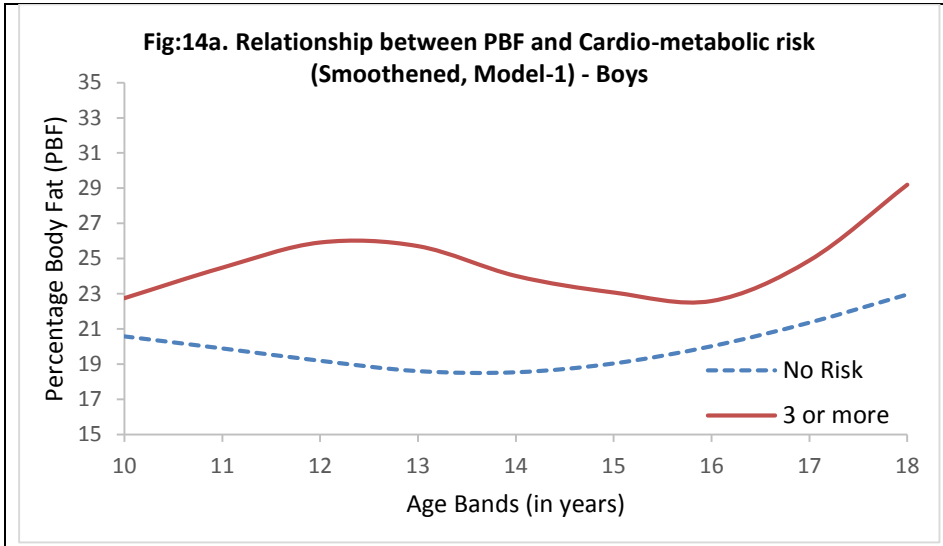


Fig:14a. Relationship between PBF and Cardio-metabolic risk
(Smoothened, Model-1) - Boys
Percentage Body Fat (PBF)
35
33
31
29
27
25
23
21
19
17
15
10
11
12
13
14
15
16
17
18
Age Bands (in years)
No Risk
3 or more

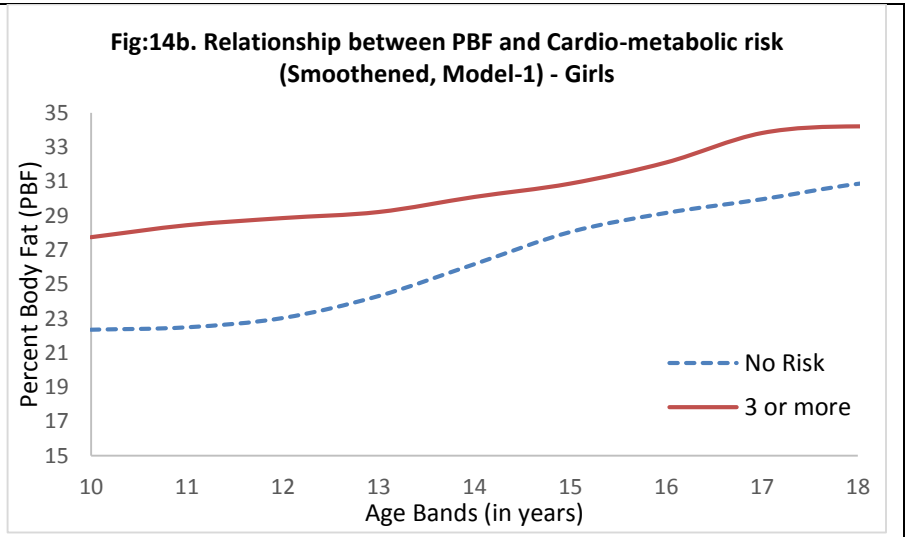


Fig:14b. Relationship between PBF and Cardio-metabolic risk
(Smoothened, Model-1) - Girls
Percent Body Fat (PBF)
35
33
31
29
27
25
23
21
19
17
15
10
11
12
13
14
15
16
17
18
Age Bands (in years)
No Risk
3 or more

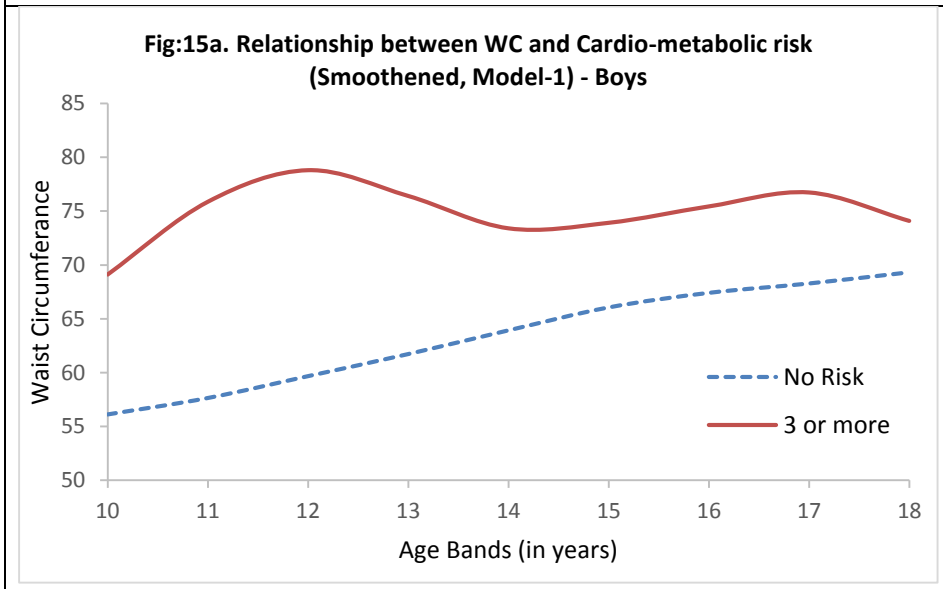


Fig:15a. Relationship between WC and Cardio-metabolic risk
(Smoothened, Model-1) - Boys
Waist Circumferance
85
80
75
70
65
60
55
50
10
11
12
13
14
15
16
17
18
Age Bands (in years)
No Risk
3 or more

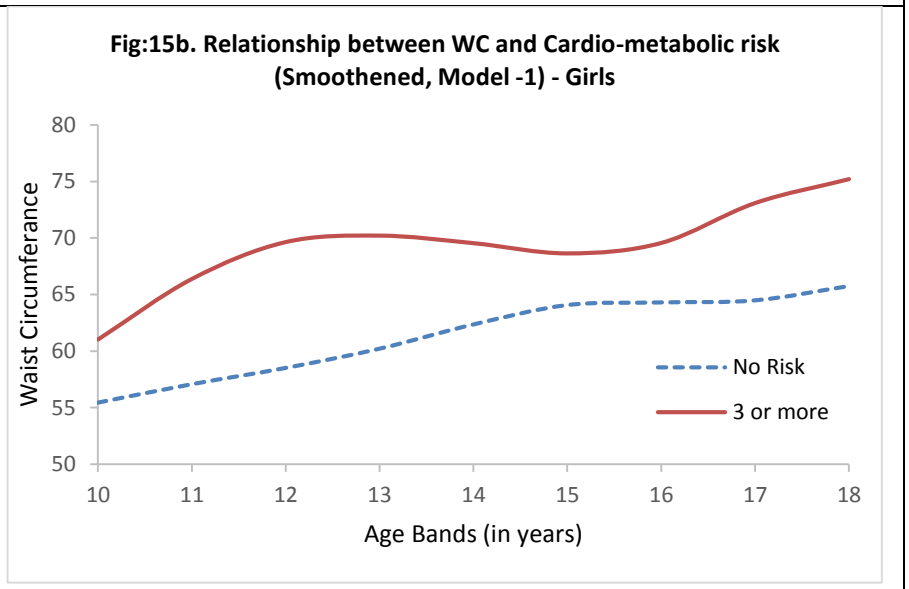
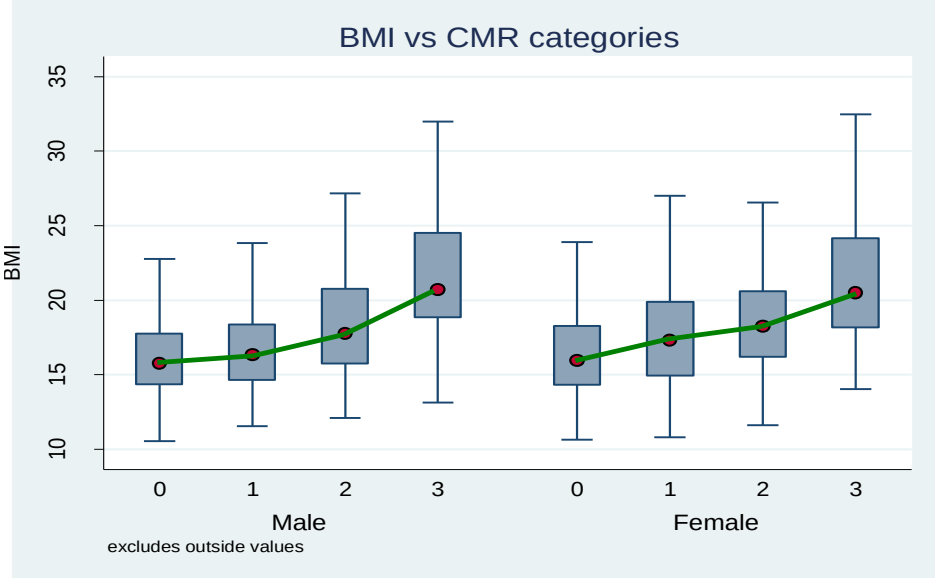


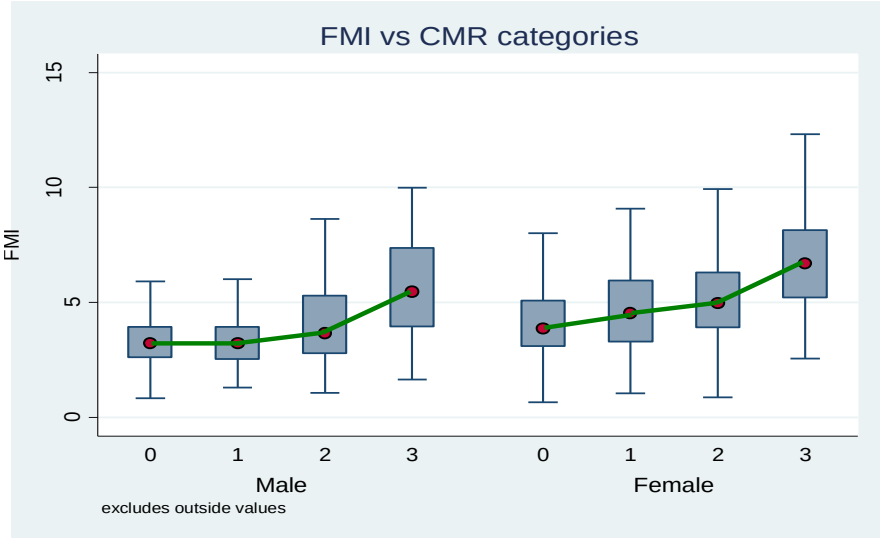
Fig:15b. Relationship between WC and Cardio-metabolic risk
(Smoothened, Model -1) - Girls
Waist Circumferance
80
75
70
65
60
55
50
10
11
12
13
14
15
16
17
18
Age Bands (in years)
No Risk
3 or more

Figure: 16a Distribution of BMI in cardio-metabolic risk categories



Kruskal Wallis: Boys - P=0.0001; Girls – P=0.0001

Figure: 16b Distribution of FMI in cardio-metabolic risk categories



Kruskal wallis: Boys P= 0.0001, Girls P= 0.0001

Fig: 16c Distribution of percent body fat in cardio-metabolic risk categories

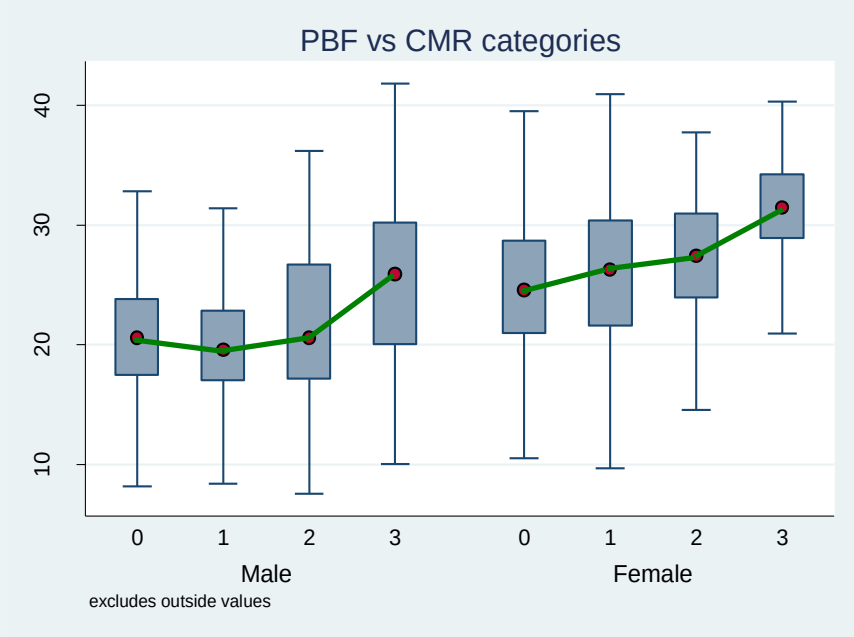


Fig: 16d Distribution of waist circumference in cardio-metabolic risk categories

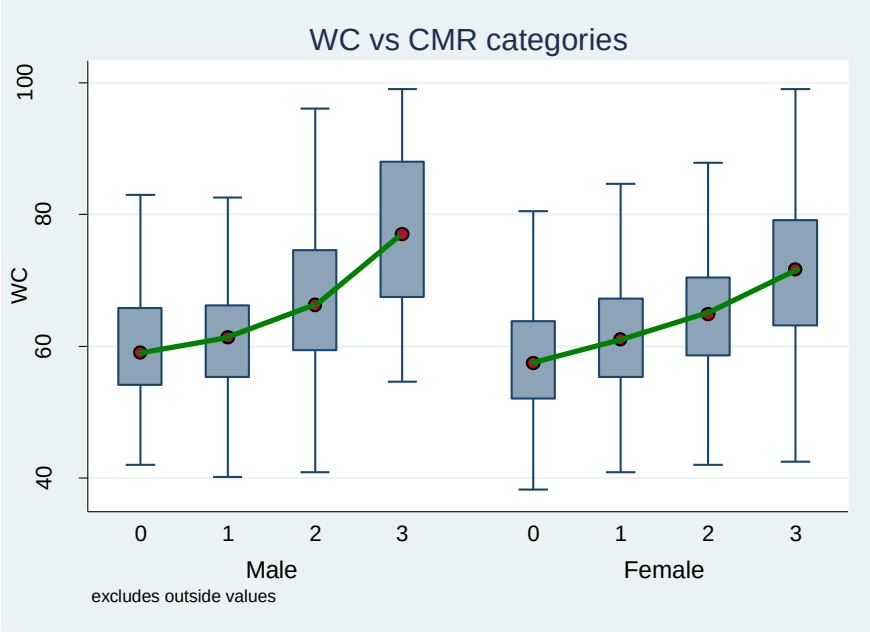


Table 22: Comparison of distribution of cardio-metabolic risk factors as per different guidelines for classifying overweight and obese

		BMI for Age_ IAP guideline, India - %(n)				BMI for Age_IOTF guideline, 23rd and 27th eqvt - %(n)				BMI for Age_ WHO guideline, 25th and 27th eqvt - %(n)			
		Thin	Normal	OW	Obese	Thin	Normal	OW	Obese	Thin	Normal	OW	Obese
Boys	0 RF	67 (46)	64.16 (852)	59.26 (80)	34.62 (27)	66.15 (424)	62.63 (496)	56.8 (71)	24 (12)	64.69 (207)	64.18 (740)	49.47 (47)	22.5 (9)
	1 RF	27.54 (19)	26.58 (353)	22.22 (30)	24.36 (19)	27.15 (174)	26.39 (209)	20.8 (26)	24 (12)	28.13 (90)	26.02 (300)	21.05 (20)	27.5 (11)
	2 RF	5.8 (4)	7.83 (104)	11.11 (15)	23.08 (18)	6.08 (39)	9.09 (72)	12.8 (16)	28 (14)	6.25 (20)	8.24 (95)	15.79 (15)	27.5 (11)
	≥ 3 RF	0	1.43 (19)	7.41 (10)	17.95 (14)	0.62 (4)	1.89 (15)	9.6 (12)	24 (12)	0.94 (3)	1.56 (18)	13.68 (13)	22.5 (9)
	Total	69	1,328	135	78	641	792	125	50	320	1,153	95	40
Girls	0 RF	50 (31)	58.03 (773)	41.62 (72)	37.1 (23)	58.43 (343)	57.62 (465)	38.95 (67)	35 (21)	57.56 (118)	56.88 (728)	37.04 (40)	30.3 (10)
	1 RF	41.94 (26)	27.85 (371)	30.64 (53)	27.42 (17)	29.98 (176)	27.39 (221)	30.81 (53)	28.33 (17)	30.24 (62)	28.44 (364)	28.7 (31)	30.3 (10)
	2 RF	4.84 (3)	10.74 (143)	16.18 (28)	12.9 (8)	9.37 (55)	11.03 (89)	17.44 (30)	13.33 (8)	9.27 (19)	11.17 (143)	12.96 (14)	18.18 (6)
	≥ 3 RF	3.23 (2)	3.38 (45)	11.56 (20)	22.58 (14)	2.21 (13)	3.97 (32)	12.79 (22)	23.33 (14)	2.93 (6)	3.52 (45)	21.3 (23)	21.21 (7)
	Total	62	1,332	173	62	587	807	172	60	205	1,280	108	33

Table 23a: Risk of clustering of risk factors (vs. no RF) among normo-weight and overweight/obese – as per IAP growth charts, 2015

OR (95% CI)	**Boys**		**Girls**	
	Among normo-weights	Among >23rd adult eqvt (Overw & Obese)	Among normo-weights	Among >23rd adult eqvt (Overweight & Obese)
Presence of 1 RF	0.93 (0.68, 1.27)*	1.11 (0.77, 1.58)*	0.63 (0.46, 0.84) *	1.49 (1.1, 2.1)
Presence of 1 & 2 RF	0.78 (0.59, 1.02) *	1.43 (1.05, 2)	0.62 (0.48, 0.81)	1.7 (1.2, 2.2)
Presence of any RF	0.66 (0.51, 0.86)	1.78 (1.32, 2.38)	0.53 (0.41, 0.69)	2.0 (1.5, 2.7)
Presence of 3 and more RF	0.14 (0.07, 0.27)	10.6 (5.6, 20)	0.20 (0.13, 0.33)	6.1 (3.8, 10)

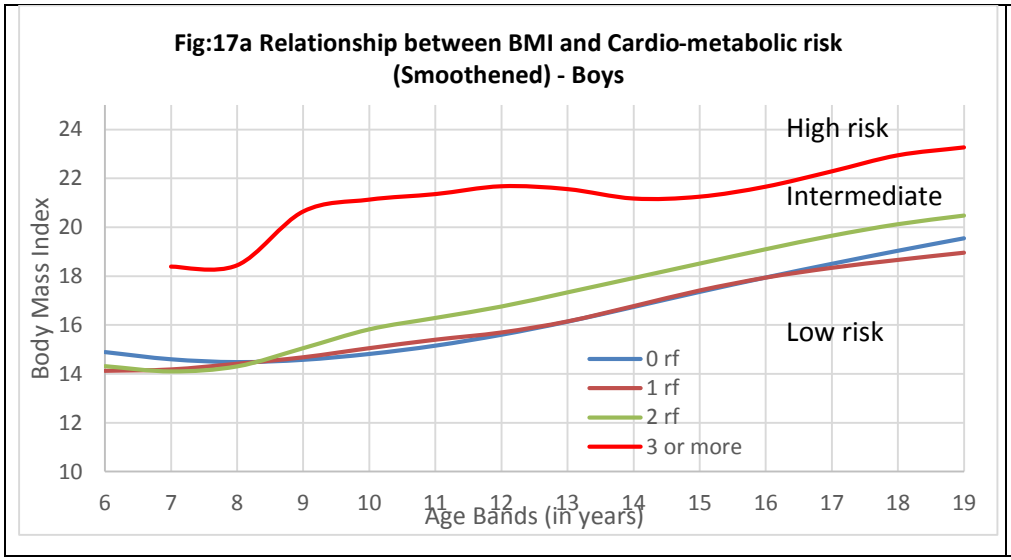
* Significant differences are highlighted (*). Rf indicates risk factors

Table 23b: Risk of clustering of risk factors among different risk categories

OR (95% CI)		**≥ 3 RF vs. 0 RF (model 1)**		**1 & 2 RF vs. 0 RF (no 3+ RF)**		**Any Rf vs. 0 RF**	
		Boys	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**
BMI for age as per IOTF cut off (23 & 27 adult eqv.t)	Thin	0.31*(0.10, 0.94)	0.56 (0.28, 1.1)	0.89 (0.71, 1.11)	1.01 (0.81, 1.26)	0.86 (0.69, 1.07)	0.97 (0.78, 1.2)
	Overweight	5.6*(2.5, 12.4)	4.8*(2.6, 8.7)	1.04 (0.69, 1.6)	1.86* (1.3, 2.6)	1.3 (0.87, 1.87)	2.13* (1.5, 2.98)
	Obese	33.1* (12.8, 85.6)	9.7* (4.5, 20.8)	3.8* (1.9, 7.7)	1.8 (0.98, .3.2)	5.3* (2.7, 10.3)	2.53* (1.46, 4.4)
BMI for age as per WHO cut off (25 & 30 adult eqvt)	Severe Thin	No child	0.70 (0.09, 5.3)	0.95 (0.61, 1.5)	1.4 (0.76, 2.5)	0.91 (0.58, 1.4)	1.32 (0.73, 2.4)
	Thin	0.85* (0.25, 2.94)	0.85* (0.33, 2.2)	1.01 (0.75, 1.4)	0.89 (0.63, 1.26)	1.0 (0.75, 1.4)	0.88 (0.64, 1.2)
	Overweight	11.4* (5.25, 24.6)	9.3* (5.1, 16.9)	1.4 (0.89, 2.2)	1.6*(1.04, 2.5)	1.8* (1.2, 2.8)	2.2* (1.5, 3.4)
	Obese	41.1* (14.6, 115.8)	11.3* (4.12, 31.1)	4.6* (2.1, 10.0)	2.3*(1.03, 5.1)	6.2*(2.9, 13.1)	3.0*(1.4, 6.4)
Height for age	Severe stunting	0.66 (0.15, 2.8)	1.9 (0.84, 4.1)	1.02 (0.67, 1.5)	1.14 (0.76, 1.74)	0.99 (0.65, 1.5)	1.2(0.82, 1.8)
	Stunting	0.64 (0.27, 1.56)	1.3 (0.75, 2.2)	0.92 (0.71, 1.2)	0.87 (0.67, 1.11)	0.89 (0.69, 1.2)	0.90 (0.71, 1.2)

* Significant differences are highlighted (*). Rf indicates risk factors. IAP=Indian Association of Pediatrics, IOTF=International Obesity Task Force, WHO= World Health Organization

Figure 17: Distribution of BMI (Smoothened graphs) in various cardio-metabolic risk categories (0 rf, 1rf, 2rf & 3rf)



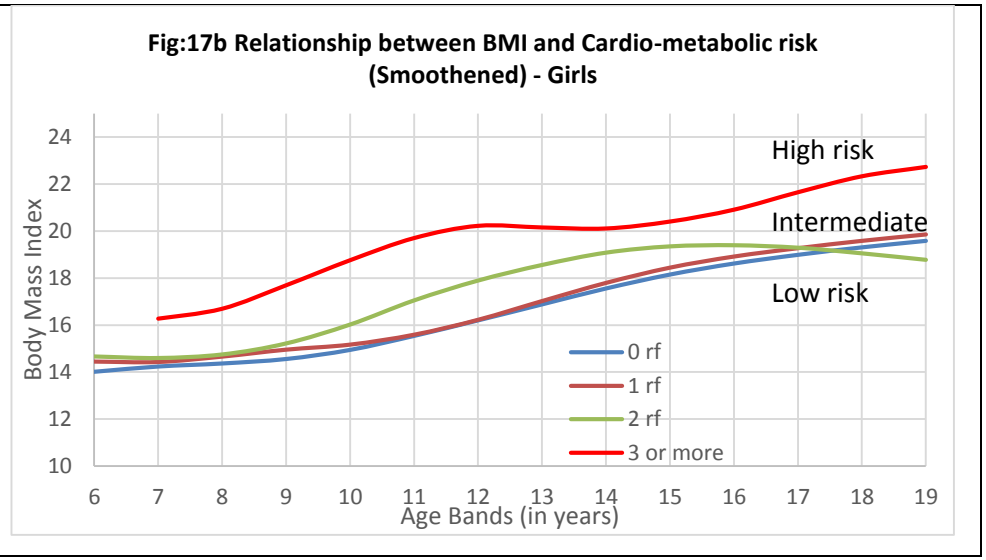
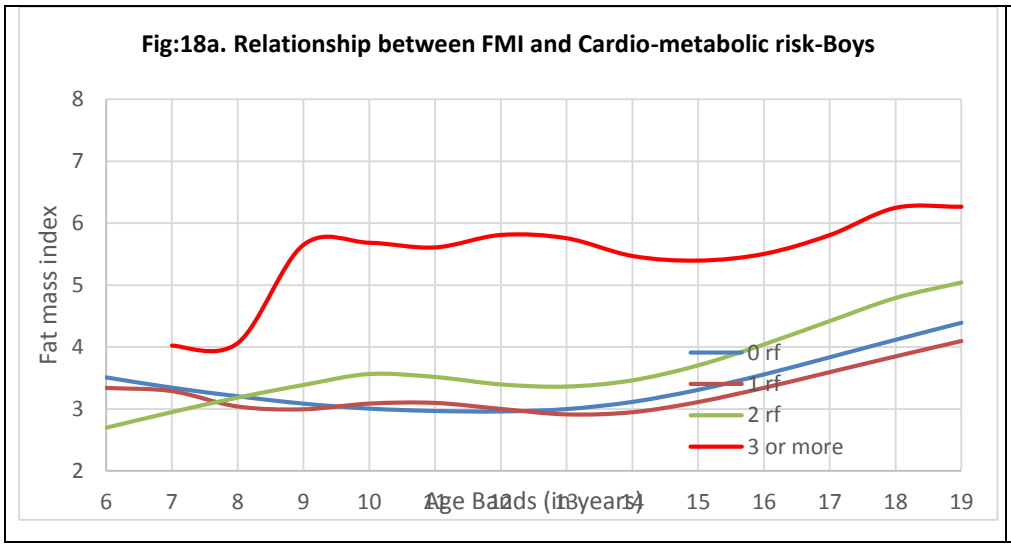


Figure 17: Distribution of FMI (Smoothened graphs) in various cardio-metabolic risk categories (0 rf, 1rf, 2rf & 3rf)



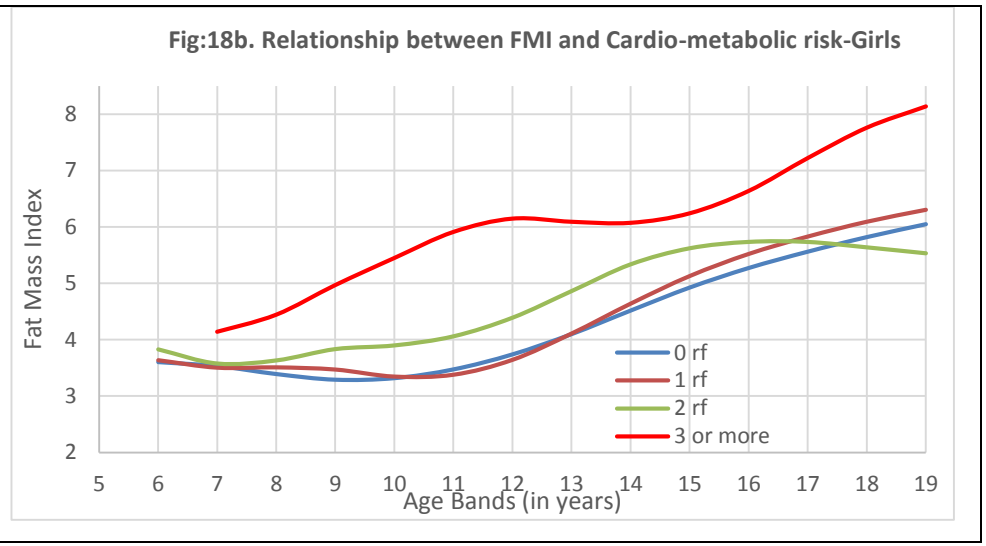
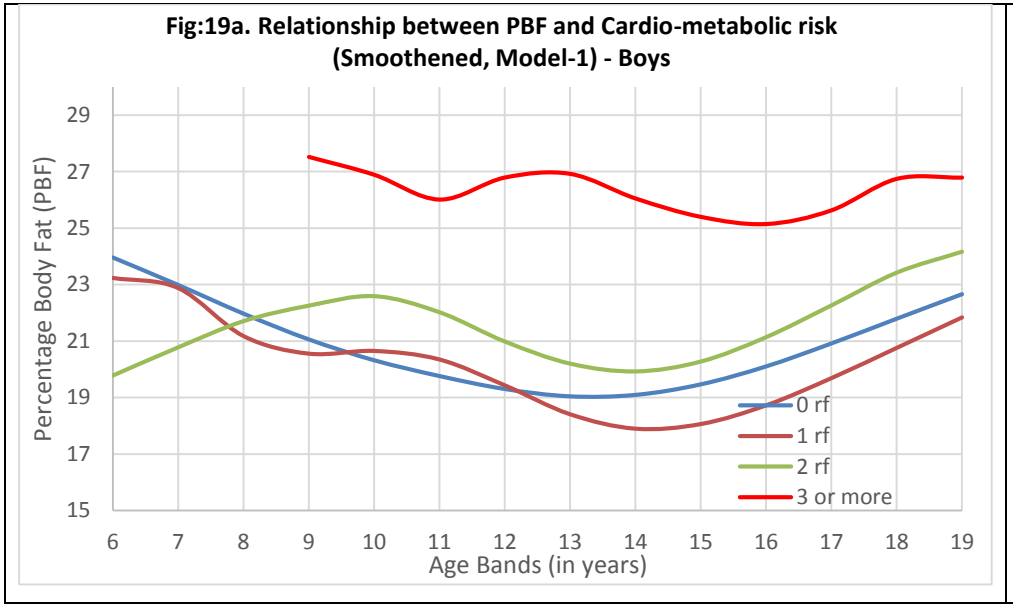


Figure 19: Distribution of **Percent Body Fat** (Smoothened graphs) in various cardio-metabolic risk categories (0 rf, 1rf, 2rf & 3rf)



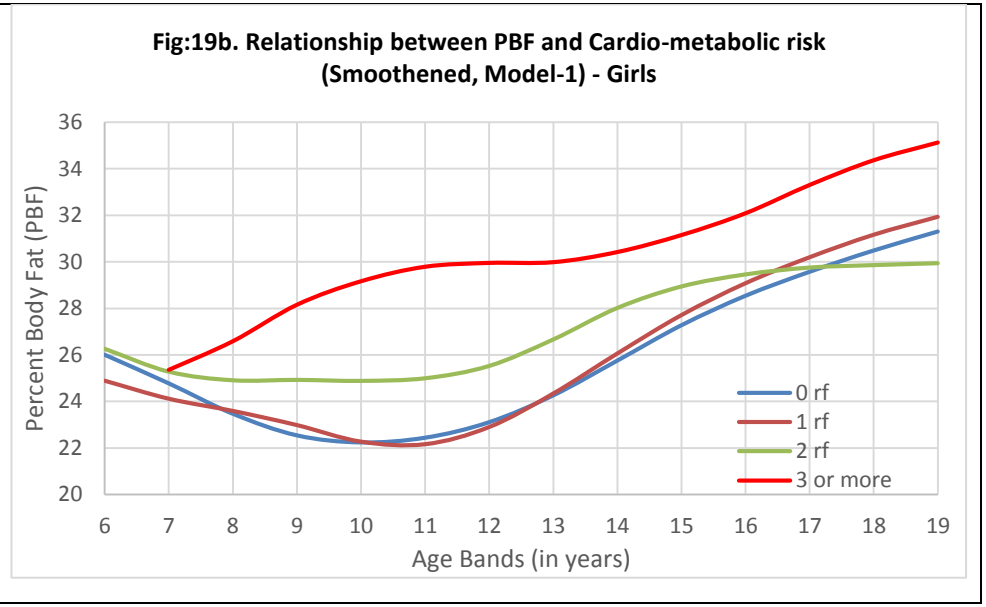
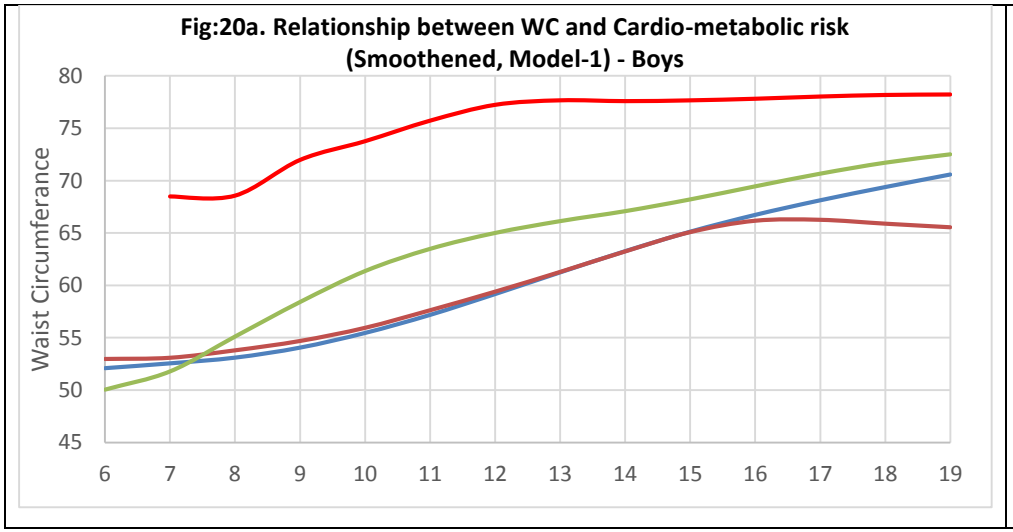


Figure 20: Distribution of **Waist Circumference** (Smoothened graphs) in various cardio-metabolic risk categories (0 rf, 1rf, 2rf & 3rf)



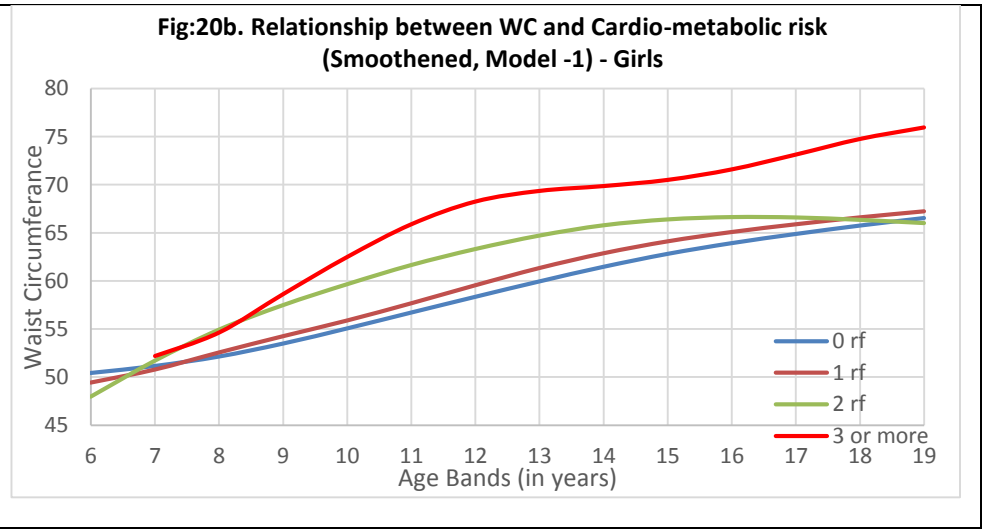


Table 24a: Relationship (AUC) between clustered risk factors and anthropometric variables

Boys	**BMI**		**Percent Body fat**		**Fat Mass Index**		**Waist Circumference**	
	≥3 RF	**0 RF**	**≥3 RF**	**0 RF**	**≥3 RF**	**0 RF**	**≥3 RF**	**0 RF**
10 to 11y	0.63	0.40	0.52	0.41	0.55	0.40	0.81	0.40
11 to 12y	0.95	0.43	0.92	0.43	0.95	0.43	0.97	0.43
12 to 13y	0.77	0.49	0.70	0.49	0.70	0.51	0.92	0.44
13 to 14y	0.80	0.37	0.84	0.43	0.86	0.40	0.71	0.42
14 to 15y	0.57	0.47	0.59	0.51	0.57	0.50	0.68	0.49
15 to 16y	0.67	0.43	0.64	0.51	0.65	0.48	0.63	0.49
16 to 17y	0.78	0.43	0.71	0.48	0.75	0.46	0.84	0.44
17 to 18y	0.84	0.40	0.73	0.51	0.80	0.46	0.79	0.50
18 to 19y	0.85	0.56	0.98	0.60	0.98	0.59	0.49	0.63
All age groups (≥10y)	0.75	0.40	0.68	0.41	0.72	0.44	0.77	0.42

Table 24b: Relationship (AUC) between clustered risk factors and anthropometric variables

Girls	**BMI**		**Percent Body fat**		**Fat Mass Index**		**Waist Circumference**	
	≥3 RF	**0 RF**	**≥3 RF**	**0 RF**	**≥3 RF**	**0 RF**	**≥3 RF**	**0 RF**
10 to 11y	0.75	0.41	0.78	0.49	0.82	0.46	0.70	0.41
11 to 12y	0.57	0.48	0.88	0.51	0.78	0.51	0.55	0.42
12 to 13y	0.84	0.46	0.82	0.47	0.85	0.45	0.78	0.42
13 to 14y	0.64	0.42	0.72	0.41	0.72	0.40	0.72	0.33
14 to 15y	0.64	0.43	0.63	0.42	0.63	0.43	0.68	0.39
15 to 16y	0.58	0.43	0.58	0.46	0.60	0.44	0.61	0.42
16 to 17y	0.63	0.43	0.64	0.44	0.62	0.42	0.61	0.37
17 to 18y	0.75	0.41	0.75	0.41	0.80	0.39	0.79	0.36
18 to 19y	0.74	0.46	0.76	0.50	0.77	0.48	0.80	0.47
All age groups (≥10y)	0.72	0.39	0.74	0.40	0.75	0.39	0.74	0.36

Table 25: Sensitivity and specificity of different BMI-for age categorization to diagnose clustering of cardio-metabolic risk

	Boys			Girls		
	Sensitivity	**Specificity**	**AROC**	**Sensitivity**	**Specificity**	**AROC**
IAP_23 & above	56 (40, 71)	89 (87, 91)	0.73	42 (31.1, 53.5)	89.4 (87.2, 91.4)	0.66
IAP_27 & above	32.6 (19, 48.5)	97 (96, 98)	0.65	17.3 (9.8, 27.3)	97.4 (96.2, 98.4)	0.57
As per current study centile values						
BMI_21 & above	65.1 (49.1, 79.0)	80.6 (78.0, 83.0)	0.73	63 (51.5, 73.4)	70.5 (67.4, 73.5)	0.67
BMI_22 & above	63 (46.7, 77)	81.5 (78.9, 83.8)	0.72	53.1 (41.7, 64)	82.7, (80, 85)	0.68
BMI_23 & above	58 (42, 73)	87.3 (85, 89.3)	0.73	44.4 (33.4, 56)	88 (86, 90)	0.66
BMI_27 & above	30 (17, 46)	98 (97, 99)	0.64	21 (12.7, 31.5)	96.9 (95.5, 97.9)	0.59

Figure 21a: New growth charts with reference to cardio-metabolic risk - Boys

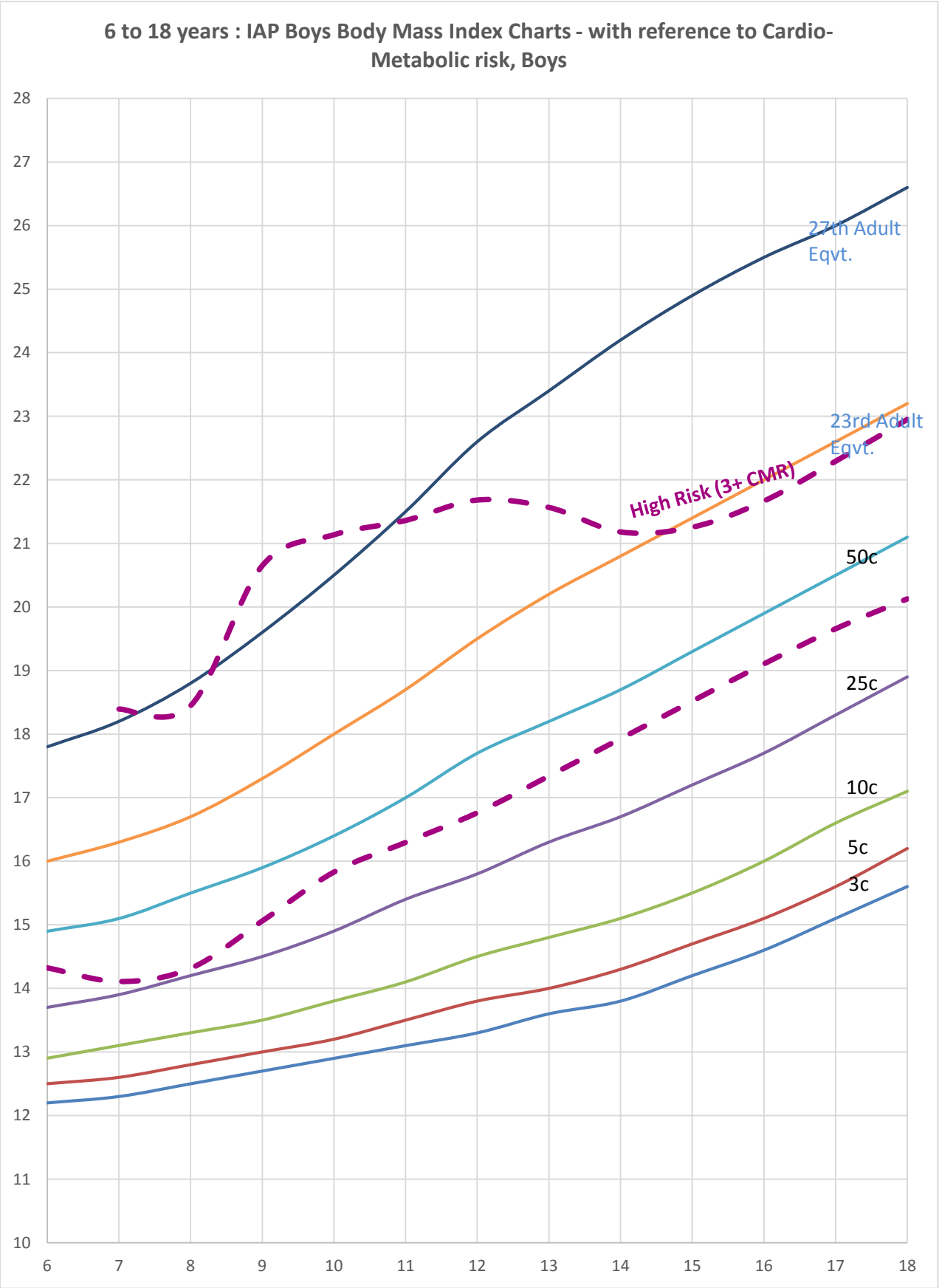


Figure 21b: New growth charts with reference to cardio-metabolic risk - Girls

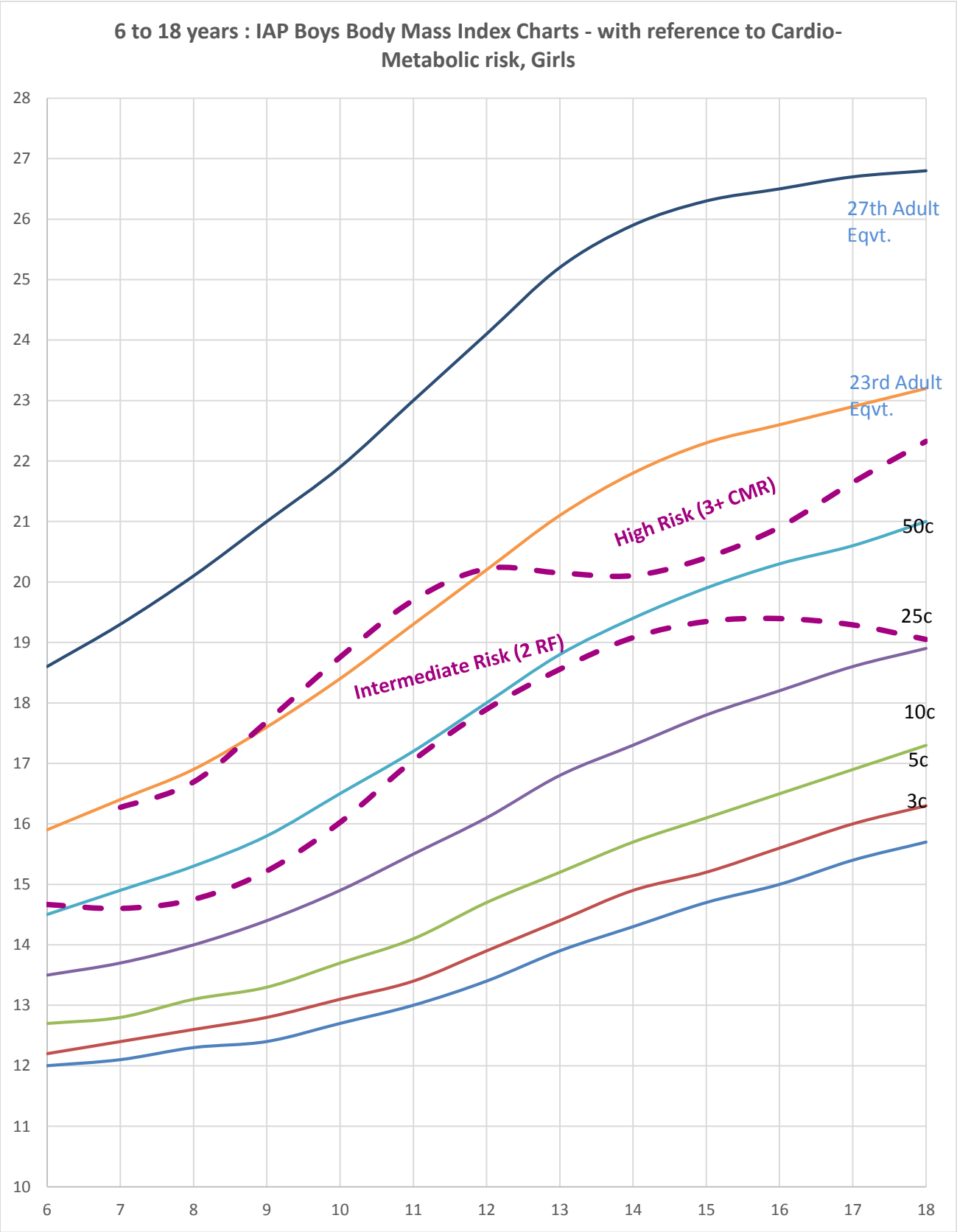


Figure 22a: FMI growth charts with reference to cardio-metabolic risk - Boys

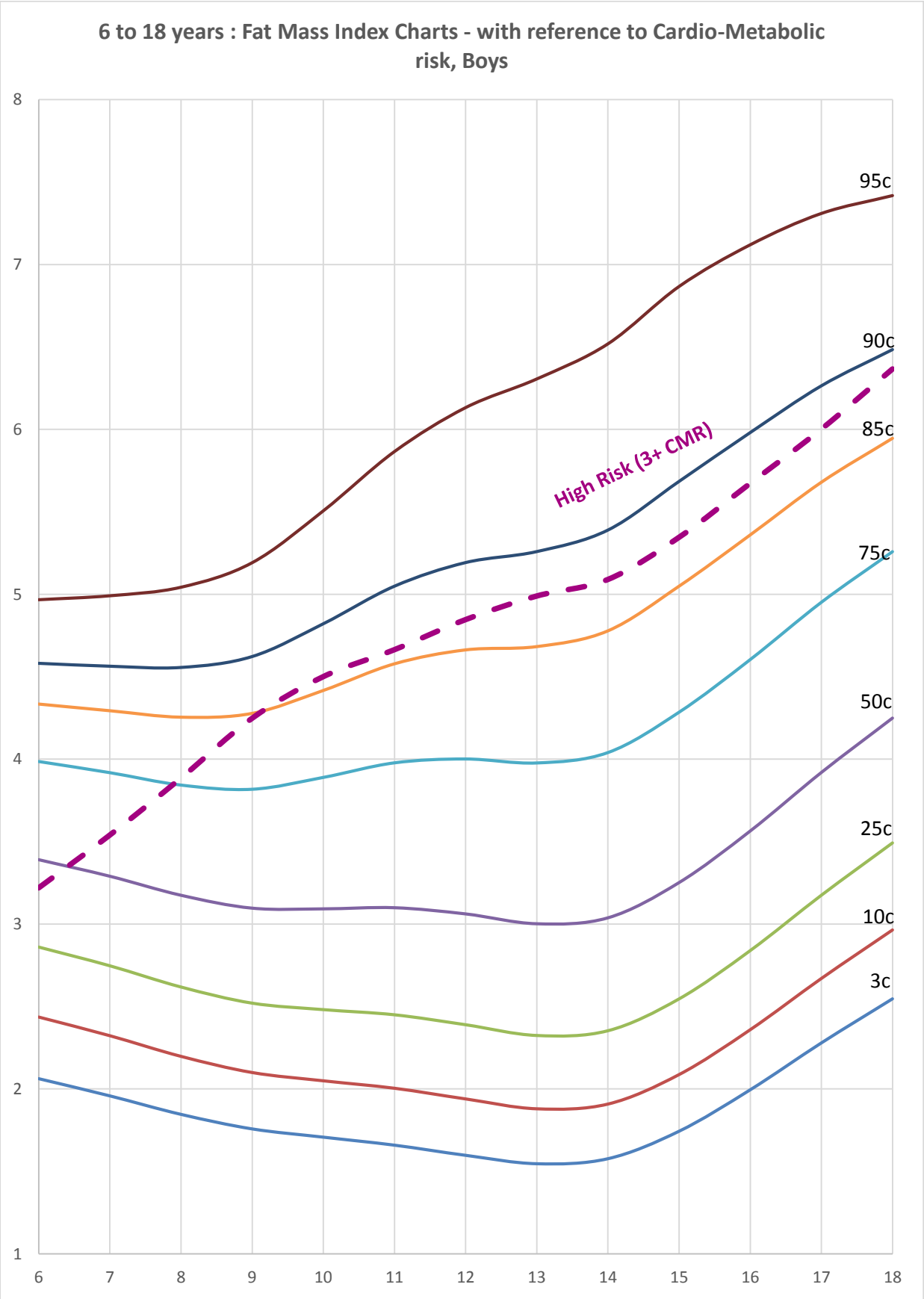
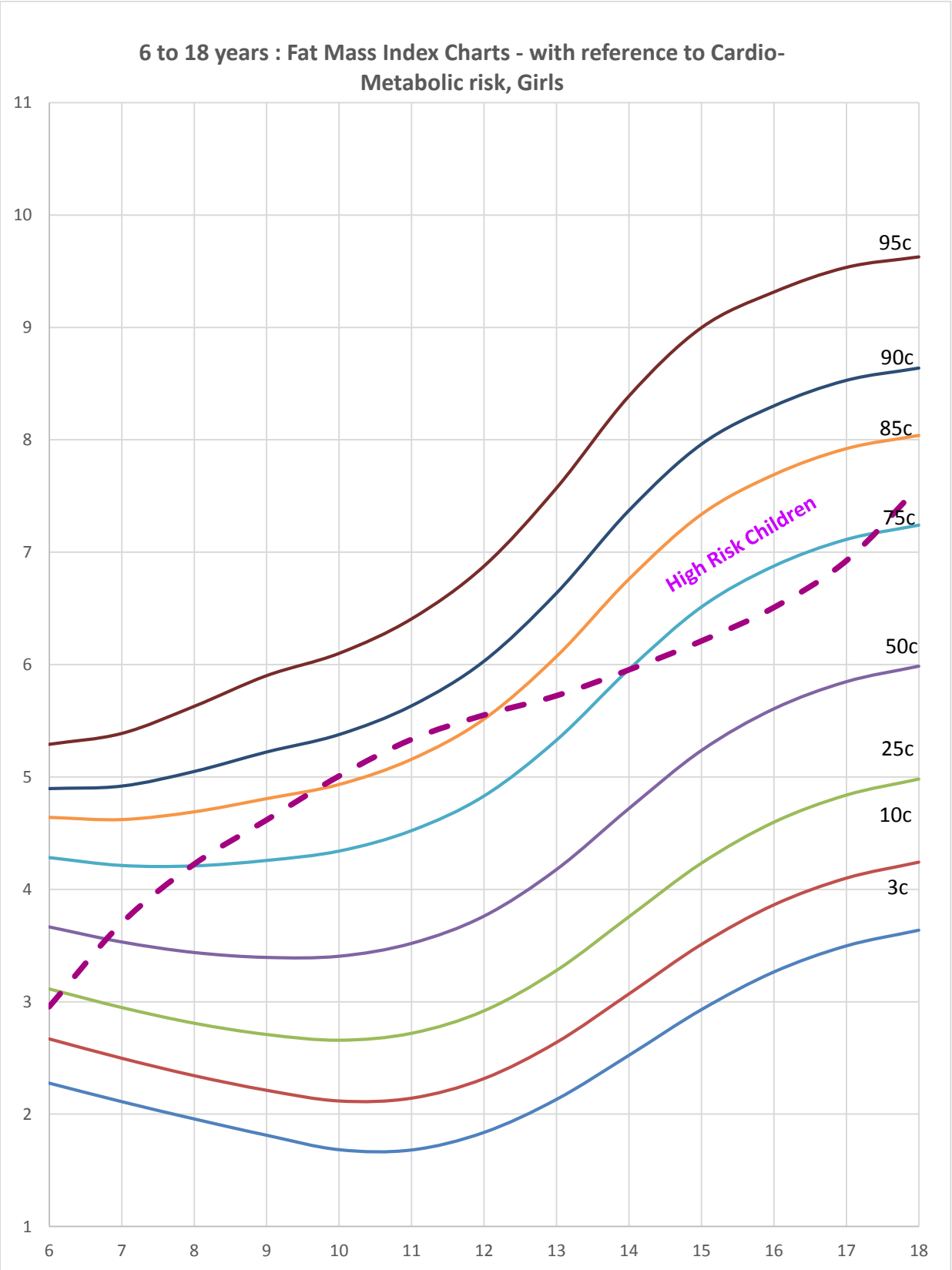


Figure 22b: FMI growth charts with reference to cardio-metabolic risk - Girls



Study 4 - A multi-level framework for monitoring cardio-metabolic risk: Proximal & distal factors associated with clustering of bio-chemical markers

4.7. Materials and Methods for study-4:

Children are influenced by physical, social, emotional, behavioural and cognitive changes influenced by several factors in the neighborhood. Influencing factors in the immediate neighborhood (home) is considered as proximal factors and those in the society are categorized under distal factors.[269] Variables attributed to child's nutritional status (Food Frequency Questionnaire), physical activity environment (at home and school), socio-economic status (standard of living index) and exposures to markets and media were captured for 3241 school children (6 to <19 years).

It is in this context, this study has attempted to understand the inter-relationships among selected factors related to clustering of cardio-metabolic risk.

1. **Specific Objectives (Study 4):** This study among 3241 children were done to understand: a) list of variables in a child's environment (individual practices, home, school and neighbourhoods) that are significantly associated with clustering of cardio-metabolic risk; b) to estimate the strength of their direct and indirect associations and c) derive a multi-level framework for monitoring cardio-metabolic risk among school children
2. **Assessments:** All 3241 children have filled a) Socio-Economic Status (SES) questionnaire; b) Food Frequency Questionnaire (FFQ); c) Children Physical Activity Questionnaire – Part A and Part B; and d) Media exposure and Marketing Behaviour Questionnaire. Interviews were conducted at schools through trained research staffs and after primary cleaning these information were used to derive:

    a. **Standard of Living Indices (SLI)**: National Family Health Survey (NFHS-round 3) has developed and used a standard of living index (SLI), using economic proxies, to measure Indian household standards based on availability and access to 38 indicators. They have used principal component analysis (PCA) and factor analysis to develop this wealth index and classified the entire population in to wealth quintiles.[270] NFHS-3 have collected data pertaining to 109,000 households; women and men separately. From this standard wealth index, in this study a subset of 11 indicators were extracted from the socio-economic status (SES) questionnaire and followed the same guidelines to create a standard of living index

(SLI) for all 3241 participants. To accommodate regional variation in standard of living this was estimated separately for each study locations and for gender. Weightage was given to each proxy variables and a composite score (matching NFHS-3 data) were derived. Finally children were categorized in to very poor, poor, middle, upper middle and higher socio-economic class based on wealth quintiles.

b. **Estimation of per-capita consumption of micro and macro nutrients:** Around 91% (2958/3241) of participants have filled food frequency questionnaires (FFQ) and self-reported approximate frequency and quantity of Indian foods, consumed in last 1 month. The list encompassed over 110 commonly consumed food recipes, targeted for each ethnic locations. Major food categories were cereals, pulses, vegetables, fruits, meat/poultry/fish, fat and oils, sugar and sweets, salted food items, nuts and beverages. Standardized bowls (cup sizes) were shown to children to capture the approximate quantity of consumption. Children had opportunity to mention additional food items within each food category. It's known fact that FFQ's are subjected for recall bias and over reporting and therefore, for cross verification of FFQ's, a 3 day 24 hour dietary recall questionnaire were administered in a subset of 371 children (boys and girls representing all 3 study locations).

   DietCAL© is a software for dietary assessment and planning, from Department of Dietetics, All India Institute of Medical Sciences (AIIMS) which was used to estimate the per-capita micro and macro nutrient contents per food items consumed. In the background, DietCAL has inbuilt recipes for most of Indian food items, for specific locations, as per the dietary guidelines by National Institute of Nutrition, Hyderabad (issued in 2010).[271] A library of standard repositories of recipes for all food items in the FFQ's were prepared and used in the DietCAL. For packaged foods the content information in the food labels were included in the repository. Per-capita consumption, approximated for a single day, for major food groups and for major nutrients were obtained from this software. Per day intake of energy (kcal), consumption of macro-nutrients (fat, proteins and carbohydrates) and micro-nutrients (minerals and vitamins) were estimated.

c. **Nutrient Adequacy:** To check for adequate consumption of nutrients per child, nutrient adequacy ratio (NAR) was calculated for energy intake, protein and 12 micro nutrients (Calcium, Iron, Magnesium, Zinc, Vit-A, Vit-B1(thiamine), Vit-B2 (riboflavin), niacin, Vit-B6(pyridoxine), Vit-C(ascorbic acid), Vit-B9(dietary folate) and Vit-B12). NAR for each nutrients were defined as the ratio of child's intake to the current recommended dietary allowance (RDA) for boys and girls in specific age groups (as explained by Hatloy A et al.,

(1998)).[272] Mean Adequacy Ratio (MAR) was calculated as an overall measure of nutrient adequacy.[273]

$$\text{NAR} = \frac{\text{Daily Nutrient Intake}}{\text{Reccomended amont of nutrients}}$$

$$\text{MAR} = \frac{\text{Sum of NAR}}{\text{Number of Nutrients}}$$

Values of nutrient adequacy (NAR and MAR) at 1 (or 100%) represents ideal situation as it mean that the intake is same as per the requirement.[274] Habte TY and Krawinkel M (2016) explains that there is no less adequate or more adequate nutrients and therefore anything below or above the recommendation can be deficient or an imbalance and in isolation and in combinations can cause adverse nutritional consequences.[275] As per our literature search, no optimal cut-offs has been established so far that could categorise over or under-consumption of nutrients.[276] As the debate continues, Armar-klemesu A et al., (1995) considered the ratio of 0.8 as a cut-off for inadequacy;[277] which was followed in this study. Most studies have truncated NAR and MAR at 1 (or 100%) however since we are more focussed on over-consumption no truncation exercise was done. We have arbitrarily selected 1.2 (120%) as a cut-off that shall indicate imbalance – those children <0.8 as inadequate, 0.8 to 1.2 as sufficient and >1.2 as over-consumption. In addition, to NAR and MAR this study have also estimated average intake (in grams) of major food groups. The results are reported for 3 age groups: 6 to <10 years, 10 to <15 years and 15 to <19 years. No dietary diversity scores were estimated. NAR and MAR in each cardio-metabolic risk categories were studied separately.

d. **Child's physical activity pattern:** In addition to nutrition adequacy healthful behaviour of child is determined by the structured and unstructured physical activity behaviour at school, household and in the neighbourhoods. This was captured through two physical activity questionnaire (Part A and B) modified from GPAQ (Global Physical Activity Questionnaire, by WHO).[278] Part A questionnaire captures the duration and frequency of outdoor and indoor sports activities, activities at school and leisure time activities while part B questionnaire focus on unstructured activities like sleep, travelling to school, neighbourhood and home related activities. All activities were reported for Monday to Friday (week days) and for Saturday and Sunday (week end) separately. These were self-reported questionnaire which are subjective to over-reporting and recall bias - for cross verification purpose a 24 hour recall of physical activity was administered in a subset of 371 children.

Across the globe, Metabolic Equivalent of Tasks (METs) are commonly used to express the intensity of physical activity. WHO defines MET as the ratio of working metabolic rate in relation to their resting metabolic rate – one MET is the energy cost of sitting quiet (resting metabolic rate, RMR) which is equivalent to 1kcal/kg/hour.[279] Sometimes it is also expressed in terms of oxygen uptake (around 3.5 ml/kg/min of oxygen for sitting quiet). Few studies report physical activity levels (PAL) which is the ratio of total energy expenditure (TEE) and child's basal metabolic rate (BMR). Total energy expenditure are also reported often while it is dependent on the child's body weight. Both TEE and PAL requires 24 hour approximation however this study have focussed only on physical activity pattern in children during week days and week end based on the MET minutes.

Each physical activity reported by children were assigned a standard MET using values described by Ainsworth et al., (2011).[280] Further, activities were categorised as sedentary (1.0 to 1.5 METs), light (1.6 to 2.9 METs), moderate (3.0 to 5.9 METs) and vigorous (≥ 6 METs) [Gibson P.E et al., (2015)].[281] Duration of time (in minutes) spent on each activities were multiplied with standard MET values to estimate the MET minutes on each type of activities. Duration on types of activity (sedentary, light, moderate and vigorous) for a single day (24 hours) during week days (Monday to Friday), week-end (Saturday and Sunday) and for the 7 day week were computed. Data are the presented as percentage time spent on each type of activity among all reported activities. Duration of sleep with clustering or risk were tested separately. No approximation for 24 hours were made as the questionnaire was designed to understand the pattern of physical activity among children. Emerging patterns were studied separately in different cardio-metabolic risk categories.

e.**Influence of environmental drivers:** In addition to nutrient and physical activity; association with clustering of cardio-metabolic risk were tested for environmental exposures like: distance of school from home, mode of transport to school (motorized transport, bicycling and walking), duration of physical training at schools, recess time activities at school, duration on study at home/tuitions, screen times (TV, computer, gadgets), separate TV in child's room, access to mobile phones etc. Frequency and intensity of different type of neighbourhood and home activities (sedentary, light, moderate and vigorous games or sports) were also tested.

Availability and access to gadgets and print media (journals/magazines, news-paper), response to food advertisements, response to branding and marketing techniques etc., were also tested. Proxies were used to assess the parenting style which includes: parental control

on gadgets (TV, internet), food purchase behaviour (packed/ready to eat foods), eating out, pocket money etc. Drivers of food choices like nutritive values, appearance, packaging and other social influencers were also tested.

Results:

Demographic characteristics of the sample is already described in study 1, 2 and 3.

a. Socio-economic conditions (SES): Among 1601 boys and 1624 girls; around 44.7% (716) boys and 42% (678) girls were from higher socio-economic (SES) condition, 31.7% (507) boys and 31.2% (507) girls were from upper middle SES conditions, 13.9% (223) boys and 15.8% (257) girls from middle SES conditions, 6.6%(106) boys and 7.7% (125) girls were from poor SES conditions and 3.1% (49) boys and 3.5% (57) girls were from very poor SES conditions - as per standard of living (SLI quartile) categorization. Among 1346 rural children, around 23.4% (315) were from high SES, 40% (537) from upper middle SES, 20.4% (275) from middle, 11% (149) from poor and 5.2% (70) were from very poor SES category. Among 1879 urban children, around 57.4% (1079) were from high SES, 25.4% (477) form upper middle SES, 10.9% (205) from middle SES, 4.4% (82) from poor SES and 1.9% (36) from very poor SES category. Distribution was similar across ethnic locations.

Among all children in higher SES households 3.6% boys (26) and 5.8% girls (39) were having 3 and more risk factors as compared to 1.4% boys (7) and 4.5% girls (23) in upper middle SES class. Around 2.7% boys (6) and 5.5% girls (14) from middle SES class were also having clustering of 3 and more risk factors. In contrary some cardio-metabolic risk factors (any risk factor) were present in 29% boys and 33% girls of very poor SES households and among 21% boys and 28% of girls in poor SES classes (as indicated in Table 26). Such distributions reiterate that cardio-metabolic risk as well as obesity is not only a problem of affluence and the risk is distributed across social strata, urban-rural settings and gender; however the pathways mediating risk may be different.

Socio-economic conditions of the family is closely associated with occurrence of overweight and obesity (Table 28). Among all children in higher SES households, around 20% boys (143/211) and 19.9% girls (135/232) were either overweight or obese. Around 8.3% (42/211) boys and 12% (61/232) girls from upper middle SES category were also overweight or obese. In addition, 8.5% of boys (19/223) and 10.9% girls (28/257) in middle SES households; 3.7% boys (4/106) and 5.6% girls (7/125) of poor SES households and 6% boys (3/49) and 1.7% girls (1/57) of very poor

SES households are also overweight or obese. This indicates that the risk of overweight/obesity is not limited to affluence.

b. Nutrient Adequacy: Studies highlights that nutrient inadequacy and cardio-metabolic risk and overweight/obese can co-exist in same individuals, families, or in communities.[282] Nutrient security exist; *"when all people, at all times, have physical, social and economic access to sufficient, safe, and nutritious food to meet their dietary needs and food preferences for an active and healthy life"*.[283] As mentioned earlier, per-capita per day consumption of energy, proteins and 11 micro-nutrients from DietCAL© were used to estimate Nutrient Adequacy Ratio and Mean Adequacy Ratio (MAR) – results are presented as median and interquartile range (Q25th and Q75th) for 3 age groups (6 to <10 years, 10 to <15 years and 15 to <19 years) (Table 29a and 29b).

Energy intake pattern: Overall, around 36.5% boys (537/1473) and 34.8% girls (517/1485) were consuming inadequate energy per day (less than 80% of recommended dietary intake). At the same time, 29% (429/1473) boys and 26.2% girls (389/1485) consume more than 120% of RDA. Inadequate consumption was higher among rural children: 39.9% boys (262/656) and 43.5% girls (262/616) as compared to 33.6% boys (275/817) and 29% girls (255/869) in urban settings. Among 429 boys consuming more than 120% of RDA; 6.7% (29) were obese and 11% (47) was overweight and among 389 girls 5.1% (20) was obese and 10.5% (41) was overweight. In contrary, among 537 boys with inadequate energy consumption around 3.5% (19) was obese, 4.8% (26) overweight and 7.1% (38) was thin and among 517 girls with inadequate energy consumption 1.6% was obese, 9.5% (49) was overweight and 4.1% (21) was thin. Energy intake was significantly higher among overweight/obese boys (P=0.003) (diff: +380 kcal/day) as compared to normo-weights; however this was not significantly different in girls (P=0.05). Among 38 boys with 3 and more cardio-metabolic risk factors, 36.8% (14) was consuming more than 120% energy and 26.3% (10) was consuming less than 80% of energy per day. Among 72 girls with clustering of 3 and more cardio-metabolic risk 16.7% (12) was consuming more 120% of recommended energy/day and 38.9% (28) was consuming inadequate energy. Energy intake among boys with 3 and more risk factors was significantly higher in boys (P=0.002) (diff: +686 kcal/day) however this was not different in girls (P=0.49) with 3+ risk factors. In boys with 3 and more risk factors carbohydrate intake was higher (P=0.001) (diff: 164 gm/day) while this was not different in girls (P=0.19).

Protein intake patterns: Median intake of proteins (grams/day) is sufficient and more than the recommended daily intake in 83% boys (1224/1473) and 81% girls (1194/1482). However there was 16.9% boys (249/1473) and 19.4% girls (288/1482) consuming protein less than the RDA. About 59.4% boys (875) and 50.7% girls (751) consume more than 120% of RDA. Among those

children consuming inadequate proteins; 5.2% boys (13/249) and 11.8% girls (34/288) were overweight or obese (above 23rd adult equivalent BMI for age). In addition 5.6% boys (14/249) and 5.2% girls (15/288) were thin and was consuming less protein. Among those children consuming more than 120% of RDA; around 16% boys (140/875) and 16.9% girls (127/751) were obese/overweight – interestingly around 3% boys (26/875) and 3.5% girls (26/751) consuming more than 120% RDA were thin, indicating mal-absorption. Protein consumption was 9.6 gms/day higher among overweight/obese boys (P=0.001) (diff: 9.6) while this was only 4 grams higher in overweight/obese girls (P=0.04) as compared to normo-weights. Among those 584 boys and 473 girls who were consuming more than 120% of RDA; around 4.8% boys (28) and 5.7% girls (27) were having 3 and more clustering of cardio-metabolic risk. Protein consumption was significantly higher in boys (P=0.001) (diff: 22.2) with 3 and more risk factors while protein was not different in girls (P=0.17) with 3+ CMR as compared to 0 risk factors.

Micro-nutrient intake patterns: Mean Adequacy Ratio (MAR) was estimated for 11 micro nutrients and the composite score less than 0.8 was considered inadequate and this above 1.2 was considered as more than sufficient. Among boys: MAR was 0.84 (95% CI: 0.80, 0.90) in 6 to <10 years, 1.0 (95% CI: 0.93, 1.07) in 10 to <15 years and 1.12 (95% CI: 1.02, 1.22) in 15 to <19 years. Among girls: MAR was 0.83 (95% CI: 0.79, 0.88) in 6 to <10 years, 0.89 (95% CI: 0.84, 0.94) in 10 to <15 years and 0.95 (95% CI: 0.88, 1.02) in 15 to <19 years. Overall 51.4% boys (788/1534) and 55% girls (864/1564) were consuming inadequate amount of micro-nutrients and 23% boys (356) and 18.5% girls (290) were consuming more than 120% of recommended dietary allowances.

Among boys and girls inadequate consumption was observed in:

- Calcium (mg/d) - boys 39.6% (608) & girls 44.4% (694)
- Iron (mg/d) - boys 63.8% (978) & girls 70.4% (1101)
- Vitamin A (µgm/d) - boys 99.5% (1527) & girls 99.7% (1558)
- Vitamin B6 (mg/d) - boys 99.6% (1514) & girls 99.7% (1549)
- Vitamin B12 (µgm/d) - boys 60.4% (926) & girls 65.9% (1,031)
- Vitamin C (mg/d) - boys 16.9% (260) & girls 17% (266)
- Vitamin B1(mg/d) - boys 40.6% (623) & girls 36.3%(568)
- Vitamin B2 (mg/d) - boys 69.2% (1,062) & girls 71.2%(1,113)
- Vitamin B3(mg/d) - boys 56.5% (866) & girls 57.2%(894)
- Magnesium (mg/d) - boys 2.7% (42) & girls 5.2%(82)
- Folate (µgm/d) - boys 22.6% (346) & girls 25.5%(398)
- Zinc (mg/d) - boys 73.5% (1,128) & girls 83.5%(1,302)

Among 788 boys with inadequate consumption 8.8% boys (69) and 11% girls (96) were overweight or obese. Mean Adequacy Rate was significantly different in boys (P=0.001) with BMI for age above 23rd adult equivalent (overweight/obese) while this was not significantly different in girls (P=0.06) with BMI above 23rd adult equivalents. Among those children with 3 and more cardio-metabolic risk clustering mean nutrient adequacy ratio (MAR) was higher among boys (P=0.004) while this was not different in girls. Children with 3 and more risk factors were consuming more foods containing:

Boys	**Girls**
Iron - (P=0.001) (diff=8.7 mg/day)	Magnesium - (P=0.03) (diff: 46.4 mg/day)
Vitamin A - (P=0.02) (diff=292.3 μgm/day)	
Vitamin B12 - (P=0.003) (diff=0.9 μgm/day)	
Vitamin C - (P=0.002) (diff= 53.7 mg/day)	
Vitamin B1 - (P=0.002) (diff=0.55 mg/day)	
Vitamin B2 - (P=0.001) (diff=0.48 mg/day)	
Vitamin B3 - (P=0.002) (diff=4.8 mg/day)	
Magnesium - (P=0.002) (diff=134.8 mg/day)	
Folate - (P=0.001) (diff=52.04 μgm/day)	
Zinc - (P=0.003) (diff=2.23 mg/day)	

c. Food Consumption Pattern: Apart from the micro-nutrients, major food groups consumed by boys and girls were also assessed (Table 30).

Sugar Sweetened Beverages (SSB): No particular trend was visible in SSB consumption among children with 3 and more risk factors: boys (P=0.84) (diff: +4.6 ml/day) and girls (P=0.37) (diff: +15.4 ml/day). Among overweight/obese children the per-capita consumption of SSBs were significantly less: among boys -64.6 ml/day (P=0.001) and among girls -24.9 ml/day (P=0.02). There was no difference in SSB consumption among poor SES boys and girls and among middle SES girls while this was lesser among middle SES boys and upper SES boys and girls. Broadly, SSB consumption is higher in boys (P=0.001) (diff: +36.8ml/day) and girls (P=0.001) (diff: +36.9 ml/day) in rural areas as compared to urban settings.

Snacks: Among those children with 3+ risk factors snacking was higher among boys (P=0.01) (diff: +52.2 g/day) while no difference was observed among girls (P=0.54) (diff: +6.5 g/day). Snacking was particularly high among urban boys from upper SES strata having 3+ CMR (P=0.008) (diff: +71.8 g/day) however no difference in urban girls. Among overweight/obese boys also the per-

capita per day consumption of snacks were higher: boys (P=0.003) (diff: +37.6 g/day) and in girls (P=0.07) (diff: +12.7 g/day). Overall snacking behaviour was higher among urban boys (P=0.008) (diff: +18.6 g/day) and urban girls (P=0.001) (diff: +28.3 g/day)

Cereals: Overall, cereal consumption was higher among boys (P=0.03) (diff: +93.6gm/day) and girls (P=0.005) (diff: +69 g/day) who were having clustering of 3 and more cardio-metabolic risk factors. Cereal consumption was particularly high among rural boys (P=0.004) (diff: +222.6g/d) and rural girls (P=0.009) (diff: +112 g/d) and also in higher SES class. Overweight/obese boys in urban higher SES class was consuming less amounts of cereals (P=0.01) (diff: -70.2 g/d) however no such trends were observed among girls.

Fruits: Among 3+ cardio-metabolic risk fruits consumption was more among urban boys from higher SES strata (P=0.006) (diff: +54.4 g/d) however no difference in consumption of fruits among girls with 3+ CMR clustering (P=0.43) (diff: +8.3). Among overweight/obese children, fruit consumption was significantly higher in boys (P=0.001) (diff: +24.1 g/day) and girls (P=0.001) (diff: +22.7 g/day). Overall fruit consumption were significantly higher among urban boys (P=0.001) (diff: +25.9 g/day) and girls (P=0.001) (diff: +44 g/day).

Vegetables: Among children with 3+ risk factors urban boys from higher SES strata were consuming more vegetables (P=0.007) (diff: 102.3 g/d). Similarly among overweight/obese boys from higher SES urban households were having more vegetables (P=0.003) (diff: +72.6 g/d). No pattern could be observed among girls. Overall vegetable consumption were higher in rural area poor SES boys (P=0.002) (diff: +69.5 g/d) and in urban high SES boys (P=0.003) (diff: +28 g/d) – no specific pattern in girl children.

Dairy Products: Per-capita consumption of dairy products were higher among 3+ CMR risk boys from urban higher SES households (P=0.001) (diff: 134.4 g/d). This was also higher among overweight/obese boys (P=0.001) (diff: +58.1 gm/day) and girls (P=0.001) (diff: +48.7 gm/day).

Pulses: Among 3+ CMR children, pulse consumption was higher among urban girls from middle SES households (P=0.04) (diff: 64.5 g/d) however no other pattern could be identified. Among overweight/obese children, pulses were consumed more by girls in urban higher SES households (P=0.02) (diff: 20.5 g/d).

Predictors of food consumption on cardio-metabolic risk: After adjusting for socio-economic conditions (SLI-3), urban-rural settings and for age groups; among boys inadequacy of micro-nutrients were significantly predicting clustering of CMR (OR=3.2; P=0.03) while among girls inadequacy of

proteins (P=0.000) and micro-nutrients (OR=7.9; P=0.001) were significantly predicting the clustering of cardio-metabolic risk. For overweight/obesity the significant predictor was also micro-nutrient deficiency (OR=1.7, P=0.04) in boys and girls (OR=2.03, P=0.03) – however urban rural settings interacts with energy consumption among boys.

Among various food groups the association with clustering of cardio-metabolic risk were tested. All food groups were poorly correlated indicating independency in the model. In the multivariate analysis on food groups after adjusting for age-groups and settings, snack eating behaviour (P=0.006) and sugar sweetened beverages consumption (P=0.019) were found to be positively associated with increase in BMI among boys. However there was no such association among girls. Similarly, per-capita cereal consumption was the only food group that was associated with 3+ clustering of cardio-metabolic risk among girls. Among boys, no food groups were significantly associated with clustering of CMR.

d. Physical activity pattern: For boys and girls, average duration (% time) and MET minutes (median) on sedentary, light, moderate and vigorous physical activities (for 3 age groups - 6 years to <10 years, 10 years to <15 years, 15 to <19 years) have been presented in Table 31a and 31b – for weekdays, weekends and 7-day average. In addition, duration of sleep (in minutes) per day reported by the child is also presented.

Sedentary activities: Duration of sedentary activities (in minutes and % time of all activities) and their MET minutes, during week days and weekends were not significantly different among children with 3+ clustering of risk factors; both in rural and urban settings. However, during week days (Monday to Friday), boys with 3+ CMR spent 3.5% more time on sedentary activities (P=0.013) while girls with 3+ CMR spent 1.8% more time on sedentary activities (P=0.09). No such pattern were observed for week-ends. Overweight/obese boys spent 15.3 % time on sedentary activities during week days (P=0.001) (diff: +3.6%) as compared to 16.1% time on sedentary activities on a week end (P=0.0002) (diff: +2.8%). At the same time overweight/obese girls spent 13.9% time on sedentary activities (of all activities reported) during week days (P=0.005) (diff: +2.3%) as compared to 14.4% time on week end (P=0.57) (diff: +0.44) (however there was no significant difference on a week end).

Light activities: No specific pattern on light physical activities (duration as well as MET minutes) could be observed between children with clustering of cardio-metabolic risk; both in rural and urban settings or across 3 age groups in boys and girls. Overall boys with 3+CMR were spending 4% time, in any week day, on light activities as compared to 3% time among boys with no risk

factors. Girls with 3+ CMR were spending 3.6% time, in a week day, on light activities as compared to 2.9% time by girls with no risk factors. Similarly, no specific trend could be observed in the duration of light physical activities and their MET minutes among overweight/obese boys and girls in urban and rural settings.

Moderate activities: No specific trend could be observed on moderate physical activities among children with clustering of risk factors as well as for overweight or obese boys and girls in urban rural settings.

Vigorous activities: Urban – rural difference and age-groups (6 years to <10 years, 10 years to <15 years, 15 to <19 years) influence vigorous physical activities – duration (percentage time) spent on vigorous physical activities (among all activities reported) among children with 3 and more clustering of risk factors are presented in table 32. No pattern in vigorous physical activities could discriminate children with clustering of risk factors. Similarly, either MET minutes or duration on vigorous physical activity could not discriminate overweight/obese children from normal weight children. Often it is reported that overweight/obese children spent more time on vigorous physical activities in urban as well as rural settings: urban overweight/obese boys claims to spent 5.4% time on vigorous activities (on a week day) as compared to 4.2% time by normal weights; rural overweight/obese boys claims to spent 3.7% time on vigorous activities as compared to 3.2% time by normal weight children. Similar trend has been observed among girls also.

Multivariate Analysis on Physical Activity types on Cardio-metabolic risk: After adjusting for age groups (6 to <10 years, 10 to <15 years and 15 to <19 years), gender and rural-urban settings the multivariate analysis could not discriminate children with 3+ clustering of risk factors vs. no risk factors on the basis of type of physical activities reported. In contrary, among overweight/obese boys, percentage time spent on sedentary physical activities during week days (P=0.014) and light physical activities during week end's (P=0.011) were positively associated with increase in BMI while percentage time spent on moderate physical activities during week days (P=0.025) were negatively associated with increase in BMI. Similarly, among overweight/obese girls, percentage time spent on sedentary activities during week days (P=0.008), week end's (P=0.02) and percentage time on vigorous physical activities during week days (P=0.026) were positively associated with increase in BMI.

e. Other Environmental Drivers of clustering of cardio-metabolic risk (Table 33):

Sleep Duration: Among boys and girls, duration of sleep was found as a protective factor for clustering of cardio-metabolic risk.

Mode of transport to school: Boys commuting to schools in motorized scooter/bike were having 5 times increased risk of clustering of cardio-metabolic risk as compared to those walking to schools – however this relationship were not significant among girls. In contrary, boys and girls commuting by bicycle are protected. There can be several other factors that needs to adjust to understand the dynamics.

Distance of school from home: Another factor which was found significantly associated with clustering of risk factors among boys is the distance of school from home however this was not significant among girls. In contrary, time taken to travel from school to home (vice versa) were found to be significantly associated in both boys and girls.

Access to gadgets: Increase access to video games, DVD, Radio/FM, Computer/laptops, separate video games and personal mobile phones were all significantly associated with clustering of risk factors. Duration of watching TV were also found associated. All these factors require further adjustments and interactions with other environmental factors.

Table 26: Distribution of overweight and obesity and cardio-metabolic risk in different socio economic strata's

BMI for Age	**Thin %(n)**		**Normoweight %(n)**		**Overweight %(n)**		**Obese %(n)**	
	Boys	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**
Very Poor SES	2.04 (1)	1.75 (1)	91.84 (45)	96.49 (55)	6.1 (3)	1.8 (1)	0	0
Poor SES	6.6 (7)	5.6 (7)	89.62 (95)	88.8 (111)	2.8 (3)	3.2 (4)	0.94 (1)	2.4 (3)
Middle SES	4.04 (9)	3.5 (9)	87.44 (195)	85.6 (220)	6.3 (14)	9.3 (24)	2.24 (5)	1.56 (4)
Upper middle SES	6.31 (32)	5.92 (30)	85.4 (433)	82.05 (416)	5.9 (30)	10.7 (54)	2.37 (12)	1.38 (7)
High SES	2.65 (19)	2.21 (15)	77.37 (554)	77.88 (528)	11.7 (84)	13.1 (89)	8.24 (59)	6.78 (46)
Clustering of CMR	**0 Clustering %(n)**		**1 Risk Factor %(n)**		**2 Risk Factors %(n)**		**≥3 Risk Factors %(n)**	
	Boys	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**
Very Poor SES	71.4 (35)	66.7 (38)	16.3 (8)	17.54 (10)	10.2 (5)	12.3 (7)	2.0 (1)	3.5 (2)
Poor SES	79.3 (84)	72.8 (91)	14.2 (15)	20 (25)	4.7 (5)	4.8 (6)	1.9 (2)	2.4 (3)
Middle SES	67.3 (150)	62.5 (161)	22 (50)	20 (51)	7.6 (17)	12.1 (31)	2.7 (6)	5.5 (14)
Upper middle SES	61.3 (311)	52.3 (265)	28.0 (142)	32.2 (163)	9.3 (47)	11.1 (56)	1.4 (7)	4.5 (23)
High SES	58.7 (420)	50.4 (342)	28.5 (204)	31.7 (215)	9.2 (66)	12.1 (82)	3.6 (26)	5.8 (39)

Table 27a: Average intake of nutrients per day, recommended dietary allowance (RDA), Nutrient Adequacy Ratio (NAR) and proportion of children with intake below 80% of RDA - Boys

Boys	Average Intake per day			Recommended Dietary Allowance as per ICMR				Median NAR			Proportion of children with not adequate intake (<80% recommendation)		
Median, (Q25, Q75)	6 to <10y	10 to <15y	15 to <19y	7 to <10y	10 to <12y	13 to <15y	15 to <19y	6 to <10y	10 to <15y	15 to <19y	6 to <10y	10 to <15y	15 to <19y
Energy (kcal/d)	1585 (1279,2049)	2120 (1557,3060)	2726 (1961, 3932)	1690	2190	2750	3020	1.0 (0.8, 1.24)	0.87 (0.65,1.25)	0.94 (0.66,1.35)	28.5 (122)	42.7 (276)	34.8 (139)
Protein (gms/d)	43.29 (33.1,56.8)	56.6 (39.5,83.2)	74.6 (54.3, 106.9)	29.5	39.9	54.3	61.5	1.58 (1.2, 2.1)	1.25 (0.90,1.81)	1.27 (0.91,1.76)	11.3 (383)	18.9 (122)	19.8 (78)
Calcium (mg/d)	576.8 (373, 788)	690 (433,1038)	828.5 (548.4, 1247)	600	800	800	800	0.96 (0.6, 1.3)	0.86 (0.54,1.30)	1.04 (0.69,1.56)	35.8 (170)	42.7 (304)	31.6 (134)
Iron (mg/d)	11.01 (6.88,16.1)	14.5 (8.62,22.9)	19.9 (10.5, 28.2)	16	21	32	28	0.70 (0.4, 1.03)	0.59 (0.37,0.89)	0.67 (0.37,0.97)	56.1 (254)	69.8 (469)	62.4 (255)
Vit-A (µgm/d)	184.5 (119,324.7)	246.4 (135.1,479.6)	328.4 (172.8, 735.8)	600	600	600	600	0.04 (0.02,0.07)	0.05 (0.03,0.10)	0.07 (0.04,0.15)	100 (453)	99 (668)	99 (406)
Vit B6 (mg/d)	0.014 (0.002,0.065)	0.021 (0.004,0.101)	0.015 (0.002, 0.069)	1.6	1.6	2	2	0.01 (0.00,0.05)	0.01 (0.00,0.06)	0.01 (0.00,0.03)	100 (452)	99.3 (664)	99.7 (398)
Vit B12 (µgm/d)	0.52 (0.28,0.94)	0.63 (0.37,1.35)	0.80 (0.46, 2.1)	0.2-1	0.2-1	0.2-1	0.2-1	0.52 (0.28,0.94)	0.63 (0.37,1.35)	0.80 (0.46,2.08)	70.6 (320)	59.7 (401)	50.3 (205)
Vit C (mg/d)	60.2 (35.0, 88.33)	75.1 (41.1,113.9)	88.8 (53.9, 143.9)	40	40	40	40	1.50 (0.87,2.21)	1.88 (1.03,2.85)	2.22 (1.35,3.60)	22.7 (103)	16.8 (113)	10.8 (44)
Vit B1 (mg/d)	0.88 (0.48, 1.23)	1.11 (0.61,1.70)	1.5 (0.83, 2.1)	0.8	1.1	1.4	1.5	1.11 (0.60,1.61)	0.89 (0.52,1.39)	1.01 (0.57,1.46)	36.4 (165)	44.4 (298)	39 (160)
Vit B2 (mg/d)	0.62 (0.40, 0.86)	0.76 (0.51,1.22)	1.03 (0.67, 1.6)	1	1.3	1.6	1.8	0.64 (0.43,0.89)	0.56 (0.37,0.85)	0.59 (0.39,0.90)	66.2 (300)	71.7 (482)	68.5 (280)
Vit B3 (mg/d)	8.30 (5.67, 11.22)	11.2 (7.14, 15.5)	14.6 (9.4, 20.0)	13	15	16	17	0.65 (0.44,0.89)	0.72 (0.47,1.00)	0.88 (0.56,1.18)	65.5 (297)	57.6 (387)	44.5 (182)
Magnesium (mg/d)	281 (195,361.8)	362.8 (255, 528)	466.9 (334.2, 667.2)	100	120	165	195	2.84 (1.99,4.03)	2.70 (1.93,3.75)	2.58 (1.81,3.53)	2.7 (12)	2.7 (18)	2.9 (12)
Folate (µgm/d)	146.8 (99.6,198.7)	181.4 (124, 274)	237.1 (152.8, 353.5)	120	140	150	200	1.30 (0.83,1.67)	1.26 (0.87,1.92)	1.27 (0.83,1.96)	23.6 (107)	21.1 (142)	23.7 (97)
Zinc (mg/d)	4.44 (3.13,5.74)	5.8 (4.1, 8.3)	7.5 (5.4, 10.4)	8	9	11	12	0.56 (0.40,0.73)	0.60 (0.43,0.84)	0.65 (0.46,0.90)	80.7 (366)	71.7 (482)	68.5 (280)

Table 27b: Average intake of micro-nutrients per day, recommended dietary intake, Nutrient Adequacy Ratio (NAR) and proportion of girls with intake below 80% of RDA - Girls

Girls	Average Intake per day			Recommended Intake				Median NAR			Proportion of children with intake not adequate (<80% recommendation)		
Median, (Q25, Q75)	6 to <10y	10 to <15y	15 to <19y	7 to <10y	10 to <12y	13 to <15y	15 to <19y	6 to <10y	10 to <15y	15 to <19y	6 to <10y	10 to <15y	15 to <19y
Energy (kcal/d)	1657 (1270,2066)	1932 (1458,2652)	2094 (1666,2762)	1690	2010	2330	2440	1.01 (0.77,1.27)	0.90 (0.68,1.27)	0.87 (0.69,1.16)	28.5 (123)	36.3 (227)	39.0 (167)
Protein (gms/d)	42.7 (33.3,55.8)	50.8 (37.9,69.1)	57.2 (44.3,75.0)	29.5	40.4	51.9	55.5	1.50 (1.15,2.01)	1.14 (0.87,1.57)	1.04 (0.83,1.36)	12.3 (53)	21.2 (132)	24.0 (103)
Calcium (mg/d)	592.6 (354.1,800.4)	634.9 (403.5,956.2)	699.1 (455.6,932.5)	600	800	800	800	0.99 (0.59,1.33)	0.79 (0.50,1.20)	0.87 (0.57,1.17)	37.6 (176)	48.5 (333)	38.9 (185)
Iron (mg/d)	11.4 (7.4,15.8)	13.9 (8.5,20.5)	16.4 (10.2,21.5)	16	27	27	26	0.72 (0.46,1.01)	0.51 (0.31,0.76)	0.63 (0.39,0.81)	56.9 (258)	77.7 (510)	73.2 (333)
Vit-A (µgm/d)	177.5 (113.0,329.8)	218.6 (123.6,389.6)	217.6 (136.8,421.7)	600	600	600	600	0.04 (0.02,0.07)	0.05 (0.03,0.08)	0.05 (0.03,0.09)	99.8 (451)	100 (656)	99.1 (451)
Vit B6 (mg/d)	0.022 (0.005,0.075)	0.019 (0.003,0.101)	0.025 (0.003,0.068)	1.6	1.6	2	2	0.02 (0.00,0.05)	0.01 (0.00,0.06)	0.01 (0.00,0.03)	99.8 (449)	99.7 (649)	99.6 (451)
Vit B12 (µgm/d)	0.526 (0.301,0.941)	0.564 (0.328,1.083)	0.544 (0.329,1.163)	0.2-1	0.2-1	0.2-1	0.2-1	0.53 (0.30,0.94)	0.56 (0.33,1.08)	0.54 (0.33,1.16)	70.6 (320)	63.9 (419)	64.2 (292)
Vit C (mg/d)	58.4 (32.7,87.7)	71.6 (42.3,118.3)	75.8 (49.6,124.5)	40	40	40	40	1.46 (0.82,2.19)	1.79 (1.06,2.96)	1.90 (1.24,3.11)	23.6 (107)	16.6 (109)	10.9 (50)
Vit B1 (mg/d)	0.839 (0.524,1.161)	1.029 (0.571,1.500)	1.258 (0.747,1.660)	0.8	1	1.2	1	1.06 (0.65,1.52)	0.96 (0.53,1.42)	1.19 (0.70,1.62)	34.2 (155)	41.6 (273)	30.8 (140)
Vit B2 (mg/d)	0.622 (0.423,0.850)	0.703 (0.482,1.023)	0.807 (0.584,1.095)	1	1.2	1.4	1.2	0.63 (0.43,0.87)	0.54 (0.37,0.80)	0.63 (0.47,0.88)	67.9 (308)	75 (492)	68.8 (313)
Vit B3 (mg/d)	8.39 (5.66,10.48)	9.91 (6.80,13.77)	11.67 (8.09,15.18)	13	13	14	14	0.66 (0.44,0.85)	0.75 (0.50,1.02)	0.83 (0.58,1.08)	69.8 (316)	56.4 (370)	45.7 (208)
Magnesium (mg/d)	275.8 (201.6,344.2)	336.0 (243.6,452.1)	380.2 (277.0,495.5)	100	160	210	235	2.79 (2.05,3.90)	1.90 (1.33,2.59)	1.68 (1.20,2.16)	1.5 (7)	5.8 (38)	8.13 (37)
Folate (µgm/d)	144.6 (105.2,192.0)	168.9 (118.8,253.4)	186.0 (131.3,259.3)	120	140	150	200	1.24 (0.88,1.63)	1.16 (0.82,1.76)	0.99 (0.71,1.46)	20.7 (94)	23.9 (157)	32.3 (147)
Zinc (mg/d)	4.40 (3.23,5.50)	5.42 (3.91,7.16)	6.21 (4.41,7.87)	8	9	11	12	0.56 (0.40,0.71)	0.55 (0.39,0.74)	0.53 (0.38,0.67)	82.8 (375)	79.3 (520)	89.5 (407)

Table 28: Food consumption pattern among children for major food groups – calculated in grams per day for boys and girls

	Boys			**Girls**		
Median, (Q25, Q75)	**Average Intake per day**			**Average Intake per day**		
	6 to <10 years	10 to <15 years	15 to <19 years	6 to <10 years	10 to <15 years	15 to <19 years
Sugar Sweetened Beverages (ml/person/day)	110 (43.6, 210.7)	140 (60.5, 219.7)	200 (105.5, 400)	106.4 (28.6, 210)	118.2 (43.6, 224)	153.2 (105, 280)
Snacks* (gm/person/day)	73.2 (23.7,119.3)	98.3 (41.1,167.2)	129.3 (38.1,272.1)	81.4 (40.8,117.6)	87.6 (35.5,163.3)	107.9 (52.2,162.5)
Cereals (gm/person/day)	366.8 (256.1,476.4)	485.7 (342.6,693.9)	634.1 (435.6,878.4)	347.4 (252.7,459.5)	435.2 (308.5,630.5)	460.0 (360.2,605.7)
Fruits (gm/person/day)	52.1 (14.8,97.1)	52.1 (16.4,116.0)	70.4 (19.7,137.4)	48.0 (13.7,101.2)	51.6 (15.2,123.5)	62.9 (17.1,117.6)
Vegetables # (gm/person/day)	43.5 (7.7,87.9)	37.7 (12.6,77.4)	50.3 (19.6,100.3)	37.7 (11.6,87.9)	25.1 (8.7,75.4)	50.3 (16.7,100.3)
Dairy Products (gm/person/day)	159.5 (37.8,234.6)	166.2 (35.0,282.6)	182.7 (35.3,337.8)	162.8 (40.3,223.7)	156.5 (30.0,274.8)	155.5 (28.8,225.4)
Pulses (gm/person/day)	75.6 (44.1,125.1)	84.4 (44.1,143.6)	88.3 (45.6,168.9)	69.1 (32.8,127.4)	68.2 (33.3,135.8)	78.9 (38.5,121.0)

Note: The consumption rates are calculated per days in gms/ml from the food frequency questionnaire. * This category include salty, fried and packaged snacks & sweets and confectionaries. # Vegetable category include green leafy vegetables (GLV), all other vegetables, and roots and tubers)

One limitation in this analysis of food groups is that consumption of food groups are overlapping with specific food recipes which cannot be discriminated using a FFQ. This can be done through a 3 day dietary recall.

Table 29a: Percentage time spent on types of physical activities (among all reported activities) - Boys

Physical activity	Boys					
	6 years to < 10 years		10 years to < 15 years		15 to < 19 years	
	Duration %	Met Minutes	Duration %	Met Minutes	Duration %	Met Minutes
	Median (P25, P75)	Median (P25, P75)	Median (P25, P75)	Median (P25, P75)	Median (P25, P75)	Median (P25, P75)
Sedentary Activity						
7- day	67 (52, 84)	120 (69, 201)	62 (43, 78)	137 (69, 216)	60 (45, 75)	159 (80, 245)
Weekday	59 (41, 72)	126 (61, 215)	52 (37, 68)	138 (66, 232)	55 (41, 68)	158 (72, 263)
Weekend	59 (42, 73)	152 (85, 230)	47 (30, 65)	158 (84, 242)	50 (33, 66)	179 (108, 294)
Light Activity						
7- day	14 (8, 22)	37 (16, 75)	12 (7, 20)	46 (21, 92)	15 (8, 25)	62 (27, 114)
Weekday	12 (7, 19)	36 (23, 64)	13 (7, 20)	46 (25, 92)	14 (7, 25)	57 (30, 110)
Weekend	15 (9, 24)	50 (29, 106)	13 (8, 21)	73 (33, 144)	16 (8, 25)	95 (48, 182)
Moderate Activity						
7- day	20 (13, 31)	98 (51, 171)	22 (13, 33)	133 (57, 229)	17 (9, 25)	104 (45, 195)
Weekday	21 (12, 33)	105 (56, 200)	20 (12, 31)	132 (66, 244)	15 (9, 23)	103 (58, 198)
Weekend	20 (11, 33)	126 (63, 236)	23 (14, 35)	210 (100, 363)	18 (10, 28)	169 (79, 315)
Vigorous Activity						
7- day	16 (10, 29)	170 (88, 303)	17 (10, 29)	226 (120, 400)	20 (11, 33)	281 (159, 453)
Weekday	13 (7, 23)	149 (78, 264)	14 (8, 24)	206 (102, 401)	16 (10, 24)	263 (142, 441)
Weekend	18 (10, 33)	253 (125, 433)	23 (11, 42)	286 (132, 585)	25 (12, 15)	396 (246, 652)
Sleep	540 minutes (480, 540)		540 minutes (480, 540)		480 minutes (420, 540)	

Table 29b: Percentage time spent on types of physical activities (among all reported activities) - Girls

Physical activity	Girls					
	6 years to < 10 years		10 years to < 15 years		15 to < 19 years	
	Duration %	Met Minutes	Duration %	Met Minutes	Duration %	Met Minutes
	Median (P25, P75)	Median (P25, P75)	Median (P25, P75)	Median (P25, P75)	Median (P25, P75)	Median (P25, P75)
Sedentary Activity						
Weekday	58 (43, 73)	120 (55, 195)	56 (38, 73)	138 (58, 237)	61 (48, 73)	168 (90, 258)
Weekend	58 (39, 75)	132 (57, 222)	54 (33, 80)	152 (84, 264)	60 (40, 78)	206 (105, 338)
7- day	66 (48, 84)	113 (57, 194)	68 (47, 86)	142 (64, 223)	68 (54, 81)	161 (93, 253)
Light Activity						
Weekday	14 (9, 24)	37 (23, 63)	15 (8, 24)	46 (24, 90)	16 (8, 25)	57 (30, 109)
Weekend	20 (11, 31)	58 (36, 111)	14 (7, 25)	53 (24, 105)	16 (9, 27)	79 (40, 148)
7- day	16 (9, 27)	34 (19, 63)	15 (8, 25)	36 (19, 73)	17 (9, 28)	57 (27, 116)
Moderate Activity						
Weekday	18 (10, 27)	90 (54, 161)	18 (11, 28)	117 (66, 188)	16 (10, 24)	117 (72, 198)
Weekend	17 (9, 26)	104 (57, 175)	17 (9, 27)	133 (65, 229)	12 (7, 21)	124 (73, 217)
7- day	17 (10, 27)	80 (43, 127)	17 (10, 27)	94 (52, 153)	14 (8, 21)	94 (49, 164)
Vigorous Activity						
Weekday	10 (5, 18)	101 (50, 211)	9 (5, 17)	106 (50, 249)	9 (5, 15)	126 (67, 221)
Weekend	13 (6, 25)	125 (64, 317)	19 (8, 38)	177 (85, 354)	17 (7, 36)	177 (105, 292)
7- day	12 (6, 22)	107 (59, 202)	12 (6, 21)	111 (71, 244)	10 (5, 21)	142 (70, 233)
Sleep	540 minutes (480, 540)		480 minutes (480, 540)		480 minutes (420, 540)	

Table 30: Percentage time spent on vigorous physical activities (among all reported activities)

Physical activity	**6 years to < 10 years**		**10 years to < 15 years**		**15 to < 19 years**	
Mean ± 95% CI	**3+ CMR**	**No Risk**	**3+ CMR**	**No Risk**	**3+ CMR**	**No Risk**
Rural Settings						
Boys						
Weekday	--	--	2.4 (-1.2, 6.0)	2.9 (2.4, 3.2)	3.0 (1.8, 4.2)	4.4 (3.6, 5.1)
Weekend	--	--	1.9 (-1.6, 5.3)	6.3 (5.0, 7.5)	9.1 (0.80, 17.5)	8.0 (6.0, 10)
Girls						
Weekday	1.4 (-2.6, 5.3)	1.8 (1.5, 2.2)	2.3 (0.89, 3.7)	1.7 (1.5, 2.0)	1.9 (0.17, 3.7)	2.0 (1.5, 2.5)
Weekend	2.3 (-13.7, 18.3)	3.4 (2.4, 4.4)	7.0 (1.03, 12.9)	5.1 (3.9, 6.3)	7.6 (0.68, 14.5)	10.5 (7.4, 13.5)
Urban Settings						
Boys						
Weekday	1.3 (0.30, 2.23)	2.8 (2.4, 3.4)	6.3 (2.6, 9.9)	5.5 (4.4, 6.6)	4.5 (1.9, 6.9)	4.1 (3.3, 4.8)
Weekend	--	--	15.3 (7.7, 22.8)	10.5 (8.4, 12.7)	9.3 (7.4, 11.2)	9.8 (3.6, 16.1)
Girls						
Weekday	1.9 (-0.01, 3.8)	1.9 (1.6, 2.2)	2.9 (1.2, 4.6)	2.9 (2.01, 3.8)	2.8 (2.14, 3.5)	2.2 (1.8, 2.6)
Weekend	2.4 (-3.34, 8.15)	3.4 (2.6, 4.14)	9.3 (0.34, 18.28)	6.9 (5.46, 8.4)	6.1 (4.1, 8.1)	5.2 (3.1, 7.5)

Table 31: Factors in the environment that are correlated with clustering of cardio-metabolic risk among children

	Boys			Girls		
	Odds Ratio	**95%CI**	**P- value**	**Odds Ratio**	**95%CI**	**P- value**
Sleep hours	0.78	0.62, 0.97	0.02	0.86	0.73, 1.01	0.07
Mode of transport from school (as compared to walking from school)						
• School bus/Van	1.91	0.93, 3.95	0.08	1.38	0.82, 2.33	0.22
• Motorized Scooter/Bike	5.63	2.09, 15.16	0.00	1.31	0.30, 5.79	0.72
• Car	1.44	0.47, 4.38	0.52	1.45	0.68, 3.10	0.34
• Bicycle	0.99	0.22, 4.40	0.99	0.82	0.11, 6.32	0.85
Distance of school from home (in kilometers)	1.07	1.00, 1.14	0.04	1.03	0.97, 1.08	0.33
Time taken in minutes from school	1.03	1.00, 1.05	0.02	1.03	1.01, 1.04	0.01
Access to video games, DVD players etc.	2.46	1.25, 4.84	0.01	1.49	0.94, 2.35	0.09
Access to Radio / FM (including FM radio in mobile phones)	2.52	1.26, 5.06	0.00	1.62	1.00, 2.61	0.05
Access to computer/laptops	2.49	1.33, 4.63	0.00	1.49	0.93, 2.39	0.10
Availability of separate video games for children	2.30	1.20, 4.40	0.01	0.97	0.49, 1.94	0.94
Availability of personal mobile phone	2.21	1.19, 4.11	0.01	2.36	1.43, 3.89	0.00
Parental control on listening to Radio	0.52	0.27, 0.98	0.04	1.17	0.69, 1.97	0.57
Duration of watching TV by children	1.35	1.07, 1.70	0.01	1.01	0.78, 1.31	0.93

Chapter 5: Discussion

Overall there was 8.4% and 10.6% overweight boys and girls; 4.9% and 3.9% obese boys and girls and 4.3% and 3.8% thin boys and girls (classification using IAP 2015, adult equivalent cut offs). These rates are relatively lower than the population prevalence reported in other studies – as summarized in a recent systematic review by Ranjani et al., (2016).[284] This could be because; the children per school were randomly selected from the BMI quartiles obtained through screening camps. In addition, most of these literatures have used different criteria's for classifying children as over-weight, obese and thin and therefore are not comparable. However the proportion of overweight and obese children in this study were closer to a recent study from South India using the adult cut-off equivalents of IAP growth charts.[285] Our rates are closer to National Nutrition Monitoring Board survey in 2009 even-though they have used different criteria for classification.[286] There are several definitions for childhood obesity and overweight and the most widely used among these are WHO child growth standards, International Obesity Task Force (IOTF) guidelines and recommendations made by the Indian Association of Pediatrics (IAP) for Indian children. Gupta et al., (2012) also conducted a systematic review among 5 to 19 years and reported overweight ranges between 6.1 and 25.2 per cent and obesity between 3.6 and 11.7 per cent.[19] It has to be reaffirmed that this systematically and purposively selected representative sample of children (6 to <19 years), selected equally from four BMI quartiles from each schools in three study locations (through a screening health camp), are not a true representation of prevalence rates of obesity, overweight and thinness in the population. However these estimates can be considered as a representation in trends prevailing in the population.

Our study reports that; generally boys are taller and have high waist-circumference while girls have higher BMI and hip circumferences. Overall, height, weight and waist-circumference were higher among urban children. There were no particular pattern in the distribution of height and weight across age-groups in both gender.[285] Obese and overweight rates were particularly higher in urban areas however these conditions are common in rural areas also. Ranjani et al., (2016) also reported that overweight and obesity rates in children and adolescents are increasing not just among the higher socio-economic groups but also in the lower income groups where underweight still remains a major concern.[12] In this study, among 258 children from poor socio-economic status there were 3.5% (n=9) overweight children and 0.8% (n=2) obese children. Among 820 children from middle socio-economic status 8% (66) was overweight and 1.7% (14) were obese. Overweight and obesity rates were higher among urban and rural boys and girls in Delhi. More recent studies among government schools highlight the fact that both underweight and overweight

(3-5%) co-exist in government schools.[287,288] The rates among urban children in Delhi were comparable with the recent study from Bhargava M et al., (2016); though they have used WHO cut-offs for classification.[289] Concomitantly, both thinness and overweight rates were higher in Hyderabad region and among urban girls in Shillong region. Age wise distribution of obese, overweight and thin children from our study was comparable with children from an affluent population in Saurashtra region (using IAP growth charts, 2015).[290]

Often, different studies use different criteria's to diagnose overweight and obesity. Shetty et al., (1999) have reviewed and highlighted major methodological weaknesses in obesity related studies, especially from developing countries.[291] In contrast to large datasets from North America and Europe; the ones from low and middle income countries (LMIC) are sporadic and scanty, mostly based on small surveys that are seldom representative in nature. Methodological variations are common among studies and this makes inter- and intra- community comparisons difficult. Additionally, ethnicity, sex, pubertal stages, socio-economic and rural-urban gradients are generally not considered while determining the burden of childhood obesity. Unlike adults, child specific growth charts, relating to height in meters square (m2) and weight in kilograms (kg) for age groups and gender are used for calculating BMI per percentiles in children. It is also known that BMI does not measure body fat directly, however, these are commonly used to make estimations of body fat. A repeated cross sectional study from Southern India, among 24,000 school children, has used WHO criteria and reported an increase in the proportion of overweight children from 4.9 percent in 2003 to 6.5 per cent in 2005 showing that it is rapidly growing into an epidemic[292, **Error! Bookmark not defined.**]

To the extent of our search there was very few studies in India who have conducted pubertal assessment among children and adolescents. Mean age of pre-adolescence (stage 1 puberty) was 9.2 years in boys and 8.9 years in girls and they achieve full growth maturation (stage 5 puberty) at 16.9 years for boys and 17 years for girls. Majority of girls achieve menarche at 12.4 years.[293] There was no urban rural difference in stages of pubertal growth among boys and girls. Surana V et al., (2017) have reported that median age of puberty among Indian boys as 10.4 years.[294] Prior to this a study on pubertal staging among Indians was reported in 1979 by Sharma JC et al.[295]

We also found that blood pressure was higher among rural children, which was reported in several other studies.[296,297] Pre-hypertensive trends in rural areas of north-east regions are also already reported.[298] Overall this study confirms that body composition is different for boys and girls with age and pubertal stages as a significant predictor of fat and lean mass depots among children.

There are several ways to estimate body fat and lean mass however there are no true reference standards; as each of these methods follow different compartment models that uses one or other assumptions. Kuriyan R et al.,[299] (2014) have compared fat estimates from different methods using 4 compartment (4C) models and reported that DEXA method can estimate fat mass with minimum bias. However it has to be noted that, DEXA also show differential predictive ability in people with low and high fats but such difference are minimal. Due to its non-invasive nature, flexibilities with segmental information and quick results it is increasingly used in field studies as a criterion standard. In the present study, we used multi-frequency, hand to foot, 8 tactile electrode bio-impedance systems to estimate fat and lean mass of different body segments which was compared with DEXA values. This BIA system has shown better accuracy in predicting fat as compared to single frequency or 4 electrode BIA machines.[300] Sum of segmental impedance index, adjusted for height $(cm)^2$, were used to estimate total body impedance.[301] In addition, height was also used in place of segmental lengths assuming that the distance of electricity flown in a segment conductor will be proportional to the body height.[302] Luque V et al., 2014 have also reported that segmental lengths do not improve the results and have used $height^2$ to segmental analysis. Having said so, Kuriyan et al., (2014) have observed that BIA machines using inbuilt manufacturer's equations provides large random errors in Indian population when compared with 4C models and therefore there is a need for developing robust, age and gender specific Indian equations. Overall, several difficulties in 2 and 3 compartment models can be addressed with a 4 compartment model however there are concerns about individual measurement errors that shall propagate to an aggregate level and produces a large error in the final estimation of fat and fat free mass.[303] Overestimation of fat and fat free mass by BIA manufacturer's equation and better agreements with derived equations are reported in several other studies.[300]

Several studies have quoted that, bio-impedance at 50 khz, the electric current, passes through both intra and extracellular spaces and changes in the impedance are closely related to changes in lean body mass (i.e., muscle mass or body cell mass) - large volume changes in the abdomen regions have less influence on the measurement of fat free mass (FFM).[95] It was also observed that frequencies above 50 khz does not improve the predictive ability of segmental impedance.[304] There are several influencing factors for BIA (hydration, fat fraction, ECW to ICW ratio etc.) and it is advised to reduce the interference effects by focusing on well-defined fractions.

In this study, we have focused on predicting lean mass (muscle mass or body cell mass) because theoretically electricity in the human body passes through soft tissues while fat and bone mass remains as non-conductors.[305,304] Use of fat mass as dependent variable from DEXA did not greatly

improve the precision of the model and equations which does not having fat measures is quoted as more practical for routine application. It has to be noted that, DEXA also indirectly estimate fat after subtracting directly observed bone and soft mass per pixel of body compartments. Generally lean mass is used as synonymous to muscle mass. From the lean mass fat mass was estimated from body weight. Most of prediction equations available in literature for FFM use a 2-component model using DEXA as the reference standard. Ideally, to reduce the influence of estimation errors, all four components as in DEXA (BMC, Lean, Fat and TBW) should have been estimated however BMC estimation from DEXA was not considered in this study - as bones are poor conductors of electricity and it do not reflects to the actual impedance measurements. In addition this was not the primary objective of this study.

Our prediction equations with BIA values adjusted to height^2 as independent variable have shown higher R2 (around 0.87) and while this along with body weight and age was 0.94 among boys and 0.96 among girls. This was highlighted in the study by Shumei et al., 2003 for estimating fat free mass. Addition of other anthropometric variables has not significantly improved the model. Kyle et al., (2004) have reviewed and summarized several BIA based prediction equations for estimating fat and fat free mass. Prediction equations under this study were having high R^2 and SEE and are comparable. In addition, we have undertaken systematic studies for proving the precision and accuracy of fat and lean mass estimations (Table 7 and 8). Our results show very good precision and accuracy as compared to several other studies. Jack-knife estimations were done to study the influence of each observations on standard error of means. Bland-Altman plots were obtained to study the distribution of residuals. From fat mass and lean mass percentage fat in children was estimated in full sample of 3241 children. Finally, fat mass and lean mass distributed among thin, normo-weight, overweight and obese categories were studied. Percentage fat in children in different stages of pubertal growth was also presented in this study.

In summary, we found that whole body composition estimation using bio-impedance is a useful technique for estimating fat and lean body mass among children. It is important that manufacturer equations, in commercially available BIA instruments, are population specific and direct outputs should not be used without validation. For epidemiological studies, multi-frequency 8 tactile electrode bio-impedance system can be used to obtain original bio-impedance values and through linear prediction equations more robust estimations of fat and lean mass proportions can be obtained. There are still several underlying assumptions while using different models (2, 3 4 and 5 compartments) and also use of DEXA as gold standard and appropriate use of BIA - therefore this area require more in-depth scientific studies.

Cardio-metabolic risk factors:

As per the consensus report from American Diabetes Association (ADA), cardio-metabolic risk refers to any individual's all-time risk of developing cardio-vascular diseases – specific factors include central obesity, hyperglycemia, hypertension, insulin resistance and dyslipidemia.[306] It is similar to metabolic syndrome however CMR definition is more inclusive (it will have a larger population than those in MetS). Several ambiguity exists within the current practices and definitions related to both conditions – often anthropometry and bio-chemical markers are combined together while they co-exist within the same individuals (co-linearity in statistics). In addition, several children and adolescents with normal anthropometry are found to have elevated markers of dyslipidemia, insulin resistance and atherogenic dyslipidemia – leading to mis-classifications especially when indices like BMI-for-age are used.[307] Most of the metabolic changes starts earlier in life (childhood) and therefore there is a need to design more robust and simple monitoring system for the surveillance of cardio-metabolic risk among children.

Reference values and percentile curves, for Indian boys and girls between 6 to 18 years, has been generated in this study. LMS method were applied as per standard protocol using templates (developed during this study) as well as using LMS Chart maker pro-version. The values were similar in both methods. Overall, this study has developed 19 percentile curves (13 for bio-chemical markers and 6 for anthropometric markers) - such extensive list of reference values and percentile curves were not available in a single study in Indian context (as per our literature search). Overall, centile curves were relatively stable across age bands indicating that there is little influence of age in the distribution of bio-chemical markers across age. It is difficult to compare the percentiles across studies as these values are dependent on demographic factors and ethnicities.

So far, very few studies have generated such curves for bio-chemical markers in Indian context however several studies have already reported values for anthropometric standards for monitoring growth among Indian children. This has been highlighted in a recent systematic review by Gupta R et al., (2017).[308] Madhavan M et al., (2005) have reported percentile for Asian Indian adolescents (14 to 18 years) for selected lipid markers (in mmol/l).[309] The graph patterns were comparable with adolescent age group in this study however the values in each percentile categories were slightly different. For example, among boys the 85th percentile at 18 years for total cholesterol in our study was 175.4 while this in Madhavan M study was 163.2. This was 139.9 at 50th percentile in our study which was 134.2 at 50th percentile. Among girls also similar trend was observed - +3.7 difference at 85th percentile and -7.5 difference at 50th percentile. This minor difference shall either be due to large samples (selected from each BMI quartiles) and due to robust methods adopted in our study

or due to the shift in body compositions attributed to demographic transition between 2005 and 2015. Bansal U et al., (2017),[310] studied school children (10 to <19years) in a district in Uttar Pradesh, India and reported reference values for 5th, 50th and 95th percentiles – though the percentile values are presented for all children (boys and girls). Total cholesterol at 50th percentile for 18 years were 146 mg/dl in this study as compared to 139.9 mg/dl in our study. Triglycerides at 50th percentile for 18 years were 97.7 mg/dl in our study as compared to 100 mg/dl in Bansal U et al., study. The trend was similar across other bio-chemical markers. Lipid profile norms for Indian children has been presented by Khalil et al., (1995) and the values obtained in our study falls within their range suggested.

Cook S et al., (2009) have also presented percentile curves and reference values for major cardio-metabolic risk markers using NHANES data from United States.[145] Most of the curves were following same bi-modal patterns across age bands however the values in each percentile categories differs. For example, total cholesterol in boys at 50th percentile were 158.3 mg/dl in US children as compared to 146 mg/dl in Indian children. Triglycerides at 50th percentiles were 75.4 mg/dl in US boys as compared to 97.7 mg/dl in Indian boys. Several studies have already reported higher cholesterol, triglycerides and low HDL levels among Indians.[311, 263] In 2013 Alberty R et al., have presented serum lipid percentile curves for children and adolescents for predicting adult dyslipidemia and values were comparable with some difference across percentile categories.[312]

For anthropometric variables, in addition to BMI-for-age indices like height-for-age, weight-for-age, weight-for-length, weight-for-height etc., are all used to monitor growth in children.[313] Most commonly used measure are BMI-for-age although they have numerous disadvantages.[314] Principally, BMI-for age fails to distinguish between fat mass, lean tissue mass and bone mass. In addition, BMI are not useful in children due to changing body shapes as they progress through normal growth trajectories. Studies suggest that overweight/obesity also exist in the normal limits of BMI basically due to increased levels percentage body fat. Since the pathology associated with obesity is driven by excess fat mass, an ideal monitoring tool should directly assess human adiposity and its risk factors.[315] Many individuals categorized as normal weights using BMI had a high percentage of body fat and also had metabolic disturbances leading to heart diseases. Some define them as "normal weight obesity"- a condition of normal BMI but having high body fat percentages.[316] In addition, due to increased genetic susceptibility among South East Asians (thrifty gene hypothesis and differential susceptibility hypothesis), Indians are reported to have more abdominal (visceral) fat than their western counterparts.[317] Indians with the same BMI values were

observed to have seven to eight per cent of higher percentage body fat, which makes them more vulnerable to cardio-metabolic risk factors.[318]

All these studies highlights that the reference values and percentile curves in this study are comparable with available centile values in literatures. Thus with the advantage of robust methodology and representative sampling process the values presented here can be used for monitoring cardio-metabolic risk among Indian children – these curves have already accounted for urban-rural differences and ethnic differences. Percentile lines corresponding to existing cut-off values (absolute values), as given in the diagnostic standards, that corresponds to currently accepted abnormal values were extracted and presented.

The results of study 3 indicates that overweight and obese children are likely to have 3 and more cardio-metabolic risk factors (in serum) however it is not clear whether changes in serum markers predisposes changes in anthropometry or vice versa. Though few children had elevated glucose levels (above diagnostic cut-offs) the insulin resistance (HOMA-IR) was high (13.3% boys and 23.3% girls). Our study reaffirms that insulin resistance are higher in Indian children and are associated with stages of growth, especially in urban locations. Mishra A et al., (2004) have also reported increased insulin resistance among post-pubertal Asian Indians in urban areas that are correlated with overweight/obesity and truncal adiposity.[319] However this correlations were not significant with percentage body fat or BMI categories in this study. In the pathophysiology of cardio-metabolic risk as well as dysglycemia the central factor considered is insulin resistance;[320] its higher rates among Indian children are worrisome especially because already India is having the largest affected population with type2diabetes. In addition, hypertension (without including pre-hypertensive) were present in 8% children in our study. A review by Uddaraju A and Ram VS (2013) have already highlighted this at around 10% among Indian children.[321]

Very few studies from India has actually evaluated lipid abnormalities and hypercholesterolemia among children. A study from Jaipur, India have reported around 6.8% prevalence of hypercholesterolemia among children. Another study among adolescents by Gupta et al., in Delhi have also reported the prevalence of high cholesterols among 14 to 15% children.[322] In addition to high cholesterols, higher levels of triglycerides and lower levels of HDL cholesterols were also observed in this study; which was also reported in several other studies and reviews targeting Indian children and adolescents.[323,324] Low HDL levels were found in 37% boys and 40% girls which was confirmed in several studies.[325] Thus our study reaffirms the hypothesis that metabolic changes occurs much earlier in life.

Clustering of cardio-metabolic risk factors:

This study reports clustering of cardio-metabolic risk among 2.2% boys and 5.5% girls who have normal body weights (BMI <23rd adult equivalent). Among these children (with normal BMI), body fat (kg) was 2.2 kg higher among boys and 4.5 kg higher among girls who had 3+ clustering of cardio-metabolic risk (P=0.001 & P=0.0001); pointing towards the thin-fat phenotypes among South Asian children. Studies have already highlighted that, at any BMI and age-bands Indians are known to have high body fat, waist circumference and low muscle mass which is exacerbated by the presence of cardio-metabolic conditions like insulin resistance, metabolic syndrome, diabetes and dyslipidemia.[326,327,328] These findings are in line with the presence of thrifty phenotype among Indian children (Hales and Barker, 1992);[329] as confirmed by Pune Maternal Nutrition Study (Yajnik CS et al., (2004).[330] This study also reported higher cardio-vascular risk among taller children (especially born for shorter parents); supplementing the hypothesis that accelerated growth in childhood (fast growing children) shall be associated with increased cardio-metabolic risk.

In this study clustering was defined as per absolute cut-offs (presently used in clinics) for diagnosing different clinical conditions as presented in Table 25. Since Apo-A and Apo-B proteins are associated with low HDL and non-HDL cholesterols this was used in a second model. Our definition on cardio-metabolic risk are different from existing definition of metabolic syndrome (syndrome X) as we have not used clinical parameters (abdominal obesity or waist circumference) in the definition – later we explored clinical parameters (like BMI, FMI, % body fat and waist circumference) for their association with cardio-metabolic risk. Similar study was conducted by Onis M et al., (2013) to find association between WHO's BMI-for age cut offs and cardio-metabolic risk – they reported clustering of 3+ risk factors among 6.9% children and 2 risk factors among 14.9% children.

Children can be classified as thin, normo-weight, overweight and obesity based on BMI-for-age centile values as in Indian Association of Pediatrics (IAP) guidelines, or as per International Obesity Task Force (IOTF) guideline or as per World Health Organization (WHO) classification system. Table 22 depicts the proportion of children with clustering of 3 and more risk factors in different classification systems. Often the current public health systems, across the globe, emphasis on obesity (above 27th adult equivalent BMI-for-age in South-east Asia and 30th adult equivalent in other countries) however it shall be too late to intervene as changes in cardio-metabolic profile starts much earlier – at the level of overweight or even lesser (BMI for age). Thus, the need of the hour is a better monitoring tool based on existing classification system that shall help to screen

and identify cardio-metabolic risk at earlier stages. Considering the applicability in clinical use, we have superimposed additional risk categorization line (high, intermediary and low risk) within the existing growth charts for BMI-for age proposed by Indian Association of Pediatrics, 2015 (Figure 21a and 21b, Page 152 & 153). In addition, growth percentile curves for fat mass index has been constituted that shall help in monitoring cardio-metabolic risk corresponding to body fat.

Proximal and distal environmental factors:

Nesbit KC et al., (2014) have studied proximal (home) and distal factors (neighborhood) influence on obesity among adolescents. Not much studies have evaluated clustering of cardio-metabolic risk among children in different socio-economic strata's from India however this has been extensively studied in the case of overweight and obesity. Major risk drivers of childhood obesity are related to eating behavior, food intake and feeding practices;[331,332] ready availability of calorie dense foods;[333] preference to and increased consumption of sweet and fatty/fried food snacks;[334,335] skipping breakfast;[18] and child's food and physical activity environment at home.

Socio-economy: Ranjani et al., (2016) have reported that overweight and obesity rates in children and adolescents are increasing not just among the higher socio-economic groups but also in the lower income groups where underweight still remains a major concern. More recent studies among government schools also highlight the fact that both underweight and overweight (3-5%) co-exist in government schools.[336,337] Pandey et al., (2014)[338] repeated a cross-sectional study (2001-02 and 2013-14) among affluent schools from Mumbai's western area and showed that the prevalence of childhood obesity among upper socio-economic stratum of society has remained high at 25-30 per cent during both the periods. Kaur et al., (2008) from Delhi have studied the prevalence of overweight and obesity with respect to income groups: it was observed that the prevalence of overweight was three times higher in high income schools (15.3%) as compared to middle income schools (6.5%) and low income schools (2.7%). Obesity was also high in high income schools (6.8%) while it was 0.6 per cent in middle income schools and was 0.1 per cent in low income schools.339This study also highlighted that 12 per cent children in high income schools consumed energy dense fast foods more than four times a week as compared to 9.8 per cent in middle income schools and 7.2 per cent in low income schools. This study reemphasizes the association of childhood obesity with the socio-economic status of families. Another Delhi based study in 2008 also reported obesity prevalence as high as 29 per cent in private schools as compared to 11.3per cent in government schools.**Error! Bookmark not defined.** Thus children in all age-groups across socio-economic strata's are at higher risk of cardio-metabolic risk.

Nutrient Adequacy: In our study, one third children was consuming inadequate amount of energy and protein (< 80% of RDA) and almost similar proportion of children were consuming more than 120% of RDA. Using the Integrated Child Development Services (ICDS) data Malhotra A (2007) also reported inadequate amount of energy intake per day (<75% of RDA) in nearly half of children.[340] Dietary food pattern analysis has increasingly been used to capture the complexities of diet and the risk of chronic diseases in adults, but limited information is available among children. NNMB (National nutrition monitoring board) surveys have documented that except for the daily consumption of rice and wheat, the intake of all other food items was found to be far below ICMR's suggested levels especially, micronutrients which was grossly inadequate. The intake of cereals and millets, other vegetables, condiments and spices, was significantly ($p < 0.05$) higher among the overweight and obese adolescents (334g, 57g and 19g) however, the average daily intake of GLV, though low, was marginally higher and that of fruits was significantly ($p < 0.05$) higher in the non-obese adolescents (16g and 56g respectively). The intake of pulses, roots and tubers, fish and flesh foods, milk and milk products, fats and oils and sugar and jaggery was marginally higher among overweight and obese adolescents as compared to the non-obese children. The intake of protein, energy, thiamin, niacin, vitamin C and iron were significantly ($p < 0.05$) higher among the overweight and obese individuals. The intake of fat, calcium, riboflavin and folic acid were marginally higher in overweight and obese individuals.

Changing Diet (food groups): The increase in westernization, urbanization and mechanization, as occurring in most other countries around the world, is associated with diet changing to one of high fat, high energy-dense foods and a sedentary lifestyle.[341] As population become more urban and income rises, diets high in sugar, salt and fat replace more traditional diets that were high in complex carbohydrates and fibers.[342] The increase in the frequency of eating meals and snacks away from home and the proportion of food budget spent on away from home foods has been associated with the increasing prevalence of obesity.[343, 344, 345] Currently an average Indian in urban areas consume around 540ml/week of sugar sweetened beverages (which accounts for around 132 kcal and 33–40g of sugars).[346] Sweetened drinks containing either sucrose alone or sucrose in combination with fructose appear to be associated with weight gain.[347] Overall the nutrition transition particularly noticeable among children has resulted in the high consumption of calories, saturated fats, trans fatty acids (TFAs), simple sugar and salts along with low intake of fiber, monounsaturated fatty acids (MUFAs), and n-3 polyunsaturated fatty acids (PUFAs) etc,; all contributing to the overweight and obesity epidemic. Broadly, individuals do not tend to decrease solid calories in compensation for increased liquid calories.[348] In addition, studies have found genetic and intra-uterine growth imbalances also associated with eating habits and occurrence of

overweight and obesity in children.[349,350] The NIN study in Andhra Pradesh found that the proportion of adolescents consuming non-vegetarian diets was significantly ($p < 0.05$) higher in overweight and obese adolescents (68%) as compared to others (60.8%). The proportion of adolescents consuming vegetarian diet + egg was marginally higher in non-obese groups (18.3%) as compared to overweight and obese adolescents (12.7%). About three fourths (69-70%) of overweight or obese adolescents preferred the consumption of fatty foods. However the study concludes that the 24 hour dietary recall and food frequency questionnaires are unlikely to estimate actual food intake among adolescents, especially among overweight children, because they generally consume outside foods frequently and ingredients of many outside foods are not known scientifically.

Several obese children overeat impulsively i.e., they continue eating even though they are not hungry. Highly impulsive children often do not think about the reactions or their consequences. Besides over eating, these children seem to be vulnerable to food triggers like the smell and taste of the food.[351] It has been suggested that poor control of neural centers related to impulsivity and/or addiction could foster impaired control of food intake leading to overeating and subsequent obesity.[352] Adaptive decision-making and the ability to delay gratification may positively influence eating behaviors, particularly in an energy rich food environment where conscious control of energy intake is essential for the maintenance of healthy body weight.[353]

Several studies have also demonstrated that school vacations and holidays are marked with less structured eating, increased access to foods and less physical activity. Weekends may represent a time when children are more likely to engage in less healthy behaviors; given that they have increased time for eating and greater access to foods at home. They consume significantly more grams of fat and fewer servings of fruits and vegetables on weekends.[354] Studies have demonstrated that diets rich in vegetables may protect against many chronic diseases and overweight. Despite these benefits, the consumption of vegetables and fruits among children and adolescents is well below the recommended levels.[355] Urban middle class school children are known to eat at times other than regular meals, preferring to snack between classes or after school. These eating episodes often include high calorie foods with little nutritional value.[356] The severity of obesity is associated with the degree of unhealthy dietary practices and difficulty in making healthy lifestyle changes.

Physical Activity: With the advent of mechanized transport, technologies to share physical activity and due to various socio-cultural changes the 'normal' amount of physical activity in humans is decreasing day by day. This has affected adults and children similarly and is a global phenomenon with literature reporting a secular trend, though inconsistent.[357,358,359] Most of the

studies estimating physical activity levels have not followed uniform methods, samples or outcomes making it difficult for across study comparisons. It has been reported that 22.4 per cent of Saudi preschool children walked 10,000 steps or more per day and nearly two thirds of Iranian adolescents aged 11–18years were physically inactive.[360,361] The trends in the decrease in physical activity among children in India are more consistent.[362] There is lower physical activity among girls compared to boys and there is a large deficit in participation in outdoor games and sports. Corder et al., in their study on adolescents in Chennai have demonstrated that double labeled water-derived energy expenditure was lower in their group than other adolescent populations in Europe and similar to those in North America. Additionally four boys and none of the girls accumulated ≥60 min/day of accelerometry-derived moderate intensity activity indicating that low levels of energy expenditure and physical activity persist.[363] Also it is alarming that Swaminathan et al., demonstrated a declining trend in moderate to vigorous physical activity (MVPA) over a single year follow up.[364] Most of them were largely attributed to a decrease in physical activity at school.

Socio-culture: In India, adolescent girls have been neglected and most of them reach adolescence through years of poverty, illiteracy, ignorance and lack of adequate nutrition/health care. The ill effects of these deprivations are further aggravated by gender discrimination - both at the household and the community level. This results in poor nutrition and health status, besides the low social status of these girls. The important nutritional challenges, currently being faced by adolescents are micro and macronutrient deficiencies (anemia and under-weight) in rural and tribal areas and overweight and obesity among urban areas. Various studies have indicated that a large number of adolescents, especially the ones from rural poor communities, are either illiterate or school drop outs and self-realization of overweight and obesity is also an area of concern. The NIN study in Andhra Pradesh highlights that about 21 per cent of obese children from adolescent age groups perceived that their body size was normal. About two third of obese children (63%) perceived that they are overweight and not obese. Similar trends were seen in all the regions. Surprisingly, about five per cent of obese adolescents still perceived, that they were lean.

Rapid physical growth and development during adolescence have to be met with special nutrition needs. They are generally ignored in the case of girls, particularly those from poor communities, resulting in their growth being stunted. If optimal nourishment is provided during the pre-pubertal growth spurt, girls are likely to undergo 'catch-up growth' and attain adult size comparable to better fed children. With the onset of menarche and in the absence of adequate dietary intake, adolescent girls become highly susceptible to anemia. Therefore, more than three-fourths of girls are anemic (NNMB 2003).[365] Even though IFA tablets supplementation is being implemented

throughout the country, its coverage is minimal. The nutritional status of adolescent girls is very important; because they are the would-be mothers of the future. Besides iron deficiency anemia, other micronutrients like iodine, vitamin A, calcium, phosphorus and magnesium may be deficient in undernourished adolescent girls, which may impair their growth and maturation and affect their reproductive life later. Promoting the use of iodized salt and green leafy vegetables takes care of the iodine, iron as well as vitamin A needs of these girls.

NNMB Surveys have shown that more than one fifth of adolescent girls in rural areas are married early, as against the government norm of age at marriage being 18 years. About a quarter of the married adolescent girls are short in stature and 18.6 per cent were underweight (NNMB 1996-97).[366] Early marriage and early pregnancy can interrupt the mother's physiological growth and can result in birth complications / low birth weight babies. About 39per cent of the adolescents were stunted (<Median -2 SD of NCHS height for age) irrespective of sex. The prevalence of under-nutrition (<median -2 SD of NCHS weight for age) is higher (53.1%) in boys than in girls (39.5%)367. Adolescent girls in the rural areas could be at greater risk of nutritional stress because of early marriage and early conception before completion of their physical growth.

Home environment: Overall home environment plays an important role in developing a child's psychological social behavior. Parenting style, reward and food restriction, attachment, personality development discipline, sibling's relationships, bullying in the household, comparisons with siblings, and high expectations from them are all factors which can contribute to depression and a stressful environment for children, which manifests in an obesogenic environment for children. Children indulge in the over consumption of unhealthy foods and less physical activity as a reaction to their environment.

Parenting /Parental stress: Psychological stress in a family may contribute to childhood obesity. Sources of such stress include serious life events, parenting stress, chronic parental conflict, divorce and separation, lack of social support, parental worries, especially in the case of a single child or single parent (e.g., the possibility of the child falling ill, being harmed, being handicapped, not developing normally, being exposed to abuse, or not surviving). Studies on overprotective dominant mothers, a diffident father and lack of warmth within the family reported these as risk factors for the development of obesity among children.[368] In the Indian context, there are many studies, which have reported the effect of the home environment on a child's psychology, but there is no such evidence, which shows the association of familial stress and childhood obesity. A study by Amritha et al., done in 2006 in Bangalore reported that the offspring of parents suffering from panic disorder and depression had a greater degree of cognitive impairment and

psychopathology.[369] Another study reported that there was a significant difference in the quality of the family environment and stress among male and female children of ill parents.[370]A recent study concluded that children with conduct disorder perceived their parents negatively as compared to normal children and simultaneously parents of the conduct disorder group showed a negative parenting style, which reflected poor parent child bondage as compared to the parents of children without conduct disorder.[371]

Maternal depressive symptoms may be related to children's nutrition and physical activity, which in turn helps determine weight status. Mothers with such symptoms are less likely to have rules about what their children eat.[372] They are also less likely to eat dinner with their children, and the children usually watch more TV per day than children with non-depressed mothers. All of these behaviors have been correlated with higher child BMI. However, identifying maternal depression early can reduce the effect on children's eating habits and weight. The association of childhood depression and obesity has not been reported in the Indian context. However maternal depression and childhood obesity was studied in Mumbai. In this study it was reported that children whose mothers were under depression were more overweight and obese as compared to the children of normal mothers.[373] The study further concluded that a mother's mental health, and unpropitious family characteristics definitely play a role in children becoming overweight and obese.

School environment: School is the second home of every child in society. A healthy school environment is required to furnish better health for children both mentally and physically. In today's world of globalization, competition among children is escalating to new heights. The pressure of competition in the classroom and entrance exams is creating huge levels of stress among students. Furthermore, peer group pressure, competition among the peer group, bullying among the peer group also adds to a stressful environment for children in school. Hence, the children of today suffer from many psychological conditions (stress, depression, anxiety), which directly and indirectly lead to increased food intake and decreased physical activity among them.

Gupta et al., in 2001 concluded that scholastic under achievement was found to be associated with maximum behavioral problems. In addition to this the authors has suggested that scholastic under achievement could be a useful starting point for identifying behavioral problems.[374] Verma et al., reported that the examination system, burden of homework and the parent's and teachers' attitude resulted in stress among the school children studied in Chandigarh. Deb reported that the parent's high expectations from their children regarding academic success, academic pressures and competition among the children leads to stress and anxiety among the school children.[375]

Chapter 6: Conclusion

This study has developed new prediction equations, for boys and girls, for monitoring body fat from bio-impedance values (linear prediction models). Absolute difference (bias) and percentage differences in predicted lean (BIA) from expected lean (DEXA lean) were tested against boys and girls among thin, normo-weight, overweight and obese children. The new BIA prediction equation could precisely predict lean mass among 82.4% (n=84) boys, moderately in 15.7% (n=16) and imprecise in 2% (2) boys. Among girls, the BIA prediction could precisely predict lean mass among 77.6% (n=76) girls, moderately in 21.4% (n=21) and imprecise in 1% (1).

For monitoring cardio-metabolic risk among children, Lambda (L), Median (Mu) and Sigma (S) were estimated across age bands for boys and girls and developed reference values at 5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 85^{th} and 95^{th} centiles (growth curves). Around 19 percentile curves are presented under two heads: a) **bio-chemical markers** [Glucose monitoring (Fasting glucose & HbA1C (Glycated Hemoglobin)); Insulin Resistance (HOMA-IR); blood pressure monitoring (Systolic BP, Diastolic BP and Mean Arterial Pressure) lipid monitoring (Total cholesterol, Low HDL-C, Triglycerides Apo-B representing non-HDL and Low Apo-A proteins representing HDL-c) and Uric acid levels] and b) **clinical markers** [Nutritional status (BMI for age, Weight for age & Height for age); Percentage body fat & Fat mass index and Waist circumference.

We define clustered cardio-metabolic risk as: *'any child (boy or girl) on or above 10 years of age having more than 3 risk markers (serum) indicating: 1) hyperglycemia (as fasting glucose ≥ 126 mg/dl or HbA1C ≥ 6.5); 2) insulin resistance (as HOMA-IR ≥ 2.5); 3) hypertension (SBP ≥ 130 or DBP ≥ 85 mmHG); 4) high total cholesterol ≥ 200 mg/dl; 5) high triglycerides ≥ 130 mg/dl; 6) low HDL cholesterols (HDL ≤ 40mg/dl for boys and girls up to 16 years and ≤ 50 mg/dl for girls ≥ 16 years) and 7) hyperuricemia (boys ≥ 7.0 mg/dl and girls ≥ 5.7 mg/dl).* These children have to be monitored irrespective of their BMI stages. HDL-C can be replaced with apo-A (≤ 115 mg/dl) and total cholesterol can be replaced by apo-B (≥ 110 mg/dl). Continuous monitoring can be done using body mass index (BMI), fat mass index (FMI), percentage body fat (PBF) and/or waist circumference.

Clustering of risk factors were studied using two models. Overall, there was substantial level of agreement between two models (boys: kappa 0.64, P=0.001) and (girls: kappa 0.63, P=0.001). Clustering of 3+ risk factors are distributed among normo-weight, overweight and obese as per existing BMI-for-age categorization. Existing classification system based on BMI-for-age could not capture all children with cardio-metabolic risk (False negatives). Often the current public

health system emphasis on obesity (above 27th adult equivalent BMI-for-age in South-east Asia and 30th adult equivalent in other countries) however it shall be too late to intervene as changes in cardio-metabolic profile starts much earlier – at the level of overweight or even lesser. Thus we recommend the use of lower BMI-for-age (at adult equivalent 21) that shall increase the sensitivity of screening tools and facilitate early diagnose of cardio-metabolic risk. Average BMI, FMI, PBF and WC was significantly higher among children with 3 and more risk factors.

We also modified existing growth charts based on BMI-for-age to diagnose and monitor cardio-metabolic risk among boys and girls (Figure 21a and 21b). The values are from existing growth charts which was superimposed with smoothened (LMS) mean values for 2 CMR and 3+CMR from this study. Dotted lines indicate those children in high risk and intermediate risk. Thus based on the existing BMI-for-age classification system (IAP growth charts), we propose to include risk categorization based on cardio-metabolic risk.

Finally, study among 3241 children were done to understand: a) list of variables in a child's environment (individual practices, home, school and neighbourhoods) that are significantly associated with clustering of cardio-metabolic risk. Standard of living index; energy, protein and micro nutrient consumption; sugar sweetened beverages and snack eating; and time spent on sedentary physical activities were found to be significantly associated with clustering of risk factors. Duration of sleep was found to have protective effect. Boys commuting to schools in motorized scooter/bike were having 5 times increased risk of clustering of cardio-metabolic risk as compared to those walking to schools – however this relationship were not significant among girls. Another factor which was found significantly associated with clustering of risk factors among boys is the distance of school from home however this was not significant among girls. Increase access to video games, DVD, Radio/FM, Computer/laptops, separate video games and personal mobile phones were all significantly associated with clustering of risk factors. Parental control and duration of watching TV were also found to be significantly associated.

Entire thesis was conceived as an effort to identify a whole of society monitoring framework that shall help in identifying and monitoring children with cardio-metabolic risk factors without actually collecting individual level data. That means, by looking at specific indicators at aggregate levels in a society the monitoring framework shall help to predict the number of children at risk of cardio-metabolic risk. Unfortunately, the current data collected have not shown such predictive properties directly and this require 'Structural Equation Models' to identify and control variables that are mutually interacting at different levels. Further, studies are required in this direction.

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