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Cardio-Metabolic Biomarkers in Adolescents: Estimating Health Risks Through Filial Ties Over Three Generations

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Keywords

- Cardio-metabolic health
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Abstract

Background: Complex etiology of various cardio-metabolic disorders involves both genetic components and environmental exposures. In most of these diseases, there is a well-documented association between family history of the disease and its development. The study estimates cardio-metabolic risk in adolescents through cardio-metabolic health of grandparent and maternal generation.

Materials and methods: A cross-sectional analysis on 463 parent-child dyads (biological mothers) was conducted through multi-staged stratified sampling from April, 2011 till September, 2013. Self-reported data on cardio-metabolic parameters was documented for grandparental generation. Binary logistic regression models estimated the children's risk for each cardio metabolic risk factor with cardio-metabolic history in parent or subsequent generation controlling for TV viewing time, age, gender and ethnicity.

Results: Odds-ratio for children in upper quartiles of SBP, DBP, WC and BMI were significantly associated with cardio- metabolic history of the grandparent and health of the mother in varying degrees. Mother-child pair analyses show that a BMI ≥ 25 kg/ m2 results in higher BMI in offspring (6.47 times), risk of WC ≥ 85th percentile increases 2.59 times and occurrence of BP ≥ 90th percentile ranges from 4.16-4.70. Hypertension in mothers might result in similar condition in her progeny.

Conclusion: The study reflects diverse associations between cardio-metabolic profiles and order of relatives. Early and timely intervention in the maternal generation might reduce the risk of high BP or metabolic diseases in children. Chronic ailments that now start early in life can be prevented or delayed, at least among children of high-risk genitors.

ABBREVIATIONS

BP: Blood Pressure; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HTN: Hypertension; BMI: Body Mass Index; WC: Waist Circumference; FDR: First Degree Relatives

INTRODUCTION

Nearly a decade ago, WHO reported at cardio-metabolic risk and chronic diseases contribute approximately 46% to the global burden of disease [1]. About half of these deaths, they said are attributable to cardiovascular diseases; obesity and diabetes which are showing disturbing trends, as they have started to appear early in life besides affecting large proportion of population. Multiple studies have used modelling to quantify the mortality and disease burden attributable to risk factors or to assign a portion of the CVD mortality trends to risk factor trends in selected populations [2], these studies have assumed that the causal effects from individual-level epidemiological studies apply to whole populations [3,4]. It has also been well demonstrated that cardiovascular risk factors frequently occur in obese adolescents and that these risk factors tend to cluster resulting in increased incidence of concomitant co-morbidities, creating a risk continuum. These defects are likely triggered or exacerbated by concurrent obesity, sedentary lifestyle, unhealthy eating habits, and hormonal changes (puberty) in genetically susceptible populations [5].

The complex etiology of various cardio-metabolic disorders involves both genetic components and environmental exposures. In most of these diseases, there is a well-documented association between family history of the disease and its development [6-9]. Maternal and paternal family histories of diabetes are both associated with an earlier age of onset [10-12] and this effect is more marked when multiple family members are affected [13]. Individuals with familial cardio-metabolic history tend to have relatively poor health statistics. An ailing genetic blue print might lead to an early age of onset which would be expected to have a prolonged negative impact on the development of chronic complications.

There has been a marked increase in cardiovascular mortalities and morbidities due to growing prevalence of risk factors like sedentary lifestyle, high caloric nutrition, psychosocial stress etc. [14,15]. The genetic profiles of individual, family and population

provide an additive effect to this over exaggerated crisis [16]. Hence the best way to control this menace is primary prevention i.e. estimation of the risk, understanding the categories of risk, identification of population specific risk factors and capturing the most vulnerable cohort at the earliest age [17].

Distinguishing genetic causes from environmental causes is difficult in chronic, multifactorial diseases. Fortunately, there is a simple way to simultaneously explore the influence of genetic and environmental factors on a condition: the use of family history. In the present study, we examined relationships among parental and grandparental cardio-metabolic health and important physiological and biochemical outcomes in their biological adolescent offspring. We hypothesized that familial cardio-metabolic parameters would indicate worse clinical outcomes in subsequent generation. We investigated potential relationships between three generations separately, as there are known differences in inheritance between first and second degree relatives. Assemblage of family history data in the community in the form of cohort studies will prove to be a tool for prevention and efficient risk modification.

MATERIAL AND METHODS

Target Population

The present study was conducted on Siddis of Gujarat and Punjabi Khatri-Aroras of Delhi, India from April 2011-September, 2013. The Siddis (Afro-Indians) are a particularly vulnerable tribal population (PVTG's) of Gujarat inhabiting rural settings. Siddis are agriculturists and daily-wage workers. Punjabi Khatri-Aroras are an urbane caste group of Delhi. The occupations range from being business to services in government or private sectors. Some females are also homemakers.

Sample size and sampling technique

Considering prevalence of metabolic syndrome to be 4.2 among adolescents [18], a sample size of 410 was required at α-error of 5%, and non-response rate 10%. The subjects were selected by using simple random sampling using computer-generated random numbers. The sampling frame available was used for generating the random numbers. Data for the present cross-sectional research was collected through an epidemiological survey through school and household study on 550 children aged 9-11 years (mean age: 9.91 ± 2.87 years) along with their biological mothers (n=550) through multi-staged stratified sampling. The families were matched for socio-economic status (inter-group) and ethnicity. Non-response rate for self-reported data on all cardio-metabolic variables of interest for grand parental generation was 15.8% in all cases. Final analysis for the present objective was performed on 463 children with complete information. Data was collected during school and household visits using a proforma that included information on anthropometry, physiological parameters, cardio-metabolic health, and reproductive performance. Only subjects who voluntarily agreed to be a part of the study post sampling and after the procedure and purpose were explained to them were included. Informed written consent was obtained from each subject. All the subjects were apparently healthy with no visible deformity.

Data collection

For each participant a general questionnaire was filled which contained demographic data, socio-economic status [19,20], family size, quality of life, TV viewing hours, smoking, physical activity, ethnicity, systolic and diastolic blood pressures, BMI, waist-hip ratio, and health records especially those of cardiovascular risks and outcomes such as ischemia of heart, cerebral vascular events (CVA), diabetes, hypertension, diabetes and other history of diagnosed conditions in parent or grand parental generation. The questionnaires recorded occurrence of any of these conditions through self-reported data by the parent for the preceding generation. Genealogies were also drawn and used, wherever possible as in when it could be traced up to the fourth generation.

Anthropometric data: Anthropometric measurements including height, weight, skin fold thicknesses, waist and hip circumference were obtained using standardized procedures for mothers and their biological children [21]. Body weight was measured by using spring balance to the nearest 500 gm, stature with the help of Martin's Anthropometer to the nearest mm. Waist circumference and hip circumference were measured with a non-stretchable flexible steel tape to the nearest mm. The body fat percentage was recorded using a body composition analyzer employing bioelectric impedance technique. WC (cm) was measured with a tape against the skin at above the crest of the ilium and hip circumference where found maximum while the children were standing upright. Measurements were recorded to the nearest 0.1 cm.

Blood chemistry: A fasting venous sample was obtained for both mothers and adolescents, after ensuring 8 hours of overnight fast, for estimation of plasma glucose and serum lipids using standard enzymatic methods (Biochemistry analyzer Cobas integra 400 plus from Roche Germany) in pathology laboratories. These samples were analyzed from serum for blood glucose by hexokinase method [22]. Fasting blood sugar for the sample population was measured with a single prick using glucometer. The sub sample was chosen randomly and on the basis of funds available. Coefficient of variation (CV) of methods under-consideration in the laboratories was found to lie within 4%-7%, indicating a good precision.

Physiological measurements: Blood pressure both systolic (SBP) and diastolic blood pressure (DBP) was measured with the help of sphygmomanometer and stethoscope. BP measurements (mm Hg) were made after the subject had been sitting quietly for a minimum of 5 minutes; children were made to sit with their arm relaxed either in their lap or on a low table. BP was measured using an appropriate cuff-size. If any readings were unusually high (for boys: systolic BP (SBP) >120 mm Hg or diastolic BP [DBP] >78 mm Hg, for girls: SBP >116mm Hg or DBP >76 mmHg) according to AAP/NHLBI [23], the cuff was removed and the child rested for at least 5 minutes prior to another measurement.

Definitions: Body mass index was calculated as weight divided by height squared (kg/m^2), and categorized as normal (≤ 25.0), overweight (≥ 25.0 but ≤30.0), and obese (≥ 30.0) [17]. Waist-to-hip ratio was calculated by dividing waist circumference by hip circumference. For serum lipids, we referred to NCEP

Table 1: Cohort characteristics of 463 children aged 9-11 years.

		N	%
Characteristics of the cohort			
Age (mean = 9.91 ± 2.87 years)	9 Years	182	39.1
	10 Years	138	29.9
	11 Years	143	30.9
Sex	Male	248	53.6
	Female	215	46.4
Ethnicity	Siddis	156	33.6
	Punjabi-Khatris	307	66.4
Child BMI z-score * (≥ 85th percentile)	Females (21.83)	97	20.85
	Males (21.45)	102	22.1
WC distribution (≥ 85th percentile)	Females (72.6cm)	107	23.2
	Males (71.5cm)	118	25.4
SBP (≥ 90th Percentile	Females (116 mm	82	17.8
	Males (118 mm Hg)	112	24.1
DBP (≥ 90th Percentile	Females (72 mm Hg)	102	22.1
	Males (74 mm Hg)	128	27.7
• BMI z score calculated from sex and age-specific points [22].			

- ATP III Guidelines [24,25]. According to these standard guidelines, hypercholesterolemia is defined as TC >200mg/dl, LDL-C as >100mg/dl, hypertriglyceridemia as TG >150mg/dl and HDL-C <40mg/dl. Dyslipidemia is defined by presence of one or more than one abnormal serum lipid concentration. For serum glucose levels, we referred to ADA Guidelines [26]. Subjects with fasting blood glucose >126mg/dl or who were on medication for diabetes was considered as having diabetes mellitus. Based on the seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure [27], normal BP is defined as less than 120/80 mmHg, prehypertension as 120–139/80– 89 mmHg, stage I hypertension as 140–159/90–99 mmHg, and stage II hypertension as equal to and above 160/100 mmHg. Measurements were conducted by trained personnel and all instruments were calibrated once weekly. Because there is no standard definition for abnormal cardio-metabolic risk factors (especially for 9 years old) in children, we classified each cardio-metabolic risk factor as increased if it was at or above the upper quartile for the outcome in question. The 85th percentile for BMI and WC was determined from sex- and age-specific distributions [28], for HTN as a risk factors 90th percentile was used from the study cohort.The differences between means for most variables for children were non-significant between sexes and ages and hence combined for the analysis.

Institutional ethical committee (Department of Anthropology, Faculty of Sciences, University of Delhi, India) issued ethical clearance certificate, and informed consent was obtained from all study subjects at least 18 years of age or from the parent of the younger subjects.

Statistical analysis

Data was analyzed in September, 2013. Separate binary logistic regression models were used to estimate child's risk of each cardio metabolic risk factor, defined at 85th percentile for BMI and WC; and at 90th for SBP and DBP. An additive feature was an estimated association with presence or absence of cardio-metabolic history in parent or subsequent generation using different models controlling for ethnicity, maternal weight and age. Analysis was performed in 2 ways, reflecting the fact that, in familial studies, the same event was documented as the dependent outcome in one analysis and as the independent exposure in the subsequent model by coding for the number risk factors present. For presence of each risk factor documented by reported status (Yes or No), in either set of grand-parents or parents, a point was added to the risk score; hence the score varied from 0-20, for presence of none or all risk factors.

This analysis has been present in Table (2). Summarizing scoring algorithm, for presence of a particular condition in all grandparents the score will be 4. Hence, the maximum score for risk of adverse event through grandparent generation is 12 and that for the parent generation is 8. Potential effect modification was assessed in the relationship between the risk score and each childhood cardio metabolic outcome by ethnicity, maternal weight and child's sex. Cross products were added on, at a time, to fully adjusted models; no cross products were found to be statistically significant.

Another analysis presented in Table (4) deals with the age-adjusted continuous descriptives, for various measurements were compared on the basis of score calculated and self-reported cardio-metabolic health status of both parents. The score varied between 0-8 for presence or absence of a particular health condition. Adolescents were divided into 3 study groups (Group 1 with Score 0, Group 2 with score 1-2, Group 3 with score ≥ 3). Both scores are characteristic approach of the present study.

Data was analyzed using Statistical Package for Social Sciences (SPSS), version 20.0. The results are given as means and t-test was used to compare the measurements between group as data was parametric. The question of how family history of cardio-metabolic factors in first degree relatives (FDR) and potential application in next generation was examined using regression analysis, controlling for TV viewing time, age, gender and ethnicity.

RESULTS

The mean age of the group is 9.13 ± 2.87 years. Nearly 21% children of both sexes lie above the normal 85th percentile according to BMI centiles. Cohort–specific 85th percentiles for

Table 2: ORs (95% CIs) for each offspring cardio metabolic risk factor meeting or exceeding the given percentile at 9-11 years of age, associated with a point increase in risk score.

Cardio-metabolic Risk Factor	Model 1	Model 2`	Model 3
BMI percentiles	1.34(1.17,1.61)	1.37 (1.17,1.71)	1.39 (1.14,1.62)
SBP	1.27 (1.05,1.52)	1.25 (1.04,1.51)	1.24 (1.01,1.54)
DBP	1.30(1.09,1.50)	1.33 (1.09,1.59)	1.35 (1.06,1.60)
WC	1.04 (1.01,1.32)	1.03(1.02,1.32)	1.05 (1.02,1.31)
Model 1 is unadjusted Model 2 is model1 plus sex and ethnicity included Model 3 is adjusted for model 2 plus maternal weight			

Table 3: Odds Ratio for HTN, dyslipidemia, obesity and diabetes in first degree relatives (FDR) and in risk percentile categories for grand-children (second degree relatives) with positive family history.

			Grand Parent Generation					
			CVD History		Diabetes		HTN	
			Odds	CI'S	Odds	CI'S	Odds	CI'S
Parents generation	HTN(SBP)	Pre Hyper Tension	5.14	3.21,6.15	-	ns	4.62	2.27,4.88
		Hypertension	11.76	8.76,12.03	-	ns	6.45	4.21,7.43
	HTN	Pre Hyper Tension	4.21	2.54,5.11	1.05	1.02,2.11	4.98	2.43,6.22
	(DBP)	Hypertension	10.47	7.22,11.78	-	ns	8.32	6.98,8.66
	Dyslipidemia	Risk	1.92	1.02,3.76	1.02	1.01,2.12	-	ns
	BMI	Overweight	9. 98	5.43,10.78	-	ns	10.86	8.64,11.57
		Obese	10.63	9.11,12.32	2.56	1.43,3.76	12.48	9.76,14.33
Children		Risk	-	ns	4.12	2.98,5.03	-	ns
	BMI percentiles	≤ 75th percentile	0.51	0.23,0.67	-	ns	-	ns
		≥90th percentile	3.42	2.95,4.04	1.76	1.25,2.39	3.89	2.78,5.43
	SBP	≥ 90th percentile	-	ns	-	ns	2.45	2.04,3.35
	DBP	≥90th percentile	2.76	1.43,2.98	-	ns	-	ns
	WC	≥85th percentile	1.56	1.32,3.04	-	ns	-	Ns

Only Significant values have been shown in the table

Table 4: Odds Ratio for risk percentile categories in children from positive parental cardio-metabolic history 4.

			Parent generation									
			BMI		Diabetes		HTN (SBP)		HTN (DBP)		Dyslipidemia	
			odds	CI's	Odds	CI's	Odds	CI's	odds	CI's	Odds CI's	
Children	BMI Percentiles	≤ 75th Percentile	–	ns	-	ns	0.78	0.34,0.97	-	ns	- ns	
		≥90th Percentile	6.47	3.54,7.78	-	ns	7.56	5.36,8.04	4.67	3.07,6.78	-	ns
	SBP	≥ 90th Percentile	4.7	2.65,5.03	-	ns	4.78	3.65,5.21	5.34	3.56,6.09	-	ns
	DBP	≥ 90th Percentile	4.16	3.23,5.44	2.72	1.23,4.06	4.23	3.45,4.87	7.76	4.78,9.43	1.23	1.09,2.76
	WC	≥ 85th Percentile	2.59	1.56,3,49	-	ns	3.56	2.23,4.12	4.43	3.22,5.34	2.21	1.43,2.89

Only significant values have been shown in the table

WC were 71.5 cm and 72.6 cm for boys and girls, respectively. For blood pressure ≥ 90th percentile, 24.1% males through SBP- 118 mm Hg and 27.7% males through DBP 76 mm Hg, while 17.8 % girls through SBP-116 mm Hg and 22.1 % girls through DBP-70 mm Hg fall in this category (Table I). ORs and 95% CIs for a unit increase in risk score of cardio-metabolic factors with adolescent cardio-metabolic markers are presented in Table (2). ORs for children belonging to the upper quartile of DBP and SBP were found to be 1.30 (95% CI, 1.09-1.50) and 1.27 (95% CI, 1.05-1.52), respectively. Odds of adverse event in the upper quartile of WC were found to be 1.04 (95% CI, 1.01-1.32) times higher while for BMI ≥85th percentile, the odds varied from 1.34 (95% CI, 1.17-1.61). Adjustment for child's gender and ethnicity did not appreciably alter the risk estimates (Table 2).

The extent of metabolic inheritance from grandparents in FDR (Figure 1) and grand-children has been presented in Table (3), through regression analysis. Occurrence of HTN and obesity in parents is significantly discernable with CVD history or with presence of HTN in grandparents. A diabetic parent might lead to 4.12 higher chances of diabetes in FDR (parent) generation. In second degree relatives (grandparent-grand-children) the results were not exclusively pronounced for most variables except for CVD history which clearly reflected in high risk BMI percentiles (OR= 3.42), DBP percentile (OR = 2.76) and WC percentiles (OR = 1.56). Risk of high SBP and obesity in children had marked risk with presence of HTN in grandparents. Mother-child pair analyses are shown in Table (4). BMI ≥ 25 kg/ m^2 results in higher BMI in off springs (6.47 times), risk of WC ≥ 85th percentile increases 2.59 times and occurrence of BP ≥ 90th percentile ranges from 4.16-4.70. Hypertension in mothers might result in similar condition in her child nearly 4 times through SBP and 5.34-7.76 times through DBP. Incidences of higher DBP and WC have small yet significant relationship with Dyslipidemia. Age adjusted clinical and biochemical characteristics of the adolescents are shown in Table IV. There was no significant difference in the mean age among the 3 study groups (Group 1 with Score 0, Group 2 with score 1-2, Group 3 with score ≥3). Adolescents in groups 2 and 3 had significantly higher BMI ($p < 0.05$), waist circumference ($p <$

0.05 for group 3), WHR ($p < 0.05$ for group 2 and group 3) when compared with group 1. Fasting plasma glucose, total cholesterol, and serum triglycerides showed a linear trend, the differences did not reach statistical significance. Group 3 had significantly higher ($p < 0.05$) low-density lipoprotein cholesterol compared with group 1. HDL cholesterol was significantly lower in groups 2 and 3 as compared to group 1 ($p < 0.05$). The mean systolic and diastolic BP was significantly higher in group 3 ($p < 0.05$).

DISCUSSION

A common assumption in the epidemiology of chronic disease is that there is a long time gap between exposure and expression of the disease. A challenge to this assumption is the increasing appearance of children with type 2 diabetes or distinctly elevated risk for cardiovascular disease (CVD) in adolescents. The appearance of signs of adult chronic diseases in children indicates that genetic factors are important, because the environment has acted only for a short time. However, environmental risk factors are also at work, with drastic deteriorations of diet and physical activity patterns in the past several decades. The foods consumed, the frequency with which we eat, and the amounts we ingest, changes in physical activity have their own sincere effort in leaving us stranded [29-31].

Our findings prove the existence of familial ties in cardio-metabolic profiles. The odds for inheritance of a chronic condition in parent or subsequent generation are high for a diseased ancestry. The extent of inheritance varied with number of factors affecting the subsequent older generations as presence of 3 chronic conditions puts nearly 75% parental generation at a risk of all chronic conditions. It is an independent risk factor for both diseases as well as for some precursors of these diseases. It has been overemphasized that the major etio-pathogenic factors contributing to childhood obesity result from an imbalance in the energy equation produced by either increased energy intake or decreased energy expenditure [32] or both [33]. Notion is that a "toxic environment" fosters the current epidemic of obesity, type II diabetes, and CVD in children. However, this imbalance in the energy equation does not explain differences in fat distribution, individual susceptibility to develop obesity -associated co -morbidities, or the dissimilar weight loss response to lifestyle and pharmacological interventions [5]. Compared to that in adults, the energy balance in children is more affected by the intrauterine environment, metabolic abnormalities, racial and genetic predisposition, familial histories, underlying conditions, medications, and other factors. It has been established that about 75% of coronary heart disease risk is explained by conventional risk factors. For the remaining 25% risk, family history of risk factors represents conclave of genetics and other molecular biomarkers [34].

Critical periods and covariates for the development of childhood metabolic vigor have been established. For a unit increase in the risk score calculated from grandparents and maternal cardio-metabolic health, the child's metabolic risk varies distinctively from 1.04 in WC to1.34 in BMI (unadjusted models). The unfavorable body composition that accompanies exposure to increased serum (glucose and lipid) levels at times, even in-utero are likely to lead to the increased cardio-metabolic risk observed in this and other studies [35-37].The increased growth velocity observed among children exposed to such a genetic blue print could also partially explain observations of higher BP and BMI in childhood. Chronic, subclinical inflammation associated with adipose tissue may be one patho-physiological mechanism explaining the increased risk of atherosclerotic CVD and diabetes associated with obesity, which in part might be inherited by the genetic mechanism [38]. Though ethnicity and sex, play roles of confounders or covariates, their effect was found to be quantifiably negligible. For two populations under the study, completely different in essentials (environmentally and on genetic basis), ethnicity is seen to play no decipherable role on the inheritance pattern. The number of individuals being affected by chronic ailments has increased manifolds over the three generations irrespective of their rural-urban backgrounds. Hence, this shows that genes which otherwise remained subdued have expressed themselves in full measure and earlier than expected, with conducive environmental conditions.

Rural-urban and ethnic comparisons were expected to crop up in the present results but they did not surface. Two populations under study, the Siddis of Gujarat are rural by nature unlike Punjabi Khatri-Aroras who reside in urban Delhi. Siddis are marked by very high physical activity levels by occupations whereas Khatris and Aroras have a job profile which is not physically demanding. While the former population finds its roots in African descent, the latter are known to have originated in Potwar plateau of Punjab (India). Siddis have borrowed urban ways in certain lifestyle factors such as nutrition and transportation. No statistically significant differences were noticed suggesting that genetic

Table 5: Age- adjusted means for adiposity indices, biochemical and physiological characteristics of the adolescents.

Variables		Adolescents	
	Score 0 (N = 131)	**Score 1-2 (N = 283)**	**Score ≥ 3 (N = 49)**
Age (in years)	9.18 ± 2.6	9.53 ± 1.8	9.6 ± 2.9
Adiposity Indices			
BMI (kg/m2)	19.32 ± 3.6	20.25 ± 3.5*	21.86 ± 4.3*^
Waist Circumference (cm)	70.6 ± 10.7	70.9 ± 12.1	72.6 ± 11.1*^
Waist-Hip Ratio	0.80 ± 3.3	0.82 ± 4.2*	0.83 ± 6.5*^
Biochemical Markers			
Fasting Plasma Glucose (mg/dL)	88 ± 6.2	89 ± 4.6	89 ± 9.2
Total Cholesterol (mg/dL)	140 ± 22.6	141 ± 32.1	143 ± 25.8
Serum Triglycerides (mg/dL)	78 ± 23.4	80 ± 16.7	81 ± 22.3
HDL (mg/dL)	44 ± 8.2	42 ± 9.4*	39 ± 7.6*^
LDL (mg/dL)	78 ± 18.6	80 ± 14.2*	80 ± 19.1*
Physiological Indicators			
Systolic Blood Pressure (mm Hg)	104 ± 12.3	107 ± 11.4*	114 ± 10.2*^
Diastolic Blood Pressure (mm Hg)	70 ± 8 .5	71 ± 9.1	74 ± 6.8*^
^ $p < 0.05$ compared with group 2			

factors are more important for inheritance of chronic condition irrespective of ethnicity, or that causative environmental factors such as diet operate similarly upon both the rural and the urban populations. Rapid economic developments have improved the availability of nutrients, together with socioeconomic and health conditions, in Siddis. A nutritional transition like high nutrient availability, and specifically an energy dense diet might have predisposed both populations to obesity, HTN, dyslipidemia, type-2, DM in comparable proportions. This study also reflects diverse associations between cardio-metabolic profiles and order of relatives. Within second degree relatives, the associations are on a lesser scale (0.5-4 times, Table 3) as against first degree relatives where the effect was profoundly decipherable (2.59-7.76 odds, Table 4) such as parent-child associations. In the older generation odds were higher (OR 1.02-12.48, Table 3) as they were more explicitly expressed in full grown adults as against a growing adolescent population of 9-11 years. Although family history has been found to contribute independently to the risk of both diabetes and CVD, it is rarely that it is used quantitatively to assess such risk over three generations, as in this study. Some epidemiologic studies have shown that people with 1 or more first-degree relatives who are affected with diabetes were 2 to 6 times as likely to have the disease compared with people who have no affected relatives [6, 39,40]. Hence, timely intervention in the maternal generation might reduce the risk of high BP or metabolic disease in children. It is paradoxical that even with numerous evidences that certain factors in childhood contribute to the later development of some important chronic diseases such as diabetes and CVD [31,41], there is a virtual lack of any intervention or screening on similar grounds for detecting and reversing the risk factors and early signs of these diseases in children with ailing cardio-metabolic descent. Hence, these conditions that start early in life can be prevented or delayed, at least among children of high-risk genitors.

The prospective design is strength of the current study and essential for examining the effect of familial links on subsequent childhood obesity withstanding ethnicities. Studies reporting effects of obesity markers on health of subsequent generations even with a simplistic score are rare. This provides conclusive evidence that obesity prevention regimes should be based on additive estimates of health risk as calculated from first order relatives and not merely binary histories (presence/absence chronicity records). The amount of bias incurred from the use of self-reported data about history of cardio- metabolic disorders in grandparent generation might be a major limitation. Estimates are likely to contain some degree of bias due to residual and unmeasured confounding; shared intergenerational lifestyle characteristics, physical activity variables, and/or nutritional parameters, as they may have contributed to some or all of the associations described. The sample size and cross-sectional epidemiological approach adopted as against a longitudinal study is another drawback of the present research work. The analysis did not involve early life of the child or gestational conditions. In addition, different percentile has been used to define children's cardio metabolic outcomes for different characteristics unlike previous publications.

CONCLUSION

The study tends to quantify the effects of cardio-metabolic history in subsequent generations and understand the magnitude of risk of predisposition irrespective of sex and ethnicity. It brings forth the importance of family history as a tool in epidemiological research pertaining to chronic ailments. Timely intervention in the maternal generation and children of high risk genitors might reduce the risk of development of some important chronic metabolic conditions.

AUTHORSHIP AND ACKNOWLEDGEMENTS

PB contributed towards the conception and design of the study and acquisition of data. SK and PB are responsible for analysis and interpretation of data. PB drafted the article; SK and YK are responsible for the intellectual content. Both authors have made a final approval of the version submitted. The authors are grateful to all the subjects and medical staff for their cooperation. Financial assistance to PB in the form of UGC fellowship is greatly acknowledged. R & D and purse grant from University of Delhi, India to SK is gratefully acknowledged. The poster associated with a part of the present article has been awarded the best poster presentation award at the Indian Science Congress, 2013.

CONFLICT OF INTEREST

The authors declare no potential, perceived, or real conflict of interest. Authors declare that there is no sponsor hence, had no involvement in the manuscript in question. The first draft was put forth by PB and no honorarium, grant, or other form of payment was given to anyone to produce the manuscript. Ethical clearance was obtained from the Department of Anthropology, University of Delhi, Delhi-07, India as per the rules.

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