Study Protocol

National and Sub-National Prevalence, Trend, and Burden of Cardiometabolic Risk Factors in Iranian Children and Adolescents, 1990 – 2013

Roya Kelishadi MD[1], Silva Hovsepian MD PhD Candidate[1], Mostafa Qorbani PhD[3,2], Fahimeh Jamshidi MD[1], Zahra Fallah MD PhD Candidate[1], Shirin Djalalinia PhD Candidate [4,2,5], Niloofar Peykari PhD Candidate [4,2,5] , Alireza Delavari MD[6] , Farshad Farzadfar MD MPH DSc•[2,4]

Abstract

Background: Non-communicable diseases (NCDs) and their risk factors are a major health threat at the global level, notably for developing countries. The tracking of cardiometabolic risk factors from childhood to adulthood is well documented. Therefore, more attention needs to be directed at primordial and primary prevention of NCDs. Given the high prevalence of NCDs and their risk factors in Iranian population, a study was designed to determine the attributable burden of cardiometabolic risk factors in Iranian pediatric population during past decades.

Methods: This paper explains the definitions, organization, data sources, methods of data gathering or generating, data analyses, and the trend analysis of the study. A national expert working group addressed unmet needs and offered consultations on the selection of risk factors and the practical definition of disease. In the later stages, during the course of the study, they will supervise the statistical modeling methods, the interpretation of results, and the publication strategy. Also an international expert advisory group will collaborate with the project team.

Conclusion: The findings of this study could provide basic information regarding NCD related risk factors, and their burden and trends in children, which is necessary for health policy decisions to reduce the burden of disease and to plan cost-effective preventive strategies.

Keywords: Cardiovascular disease, pediatrics, prevalence, risk factors

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Introduction

During last decades, the global pattern of diseases has markedly shifted towards non-communicable diseases (NCDs). This is of special concern for developing countries which are facing an epidemiologic transition along with rapid lifestyle changes and an emerging epidemic of NCDs in the near future.[1–4] Cardiovascular diseases (CVDs) are predicted to become the most important cause of mortality worldwide and to account for approximately three-quarters of all deaths in the low- and middle-income countries by the year 2020.[5] Moreover, according to the report of Global Burden of Disease Study, 2010, Ischemic CVDs were the leading cause of the disability-adjusted life years (DALYs) worldwide with a growing rate of 29 % compared with 1990.[6] These data justify the necessity of determining and controlling major CVD risk factors. A growing body of evidences suggests that early-life environment is probably the most important causal component in the aetiology of many chronic adult diseases such as CVDs. It is proposed that epigenetic rearrangements may play an equally essential role in the disease development particularly at the key developmental stages.[7,8]

Several epidemiological, clinical and pathological studies have confirmed the beginning of the atherosclerosis process from early life. The presence of aortic fatty streaks and fibrous plaques even in children aged less than 10 years,[9,10] and the tracking of CVD risk factors from childhood to adulthood [7,11] are well documented. Most NCDs have common modifiable risk factors; therefore, more attention needs to be directed at primordial and primary prevention of NCDs including CVDs. The goal would be achieved properly if modifiable risk factors would be screened and managed from early life.[12,13]

Many epidemiological studies worldwide reported ethnic and geographical differences regarding the frequency and magnitude of CVD risk factors due to the effect of ethnic and regional factors.[14] Such differences are even documented in the pediatrics age group.[15,16] Therefore, preventative strategies in each country should be designed according to the role of each CVD risk factors in that population.

CVDs and their major risk factors are highly prevalent in the Middle East.[17] However, a recent review revealed that among developing countries, the lowest number of articles published on NCD priority intervention comes from this region.[18] As one of the countries in this region, Iran is experiencing alarming prevalence

Authors' affiliations: [1]Child Growth and Development Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Non-communicable Diseases Research Center, Endocrinology and Metabolism Population Science Institute, Tehran University of Medical Sciences, Tehran, Iran, [3]Alborz University of Medical Sciences, Alborz, Iran, [4]Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Research Institute, Tehran University of Medical Sciences, Tehran, Iran, [5]Development of Research & Technology Center, Deputy of Research and Technology, Ministry of Health and Medical Education, Tehran, Iran, [6]Digestive Oncology Research Center, Digestive Disease Research Institute, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.
•Corresponding author and reprints: Farshad Farzadfar MD MPH DSc, Non-communicable Diseases Research Center, Endocrinology and Metabolism Research Institute, Tehran University of Medical Sciences, Tehran, Iran. Address: 4th floor, No. 4, OstadNejatollahi St, Enqelab Ave, Tehran, Iran. Postal code: 1599666615, Tel/Fax: 98-21-88913543; E-mail: f-farzadfar@tums.ac.ir.
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rates of cardiometabolic risk factors, as documented by nationwide studies conducted among adult populations.[19–22]

Many studies have determined the prevalence of cardiometabolic risk factors in Iranian children and adolescents, but they have been limited to one area; only one of these studies has been conducted at the national level. This surveillance program entitled Child and Adolescent Surveillance and Prevention of Adult Non-communicable diseases (CASPIAN) study was consisted of national surveys conducted every two years. It showed that the most frequent CVD risk factors among Iranian pediatrics population were low levels of high density lipoprotein- cholesterol (HDL-C), hypertriglyceridemia and overweight, respectively.[23]

According to the results of the first survey of the CASPIAN study, the prevalence of hyperlipidemia, systolic hypertension, diastolic hypertension, systolic or diastolic hypertension, overweight, obesity and metabolic syndrome were 45.7 %, 4.2 %, 5.4 %, 7.7 %, 18.1 % , 4.8 % and 14.1 % ,respectively.[24–27]

The prevalence of dyslipidemia, high blood pressure, and metabolic syndrome were higher in obese children than in their other counterparts; however CVD risk factors, notably low HDL-C and hypertriglyceridemia, also existed in some of the normal weight students.[27] The factor analysis of CVD risk clustering in pediatric metabolic syndrome of the CASPIAN study population indicated that cholesterol/triglycerides (TG), metabolic/adiposity, and blood pressure were loaded in children with metabolic syndrome.[28]

Though there are many epidemiological studies regarding the prevalence and point estimates of metabolic risk factors among Iranian children and adolescents, there are a little information on their exposure distribution at the sub-national level, on the trends of cardiometabolic risk factors and their effects on the population health. Recent comprehensive systematic reviews showed that developing countries had limited data, especially longitudinal data, on metabolic risk factors. The study supported the value of population-based periodic risk factor surveillance studies not only for comparative cross-country analysis, but also for national and subnational priority setting.[29]

Trend analysis of the metabolic risk factors is a sub-component of National and Sub-nation Burden of Diseases, Injuries, and Risk Factors from 1990 to 2013 (NASBOD) study which is aimed to quantify metabolic risk factors exposures and related attributed burdens and their trends and inequalities at the national and sub-national levels.[30] To the best of our knowledge, there are few studies in developed and developing countries providing the estimates on the trends of the risk factors exposure at the sub-national level (small area estimation).[31–33]

Considering the importance of exploring different aspects of this emerging phenomenon, this study was designed to determine the attributable burden of cardiometabolic risk factors in Iranian pediatric population during past decades. This paper explains the definitions, organization, data sources, methods of data gathering or generating, data analyses, and the trend analysis of the study.

Materials and Methods

Organizing working group

A national expert working group, consisted of public health experts, pediatricians, global health experts and epidemiologists, was created to address unmet needs. The national expert working group offered consultations on the selection of risk factors, the practical definition of diseases, and in the later stages during the course of the study they will supervise the statistical modeling methods, the interpretation of results, and the publication strategy. Also an international expert advisory group will collaborate with the project team.

Risk factor selection process

We focused on the important risk factors of non-communicable diseases such as dyslipidemia, high blood pressure, high BMI, WC and metabolic syndrome which can lead to cardiovascular diseases like coronary heart disease, stroke and peripheral artery occlusive disease. In addition, these risk factors can enhance the development and progress of other disease like chronic kidney insufficiency, diabetes, NAFLD, osteoporosis, and cancers.

The emergence of abnormal levels of risk factors by adult criteria begins to occur in young adults. Retrospective studies, interestingly, have revealed the evidences of the presence of some diseases already from childhood including obesity, high blood pressure, and dyslipidemia. These findings have strong implications for undertaking preventive measures from early life.[34] Overall, dietary risks, high blood pressure, and high body-mass index are the three risk factors that account for the major part of disease burden in Iran.[6]

We considered cardiometabolic risk factors other than abnormalities in fasting plasma glucose (FPG) because in the pediatric age group, the most overt type of diabetes is insulin- dependent which becomes symptomatic soon. Thus universal screening of FPG is not necessary; instead, targeted screening is recommended for individuals with a family history of diabetes and patients who met the criteria of the American Diabetes Association (ADA).[35]

Definitions

Table 1 presents the ninety-fifth percentiles of blood pressure for 50th and 75th height percentiles in children and adolescents.[36] Table 2 shows the National Heart, Lung, and Blood Institute (NHLBI) recommendations for pediatric hypertension diagnosis and Table 3 shows the acceptable, borderline-high, and high plasma lipid, lipoprotein, and apolipoprotein concentrations for children and adolescents.[37] The components of pediatric MetS are presented in Tables 4 and 5 based on two different references.[37,38]

Pediatric hypertension

The Task Force on Blood Pressure Control in Children, commissioned by the NHLBI of the National Institutes of Health (NIH) of America, developed standards for BP. Based on the definitions by Task Force, BP is considered normal when the systolic and diastolic values are less than the 90th percentile for the child's age, sex, and height. The Fourth Report introduced a new category, prehypertension, which is diagnosed when a child's average BP is above the 90th percentile but below the 95th. Every adolescent with a BP greater than 120/80 mm Hg is also diagnosed the same, even if the BP is below the 90th percentile. This classification was designed to align children and adult categories based on the recommendations mentioned in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Stage I hypertension will be diagnosed if a child's BP is greater than the 95th percentile but less than or equal to the 99th percentile plus 5 mm Hg. Stage II hypertension will be diagnosed if a child's BP is greater than the 99th percentile plus 5 mm Hg. If the systolic and diastolic pressures give rise to a

Table 1. Ninety-Fifth Percentiles of Blood Pressure for 50th and 75th Height Percentiles in Children and Adolescents[37]

Age, y	95th BP Percentile for Girls, mm Hg		95th BP Percentile for Boys, mm Hg	
	50th Height Percentile	75th Height Percentile	50th Height Percentile	75th Height Percentile
1	104/58	105/59	103/56	104/58
6	111/74	113/74	114/74	115/75
12	123/80	124/81	123/81	125/82
17	129/84	130/85	136/87	138/87

Table 2. Age-Specific Recommendations for Diagnosis of Hypertension[38]

Birth to 3 y ;
If BP ≥ 90th percentile by oscillometry, confirm by auscultation،If BP confirmed ≥90thpercentile, initiate evaluation for etiology and treatment per algorithm
3 to 11 y ;
If BP confirmed > 90th percentile, <95th percentile = **prehypertension (Pre-HTN)**
If BP confirmed > 95th percentile, <99th percentile + 5 mmHg = **stage 1 HTN**
If BP confirmed > 99th percentile + 5 mmHg = **stage 2 HTN:**
12 to 17 y Annual;
If BP confirmed > 90th percentile, < 95th percentile or >120/80 = **pre-HTN**
If BP confirmed ≥ 95th percentile, < 99th percentile + 5 mmHg=**stage 1 HTN**
If BP confirmed > 99th percentile + 5 mmHg = **stage 2 HTN**
18 to 21 y ;
BP ≥ 120/80 to 139/89 = **pre-HTN**
BP ≥140/90 to 159/99 = **stage 1 HTN**
BP ≥160/100= **stage 2 HTN**
BP recommendations are based on the NHLBI's "The Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood

Table3. Acceptable, Borderline-High, and High Plasma Lipid, Lipoprotein, and Apolipoprotein Concentrations for Children and Adolescents[38]

Category	Low, mg/dL[a]	Acceptable, mg/dL[a]	Borderline-High, mg/dL[a]	High, mg/dL[a]
TC	- - -	< 170	170–199	≥ 200
LDL cholesterol	- - -	< 110	110–129	≥ 130
Non-HDL cholesterol	- - -	< 120	120–144	≥ 145
Apolipoprotein B	- - -	< 90	90–109	≥ 110
Triglycerides				
0–9 y	- - -	< 75	75–99	≥ 100
10–19 y	- - -	< 90	90–129	≥ 130
HDL cholesterol	< 40	> 45	40–45	- - -
Apolipoprotein A-1	< 115	> 120	115–120	- - -

Values for plasma lipid and lipoprotein levels are from the NCEP Expert Panel on Cholesterol Levels in Children. Non-HDL cholesterol values from the Bogalusa Heart Study are equivalent to the NCEP Pediatric Panel cut points for LDL cholesterol.
Values for plasma apolipoprotein B and apolipoprotein A-1 are from the National Health and Nutrition Examination Survey;
III. Note that values shown are in mg/dL; to convert to SI units, divide the results for TC, LDL cholesterol, HDL cholesterol, and non-HDL cholesterol by 38.6; for triglycerides, divide by 88.6;
a. Low cut points for HDL cholesterol and apolipoprotein A-1 represent approximately the 10th percentile. The cut points for high and borderline-high represent approximately the 95th and 75th percentiles, respectively.

discrepancy with respect to the classification, the child's condition should be categorized using the higher value.[36,39,40]

Data sources

a) Systematic Literature Review

The search protocol was designed by the scientific committee in cooperation with information specialists' subgroups based on the objectives of the project and using the "Guide to the search strategy" by COCHRANE collaboration.

a-1) Sources to be searched

In order to obtain the highest level of access to the published, available unpublished and grey literature, the systematic search of electronic databases would be followed through the comprehensive hand searching process.

a-2) Databases we intended to search

PubMed and the NLM Gateway (for MEDLINE), Institute of Scientific Information (ISI), and SCOPUS will be searched as the main international electronic data sources. Moreover Iranmedex, Irandoc, and Scientific Information Database (SID) are considered as the main domestic databases with systematic search capability and with the widest coverage on national indexed or even non indexed Iranian scientific journals. The medical subject headings (Mesh) including Entry Terms of PubMed and Emtree of Scopus were used for conducting the most comprehensive and efficient searches. Persian keywords equivalent to their English search terms were use for searching in the national search engines.

a-3) Executive details

The project research team will undertake the defined tasks in about 6 months. For each data base, strategies will be run separately regarding the detailed practical instruction including filters and

Table4. Metabolic Syndrome Component Levels for Evaluation of Children With Multiple Cardiovascular Risk Factors[38]

Risk Factor	Cut Point	Reference
Obesity, percentile		
BMI	≥ 85th to < 95th	CDC growth charts
Waist Circumference	≥ 90th to < 95th	NHANES
Blood Pressure, percentile	≥ 90th to < 95th	"The Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents"
Dyslipidemia, mg/dL		See "Table 3" for normative values
HDL cholesterol	≥ 40 to ≤ 45	
Triglycerides		
0–9 y	≥ 75 to <100	
≥10 y	≥ 90 to < 130	
Non-HDL cholesterol	≥ 120 to <144	
Glycemia, mg/dL		ADA screening recommendations
Fasting glucose	≥ 100 to <126	
Fasting insulin	Elevated fasting insulin level, above normal for gender, race, and pubertal status, is considered evidence of insulin resistance	

NHANES indicates National Health and Nutrition Examination Survey; ADA, American Diabetes Association

Table5. Proposed Pediatric Definitions of MetS[39]

	Adult Definition*	Percentiles	Proposed Pediatric Definition
Hypertriglyceridemia	≥ 1.65 mmol/L	75th (male); 85th (female)	≥1.1 mmol/L
Low HDL	< 1.04 mmol/L (men); < 1.3 mmol/L (women)	40th	HDL < 1.3 mmol/L (boys aged 15–19 years, < 1.17 mmol/L)
High fasting glucose	≥ 6.1 mmol/L	NA	≥ 6.1 mmol/L
Central obesity (waist circumference)	> 102 cm (men) > 88 cm (women)	72nd (male) 53rd (female)	> 75th percentile for age and gender
Hypertension	SBP ≥ 130 mm Hg DBP ≥ 80 mm Hg	NA	> 90th percentile forage, gender, and height

*ATP III. To convert SI to conventional units, divide mmol/L by 0.0113 for triglycerides, 0.0259 for HDL, and 0.0555 for glucose

refining processes. There will be filters for ongoing searches in the national and international electronic databases, inclusion criteria for data and researches and all of other published/ available unpublished reports or thesis. We will limit the search terms to national, provincial, district, community population based studies in child and adolescence), to Iran, to human subject and there is no restriction on language. All research papers, abstracts, conference proceedings, titles of thesis, dissertations and reports included to our inclusion criteria for document types. Databases will be searched for the related data recorded from 1985 to the present. For more data availability through register system of international data bases the new cases would be added. We will use Endnote reference management software, version 11. All Iranian scientific journals of medical universities, which are not registered in the domestic electronic databases, governmental reports, projects reports, conferences and reference lists will be reviewed through hand searching.

a-4) Study selection process

Generally, all papers that reported any relevant data on risk factors (incidence, and prevalence) from population-based or cross-sectional studies would be potentially eligible for the review. Our target population is children and adolescents (6 – 19 years).

a-5) Data extraction

After determination of eligible papers, using standardized data extraction sheet, data would be extracted and entered into predefined electronic data extraction sheets. For more accuracy it will be conducted independently by two researchers and probable discrepancy between researchers will be resolved by consensus. The data extraction sheet contains the following items: General information about the study and its citations, detailed characteristics of population, Methodological information about designing and conducting the study, and study outcomes indicators.

b) National data Sources

b-1) Childhood and Adolescence Surveillance and Prevention of Adult Non-Communicable Disease (CASPIAN) study

The main data source for children and adolescents cardiometabolic risk factors in Iran is the CASPIAN study which was a joint collaborative study by WHO regional office for the Eastern Mediterranean (WHO/EMRO), the Iranian Ministry of Health and Medical Education, and the Ministry of Education.[41] Data

was collected in four different surveys during 2003 to 2012 in four different years at the national and subnational levels in Iran. The methodological characteristics of four CASPIAN studies are as bellow:

b-1-1) CASPIAN I: This national study was performed from 2003 to 2004 in 23 provinces of Iran.[41,42] In this survey, according to the WHO/MONICA protocol, approximately 22000 students aged 6–18 years were selected via multistage cluster sampling method. In this survey, to take the socioeconomic status into consideration, sampling was based on living place (urban/rural) and type of school (public/private). Data were collected via questionnaire, physical measurements, and biochemical tests. The questionnaire was based on the WHO STEPwise approach and the WHO Global School Health Survey which included questions about socio-demographic characteristics, family history of NCD, family dietary habits, food frequency questionnaire, as well as questions about the behavior, attitude, skills and knowledge of students and parents about a healthy lifestyle. In the physical measurement part, anthropometric measures including height, weight, waist circumference and hip circumference, and blood pressure were measured using a standard protocol. Fasting blood sugar (FBS), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and low-density lipoprotein-cholesterol (LDL-C) were measured in a subsample of 4811 students aged 6 – 18 years from six provinces located in diverse parts of the country by a WHO collaborating center in Tehran and using the standards of the National Reference Laboratory. Since the quality of study processes was monitored by the Data and Safety Monitoring Board of the project, the quality of data was acceptable. The results of this study are representative of sub-provincial and provincial levels.

b-1-2) CASPIAN II: This study was conducted from 2007 to 2008 in 28 provinces.[43] In this study, 10000 students aged 11 – 18 years from urban and rural areas were selected via multistage sampling method. In this study data were collected using a questionnaire and physical measurements. Blood sampling and biochemical tests were not performed in this survey. The questionnaire was based on Global School Health Survey (GSHS) and Youth Risk Behavior Surveillance (YRBS) and in addition to the CASPIAN I questions, it also included questions about the relationship with peers, psychosocial status of school, physical activity pattern, hygiene, violence and unintentional injury, protective factors, mental health, tobacco use, and sexual behaviors. In this study height and weight were measured and other anthropometric indexes, blood pressure, and blood sampling were not considered. Individuals' data collected by the study are not available and only the aggregated data of the study is available to be used for the estimation of cardiometabolic risk factors burden in children and adolescents.

b-1-3) CASPIAN III: This survey was conducted in 27 provinces of Iran from 2009 to 2010.[44] The survey was conducted on 5570 students aged 10 – 18 years from urban and rural areas, who were selected by multistage random cluster sampling. In this study data were collected via questionnaire, physical measurements and biochemical measurements. The study questionnaire was similar to that of CASPIAN II study. In this study anthropometric measures (including height, weight and waist circumference) and blood pressure and blood sampling (FBS and lipid profile) were measured using a standard protocol. The quality of study processes is acceptable and the results are representative of provincial level.

b-1-4) CASPIAN-IV: The forth study of the school-based surveillance system entitled CASPIAN-IV study was conducted from 2011 to 2012 in rural and urban areas of 30provinces.[45,46] In this study 14880 students aged 6 – 18 years were selected via multi-stage cluster sampling method from 31 provinces of Iran. The Questionnaires was similar to that of CASPIAN II and III. In this study, similar to CASPIAN I, height, weight, waist circumference, hip circumference and blood pressure were measured. In addition, the wrist circumference was also measured. In this study biochemical tests were not performed and the results are representative of sub-provincial and provincial levels.

b-2) School students' examination project

This project was established in 2003 – 2004 for first time, to examine students at the beginning of each grade (elementary, guidance school and high school). In this project, weight and height of all students aged 6 – 18 were measured at the beginning of the school annually based on a standard protocol.

b-3) Surveys of Risk Factors of Non-Communicable Diseases (SuRFNCD)

This data source included six national surveillance SuRFNCDs which were collected during 2005 to 2009 and in 2011 in six different years at provincial and sub-provincial levels in Iran. In these studies a total of 221000 subjects aged 15 – 65 years from urban and rural population of Iran were selected via multistage cluster sampling method.[47] In all surveys, anthropometric indices (including height, and weight) and blood pressure were measured using a standard protocol and biochemical measures (FBS and lipid profile) were collected in only three SuRFNCDs in 2005, 2007 and 2011. SuRFNCDs' data about individuals aged 15 – 18 years old can be used for the estimation of cardiometabolic risk factors burden in adolescents.

b-4) Tehran Lipid and Glucose (TLGS) study

The study is a cohort study which was started in 1999 and in the first survey, 15000 individuals over three years of age were selected randomly from residents of district 13 of Tehran (urban population) in order to assess cardiovascular risk factors, diabetes mellitus, and serum lipid disorders.[48] In this study anthropometric measures (including height, weight, waist circumference, and hip circumference) and blood pressure, and blood sampling (lipid profiles, fasting blood sugar and 2-hours-postload-glucose) were measured using a standard protocol. In the second phase of the study, lifestyle interventions were implemented.[49]

Statistical methods and analysis plans

To overcome the limitation of lack of representative data in provincial level, in some age or sex groups, and in urban or rural areas, two distinct statistical models (Spatio-temporal model and multilevel autoregressive model) will be used to estimate mean and its confidence interval. To estimate mean and uncertainty interval for interest data of a specific age, year, and province as well as that of other ages, years, and provinces will be entered to the models. For the provinces, which have been separated from other provinces in the under research period of time, we will face

the problem of misaligned areal units, in both models. Benefiting from two different models will reduce model dependency in the results.

Spatio-temporal Bayesian Hierarchicalmodel

To overcome the abovementioned limitations we will apply Spatio-temporal Bayesian hierarchical modeling with Conditional Auto Regressive prior for spatial random effects.[50] In spatial framework, observations that are closer in space are assumed to be more correlated than observations farther away. Such structure enables model to "borrow information" from neighboring areal units to improve estimates for areas with missing values and/or small number of observations. Moreover, Spatio-temporal misalignment modeling combines incompatible areal units between data sources and/or over the years. The model includes covariates effects, non-linear age trend, and study quality and source of data variations.

Bayesian Multilevel Autoregressive model

Another advanced method to handle the challenges mentioned is Bayesian multi-level autoregressive model.[51] Through which, observations are hierarchically nested in districts, provinces, sub-regions, regions, and national levels, respectively. In this hierarchical model, lower levels borrow information from higher levels and units of each level borrow information to each other depending on the degree of data availability. The model benefited from several different components including linear time trends, nonlinear change over time, covariate effects, and non-linearity associated with age, heterogeneity of data sources, and age-by-study variability. If necessary, estimates will be obtained using time-varying district-level or province-level covariates.

To perform Bayesian inference for both modeling frameworks, the Markov Chain Monte Carlo (MCMC) methods for their general applicability and ease of implementation will be used. All programs will be written in R-statistical packages (version 3.0.1).

In addition to these challenges, the other problem is the summary statistics that have been reported in different classification. Using regression models, we will benefit from cross walk between continuous and categorical measures of interest variables.

Ethical Considerations

This is a secondary research on observational studies which is compatible with the relevant socio-cultural concerns. The study protocols will be submitted to the Institutional Ethical Review Boards for approval. Data will be gathered in two main ways: First, through systematic reviews on related published data and second through searching datasets of national, subnational or regional studies with the permission and/or supervision of main researcher(s). Any required additional data will be asked from original authors in a moral manner. Data will be used de-identified if it is due. In probable archive searches, relevant ethical consideration such as confidentiality will be considered. All data sources will be cited in our reports. Findings will be disseminated to relevant stakeholders.

Discussion

In recent decades, Iran like other developing countries has been experiencing a rapid epidemiological transition, and is facing a double burden of diseases due to urbanization and nutrition transition.[52] The double burden of diseases among children especially in nutritional disorders could significantly affect the emergence of NCD and the pattern of morbidity and mortality.

Findings from developing countries have provided evidence-based data on the considerable prevalence of childhood overweight and its metabolic consequences in countries which are still challenging with malnutrition and micronutrient deficiencies. In fact, Iran is in an epidemiologic transition from older stages of communicable and poverty-related diseases to fifth stage of alarming increase in overweight and obesity and continuous decreases in physical activity; thus Iran is facing both side consequences.[53,54]

Evidences suggest that the interaction between genetic, intrauterine, and environmental factors lead to NCDs and related metabolic disorders.[55]

An ethnic comparisons between three large population-based samples of European, Asian and South-American children and adolescents revealed that the prevalence of the MetS components differ among children and adolescents of the three studied ethnicities, with special focus on the context of low HDL-C and high TG levels, as well as abdominal obesity.[16]

In a review study, findings from developing countries showed that among children and adults studied in Iran and Turkey, the most frequent components of the metabolic syndrome were high triglyceride levels and low HDL-C levels. This can reflect an ethnic predisposition toward this type of dyslipidemia in this region. On the other hand, prevalence rates of high total and low density lipoprotein cholesterol were reported to be considerably higher in Western countries than in Iran and Turkey.[56]

Though genetic susceptibility is not similar in different ethnic populations, but it is proposed that individuals with higher susceptibility develop NCDs and the related metabolic disorders if they would be exposed to Westernized lifestyle.[55] Therefore, age-appropriate and culture-sensitive interventions in modifiable environmental factors, such as lifestyle modification and increasing physical activity from childhood, are probably the best choice for primary prevention of NCDs.[57] Considering that long term life style modification in adult population is difficult to achieve, it is more favourable to plan preventive strategies which target young people.[58,59] Thus to achieve this goal, providing a baseline epidemiologic information is necessary for different cardiometabolic risk factors in the pediatric age group.

Considering the fact that early-life environment is probably the most important causal component in the etiology of some diseases including metabolic and cardiovascular disorders[60] and the importance of planning preventive measures from early life, this study was designed to estimate the distribution, contribution and the role of metabolic risk factors including metabolic syndrome, dyslipidemia, obesity and blood pressure in the burden of diseases among pediatric population at subnational level in Iran, from 1990 to 2013.

The findings of the study would help us to determine inequalities between regions, ethnicities, ages, and sexes in children and adolescents, to design health policies and programs especially in the field of prevention accordingly. This study is a part of NASBOD study, a comprehensive project, which was designed to use many sources of data for the estimation of burden of diseases, injuries, and risk factors from 1990 to 2013, using new quantitative methods to adjust low quality of data.

In the current study, different nationally reported source of data

were used for estimating the burden of mentioned cardiometabolic risk factors in Iranian children and adolescents. The most commonly used sources of data were different surveys of the CASPIAN study, as the only nationwide study in this field in Iran.[43–45] In addition, the data of a number of community-based epidemiological studies at smaller scales were considered as well.[47,48,61–63]Availability of various nationally representative sources of data is considered as the advantages of this study.

Using a systematic review study, the obtained data will be used to estimate YLD, YLL and consequently DALYs of cardiometabolic risk factors in children. Moreover, considering different background variables and exposures in different regions and ethnic groups, the inequalities in studied burden of CVD will be estimated.

Relative risks are taken from large international meta-analyses and there may be cross-country differences. However, there are studies demonstrating that despites other lifestyle and environmental risk factors for infectious diseases, the relative risks of metabolic risk factors are somehow similar between countries.[64] Moreover, heterogeneity analysis can be used to reduce uncertainty of the results. Third, relative risks are different between mortality and incidence of the disease. And finally, disability weights are not calculated specifically for the country under the study and are taken from global studies.[33] There are also some limitations which are specific to our country. Data on incidence and duration of non-fatal diseases, and non-fatal sequelea are scant, which increases the uncertainty of estimations of disability. There is limited access to data at the provincial scale, which can be somehow corrected by using hierarchical models. The limited access to the level of risk factor can be adjusted through crosswalk analysis. There may be limited access to the fulltexts of certain published or unpublished epidemiological studies, which will be resolved through contacting investigators of those studies. Finally, there may be distinct heterogeneity between data sources, which will be managed via methodological strategies.

Meanwhile collecting data and conducting the study, our health information system situation and pitfalls will become more apparent. It is expected to face many deficiencies and irregularities in this regard. This can help us to decide what the problems are and how they can be solved. In addition we can propose an information system infrastructure specific to our study goals based on what we need.

The findings of this study could provide basic information regarding cardiometabolic risk factors in children and their burden and trends, which are necessary for health policy decisions to reduce the burden of diseases, and to plan cost-effective preventive strategies. However, effective strategies could reduce the burden of diseases in adult population of country in the future. The results also could be used for future subnational, national, regional and global studies. Obtained data will be presented via web site, publications, workshops, symposiums, and training courses.

Abbreviations

NCDs: Non-communicable diseases; CVDs: Cardiovascular diseases; DALY: Disability-Adjusted Life Years; GBD: Global Burden of Disease; NASBOD: National and Sub-national Burden of Disease; YLL: Years of Life Lost due to premature mortality; YLD: Years of Life Lost due to Disability; TLGS: Tehran Lipid and Glucose; CASPIAN study: Childhood and Adolescence Surveillance and Prevention of Adult Non-Communicable Disease.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

General designing of the paper was by the NASBOD core team and the Child Growth and Development ResearchCenter expert panel. All co-authors had contribution in the primary draft preparation and revision. All authors have given approval to the final version of the manuscript.

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Appendix A. Search Strategy of Metabolic Risk Factors

High Body Mass Index (BMI) / Waist Circumference/ waist-hip ratio/ waist-to-height ratio
Search strategy in PubMed/Medline (“Body Mass Index”[Mesh] OR “Body Mass Index”[All Fields] OR “Overweight”[Mesh]) OR “Overweight”[All Fields] OR “Obesity”[Mesh] OR “Obesity”[All Fields] OR “Quetelet* Index”[All Fields] OR “Waist Circumference “[Mesh] OR “ Waist Circumference “[All Fields] OR “waist-hip ratio”[MeSH Terms] OR waist hip ratio[All Fields] OR “waist to hip ratio”[MeSH Terms] OR waist to hip ratio[All Fields] OR waist to height ratio[All Fields]) AND (“Iran”[Mesh] OR “iran”[All Fields]) OR Iranian[All Fields] OR I.R.Iran[All Fields] OR “I.R Iran”[All Fields] OR (“persia”[MeSH Terms] OR “persia”[All Fields])) AND ((“1985/01/01”[PDAT] : “2013/12/31”[PDAT]) AND “humans”[MeSH Terms])
Search strategy in ISI Web of Science Time span=1990-2013. Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH. Topic= (“Body Mass Index” OR “Overweight” OR “Obesity” OR “Quetelet* Index” OR “ Waist Circumference “ OR “ waist hip ratio “ OR “ waist to hip ratio “ OR “ waist-hip ratio “ OR “ waist to height ratio”) AND ((“Iran” OR Iranian OR I.R.Iran OR “persia”) OR Address= (Iran))
Search strategy in Scopus (TITLE-ABS-KEY (“Body Mass Index” OR “Overweight” OR “Obesity” OR “Quetelet* Index” OR “ Waist Circumference “ OR “ waist hip ratio “ OR “ waist to hip ratio “ OR “ waist-hip ratio “ OR “ waist to height ratio “ OR “ waist-to- height ratio “)) AND (TITLE-ABS-KEY (Iran OR Iranian OR I.R.Iran OR Persia) OR (AFFIL (Iran)) AND PUBYEAR > 1989 AND PUBYEAR < 2013
IranMedex, SID and Irandoc: “Body Mass Index”, “BMI”, “Overweight”, “Obesity”, “Quetelet* Index”, “waist-hip ratio”, “waist to ratio”, “Chaghi”, “Shakhese tudeh e badani”, “ezafe vazn”, “Dore kamar” , “Dore kamar be lagan” , “Dore kamar be basan”, “Dore kamar be ghad”, in combination with terms pediatr* OR child* OR adolescent OR student OR teenager OR boys OR girls koodak , atfal , nowjavan, daneshamooz, madreseh, madares, dokhtar, pesar in Persian language search.
Dyslipidemia / hyperlipidemia / lipid profile/ HDL-C /LDL-C /cholesterol /triglyceride
Search strategy in PubMed/Medline (TITLE-ABS-KEY (Dyslipidemia **OR** hyperlipidemia **OR** lipid profile **OR** HDL-C **OR** LDL-C **OR** cholesterol **OR** triglyceride)) AND (TITLE-ABS-KEY (Iran OR Iranian OR I.R.Iran OR Persia) OR (AFFIL (Iran)) AND (TITLE-ABS-KEY(Children **OR** student **OR** School-aged **OR** Preschool **OR** Pre-school **OR** youth **OR** Teenagers **OR** Adolescent **OR** Boy **OR** Girl))
Search strategy in ISI Web of Science (TITLE-ABS-KEY (Dyslipidemia **OR** hyperlipidemia **OR** lipid profile **OR** HDL-C **OR** LDL-C **OR** cholesterol **OR** triglyceride)) AND (TITLE-ABS-KEY (Iran OR Iranian OR I.R.Iran OR Persia) OR (AFFIL (Iran)) AND (TITLE-ABS-KEY(Children **OR** student **OR** School-aged **OR** Preschool **OR** Pre-school **OR** youth **OR** Teenagers **OR** Adolescent **OR** Boy **OR** Girl))
Search strategy in Scopus (TITLE-ABS-KEY (Dyslipidemia **OR** hyperlipidemia **OR** lipid profile **OR** HDL-C **OR** LDL-C **OR** cholesterol **OR** triglyceride)) AND (TITLE-ABS-KEY (Iran OR Iranian OR I.R.Iran OR Persia) OR (AFFIL (Iran)) AND (TITLE-ABS-KEY(Children **OR** student **OR** School-aged **OR** Preschool **OR** Pre-school **OR** youth **OR** Teenagers **OR** Adolescent **OR** Boy **OR** Girl))
IranMedex, SID and Irandoc: “Dyslipidemia” , “hyperlipidemia”, “lipid profile” “HDL-C”, “LDL-C”, “cholesterol”, “triglyceride”, “charbi e khun”, “student”, “children”, “adolescent” , “daneshamouzan”, “koudakan”
Blood pressure related risk

Search strategy in PubMed/Medline
("high blood pressure"[MeSH Terms] OR " high blood pressure"[Title/Abstract] OR "blood pressure"[MeSH Terms] OR "blood pressure"[Title/Abstract] OR hypertens*[MeSH Terms] OR hypertens*[Title/Abstract] OR prehypertens*[MeSH Terms] OR prehypertens*[Title/Abstract] OR pre-hypertens*[MeSH Terms] OR pre-hypertens*[Title/Abstract] OR "systolic pressure"[MeSH Terms] OR "systolic pressure"[Title/Abstract] OR "diastolic pressure"[MeSH Terms] OR "diastolic pressure"[Title/Abstract] OR "arterial pressure"[MeSH Terms] OR "arterial pressure"[Title/Abstract]) AND (pediatric[Title/Abstract] OR child*[Title/Abstract] OR adolescent[Title/Abstract] OR school[Title/Abstract] OR preschool[Title/Abstract] OR pre-school[Title/Abstract] OR teenager[Title/Abstract] OR "teen-ager"[Title/Abstract] OR boys[Title/Abstract] OR girls[Title/Abstract]) AND ("Islamic Republic of Iran" [All Fields] OR Iran*[All Fields] OR Persia*[All Fields] OR "I.R Iran"[All Fields] OR "I.R.Iran"[All Fields] OR Iran[Affiliation]) AND ("1985/01/01"[Date - Publication] : "2013/12/31"[Date - Publication])

Search strategy in ISI Web of Science
Time span=1985-2013. Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH.
Topic= ("blood pressure" OR "hypertens*" OR "prehypertens*" OR "pre-hypertens*" OR " systolic pressure " OR " diastolic pressure " OR " arterial pressure " OR " high blood presure ")
AND Topic=(pediatr* OR child* OR adolescent OR student OR teenager OR boys Or girls)
AND (("Iran" OR Iranian OR I.R.Iran OR "persia") OR Address= (Iran))

Search strategy in Scopus
(TITLE-ABS-KEY ("high blood pressure" OR "blood pressure" OR "hypertension" OR "prehypertension" OR " pre-hypertension " OR "systolic pressure " OR "diastolic pressure " OR " arterial pressure ")) AND TITLE-ABS-KEY (pediatr* OR child* OR adolescent OR student OR teenager OR boys OR girls) AND (TITLE-ABS-KEY (Iran OR Iranian OR I.R.Iran OR Persia) OR (AFFIL (Iran)) AND PUBYEAR > 1985 AND PUBYEAR < 2013

IranMedex, SID, Irandoc, magiran, medlib:
"high blood pressure" OR "blood pressure" OR "hypertension" OR "prehypertension" OR " pre-hypertension " OR "systolic pressure " OR "diastolic pressure " OR "arterial pressure "" in combination with terms pediatr* OR child* OR adolescent OR student OR teenager OR boys OR girls in English language search and "feshare khoon", "Feshare khoone bala","porfeshariye khoon", "pishporfeshariye khoon","feshare systoli(k)","feshare diastoli(k)", "feshare sharyani", perehipertansioon,pereh hipertansioon,pere-hipertansioon,hipertansioon, haypertansioon,haypertenshen,perehaypertansioon,perehaypertenshen with different letter spacings in combination with terms "koodak","atfal","nowjavan", "daneshamooz","madreseh","madares","dokhtar", "pesar" in Farsi (Persian) language search.

Metabolic Syndrome

Search strategy in PubMed/Medline
("metabolic "[Mesh] OR "insulin resistance"[Mesh]) OR "dysmetabolic"[Mesh] OR "reaven"[Mesh] OR "cardiovascular"[Mesh]) AND "syndrome*"[Mesh] AND "humans"[MeSH Terms] AND (Iran* OR "I.R.Iran" OR "IR.Iran" OR Persia*)

Search strategy in ISI Web of Science
("metabolic " OR "insulin resistance" OR "dysmetabolic" OR " reaven" OR "cardiovascular")AND "syndrome*" AND (Iran* OR "I.R. Iran" OR persia*)

Search strategy in Scopus
((AFFIL(iran* OR "I.R. Iran" OR persia*) AND PUBYEAR > 1984) OR (TITLE-ABS-KEY(iran* OR "I.R. Iran" OR persia*) AND PUBYEAR > 1984)) AND ((TITLE-ABS-KEY(("metabolic" OR "insulin resistance" OR "dysmetabolic" OR "reaven" OR "cardiovascular") AND "syndrome*") AND PUBYEAR > 1984)

IranMedex, SID and Irandoc
"Metabolic syndrome", "Dysmetabolic syndrome"," Cardiovascular syndrome", "Insulin resistance syndrome", "sandrome metabolic", "sandrome moghavemat be Insulin", "moghavemat be Insulin"