

Review Article



Asian Cohort Studies on Cardiovascular Risk Factors in Childhood

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Conflict of Interest

The authors have no financial conflicts of interest.

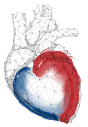
ABSTRACT

Long-term cohort studies have shown that cardiovascular risk factors measured during childhood were associated with levels of adult cardiovascular risk factors and also with the lifetime risk of cardiovascular disease (CVD). However, most of the epidemiologic evidence was from Western studies and relatively small in the Asian population. From the literature, we identified and reviewed 8 Asian cohort studies focusing on cardiovascular risk factors among children. The Asian cohort studies have confirmed that childhood risk factors can predict later levels of adult risk factors. Besides, it has been shown that childhood risk factors are associated with intermediate phenotypes, such as metabolic disturbance and degenerative vascular changes, in adulthood. These findings reaffirmed the importance of screening and managing cardiovascular risk factors from early life in Asia. However, there is little evidence on CVD incidence and mortality because there is no Asian cohort study, which observed from childhood until middle-aged or old ages. Longer follow-up data are required to measure the impact of childhood cardiovascular risk factors, especially since obesity and other cardiovascular risk factors are increasing in Asian children and adolescents.

Keywords: Child; Adolescent; Cardiovascular disease; Asia

INTRODUCTION

The risk factors associated with adult atherosclerotic cardiovascular disease (CVD) have also been implicated in children, and contribute to the earlier development of disease in children. As the childhood is the formative period of diet and lifestyle patterns, this time is important for the health of the rest of life.¹⁾ On the same hand, the risk factors common in adulthood cardiovascular factors also exist from very early stage of childhood, including obesity, hypertension, abnormal lipid levels, inflammatory change, prothrombotic change, and vascular alterations. Early identification of risk factors and modification of lifestyles can decrease the risk of atherosclerotic CVD in later life since atherosclerosis begins as early as childhood, and typically manifesting clinically during adulthood.²⁻⁵⁾ Thus, there is vital importance to examine the childhood cardiovascular risk factors and their association with future adult cardiovascular outcome. One of the best ways to evaluate the impact of cardiovascular risk factors on the risk of disease is a community-based prospective cohort



Author Contributions

Conceptualization: Kim HC; Formal analysis: Jung SJ; Investigation: Jung SJ; Writing - original draft: Jung SJ; Writing - review & editing: Suh I.

Table 1. Cardiovascular cohort studies in Western children

Study name	Country	No. of inclusion	Starting year	Baseline age (years)
Muscantine study ⁶⁾	USA	11,377	1970	5–18
Bogalusa Heart Study ⁷⁾	USA	12,000	1973	0–14
Young Finns Study ⁸⁾	Finland	3,596	1980	3–18
Young-HUNT Study ⁹⁾	Norway	17,820	1995	13–19
Amsterdam Growth and Health Longitudinal Study ¹⁰⁾	Netherlands	600	1976	13–16
GECKO Drenthe study ¹¹⁾	Netherlands	2,997	2006	At birth
Pelotas birth cohort ¹²⁾	Brazil	5,265	1993	At birth
TARGET Kids ¹³⁾	Canada	5,062	2008	At birth
QUALITY cohort ¹⁴⁾	Canada	630	1999	8–10
Saguenay Youth Study ¹⁵⁾	Canada	1,092	2003	12–18

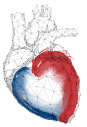
study. Several Western cohort studies^{6–15)} measured the childhood cardiovascular risk factor, demonstrating valuable knowledge of early cardiovascular risk factors for public intervention (Table 1); however, there was a relatively short amount of studies done in Asia. In many Asian countries, the prevalence of childhood obesity reached epidemic proportions¹⁶⁾ and the cardiovascular risk factors in children is concerning.¹⁷⁾ Thus we aimed to review cohort studies with relatively longer follow-up, and their findings in exploring the effect of cardiovascular risk factors in Asian children.

SELECTION OF THE COHORTS

For identifying Asian cardiovascular cohort study in children, we searched MEDLINE/ PubMed data from Feb 17, 2019 to Mar 6, 2019 with following Medical Subject Headings (MeSH) terms: "asia"[MeSH Terms] OR "asia"[All Fields]) AND ("cohort studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields]) OR "cohort studies"[All Fields] OR "cohort"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields]) AND ("adolescent"[MeSH Terms] OR "adolescent"[All Fields]) AND ("cardiovascular system"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "system"[All Fields]) OR "cardiovascular system"[All Fields] OR "cardiovascular"[All Fields]). Also, Google Scholar¹³⁾ was searched with following search keywords: "asia[OR]children[OR]cohort[OR]cardio\$," "asia[OR]adolescent[OR]cohort[OR]cardio\$," "asia[OR]adolescent[OR]longitudinal[OR]cardiovascular." We added additional literatures from hand-search, with citations in a meta-analysis.¹⁸⁾ We found 8 Asian cohort studies^{19–26)} observing cardiovascular risk factors and their effects on CVD in childhood or adolescent populations (Table 2).

STUDY DESIGN AND MEASUREMENTS OF THE SELECTED ASIAN COHORTS

We identified 3 birth cohort studies which measured cardiovascular risk factors of children: Vellore birth cohort study²⁰⁾ (India, started in 1969), Andhra Pradesh Children and Parents Study²¹⁾ (APCPS) (India, started in 1987), and Mysore Parthenon birth cohort²³⁾ (India, started in 1997). These birth cohorts examined mainly the nutritional deficit of mothers and children in association with offspring's cardiovascular outcomes, including blood pressure (BP). Vellore birth cohort study aimed to examine the relationship between maternal BP before and during pregnancy and the incidence of toxemia. The study enrolled 10,691 singleton live birth children and their mothers during 1969–1973 in Vellore district in India and measured



Childhood Cardiovascular Cohort Studies

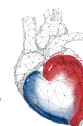
Table 2. Summary of children's cardiovascular cohort studies in Asia

Name of the cohort	Country	Initiation (year)	Participants	Follow-up	Measurement
Vellore birth cohort study ⁽²⁰⁾	India	1969	10,691 Singleton live birth enrolled during 1969–73 in Vellore district, India	1977–80, 1982–88, 1998, 1998–2002	Socioeconomic status, diet, life-style, medical history, anthropometry, skin folds thickness, BP, blood sample
Kangwha Study ⁽¹⁹⁾	South Korea	1986	484 school children (6-year-old)	Annual follow-up until 1997, 1999, 2005, 2010–11, 2014–18	Anthropometry, BP, electrocardiogram, blood test, urine test, sexual maturation, lifestyle factors, carotid intima-medial thickness, abdominal CT, quantitative ultrasound-bone mineral density
Andhra Pradesh Children and Parents Study ⁽²¹⁾	India	1987	2,061 children of traced families in Hyderabad Nutritional Trial, born during 1987–90 in Andhra Pradesh, India	2003–05, 2009–10, 2010–12	Mother's anthropometry, socio-demographics, lifestyle, general health, medical and family history, atopic history, birth, feeding, immunization, BP, arterial stiffness, lung function, fasting blood sugar, lipids, insulin, DNA (selected single nucleotide polymorphism)
Rural Japanese Children Cohort ⁽²²⁾	Japan	1992	1,084 school children in Eastern Shimane Prefecture, Japan, enrolled during 1992–93 (mean age 8.35 years)	1996–97	Physical examination, blood test, BP, height, weight, total cholesterol, HDL-cholesterol, non-fasting blood samples, lifestyle, family history, atherogenic index
Mysore Parthenon birth cohort ⁽²³⁾	India	1997	1,233 women with oral glucose test in Mysore, India and their children (n=663) in 1997	At age 5, 9.5, and 13.5 years	Serial anthropometry and body composition, physiological and biochemical measures, dietary intake, nutritional status, physical activity measures, stress reactivity measures and cognitive function, and socio-demographic parameters
Chinese Metabolic Syndrome Twin Cohort Study ⁽²⁴⁾	China	1998	953 children in Anqing and Luan areas of Anhui Province, China enrolled during 1998–2000, aged 6–13 years	2005–07	Demographics, disease history, lifestyle, International Physical Activity Questionnaire-short, anthropometry, dual-energy X-ray absorptiometry measures of adiposity, and Tanner stage, adipokine, zygosity
Ho Chi Minh City Youth Cohort ⁽²⁵⁾	Vietnam	2004	759 school children in urban districts, enrolled in 2004, aged 13–18 years	Annual follow-up until 2009	Anthropometry, dietary intake and behaviors, physical activity and sedentary behaviors, family social and physical environment, school environment, socioeconomic status and parental characteristics
Korean Child-Adolescent Study ⁽²⁶⁾	South Korea	2005	3,968 elementary school students from 9 schools in in Seoul and Gwacheon, South Korea, aged 9–10 years	Annual follow-up from 2008 to 2014	Height, weight, body component, waist circumference, BP, triglyceride, HDL-cholesterol

BP = blood pressure; CT = computed tomography; HDL = high-density lipoprotein.

maternal nutritional status with children's anthropometry including skin-folds thickness. The APCPS aimed to assess the long-term effects of early-life undernutrition on risk of CVD. The study enrolled 2,061 children of traced families in a nutritional trial, and measured the arterial stiffness and insulin resistance after nutritional supplement. The Mysore Parthenon birth cohort⁽²³⁾ aimed to explore the long-term effects of maternal glucose tolerance and nutritional status on cardiovascular risk factors in the offspring. The study enrolled 1,233 pregnant women and measured their nutritional status along with their offspring's anthropometry and body composition. Also, this study utilized 7-day accelerometer recordings for physical activity measurement.

The Kangwha Study⁽¹⁹⁾ was started in 1986 to identify distribution and determinants of BP among Korean children and to analyze the tracking patterns of BP and cardiovascular risk factors from childhood to adulthood. It was originally designed to include 484 elementary school students (6 years old) residing in Ganghwa island, and it has been expanded to 784 with 3 additional recruitment sessions in 1987, 1992, and 1995. From 1986 (age 6) to 1997 (age 17), questionnaire surveys and physical examinations were conducted annually at schools of the cohort participants. There have been a total of 4 follow-up surveys during adulthood (1999–2001, 2005, 2010–2011, and 2014–2018). BP and anthropometric measurements were made at baseline and all follow-up surveys. Blood and urine tests, sexual maturation, electrocardiogram were added from the 1992 follow-up survey, and carotid ultrasonography, abdominal computed tomography, and ultrasound bone densitometry were also added in the adult follow-up survey.



The Rural Japanese Children Cohort²²⁾ was established in 1992 to understand the tracking tendency of cardiovascular risk factors in Japanese children, enrolling about 1,000 school children in Japan. They measured the results of physical examination, blood measurements including lipid profiles, lifestyle factors, and calculated atherogenic index.

The Korean Child-Adolescent Study²⁶⁾ started in 2005 to identify early risk factors for obesity and metabolic disease in Korean children. Similar to the Rural Japanese Children Cohort which measured intermediate biomarkers related to the cardiovascular health, the Korean Children-Adolescent Study measured anthropometric data including body component and waist circumference along with lipid biomarkers such as triglyceride and high-density lipoprotein (HDL)-cholesterol.

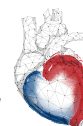
Chinese Metabolic Syndrome Twin Cohort Study²⁴⁾ (China, started in 1998) aimed to examine the associations of longitudinal adiposity measures with 2 adipokines (leptin and adiponectin), and their ratio in children adolescents. They enrolled about 953 children aged 6–13 years and measured anthropometry, lifestyle factors, Tanner stage, standard whole-body scan with dual-energy X-ray absorptiometry (DXA), and adipokines including leptin and adiponectin. For measuring physical activity, a short version of the International Physical Activity Questionnaire²⁷⁾ was applied.

Ho Chi Minh City Youth Cohort²⁵⁾ was started in 2004 and aimed to assess the change in nutritional status, indicators of adiposity, diet, physical activity and sedentary behaviors, and their complex relationships in adolescents in urban areas of Ho Chi Minh City, Vietnam. It utilized Adolescent Physical Activity Recall Questionnaire²⁸⁾ to capture the physical activity information. Concerning the results from the physical activity measurements, the overall descriptive trend of physical activity among children in Vietnam was analyzed, utilizing the information from 759 school children from urban area.

KEY FINDINGS OF THE SELECTED ASIAN COHORT STUDIES

The Vellore birth cohort study²⁰⁾ explored the magnitude of maternal undernutrition with cardiovascular risk factors in babies, and suggested that shorter maternal height was associated with impaired glucose tolerance (IGT) in young adults. Also, IGT, diabetes, and insulin resistance were associated with rapid body mass index (BMI) gain throughout childhood, adolescence, and adult life in the same cohort. The APCPS²¹⁾ suggested that a lower risk of CVD (i.e., arterial stiffness and insulin resistance) in adolescents from the nutritional supplementation group. In Mysore Parthenon birth cohort,²³⁾ there were higher cardiovascular risk markers, such as body fat/glucose, insulin level, homeostatic model assessment of insulin resistance, and BP in children of diabetic mothers than control offspring during childhood.

The Kangwha Study reported the long-term tracking patterns, from childhood to adulthood, of cardiovascular risk factors including BP¹⁹⁾ and blood lipid.²⁹⁾ Even though the BP tracking from childhood to adulthood in the Korean population seemed to be stable,¹⁹⁾ the patterns from the blood lipid from adolescent to adulthood were notable.²⁹⁾ High triglyceride to HDL-cholesterol ratio in adolescence was significantly associated the risk of developing



hypertension in adulthood.³⁰⁾ Elevated adulthood central systolic BP was significantly associated with brachial artery BP level from childhood to adulthood.³¹⁾ Adolescent obesity was associated with increased carotid artery intima-media thickness at age 25.³²⁾

In Rural Japanese Children Cohort,²²⁾ the stability of tracking was suggested to be acceptable for BMI, total cholesterol, atherogenic index, and HDL-cholesterol. Moreover, children with more than 3 CVD risk factors (BMI \geq 75th percentile, high frequency of eating meat and eggs, and a low frequency of playing outside) showed the increased risk (relative risk, 8.39; 95% confidence interval, 1.20–38.70) for CVD. The Korean Child-Adolescent Study²⁶⁾ suggested that a higher intake of fruit sugar at baseline was independently associated with a decreased risk of adiposity, and such individual factors (i.e., obesity in childhood and short sleep duration) along with parental factors (i.e., low socioeconomic status and parental history of CVD) increased the risk of obesity in adolescence, significantly.

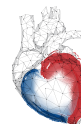
In Chinese Metabolic Syndrome Twin Cohort Study,²⁴⁾ the different effect of adiposity trajectory was measured with standard whole-body scan with DXA on leptin, adiponectin, and their ratio. It was concluded that, compared to leptin and adiponectin individually, the leptin/adiponectin ratio could serve as a more stable indicator of adipocyte dysfunction, and the longitudinal change in adiposity measures was a significant predictor for follow-up plasma adipokine levels.

The Ho Cho Minh City Youth Cohort²⁵⁾ reported the overall reduction of time spent on physical activity throughout the study period. Simultaneously, the results from the cohort suggested that time spent on sedentary behaviors increased significantly, which was in line with the results indicating the prevalence of combined overweight/obesity increased from 14.2% to 21.8% in the 5 years.

Majority of the studies were conducted with a systematic assessment of the target population, having relatively sufficient inclusion numbers and measuring anthropometry and applied adequate intermediate biomarkers for CVD outcome. Initial studies included nutritional assessment, considered physical activity measurement, and made a descriptive analysis to capture the change in cardiovascular risk factors. However, there is limited evidence from these cohorts demonstrating the causal association between childhood cardiovascular risk factors and CVD incidence or mortality, since the participants in these cohorts were not followed until their late adulthood and old ages.

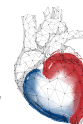
CONCLUSION

It is known that childhood cardiovascular risk factors are associated with adulthood CVD incidence and mortality, and obesity and other cardiovascular risk factors are increasing in Asian children and adolescent. We searched 8 Asian cohort studies among children which were followed-up relatively in longer period. These studies suggested that cardiovascular risk factors in childhood were associated with later adulthood risk factors. Additionally, childhood risk factors were associated with intermediate phenotypes including degenerative vascular change and metabolic disturbance. However, as there is no study which followed participant until mid to elderly adulthood among these studies, more long-term follow-up studies with cardiovascular outcomes are warranted.



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