

The Cuban National Child Cohort Study 1973-2025. Background and Design of the sixth follow-up

Estudio nacional de cohorte del niño cubano 1973-2025. Antecedentes y diseño del sexto seguimiento

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ABSTRACT

Introduction: The concept of Developmental Origins of Health and Disease is now widely recognized. Cuba has a valuable database to analyze this phenomenon from the National Cuban Child Cohort Study which included all those born in the country during the first week of March 1973 that were the product of simple pregnancies and survived beyond the first week (n = 4299), who were studied at birth, at 7 months and at 7, 11 and 17 years.

Objective: To provide an overview of the National Cuban Child Cohort Study and describe the design to be used in the sixth follow-up of its participants, which will include all those who currently reside in Havana, Cuba (n = 600).

Methods: Each participant will be asked to visit the "Hospital Hermanos Ameijeiras" to complete a questionnaire covering sociodemographic data, lifestyle, eating habits and current health conditions. In addition, a physical examination, anthropometric measurements, evaluation of body composition through bioimpedance, blood chemistry, electrocardiogram and carotid ultrasound will be performed. Information about the health of the descendants and parents of the participants will also be collected. These data will be correlated with those obtained at birth and during childhood and adolescence.

Conclusions: This research represents a unique opportunity to delve deeper into the patterns and mechanisms involved in Developmental Origins of Health and Disease and to develop strategies aimed at improving the health of the Cuban population.

Keywords: Cohort study; Non-communicable diseases; Life Course; Developmental Origins of Health and Disease.

RESUMEN

Introducción: El concepto de Orígenes del Desarrollo de la Salud y la Enfermedad es ahora ampliamente reconocido. Cuba cuenta con una valiosa base de datos para analizar este fenómeno, proveniente del Estudio Nacional de Cohorte del Niño Cubano, que incluyó a todos los nacidos en el país, durante la primera semana de marzo de 1973, que fueron resultado de embarazos simples y que sobrevivieron más allá de la primera semana (n = 4 299). Estos fueron estudiados al nacer, a los 7 meses, y a los 7, 11 y 17 años.

Objetivo: Brindar una visión general del Estudio Nacional de Cohorte del Niño Cubano y describir el diseño a utilizar en el sexto seguimiento de sus participantes, que incluirá a todos los que actualmente residen en La Habana, Cuba (n = 600).

Métodos: A cada participante se le solicitará que visite el "Hospital Hermanos Ameijeiras" para completar un cuestionario que abarca los datos sociodemográficos, el estilo de vida, los hábitos alimentarios y las condiciones de salud actuales. Además, se realizará un examen físico, las mediciones antropométricas, la evaluación de la composición corporal mediante bioimpedancia, la química sanguínea, el electrocardiograma y la ecografía carotídea. También, se recopilará información sobre la salud de los hijos y de los padres de los participantes. Estos datos se correlacionarán con los obtenidos al nacer, durante su infancia y la adolescencia.

Conclusiones: Esta investigación representa una oportunidad única para profundizar en los patrones y mecanismos implicados en Orígenes del Desarrollo de la Salud y la Enfermedad, y para el desarrollo de estrategias dirigidas a mejorar la salud de la población cubana.

Palabras clave: estudio de cohorte; enfermedades no transmisibles; curso de vida; Orígenes del Desarrollo de la Salud y la Enfermedad.

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Introduction

The importance of early life stages for an individual's health is widely recognized today. The concept of Developmental Origins of Health and Disease (DOHaD), which proposes that exposure to adverse environmental conditions in early life can result in unfavorable health consequences in the short and long term, is internationally accepted. Numerous pieces of evidence support the importance of attention to the first 1 000 days of life, from preconception to the first two years, as a window of opportunity for achieving healthy development.^(1,2)

This area of research was initiated by the studies of David Barker (1938-2013), who made a significant contribution to biomedical research in the late 20th century by shifting the focus on the genesis and prevention of non-communicable diseases (NCDs) from a gene and adult lifestyle-centered view to a more holistic perspective that emphasizes the importance of development. Barker presented a set of evidence about the risk of ischemic heart disease in adults with a history of low birth weight, leading him to propose the so-called Barker Hypothesis - also known as the "thrifty phenotype hypothesis" - to refer to the changes generated in fetal development in a nutrient-scarce environment. This, through modifications in the metabolic programming of the fetus and the "plasticity" of this process, causes uneven growth that benefits key organs, such as the brain, at the expense of the growth of others like the liver, heart, pancreas, and kidneys. The consequences of this uneven growth, particularly when there are differences between the child's prenatally "programmed" characteristics and the quality of the postnatal environment, can result in broad dysfunctions that are the genesis of multiple NCDs that can affect health from early stages of life.^(3,4)

The Barker Hypothesis was refined over time and evolved into what is now known as the DOHaD concept. This describes how various environmental factors, not only nutrient deficiency but also overnutrition, stress, and various maternal diseases, a set of drugs and environmental toxins, drug use, or adverse childhood experiences,

among others, can generate epigenetic changes in the metabolic programming of development that largely determine health as well as intellectual and social achievements in people's lives. These effects can manifest in the course of an individual's life or even in that of their offspring and allow us to understand the origin of numerous metabolic diseases, such as diabetes and obesity, certain cardiovascular conditions and types of cancer, as well as disorders in reproductive health, mental health, learning ability, or child neurodevelopment.^(5,6,7,8,9)

Identifying individuals at higher risk of suffering from these conditions from early childhood would allow the implementation of specific and validated interventions to reverse these disease trajectories.^(10,11) However, there is still much to learn about the potential role of early life factors in the onset of NCDs, which, on the other hand, are currently the leading cause of morbidity and mortality worldwide.⁽¹²⁾ With this objective, numerous studies have been developed, among which, in addition to those of D. Barker, those carried out from the famine suffered by the Netherlands at the end of the Second World War that affected the western part of those countries, the Bogalussa cohort study, or the Rayne study, to mention just a few of the most relevant ones.^(13,14,15)

Cuba has a valuable national database derived from a cohort study integrated by all children born in the country during the first week of March 1973, who were born from single pregnancies and survived beyond their first week, they were studied during their childhood and adolescence at 7 months, 7, 11, and 17 years.⁽¹⁶⁾ The info from this research has been kept intact all these years by the Research Group of Human growth and Development at the University of Medical Sciences in Havana. These findings were considered really valuable because they gave us a detailed and in-depth look into the fundamental aspects of children's health and development. It covered everything from their environment, family dynamics, illnesses, physical growth, psychological aspects, healthcare, dental development, school progress, as well as a wide selection of educational and intelligence tests for Cuban children and teenagers during their formative years. These findings also provided a solid national benchmark for comparison.

Since the development of the DOHaD hypothesis, the information from this research became more relevant as it allowed understanding the influence of health and living conditions during the early years of these individuals' lives on the health, educational achievements, and social outcomes of adult individuals. Therefore, a decision was made to conduct a new follow-up of the cohort as they reached their fifth decade of life. The purpose of this article is to provide an overview of the CNCS and describe the design and methods that will be used for the sixth follow-up of its participants.

The Cuban National Child Cohort Study (CNCCS): Background

The Cuban National Child Cohort Study (CNCCS) was initiated in 1973 as a research project aimed at gathering information about perinatal mortality in the country. This study was part of the activities associated with the development of a program for the reduction of infant mortality. In 1970, Cuba had an infant mortality rate of 40 per 1000 live births, and the goal of the program was to halve this figure within a decade, a goal that was ultimately achieved.^(17,18)

This comprehensive program covered a range of areas, from family planning to the psychological issues of children and adolescents. It was projected that, in conjunction with the progress of the program, studies would be conducted to deepen the understanding of children's health, growth, and development from the perinatal stage to adolescence. The search within such a broad scope resulted in a research project named Perinatal Research. This project drew on the experience of the "1958 National Child Development Study (NCDS)" in the United Kingdom, with advice from distinguished English researchers Neville Buttler and Harvey Goldstein.⁽¹⁹⁾

The study aimed to investigate the biological, social, and medical care factors that operated from gestation, childbirth, and the perinatal period on the mother and the product of gestation. Its results, while providing valuable information on the mentioned aspects, were of extraordinary value in deepening the understanding of

these processes in the country, improving maternal and child health programs, enhancing the quality of services, and adapting educational programs for both paramedical personnel and undergraduate and specialist training programs.

The study was conducted during the first week of March 1973 through a survey of all children born in the country who survived for 7 days ($n = 4378$). 79 children from twin pregnancies were excluded, and low birth weight births during the remaining three weeks of March were included in the recruitment process. In 27 cases, it was not possible to carry out the survey, resulting in a final figure of 4299 participants. Its results were published in the book *Perinatal Research*, which has been a reference work in the country for over a generation of obstetricians, pediatricians, neonatologists, health administration specialists, health statisticians, nursing professionals, and others.⁽²⁰⁾

The Cuban National Child Cohort Study (CNCCS): Follow-Up

Following the inception of the initial research at birth, four additional studies were conducted during the participants' childhood and adolescent stages. Figure illustrates the progression of the CNCCS and the participation of its subjects over time. There's a clear pattern of consistent engagement from the study population. While there were some dropouts between the inception of the study and subsequent follow-ups, these reductions were minimal, especially given the study's nationwide scope. Seventeen years post-initiation, the participation stood strong at 69.8 % of the original sample. This remarkable engagement can be attributed in part to the robust prenatal care system in place as of 1973. On average, each birth was preceded by more than eight prenatal consultations, and a staggering 98 % of all births occurred within health institutions.

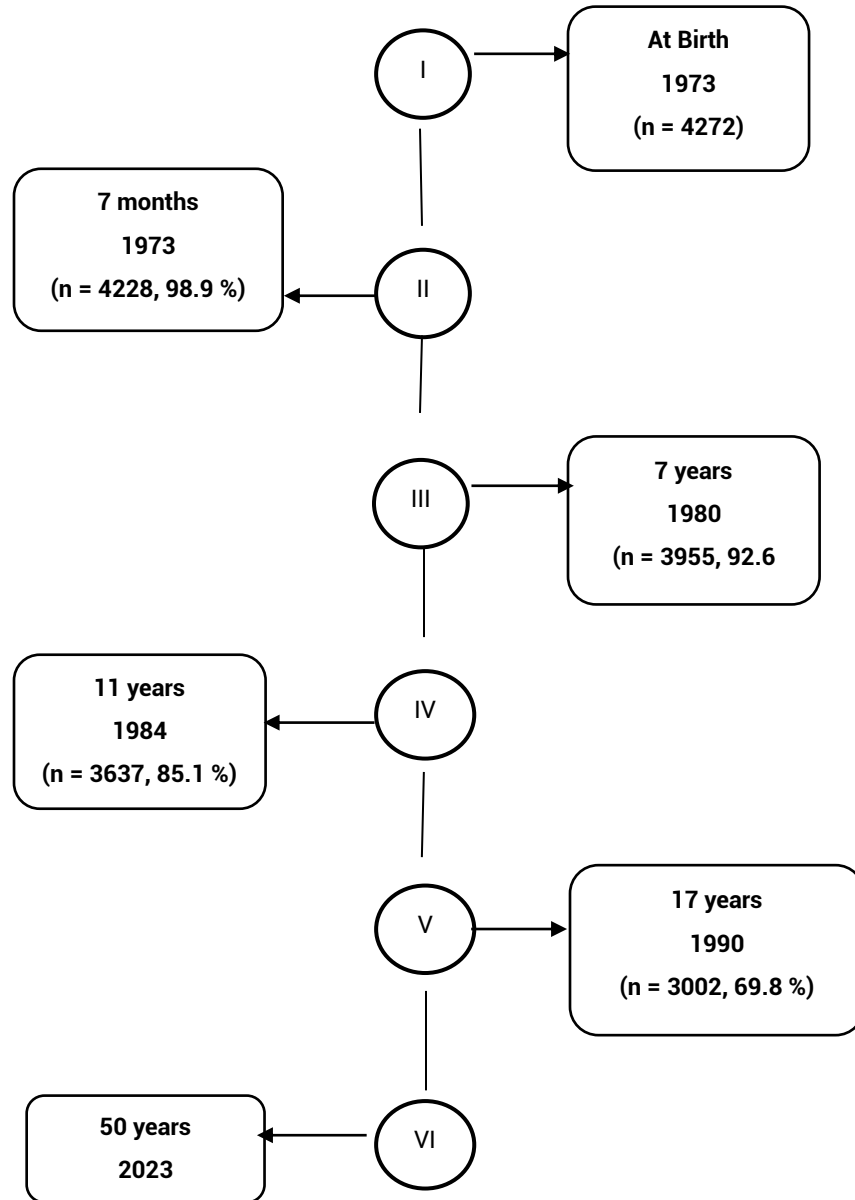


Fig. - Cuban National Child Cohort Study (CNCCS) 1973-2025: Follow-ups conducted with participants.

Second Follow-up (7 Months)

The cohort's second follow-up was executed when the children reached 7 months of age. This study aimed to gather information regarding basic health aspects from birth up to the research age. It also sought insights into how specific socioeconomic factors influenced these early stages. Emphasis was placed on understanding prevalent illnesses during this life stage, dietary habits-particularly breastfeeding and the transition to supplementary foods, immunizations, childcare, hospital admissions, mortality between birth and seven months, and its correlation with parents' educational levels. This wealth of data proved vital for guiding child health programs and subsequent research endeavors.⁽²¹⁾

Third Follow-up (7 Years)

By the time the third cohort study was conducted, most participants were seven years old, having mostly completed preschool and first grade, and were now in the second grade of primary education. This study was pivotal as it not only expanded upon the data gathered since pregnancy, birth, and the initial seven months but also delved into the realm of the participants' education and behavior. This necessitated collaboration with education experts and the Ministry of Education, who provided invaluable support-ranging from the inclusion of their researchers and resources to promoting and implementing the research findings.

The 7-year study encompassed eight main subjects: Home environment, morbidity, accidents, health care, physical development, dental health, an educational assessment by teachers, and a set of school tests covering reading, writing, math, school readiness, mental work capacity, and language skills. Out of the initial cohort, 3.906 children (almost 92 %) participated, though 49 were either deceased or had left the country.⁽²¹⁾

Fourth Follow-up (11 Years)

The next phase of the study was initiated when the children turned 11, with most of them in fifth grade. The research themes largely mirrored those of the 7-year study.

However, due to the children's growth and maturity, the introduction of new variables and investigative methods was necessitated to better understand the evolving capabilities of the participants at this age.⁽²¹⁾

Fifth Follow-up (17 Years)

The final study occurred when participants were 17 years old. At this stage, most were in the eleventh grade of pre-university education. Of the participants, 1.100 (36 %) had discontinued their education, with some having entered the workforce. 3.002 adolescents (representing 69.8 % of the initial survey) participated, of which 1,902 were still students. In addition to medical examinations, teacher surveys, and academic tests, participants were also queried about their perspectives on education, instructors, aspirations, interests, views on family, and societal opinions.⁽²¹⁾

This structured approach allowed for a comprehensive understanding of the participants' development and the influencing factors over a significant duration of their lives.

The Sixth Cohort Follow-Up

Rationale

As the cohort members reach their half-century milestone, executing the sixth follow-up provides a unique opportunity for Cuba to compare the evidence from previous studies in the DOHaD field with results from this research study. This follow-up will not only enhance our understanding of human development and the origins and emergence of NCDs, but its findings will also shape strategies and interventions to improve the well-being and quality of life of the Cuban population. Another focal point entails comparing the cohort's developmental characteristics, health, and educational achievements during their childhood and adolescence to those of their direct descendants at the time of this study. This approach aims to delve deeper into the influence of genetic factors, epigenetics, and social determinants on health.

The CNCCS's orientation has evolved from a descriptive and epidemiological lens to one emphasizing the "origins of development" and "lifespan course." The goal is to further explore the health and behaviors of the cohort in adulthood and examine their influence on their descendants.

Methods

This represents the sixth follow-up of the CNCCS, a multicenter, prospective cohort research study. Several national institutions will collaborate, including the University of Medical Sciences of Havana, the Clinical Surgical Hospital "Hermanos Ameijeiras", and the Cuban Neurosciences Center. Additionally, there will be an international collaboration with the Lunenfeld-Tanenbaum Research Institute in Toronto, Canada.

Study Population

The study will consider all cohort members who participated in previous follow-ups, as well as their direct descendants, as the research universe. The sample for the sixth follow-up includes all participants of the original cohort who have consented to be contacted for the current follow-up. Due to feasibility, only those currently residing in the city of Havana will be included, regardless of their birthplace or where they spent their childhood and adolescence. Direct descendants of these individuals living in this province will also be studied, considering only one descendant per cohort member. In cases where a member has multiple descendants, the youngest will be selected.

The CNCCS has numerous variables, with modifications made during each follow-up based on the life stage under scrutiny. Tables 1 and 2 shows a summary of variable proposed for the six-follow up cohort.

Table 1 - Summary of variables proposed for the six-follow-up cohort

Topic	Detailed items
General Information	Registration (email, code) Participant Contact information (address, phone number)
Demographic Information	Skin color, educational level, occupation, marital status
Household Characteristics	Overcrowding, housing materials, appliances, internet access, water source, sanitary facilities
Functional Capacity	Use of glasses, use of hearing aids, motor difficulties, concentration difficulties, self-care, communication difficulties
Toxic Habits	Tobacco use, alcohol consumption
Sleep Pattern	Daily sleep hours, difficulty falling sleep, previous diagnosis of a sleep disorder
Physical activity	Intense or moderate activity, engaging in physical activities
Dietary Habits	Type of diet (obesogenic or not)
Medical History	Family medical history, personal medical history, previous hospital admission, current medications, COVID-19 diagnosis
Mental Health	Anxiety, Depression, Cognitive state
Physical Examination	General physical examination and blood pressure
Anthropometric Measurements	Weight, Height, waist, arm and hip circumference skin folds: biceps, triceps, subscapular, supra-iliac
Body Composition (Bioimpedance)	Body Fat Mass (BFM), Fat Free Mass (FFM), Lean Body Mass (LBM), Body Fat Percentage (BFP), Muscle mass, Total Body Water (TBW), Body Fat percentage (BFT), Bone Mineral Content (MBC), Basal Metabolic Rate (BMR).
Blood Chemistry	Fasting glycemia, creatinine, hemogram, lipogram: cholesterol, LDL, HDL, Triglycerides.
Biomarkers degenerative disease	ε4 allele of the ApoE (apolipoprotein E)
Electrocardiogram	ECG of 12 derivations
Carotid Doppler Ultrasound	Non-invasive diagnostic imaging procedure used to evaluate the flow of blood through the carotid arteries and atherosclerosis

Table 2 - Summary of variables proposed for the six-follow-up participants' descendants

Topic	Detailed items
General Information	Registration (email, code) Participant Contact information (address, phone number)
Demographic Information	Skin color, educational level, occupation >18years
Toxic Habits	Tobacco use, alcohol consumption
Medical History	Family medical history, personal medical history, previous hospital admission, current medications, COVID-19 diagnosis
Physical Examination	General physical examination and blood pressure
Anthropometric Measurements	Weight, Height, waist, arm and hip circumference Skin folds: biceps, triceps, subscapular, supra-iliac

Information Collection

For data collection, a general questionnaire has been created. Socio-demographic data, family and personal medical history, lifestyle, dietary habits, and toxic habits will be collected through interviews. To assess anxiety and depression STAI scale⁽²²⁾ and Patient Health Questionnaire PHQ-9⁽²³⁾ respectively will be used. Also, to assess cognitive impairment the Montreal Cognitive assessment scale (MoCA) will be used.⁽²⁴⁾ Physical examination information will be obtained using standard clinical procedures. The measurement techniques for obtaining anthropometric dimensions are those used by the Research Group on Human Growth and Development.⁽²⁵⁾ Body composition will be evaluated through estimation by bioimpedance.⁽²⁶⁾ The standard techniques from Hermanos Ameijeiras Hospital will be utilized for variables associated with blood chemistry, ECG, and carotid ultrasound.^(27,28) To identify biomarkers, the presence of the $\epsilon 4$ allele of the ApoE (apolipoprotein E) gene will be determined.⁽²⁹⁾

Before starting data collection, a pilot study was conducted with 50 cohort members to test the logistics of the new follow-up and address potential uncertainties in the

questionnaire application. Based on its findings, necessary modifications and adjustments were made for the main research study.

Data Processing

Data will be recorded in an Excel database, which will then be exported to SPSS software, version 22.0. Qualitative variables will be statistically described using absolute frequencies and percentages, while quantitative variables will be described using mean or median as measures of central tendency and standard deviation (SD) and interquartile range (IQR) as measures of dispersion. The median and IQR will be used when the Kolmogorov-Smirnov statistic indicates a non-normal distribution of the variable. To identify statistically significant associations between the information on the variables studied in previous follow-ups and the current status of the cohort members and their descendants, mean or median comparisons and the non-parametric Chi-square independence test will be employed with a significance level of 5 % ($p < 0.05$). When an association is demonstrated, its strength will be estimated using the Odds Ratio (OR) with a 95 % Confidence Interval (CI 95 %).

Ethical Considerations

Approval was obtained from the Ethics Committee of the Julio Trigo López Faculty of Medical Sciences at the University of Medical Sciences of Havana for the new cohort follow-up. Furthermore, the study is conducted in accordance with the Helsinki Declaration of the World Medical Association adopted at the 64th General Assembly held in Brazil, 2013.⁽³⁰⁾ Informed consent will be obtained from all participants.

General characteristics of the cohort

Over recent decades, the prevalence of non-communicable diseases (NCDs) has reached epidemic proportions worldwide. This rapid increase challenges the notion that genetic factors are the main contributors to these diseases. There is compelling evidence, based on numerous clinical observations and animal experiments, that a new dimension known as the DOHaD plays a role. This requires a paradigm shift in maternal and child health care that takes into account the contribution of developmental epigenetic programming in the prevention of these diseases.⁽³¹⁾

In Cuba, there has also been a noticeable increase in morbidity and mortality from NCDs. According to the 2023 Statistical records, the death rate due to NCDs is the highest, with 942.3 deaths per 100,000 inhabitants. Regarding the top ten causes of death, heart diseases rank first with a rate of 313.5 per 100,000 inhabitants, followed by deaths due to malignant tumors, which have a rate of 246.0. Both account for 48.7 % of all deaths in 2023. Furthermore, there's a rising prevalence of overweight, obesity, diabetes, and hypertension from childhood and adolescence.⁽³²⁾

Currently, there are three types of models used for experimentation and grounding of the DOHaD concept: human models (epidemiological studies), animal models, and cell line models. Each, according to their specifications, aims to identify factors involved in the programming of health and disease during development.^(33,34)

Epidemiological studies, including prospective cohort studies like the CNCCS, primarily evaluate how maternal nutrition, either due to deficiency (malnutrition) or excess (overweight and obesity), along with various environmental factors, result in changes in the metabolic programming of the fetus. This leads to the early onset of NCDs and can also affect the subsequent generation.^(6,35)

An analysis of the initial cohort's demographics at birth revealed several significant characteristics: it's noteworthy that just over a fifth of the mothers were under 20 years old, accounting for 22.6 %. Three out of every four mothers had only completed primary-level education 75.3 %. More than half, 59.2 %, were married. Only a minority, 29.7 %, had three or more children. In 87 % of the cases, childbirth proceeded without complications (Table 3).

Table 3 - Selected Demographic Characteristics

Variable	No.	%
Mother's Age		
< 20 years	966	22.6
20-34 years	2930	68.6
≥ 35 years	367	8.6
Unknown	9	0.2
Mother's Education		
0-6	3217	75.3
≥ 7	1042	24.4
Unknown	13	0.3
Marital Status		
Married	2529	59.2
Living with a partner	1679	39.3
Other	64	1.5

Analyzing the obstetrical medical history, delivery details and outcome. Most of the new-borns were male (52.9 %), 7.8 % were preterm or with a birth weight of less than 2500 grams and practically 90 % reached an Apgar score one minute after birth 7 or more (Table 4).

Table 4 - Selected Obstetric Characteristics from CNCCS

Variable	No.	%
Number of Deliveries		
0	1230	28.8
1-2	1773	41.5
≥ 3	1269	29.7
Mode of Delivery		
Spontaneous vaginal	3712	86.9
Caesarean	406	9.5
Assisted vaginal	150	3.5
Unknown	4	0.1
Gestational Age (weeks)		
< 37	333	7.8
37-42	2880	67.4
> 42	555	13.0
Unknown	504	11.8
Infant sex		
Male	2260	52.9
Female	2012	47.1
Birthweight (grams)		
< 2500	333	7.8
2500-3990	3627	84.9
> 4000	171	4.0
Unknown	141	3.3
Apgar 1 minute		
0-3	77	1.8
4-6	239	5.6
≥ 7	3794	88.8
Missing	115	2.7
Unknown	47	1.1

Subsequent follow-ups of the CNCS cohort revealed several significant trends:

- **Morbidity and Mortality Rates:** Male children and those who weighed less than 2500 grams at birth exhibited higher mortality rates. These groups were also more prone to diarrheal and respiratory diseases, looked for medical attention more frequently, and had a higher number of hospital admissions during their first few months of life.
- **Socio-economic Influences on Development:** During school ages, socio-economic factors, including parents' educational levels, occupations, and living conditions, played a pivotal role in the children's physical and academic development. For instance, Table 5 illustrates the clear differences in average heights attained at different ages based on the mothers' educational levels at the time of their child's birth. It's worth noting that height is often a comprehensive indicator of overall health, nutrition, and well-being in populations.⁽³⁶⁾
- **Intellectual Development and Learning Abilities:** There was a positive correlation between the aforementioned socio-economic determinants and the children's performance in intellectual development tests, like the Goodenough's Draw-a-Person test and the Wechsler Intelligence Scale for Children (WISC). The same was observed in other tests measuring knowledge, skills, school readiness, and mental work capacity.

Table 5 - Average Heights at Ages 7, 11, and 17 years old of CNCCS participants according to gender and sex and mother's level of education

SEX	Age (years)	Mother's level of Education (grades)				
		1-3	4-6	7-9	10-12	< 12
Male	7	119.9	121.7	123.6	125.2	126.9
	11	136.7	138.0	139.7	140.0	141.6
	17	167.5	168.8	169.5	170.2	171.4
Female	7	119.4	121.4	123.4	124.1	124.5
	11	139.0	140.8	143.6	144.6	146.4
	17	157.1	157.31	158.2	158.3	160.1

Throughout childhood and adolescence, the health status of the CNCCS cohort members was assessed using parental interviews and physical examinations by pediatricians involved in each follow-up. Despite Cuba's impressive advancements in healthcare since the 1960s, infectious and parasitic diseases were predominant among this population. The most commonly encountered infectious diseases included measles, mumps, chickenpox, dengue, rubella, whooping cough, hepatitis, and meningitis. Among chronic illnesses, asthma was prevalent; 8.7 % of male members and 5.6 % of female members suffered from persistent asthma. Notably, asthma was more frequently observed in urban areas and among male participants. This health landscape provides a foundational framework for exploring how environmental factors during cohort members' upbringing influenced their health, educational achievements, and social outcomes as they reached their 50th birthday. These findings could significantly contribute to the DOHaD hypothesis, enhancing our understanding of how early life exposures impact later-life outcomes

The health panorama of the Cuban population that the CNCCS can provide, as well as the identification of environmental factors during the upbringing of the members of the cohort that influenced their health, educational achievements and social results upon reaching age 50, could contribute to increase our knowledge about the

DOHaD concept and to improve our understanding of how early life exposures impact later life outcomes.

A significant strength of the CNCCS is the extended period that has elapsed since the birth of the cohort members. This duration enables not just the study of short and medium-term effects of certain exposures of interest, which had been identified in previous follow-ups, but also the examination of the effects of certain variables over the long term in the lives of individuals.

One limitation is the difficulties to locate all the members of the initial cohort. This restriction will limit the statistical analysis to investigate exposure effects. Potential biases could arise due to selective participation of individuals in this new follow-up. There is no information available regarding the period between the last follow-up at 17 years old and the current one at 50 years old. This gap constrains the ability to adjust for potential confounding factors that might have influenced the participants during that phase of their lives.

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Conflict of interest

The authors declare no conflicts of interest.

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