

## Birth Cohort Studies and the Early Origins of Adult Health and Disease

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### Education Gap

Preconception, prenatal, and birth cohort studies are time, effort, and money consuming, and are less common than other epidemiologic study designs. Clinicians need to be aware of the main characteristics and availability of preconception, prenatal, and birth cohort studies to prioritize evidence from this type of research when studying early-life origins of adult disease.

### Abstract

Prenatal and birth cohort studies, including those that start before conception, are an epidemiologic study design that best allows for the investigation of early-life origins of adult disease. This article reviews the definition and methodology of a cohort study. We also identify the worldwide locations of the most important preconception, prenatal, and birth cohorts that have been studied, as well as describe their characteristics. Finally, we examine the importance of these studies in the context of life-course epidemiology research and discuss why new studies of this type are needed. Preconception, prenatal, and birth cohorts provide insights into the mechanism of risk and protection across the life course and between generations, and have contributed significantly to what is known today regarding the developmental origins of health and disease hypothesis.

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#### ABBREVIATIONS

ALSPAC Avon Longitudinal Study of Parents and Children  
IJE International Journal of Epidemiology

### Objectives After completing this article, readers should be able to:

1. Define a cohort study and describe its main methodologic characteristics.
2. Identify the most important preconception, prenatal, and birth cohort studies worldwide and their chief characteristics.
3. Recognize the relevance of cohort studies for the study of early-life origins of adult health and disease.
4. Describe why new preconception, prenatal, and birth cohort studies are needed in different settings (ie, low-, middle-, and high-income countries).

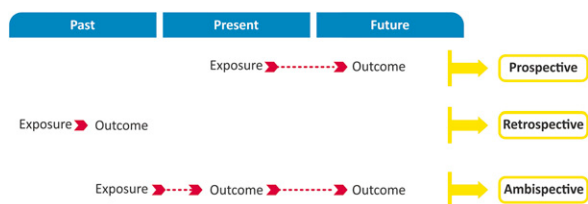
## WHAT IS A COHORT STUDY?

A cohort study is a type of observational epidemiologic study in which the status of individuals regarding the exposure of interest determines their selection for the study. Members of the cohort are then tracked from the time of exposure until the occurrence of the outcome(s) of interest. The presence or absence of exposure to a particular event/variable results in the formation of 2 groups: exposed and unexposed. At the end of the follow-up period, the exposed and unexposed groups are compared in terms of the frequency of illness/injury and other outcomes of interest. (1)

Depending on the reference time point for the exposure of interest and the time at which the study starts, cohort studies can be classified as prospective, retrospective, or ambispective (Fig 1). In a prospective cohort study, exposure data are collected at study entry (in the present), and cohort members are then followed until the outcome is achieved (in the future). In a retrospective cohort study, exposure and outcome are defined on the basis of data collected before the study outset (in the past). A cohort study can present characteristics of both designs, in which case it is considered an ambispective study. In an ambispective cohort study design, exposure is defined at a time in the past, the outcome is identified in the present, and cohort members can be followed to identify the incidence of new cases. (2)

Cohort membership can be classified as fixed or dynamic, depending on the period during which the subjects are enrolled. Fixed cohorts are those in which the subjects are enrolled at the beginning of the study (recruitment period) and no new subjects are enrolled during the follow-up period. Dynamic cohorts allow the entry and exit of subjects during the follow-up period. (3)

To create a cohort, the sample can be selected from the general population or from special exposure groups, depending on the purpose of the study and the exposure of interest. Cohorts selected from the general population allow quantification of exposure and outcome variables, and examine their relationship at the population level. However, for rare or unusual exposures, the selection of special exposure groups is more likely to provide adequate number



**Figure 1.** Representation of the reference time points for exposure data and outcomes of interest in cohort studies.

of subjects and individual exposure data compared with a cohort selected from the general population. First, an exposed cohort (eg, a group of individuals exposed to a specific environmental contaminant) and a sample of unexposed individuals are identified. Subsequently, the 2 groups are followed longitudinally to assess the incidence of the outcome of interest. (1)(2)(3)

The necessary prerequisite of a cohort study is the guarantee of a temporal relationship, given that the exposure necessarily precedes the occurrence of the outcome. Risk can be assessed directly by calculating incidence measures. (4) Frequent follow-up evaluations of the cohort over time allow the formulation of new hypotheses and the investigation of multiple outcomes throughout life. (1)

One of the main disadvantages of a prospective cohort study is the virtually inevitable loss of members during follow-up (attrition bias). If the losses to follow-up differ between the exposed and unexposed groups, the risk can be under- or overestimated, depending on whether the losses are attributable to the outcome measure. (4) The high cost of long follow-up periods is another major disadvantage of cohort studies. Cohort studies often require relatively large samples to obtain scientifically relevant evidence, especially for outcomes with a low prevalence in the population. (5) The primary disadvantage of retrospective cohort studies is the investigator's inability to control data collection. As a result, the data may be incomplete, imprecise, or inconsistently measured between subjects; retrospective cohort studies are also susceptible to recall or information bias.

## BASIC STAGES OF A COHORT STUDY

The execution of a cohort study involves the meticulous planning of all its stages: the definition of the study objectives; selection of the study population and the exposures and outcomes that will be investigated; creation of instruments for data collection and measurement; development of strategies to avoid losses to follow-up; execution of a pilot study before beginning definitive data collection, and the data analysis plan after completion of the follow-up (Fig 2). (6)

It is necessary to define the population in which the effects of a given exposure on a given outcome will be investigated. Depending on the purpose of the study and the hypotheses to be tested, the sample can be selected from the general population or from specific exposure groups. After the cohort with the relevant exposure groups has been defined and recruited, the cohort members are followed over time for assessment of outcomes of interest. The exposure and outcome variables should be measurable and clearly defined. In prospective cohorts, losses to

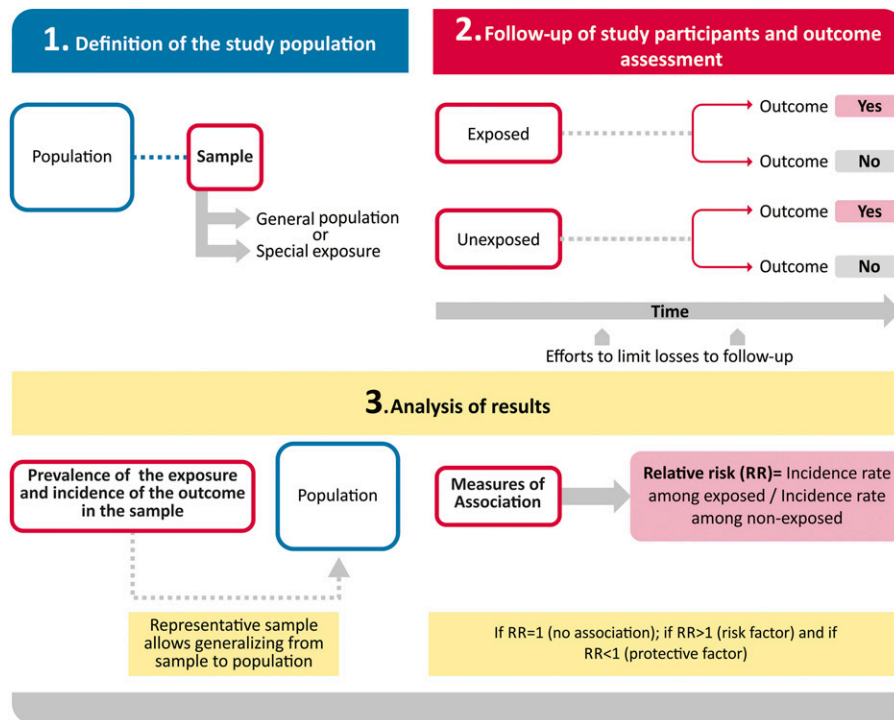


Figure 2. Basic procedures of a cohort study.

follow-up should be minimized so that risk measures can be estimated without bias. Subsequently, the incidence of the outcome among exposed and unexposed groups is compared through an association measure such as relative risk. (1)

### PRECONCEPTION, PRENATAL, AND BIRTH COHORT STUDIES

The types of cohort studies that best allow the study of early predictors of disease risk are preconception, prenatal, and birth cohorts. Birth cohorts are composed of individuals whose common event is birth at a given place and time. In these studies, data related to prenatal exposures are collected retrospectively. Cohort studies that begin in pregnancy and those that begin in the preconception period are particularly interesting because they identify fetal and preconception exposures in real time. However, the gathering of information related to pregnant women requires greater logistical planning and incurs higher costs than maternal/newborn data assessed at birth. (2)(7)

Birth and prenatal cohorts have contributed much of what is known today about the early-life origins of adult disease, and are the main source of data for life course epidemiology. The life course epidemiology framework encompasses the biological, behavioral, and psychosocial processes that occur throughout the life of individuals, linking adult health and

the risk of becoming ill with physical or social exposures that occurred earlier in life (during gestation, infancy, childhood, adolescence, or the early stages of adulthood) or in previous generations. (8)

### LOCATION OF THE MAIN PRECONCEPTION, PRENATAL, AND BIRTH COHORTS WORLDWIDE

The *International Journal of Epidemiology* (IJE) features a Cohort Profile section, in which it publishes the methodology of cohort studies conducted around the world. The studies published in that section are those for which the baseline data collection has been completed, basic descriptive data have been provided, and follow-up plans for cohort members have been clearly outlined. Preference is given to studies involving cohorts of more than 1,000 members and for whom study-specific follow-up data were collected. In that same section, the IJE also publishes profiles of cohort consortia as long as they present aggregate data. (9)

With the objective of identifying preconception, prenatal, and birth cohort studies with published methodology, we performed a bibliographic search of the PubMed database. The search strategy included title and journal searches with the terms “cohort profile” and “*International Journal of Epidemiology*,” respectively. Cohorts and cohort consortia in which the members were enrolled during childhood or

thereafter were excluded. We screened the articles by reading the titles and the full text. The cohort data, which were extracted and imported into a spreadsheet, included the following:

- Cohort name
- Year of publication of the study
- First year of member recruitment
- City and country
- Stage of life during which members were recruited (preconception, prenatal, or at birth)
- Birth data collection (prospective or retrospective)
- Type of membership (fixed or dynamic)
- Sample selection (from the general population or from specific exposure groups)
- The initial number of members
- The age of the members at the most recent follow-up evaluation.

We considered all articles published until November 14, 2017.

Figure 3 shows a flow chart of the study selection process. After the removal of duplicates, we identified 352 studies published in the IJE Cohort Profile section. Of those, 84 were preconception, prenatal, or birth cohorts and 4 were birth cohort consortia.

Of the 84 cohorts identified, 41 were birth cohorts, 41 were prenatal cohorts, and 2 were preconception cohorts. A prospective design was used in 64 studies, 38 were population-based, and 72 studies involved cohorts with fixed membership. We identified 19 multicenter cohort studies, 14 of which were single-country studies and 5 of which were conducted in 2 or more countries. The cohorts comprised members who were born before the 1950s ( $n=13$  studies), between 1950 and 1989 ( $n=19$  studies), and in the 1990s ( $n=52$  studies). More than a third of the identified cohort studies published their methodology between 2015 and November 2017 (Table 1).

Of the 84 cohorts identified, 40 were located in Europe, 4 in Africa, 13 in the Americas, 15 in Asia, and 12 in Oceania (Table 2). Most of the European cohorts were in England. In the Americas, most of the cohorts were in the United States or Brazil. In Asia, most of the cohorts were in East Asia (China or Japan) and South Asia (India). In Oceania, most of the cohorts were in Australia. According to the World Bank classification of countries by income group, (10) 63 of the cohorts belonged to high-income countries, 15 to upper middle-income countries, and 6 to lower middle-income countries. The number of individuals enrolled at the beginning of the studies was significantly higher in the cohorts in high-income countries compared with those from low- and middle-income countries (Table 3). Figure 4 shows the location of the 84 cohorts on a world map.

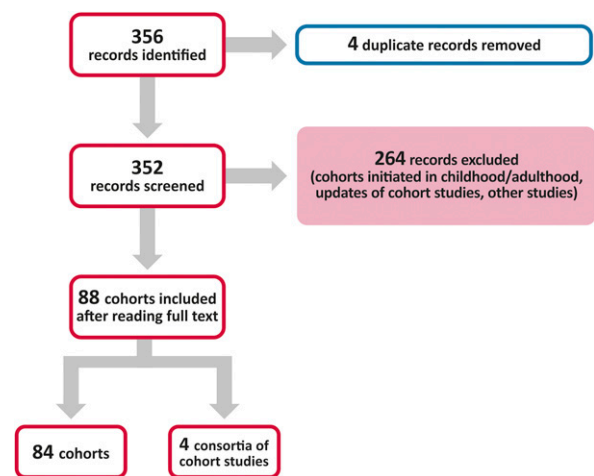


Figure 3. Flow chart for the search and selection stages of the preconception, prenatal, and birth cohort studies.

The characteristics of the cohorts varied according to the income level of the country in which they were located. One of the characteristics of high-income countries is the development of cohorts with birth registration data and national databases. In these countries, data related to births occurring decades ago are available in historical records, usually tracked by a personal record number. The availability of such data creates the opportunity for monitoring large populations and participants at advanced ages. For example, the retrospective Nordic Perinatal Bereavement Cohort study, which was conducted in Denmark, Finland, and Sweden, used decades of follow-up data obtained from population records and involved more than 7 million individuals born between 1973 and 2007. (11) In addition, the Hertfordshire cohort studies, conducted in England, included 3,225 individuals born between 1931 and 1939, (12) as well as 3,477 individuals born between 1920 and 1930. (13) Other characteristics that differentiate cohort studies conducted in high-income countries from those conducted in other countries include the greater number of follow-up evaluations performed, longer follow-up periods, and greater sophistication of relevant measurements. (14)(15)(16)(17) Another interesting aspect of such cohort studies is that the life course epidemiology approach is not limited to individuals of a single generation; the descendants of cohort members are often being monitored as well, which allows analyses across generations. For example, monitoring of the second generation of participants has already begun for the United Kingdom-wide 1946 and 1970 cohorts, (14)(16) as well as for the Avon Longitudinal Study of Parents and Children (ALSPAC). (17)

Although prenatal and birth cohorts in upper middle-income countries are less common than are those in high-income

**TABLE 1. Main Characteristics of the Preconception, Prenatal, and Birth Cohorts Identified**

VARIABLE	NO.	%
Initiation of the cohort		
Birth	41	48.8
Prenatal	41	48.8
Preconception	2	2.4
Study design		
Prospective	64	76.2
Retrospective	20	23.8
Cohort membership		
Fixed	72	85.7
Dynamic	12	14.3
Base		
Sample of the target population	46	54.8
All of the target population	38	45.2
Multicenter		
No.	65	77.4
In a single country	14	16.7
In $\geq 2$ countries	5	5.9
Birth year		
Pre-1950	13	15.5
1950–1989	19	22.6
1990 or after	52	61.9
Year of publication		
2005–2009	21	25.0
2010–2014	28	33.3
2015–2017 <sup>a</sup>	35	41.7
Total	84	100.0

<sup>a</sup>Through November 2017.

countries, some of the former are noteworthy. This is especially true of the cohorts in the city of Pelotas, Brazil, located in the southern region of the country. The first Pelotas birth cohort was initiated in 1982 and involved 5,914 children. (18) Subsequent cohorts were initiated in 1993, 2004, and 2015. With 3 decades of work, more than 24,000 individuals studied throughout their life, hundreds of follow-up evaluations performed, and thousands of variables collected, the Pelotas birth cohort studies are the

largest population-based birth cohort studies in developing countries and have the lowest rates of loss to follow-up of such studies. (18)(19)(20)(21) Some cohort studies conducted in other upper middle-income countries, including South Africa, (22) Jamaica, (23) and the Philippines, (24) have cited problems with family migration, early childhood deaths, and a lack of financial resources as reasons for losses to follow-up.

In cohort studies conducted in lower middle-income countries, the collection of data related to individuals at birth is hampered by cultural practices of delivery outside the hospital setting and incomplete or absent birth records. (25)(26)(27) In such countries, cohort studies also encounter problems with losses to follow-up, mainly due to high infant mortality and internal migration. (25)(26)(27)(28)

Of the 84 cohort studies identified, only 2 involved preconception cohorts. In the 2007 Smart-Gravid cohort from Denmark, 2,288 women of reproductive age were evaluated before and after conception and were monitored until delivery. (29) The 2009 “LIFE” cohort study conducted in India collected data on 980 women before gestation and their offspring up to 5 years of age. (30)

Four consortia of birth and/or prenatal cohorts were also identified:

The International Childhood Cancer Cohort Consortium, comprising 11 cohorts, designed to study the role of various environmental and genetic exposures in the etiology of childhood cancer, has evaluated data related to approximately 700,000 children. (31)

The Environment and Childhood consortium, composed of 7 birth cohorts in Spain, aimed to evaluate the role of environmental pollutants in childhood growth and development, on the basis of data related to 3,768 children. (32)

The Consortium of Health-Oriented Research in Transitioning Societies, encompassing 5 of the largest birth cohorts located in low- and middle-income countries (Brazil, Guatemala, India, the Philippines, and South Africa), with the fundamental objective of providing high-quality scientific data on the early origins of chronic diseases and on human capital, has evaluated data related to approximately 22,840 children. (33)

The Nausea and Vomiting During Pregnancy Genetics Consortium, composed of 7 cohorts in Australia, Finland, Spain, Denmark, and the United Kingdom, designed to aggregate knowledge on genetic and environmental causes (with special attention to psychological causes) of nausea, vomiting, and hyperemesis in pregnant women, as well as on their incidence and severity, has evaluated data related to 25,830 women. (34)

TABLE 2. Preconception, Prenatal, and Birth Cohorts by Region and Country

REGION (TOTAL)	
Country	No.
Africa (n=4)	
Kenya	1
Mauritius	1
South Africa	2
The Americas (n=13)	
Brazil	4
Canada	1
Chile	1
Ecuador	1
Jamaica	1
United States	5
Asia (n=15)	
China	4
India	5
Israel	2
Japan	3
The Philippines	1
Europe (n=40)	
Belarus	1
Belgium	1
Czech Republic	1
Denmark	5
Denmark, Sweden, and Finland	1
England	7
Finland	4
France	2
Greece	1
Ireland	1
Norway	1
Scotland	2
Sweden	1
Switzerland	1
The Netherlands	5
Wales	1

Continued

TABLE 2. (Continued)

REGION (TOTAL)	
England, Scotland and Wales	3
Isle of Man	1
United Kingdom (England, Scotland, Wales and Northern Ireland)	1
Oceania (n=12)	
Australia	10
New Zealand	2
<b>Total</b>	<b>84</b>

### PRECONCEPTION, PRENATAL, AND BIRTH COHORT STUDIES AND EARLY-LIFE ORIGINS OF ADULT HEALTH AND DISEASE

Preconception, prenatal, and birth cohort studies provide a unique opportunity to assess the consequences of early life exposures on adult health and disease. By repeatedly assessing exposures and outcomes in individuals over time, such studies have the potential to identify early environmental exposures (physical, chemical, biological, social, or psychosocial factors) that influence health throughout life. (35) They allow the study of certain critical windows of time during which individuals are especially sensitive to their environment (critical development periods), (35) as well as the cumulative effects of exposures on health and disease throughout life. (36) Below are some examples of studies examining consequences of early-life exposures on later-life outcomes.

The investigation of the effects of the Dutch Hunger Winter of 1944-1945 on human development, particularly on mental performance, has become a classic study in the life course epidemiology literature, showing how a starvation diet during pregnancy influences subsequent health of the offspring. The information collected in the Dutch national psychiatric records made it feasible to examine psychiatric outcomes during adulthood among people exposed to hunger at different gestational periods during pregnancy. The best-known finding concerns the increased risk of schizophrenia among individuals exposed to the famine during the first trimester of gestation, (37) a finding that years later was replicated with data from the famine period faced by China between 1959 and 1961. (38)

Using data from ALSPAC, investigators reported that maternal prenatal fish consumption was associated with

**TABLE 3. Number of Preconception, Prenatal, and Birth Cohorts and Initial Number of Cohort Members, by Economic Status of the Respective Countries**

COUNTRY INCOME LEVEL <sup>a</sup>	COHORT STUDIES	ESTIMATED INITIAL COHORT MEMBERSHIP <sup>b</sup>
	N (%)	N
High	63 (75.0)	9,993,904
Middle	15 (18.0)	422,288
Low	6 (7.0)	46,139
Total	84 (100%)	10,462,331

<sup>a</sup>Classified by the income criterion established by the World Bank (updated in June 2017).

<sup>b</sup>Estimates obtained by calculating the sum of the numbers of initial members of each cohort reported in the cohort profile.

lower frequency of maternal depressive and anxiety symptoms, as well as lower frequency of intrauterine growth restriction and better neurocognitive child development. (39) Another example of an early environmental exposure that has an impact in later stages of life is breastfeeding. Studies using data from the Pelotas birth cohorts have reported that a longer duration of breastfeeding is associated with a higher level of education, higher IQ, and higher income in adulthood, (40) as well as a lower probability of presenting with severe depressive symptoms in adult life. (41)

The cumulative risk effect of early life exposures was examined using data from the 1958 British birth cohort. Investigators showed that child maltreatment (abuse and neglect) was associated with reduced adult socioeconomic outcomes and this was more extreme if there were multiple maltreatments. (42)

The long-term effects of environmental exposures may not be limited to individuals who have been exposed directly to the relevant exposure. (43)(44)(45) Emanuel et al (46) observed that the height of the grandmother (Fo generation) is a determinant of the birthweight of the mother (F1 generation), which in turn influences the birthweight of her child (F2 generation), establishing a chain of intergenerational associations. (46) The intergenerational approach is fundamental for understanding the intergenerational transfer of risk long after the initial environmental exposure has occurred.

### WHY ARE NEW PRECONCEPTION, PRENATAL, AND BIRTH COHORT STUDIES NEEDED?

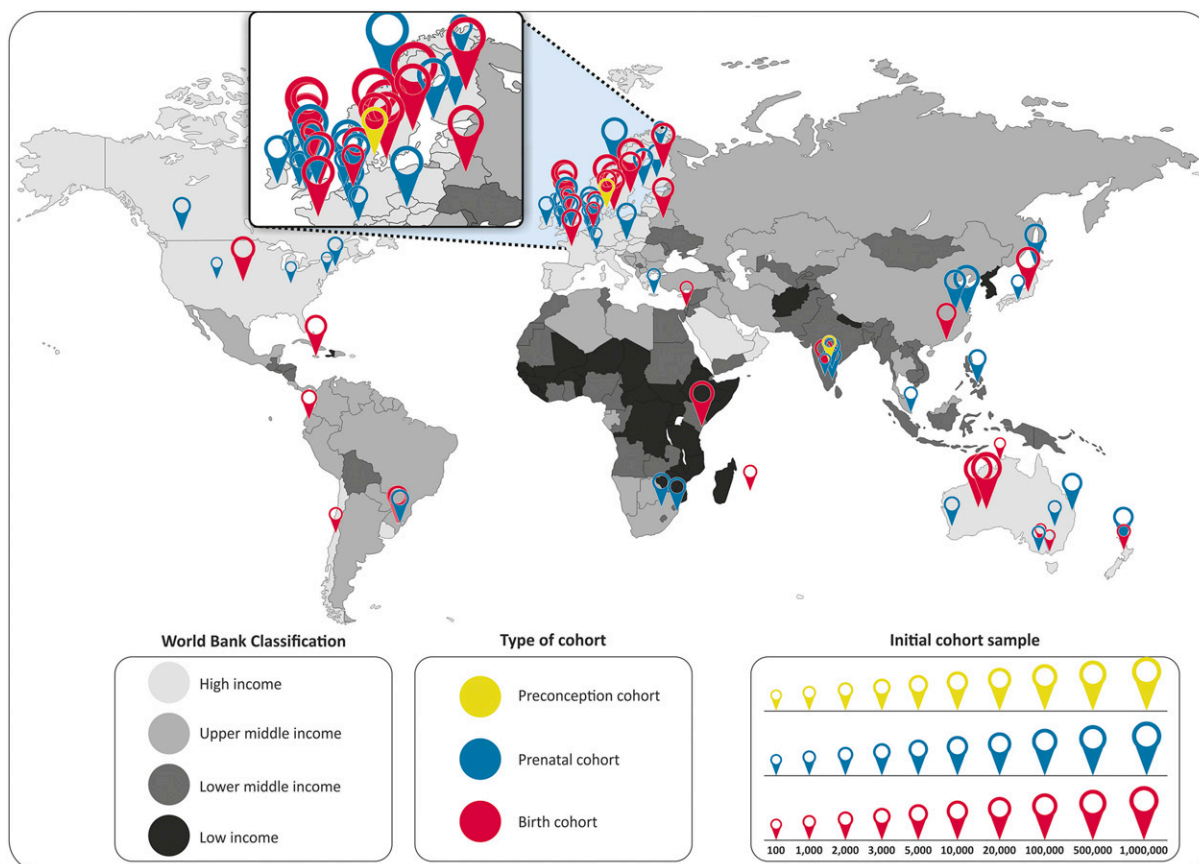
The epidemiologic, nutritional, and economic transitions experienced by most countries in the world justify the

addition of new birth cohorts, mostly for measuring new exposures or exposures that have not been evaluated in previous decades, and for comparing associations between exposures and outcomes at different points in time and between cohorts. (47) The nature of the exposures can differ between higher-income and developing countries. For example, in higher-income countries, physical activity is predominantly leisure-related, whereas in poor countries, individuals engage in physical activity primarily on the way to work or in the working environment. (7) In low- and middle-income countries, certain exposures may have increased relevance because of the high prevalence of risk factors such as low birthweight, malnutrition, poverty, and violence. (7)(48) Finally, the confounding structures in middle- and low-income countries can be different from those found in high-income countries. (7) In exploring the confounding biases in the association between breastfeeding and IQ, Brion et al (49) found that socioeconomic status was a confounding variable in the England-based ALSPAC cohort (17) whereas no such bias was identified in the 1993 Pelotas cohort. (19) By comparing associations between exposures and outcomes in different contexts, it is possible to explore the probability of residual confounding and to improve causal inference. (49)

One important contribution of cohort studies is their ability to generate feedback for decision makers. Results of birth cohort studies can assist managers in monitoring population health indicators, analyzing health determinants, and strengthening health care and surveillance services. (20) In addition, the development of birth cohorts promotes improvements in the process of collecting and analyzing epidemiologic data, as well as in research and development of the scientific capacity of a country. (35)

### CONCLUSION

Preconception, prenatal, and birth cohorts are extremely useful for the study of social and biological pathways linking early life and adult health and disease. The study of many biological, behavioral, and psychosocial processes that occur in childhood, adolescence and adulthood has been made possible through the analyses of environmental exposures from prenatal and birth cohort studies. However, the majority of such cohort studies have been conducted in high-income countries. Studying the relationship between exposure and disease and taking into account the specificities of each region makes it possible to adequately evaluate the mechanisms of risk and protection throughout a lifetime. The challenges that face cohort studies in the context of life course epidemiology include the availability of adequate data from environmental exposures at various stages



**Figure 4.** Map of the world showing the location of the preconception, prenatal, and birth cohorts identified. The size of each marker is proportional to the initial membership of each cohort, and the colors of the markers indicate whether the study involved a preconception, prenatal, or birth cohort. High-income, upper middle-income, and lower middle-income countries are identified by different shades of gray.

of the individuals' lives and the application of techniques capable of dealing with the complexity of the theoretical models involved. Sustainable financial support is mandatory to initiate and properly follow a preconception, prenatal, or birth cohort.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Recognize a cohort study.
- Understand the strengths and limitations of cohort studies.

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