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Methodological aspects of the 1993 Pelotas (Brazil) Birth Cohort Study

Aspectos metodológicos da Coorte de Nascimentos de 1993 em Pelotas, RS

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Keywords

Longitudinal studies. Cohort studies. Prospective studies. Child development. Follow-up studies. Epidemiologic methods.

Abstract

This paper describes the main methodological aspects of a cohort study, with emphasis on its recent phases, which may be relevant to investigators planning to carry out similar studies. In 1993, a population based study was launched in Pelotas, Southern Brazil. All 5,249 newborns delivered in the city's hospitals were enrolled, and sub-samples were visited at the ages of one, three and six months and of one and four years. In 2004-5 it was possible to trace 87.5% of the cohort at the age of 10-12 years. Sub-studies are addressing issues related to oral health, psychological development and mental health, body composition, and ethnography. Birth cohort studies are essential for investigating the early determinants of adult disease and nutritional status, yet few such studies are available from low and middle-income countries where these determinants may differ from those documented in more developed settings.

Descritores

Estudos longitudinais. Estudos de coorte. Estudos prospectivos. Desenvolvimento infantil. Estudos de acompanhamento. Métodos epidemiológicos.

Resumo

Descrever aspectos metodológicos do estudo da coorte de crianças que podem ser relevantes para pesquisadores que estejam planejando investigações semelhantes. Em 1993, uma coorte de base populacional foi recrutada em Pelotas, RS. Os 5.249 recém-nascidos nos hospitais da cidade foram acompanhados com um, três e seis meses, e com um e quatro anos de idade. Subestudos estão sendo realizados sobre saúde bucal, desenvolvimento psicológico e saúde mental, composição corporal e aspectos etnográficos. Em 2004-5 foi possível entrevistar 87,5% da coorte inicial, com a idade de 10-12 anos. Estudos de coortes de nascimentos são essenciais para investigar os determinantes precoces da morbidade e estado nutricional de adultos. No entanto, há poucos estudos com esta metodologia em países de renda média e baixa, e alguns dos determinantes da situação de saúde podem ser distintos daqueles observados em países ricos.

INTRODUCTION

Birth cohort studies are receiving growing attention. Early life characteristics such as birthweight, infant and childhood growth patterns, and breastfeeding practices have been linked to morbidity in child-

hood, adolescence and adulthood. In the 1980's, Barker proposed the "fetal origins of adult diseases" hypothesis, based on studies associating birthweight and weight at one year with cardiovascular disease risk later in life.¹ A modified version of this hypothesis was proposed by Lucas⁸ in the 1990s, which he

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referred to as the “programming” hypothesis. More recently, Singhal & Lucas,¹¹ based on experimental and observational data, proposed the “growth acceleration hypothesis”, shifting the focus from intrauterine growth restriction to the velocity of growth in early life. The debate on these issues is still rife.

The vast majority of birth cohort studies are from high-income countries. However, newborns from low and middle-income countries may differ substantially from those. For example, intrauterine growth retardation is much more frequent,¹⁰ as are anthropometric deficits, slow growth in childhood and infectious diseases.¹⁵ This stresses the need to carry out studies in less-developed settings.¹⁴

Cross-sectional, case-control and retrospective cohort designs have been used to investigate these issues, but the quality of data on early exposures is often poor and may lead to bias or misclassification. Therefore, prospective studies are warranted, particularly those that follow a group of people since birth to adulthood. The first national prospective birth cohort study was started in 1946 in the United Kingdom¹⁶ and was followed by many similar studies in high-income countries. The high costs of such studies, and the complex logistics involved in following up a large number of individuals over long time periods, has limited the number of such studies in low and middle-income countries.⁶

In Pelotas, Southern Brazil, a population-based birth cohort study was started in 1982, and subjects have been followed up at several points in time during infancy, childhood, adolescence and young adulthood. The Pelotas 1982 Birth Cohort Study became the largest and longest running birth cohort study in a developing country.⁶ The success of this study encouraged us to plan a new birth cohort one decade later. Due to funding issues, it was not possible to start the new cohort in 1992, but only in 1993.

Pelotas currently has 320,000 urban inhabitants, being located at the extreme South of Brazil, near the Uruguayan border. Its main economic activities are rice production, commerce and education. At the time of the study, the infant mortality rate was 21 deaths per thousand births.

The main objectives of the 1993 cohort were: (a) to evaluate time trends in health indicators throughout the lifespan, through a comparison with results of the 1982 study; (b) to test specific hypotheses which were not possible to address in the 1982 cohort; (c) to improve data quality with the lessons learned from the 1982 study.

The early phases of the Pelotas 1993 Birth Cohort Study were described in previous publications.^{3,13} In the present paper, we provide a summary of the methods of the early visits (1993-94) as well as a detailed description of the visits and sub-studies that took place since 1997.

Lessons learned from the 1982 cohort

The 1982 study was originally designed as a perinatal health survey, rather than a birth cohort. As a consequence, detailed information necessary for long-term follow-up were not initially collected. In contrast, the initial interview for the 1993 cohort included information on the address and telephone number of the cohort member's family; address and telephone number of at least two relatives or close family friends; and place of employment of the parents. The research team also asked families if they were planning to move, and if so, where to. In addition, the full names of the child and of both parents were collected – in 1982 only the mother's name was recorded; because many children still did not have a name on the occasion of the hospital interview, the child's name was often missing. Names, addresses and phone numbers were confirmed in all follow-up visits. It is important to note that all these contact data were kept in a confidential database with restricted access.

The 1982 cohort showed that most infant deaths and hospital admissions were concentrated in the first few months of life, and also that critical events related to feeding patterns took place at these early ages. By the early 1990s, the international literature was starting to highlight the importance of early “critical windows” in which exposures would affect long-term health.⁷ To allow such analyses, the 1993 cohort included visits at the ages of one, three, six and 12 months, in contrast to the 1982 cohort for which the first follow-up visit took place at 12 months. Also, the high burden of disease faced by low-birthweight children in the 1982 cohort led us to oversample these children in the 1993 follow-up visits.

The 1993 study also allowed to correct some of the pitfalls of the earlier cohort. In 1982, birth length was not collected because it was deemed to be a complex measurement requiring special equipment and training. Birthweight was obtained in 1982 from the regular hospital scales (that were periodically calibrated by the research team). In 1993, birth length was measured using standard equipment and protocols, and each hospital was provided with a new electronic scale. In 1982, gestational age was based on the reported date of the last menstrual period, but this information was missing for 20% of the cohort. In 1993, we also

Table 1 - Main follow-up visits in the Pelotas 1993 Birth Cohort Study.

Year	Age	Sampling strategy	Eligible subjects N	Follow-up rate* %
1993	Birth	All 1993 births in five maternity hospitals in Pelotas, Brazil	5,249	—
1993-4	1 month	Systematic sample of 13% of all cohort members	655	99.1
1993-4	3 months	As in the previous visit	655	98.3
1993-4	6 months	All low birthweight children (<2,500 g) and 20% of the remaining cohort members (including those followed-up at one and three months)	1,460	96.8
1994-5	12 months	As in the previous visit	1,460	93.4
1997-8	4 years	As in the previous visit	1,460	87.2
2004-5	11 years	All cohort members	5,249	87.5

*Percent of original cohort members eligible for the follow up visit who were either interviewed or known to have died

collected this variable for comparison purposes, but in addition the interviewers were trained on the Dubowitz scale based on the physical examination of the newborn.⁴ This allowed us to use the first variable in reports comparing both cohorts, and the second indicator when analyzing the 1993 cohort alone.

Main follow-up visits

Table 1 shows the main follow-up visits of the 1993 cohort study, including year of data collection, target ages, sampling strategies, as well as the number of eligible individuals and follow-up rates.

The perinatal study and first-year visits

All five maternity hospitals were visited daily during 1993. Mothers who lived in the urban area answered a questionnaire containing demographic, socioeconomic, reproductive, behavioral, care seeking and morbidity variables (Table 2). Weight (precision of 10 g), length (precision of 1 mm) and head circumference (precision of 1 mm) of all newborns were measured. There were 16 refusals, and information was obtained on 5,249 live births and 55 fetal deaths. The latter were included in the mortality statistics, but are not computed in the birth cohort study. This phase of the study, as well as the home visits at six and 12 months, were financed by the European Economic Commission.

For the one and three-month visits, a systematic sample of 655 cohort members was selected. The one-month visit started in February 1993 (when children born in January completed one month) and ended in January 1994 (when children born in December 1993 completed one month). The three-month visits were carried out between April 1993 and March 1994. Follow-up rates were 99.1% and 98.3%, for one and three months, respectively. Standardized questionnaires were applied to the mother, with emphasis on morbidity, feeding patterns, health services and medicines utilization. Children were weighed and their length, head and abdominal circumferences were measured (Table 2). These visits were funded by the

World Health Organization for assessing breastfeeding patterns, early growth and related factors. Because of funding limitations, it was only possible to follow up a smaller number of children at these ages than in the other visits.

A different sampling approach was used in the six and 12-month visits, for which larger funds were available. To better assess the consequences of low birthweight, all 510 children with this condition were visited, as well as a 20% systematic sample of the remaining children. The 655 children eligible for the one and three-month visits were included in the sample, so that these children were examined five times – at birth and at one, three, six and 12 months. The different sampling fractions for low birthweight and other children required weighted analyses of these datasets. The questionnaires used in the previous follow-ups were adapted and information on the same variables was collected (Table 2). In addition, the Denver II motor development scale⁵ was applied to all children. Response rates were 96.8% at six and 93.4% at 12 months. There were very small differences in follow-up rates according to family income and to birthweight;¹³ at least 92.2% of the children in any category of these variables were traced.

1997-8 follow-up visit

In 1997-8, we attempted to locate the 1,363 children examined at 12 months; 1,273 (93.4%) were identified, representing a cumulative response rate of 87.2%. Out of the 90 children who were not interviewed, 61 had moved out of the city. Other reasons for non-response were incorrect addresses (18 children) and refusals (five children).

During the home visit, mothers were interviewed about socioeconomic and demographic variables, environmental characteristics; health services utilization and morbidity; nutrition and psychological development; and child care. The children were weighed with portable digital scales and measured with locally made stadiometers (Table 2). Standardization sessions for anthropometric measurements were

carried out prior to and during data collection. In addition, quality control included a short questionnaire repeated for 5% of the interviews. This phase of the study was funded by the Brazilian Program for Centers of Excellence in Research (PRONEX).

2004-5 follow-up visit

The experience gained with the 1982 cohort suggested the whole cohort, rather than subsamples,

should be visited. Use of subsamples meant that full data were only available for a very small subgroup of the whole cohort, those seen in every visit. Also, for prospective studies of rare events such as morbidity or mortality, it is essential to have information on the whole cohort at key points in time. Therefore, unlike all previous visits to the cohort, the 2004-5 visit was aimed at locating all children born in 1993.

Our previous experience, particularly the difficulty

Table 2 - Variables collected in the main follow-up visits to the Pelotas 1993 Cohort Study members.

Variable	Perinatal	1 month	3 month	Visit 6 month	12 month	4 year	11 year
Family variables							
Family income	X				X	X	X
Wealth assets index		X		X		X	X
Parental variables							
Maternal employment	X	X	X	X	X	X	X
Maternal schooling	X					X	X
Paternal schooling	X					X	X
Maternal age	X						X
Maternal marital status	X		X	X	X	X	X
Maternal skin color	X						
Paternal skin color	X						
Maternal reproductive history	X					X	X
Gestational age	X						
Type of delivery	X						
Antenatal care	X						
Maternal weight	X					X	X
Maternal height	X					X	X
Maternal hospitalization	X						
Social support during pregnancy	X						
Maternal smoking	X	X	X	X	X	X	X
Paternal smoking	X	X	X	X	X	X	X
Maternal alcohol intake	X						X
Paternal alcohol intake							X
Maternal mental health		X	X				X
Parental chronic diseases							X
Maternal physical activity							X
Child / adolescent variables							
Sex of the child	X						
Child skin color						X	X
Weight	X	X	X	X	X	X	X
Length / Height	X	X	X	X	X	X	X
Triceps skinfold							X
Subscapular skinfold							X
Abdominal circumference	X	X	X	X	X		
Head circumference	X	X	X	X	X		
Chest circumference	X						
Breastfeeding	X	X	X	X	X	X	
Dietary patterns		X	X	X	X	X	X
Pacifier use		X	X	X	X	X	
Child care		X	X	X	X	X	X
Child morbidity		X	X	X	X	X	X
Child hospitalization		X	X	X	X	X	X
Child medicine intake		X	X	X	X	X	X
Neurological development				X	X	X	X
Number of teeth				X	X		
Accidents and injuries					X	X	
Blood pressure							X
Child schooling							X
Religion							X
Gynecologic consultations							X
Age of first period							X
Child physical activity							X
Sedentary behaviors							X
Child labor							X
Oral health and aesthetics							X
Stressful events							X
Body image							X
Resting pulse							X
Child smoking							X
Child alcohol intake							X
Violence inside and outside home							X
Knowledge on HIV infection							X

Table 3 - Sub-studies nested in the Pelotas 1993 Birth Cohort Study, 1993-2002.

Year	Topic (age)	Sampling strategy	Main objective	Sample size
1993	Hospital admissions (<1 year)	Nested case-control study of hospital admissions during infancy	To identify risk factors for hospital admissions in infancy according to type of illness	152 cases 2,391 controls
1994	Ethnographic (1 year)	Sample stratified by maternal schooling and family income	To explore issues related to health care seeking patterns and to infant feeding, social support and social organization.	80
1997	Asthma (4 years)	All 1,363 individuals included in the 1-year main visit	To identify prevalence and risk factors for asthma in Brazilian children.	1,273
1997	Development and behavior (4 years)	Half of the 1,273 individuals included in the 4-years main visit	To investigate variables associated with behavioral problems and intelligence	634
1997	Injuries (4 years)	Half of the 1,273 individuals included in the 4-years main visit	To measure the main risk factors associated with the occurrence of accidental injuries in children	620
1999	Oral health (6 years)	One quarter of the 1,273 individuals included in the 4-years main visit	To test the effect of early social, biological and behavioral factors on dental caries and malocclusion in primary dentition	359
1999	Asthma and lung function (6 years)	Half of the 1,273 individuals included in the 4-years main visit	To investigate the association of respiratory symptoms and lung function with atopy, demographic, socioeconomic, environmental and gestational factors.	532
2002	Body composition and symmetry (9 years)	Sample stratified by birth-weight (<2,500; ≥2,500 g) and weight gain 1-4 years (below or above median)	To test the effect of birthweight, early and late growth on body composition and symmetry at 9 years	172

of tracing subjects based on old addresses (due to high mobility), suggested a multi-pronged strategy for locating the adolescents:

- School census:** All 97 city schools, public and private, were visited in early 2004 to identify adolescents born in 1993. School databases were searched. All students belonging to the cohort were linked to their records. Folders were sent to the families of students born in 1993 who could not be linked, inquiring where they had been born, and – if born in Pelotas – asking for confirmation of names of parents, date of birth, hospital of delivery, current address, and others. Approximately 4,400 children were identified in the schools. Another 200 children were reported to have been born in Pelotas but could not be linked, possibly their mothers lived outside the urban area at birth and therefore did not belong to the original cohort.
- City census:** The approximately 98,000 households in the urban area were visited in 2004-5, in search of adolescents born in 1993. Subjects belonging to the 1982 cohort were also sought during this visit. Individuals born in 1993 were linked to their cohort records, and if this was not possible, a second home visit was carried out to confirm the information. This strategy identified 3,254 cohort members, most of whom (93%) had already been located in their schools.
- Search at previous addresses:** After the two above strategies were used, approximately 600 children were yet to be traced. Previous home addresses were available either from the perinatal or from follow up interviews to sub-samples. Another 250 children were identified, who had not been traced by the previous strategies.

As in the previous phases of the study, field supervisors repeated 10% of the interviews for quality control purposes. Half of the families who had a telephone (72% of those interviewed) were contacted to confirm that the interview had taken place, and any criticisms on the questionnaire or on the interviewer were recorded.

The 2004-5 questionnaire was divided into four blocks. The first collected detailed contact information, including at least three different addresses of the family and relatives, phone numbers and place of work. In the second block, mothers were asked about family characteristics, maternal and paternal variables, and morbidity history of the adolescent. The third block was an interviewer-applied questionnaire to the adolescent, including diet, physical activity and other variables. Confidential information – including smoking, alcohol and drug use – was included in a fourth questionnaire that was self-applied and identified only by the adolescent's serial number. Table 2 provides a list of the main topics of the questionnaire.*

In this visit, physical examination comprised measurements of weight, height, subscapular and triceps skinfolds, blood pressure and pulse (Table 2). Interviewers were standardized prior to the start of the field work, and standardization sessions were repeated every two months. The measurement equipment was calibrated weekly.

Sub-studies

Several sub-studies including the cohort members were also carried out. Table 3 shows these studies, with

*Full version in Portuguese is available from http://www.epidemiio-ufpel.org.br/_projetos_de_pesquisas/coorte1993/ [2005 out 31]

Table 4 - Follow up rates in the 2004-5 visit, according to baseline characteristics of the cohort. Pelotas, Southern Brazil.

Variable	Original cohort N (%)	% located*	P**
Gender			0.18
Boys	2,580 (49.2%)	86.9	
Girls	2,667 (50.8%)	88.1	
Family income (minimum wages)			<0.001
≤1	967 (18.4%)	88.3	
1.1-3.0	2,260 (43.1%)	88.7	
3.1-6.0	1,204 (22.9%)	88.9	
6.1-10.0	433 (8.3%)	79.9	
>10.0	385 (7.3%)	82.6	
Maternal schooling at birth (years)			<0.001
0	134 (2.6%)	82.1	
1-4	1,338 (25.5%)	88.7	
5-8	2,424 (46.2%)	89.9	
≥9	1,350 (25.7%)	82.5	
Birth weight (g)			0.16
<2,500	510 (9.8%)	89.8	
2,500-3,499	3,361 (64.2%)	86.9	
≥3,500	1,361 (26.0%)	87.9	
Overall	5,249 (100.0%)	87.5	

*Including 141 deaths

**Chi-square test

respective years, target ages, sampling strategies, main objectives, and number of individuals included. As described in a previous publication, infant mortality was actively monitored by weekly visits to all hospitals, civil registration offices and the local health authorities.⁹ Deaths continued to be monitored after the first year, except for the hospital visits.

Four sub-studies (not shown in Table 3) are currently underway or will be started shortly. These include:

- Ethnographic study. This consists of repeat visits to the 80 subjects who were part of the original ethnographic study. The main objective is explore how the general process of socialization, maturation and life cycle events impinges on health events, including substance use and abuse, smoking, injury and violence, mental well being, stressful life events, chronic diseases, and sexuality. A similar study is being carried out for the 1982 cohort to assess trends over time in cultural patterns.
- Oral health study. The 359 subjects examined in the 1999 oral health study are being visited to estimate the prevalence of oral disease and to identify social, biological and behavioral risk factors, with emphasis on early life exposures.
- Development and behavioral study. This is aimed at estimating the prevalence, prognosis and early determinants of developmental and psychiatric disorders. All 634 subjects examined in the 1997 development and behavior sub-study were revisited and 601 (95%) were interviewed again in 2005.
- Body composition study. This includes the administration of deuterium to 560 cohort members who were followed up in all cohort visits so far. The main objective is to measure body composition in adolescence and its early determinants, particularly growth velocity in different age intervals.

Data management

The complete 1993 cohort database now includes over 2,500 variables. A data dictionary is available in two versions. In the first, variables are organized according to when they were collected, that is, by visit. In the second, they are grouped by categories (e.g. socioeconomic, anthropometric, and others). The initial letter of each variable name indicates the follow-up visit, e.g. A for the perinatal survey, B for the 1-month visit, C for the 3-month visit) and so on. As far as possible, each indicator has the same variable name in the different follow-ups, differing only regarding the first letter. The main database is available both in Stata and SPSS formats. All questionnaires and interviewer guides used in previous follow-up visits are also available in electronic and paper formats.

Follow up rates

Of the 5,249 live born children, 141 (2.7%) are known to have died; other children may also have died after migrating out of the city, but no information on these deaths is available. In 2004-5, 4,482 adolescents were contacted. Among these, there were 30 refusals (0.7%) and 4,452 adolescents were interviewed. By adding those who are known to have died to those interviewed, the follow-up rate was 87.5%.

An unexpected finding was that the door-to-door visits to all households in the city, leading to the identification of 3,254 cohort subjects, failed to locate 27.4% of the 4,482 adolescents who were eventually traced.

Table 4 shows follow up rates in the 2004-5 visit according to key baseline characteristics. No differences

were observed according to sex or birthweight. Follow-up rates tended to be higher for adolescents belonging to low and middle-income families, and those born to mothers with intermediate levels of education. At least 79.9% of all children in each subgroup were traced.

CONCLUSIONS

Prospective birth cohort studies provide evidence on life-course determinants that are difficult, if not impossible, to investigate through other study designs. In the oldest available prospective birth cohort, the 1946 British Births Study, subjects are now approaching their seventh decade of life.¹⁶ Several new birth cohorts have been launched around the start of the new millennium, including one in Britain¹² and another in the USA.* Three birth cohorts are currently being followed up in Pelotas: the 1982 and 1993 cohorts, and a new one launched in 2004.² In addition to providing evidence on the life-course approach, the existence of three cohorts allows the investigation of secular trends by comparing children of the same age in the three cohorts.

These cohorts have addressed not only the study of biological determinants of adult disease, but also emphasized the study of social and cultural factors. The broad social inequalities that characterize our country allow the demonstration of the long term effect of early-life poverty.

Several lessons were learned in the recent phases of the study. The overall follow up rate was quite high and almost nine out of 10 cohort members were traced. However, the fact that the door-to-door visits failed to identify about one quarter of the adolescents who were eventually located suggests that this strategy alone is insufficient for the future phases of the study. In the past, we had successfully used this approach to locate a high proportion of the 1982 cohort. It is possible that increased concerns with security are responsible for many families failing to provide information to the interviewers.

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A multidisciplinary study team is essential for birth cohort studies. Epidemiologists, clinicians, nutritionists, anthropologists, psychologists, biologists, physical educators, dentists and statisticians have played essential roles in the study. In the future, further inputs will be sought from economists, sociologists and educators.

A critical issue affecting long-term cohort studies is "funder fatigue", namely the fact that no single funding agency is likely to provide long-term support to a single study, regardless of how successful it may be. Over the last 12 years, five different agencies provided financial support.

The next visit to the cohort is planned for 2008, when the adolescents will be 15 years old. In addition to collecting information on variables measured in the 2004-5 visit, special emphasis will be given to sexual and reproductive factors. Because the 1982 cohort members were visited at the age of 15 years, this visit will allow a direct comparison between the two cohorts at the same age. DNA samples will be collected in that visit, to create a bank for future studies of chronic diseases. We look forward to continuing this study for many years to come.

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