

COHORT PROFILE

Cohort Profile: The Limache, Chile, birth cohort study

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The Limache cohort was set up to assess the programming and life course events hypotheses in relation to cardiovascular risk factors and chronic respiratory conditions, especially asthma, in the context of an unprecedented economic growth in Chile. The cohort was a representative sample of 1232 participants born between 1974 and 1978 in the hospital of Limache. The study includes data collected at birth, during the 1st year of life, at 22 to 28 years (collected between 2000 and 2002) and at 32 to 38 years (collected between 2010 and 2012). The data collected include anthropometric measurements at birth, 1st year of life and in adulthood, socio-economic and demographic data, lifestyle information including smoking, alcohol consumption and food intake, respiratory symptoms, lung function, broncho-reactivity to methacholine and skin prick reaction to eight allergens, measurement of cardiovascular risk factors and information on common mental health, mainly in the most recent study. The principal researchers welcome collaborative projects, especially those that will compare similar data sets in other settings [E-mail: hamigo@med.uchile.cl].

Why was the cohort set up?

In 1999 the principal investigators conceived a study which would assess the impact of the accelerated socio-economic development taking place in Chile. Infant mortality, low birthweight, undernutrition and infectious diseases in those under 3 years of age were markedly decreasing. Infant mortality decreased from nearly 80 per 1000 in the early 1970s to around 10 per 1000 at the end of the 1990s, and birthweight below 2500 g decreased to approximately 6%.^{1–3} These changes in health status of the Chilean population provided a unique opportunity to appraise whether the improvement in living conditions would have an impact on the pattern of chronic diseases in adulthood.

At the time, the programming and the life course events hypotheses were being studied in developed countries,^{4–6} but very few countries from the

intermediate developed nations were involved in this area of research. A Chilean study considering the fast socio-economic and health changes taking place could contribute to our understanding of the aetiology of chronic disease in adults.

A consideration in our study was the inclusion of the period of accelerated health changes that took place in Chile from the early 1970s.⁷ This was the reason why we chose a non-concurrent design which would capture over a short period of time information on birth variables in young adults. This was possible because details were collected for all births in the country including duration of gestation, birthweight and birth length.⁸ Limache, a semirural agricultural area relatively near Santiago and close to Viña del Mar and Valparaíso, was chosen because: a birth register in the hospital has been kept since the 1970s; paediatric clinical records were kept in the local hospital (Figure 1); and there was demographic information that emigration from this



Figure 1 Paediatric clinical records in the local hospital

area was low so that we would be able to find most participants born in the 1970s still living in Limache and in Olmué, a neighbouring area.

Two grants obtained within a year of each other, in 2001 and 2002, from the Wellcome Trust and the National Research Fund of Chile (Fondecyt) respectively, allowed us to start the project to study asthma and lung function, and later on to study cardiovascular risk factors. The Fondecyt grant was awarded after the study had begun. The staggered start of the two components of the study may explain why the initial sample of the asthma study was 1232 participants whereas the cardiovascular risk component included only 998 participants for whom a blood sample was obtained.

Although the programming and life course events hypotheses are the two main themes of the Limache birth cohort, several other issues are also part of the study, such as socio-economic background, common mental illness, nutritional status, food intake and smoking.

Cardiovascular risk factors

The aim of the first cardiovascular study was to assess the associations between birth weight and length, and their increments during the 1st year of life, with risk factors for cardiovascular diseases (blood pressure, glycaemia, insulin, the Homeostasis

Model Assessment (HOMA), lipoproteins, smoking, obesity) in young adults, and also to explore the possible effect modifier between these growth measures on the outcomes of interest.^{9,10}

In 2010, 10 years after our initial study, we obtained a second Fondecyt grant which also focused on the programming hypothesis, specifically to assess whether an amplification effect of fetal injury on cardiovascular risk factors reported by Barker and colleagues¹¹ can be identified in our cohort, taking into account the increasing variability of blood pressure, insulin resistance and blood lipoproteins with age. This second survey was also concerned with the impact of changes in socio-economic level on health, as social inequalities in Chile although decreasing are extreme.¹² We were also concerned by the epidemic levels of obesity.¹³

Asthma and lung function

The aim of the asthma study was to assess the possible impact of anthropometric measures at birth (weight and length) and 1st-year growth on asthma symptoms and bronchial hyper-reactivity (BHR) to methacholine¹⁴ and lung function.¹⁵ We were also interested: to learn whether variables which may act as proxy measures of the environment, such as infections and overcrowding, would increase the risk of asthma, atopy and BHR;¹⁶ and to study the relationship between socio-economic status and asthma;¹⁷ and the association between obesity and asthma.⁸

Who is in the cohort?

The study was carried out in Limache and Olmué which are located in the Valparaíso Region of Chile, 108 km from the capital city, Santiago. The economy is heavily dependent on agriculture and an increasing leisure industry based on holiday properties ('parcelas'), 10% of the Limache population and 25.3% of Olmué are considered rural, 11% of the population are defined as very poor (families that don't have enough money to cover their basic necessities).¹⁸ The two towns are increasingly becoming commuting towns since a large proportion of the population work in the nearby cities.

The sampling frame consisted of 3092 live birth deliveries in the Limache Hospital between January 1974 and December 1978. The catchment area of the hospital included Limache and Olmué and the agricultural area around these two towns. Most pregnant women delivered their babies in the local hospital, but a small number of them may have delivered in neighbouring hospitals including Valparaíso. A simple random sample of 1232 participants was obtained for our initial study based on statistical power estimates using the effects of birthweight differences on lung function as outcome for the respiratory study. For the cardiovascular study, a sample of 998 of the 1232 selected were studied based also on statistical

power considerations and the resource implications of tracing the participants already studied in the respiratory study.

One quarter (305) of the individuals randomly selected for the study did not participate (Figure 2).¹⁹ They were randomly replaced from the hospital register sampling frame following the same procedure as for the original sample.

How often have they been followed up, and what was attrition like?

The cohort was first assessed between January 2000 and the end of 2002 when the participants were aged between 22 and 28 years. The initial effort was focused on data extraction from the birth register (Figure 3), paediatric clinical notes which provided anthropometric data at birth and the 1st year of life, and diseases diagnosed in the primary care centre. We have just finalized a follow-up study of the cohort which started in June 2010 and ended in December 2012. We have obtained follow-up information for 800 (65%) participants of the initial sample, and 756 of them provided a blood specimen, but we are still trying to get a blood specimen for some of the 43

participants (Figure 2). The data collection in phase 2 has been more resource intensive than in phase 1. Emigration at the beginning of the study was low, with only 11% of participants not located 25 years after birth. However, the economic development of Chile and the family formation period of the study participants have greatly increased the migration of people in the past 10 years; 166 (14%) participants who participated in phase 1 of the study emigrated, and the current address was unavailable in 116 (9.4%) of those who participated in phase 1 (Figure 2). However, 45 (6%) of those who participated in phase 1 and emigrated were traced and participated in phase 2. The percentage not consenting to participate for the latest follow-up continues to be low, 29 (2%), but 115 (9.3%) of those whom we visited on multiple occasions unsuccessfully may also have been unwilling to participate.

The attrition rate was greater for males at 266 (48%) out of 556, than for females, at 166 (25%) out of 676; for those in the poorest group by number of belongings (30% in participants of phase 2 and 41% in non-participants). There was a lower percentage of smokers among participants of phase 2 (54%) than among non-participants (64%). There were also small differences in the attrition rate by blood pressure, total cholesterol and insulin resistance, which

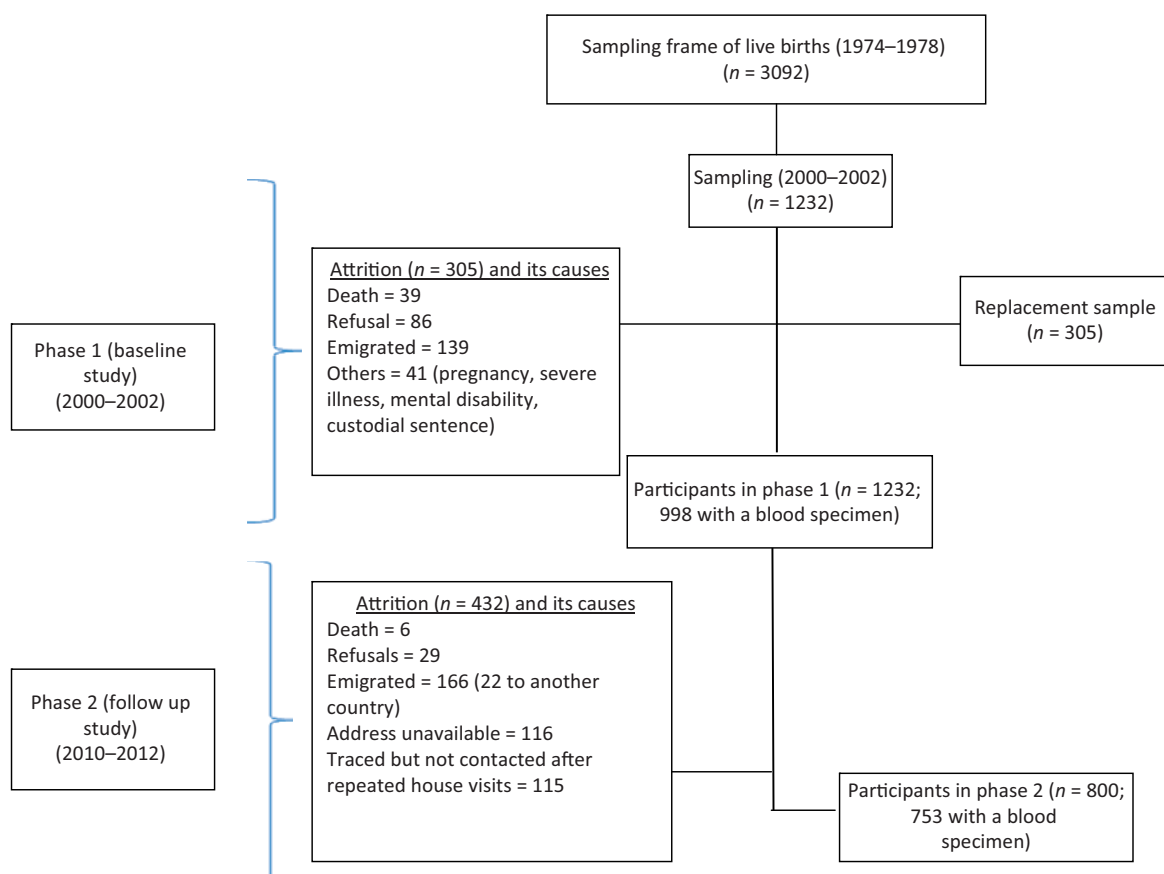


Figure 2 Sampling, participation and attrition rates over the study period of the Limache birth cohort (1974–1978)

Date	Sex	Age	Profession/Occupation
10/10/74	M	10	Handicraft - PVE
11/10/74	M	11	PVE - pintura
12/10/74	M	12	PVE - agricultura
13/10/74	M	13	PVE - agricultura
14/10/74	M	14	PVE - agricultura
15/10/74	M	15	PVE - agricultura
16/10/74	M	16	PVE - agricultura
17/10/74	M	17	PVE - agricultura
18/10/74	M	18	PVE - agricultura
19/10/74	M	19	PVE - agricultura
20/10/74	M	20	PVE - agricultura
21/10/74	M	21	PVE - agricultura
22/10/74	M	22	PVE - agricultura
23/10/74	M	23	PVE - agricultura
24/10/74	M	24	PVE - agricultura
25/10/74	M	25	PVE - agricultura
26/10/74	M	26	PVE - agricultura
27/10/74	M	27	PVE - agricultura
28/10/74	M	28	PVE - agricultura
29/10/74	M	29	PVE - agricultura
30/10/74	M	30	PVE - agricultura
31/10/74	M	31	PVE - agricultura
1/11/74	M	32	PVE - agricultura
2/11/74	M	33	PVE - agricultura
3/11/74	M	34	PVE - agricultura
4/11/74	M	35	PVE - agricultura
5/11/74	M	36	PVE - agricultura
6/11/74	M	37	PVE - agricultura
7/11/74	M	38	PVE - agricultura
8/11/74	M	39	PVE - agricultura
9/11/74	M	40	PVE - agricultura
10/11/74	M	41	PVE - agricultura
11/11/74	M	42	PVE - agricultura
12/11/74	M	43	PVE - agricultura
13/11/74	M	44	PVE - agricultura
14/11/74	M	45	PVE - agricultura
15/11/74	M	46	PVE - agricultura
16/11/74	M	47	PVE - agricultura
17/11/74	M	48	PVE - agricultura
18/11/74	M	49	PVE - agricultura
19/11/74	M	50	PVE - agricultura
20/11/74	M	51	PVE - agricultura
21/11/74	M	52	PVE - agricultura
22/11/74	M	53	PVE - agricultura
23/11/74	M	54	PVE - agricultura
24/11/74	M	55	PVE - agricultura
25/11/74	M	56	PVE - agricultura
26/11/74	M	57	PVE - agricultura
27/11/74	M	58	PVE - agricultura
28/11/74	M	59	PVE - agricultura
29/11/74	M	60	PVE - agricultura
30/11/74	M	61	PVE - agricultura
1/12/74	M	62	PVE - agricultura
2/12/74	M	63	PVE - agricultura
3/12/74	M	64	PVE - agricultura
4/12/74	M	65	PVE - agricultura
5/12/74	M	66	PVE - agricultura
6/12/74	M	67	PVE - agricultura
7/12/74	M	68	PVE - agricultura
8/12/74	M	69	PVE - agricultura
9/12/74	M	70	PVE - agricultura
10/12/74	M	71	PVE - agricultura
11/12/74	M	72	PVE - agricultura
12/12/74	M	73	PVE - agricultura
13/12/74	M	74	PVE - agricultura
14/12/74	M	75	PVE - agricultura
15/12/74	M	76	PVE - agricultura
16/12/74	M	77	PVE - agricultura
17/12/74	M	78	PVE - agricultura
18/12/74	M	79	PVE - agricultura
19/12/74	M	80	PVE - agricultura
20/12/74	M	81	PVE - agricultura
21/12/74	M	82	PVE - agricultura
22/12/74	M	83	PVE - agricultura
23/12/74	M	84	PVE - agricultura
24/12/74	M	85	PVE - agricultura
25/12/74	M	86	PVE - agricultura
26/12/74	M	87	PVE - agricultura
27/12/74	M	88	PVE - agricultura
28/12/74	M	89	PVE - agricultura
29/12/74	M	90	PVE - agricultura
30/12/74	M	91	PVE - agricultura
31/12/74	M	92	PVE - agricultura
1/1/75	M	93	PVE - agricultura
2/1/75	M	94	PVE - agricultura
3/1/75	M	95	PVE - agricultura
4/1/75	M	96	PVE - agricultura
5/1/75	M	97	PVE - agricultura
6/1/75	M	98	PVE - agricultura
7/1/75	M	99	PVE - agricultura
8/1/75	M	100	PVE - agricultura

Figure 3 Birth Register of the Limache Cohort 1974–1978

were explained by the difference in attrition between the sexes. This difference in attrition rate between phases 1 and 2 of the study indicates that analyses should be carried out by weighing by attrition fraction by sex and poverty.

We anticipate that in an eventual third survey in 10 years' time, the emigration out of the area would have diminished as most participants would be settled. However, the building stock in the area has greatly increased and we expect this trend to continue, leading to frequent changes of address within the area and thus increasing the difficulty of tracing the cohort members. Our expectation is that an eventual third survey will be performed using modern communication facilities, as internet and telephone facilities keep improving.

What has been measured?

Table 1 shows the range of variables included in phases 1 (2000–02) and 2 (2010–12) of the study.

Socio-economic background

Socio-economic level was a key variable to measure, but we found it difficult conceptually

to use the information available for young adults in Limache. In our first survey (2000–02), when the cohort members were aged between 22 and 28 years, there was educational homogeneity; most participants completed secondary education but very few pursued further education; and the income of the individual and their family was difficult to interpret because some individuals who were starting a family would appear to be poor but able to manage independently whereas others would appear to have greater resources but were heavily dependent on their family. We needed to balance also the quality of housing with the type of tenancy (ownership, letting, lent house, illegally occupied plot of land, etc.). Thus it was cumbersome to decide for a large proportion of the sample what access to family resources a participant in our study would have. For most of our analyses we used five household belongings to assess socio-economic level: gas-fuelled water heater, personal computer, refrigerator, washing machine and microwave oven, and car ownership.

In the most recent survey (2010–12) many of the variables were retained but more detailed information was requested. For example, in the current study information on 19 items was collected including TV cable, broadband connection and credit card use,

Table 1 Range of variables in the study

	Phase 1 (age 22 to 28 years)	Phase 2 (age 32 to 38 years)
Socio-economic variables		
Full-time education participant	Yes	Yes
Parents	Yes	
Type of working contract	No	Yes
Personal and family income	Yes	Yes, more detailed
Type of house, tenancy and number of rooms	Yes	Yes
Household goods and services	Yes	Yes, more detailed
Family and social support	No	Yes
Anthropometric measurements		
Weight, length or height	Birth, 1st year, 22 to 28 years	32 to 38 years
Body mass index (BMI)	Birth, 1st year, 22 to 28 years	32 to 38 years
Waist circumference and skinfold thickness	Yes	Yes
Food Frequency Questionnaire (FFQ)	Yes, FFQ, mainly on antioxidants	Yes, full FFQ
Smoking behaviour	Yes	Yes
Physical activity (IPAQ questionnaire)	Yes	Yes
Multiple physical symptoms	Yes, in a subsample	No
General health questionnaire-12	Yes, in a subsample	No
Anxiety	Yes, in a subsample	No
Behavioural and mental health items		
Patient Health Questionnaire-9 (PHQ-9)	No	Yes
PHQ-15	Yes, in a subsample	Yes
Generalized anxiety questionnaire (GAD)	No	Yes
Blood markers		
Ferric reducing ability of plasma, uric acid, protein carbonyls, F2 isoprostanes	Yes	No
Glycaemia, insulin, proinsulin, HOMA, lipids	Yes	Yes
Protein C-reactive	No	Yes
Respiratory items		
Symptoms (European Community Respiratory Health Survey (ECRHS))	Yes	Yes, but slightly modified
Bronchial hyper-reactivity to methacholine	Yes	No
Skin prick test	Yes	No
Lung function (FEV ₁) and forced vital capacity (FVC) and the FEV ₁ /FVC ratio)	Yes	No
Other aspects		
Infectious diseases, antecedents of malnutrition in the first years of life	Yes	No
Contact with pets and farm animals in childhood	Yes	No
Parent history of non-communicable diseases	Yes	Yes
Body image	No	Yes
Blood pressure	Yes	Yes

reflecting the unprecedented economic growth of the country in the past 10 years.²⁰ Information on self-perception of socio-economic changes between the two periods was added.

Anthropometric measurements

The measurements at birth were assessed by trained nurses and midwives.²¹ We obtained information on preterm status from the birth register and on duration of pregnancy from clinical records. The clinical notes also provided information on weight and length from birth to 12 months old for most of the participants in the study. Thus we were in the favourable position of having information on length and weight at delivery, during the 1st year of life and in adult life. In adults we have included anthropometric measures in the two surveys: weight, height, waist circumference and skinfold thickness in four sites (Table 1).

Behavioural measures

We included smoking status, food frequency questionnaires, a physical activity questionnaire and mental health status using a variety of tests (Table 1). We decided to include a different set of validated tests of mental status in the latest survey to assess a somatic symptom score [Patient Health Questionnaire-15 (PHQ-15)],²² possible depression (PHQ-9)²³ and possible anxiety [Generalized Anxiety Disorder-7 (GAD-7)].²⁴ The tests of mental health status in the first survey were applied to a subsample only and some were not specific to a condition.²⁵ We have also collected information on what social and family support subjects feel is available to them.

Cardiovascular risk factors:

As shown in Table 1, a wide range of measurements was included such as systolic and diastolic blood pressure, glycaemia, insulin, HOMA, total cholesterol, triglycerides, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol.

Asthma and lung function

We collected a wide range of variables on: respiratory symptoms and measurements (Table 1) using the Spanish version of the European Community Respiratory Health Survey (ECRHS) questionnaire adapted to the Chilean lexicon; bronchial hyper-reactivity to methacholine (BHR) using the tidal breathing method;²⁶ skin prick reaction to eight allergens; and lung function. Total and specific IgE were not included for reasons of cost, but atopy status based on skin prick test was available.

What has it found?

We have published 20 papers (a list is available from the authors).

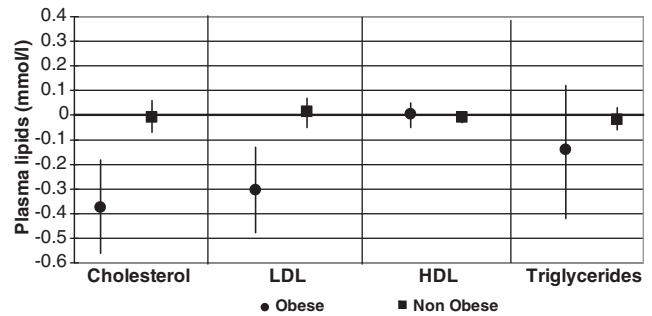


Figure 4 Plasma lipid changes (β coefficient 95% CI) related to the birthweight increase of one Kg in the obese and non obese groups

From the cardiovascular perspective

It is worth noting the high prevalence for cardiovascular risk factors such as cholesterol level above 200 mg/dl (5.2 mmol/l) (25%), insulin resistance (35%) and low HDL cholesterol levels (49%) [40 mg/dl (1.04 mmol/l) in men and 50 mg/dl (1.3 mmol/l) in women]. There was a lower prevalence of hypertension (defined as ≥ 140 mmHg for systolic blood pressure and/or ≥ 90 mmHg for diastolic blood pressure) (6%) and of metabolic syndrome (10%).^{27–29} Smoking was common in our sample (58%), but the number of cigarettes smoked was relatively low [4 (IQR 2 to 9)] and even lower in women,³⁰ and there was a high prevalence of BMI above 25 (50%) and sedentarism (38%).³¹ Data from the 2010–12 follow-up study show that the mean BMI in men was 27.6 and women was 29.3, an astonishing increase of 2.8 units over the past 10 years. Overall this population is characterized by a high risk profile for coronary heart disease and other chronic diseases.

We were able to document an inverse association between birthweight and glycaemia, blood pressure and cholesterol in adult life.^{9,10} These associations were higher in women. There was no association between birthweight and insulin resistance or metabolic syndrome. There was no association between weight at 12 months of age and blood pressure or lipids in adulthood. Obesity among adults who had been heavier in the second 6 months of their 1st year was associated with a higher level of glycaemia.

An interesting finding from our study was the associations between birthweight and levels of total cholesterol and low-density lipoproteins in plasma in those who were obese (Figure 4). These associations were not observed for high-density lipoproteins or triglycerides. These findings were consistent with the results of the Ribeirao Preto study (Brazil).⁹ This example illustrates our efforts to collaborate with other groups sharing anonymized databases. In this study the Chilean group took the lead, but in another study about insulin resistance our Brazilian partners took the lead.¹⁰

Asthma and lung function study

Asthma symptoms were common (27.4% for wheeze and 13.7% for waking with breathlessness); the prevalence of atopy based on skin prick tests to eight allergens was 26.3%, but only 7.8% of the participants had a positive BHR to methacholine.³² Very few associations were found between atopy, wheeze and bronchial responsiveness, and dietary antioxidants.³³

In the aetiological analyses, we found that there was an association between BMI and asthma symptoms, but waist circumference was not associated with asthma symptoms.⁸ Poverty was associated with asthma symptoms, and, in support of the hygiene hypothesis, overcrowding was negatively related to atopy; and atopy with asthma symptoms and BHR.¹⁷ Indoor exposures including tobacco were associated with asthma symptoms.^{30,34} Some evidence was found that a rapid rate of growth in length, especially in newborns of short length, was associated with asthma.¹⁹ BMI and waist circumference in adulthood were negatively associated with FEV₁ and FVC¹⁵ and, among the eight specific allergens, the allergens *D. Pteromyssinus* and dog and cat allergens had the greatest impact on asthma and BHR.¹⁶ The levels of oxidative stress-related biomarkers and antioxidant status in plasma were not related to asthma in the general population in the absence of more severe symptoms or exacerbations.³⁵

What are the main strengths and weaknesses of the study?

This study is one of the few cohort studies in South America based on a representative random sample of newborns between 1974 and 1978. The study has benefited from data available in the hospital birth register and from the clinical notes of infants. The range of health and socio-economic information is comprehensive. At the time when the participants of this cohort were born, malnutrition and poverty in Chile were widespread. Thus this cohort suffered the experience of malnutrition followed by an excess food supply which may have influenced the high prevalence of obesity. Only 7% in the initial survey did not consent to participating in the study. Measurements in adults were taken by trained personnel and the quality of the measurements taken was closely monitored.

An aspect worth noting among the strengths of the study is that it has served as the vehicle for training a large number of professionals. Material from this cohort study has been used or is being used for two PhD and 17 MSc projects, three medical doctors and six undergraduate students with an interest in

epidemiology. We envisage that this spin-off aspect of our study will continue.

Our study is based on a sample with a somewhat restricted socio-economic and educational heterogeneity because extreme poverty does not exist in Limache and the more affluent group is small and did not use the local hospital in the 1970s. Some of the measurements in the birth register and in the clinical notes could have been inaccurate as quality control was unavailable and the variation between measurers is unknown. A major challenge for a future eventual follow-up will be to find a large number of cohort members. We hope that younger colleagues will take up the study and be able to carry out further follow-ups, especially as major health events will start to occur at a higher rate in 20 to 30 years from now. Genetic markers have not been included in the study.

Can I get hold of the data? Where can I find more?

We welcome collaboration on the basis that colleagues can provide similar data or complementary data to contrast findings using similar approaches or to provide an exchange of ideas. Collaboration with Brazilian colleagues has been fruitful in comparing prevalence and aetiology in populations of similar age in relation to insulin sensitivity,¹⁰ lipoproteins,⁹ metabolic syndrome²⁸ and atopic status.³⁶ We do not provide our data to researchers whose aim is to work independently from the team, but we are happy to learn from those who are looking for genuine collaboration.

If you wish to obtain further information on details not included in this paper, please contact the corresponding author at hamigo@med.uchile.cl.

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So far we have obtained three grants, one from the Wellcome Trust (grant 059448Z7) to study the aetiology of asthma and lung function in Chile (2000), and two grants from the National Research Fund of Chile (Fondecyt) to study cardiovascular risk factors (2001 and 2010); grants 1010572 and 1100414 respectively. We are indebted to them for their generosity.

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We are indebted to our colleagues who helped in the data collection, analysis and report writing, and last but not least to the cohort members for their willingness to participate and to trust us.

Conflict of interest: None declared.

KEY MESSAGES:

- The Limache sample is characterized by a high prevalence of smoking, obesity and lack of exercise.
- Birthweight was inversely associated with blood pressure, glycaemia and cholesterol level, albeit only in those who were obese.
- Poverty was associated with severe respiratory symptoms.
- There was only partial support for the hygiene hypothesis and programming hypothesis in relation to respiratory symptoms of young adults.

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