

Addressing geographical variation in the progression of non-communicable diseases in Peru: the CRONICAS cohort study protocol

J Jaime Miranda,^{1,2} Antonio Bernabe-Ortiz,^{1,3} Liam Smeeth,^{1,4} Robert H Gilman,^{1,5,6} William Checkley,^{1,5,7} CRONICAS Cohort Study Group*

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*Members of the CRONICAS Cohort Study Group listed in appendix 1.

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For numbered affiliations see end of article.

Correspondence to

Dr J Jaime Miranda;
jaime.miranda@upch.pe

ABSTRACT

Background: The rise in non-communicable diseases in developing countries has gained increased attention. Given that around 80% of deaths related to non-communicable diseases occur in low- and middle-income countries, there is a need for local knowledge to address such problems. Longitudinal studies can provide valuable information about disease burden of non-communicable diseases in Latin America to inform both public health and clinical settings.

Methods: The CRONICAS cohort is a longitudinal study performed in three Peruvian settings that differ by degree of urbanisation, level of outdoor and indoor pollution and altitude. The author sought to enrol an age- and sex-stratified random sample of 1000 participants at each site. Study procedures include questionnaires on socio-demographics and well-known risk factors for cardiopulmonary disease, blood draw, anthropometry and body composition, blood pressure and spirometry before and after bronchodilators. All participants will be visited at baseline, at 20 and 40 months. A random sample of 100 households at each site will be assessed for 24 h particulate matter concentration. Primary outcomes include prevalence of risk factors for cardiopulmonary diseases, changes in blood pressure and blood glucose over time and decline in lung function.

Discussion: There is an urgent need to characterise the prevalence and burden of non-communicable diseases in low- and middle-income countries. Peru is a middle-income country currently undergoing a rapid epidemiological transition. This longitudinal study will provide valuable information on cardiopulmonary outcomes in three different settings and will provide a platform to address potential interventions that are locally relevant or applicable to other similar settings in Latin America.

INTRODUCTION

In recent years, non-communicable diseases in low- and middle-income countries (LMIC) have received increasingly more global attention by scientists and by public health

ARTICLE SUMMARY

Article focus

- Compare prevalence and risk factors of cardiovascular and chronic obstructive pulmonary disease among three different populations.
- Compare rate of disease progression to hypertension and diabetes from a disease-free baseline status between populations.
- Compare rate of lung function decline between populations.

Key messages

- Our longitudinal study will provide valuable information on cardiopulmonary outcomes in three different settings and will provide a platform to address potential interventions that are locally relevant or applicable to other similar settings in Latin America.

Strengths and limitations of this study

- The CRONICAS cohort is the first longitudinal study in Peru to assess cardiopulmonary risk factors among population from different geographical settings.

advocates and policy makers. Several publications underscore the high burden of disease associated with non-communicable diseases^{1–22} and its economic impact in LMIC.^{23–25} The topic has even reached to the higher political agenda at the United Nations in September 2011.²⁶

Whole determinants of many non-communicable diseases in LMIC are likely to be similar to those in affluent countries, yet population attributable fractions may differ due to differences in risk factor distributions.²⁷ There is urgent need to better characterise current rates of non-communicable disease morbidity and mortality in LMIC to properly assess future projections.²⁸ Most of the current approaches to understand non-communicable disease trends in LMIC are extrapolations of data obtained from

high-income countries; however, since 80% of deaths related to non-communicable diseases occur in LMIC,² generation of local knowledge to address such problems is needed. This has been recommended by WHO in its recent 'Prioritised Research Agenda for Prevention and Control of Non-Communicable Diseases'.²⁹

Peru is a middle-income country where non-communicable diseases are responsible for 42% of total years of life lost³⁰; however, mortality profiles are heterogeneous throughout the country and have rapidly shifted from a pattern dominated by infectious diseases to one dominated by non-communicable diseases and injuries over the last decade.³¹ As with other countries, cardiovascular disease (CVD) risk factors are strongly associated with lower socioeconomic status in Peru.³²⁻³³ Peru's diverse geography along with unequal societal development accounts for different stages of the epidemiological transition in different populations.³⁴⁻³⁵ In the same way, there is limited information about the burden of chronic obstructive pulmonary disease (COPD) in Peru. The PLATINO Study, which excluded Peru, found that the prevalence of COPD varied from 8% to 20% in individuals aged 40 years and older in five large Latin American cities, suggesting that COPD poses a considerable health burden in Latin America.³⁶ Smoking was relatively prevalent (23%–29%) across the five cities included in PLATINO.³⁷ In contrast, in Peru, we have recently found that overall rates of daily tobacco smoking are substantially lower than in other Latin American countries.³⁸ However, other risk factors unique to LMIC such as biomass fuel exposure can contribute equally to the burden of COPD.³⁹⁻⁴⁰

Understanding the effects of rapid urbanisation is one of the grand challenges concerning chronic non-communicable diseases.⁴¹ Peru offers a unique opportunity to assess the impact of geographical variation on non-communicable diseases.

METHODS

Study design and settings

The CRONICAS cohort is a longitudinal study that started in September 2010. This study is currently being performed in three settings in Peru (table 1). Pampas de San Juan de Miraflores is a periurban community located 25 km south of Lima's city centre, with approximately 60 000 people in about 4 km², consisting mostly of Andean immigrants. This area is physically diverse and has experienced significant but unplanned population

growth, with residents living on both low and high ground. The site in Tumbes is located in the northern coast of Peru and comprised by a group of communities with about 20 000 people spread over 80 km², where the traditional agricultural landscape has become intermixed with rapidly growing urban sections. Puno is a city in southeastern Peru, located on the shore of Lake Titicaca. With a population of approximately 150 000 inhabitants, many villages surround the urban area. Use of biomass fuels is highly prevalent in these villages. Houses are made of adobe, and the majority does not have chimneys, with small windows kept closed, especially in the winter, due to the low temperatures at high altitudes.

Study objectives

This study has the following objectives: to compare the (1) prevalence and risk factors of CVD and COPD, (2) rate of disease progression to hypertension and diabetes from a disease-free baseline status and (3) rate of lung function decline between populations.

Participants and selection criteria

All participants had to be aged 35 years and older, be a full-time resident in the area and be capable of understanding procedures and of providing informed consent. Participants who were pregnant, were cognitively incapable of providing informed consent or responding to a questionnaire, had any physical disability that would prevent measurements of anthropometrics and blood pressure and had active pulmonary tuberculosis were excluded. We enrolled only one participant per household.

Fieldwork personnel selection and training

Fieldwork personnel were trained in a course including modules on participant selection, human subjects protection and ethics, informed consent procedures, interviewing, clinical assessment and coding. The modules included formal lectures and demonstrations. Fieldworkers received a copy of an Interviewer's Manual. A team of approximately 30 field interviewers (10 per site) was selected. Additionally, a coordinator for each site was trained in this course. Thus, field personnel and coordinators were capable of conducting interviews and performing clinical assessments.

Sampling method

We identified a sex- and age-stratified random sample (35–44, 45–54, 55–64, ≥65 years of age) of potentially

Table 1 Characteristics of the CRONICAS Study settings

Setting	Degree of urbanisation	Use of biomass fuels	Outdoor air pollution	Altitude
Lima	Highly urbanised	Rare	High	Sea level
Tumbes	Semi-urban	Highly prevalent	Low	Sea level
Puno, urban	Urban	Rare	Low	3825 m above sea level
Puno, rural	Rural	Highly prevalent	Low	3825 m above sea level

eligible subjects. We aimed to enrol 1000 subjects at each location. In Puno, we stratified recruitment to include 500 participants each from the urban and rural settings.

Timeline: enrolment, baseline and follow-up visits

Enrolment and baseline data collection started in September 2010. Follow-up visits will begin in February 2012 and an additional evaluation is planned to start in June 2013.

At baseline, fieldworkers visited households to contact potential participants, verify inclusion and exclusion criteria, invite them to the study, read consent forms, apply questionnaires to participants and make an initial appointment for clinical evaluation. If potential participant was not found after three visits, a subject from the same age and sex group was randomly selected for replacement. The team had the responsibility to complete all clinical measurements and laboratory blood samples following standardised protocols. Recruitment of participants continued until the age- and sex-specific sample size was reached.

Follow-up visits will be conducted at 20 and 40 months from enrolment. Sub-sections of the questionnaire as well as anthropometry, blood pressure and spirometry will be performed in all three visits. Blood sample collection will be undertaken only at baseline and at 40 months.

Study procedures

Questionnaires, informed consents, clinical forms and blood samples were labelled using alphanumeric codes to identify the site and participant.

Questionnaires

After informed consent was obtained, participants responded to a face-to-face questionnaire applied by a trained community health worker using paper-based formats. Data collected included several factors potentially associated with CVD and COPD, such as age, sex, years of education and other socioeconomic variables, smoking and alcohol habits, cardiovascular and respiratory symptoms, biomass fuel use and physical activity patterns. We used a modified version of WHO's STEP approach questionnaire for surveillance of non-communicable disease.⁴² Detailed information regarding sections and topics of the questionnaire is in [table 2](#). In addition to the detailed survey, a rejection questionnaire comprising relevant questions to assure comparability between participants and non-responders was also applied to those who refuse to participate.

Phlebotomy and laboratory analyses

A trained technician explained procedures for sample collection and then participants were asked to provide venous blood sample for specific tests (see [table 3](#)) in fasting conditions, at least 8 but <12 h. New appointments were scheduled if the fasting period was not appropriate. A total of 13.5 ml of blood were collected.

Table 2 Sections and topics of the questionnaire in the CRONICAS Study

Type of data	Components
Demographic assessment form:	<ul style="list-style-type: none"> – Place and date – Language and informed consents – Contact information
Socioeconomic assessment form:	<ul style="list-style-type: none"> – Demographic information – Family and expenses – Household information – Biomass fuel use
Lifestyle assessment form:	<ul style="list-style-type: none"> – Short version of food frequency questionnaire – Salt consumption – Dietary behaviour questionnaire – Tobacco use and smoking – Alcohol use – Self-perception about health and obesity – Physical activity
Neighbourhood walkability form:	<ul style="list-style-type: none"> – Stores and facilities in the neighbourhood – Crime and traffic safety – Neighbourhood cohesion – Support
Mental health form:	<ul style="list-style-type: none"> – Depressive symptoms – Anxiety
Migration assessment form:	<ul style="list-style-type: none"> – Migration – Language use
Treatment assessment form:	<ul style="list-style-type: none"> – Cardiovascular medication – Pulmonary medication
Cardiovascular form:	<ul style="list-style-type: none"> – Personal and familial history – Stress chest pain – Intermittent claudication
Respiratory symptoms form:	<ul style="list-style-type: none"> – Respiratory symptoms – Sleep disorders – Snoring and apnoea
Biomass exposure form:	<ul style="list-style-type: none"> – Cooking – Type of cook stoves – Use of cook stoves – Biomass fuel use
Clinical examination:	<ul style="list-style-type: none"> – Anthropometric assessment form – Blood pressure assessment form – Ankle– brachial index form – Spirometry test form

Plasma glucose was measured using an enzymatic colorimetric method (GOD-PAP; Modular P-E/Roche-Cobas, Grenzach-Whylen, Germany), serum insulin using electrochemiluminescence (Modular P-E/Roche-Cobas), highly sensitive C reactive protein using Latex (Tina-quant CRP-HS Roche/Hitachi analyzer, Indianapolis, IN, USA) and haemoglobin A1C using high-performance liquid chromatography (D10, BioRad, Munich, Germany), which is traceable to the Diabetes Control and Complications Trial reference study as certified by the National Glycohemoglobin Standardisation Program. All samples were analysed in a single facility, and, for quality assurance, the quality of assays was checked with regular external standards and internal duplicate assays and monitored by BioRad (<http://www.>

Table 3 Information about biological tests and sample type

Test	Units	Sample type
Haemoglobin	g/dl	Whole blood
Glycated haemoglobin	%	Whole blood
Fasting glucose	mg/dl	Plasma with Na fluoride
Insulin	μU/ml	Serum
Total cholesterol	mg/dl	Serum
HDL cholesterol	mg/dl	Serum
LDL cholesterol*	mg/dl	Serum
Triglycerides	mg/dl	Serum
C reactive protein (HS)	mg/l	Serum

*Calculated using Friedewald equation. In individuals with triglycerides >400 mg/dl, LDL was measured in serum. HDL, high-density lipoprotein; HS, high sensitive; LDL, low-density lipoprotein.

biorad.com). Information about sampling process is detailed in figure 1.

Clinical assessment

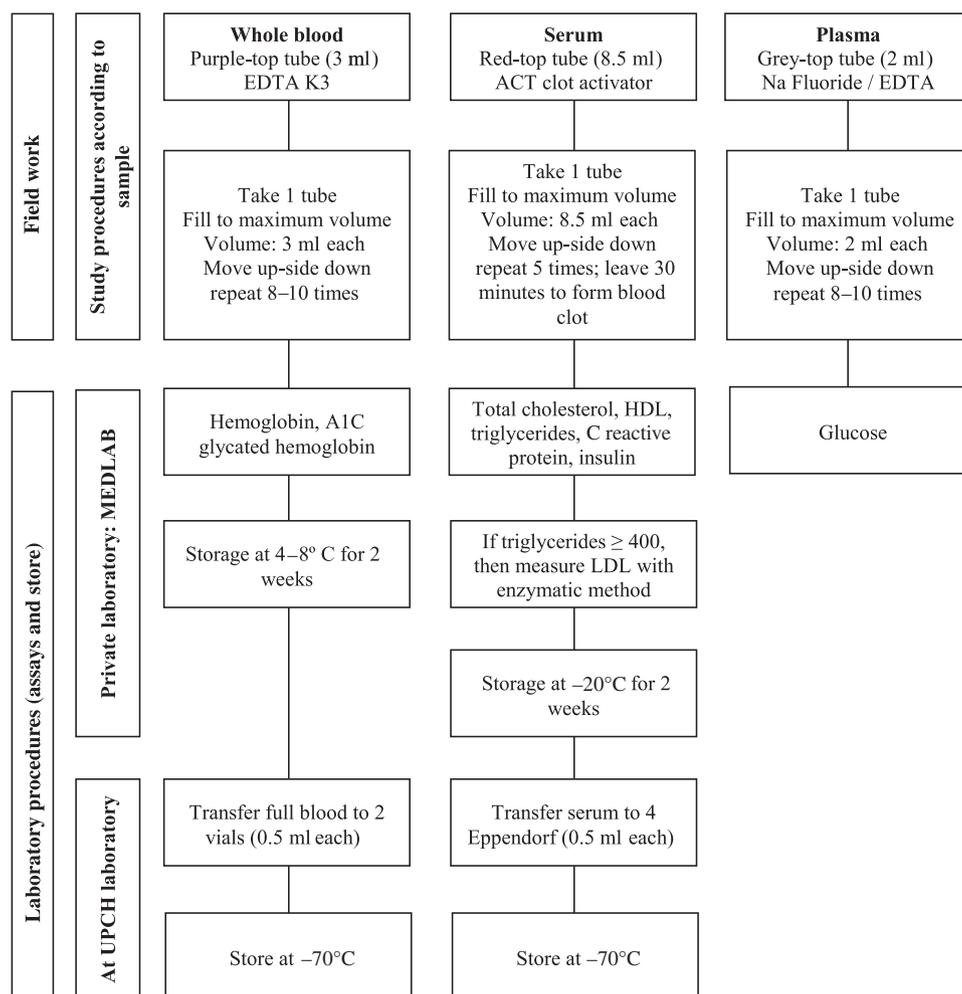
We measured standing and sitting height, waist and hip circumference in triplicate using standardised techniques, heart rate, systolic and diastolic blood pressure were in triplicate using an automatic monitor OMRON

HEM-780, previously validated for adult population.⁴³ Ankle–brachial index, a marker of subclinical atherosclerosis that predicts the risk of future vascular events,⁴⁴ was also measured using the same device. We measured weight and bioelectrical impedance using the TBF-300A body composition analyzer (TANITA Corporation, Tokyo, Japan). Measurements were carried out according to manufacturer’s specifications.

Spirometry

We measured lung function using the Easy-On-PC spirometer (nidd, Zurich, Switzerland; <http://www.nidd.ch>). This device uses a flow metre that is not affected by changes in barometric pressure and therefore independent of gas density and suitable for use at high altitudes. We trained technicians to comply with the joint European Respiratory Society and American Thoracic Society guidelines.⁴⁵ After training, three of the most skilful technicians were selected to perform procedures. In addition, we had a centralised quality control system in which all tests were graded according to standard guidelines⁴⁶ to ensure that data collected is of highest quality. Regular calibration checks were performed. We also provided feedback to fieldworkers regarding spirometry activities. We recorded forced vital capacity (FVC), forced expiratory volume in one second (FEV₁) as well as store individual flow–volume curves for

Figure 1 Flow chart of biological samples processing at laboratory.



quality control assessment and further analysis. All patients underwent bronchodilator-response testing. We administered two puffs from a salbutamol inhaler (100 mcg/puff) via a spacer and repeated spirometry 10–15 min later (a generic salbutamol inhaler was used for this project).

We did not perform spirometry to any subject who had surgery of heart, chest, lungs or eyes in the past 3 months, or heart attack in the past 3 months, and a blood pressure greater than 180 (systolic) or 100 (diastolic). We did not use bronchodilators in participants with a heart rate >120 beats for minute. We rescheduled spirometry at a later date for participants who reported having a respiratory infection in the last 2 weeks, who had used a short-term bronchodilators in the last 4 h or a long-term bronchodilators in the last 12 h or who had smoked in the last hour.

Measures of indoor air pollution

In the second round of assessments, we plan to measure particulate matter (PM) in a random sample of 10% of households (100 per site) by placing PM monitors in the kitchen area. Average PM concentrations will be measured with the DataRAM pDR-1000 (Thermo Fisher Scientific, Waltham, Massachusetts, USA). We expect to collect PM data over a 48 h period. We will also assess aspects of household ventilation by measuring size of room and any windows or doors, as well as noting their state (open or closed) and the location of the kitchen and proximity to the living space. We will also record whether there is a fan in the room and if it was used during the 48 h of data collection.

Study outcomes

The primary outcomes for the baseline assessment are prevalence of major risk factors for cardiopulmonary diseases. The primary outcomes for the follow-up include longitudinal changes in blood pressure, blood glucose and lung function over 40 months. We will also be able to assess traditional risk factors for CVD and COPD in all follow-up visits.

Hypertension rates will be calculated using the average of the second and third blood pressure measures. Hypertension will be defined as the systolic blood pressure ≥ 140 mm Hg, and/or diastolic blood pressure ≥ 90 mm Hg, and/or self-report of current use of anti-hypertensive drugs.⁴⁷ Diabetes mellitus will be defined as a fasting glucose ≥ 126 mg/dl (or ≥ 7 mmol/l) or self-report of physician diagnosis and currently receiving antidiabetic medication.⁴⁸ As local references do not exist, we will define COPD as the presence of airflow limitation characterised by $FEV_1/FVC < 70\%$.^{49–50} We will define reversibility as an improvement of >12% or >200 ml in baseline FEV_1 or FVC in the post-salbutamol assessment.⁵¹

Sample size and power

Calculations for CVD outcomes were derived using prevalence estimates of hypertension from PERU MIGRANT Study.^{38–52} Prevalence in urban (Lima),

migrant and rural groups was 30%, 13% and 12%, respectively. With 1000 people in each study site, the study would have power $\geq 80\%$, at the 5% significance level, to detect a 3% absolute difference in the prevalence of progression to hypertension between the sites over 4 years (ie, 8% will develop hypertension in Lima, 5% in Puno and 2% in Tumbes).

To calculate the sample size for determining a difference in prevalence of COPD between site, we assume a prevalence ranging from 6% in Lima to 12% in Tumbes or Puno, with 5% significance and 90% power. We estimate a sample size of approximately 509 participants per site.

Sample size calculations for lung function assessment over time included parameter and variances estimates from the UPLIFT trial,⁵³ a 4-year study of tiotropium in COPD, using the following model:

$$\frac{FEV_{1ij}}{height_{ij}^2} = \beta_0 + \beta_1 t_{ij} + b_{0i} + b_{1i} t_{ij} + \varepsilon_{ij},$$

$$b_i \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_0^2 & \sigma_c \\ \sigma_c & \sigma_1^2 \end{pmatrix}\right) \text{ and } \varepsilon_{ij} \sim N(0, \sigma^2 I).$$

In this model, FEV_1 is expressed in millilitres and height in metres. The outcome is equivalent to a height-adjusted FEV_1 . FEV_1 is also affected by age, and this relationship is unlikely to be linear. However, we assume that the rate of decline over 40 months for each individual will be approximately linear. The values t_{ij} represents the j th measurement time for the i th participant. The β s are the regression parameters, and b_i is the random effects. We used estimates obtained for male participants given that 75% of trial participants were male and that these estimates are likely to have the least amount of variability given the sample size of about 4000 participants. To calculate the sample size needed to detect a difference in our study from UPLIFT estimates, we used the following equation:

$$n_{new} = \frac{SE_{\beta_1}^2(UPLIFT)}{SE_{\beta_1}^2(new)} \left(\frac{L_{UPLIFT}}{L_{new}}\right)^2 n_{UPLIFT},$$

where n_{new} is the sample size for our study; n_{UPLIFT} is the sample size in UPLIFT trial; the SEs are the estimate of the SE for the expected β_1 in our study and in UPLIFT, respectively and L is the follow-up duration in our study and in UPLIFT. Since we expect to follow all individuals for approximately 4 years, our study duration is similar to that of UPLIFT. We obtained the sex-stratified estimates from UPLIFT investigators.⁵³ The SE for our study can be estimated as:

$$SE_{\beta_1}(new) = \frac{\widehat{\delta\beta_1}}{Z(1 - power) - Z(\alpha)},$$

where δ is the per cent difference between sites, $\hat{\beta}_1$ is the estimate of annual decline in FEV₁ estimated from UPLIFT, $Z_{(1-\text{power})}$ and $Z_{(\alpha)}$ are the associated power and confidence level. Therefore, to detect a 50% change in the rate of decline in FEV₁/height² between sites with 5% significance and 90% power requires a total of 332 participants at each site followed longitudinally for 48 months. We assume that the rate of lung function decline for Tumbes will be similar to that of Lima. Assuming at 20% loss to follow-up, this would require approximately 400 participants. Even if we reduce the overall rate of decline in lung function by 25%, this would only increase the sample size requirement to 590 participants. Assuming at 20% loss to follow-up, this would require approximately 700 participants.

Statistical methodology and analysis

Following double data entry and careful data cleaning and consistency checking, descriptive statistics using tabulations and graphical methods will be performed. Direct standardisation to WHO standard population⁵⁴ will be used to calculate age-standardised prevalences by specific age groups. Standardised mean differences, a unit-free comparison technique, will be used to evaluate the magnitude of difference between risk factors.^{55 56} The analysis will take into account the stratified nature of the sample at all stages and the repeated measures in individuals.

Logistic regression (for binary outcomes) and multi-variable linear regressions (for continuous normally distributed outcomes) will be used to assess the relationship between urbanisation and major cardiovascular and COPD risk factors. Appropriate longitudinal data methods will be used for the assessment of disease progression from baseline disease-free status to disease at follow-up. Multivariable models will look for risk factors that explain the relationship, such as blood pressure or fasting glucose when appropriate, body mass index, fasting total cholesterol, alcohol consumption, smoking status, regular exercise, income and other socioeconomic indicators as well as area of residence, will be pursued. Multilevel analysis to compare disease progression for site will be also considered.

Ethical aspects

This protocol and informed consent forms were approved with respect to scientific content and compliance with applicable research and human subjects' regulations. Protocol and consent forms were reviewed and approved by Institutional Review Boards at Universidad Peruana Cayetano Heredia and Johns Hopkins University.

All investigators and personnel in the study have completed a training course in ethics and human subjects protection, certified by the National Institutes of Health. Informed consents were verbal because of sites included in this study were semi-urban and rural with

significant rates of illiteracy; thus, interviewer signed the form to document participants' approval.

DISCUSSION

This work emphasises the need of studies in different parts of the world, especially in LMIC to understand and assess non-communicable diseases and their risk factors. Peru is a very diverse country with different rates of urbanisation; thus, progression towards non-communicable conditions can vary widely from one geographical area to another. To our knowledge, two different cohorts are assessing non-communicable diseases in Latin America. The first one, the ELSA Study, a Brazilian cohort, has involved 'white-collar' volunteers to evaluate cardiovascular events.⁵⁷ The second one, the CESCAS I Study, has started a cohort of participants focused in urban settings from Argentina, Chile and Uruguay to obtain CVD incidence using a multistage probabilistic sample.⁵⁸

The burden of non-communicable in LMIC is only expected to increase, yet limited data are available in these settings. Extrapolation of trends using data from high-income countries, where age profiles, risk factors and body composition differ, is unlikely to provide reasonable estimates or public health strategies to decrease disease burden. Generation of local knowledge to address such problems is needed to measure the magnitude of the problem, assess risk factors, which might be completely different from developed countries, and identify high-risk groups.⁵⁹ The CRONICAS cohort has established a large cardiopulmonary cohort of adults, who will be followed-up over at least 4 years, with the possibility of longer term follow-ups and thus establishing itself as a unique resource arising from one LMIC in an area of major public health concern.

There are several strengths that distinguish our study from other large-scale studies in Latin America. On the cardiovascular side, the assessment of risk using scores derived from developed countries has shown limitations in developing societies and may have limited application in settings like Peru. Determination of non-communicable disease epidemiology requires context-specific evaluation and follow-up of subjects over time, and this information is not available for Peru. On the pulmonary side, our study findings will complement that of BOLD and PLATINO as we will be able to provide an evaluation of longitudinal assessments of lung function across several settings according to degree of urbanisation, levels of outdoor and indoor air pollution and altitude. Specifically, our research will expand on the knowledge base of the epidemiology of lung function in LMIC with a high prevalence of biomass fuel exposure. Moreover, our data can also be used to generate local references for lung function among healthy, non-smoking non-biomass fuel-exposed adults, which currently do not exist for Peru. Most importantly, the uniqueness of geographical settings, the variety of stages of urbanisation, the long-term design of the study in an

LMIC and the integration of cardiovascular- and pulmonary-related assessments will generate comprehensive data that will, in turn, provide important advances for public health and for the field of non-communicable diseases in LMIC.

In Peru, according to WHO's 2011 non-communicable diseases country profile, there is no data regarding behavioural risk factors, especially in current daily tobacco smoking and physical inactivity prevalences.⁶⁰ In addition, this report highlights the lack of an integrated policy programme for CVD, chronic respiratory diseases, diabetes, cancer, alcohol, tobacco, unhealthy diet, obesity and physical inactivity.⁶⁰ Therefore, reducing the impact of non-communicable diseases will require alliances between different groups of research beyond national boundaries. With the support of the National Heart, Lung, and Blood Institute, we have the opportunity to establish initial steps towards an appropriate surveillance system for chronic diseases in Peru. The information gathered in this protocol will provide a strong platform to address potential interventions that are locally relevant and that could be applicable to other settings in Latin America, other LMIC and eventually potentially relevant for Latin population in the USA.

Author affiliations

¹CRONICAS Center of Excellence in Chronic Diseases, Universidad Peruana Cayetano Heredia, Lima, Peru

²Department of Medicine, School of Medicine, Universidad Peruana Cayetano Heredia, Lima, Peru

³Epidemiology Unit, School of Public Health and Administration, Universidad Peruana Cayetano Heredia, Lima, Peru

⁴Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK

⁵Department of International Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, USA

⁶Área de Investigación y Desarrollo, Asociación Benéfica PRISMA, Lima, Peru

⁷Division of Pulmonary and Critical Care, School of Medicine, Johns Hopkins University, Baltimore, Maryland, USA

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Competing interests None.

Patient consent Obtained.

Contributors JJM and AB-O drafted the first version of the manuscript. JJM, LS, RHG and WC conceived, designed and supervised the overall study. All authors participated in writing of the manuscript, provided important intellectual content and gave their final approval of the version submitted for publication.

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APPENDIX 1
CRONICAS cohort study group (members listed in alphabetical order)

Cardiovascular Disease: Antonio Bernabé-Ortiz, Juan P Casas, George Davey Smith, Shah Ebrahim, Raúl Gamboa, Héctor H García, Robert H Gilman, Luis Huicho, Germán Málaga, J Jaime Miranda, Víctor M Montori, Liam Smeeth; Chronic Obstructive Pulmonary Disease: William Checkley, Gregory B Diette, Robert H Gilman, Luis Huicho, Fabiola León-Velarde, María Rivera, Robert A Wise; Training & Capacity Building: William Checkley, Héctor H García, Robert H Gilman, J Jaime Miranda, Katherine Sacksteder.