Detection and Follow-up of Cardiovascular Disease and Risk Factors in the Southern Cone of Latin America. The CESCAS I study

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Title

Detection and Follow-up of Cardiovascular Disease and Risk Factors in the Southern Cone of Latin America. The CESCAS I study

Abstract

Objectives

Cardiovascular diseases (CVD) are increasing throughout the world and are the cause of almost 16.7 million deaths each year, of which 80% occur in low and middle-income countries. In Argentina, Chile and Uruguay the available data about cardiovascular risk factors come predominantly from cross-sectional studies that are principally based on self-reporting or studies conducted with small convenience samples, which do not give precise estimates. The CESCAS I study will generate reliable estimates of the prevalence, distribution, and secular trends of CVD and its risk factors in this region.

Methods and results

CESCAS I is an observational prospective cohort study. This study entails a multistage probabilistic sample of 8000 participants between the ages of 35 and 74 years old from four mid-sized cities representing the Southern cone of Latin America: two in Argentina (Bariloche and Marcos Paz), one in Chile (Temuco), and one in Uruguay (Pando-Barros Blancos). In the first phase, baseline data will be collected regarding exposure to risk factors and prevalence of CVD. Baseline data collection is conducted in two stages: 1) household and 2) health center, in order to collect information on medical history, risk factors, lifestyles, and health utilization through specific questionnaires, physical measurements, electrocardiogram and an

overnight, fasting blood sample to measure levels of serum lipids, glucose, and creatinine. In the second phase, annual follow-up data will be obtained on the incidence rate of CVD events and the association between exposure and events.

Conclusions

The lack of follow-up studies prevents our countries from implementing risk factor stratification and management strategies at a population level. The CESCAS I study data will contribute to the improvement of public health strategies based on the application of primary care interventions, thus helping to improve cardiovascular health in this region.

Article Summary

Article Focus

- Estimate the prevalence, distribution, and secular trends in major CVD events and risk factors in four cities in Argentina, Chile and Uruguay.

Key Messages

- Lack of follow-up studies prevents our countries not only from assessing local risk estimates and obtaining reliable data for burden of cardiovascular disease, but also from implementing risk factor stratification and management strategies at a population level.
- There is a strong need in the region to build the capacity and infrastructure to undertake a population based cohort study to address the knowledge gaps and to inform policy-making on the impact of CVD in the Southern Cone of Latin America

Strengths and limitations of this study'

- CESCAS I will be the first study to estimate the longitudinal trend of CVD and risk factors in Argentina, Chile and Uruguay

Introduction

Cardiovascular diseases are increasing throughout the developing world and are the cause of almost 16.7 million deaths each year, of which 80% occur in low and middle-income countries. (1) In fact, CVD deaths represent 34% of the total annual mortality rate. (2) It has been projected that in 2015, 41 million people world-wide will die of chronic diseases if effective concerted actions are not put into place for their prevention and treatment. (3) In low and middle-income countries, almost half of these deaths will occur in people younger than 70 years old, compared with only 27% amongst corresponding age groups in high-income countries.(4) Furthermore, although in recent decades age-adjusted rates for cardiovascular mortality have diminished in developed countries, rates have increased in low and middle-income countries. (1, 5)

In Latin America, it is estimated that from 1990 until 2020, death from CVD, including coronary heart disease (CHD) will increase by approximately 145% (for both men and women), compared with an increase of 28% for women and an increase of 50% for men in developed countries during the same period. (6) Moreover, at least 75% of CVD may be explained by more proximal risk factors like unhealthy diet, low physical activity and tobacco use. (7)

In the World Health Report 2002 (WHO), 26 risk factors were evaluated and ranked by their importance. Major risk factors identified for most Latin American

countries were hypertension, an elevated body mass index, and alcohol and tobacco use. (8) The Latin American INTERHEART study showed that the majority of cardiovascular risk in the Southern Cone could be explained by tobacco use, abnormal lipids, abdominal obesity and high blood pressure. (9) In Argentina, recent estimates showed that more than 600,000 Disability Adjusted Life Years (DALY) and almost 400,000 Years of Potential Life Lost (YPLL) were lost in 2005 due to CHD and stroke, where modifiable risk factors explained 75% of fatal and non-fatal acute CHD and stroke events, 82% of acute CHD events and 62% of strokes. Similarly, modifiable risk factors explained 76% of costs due to acute events and 71% of DALY lost.(10) In Argentina, Chile and Uruguay the available data about CVD risk factors come predominantly from cross-sectional studies that are principally based on self-reporting or studies conducted with small convenience samples, which do not give reliable estimates. (11-13). None of these studies mentioned above utilized a prospective follow-up. While the ongoing ELSA study, a recently established cohort in Brazil, will provide data on cardiovascular events, its population is composed of employee volunteers from 6 Brazilian universities, and thus it will not be able to offer population-based estimates of the impact of CVD risk factors on the incidence of CVD (14)

The CESCAS I study will generate reliable estimates of prevalence, distribution, and secular trends in CVD and its risk factors in this region. These data will contribute to the improvement of public health strategies thus helping to improve cardiovascular health in Latin America.

Methods

Study Design

CESCAS I is an observational, prospective cohort study initiated in November 2010. The study is composed of two phases. In the first phase, baseline data will be collected regarding exposure to risk factors and prevalence of cardiovascular disease. In the second phase, annual follow-up data will be obtained on the incidence rate of CVD and the association between exposure and the event.

Study Population

This study entails a probabilistic sample of 8000 non-institutionalized mainly urban men and women, between the ages of 35 and 74 years old representing the general adult population in Argentina, Chile and Uruguay. Four mid-sized cities were selected: two in Argentina (Bariloche and Marcos Paz), one in Chile (Temuco), and one in Uruguay (Pando-Barros Blancos).

Sampling Method

As the prevalence of CVD risk factors is considered likely to vary by age, gender, and geographic area, the sampling method was stratified accordingly, following a complex sampling design that consisted of four stratified stages to obtain a representative sample from each of these locations (Figure 1). The first stage consisted in randomly sampling census radii from each location, stratified by socio-economic level. In the second stage a number of blocks proportional to the radius size were randomly selected. The third stage sampled households from each block using systematic sampling. If the selected house did not include a permanent residence (for example, weekend or business housing, abandoned or demolished

dwellings, those under construction, or addresses which were not identified) this was replaced by another house. In the selected households all members between 35-74 yrs old were listed to create the final sampling frame. In the fourth stage one listed member per household was randomly selected. The final sampling frame was composed of one subject per household, stratified by gender (50% women and 50% men) and age categories (35-44, 45-54, 55-64, and 65-74 years old) constituting a total of 2,000 subjects per site, all of them meeting the following criteria: a permanent resident at the location for at least 6 months per year, willing to sign a written consent to participate, not expressing an intention to relocate within the next two years, and able to respond autonomously to the questionnaire (without cognitive impairment or language problems) . Replacement of selected participants because of refusal to participate or inability to be located was not allowed. (15, 16)

Recruitment Plan

Participants are invited to participate through a letter from the site institution. The interviewer makes the first contact with the household and arranges an appointment for a home visit to collect questionnaire data and schedule a follow-up clinical visit. A clinical visit is scheduled to obtain physical measurements, an electrocardiogram (EKG) and overnight fasting blood samples. To minimize non-participation and the potential for bias in the results, the following measures will be taken to facilitate and encourage the participation:

•Travel assistance or home assessment for those unable to travel to the examination centers.

•Variety of appointment times to suit all members of the community.

•Feedback of blood test and examination results to participants.

Data collection

Baseline data collection is conducted in two stages: household and health center. In the household, an interviewer conducts a survey to collect the required information through specific questionnaires. Once the survey is complete, the interviewer proceeds to arrange the visit to the health center where the physical measurements, EKG and blood sample is obtained.

Questionnaires

A trained interviewer gathers information regarding participant characteristics including demographic, socioeconomic and health care utilization data, personal and family history of CVD and risk factors like high blood pressure, dyslipidemia, diabetes, as well as current pharmacologic and non-pharmacologic treatment. Data are also collected regarding intermittent claudication, cancer, respiratory disease, alcohol consumption and weight history using cross-culturally adapted questionnaires from the Hispanic Community Health Study / Study of Latinos (HCHS/SOL) study (17). Physical activity will be assessed through the HCHS/SOL study questionnaire adapted from the International Physical Activity questionnaire (IPAQ). (18) Information about current and former cigarette smoking, including age at which smoking was initiated, years of smoking, amount of cigarettes smoked per day, cessation attempts and treatments will be assessed using the Global Adult Tobacco Survey (GATS).(19) Use of other forms of tobacco, exposure to passive cigarette smoking and indoor pollution will also be assessed. Nutrition information will be collected using a semi-quantitative food frequency questionnaire (FFQ)

adapted from the National Cancer Institute Diet History Questionnaire, which has been validated by our research team to be used in Argentina, Chile and Uruguay. (20) Depression and anxiety will be assessed by the 9 item Patient Health Questionnaire (PHQ-9) (21), which has been validated in Argentina. (22). Stressful events and spirituality will be assessed through the HCHS/SOL study questionnaire, cross-culturally adapted (17).

Locally validated versions of the SF-12 and EQ5D are used to measure health-related quality of life and social utilities and preferences, respectively (23, 24). All the questionnaires used in the study and their sources can be seen in Table 1.

Blood Pressure and Anthropometric Measurements

Trained and certified observers will measure blood pressure (BP) during the health center visit following the recommendations of the American Heart Association (25). According to study protocol, before BP is measured, the participant remains seated and at rest for 5 minutes. Tea, mate or coffee consumption, as well as smoking or exercising, in the 30 minutes prior to the testing are not permitted. A standardized mercury or aneroid sphygmomanometer with an adequate cuff size will be used. The cuff will be placed on the right arm of the participant, inflated to 10 mm Hg, and then must be inflated until reaching a pressure of 30 mmHg above the level at which the radial pulse can no longer be palpated. Three measurements are obtained, with 30 seconds intervals between them. Korotkoff sounds are recorded, and used to identify systolic and diastolic BP.

The weight measurement will be obtained with undergarments and without shoes. The weight will be recorded in kilograms to one decimal place, using standing scales supported on a steady surface.

The height measurement will be recorded without shoes, in centimeters to one decimal place, on a Frankfort plane positioned at a 90-degree angle against metallic metric tape mounted on the wall. The abdominal circumference measurement will be recorded in centimeters to one decimal place, on a horizontal plane at 1 cm above the belly button that generally coincides with the narrowest circumference.

Laboratory Measurements

Overnight, fasting blood samples are drawn by venipuncture to measure levels of serum lipids, glucose, and creatinine. The samples will be processed and temporarily stored at the extraction site to be sent later for analysis and storage (in ultra freezers at -80°C) in the central laboratory at the Hospital Italiano of Buenos Aires. LDL cholesterol levels will be calculated utilizing the Friedewald equation for the participants who have a triglyceride level <400 mg/dL. According to this equation, total LDL cholesterol is equal to: total cholesterol – HDL cholesterol – triglycerides/5.

Electrocardiogram

The study will employ a 12-lead EKG standardized at 25 mm/sec and at 1 mV of amplitude.

Study outcomes

Hypertension is defined as the mean systolic BP ≥140 mm Hg, and/or diastolic BP≥90 mm Hg, and/or self-report of current use of antihypertensive medications. (26). Obesity was defined as BMI ≥ 30 kg/m^2 and overweight was defined as BMI ≥ 25kg/m^2. (27-30). Dyslipidemia is defined as a total cholesterol ≥ 200 mg/dL or 11.1 mmol/l, or LDL cholesterol ≥130 mg/dL or 7.2 mmol/l or HDL cholesterol <40 mg/dL or 2.2mmol/L.(31). Diabetes mellitus is defined as a fasting glucose ≥126 mg/dL or 7 mmol/l. Glucose intolerance is defined as a fasting glucose levels between 110 mg/dL and 125 mg/dL or 6.1 mmol/L to 6.9 mmol/L.(32) Current smoking is defined as smoking at least one cigarette per day at the time of the survey. Former-smoking is defined as a person who has been a smoker and does not smoke at the time of the survey. Passive smoking is defined as involuntarily breathing air that is contaminated by tobacco smoke. (28, 33) During the follow-up a person is categorized as having CVD if self-reported or their self-assigned proxy reported any of the following conditions diagnosed by a physician: CVD death, acute myocardial infarction, angina, heart failure, cerebro-vascular events, peripheral vascular disease or coronary or peripheral revascularization. The study Outcome Committee will review the source documents collected related to the reported event and adjudicate all CVD outcomes independently.

Training and Quality Assurance

Field work quality assurance

Data collection will be conducted following the standardized operations manual. Between 5 and 10% of participants will have repeated measurements of arterial pressure, height, weight and waist circumference to adjust for the effect of measurement error on selected variables. All the equipment used will be certified by international standardization norms. Periodic monitoring of data collection procedures will be performed by the coordinating center.

Laboratory quality control

All laboratory measurements (total cholesterol, HDL, LDL, triglycerides, glucose and plasma creatinine) will be performed by the central laboratory. Every laboratory technician must complete a training program.

Processing of data

The database was designed using the "OpenClinica" system. (34). This is a computerized system of related databases with web interface. The data will be entered from each site, via the web, into electronic forms. Double data entry with independent operators will be performed to eliminate data entry errors. The data will be stored on a central server. Validation rules will be generated in accordance with the nature of the variables. Automatic queries will be generated in response to out-of-range entries to be investigated by study personnel at each site.

Statistical Analysis

Sample size

The calculated sample size is 8000 participants (2000 per site) which is consistent with the recommended requirements for precision for complex surveys. This sample will be sufficient to provide precise estimates of the prevalence of major CVD risk factors by gender and site, in four age-defined categories: from 35 to 44, 45 to 54, 55 to 64 and 65 to 74 years old, as well as their association with the development of CVD (35-37). The proposed sample size is sufficient to comply with precision requirements of a complex sample that assumes that the design effect is 1.5 and the prevalence of the risk factors of interest is 5% or greater (Table 2).

For analysis, the capacity to detect risk factors was calculated using a statistically significant alpha level of 0.05 and a statistical power of 85%, which will permit detection of moderate and large relative risks.

Statistical Analysis

General characteristics of the population will be described. For continuous variables, mean and median, range, standard deviation, and/or quartile range will be calculated according to the distribution of each variable. In the case of categorical variables, absolute and relative frequencies will be calculated.

In order to determine the prevalence and incidence of risk factors, CVD events and the association between risk factors and CVD events, the design effect of the first stage unit of sampling will be considered. Weighting will be based on the relation between the number of individuals finally included in the study and the population size and composition of each site according to the most recent census data.

Likewise, the analysis will be carried out by socioeconomic strata, according to gender and four age categories (35–44, 45–54, 55–64, and 65–74 years old).

To assess association between risk factors and CVD events, linear regression and simple and multiple logistic regressions will be used according to the nature of the response variables. Continuous variables that are not normally distributed will be evaluated by the application of transformations and categorizations wherever applicable. (38)

The secular trends in risk factors over time will be evaluated with methods of statistical analysis that take into account the correlation between repeated measures. To evaluate the changes in risk factors over time by sub-groups of interest, generalized estimation equations will be used. To estimate the rate of accumulated cardiovascular incidents, the Kaplan-Meir method will be used. The log rank test will be used to compare the differences between the curves of accumulated incidence events. In order to quantify the relationship between risk factors and the incidence of CVD events, the Cox Proportional Hazards method will be used. Potential confounders and interactions will be explored. Appropriate diagnostics will be carried out to test goodness of fit, collinearity, and atypical observations in each model. In all cases, fulfillment of assumptions in the model by means of exploration of residual behavior will be verified.

Statistical analysis software STATA 10.0 and SAS 9.0 will be used.(38-40)

Ethical Aspects

The study is carried out following the guidelines for the protection of the rights of human volunteers. All investigators and personnel in the study have completed a

training course, certified by NIH. All participants will sign an informed consent during the initial visit. To protect participant confidentiality the information included in the database will not contain personal identifiers.

Timeline of the study

The baseline data collection is projected to be performed during 2011. The follow-up phase will begin in 2012 and will consist of an annual telephone interview continuing up to the 4th year with a second round of physical and biochemical measures and an EKG, 2 to 3 years after the baseline measurements.

Conclusions

Despite the increasing burden of CVD in the Southern Cone, ranking first over the last decades as a cause of mortality and morbidity, national health programs and policies are still mostly focused on interventions aimed to tackle communicable diseases or perinatal or childhood conditions. Therefore the actions and programs targeted to lifestyle and nutritional changes in the population attempt to reduce cardiovascular disease burden in high risk people (37). The lack of follow-up studies prevents our countries not only from assessing local risk estimates and obtaining more reliable data for burden of CVD, but also from implementing risk factor stratification and management strategies at a population level. Accordingly, and based on this limited and imprecise evidence, there is a strong need in the region to build the capacity and infrastructure necessary to undertake a population-based cohort study to address these remaining knowledge gaps and to inform public health policy-making on the impact of CVD in our countries. The CESCAS I

study data will contribute to the improvement of public health strategies based on the application of primary care interventions, thus helping to improve cardiovascular health in this region.

Contributory statement

AR contributed to the conceptualization and design of the study and revised this manuscript critically. JH contributed to the conceptualization and design of the study and revised this manuscript critically. VI contributed to the conceptualization and design of the study and revised this manuscript critically. RP contributed to the conceptualization and design of the study and revised this manuscript critically. LB contributed to the conceptualization and design of the study and revised this manuscript critically. FL contributed to the conceptualization and design of the study JM contributed to the conceptualization and design of the study. MC contributed to the conceptualization and design of the study and acquisition of data. HO contributed to the conceptualization and design of the study. PS contributed to the conceptualization and design of the study. JP contributed to the conceptualization and design of the study

All authors gave final approval of the version to be published.

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TABLE 1. Data collection items in the CESCAS I study

Type of data	Components	Instrument
General information	Socio-demographic and economic data, type and health services utilization	SOL/HCHS*
Claudication	Location, Functional class	SOL/HCHS*
History	Cardiovascular, respiratory, hypertension, dyslipidemia, diabetes, pharmacologic and non-pharmacologic treatment and cancer	SOL/HCHS*
Alcohol	Level of consumption (daily quantity, frequency, type of alcoholic beverage)	SOL/HCHS*
Physical Activity	Type of activity, frequency and intensity, in free time and work	IPAQ
Spirituality	Importance, religious practice	SOL/HCHS*
Nutrition	Types of foods, quantity and frequency	FFQ
Smoking	Current, former and passive smoker. Other types of tobacco use (pipe, cigar)	GATS
Mental health	Depression, traumatic events, anxiety	PHQ-9/ SOL/HCHS*
Global health		SF-12
Quality of life		EQ5D
Physical examination	Blood pressure, weight, height and waist circumference	
Laboratory	Total cholesterol, HDL cholesterol, triglycerides, glucose and creatinine	
Electrocardiogram	25 mm/sec and at 1 mV of amplitude	

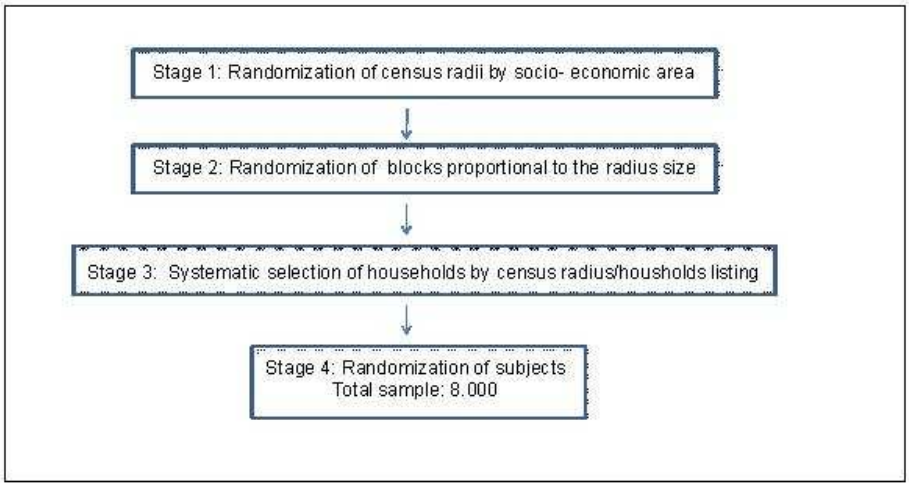
*Forms from Hispanic Community Health Study / Study of Latinos, cross-culturally adapted for use in Argentina, Chile and Uruguay

TABLE 2. Sample size for a highly complex study design for effect and design of specific proportion

Proportion	Design Effect				
	1.0	1.5	2.0	2.5	3.0
0.26-0.50	30	45	60	75	90
0.25	32	48	64	80	96
0.20	40	60	80	100	120
0.15	53	80	107	133	160
0.10	80	120	160	200	240
0.05	160	240	320	400	480

This cohort study will comply with the STROBE statement for this type of observational studies

FIGURE 1. Sampling procedure in CESCAS I study



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Cardiovascular diseases (CVD) are increasing throughout the world and cause 16.7 million deaths each year, of which 80% occur in low-middle income countries. In Argentina, Chile and Uruguay the available data about cardiovascular risk factors come predominantly from cross-sectional studies that are principally based on self-reporting or studies conducted with small convenience samples. The CESCAS I study will generate reliable estimates of the prevalence, distribution, and secular trends of CVD and its risk factors in this region.

Methods and analysis

CESCAS I is an observational prospective cohort study. This study entails a multistage probabilistic sample of 8000 participants between the ages of 35 and 74 years old from four mid-sized cities representing the Southern cone of Latin America: two in Argentina (Bariloche and Marcos Paz), one in Chile (Temuco), and one in Uruguay (Pando-Barros Blancos). In the first phase, baseline data will be collected regarding exposure to risk factors and prevalence of CVD. Baseline data collection is conducted in two stages: 1) household and 2) health center, in order to collect information on medical history, risk factors, lifestyles, and health utilization through specific questionnaires, physical measurements, electrocardiogram and an overnight, fasting blood sample to measure levels of serum lipids, glucose, and

creatinine. In the second phase, annual follow-up data will be obtained on the incidence rate of CVD events and the association between exposure and events.

Ethics and Dissemination

The protocol has obtained formal ethical approval from the IRB's in Argentina, Chile, Uruguay, and USA.

The lack of follow-up studies prevents our countries from implementing risk factor stratification and management strategies at a population level. The CESCAS I study data will contribute to the improvement of public health strategies based on the application of primary care interventions, thus helping to improve cardiovascular health in this region.

Article Summary

Article Focus

- Estimate the prevalence, distribution, and secular trends in major CVD events and risk factors in four cities in Argentina, Chile and Uruguay.

Key Messages

- Lack of follow-up studies prevents our countries not only from assessing local risk estimates and obtaining reliable data for burden of cardiovascular disease, but also from implementing risk factor stratification and management strategies at a population level.
- There is a strong need in the region to build the capacity and infrastructure to undertake a population based cohort study to address the knowledge

gaps and to inform policy-making on the impact of CVD in the Southern Cone of Latin America

Strengths and limitations of this study'

- CESCAS I will be the first study to estimate the longitudinal trend of CVD and risk factors in Argentina, Chile and Uruguay

Introduction

Cardiovascular diseases are increasing throughout the developing world and are the cause of almost 16.7 million deaths each year, of which 80% occur in low and middle-income countries. (1) In fact, CVD deaths represent 34% of the total annual mortality rate. (2) It has been projected that in 2015, 41 million people world-wide will die of chronic diseases if effective concerted actions are not put into place for their prevention and treatment. (3) In low and middle-income countries, almost half of these deaths will occur in people younger than 70 years old, compared with only 27% amongst corresponding age groups in high-income countries.(4) Furthermore, although in recent decades age-adjusted rates for cardiovascular mortality have diminished in developed countries, rates have increased in low and middle-income countries. (1, 5)

In Latin America, it is estimated that from 1990 until 2020, death from CVD, including coronary heart disease (CHD) will increase by approximately 145% (for both men and women), compared with an increase of 28% for women and an increase of 50% for men in developed countries during the same period. (6) Moreover, at least 75% of CVD may be explained by more proximal risk factors like unhealthy diet, low physical activity and tobacco use. (7)

In the World Health Report 2002 (WHO), 26 risk factors were evaluated and ranked by their importance. Major risk factors identified for most Latin American countries were hypertension, an elevated body mass index, and alcohol and tobacco use. (8) The Latin American INTERHEART study showed that the majority of cardiovascular risk in the Southern Cone could be explained by tobacco use, abnormal lipids, abdominal obesity and high blood pressure. (9) In Argentina, recent estimates showed that more than 600,000 Disability Adjusted Life Years (DALY) and almost 400,000 Years of Potential Life Lost (YPLL) were lost in 2005 due to CHD and stroke, where modifiable risk factors explained 75% of fatal and non-fatal acute CHD and stroke events, 82% of acute CHD events and 62% of strokes. Similarly, modifiable risk factors explained 76% of costs due to acute events and 71% of DALY lost.(10) In Argentina, Chile and Uruguay the available data about CVD risk factors come predominantly from cross-sectional studies that are principally based on self-reporting or studies conducted with small convenience samples, which do not give reliable estimates. (11-13). None of these studies mentioned above utilized a prospective follow-up. While the ongoing ELSA study, a recently established cohort in Brazil, will provide data on cardiovascular events, its population is composed of employee volunteers from 6 Brazilian universities, and thus it will not be able to offer population-based estimates of the impact of CVD risk factors on the incidence of CVD (14)

The CESCAS I study will generate reliable estimates of prevalence, distribution, and secular trends in CVD and its risk factors in this region. These data will contribute to the improvement of public health strategies thus helping to improve cardiovascular health in Latin America.

Methods

Study Design

CESCAS I is an observational, prospective cohort study initiated in November 2010. The study is composed of two phases. In the first phase, baseline data will be collected regarding exposure to risk factors and prevalence of cardiovascular disease. In the second phase, annual follow-up data will be obtained on the incidence rate of CVD and the association between exposure and the event.

Study Population

This study entails a probabilistic sample of 8000 non-institutionalized mainly urban men and women, between the ages of 35 and 74 years old representing the general adult population in Argentina, Chile and Uruguay. Four mid-sized cities were selected: two in Argentina (Bariloche and Marcos Paz), one in Chile (Temuco), and one in Uruguay (Pando-Barros Blancos).

Sampling Method

As the prevalence of CVD risk factors is considered likely to vary by age, gender, and geographic area, the sampling method was stratified accordingly, following a complex sampling design that consisted of four stratified stages to obtain a representative sample from each of these locations (Figure 1). The first stage consisted in randomly sampling census radii from each location, stratified by socio-economic level. In the second stage a number of blocks proportional to the radius size were randomly selected. The third stage sampled households from each block

using systematic sampling. If the selected house did not include a permanent residence (for example, weekend or business housing, abandoned or demolished dwellings, those under construction, or addresses which were not identified) this was replaced by another house. In the selected households all members between 35-74 yrs old were listed to create the final sampling frame. In the fourth stage one listed member per household was randomly selected. The final sampling frame was composed of one subject per household, stratified by gender (50% women and 50% men) and age categories (35-44, 45-54, 55-64, and 65-74 years old) constituting a total of 2,000 subjects per site, all of them meeting the following criteria: a permanent resident at the location for at least 6 months per year, willing to sign a written consent to participate, not expressing an intention to relocate within the next two years, and able to respond autonomously to the questionnaire (without cognitive impairment or language problems) . Replacement of selected participants because of refusal to participate or inability to be located was not allowed. (15, 16)

Recruitment Plan

Participants are invited to participate through a letter from the site institution. The interviewer makes the first contact with the household and arranges an appointment for a home visit to collect questionnaire data and schedule a follow-up clinical visit. A clinical visit is scheduled to obtain physical measurements, an electrocardiogram (EKG) and overnight fasting blood samples. To minimize non-participation and the potential for bias in the results, the following measures will be taken to facilitate and encourage the participation:

•Travel assistance or home assessment for those unable to travel to the examination centers.

•Variety of appointment times to suit all members of the community.

•Feedback of blood test and examination results to participants.

Data collection

Baseline data collection is conducted in two stages: household and health center. In the household, an interviewer conducts a survey to collect the required information through specific questionnaires. Once the survey is complete, the interviewer proceeds to arrange the visit to the health center where the physical measurements, EKG and blood sample is obtained.

Questionnaires

A trained interviewer gathers information regarding participant characteristics including demographic, socioeconomic and health care utilization data, personal and family history of CVD and risk factors like high blood pressure, dyslipidemia, diabetes, as well as current pharmacologic and non-pharmacologic treatment. Data are also collected regarding intermittent claudication, cancer, respiratory disease, alcohol consumption and weight history using cross-culturally adapted questionnaires from the Hispanic Community Health Study / Study of Latinos (HCHS/SOL) study (17). Physical activity will be assessed through the HCHS/SOL study questionnaire adapted from the International Physical Activity questionnaire (IPAQ). (18) Information about current and former cigarette smoking, including age at which smoking was initiated, years of smoking, amount of cigarettes smoked per day, cessation attempts and treatments will be assessed using the Global Adult

Tobacco Survey (GATS).(19) Use of other forms of tobacco, exposure to passive cigarette smoking and indoor pollution will also be assessed. Nutrition information will be collected using a semi-quantitative food frequency questionnaire (FFQ) adapted from the National Cancer Institute Diet History Questionnaire, which has been validated by our research team to be used in Argentina, Chile and Uruguay. (20) Depression and anxiety will be assessed by the 9 item Patient Health Questionnaire (PHQ-9) (21), which has been validated in Argentina. (22). Stressful events and spirituality will be assessed through the HCHS/SOL study questionnaire, cross-culturally adapted (17).

Locally validated versions of the SF-12 and EQ5D are used to measure health-related quality of life and social utilities and preferences, respectively (23, 24). All the questionnaires used in the study and their sources can be seen in Table 1.

Blood Pressure and Anthropometric Measurements

Trained and certified observers will measure blood pressure (BP) during the health center visit following the recommendations of the American Heart Association (25). According to study protocol, before BP is measured, the participant remains seated and at rest for 5 minutes. Tea, mate or coffee consumption, as well as smoking or exercising, in the 30 minutes prior to the testing are not permitted. A standardized mercury or aneroid sphygmomanometer with an adequate cuff size will be used. The cuff will be placed on the right arm of the participant, inflated to 10 mm Hg, and then must be inflated until reaching a pressure of 30 mmHg above the level at which the radial pulse can no longer be palpated. Three measurements are

obtained, with 30 seconds intervals between them. Korotkoff sounds are recorded, and used to identify systolic and diastolic BP.

The weight measurement will be obtained with undergarments and without shoes. The weight will be recorded in kilograms to one decimal place, using standing scales supported on a steady surface.

The height measurement will be recorded without shoes, in centimeters to one decimal place, on a Frankfort plane positioned at a 90-degree angle against metallic metric tape mounted on the wall. The abdominal circumference measurement will be recorded in centimeters to one decimal place, on a horizontal plane at 1 cm above the belly button that generally coincides with the narrowest circumference.

Laboratory Measurements

Overnight, fasting blood samples are drawn by venipuncture to measure levels of serum lipids, glucose, and creatinine. The samples will be processed and temporarily stored at the extraction site to be sent later for analysis and storage (in ultra freezers at -80°C) in the central laboratory at the Hospital Italiano of Buenos Aires. LDL cholesterol levels will be calculated utilizing the Friedewald equation for the participants who have a triglyceride level <400 mg/dL. According to this equation, total LDL cholesterol is equal to: total cholesterol – HDL cholesterol – triglycerides/5.

Electrocardiogram

The study will employ a 12-lead EKG standardized at 25 mm/sec and at 1 mV of amplitude.

Study outcomes

Hypertension is defined as the mean systolic BP ≥140 mm Hg, and/or diastolic BP≥90 mm Hg, and/or self-report of current use of antihypertensive medications. (26). Obesity was defined as BMI ≥ 30 kg/m^2 and overweight was defined as BMI ≥ 25kg/m^2. (27-30). Dyslipidemia is defined as a total cholesterol ≥ 200 mg/dL or 11.1 mmol/l, or LDL cholesterol ≥130 mg/dL or 7.2 mmol/l or HDL cholesterol <40 mg/dL or 2.2mmol/L.(31). Diabetes mellitus is defined as a fasting glucose ≥126 mg/dL or 7 mmol/l. Glucose intolerance is defined as a fasting glucose levels between 110 mg/dL and 125 mg/dL or 6.1 mmol/L to 6.9 mmol/L.(32) Current smoking is defined as smoking at least one cigarette per day at the time of the survey. Former-smoking is defined as a person who has been a smoker and does not smoke at the time of the survey. Passive smoking is defined as involuntarily breathing air that is contaminated by tobacco smoke. (28, 33) During the follow-up a person is categorized as having CVD if self-reported or their self-assigned proxy reported any of the following conditions diagnosed by a physician: CVD death, acute myocardial infarction, angina, heart failure, cerebro-vascular events, peripheral vascular disease or coronary or peripheral revascularization. The study Outcome Committee will review the source documents collected related to the reported event and adjudicate all CVD outcomes independently.

Training and Quality Assurance

Field work quality assurance

Data collection will be conducted following the standardized operations manual. Between 5 and 10% of participants will have repeated measurements of arterial pressure, height, weight and waist circumference to adjust for the effect of measurement error on selected variables. All the equipment used will be certified by international standardization norms. Periodic monitoring of data collection procedures will be performed by the coordinating center.

Laboratory quality control

All laboratory measurements (total cholesterol, HDL, LDL, triglycerides, glucose and plasma creatinine) will be performed by the central laboratory. Every laboratory technician must complete a training program.

Processing of data

The database was designed using the “OpenClinica” system. (34). This is a computerized system of related databases with web interface. The data will be entered from each site, via the web, into electronic forms. Double data entry with independent operators will be performed to eliminate data entry errors. The data will be stored on a central server. Validation rules will be generated in accordance with the nature of the variables. Automatic queries will be generated in response to out-of-range entries to be investigated by study personnel at each site.

Statistical Analysis

Sample size

The calculated sample size is 8000 participants (2000 per site) which is consistent with the recommended requirements for precision for complex surveys. This sample will be sufficient to provide precise estimates of the prevalence of major CVD risk factors by gender and site, in four age-defined categories: from 35 to 44, 45 to 54, 55 to 64 and 65 to 74 years old, as well as their association with the development of CVD (35-37). The proposed sample size is sufficient to comply with precision requirements of a complex sample that assumes that the design effect is 1.5 and the prevalence of the risk factors of interest is 5% or greater (Table 2).

For analysis, the capacity to detect risk factors was calculated using a statistically significant alpha level of 0.05 and a statistical power of 85%, which will permit detection of moderate and large relative risks.

Statistical Analysis

General characteristics of the population will be described. For continuous variables, mean and median, range, standard deviation, and/or quartile range will be calculated according to the distribution of each variable. In the case of categorical variables, absolute and relative frequencies will be calculated.

In order to determine the prevalence and incidence of risk factors, CVD events and the association between risk factors and CVD events, the design effect of the first stage unit of sampling will be considered. Weighting will be based on the relation between the number of individuals finally included in the study and the population size and composition of each site according to the most recent census data.

Likewise, the analysis will be carried out by socioeconomic strata, according to gender and four age categories (35–44, 45–54, 55–64, and 65–74 years old).

To assess association between risk factors and CVD events, linear regression and simple and multiple logistic regressions will be used according to the nature of the response variables. Continuous variables that are not normally distributed will be evaluated by the application of transformations and categorizations wherever applicable. (38)

The secular trends in risk factors over time will be evaluated with methods of statistical analysis that take into account the correlation between repeated measures. To evaluate the changes in risk factors over time by sub-groups of interest, generalized estimation equations will be used. To estimate the rate of accumulated cardiovascular incidents, the Kaplan-Meir method will be used. The log rank test will be used to compare the differences between the curves of accumulated incidence events. In order to quantify the relationship between risk factors and the incidence of CVD events, the Cox Proportional Hazards method will be used. Potential confounders and interactions will be explored. Appropriate diagnostics will be carried out to test goodness of fit, collinearity, and atypical observations in each model. In all cases, fulfillment of assumptions in the model by means of exploration of residual behavior will be verified.

Statistical analysis software STATA 10.0 and SAS 9.0 will be used.(38-40)

Ethical Aspects

The study is carried out following the guidelines for the protection of the rights of human volunteers. All investigators and personnel in the study have completed a

training course, certified by NIH. All participants will sign an informed consent during the initial visit. To protect participant confidentiality the information included in the database will not contain personal identifiers.

Timeline of the study

The baseline data collection is projected to be performed during 2011. The follow-up phase will begin in 2012 and will consist of an annual telephone interview continuing up to the 4th year with a second round of physical and biochemical measures and an EKG, 2 to 3 years after the baseline measurements.

Conclusions

Despite the increasing burden of CVD in the Southern Cone, ranking first over the last decades as a cause of mortality and morbidity, national health programs and policies are still mostly focused on interventions aimed to tackle communicable diseases or perinatal or childhood conditions. Therefore the actions and programs targeted to lifestyle and nutritional changes in the population attempt to reduce cardiovascular disease burden in high risk people (37). The lack of follow-up studies prevents our countries not only from assessing local risk estimates and obtaining more reliable data for burden of CVD, but also from implementing risk factor stratification and management strategies at a population level. Accordingly, and based on this limited and imprecise evidence, there is a strong need in the region to build the capacity and infrastructure necessary to undertake a population-based cohort study to address these remaining knowledge gaps and to inform public health policy-making on the impact of CVD in our countries. The CESCAS I

study data will contribute to the improvement of public health strategies based on the application of primary care interventions, thus helping to improve cardiovascular health in this region.

Contributory statement

AR contributed to the conceptualization and design of the study and revised this manuscript critically. JH contributed to the conceptualization and design of the study and revised this manuscript critically. VI contributed to the conceptualization and design of the study and revised this manuscript critically. RP contributed to the conceptualization and design of the study and revised this manuscript critically. LB contributed to the conceptualization and design of the study and revised this manuscript critically. FL contributed to the conceptualization and design of the study and revised this manuscript critically. JM contributed to the conceptualization and design of the study and revised this manuscript critically. MC contributed to the conceptualization and design of the study and revised this manuscript critically. HO contributed to the conceptualization and design of the study and revised this manuscript critically. PS contributed to the conceptualization and design of the study and revised this manuscript critically. JP contributed to the conceptualization and design of the study and revised this manuscript critically.

All authors gave final approval of the version to be published.

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TABLE 1. Data collection items in the CESCAS I study

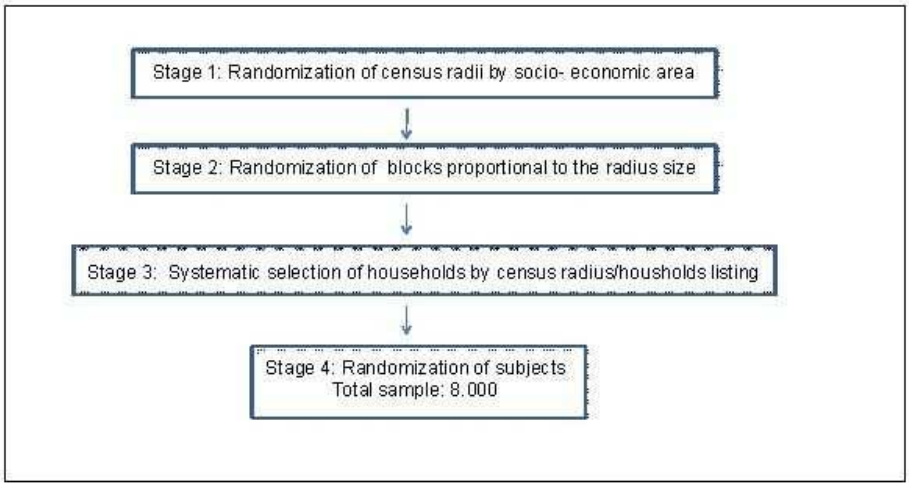
Type of data	Components	Instrument
General information	Socio-demographic and economic data, type and health services utilization	SOL/HCHS*
Claudication	Location, Functional class	SOL/HCHS*
History	Cardiovascular, respiratory, hypertension, dyslipidemia, diabetes, pharmacologic and non-pharmacologic treatment and cancer	SOL/HCHS*
Alcohol	Level of consumption (daily quantity, frequency, type of alcoholic beverage)	SOL/HCHS*
Physical Activity	Type of activity, frequency and intensity, in free time and work	IPAQ
Spirituality	Importance, religious practice	SOL/HCHS*
Nutrition	Types of foods, quantity and frequency	FFQ
Smoking	Current, former and passive smoker. Other types of tobacco use (pipe, cigar)	GATS
Mental health	Depression, traumatic events, anxiety	PHQ-9/ SOL/HCHS*
Global health		SF-12
Quality of life		EQ5D
Physical examination	Blood pressure, weight, height and waist circumference	
Laboratory	Total cholesterol, HDL cholesterol, triglycerides, glucose and creatinine	
Electrocardiogram	25 mm/sec and at 1 mV of amplitude	

*Forms from Hispanic Community Health Study / Study of Latinos, cross-culturally adapted for use in Argentina, Chile and Uruguay

TABLE 2. Sample size for a highly complex study design for effect and design of specific proportion

Proportion	Design Effect				
	1.0	1.5	2.0	2.5	3.0
0.26-0.50	30	45	60	75	90
0.25	32	48	64	80	96
0.20	40	60	80	100	120
0.15	53	80	107	133	160
0.10	80	120	160	200	240
0.05	160	240	320	400	480

FIGURE 1. Sampling procedure in CESCAS I study



54x43mm (300 x 300 DPI)

This cohort study will comply with the STROBE statement for this type of observational studies