American Journal of Epidemiology Advance Access published January 10, 2012

American Journal of Epidemiology

DOI: 10.1093/aje/kwr294

Practice of Epidemiology

Brazilian Longitudinal Study of Adult Health (ELSA-Brasil): Objectives and Design

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Initially submitted May 4, 2011; accepted for publication July 29, 2011.

Although low- and middle-income countries still bear the burden of major infectious diseases, chronic noncommunicable diseases are becoming increasingly common due to rapid demographic, epidemiologic, and nutritional transitions. However, information is generally scant in these countries regarding chronic disease incidence, social determinants, and risk factors. The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) aims to contribute relevant information with respect to the development and progression of clinical and subclinical chronic diseases, particularly cardiovascular diseases and diabetes. In this report, the authors delineate the study's objectives, principal methodological features, and timeline. At baseline, ELSA-Brasil enrolled 15,105 civil servants from 5 universities and 1 research institute. The baseline examination (2008–2010) included detailed interviews, clinical and anthropometric examinations, an oral glucose tolerance test, overnight urine collection, a 12-lead resting electrocardiogram, measurement of carotid intima-media thickness, echocardiography, measurement of pulse wave velocity, hepatic ultrasonography, retinal fundus photography, and an analysis of heart rate variability. Long-term biologic sample storage will allow investigation of biomarkers that may predict cardiovascular diseases and diabetes. Annual telephone surveillance, initiated in 2009, will continue for the duration of the study. A follow-up examination is scheduled for 2012–2013.

cardiovascular diseases; chronic disease; cohort studies; developing countries; diabetes mellitus; epidemiologic methods; longitudinal studies; occupational health

Abbreviations: CI, confidence interval; CIS-R, Clinical Interview Schedule—Revised; ECG, electrocardiogram; ELSA-Brasil, Brazilian Longitudinal Study of Adult Health.

Chronic noncommunicable diseases are a global health problem and a leading threat to human health and development. The 4 main chronic noncommunicable diseases—cardiovascular disease, cancer, chronic respiratory disease, and diabetes—are responsible for 60% of all deaths globally, with 80% of these occurring in low- and middle-income countries (1). Chronic diseases have major adverse effects on the quality of life, cause premature death, and create large and underappreciated economic effects on families, communities, and societies (2).

Brazil, a middle-income country, has over the past several decades undergone one of the world's most rapid demographic transitions (3). More than 85% of Brazilians currently live in urban areas, facing risks typical of urban contexts (4). Although age-standardized rates of mortality from chronic diseases, especially cardiovascular and respiratory diseases, have declined (5), population aging has resulted in an increased chronic disease burden. Within this context, Brazil is also experiencing a rapid nutritional transition, with marked increases in overweight and obesity (6). Its Gini coefficient of inequality, like that of many other Latin American and Caribbean countries, remains among the highest in the world (7). As chronic diseases concentrate among the poor, their rising burden threatens to widen the already huge gap in health care.

Most of our knowledge about chronic disease epidemiology comes from large cohort studies conducted in the United

States and Western Europe. Very few such studies have been conducted in low- and middle-income countries, where the prevalences of effect modifiers may differ from those in high-income countries and novel risk factors may be present. Accordingly, we are conducting a large multicenter cohort study, the Brazilian Longitudinal Study of Adult Health (in Portuguese, Estudo Longitudinal de Saúde do Adulto (ELSA)-Brasil)), that is focused on the risk of obesity, diabetes, and cardiovascular diseases in Brazilian adults aged 35–74 years. Here we describe the objectives and main methodological aspects of this study.

MATERIALS AND METHODS

The main study objectives of ELSA-Brasil are to investigate the incidence and progression of diabetes and cardiovascular diseases and their biologic, behavioral, environmental, occupational, psychological, and social factors. Both upstream (social patterns and structures that shape people's chances to be healthy) and downstream (individual characteristics) risk factors will be assessed for their possible associations with subclinical and clinical outcomes.

Study design

ELSA-Brasil is a cohort study of 15,105 civil servants from 5 universities and 1 research institute located in different regions of Brazil: the federal universities of Bahia, Espirito Santo, Minas Gerais, and Rio Grande do Sul; the University of Sao Paulo; and the Oswaldo Cruz Foundation.

Study population: recruitment and sample size

All active or retired employees of the 6 institutions aged 35–74 years were eligible for the study. Exclusion criteria were current or recent (<4 months prior to the first interview) pregnancy, intention to quit working at the institution in the near future, severe cognitive or communication impairment, and, if retired, residence outside of a study center's corresponding metropolitan area. The first examination was carried out from 2008 through 2010. Annual telephone surveillance for outcomes is now in its second year, and the first follow-up examination will be conducted in 2012 and 2013. Table 1 shows the recruitment goals, which aimed at achieving reasonable variability pertaining to gender, age, and socioeconomic status. In general, these goals were achieved, though with slightly more women and younger persons and slightly fewer unskilled workers. As measured by self-rated race/color, 52% of participants are white, 28% are pardos (''browns'' or of mixed color), 16% are black, 3% are Asian (mainly Japanese Brazilians), and 1% are indigenous.

Our sample includes volunteers (76% of the final sample) and actively recruited participants (24%), the latter being recruited from listings of civil servants. The total sample will be used to examine associations between risk factors and outcomes that are probably free of bias (8), whereas those actively recruited will be used to assess the likelihood of bias in our estimations.

Sample size estimation was based on the main study outcomes—type 2 diabetes and myocardial infarction. Since the incidence of diabetes in our Brazilian populations is unknown, we conservatively estimated a 3-year cumulative incidence of 1.4%, which is considerably lower than that found in the Atherosclerosis Risk in Communities Study (9), given that the prevalence of overweight/obesity in Brazil (10) is lower than that in the United States. Considering an alpha value of 5%, statistical power of 80%, exposure prevalence of 20%, and a relative risk of 2.0, we estimated the necessary sample size at approximately 6,400 subjects. This sample size would also allow for an adequate number of incident myocardial infarctions, as the estimated incidence of myocardial infarction, based on mortality data, is expected to be slightly higher than that of diabetes. In order to present gender-specific analyses and allow for possible losses to follow-up, we defined the desired sample size as approximately 15,000 persons.

Table 1. Study Goals and Baseline Distributions of Cohort Participants by Gender, Age, and Occupation, Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008–2010

Variable	Study Goal, %	Actual Distribution, %
Gender		
Women	50	54
Men	50	46
Age group, years		
35–44	15	22
45–54	30	39
55–64	40	28
65–74	15	11
Occupation		
Unskilled	35	28
Technical/clerical	35	36
Faculty and professional staff	30	36

Baseline examination

Data are collected in 2 phases. The first, lasting approximately 1 hour, includes obtaining informed consent and conducting the initial interview at the participant's job site. The second, comprising additional interviews and examinations, lasts approximately 6 hours and is conducted at a study clinic. To be considered a participant, an individual must complete the following procedures: the initial interview, an electrocardiogram (ECG), fasting blood collection, and blood pressure measurement.

The main exposure areas ascertained through interviews are presented in Table 2. Considering the singular social characteristics of the Brazilian population, as well as the socioeconomic disparities prevailing in the country, ELSA-Brasil questionnaires include a wide range of social items in addition to biologic items. Criteria such as life-course exposures influenced the choice of questions or specific questionnaire modules and scales included in the interviews. Social determinants of health, such as social mobility, adverse socioeconomic conditions across the life course, experience of discrimination, job stress, gender and family context, and

health-related neighborhood context, are included. Recording of current and past addresses permits geocoding and consideration of neighborhood data in the study.

Data on mental health and cognitive status are also obtained. The Portuguese version of the Clinical Interview Schedule—Revised (CIS-R) and cognitive tests are included in the second phase of the interview. The CIS-R is a structured interview for measurement and diagnosis of nonpsychotic psychiatric morbidity in community and primary-care settings (11) and can be administered by non-clinically trained interviewers. Slightly different versions of the CIS-R have been used in previous studies in Brazil (12–14). The version used in ELSA-Brasil was translated into Portuguese and then back-translated.

ELSA-Brasil uses 3 cognitive tests, which are all included in the Brazilian version of the cognitive battery of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (15). Memory is evaluated by means of the word learning and retention test. The validated version of the Semantic Verbal Fluency Test (category of animals) evaluates language, in addition to memory and executive functions. Phonemic verbal fluency is evaluated by means of the word counts test–letter F (i.e., the number of words produced that begin with the letter F), which has also been used in the Whitehall II Study (16). Executive functions related to attention, concentration, and psychomotor speed are evaluated by means of Trail Making Test B (17). This cognitive battery was validated in a sample of elderly (age $\geq$65 years) Brazilians (15). The best sensitivity and specificity results compared with clinical evaluation (Clinical Dementia Rating) were approximately 75% for memory and verbal fluency tests, and the worst results were for executive functions, with sensitivity and specificity values of approximately 55% (15).

A comprehensive set of examinations and measurements (Table 3) is carried out. The anthropometric parameters—weight, height, sitting height, and waist and hip circumferences—are measured using standard equipment and techniques (18). Resting blood pressure and heart rate are measured 3 times in the seated position after 5 minutes' rest. The average of the second and third measurements will be used in the analyses. Positional blood pressure is also measured. Ankle-brachial index is defined as the ratio between ankle blood pressure and arm blood pressure (19). A standard 12-lead ECG is administered and will be analyzed using the Minnesota code (20). A 10-minute ECG rhythm strip is obtained in the supine position for determination of heart rate variability. Lead II ECG signals are recorded at 250 Hz and processed to produce temporal and spectral indexes, with the power spectrum being modeled using autoregressive analysis.

Transthoracic echocardiography (Aplio XG; Toshiba Corporation, Tokyo, Japan) is performed by echocardiographers with the subject at rest in left lateral decubitus. Cine loops and static images of 3 cardiac cycles under regular cardiac rhythm are selected following a standard protocol based on current recommendations for use of echocardiography in research (21). These images are then transmitted to and read at a central reading center. In addition to standard measurements, epicardial fat thickness is also estimated (22). The stiffness of large arteries is evaluated by means of carotid-to-femoral pulse wave velocity using a validated and noninvasive automatic device that calculates velocity by dividing the suprasternal notch-femoral distance by the difference in recorded transit time between pulse waves measured at the carotid and femoral arteries (23). The intima-media thicknesses of 1-cm portions of the distal left and right common carotid artery far walls are obtained by ultrasonography and calculated automatically by MIA software (Medical Imaging Applications, Coralville, Iowa) over 3 cardiac cycles. The carotid bifurcation is examined over a length of 3 cm (1.5 cm proximal and distal to the flow divider) for plaques. Nonalcoholic fat steatosis is assessed by ultrasonography of the liver. The preperitoneal fat layer and subcutaneous fat layer are measured by ultrasonography. Nonmydriatic retinal images are obtained in order to evaluate arteriolar and venular diameters and retinal lesions.

The ECG, heart rate variability, pulse-wave velocity tracings, carotid artery intima-media thickness, echocardiography, retinal photography, nonalcoholic fat steatosis, and abdominal wall adiposity are all identified and/or measured and interpreted at central reading centers, after careful evaluation of their quality.

ELSA-Brasil also investigates biochemical and genetic factors. Blood samples are collected after a 12-hour overnight fast. A standard 75-g oral glucose tolerance test is administered to all participants without known diabetes, and a meal challenge test is administered to those with diabetes. Fasting and 2-hour postload samples are collected for baseline laboratory determinations and for long-term storage. A 12-hour urine sample is collected for determination of sodium, potassium, calcium, phosphorus, and creatinine levels and microalbuminuria. Table 4 shows the results of the baseline laboratory determinations performed on all ELSA-Brasil participants. All analyses are performed at the University of Sao Paulo. Approximately 28 aliquots per participant are prepared for storage in liquid nitrogen at 2 different facilities (University of Sao Paulo and Oswaldo Cruz Foundation); and 14 aliquots are stored in freezers at -80°C at each of the 6 research centers. Samples include heparin and citrated plasma for measures of thrombogenesis and fibrinolysis. The study protocol also includes DNA extraction.

Cohort surveillance and follow-up for events

ELSA-Brasil's clinical cardiovascular endpoints include acute myocardial infarction, unstable angina pectoris, cardiac revascularization, resuscitated cardiac arrest, heart failure, peripheral arterial disease, stroke, transient ischemic attack, incident diabetes, and chronic kidney disease. The study also ascertains diabetes-related events (blindness, amputation) and acute complications resulting in hospitalization (ketoacidosis, hyperosmolar state, severe hypoglycemia). In addition, by direct comparison of data from repeated examinations over time, the study also investigates changes in weight, dyslipidemia and other metabolic disorders, and the occurrence of microalbuminuria, retinopathy, cognitive dysfunction, and psychiatric illnesses.

Surveillance is being conducted through annual telephone interviews, return visits to ELSA-Brasil clinics, employer reports, and linkage to national databases, such as the National Mortality System. Annual telephone calls are made to verify the overall state of participants' health, including new diagnoses, deaths, hospitalizations, and emergency department

Table 2. Components of Baseline Interviews in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008–2010

Questionnaire	Source of Data	Variable(s)
Sociodemographic characteristics	Both phase 1 and phase 2 interviews[a,b]	Age, gender, and race/ethnicity
		Social class (37)
		History of migration, location and duration of residence
		Educational and occupational history (participant and spouse)
		Family income and household assets
		Household characteristics and family composition (present and past)
		Marital history and partner characteristics
		Family caregiving
		Religion (both present and past)
		Parents' schooling and occupation
		Life conditions during childhood
Health and medical history	Both phase 1 and phase 2 interviews	Self-rated health, medical history of cardiovascular illnesses, diabetes, kidney disease, cancer, and other selected chronic diseases and medical procedures of interest
		Rose angina questionnaire (38) and questionnaires for intermittent claudication (38) and heart failure
		Headache questionnaire (39)
Occupational exposure	Both phase 1 and phase 2 interviews	Job stress (40)
		Job characteristics (degree of autonomy, access to funds and authority) (40)
		Retirement status
		Conflicts between work and family demands (41)
Family history of disease	Phase 1 interview[a]	History of specific diseases such as cardiovascular disease, diabetes, and sudden death
Reproductive health	Phase 2 interview[b]	Menarche, menstrual cycles, and menopause
		Contraceptive use
		Reproductive history
		Hormone therapy
		Infertility

Table continues

visits that have occurred since the baseline examination or last contact. All hospital discharge diagnoses are recorded. Full hospital information is abstracted by trained personnel if diagnoses include any *International Classification of Diseases* code related to ELSA-Brasil endpoints.

Cohort participants will be reinterviewed and reexamined at the ELSA-Brasil clinics every 3–4 years. During each examination, we will obtain data on exposures and clinical and subclinical outcomes of interest. At follow-up visits, new questions may be added to the interview schedule, and new examinations may be performed.

Events are classified according to the study protocol by a panel of physicians trained according to the ELSA-Brasil classification criteria. These criteria were selected for comparability with those of other pertinent epidemiologic studies and in collaboration with investigators from the Multi-Ethnic Study of Atherosclerosis (24) and the Atherosclerosis Risk in Communities Study (25). Deaths are identified primarily from reports by next of kin and employers. Underlying and contributing causes of deaths are classified according to death certificates and available hospital records and, for out-of-hospital deaths, according to information obtained from interviews with next of kin and physicians.

Quality assurance and control

A series of small pilot studies of increasing complexity were performed to identify and correct potential problems in the data collection instruments and procedures. Central training, certification, and recertification of interviewers and health professionals responsible for the clinical and laboratory examinations are performed according to the study protocol. The standardized study procedures are detailed in the ELSA-Brasil operations manuals (available upon request).

During data collection, periodic staff meetings are held to discuss problems and check whether standardized procedures are being correctly implemented. Supervisors systematically observe techniques using previously prepared checklists, utilizing this information when recertifying staff. Interviews carried out during 1 week are taped, and a sample of the recordings is reviewed by experienced interviewers from other centers. In periodic conference calls, clinic coordinators

Table 2. Continued

Questionnaire	Source of Data	Variable(s)
Health care	Phase 2 interview	Access to preventive health care/examinations, health insurance, and utilization of health-care services
Psychosocial factors	Both phase 1 and phase 2 interviews	Neighborhood characteristics (leisure, sports, access to food purchasing) (42, 43)
		Social networks (44, 45)
		Experience of discrimination
		Social capital (46)
		Stressful life events (47)
		Self-rated social status (48)
		Birth weight and weight at age 20 years
Body weight history and body image	Phase 2 interview	Body image (current and desired) (49)
Food consumption	Phase 2 interview	Food frequency questionnaire (50)
Smoking	Phase 1 interview	Past and current cigarette smoking, exposure to secondhand smoke
Alcohol consumption	Phase 2 interview	Usual type and frequency of intake; drinking patterns
Physical activity		Current physical activity, including leisure and sport-related activity (51)
Medication use	Phase 2 interview	Prescription and nonprescription drugs, vitamin/dietary supplements, and other medications taken in the past month
		(Participants are instructed to bring all medications and prescription forms to the examination.)
Cognitive function	Phase 2 interview	3 standardized tests from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), validated for the Brazilian population (15): a word learning and retention test to evaluate memory; verbal fluency tests (semantic and phonemic) (16); and Trail Making Test B to evaluate executive functions related to attention, concentration, and psychomotor speed (17)
Mental health	Phase 2 interview	All 14 sections of the Clinical Interview Schedule—Revised (12): somatic symptoms, fatigue, concentration, depression, irritability, sleep, worry over physical health, depressive ideas, worry, anxiety, phobia, panic, compulsions, and obsessions

[a] Phase 1 interview at the work site.
[b] Phase 2 interview plus examinations carried out at a study research center.

review issues related to standardization of procedures. Reliability of instruments and measurements is assessed by obtaining duplicate measurements in subsamples. Protocols differ slightly for different blocks of measurements. Reliability coefficients estimated by bootstrap techniques for some clinical measurements taken during the same visit are 0.883 (95% confidence interval (CI): 0.823, 0.907) for systolic blood pressure, 0.893 (95% CI: 0.826, 0.923) for diastolic blood pressure, 0.995 (95% CI: 0.991, 0.996) for waist circumference, and 0.903 (95% CI: 0.768, 0.945) for pulse wave velocity.

Study management

The study's steering committee is responsible for the overall conduct of the study. Its members include study investigators, representatives of the Brazilian Ministry of Health and the funding agency, and an external consultant. Technical working committees have developed operations manuals and were responsible for training and certifying staff. The data center has developed data entry and management systems, as well as a system for transmission and storage of images. The 5 reading centers are based in the different research centers. Two repositories have been created for long-term storage of biologic samples. In addition to a central laboratory, each of the 6 research centers stores a fraction of the biologic samples.

Data management

Data are entered using a Web-based system structured on a Java platform with open-source software. Backup paper forms permit subsequent data entry. Echocardiographic, ultrasound, and retinal images are transmitted to a central storage location within an electronic picture archiving and communications system, with transfer in DICOM (Digital Imaging Communications in Medicine) format, based on the open-source software DCM4CHEE (http://www.dcm4che.org/). Investigators at the reading centers can download images from this storage location for processing. ECGs are transmitted electronically to the reading center in XML format and are received and stored using a dedicated proprietary system (Pyramis ECG Data Management System; Cardiac Science, Bothell, Washington). Laboratory specimens are identified by bar codes. We periodically extract data from a central SAS

Table 3. Components of Baseline Examinations and Measurements in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008–2010

Procedure	Description
Anthropometry	Weight, height, sitting height, and measurement of waist, hip, and neck circumferences (18, 52)
Blood pressure	Standard procedures (5 minutes' rest, 3 determinations), obtained using an oscillometric sphygmomanometer (Omron 765CP; Omron, Kyoto, Japan)
Ankle-brachial index	Ankle and arm blood pressures, obtained using standardized Doppler procedures (53)
Orthostatic hypotension	After a 20-minute rest with the participant lying supine, a blood pressure measurement was taken, and the measurement was repeated with the participant in a standing position.
Electrocardiography	Standard digital 12-lead ECG and 2-minute rhythm strip (Burdick Atria 6100; Cardiac Science, Bothell, Washington). Readings and diagnostic criteria are based on the Minnesota code definitions (20).
Heart rate variability	Temporal and spectral indexes determined from a 10-minute ECG recording obtained in the supine position from DII derivation at 250 Hz (WinCardio; Micromed, Brasila, Brazil)
Transthoracic echocardiography	Obtained with a commercially available ultrasound system with a 2- to 3.5-mHz transducer (Aplio XG; Toshiba Corporation, Toshigi, Japan)
Carotid-to-femoral pulse wave velocity	Aortic stiffness is measured using a validated and noninvasive automatic device (Complior SP; Artech Medical, Paris, France).
Carotid artery intima-media thickness	Carotid ultrasonography of both common carotid arteries with a linear transducer (nominal center transducer frequency of 7.5 MHz) (Aplio XG) with axial resolution of approximately 0.10 mm
Abdominal wall fat layers	Preperitoneal fat layer and subcutaneous fat layer obtained with a linear transducer (nominal center transducer frequency of 7.5 MHz) (Aplio XG)
Nonalcoholic fat steatosis	Liver ultrasonography (Aplio XG)
Retinal fundus photography	Images centered on the macula and optic disc of each eye obtained with a Canon CR-1 nonmydriatic system with an EOS 40D (10-megapixel) digital camera (Canon, Tochigiken, Japan)
Oral glucose tolerance test	Standard 75-g oral glucose tolerance test following an overnight fast, with fasting and 2-hour postload glucose determinations
High-saturated-fat, high-glycemic-index meal challenge in diabetes	435-kcal snack including 24 g of fat (14 g saturated) and 47 g of carbohydrate of rapid absorption, administered after an overnight fast, with measurement of fasting and 2-hour glucose and triglycerides and storage of postload samples for future determinations

Abbreviation: ECG, electrocardiogram.

database (SAS Institute, Inc., Cary, North Carolina). SAS programming generates queries related to questionable data values, permitting data editing. Specific databases for analyses can then be created from the central database.

Ethical issues

Because it is a multicenter study, ELSA-Brasil's research protocol was approved not only by the ethics committee of each institution but also by the National Research Ethics Committee. In addition to the usual informed consent, participants are also asked to consent to the storage of biologic samples.

Notification of study results and referral of participants

Participants receive a brief report at the end of the clinic visit, including data on height, weight, blood pressure, and preliminary ECG and other routine test results. Referral to the Brazilian health-care system follows procedures described in our manual of clinical procedures (available upon request). ''Alert'' findings, which require clinical referral on an urgent basis, are reported to the participants, who are then accompanied to the emergency department of a university hospital by a member of the study staff.

DISCUSSION

ELSA-Brasil has the potential to provide important new information about the development and progression of cardiovascular disease and diabetes in a middle-income country facing accelerated changes in its demographic, nutritional, and epidemiologic profiles and huge social and economic inequities. The study represents a shift in research priorities in South America, which have traditionally focused on maternal and child health and infectious diseases. To our knowledge, ELSA-Brasil is the first large multicenter cohort study of adult health to be conducted in Brazil and funded by its health ministry.

A few characteristics of the study population and the scenario in which its members live deserve comment. By initiating enrollment at age 35 years, ELSA-Brasil allows investigation of early processes and subclinical disease

Table 4. Components of Baseline Laboratory Measurements in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008–2010

Analyte	Technical Reference
Whole blood cell count	Automatic method (center-specific)
Glucose	Hexokinase method (ADVIA Chemistry; Siemens, Deerfield, Illinois)
Total and high density lipoprotein cholesterol	Enzymatic colorimetric assay (ADVIA Chemistry)
Low density lipoprotein cholesterol	Calculated by means of the Friedewald equation
	If triglyceride levels >400 mg/dL: enzymatic colorimetric assay (ADVIA Chemistry)
Triglycerides	Enzymatic colorimetric assay (glycerol phosphate peroxidase) (ADVIA Chemistry)
Creatinine	Enzymatic colorimetric assay (Jaffé) (ADVIA Chemistry)
Gamma-glutamyltransferase	Kinetic colorimetric assay
Aspartate aminotransferase and alanine aminotransferase	Modified International Federation for Clinical Chemistry (enzymatic) assay (ADVIA Chemistry)
Uric acid	Enzymatic colorimetric assay (ADVIA Chemistry)
Calcium	Colorimetric assay (ADVIA Chemistry)
Glycated hemoglobin (hemoglobin A_{1c})	High pressure liquid chromatography (Bio-Rad Laboratories, Hercules, California)
High-sensitivity C-reactive protein	Immunochemistry (nephelometry) (Dade Behring; Siemens)
Thyroid-stimulating hormone and thyroxin	Immunoenzymatic assay (third generation) (Siemens)
Insulin	Immunoenzymatic assay (ELISA) (Siemens)
Chagas' disease antibody	Microplate ELISA (Chagatest ELISA; Wiener Laboratories, Rosario, Argentina)
Urinary sodium and potassium	Potentiometry (ion-selective electrodes) (ADVIA Chemistry)
Microalbuminuria	Immunochemical assay (nephelometry) (Dade Behring)

Abbreviation: ELISA, enzyme-linked immunosorbent assay.

manifestations, possibly minimizing the survival bias observed in older cohorts, in which a greater degree of left-censoring occurs. More specifically, a lower limit for age at enrollment also helps in capturing early-onset disease (26, 27). Studying both men and women permits investigation of societal changes in gender relationships which have occurred over recent decades, as well as gender as an association modifier. Collection of data on patterns of reproduction, marriage, family composition and caring, and work-family interactions allows investigation of the role of these frequently less-studied exposures. ELSA-Brasil's baseline is set squarely within the obesity epidemic—almost 50% of Brazilians are currently overweight or obese (10). The study can investigate the role of interactions between obesity and other risk factors, particularly

Table 5. Some Novel Aspects of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)

Measurement	Innovative Aspects
Standardized meal test with stored postload blood samples for persons with known diabetes	Investigation of the role of postprandial oxidative stress and inflammatory and metabolic responses to energy and fat ingestion in the development of diabetes complications
Oral glucose tolerance test with stored postload blood samples and measurement of hemoglobin A_{1c} at baseline and follow-up	More detailed characterization of the role of the postprandial state in disease processes
Social class, religion (both present and past), work-family interface, neighborhood characteristics	Evaluation of selected social and cultural exposures in the development of outcomes of interest in a Latin American cohort
Clinical Interview Schedule—Revised	Evaluation of the role of common psychiatric disorders in the development of various outcomes
Multiple cognitive function tests applied throughout the whole cohort age range	Widened evaluation of the natural history of cognitive function and risk factors for minor and major declines over time
Overnight urine collection	More precise measurement of sodium and potassium intakes in the investigation of their role in disease outcomes
Epicardial fat	Investigation of this newly measurable risk factor in the etiology of cardiovascular disease, as well as diabetes and its complications

those related to social determination and low levels of physical activity.

In addition, the social and ethnic diversity of the cohort and its large sample size are strengths that will allow insights into interactions between social and biologic risk factors with regard to subclinical and clinical manifestations of diabetes and cardiovascular diseases. The fact that our study is being carried out in major cities with large and heterogeneous populations of mostly low and middle income levels suggests that our external validity may extend to urban centers of similar characteristics both within and outside of Brazil.

We designed a cohort study of workers with stable employment and retirement benefits in order to ensure a satisfactory level of retention of participants during follow-up. Furthermore, the choice of such a cohort allows the application of relatively complex questionnaire strategies, which might not be readily grasped by participants of a lower educational status.

Additionally, given the extensive nature of its measurements, ELSA-Brasil is poised to contribute to the basic understanding of psychosocial and pathophysiologic pathways of causation and progression of these diseases. Some novel features in this regard are highlighted in Table 5. Postload samples in participants with diabetes will allow a closer assessment of postprandial processes in the development of chronic complications of this disease. Investigation of pathways centered on chronic inflammation, as developed within a conceptual framework postulating their role in the development of atherosclerotic diseases and diabetes (28), can be extended to incorporate additional dimensions of causality such as neighborhood and life-course adversities (29). Additionally, ELSA-Brasil will ascertain the presence of chronic kidney disease, cognitive deficits, and psychiatric morbidity at baseline—conditions that are related to and frequently have risk factors similar to those for cardiovascular diseases and diabetes (30, 31). Because these conditions represent important components of disease burden, new analyses of special interest can be performed; for example, by evaluating the role of incident and recurrent psychiatric morbidity in the development and progression of kidney disease (32) and cognitive disorders (33), or the role of inflammatory and neurodegenerative processes in depression (34). Overnight urine collection will permit more precise examination of the role of sodium intake in disease outcomes, a question of recently renewed interest (35). Furthermore, echocardiographic measurement of epicardial fat will permit examination of the association of this new risk marker (22) with many disease processes and outcomes. Among the sociocultural and psychological factors, stress in the workplace, ethnicity and discrimination, work-family interface, religion (both present and past), neighborhood characteristics, social class, social capital, and social networks can be examined as social risk factors, either individually or as modifiers of biologic risk factors.

The availability of various stored biologic specimens—plasma (citrate, heparin, ehtylenediaminetetraacetic acid), serum, urine, and DNA, obtained in both fasting and postload states—will permit the consideration of markers of both currently known and novel predictors of chronic diseases. These investigations can proceed not only within the current organizational structure of the project but also through ancillary studies. The study design allows assessment of hypotheses using a case-cohort strategy (36), as has been successfully done in other cohort studies. Although some measures (e.g., accelerometry) were strongly considered for the baseline examination, either cost or operational aspects impeded their implementation. Subsequent follow-up visits will permit incorporation of additional measurements.

In sum, ELSA-Brasil will permit innovative investigation of multiple exposures and outcomes and will assist in the establishment of prevention and control policies aimed at reducing the chronic disease burden in Brazil and other low- and middle-income countries.

ACKNOWLEDGMENTS

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The ELSA-Brasil baseline study was supported by the Brazilian Ministry of Health (Science and Technology Department) and the Brazilian Ministry of Science and Technology (Financiadora de Estudos e Projetos and CNPq National Research Council) (grants 01 06 0010.00 RS, 01 06 0212.00 BA, 01 06 0300.00 ES, 01 06 0278.00 MG, 01 06 0115.00 SP, 01 06 0071.00 RJ).

The authors thank the research team of the ELSA-Brasil baseline study for their contribution.

Conflict of interest: none declared.

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