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Medical assessments and measurements in ELSA-Brasil

Jose Geraldo Mill[I]
Karina Pinto[II]
Rosane Härter Griep[III]
Alessandra Goulart[IV]
Murilo Foppa[V]
Paulo Lotufo[IV]
Marcelo K Maestri[VI]
Antonio Luiz Ribeiro[VII]
Rodrigo Varejão Andreão[VIII]
Eduardo Miranda Dantas[I]
Ilka Oliveira[IX]
Sandra C Fuchs[VI]
Roberto de Sá Cunha[I]
Isabela M Bensenor[IV]

[I] Departamento de Ciências Fisiológicas. Centro de Ciências da Saúde. Universidade Federal do Espírito Santo. Vitória, ES, Brasil

[II] Instituto de Saúde Coletiva. Universidade Federal da Bahia. Salvador, BA, Brasil

[III] Laboratório de Educação em Ambiente e Saúde. Instituto Oswaldo Cruz. Fundação Oswaldo Cruz. Rio de Janeiro, RJ, Brasil

[IV] Centro de Pesquisa Clínica e Epidemiológica. Hospital Universitário, Universidade de São Paulo. São Paulo, SP, Brasil

[V] Programa de Pós-Graduação em Ciências Cardiovasculares, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul. Porto Alegre, RS, Brasil

[VI] Hospital de Clínicas de Porto Alegre. Universidade Federal do Rio Grande do Sul. Porto Alegre, RS, Brasil

[VII] Hospital das Clínicas. Departamento de Clínica Médica. Faculdade de Medicina. Universidade Federal de Minas Gerais. Belo Horizonte, MG, Brasil

[VIII] Coordenadoria de Engenharia Elétrica. Instituto Federal do Espírito Santo. Vitória, ES, Brasil

[IX] Departamento de Radiologia. Faculdade de Medicina. Universidade de São Paulo. São Paulo, SP, Brasil

Correspondence:
José Geraldo Mill
Departamento de Ciências Fisiológicas
Centro de Ciências da Saúde
Universidade Federal do Espírito Santo
Av. Marechal Campos, 1468 Maruípe
29042-755 Vitória, ES, Brasil
E-mail: jgmill@npd.ufes.br

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ABSTRACT

The article describes assessments and measurements performed in the Brazilian Longitudinal Study for Adult Health (ELSA-Brasil). Some assessments including anthropometric assessment, casual blood pressure measurement, and ankle-brachial index have an established clinical application while others including pulse wave velocity, heart rate variability, and carotid intima-media thickness have no established application and do not have reference values for healthy Brazilian population but may be important predictors of cardiovascular outcomes. Blood pressure measurement following postural change maneuver was included in the ELSA-Brasil because it has not been much tested in epidemiological studies. Innovative approaches were developed for assessing the ankle-brachial index using an automatic device instead of the mercury column to measure blood pressure and for assessing the anterior-posterior diameter of the right lobe of the liver by ultrasound for quantitative assessment of nonalcoholic fatty liver disease. All ELSA-Brasil subjects were younger (35 years or more) than those included in other cohorts studying subclinical atherosclerosis. The inclusion of younger individuals and a variety of assessments make the ELSA-Brasil a relevant epidemiology study nationwide and worldwide.

DESCRIPTORS: Diagnostic Techniques and Procedures. Diagnostic Techniques, Cardiovascular, utilization. Diagnostic Techniques, Endocrine, utilization. Multicenter Studies as Topic, methods. Cohort Studies.

INTRODUCTION

The Longitudinal Study for Adult Health (ELSA) is a prospective cohort study designed to assess the incidence of cardiovascular diseases and diabetes as well as their biological and social determinants. The study originally included 15,105 subjects aged 35–74 years (2008–2010) for long-term follow-up.[3] The ELSA was designed based on the cohort model: subjects are required to attend visits at the Investigation Center (IC) for the assessment of clinical or subclinical parameters at baseline including diseases of interest. They all undergo a wide range of measures to assess cardiovascular diseases and diabetes. Some assessments including anthropometric assessment, casual blood pressure (BP) measure, and ankle-brachial index (ABI) have established clinical application.[7,8,10,16,27,30] Although BP measure following postural change maneuver has an established clinical application, it has not been much applied in epidemiological studies.[2,21] Other assessments including pulse wave velocity (PWV), heart rate variability (HRV), and carotid intima-media thickness (IMT) have no established clinical application but have been applied in cohort studies[9,19,30,31] and may be important predictors of cardiovascular outcomes. However, there are no reference values in the general population, especially in the Brazilian population. One of the purposes of the ELSA is to estimate reference values for these measurements in healthy individuals, which can be a major epidemiological contribution in Brazil. Innovative approaches were developed for assessing the ABI using an automatic device instead of the mercury column to measure blood pressure and for assessing the anterior-posterior diameter of the right lobe of the liver by ultrasound for quantitative assessment of nonalcoholic fatty liver disease (NAFLD). Standard sample collections and readings in specialized laboratories are key strategies for ensuring quality measurements. The issue of quality measurements in the ELSA is detailed elsewhere in this supplement.[28]

This article summarizes the ELSA-Brasil assessment protocols focusing on those with innovative approaches that could be incorporated into medical practice and on those that do not have established clinical applications. Thus, it is required to estimate reference values for healthy populations, one of ELSA's goals. The assessments are here categorized according to their established clinical application, established application in epidemiological studies and innovative approaches. Table 1 lists all assessments according to this categorization and Table 2 lists cohort studies using similar approaches.

ASSESSMENTS WITH ESTABLISHED CLINICAL APPLICATION

Anthropometric assessment

Anthropometric measures included weight and height measures, waist and hip circumference, sitting height and neck circumference taken following standard techniques.[20] The body mass index (BMI) was weight (kg) divided by height squared (m^2).

Casual blood pressure

BP was taken using a validated oscillometric device (Omron HEM 705CPINT) after a 5-minute rest with the subject in a sitting position in a quiet, temperature-controlled room (20–24°C).[22] Three measurements were taken at one-minute intervals. The mean of the two latest BP measurements was casual BP.

Ankle-brachial index

ABI is a noninvasive test recommended for assessment of peripheral arterial disease.[27] Three systolic BP measurements were taken with the subject in the supine position at each ankle, alternating between right and left ankles every two minutes. Then three BP measures were taken at the right arm every two minutes (Omron HEM 705CPINT). The total time for all measurements was 20–25 minutes. The ABI at each leg was calculated by dividing the systolic BP measured at the ankles by the highest pressure obtained at the right arm. Measures lower than 0.9 require clinical investigation while those lower than 0.5 are suggestive of severe obstructive vasculopathy.[27] An innovative approach was applied in the present study: ABI was measured using an automated device rather than the mercury column. The use of mercury-containing devices have been subjected to restrictions due to environmental safety concerns in Brazil and the use of mercury columns was not allowed at the São Paulo study site (IC-SP) following the Brazilian Ministry of Labor requirements. The original technique was thus adapted for use with an automated device, which reduced the duration of the test by five minutes.

Conventional electrocardiogram

Conventional 12-lead electrocardiograms (ECG) were performed using a digital device (Atria 6100, Burdick, Cardiac Science Corporation, USA) with automated readings of heart rate, duration, amplitude, and axis of P wave, QRS complex and T wave in addition to QT, QTc, and QT dispersion. All precordial electrodes were positioned after identifying the location for V4 electrode with a square. The Electrocardiogram Reading Center (ERC) at the IC-MG provided all ECG readings in the ELSA following the Minnesota ECG Coding.[25]

Blood pressure measurement following postural change maneuver

Although blood pressure following postural change maneuver is usually measured as part of medical

Table 1. Classification of assessments and measurements. ELSA-Brasil.

Assessments with established clinical application used in cohort studies
No technical innovation
Anthropometric measurements
Casual blood pressure measurement
Conventional electrocardiogram
Technical innovation
Ankle-brachial index
Assessments with established clinical application rarely used in cohort studies
Blood pressure measurements following postural change maneuver
Assessments with no established clinical application
Pulse wave velocity (PWV)
Carotid intima-media thickness (IMT)
Abdominal wall fat thickness
Heart rate variability (HRV)
Retinography
Assessments with an innovative approach
Measurement of anteroposterior diameter of the right lobe of the liver

Table 2. Assessments/measurements included in the ELSA-Brasil and other cohort studies with similar methods

Anthropometric assessmenta	All cohort studies
Blood pressure measurementa	All cohort studies
Ankle-brachial index[10,15,30]	Atherosclerosis Risk in Communities Study (ARIC), Framingham Heart Study (offspring), Multiethnic Atherosclerosis Study (MESA)
Electrocardiogram[10,15,26,30,33]	All studies with subject visits at the study site
Blood pressure measurement following postural change maneuver[8,14,26]	ARIC, Honolulu Heart Study, Malmö Preventive Project
Pulse wave velocity(PWV)[1,9,26,31,33]	ARIC, Cardiovascular Risk in Young Finns Study, Rotterdam Study, Bogalusa Heart Study, Framingham Heart Study
Carotid intima-media thickness (IMT)[9,10,16,17,26,31]	ARIC, Bogalusa Heart Study, Cardiovascular Risk in Young Finns Study, Coronary Artery Risk Development in Young Adults (Cardia Study), Guangzhou Biobank Cohort Study, MESA, Whitehall II Cohort Study
Heart rate variability(HRV)[9,15,19]	Bogalusa Heart Study, Cardia Study, Framingham Heart Study (original and offspring), Whitehall II Cohort Study
Retinography[10,26]	ARIC, MESA

[a] This information is self-reported and validated in a small study in studies using questionnaires for data collection where subjects did not come for visits at the study sites.

evaluation of patients with heart or neurological conditions, few studies have included this measure as a predictor of cardiovascular disease.[11] Two studies − the Honolulu Heart Program and the Atherosclerosis Risk in Communities (ARIC) − investigated this relationship and showed that postural hypotension was positively associated with hypertension, ischemic heart disease, and stroke.[21,26,30] In the ELSA, BP after postural change was measured following the ARIC technique and after ABI measures were taken while the patient was at rest in the supine position. BP in the right arm was first measured in the supine position (Omron HEM 705CPINT) and the subject was then asked to stand up at once (with the evaluator's help as needed). BP was reassessed within two, three, and five minutes of standing. Orthostatic hypotension was defined as ≥ 20 mm Hg decrease in systolic BP and/or ≥ 10 mm Hg decrease in diastolic BP within 3 minutes of orthostasis.[11,21]

ASSESSMENTS WITH NO ESTABLISHED CLINICAL APPLICATION USED IN OTHER COHORT STUDIES

In this group there were included assessments that were likely to provide other relevant input related to cardiovascular disease and diabetes by evaluating structural and functional parameters of the heart and blood vessels and central fat accumulation. Some assessments (PWV, HRV, IMT) have been used in other cohort studies but have no established clinical application. This is mostly because many parameters obtained in these assessments including PWV, IMT, density of the liver, ABI and temporal and spectral parameters of HRV do not have well-defined normal ranges in healthy populations in general and in the Brazilian population in particular.

Assessment of structure and function of blood vessels

Atherosclerosis is the most prevalent cardiovascular condition worldwide causing cardiovascular events of great impact such as myocardial infarction and stroke.[18] The ELSA protocol included assessments to evaluate large artery stiffness (PWV), subclinical atherosclerosis (IMT), and arteriolosclerosis of retinal blood vessels.

1. Pulse wave velocity

Large arteries act as a pressure reservoir during systole due to the predominance of elastic fibers over collagen fibers in their walls. A decrease in arterial elasticity with aging is a result of both fragmentation and disorganization of elastic fibers in the vascular wall.[5] Artery stiffness has been used as a marker of arterial aging but pressure inside the blood vessel and endothelial dysfunction can also cause stiffness.[24,32] Sudden distention of the aortic root during systole generates a wave that propagates through the arterial wall at a speed ten times greater than that of blood. According to the Moens-Korteweg equation, PWV is proportional to the elastic modulus of the medium:

$PWV = \sqrt{(Eh/2\rho R)}$

where:

E = Young's modulus

h = vascular wall thickness

R = radius of the vessel

ρ = blood density

Thus, the single effective determinant of PWV in the arterial vascular network is the elastic modulus as all other factors can be roughly considered constant. Therefore, increased carotid-femoral PWV indicates loss of elasticity of the aortic wall.

The carotid-femoral PWV was measured using a validated automated device (Complior, Artech Medicale, France) with the subject in the supine position in a temperature-controlled room (20°C–24ºC).[4] First, BP was taken in the right arm with the subject in the supine position using an oscillometric device (HRM Onrom 705 CP). The distance from the sternal furcula to the right femoral pulse was measured with a metric tape regardless of abdominal curvature. Pulse sensors were positioned in the right carotid and femoral arteries so that pulse waves were recorded and visualized on a computer screen. A computer program that can adequately detect and record pulse waves was used. PWV is calculated by dividing the distance from the sterna furcula to the femoral pulse by the difference between the rise delay of carotid and femoral pulses. A subject's PWV was the arithmetic average of readings obtained in ten consecutive cardiac cycles at regular heart rate.

PWV is affected not only by stiffness of large arteries (mainly aorta), but also by the pressure inside the artery which determines elastic and collagen fibers that are recruited.[5,23] PWV must be adjusted for BP using the pressure measure that is closest to the stiffness measure. All PWVs were measured and recorded at study sites and sent to the central cardiovascular physiology laboratory (IC-ES) for analysis and validation. ELSA is the largest study where PVW data was recorded and analyzed centrally generating robust data to construct normal references ranges and on the effect of biological and environmental factors on arterial aging.

2. Carotid intima-media thickness

The etiology of atherosclerosis is not yet fully understood, but its development and progression are dependent on the interaction between genetic and lifestyle factors.[15,18,33] Atherosclerosis is a systemic disease that involves different arterial territories with varying degrees of severity.[33] Atherosclerotic plaques are slowly progressive, starting with the transport of low density lipoproteins across the endothelium into the subendothelial space. Endothelial dysfunction is characterized by increased permeability of the endothelium to lipoproteins and may initiate the process of atherosclerotic plaque formation. Oxidation of LDL-cholesterol would be the next step in plaque formation triggering a local inflammatory reaction.[18] The degree of fibroblast proliferation and migration of smooth muscle cells from the medial layer to the subendothelial space can be inferred by IMT. IMT has been used in epidemiological research as a marker of subclinical atherosclerosis and an independent risk factor for ischemic heart disease.[1,9,10,23] In ELSA, IMT was assessed in all subjects in a standardized manner using a device (Aplio XG™, Toshiba) with a 7.5 MHz linear transducer. The carotid bifurcation was examined over a length of 3 cm for plaques. In addition, images of common carotids were acquired

over a length of 1 cm, starting 1 cm below the carotid bifurcation.[17] They were collected and recorded at study sites and send to the central ultrasound imaging laboratory (SS-SP) for analysis. Image data of three cardiac cycles were analyzed centrally using an automated computer program (MIA™), and IMT was calculated by averaging measures taken in the right and left carotids.

3. Retinography

The retina is a unique body site where the microcirculation can be imaged directly, providing an opportunity to detecting vascular diameter changes, microaneurysms, micro-hemorrhages, among others. The finding of arteriolar narrowing is associated with the development of diabetes, hypertension and dyslipidemia and can be correlated with myocardial infarction, stroke, and cardiovascular mortality.[10,14,18,34] The ELSA is an excellent opportunity to assess retinal vascular changes and their association with large artery changes. Data from cohort follow-up will also allow to prospectively assessing the association of retinal changes with cardiovascular outcomes in coronary and cerebral circulations.

Retinography was performed using a nonmydriatic retinograph (CR-1, Canon, Japan) with a 10-megapixel digital camera (Canon EOS 40 D). The subjects had their pupils naturally dilated (about four minutes in a dark room), and for each eye two 45º fundus images were obtained, one centered on the optical disk and the second one on the macula. The central retinography laboratory (IC-RS) developed standardized image acquisition and reading protocols and DICOM (~30MB) and JPEG (~3MB) images were acquired. DICOM images were transferred and stored in the ELSA's Picture Archiving and Communication System (PACS); JPEG images were recorded on CD/DVD at study sites and mailed to the central retinography laboratory.

All retinal images were processed using an imaging program (Canon CR-1 Retinal Imaging Control Software, Canon, USA). First, medical cues were identified using Image J (Java-Based Image Processing and Analysis Program, National Health Institute, USA) and then vascular caliber was measured using a measurement system for retinal blood vessels (IVAN, Nicola J. Ferrier, College of Engineering, Fundus Photography Reading Center, University of Wisconsin-Madison, USA), provided by the University of Wisconsin (USA).[14] The Retinal Assessment System (RAS), developed at the Universidade Federal do Rio Grande do Sul, will be used to assess a selected group of subjects.[24] The severity of retinal changes will be rated for microvascular complications in subgroups of subjects such as diabetics.

Assessment of heart structure and function

Echocardiograms were performed to assess heart structure and function and a 10-minute continuous ECG recording to determine HRV.

1. Echocardiogram

The echocardiogram is an ultrasound test performed to assess heart structure and function and can provide diagnostic and prognostic parameters. It can detect the development and impact of maladaptive processes in cardiovascular diseases and common pathophysiological mechanisms of cardiovascular and metabolic conditions. Echocardiograms were performed in all ELSA study sites, giving priority to tthis exam in a random subsample of the cohort (10% of the sample) and in subjects older than 55 years. All tests were performed by echocardiographers following a standard acquisition protocol developed in line with current research recommendations.[13]

Echoimages were obtained using a device (Aplio XG, Toshiba) with a 2.5 MHz sector transducer. They were sent to ELSA PACS and staff at the central echocardiogram laboratory (IC-RS) performed all readings at their end (ComPACS, Medimatic, Srl, Italy). The readings consisted of qualitative analysis of echocardiographic findings and measurements of quantitative parameters to define outcomes of interest including left ventricle (LV) geometry and size, left atrial size, LV systolic and diastolic function, segmental LV dysfunction, valvular heart disease, and fibrocalcific degeneration and epicardial fat thickness.

2. Heart rate variability

HR is continuously modulated by the degree of sympathetic and parasympathetic nerve discharge to the sinus node. HR fluctuations provide information on autonomic balance to the heart, which depends on the integration of efferent signals to brainstem nuclei from carotid pressoreceptors, chemoreceptors, and atrium volume and pulmonary artery sensors, among others. The predominance of vagal control increases HRV, which is associated with better prognosis in patients with heart failure, myocardial infarction, and other cardiovascular diseases. In contrast, increased sympathetic activity is associated with decreased HRV and poor prognosis in patients with these same conditions.[29]

For HRV determination a 10-minute continuous ECG was obtained with subjects in the supine position in a quiet, temperature-controlled room (20–24ºC). All recordings were obtained from a single lead (usually D2) using a digital electrocardiograph (Micromed, Brazil) at a frequency of 250 Hz. A computer program (WinCardio) was used to generate time series of RR intervals that were sent to the central cardiovascular physiology laboratory (IC-ES). All readings were

performed in a computer program that eliminated artifacts and selected RR intervals lasting 0.5 to 2.0 seconds and then temporal and spectral analysis of HRV was performed using an autoregressive model to identify very low-frequency (VLF, 0 to 0.04 Hz), low-frequency (LF, 0.04 to 0.1 Hz) and high-frequency spectral bands (HF, 0.1 to 0.4 Hz). HF amplitude[29] relates to vagal modulation of HR while LF band depends on both sympathetic and vagal modulation.[29] A 10-minute standing ECG was also obtained in about 5% of the subjects because there is a major increase of LF energy and increased sympathetic control of HR in the standing position.[12]

Abdominal ultrasound imaging

Abdominal fat accumulation is strongly correlated with chronic diseases including cardiovascular diseases and diabetes. It has been postulated that abdominal fat accumulation induces a chronic proinflammatory state leading to the development of hypertension, diabetes, and atherosclerosis. Thus, one of ELSA's focus of interest was to measure fats deposits in the abdominal wall and omentum.

Like in NAFLD, visceral mesenteric and omental fat has been associated to endocrine, metabolic, and cardiovascular risk factors. Ultrasound imaging has been used in recent years for biometric profiling abdominal fat distribution. Central obesity in ELSA subjects was assessed by measuring fat layers in the abdominal wall (subcutaneous and preperitoneal fat) and intra-abdominal fat (visceral fat) through ultrasound images obtained in a Toshiba Aplio XG™ scanner with a 7.5 MHz linear transducer. Three lines were traced in two abdominal wall images (xiphoid and umbilical) to measure subcutaneous and preperitoneal fat layers below the xiphoid process. All images were saved and sent to the central ultrasound imaging laboratory (IC-SP) for analysis using the MIA™ program. ELSA data will allow correlating omental fat with standard anthropometric measurements (waist circumference and waist-to-hip ratio) that have been used as indicators of abdominal obesity.[18,20]

ASSESSMENT WITH AN INNOVATIVE APPROACH

NAFLD is the most common liver disease associated with insulin resistance.[6] It is usually quantitatively assessed by medical imaging specialists through increased echogenicity in liver ultrasound examinations . These assessments, however, are evaluator-dependent. An innovative quantitative approach was proposed in ELSA to assess NAFLD: measurement of the antero-posterior (AP) diameter of the right lobe of the liver. Subjects with NAFLD are expected to have increased AP diameters. Liver images were obtained using standard equipment (Toshiba SSA-770A Aplio, Japan) and a broadband, convex transducer (PVT-375BT) at a center frequency of 3.5 MHz (2.5 to 5.5 MHz). The transducer was placed in the intercostal space and the gallbladder and the inferior vena cava were used as anatomical landmarks for gain control settings, which allowed to making adjustments according to the subject biotype. Steatosis was diagnosed by liver parenchymal echogenicity and increased ultrasound attenuation. The semi-quantitative assessment of attenuation of the acoustic beam was based on the visualization of the diaphragm: good visualization (normal); partial visualization; and non-visualization.

Static images of the right lobe of the liver in axis oblique sections including anatomical structures aligned in the AP axis − the anterior surface of right liver lobe, gallbladder, inferior vena cava and diaphragmatic angle of the liver − were acquired and saved on CD/DVD. If the gallbladder was not visualized inferior vena cava blood flow was used as an anatomical landmark for gain control settings.

The saved images were sent to the central ultrasound imaging laboratory (IC-SP) and then analyzed using TomTec's Image-Arena. It was measured by drawing a straight line perpendicular to the skin in the AP axis of the right lobe of the liver from the surface to the posterior diaphragmatic angle of the liver. All images were assessed for three sonographic parameters: echogenicity, echotexture and acoustic beam attenuation. Increased echogenicity is seen when liver parenchyma is brighter than usual. Heterogeneous echotexture occurs when there are coarse echoes compared to the usual pattern. Abnormal acoustic beam attenuation occurs when visualization of intrahepatic vessels or the posterior diaphragm is reduced, partial (mild) or absent (severe).

FINAL CONSIDERATIONS

The ELSA-Brasil protocol included assessments with well-established clinical and epidemiological research application that can provide data that are relevant and comparable with those already available from other populations. There were also included assessments/measurements applied in other cohorts to assess whether they have predictive ability for cardiovascular diseases and diabetes in the Brazilian population. The inclusion of subjects from age 35, i.e., younger compared to other cohort studies with similar goals to the ELSA,[10,30] was a strategy to identify early predictors of atherosclerosis and subclinical atherosclerosis that could possibly be incorporated into more effective prevention policies. The ELSA stands out for including younger subjects and a wider variety of assessments/measurements compared to other cohort studies investigating the epidemiology of chronic diseases.

Suitable spaces at each study site were required to conduct all assessments and specialized teams were trained in data collection centrally. All ELSA-Brasil procedures are detailed elsewhere.[7] Furthermore, the ELSA took an innovative approach by assessing ABI using an automated BP device successfully. Another novel approach was the proposed quantitative assessment for NAFLD, which is being validated using computed tomography as the gold standard. If the results are satisfactory, it would provide an easier to perform diagnostic tool that is evaluator-independent. Finally, the centralized readings of imaging assessments required the implementation of internet transmission of DICOM images collected in the ELSA study sites to the study's central laboratories. These laboratories provided training and certification of data collection teams and developed algorithms for standard readings of all assessments.

Some of the assessments included in the ELSA such as PWV, IMT, and spectral indices of HRV do not have normal reference values for general population. Since this cohort study comprises mostly healthy subjects, reference values in apparently healthy Brazilian population can be established.

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