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COHORT PROFILE

Cohort Profile: The Bambuí (Brazil) Cohort Study of Ageing

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How did the study come about?

Ageing of the population is the most important demographic change facing many countries around the world. The speed of demographic ageing in Latin American and the Caribbean, however, will be unprecedented in comparison with Western European and North American countries.[1] This demographic change will generate populations with large numbers of elderly who at some time in their lives have been exposed to infectious diseases. Infections may affect ageing in different ways. Most important postulated mechanisms include enhanced inflammation, pathogen-dependent tissue destruction or accelerated cellular ageing through increased turnover.[2] Most epidemiological studies of ageing have, understandably, focused on non-communicable diseases and related conditions. To our knowledge, no previous population-based cohort study had examined the consequences of the double burden of non-communicable diseases and a parasitic chronic infection in old age.

Chagas disease, which is caused by the protozoan *Trypanosoma cruzi*, is endemic in Latin American countries, with about 8 million people infected.[3] As a consequence of immigration from endemic countries, Chagas disease is an emerging issue in North America and Europe, and an example in the era of globalization of how infectious diseases extend beyond endemic areas.[4] Chagas disease is related to poor socio-economic circumstances in early life. In endemic areas, the main source of infection is a bloodsucking triatomine insect that colonizes poor households. Most individuals in these areas acquire the infection at <20 years of age, and ~30% develop chronic chagasic cardiomyopathy.[5] The ageing of the population, together with a cohort effect observed in endemic areas where the household insect transmission has been interrupted, will lead to increases in the number of older adults who are already infected by *T. cruzi*.[3,6,7] The main objective of the Bambui Cohort Study of Ageing is to examine the separate and joint effects of chronic *T. cruzi* infection and non-communicable diseases on health outcomes in old age.

Where is the study area?

The study has been conducted in Bambuí, a city of approximately 15 000 inhabitants located in the state of Minas Gerais in southeastern Brazil, an area long known to be endemic for Chagas disease.[8] The intensive use of insecticides interrupted the household transmission of *T. cruzi* infection in the study area by 1970. As a consequence, by mid-1990s, seropositive cases were no longer seen in young people, but the infection remained highly prevalent among elderly residents who had acquired the infection in their youth.[7]

Who is in the sample?

The eligible population for the cohort study consisted of all residents in Bambui aged ⩾60 years on 1 January 1997, who were identified by a complete census in the city. Of 1742 older residents, 92.2% participated in the baseline interview. Blood collection and other examinations were performed in 85.8% of the eligible elderly. Selected baseline characteristics of participants are presented in Table 1. Further details are described in a previous publication.[9]

Participants signed an informed consent at baseline and at each subsequent visit and authorized death certificate and medical records verification. The Bambuí Cohort Study of Ageing was approved by the Ethics Board of the Fundação Oswaldo Cruz in Rio de

Table 1 Selected baseline characteristics of participants, The Bambuí Cohort Study of Ageing, 1997

Characteristic	Percentage or mean (SD) or median (IQR)
Socio-demographic	
Age, mean (SD)	69.3 (7.4)
Female sex, %	60.0
Schooling inferior to 4 years, %	65.3
Marital status: widowed, %	35.4
Trypanosoma cruzi infection[a]	37.7
Classical cardiovascular risk factors	
Current smokers	18.7
Systolic blood pressure in mmHg, mean (SD)	137.3 (22.6)
Total cholesterol in mg/dl, mean (SD)	233.0 (40.1)
HDL cholesterol in mg/dl, median (IQR)	47 (39–57)
Diabetes mellitus, %	14.5
Left ventricular hypertrophy by ECG, %	3.2

N varies from 1484 to 1606, depending on missing values. HDL: high-density lipoprotein; IQR: inter-quartile range; ECG: electrocardiogram.
[a]Positive results in three assays: hemagglutination assay (Biolab-Mérieux SA, Brazil) and two enzyme-linked immunoabsorbent assays (ELISAs) (Abbott, USA and Viener Lab, Argentina).
[b]Fasting blood glucose $\geqslant$126 mg/dl and/or treatment.

Table 2 Follow-up rates according to key baseline variables, The Bambuí Cohort Study of Ageing, 1997–2007

Variables	Baseline participants (*N*)	Followed-up (%)	*P*-value
Age, years			0.030
60–64	492	93.4	
65–69	374	92.1	
70–74	286	94.1	
$\geqslant$75	358	97.0	
Sex			
Male	642	93.2	0.227
Female	964	94.6	
Schooling in complete years			0.306
<4	1048	94.7	
4–7	430	93.0	
$\geqslant$8	126	92.1	
Trypanosoma cruzi infection			0.027
No	850	92.8	
Yes	539	95.7	
BNP values in tertiles			0.273
Lowest (<55 pg/ml)	463	93.0	
Second	466	95.3	
Highest (>118 pg/ml)	455	93.4	

Subjects known to have died were considered as traced. *P*-value: chi-square test.

Janeiro (initial project) and by the Ethics Board of the Instituto René Rachou of the Fundação Oswaldo Cruz in Belo Horizonte (procedures that the initial project did not cover), Brazil.

How often they have been followed up, and what is the attrition rate?

Cohort members undergo annual follow-up visits, which consist of an interview and verification of death certificates. Other procedures were repeated in selected years (2000, 2002 and 2008). From 1997 to 2007, during a mean follow-up of 8.6 years, 641 participants died and 96 (6.0%) were lost to follow-up. Those who were lost were more likely to be younger and not infected with *T. cruzi*. Losses to follow-up were not associated with sex, schooling or B-type natriuretic peptide (BNP) level at baseline (Table 2).

What does it cover—and how has this changed?

Table 3 summarizes the variables included in the cohort baseline and follow-up visits. The main outcome variables include major geriatric syndromes, such as cognitive decline, functional dependence and falls, as well as death, use of health services, and use of medications. Exposure variables cover social and demographic characteristics, psychosocial factors, lifestyle, mental health, classical cardiovascular risk factors, some novel biomarkers and Chagas disease-related measures. Genome wide scanning (~1 million single nucleotide polymorphisms) of the study population is in process, and this variable will be incorporated to the cohort data set in the future. Serum, plasma, buffy coat and DNA aliquots collected in 1997 and 2008 were stored at −80°C in freezers for future use. A previous publication provides more detailed information on the baseline variables and how they were measured.[9]

What has been found?

Publications using data from the baseline survey concentrated mainly on three themes: cardiovascular diseases and risk factors, mental health, and social inequalities in health. Three studies showed that the prevalence of hypertension,[10] diabetes mellitus[11] and

Table 3 Information collected at baseline and at follow-ups, The Bambuí Cohort Study of Ageing, 1997–2008

Source	Variables
Baseline (1997) interview	Social and demographic characteristics (age, sex, ethnicity, recent history of migration, conjugal status, schooling, schooling of the spouse, religion, living arrangements, personal and family income, occupational history and current occupation). Psychosocial factors (social support and social network, life events and selected psychological traits). Lifestyle (smoking, alcohol consumption, dietary habits and physical activity). Self-reported health conditions (self-rated health and prior medical diagnosis for selected diseases or conditions). Physical symptoms (angina, intermittent claudication, chronic hand and knee pain, and stroke). Mental symptoms and sleep (common mental disorders, insomnia, daytime sleepiness and sleep habits). Reproductive health history (for women). Functioning (cognition, ability to perform activities of daily living and instrumental activities of daily living). Falls. Use of health services and of medication.
Trypanosoma cruzi infection at baseline	Seropositivity for *T. cruzi* at baseline was assessed by three different assays performed concurrently: a hemagglutination assay and two ELISAs.
Other baseline measures	Anthropometric measures (weight, height, arm circumference, wrist circumference, waist circumference, hip circumference, triceps skinfold and demi-span). Blood pressure measures (three measurements). ECG. Biochemical analysis (fasting glucose, blood creatinine, urea, total protein, albumin, uric acid, calcium, phosphorus, magnesium, total, high-density lipoprotein, and low-density lipoprotein cholesterol, tryglicerides, high-sensitive C-reactive protein and B-type natriuretic peptide). Haematological tests (red blood cell count, haemoglobin, haematocrit, red blood cell indices, white blood cell count and platelet count). Antibodies against muscarinic receptors. Genetics (Apolipoprotein E polymorphism and genomewide scanning [in process]).
Annual follow-up interviews	Vital status. Self-rated health. Common mental disorders. Cognition. Ability to perform activities of daily living and instrumental activities of daily living. Use of health services and of medication. Changes in lifestyle. Other questions from the baseline interview are part of some but not of all follow-up interviews.
Examinations at follow-up	Anthropometric and blood pressure measurements were repeated in years 2000, 2002 and 2008. ECGs were repeated in years 2002 and 2008. Blood collection and selected biochemical and haematological tests were repeated in 2008.
Verification of death certificates	Continuous
Samples storage	Serum, plasma, buffy-coat and DNA aliquots were stored at baseline and in 2008.

intermittent claudication[12] were comparable with those in high-income countries. Another publication showed a very high prevalence of *T. cruzi* infection,[7] revealing a double burden of a chronic infectious disease and non-communicable diseases in the study population. An additional burden was mental health. The prevalence of depressive symptoms, common mental disorders[13,14] and insomnia[15] were similar to—or even higher than—that of other elderly populations. Furthermore, the prevalence of Parkinsonism and Parkinson's disease was higher than that observed in other populations worldwide, especially because of the high rates of drug-induced and vascular Parkinsonism.[16] Other studies provided new insights on the performance of some instruments to measure cognitive performance[17–19] and common mental disorders[20] in a population with very low levels of schooling.

Social inequalities in health were remarkable. The results indicated that even small differences in family income were sufficient to produce inequalities in health and health-related conditions. Monthly family income in the lowest tertile (<240.00 USD) was associated with unhealthy lifestyle, worse mental and physical health, worse functioning, greater use of non-prescribed medications, and higher hospitalizations rates.[21]

Recent studies have incorporated genetic data. The distribution of Apo E genotypes among cohort members was similar to that of most Western populations.[22] African-Brazilian elderly were more likely to be E4 allele carriers, as observed in individuals from Africa.[22] Individuals carrying the E2 allele had higher tryglicerides and lower low-density lipoprotein (LDL) cholesterol levels.[23] The E4 carriers had higher LDL cholesterol levels.[23] The ApoE polymorphism was

not found to be associated with prevalent hypertension,[23] 3-year incident hypertension[24] and 9-year all-cause mortality.[25]

Another set of publications focused on Chagas disease. An initial cross-sectional study showed that seropositive elderly were more likely to report worse self-rated health, to have stayed recently in bed, to use more prescribed medications and to be hospitalized independently of other relevant factors.[7] Cardiac vagal impairment, a typical feature of Chagas disease, was found to be associated with *T. cruzi* infection in young elderly but not in the oldest old.[26]

Other recent publications of this cohort are focused on other consequences of Chagas disease and on new prognostic biomarkers. BNP, which is released from cardiomyocytes in response to ventricular wall stretch, has emerged as a novel biomarker to predict cardiovascular events in the context of non-transmissible diseases[27]; two publications using longitudinal data of the Bambui cohort examined the prognostic value of BNP in Chagas disease. The main findings were:

(i) There was a graded cross-sectional association (odds ratio estimated by ordinal logistic regression = 1.99; 95% CI 1.43–2.76) between *T. cruzi* infection and cognitive impairment, which is biologically plausible. This association was independent of several known risk factors and was not mediated by either digoxin use (the drug most frequently used to treat heart failure among study participants) or the presence of a major alteration on electrocardiogram (ECG).[28] To our knowledge, this was the first epidemiological study that established an association between a protozoan infection and cognitive impairment. Further longitudinal analysis is ongoing to confirm this observation and to identify underlying mechanisms.

(ii) *Trypanosoma cruzi* infection was a strong predictor of 10-year mortality in the elderly, independent of age, sex and traditional cardiovascular risk factors [hazard ratio (HR) = 1.56; 95% CI 1.32–1.85]. This association was consistently observed in those aged 60–69, 70–79 and $\geqslant$80 years. Overall, the population-attributable risk for mortality due to *T. cruzi* infection was 13.2%.[29] These results contradict classical studies that reported an increased risk for mortality in *T. cruzi*–infected young and middle-aged adults, but not in the elderly, and indicates that Chagas disease is an individual and population health issue in old age.

(iii) BNP was found to have prognostic value for 10-year mortality in Chagas disease. Infected persons with baseline BNP levels in the top quartile had a risk of death twice as that of those in the bottom quartile (HR = 2.07; 95% CI 1.29–3.32) independent of traditional cardiovascular risk factors and other relevant variables. The ability of BNP in predicting mortality was similar to that of ECG with reasonably stable risk discrimination over time. These findings suggest that BNP might be useful to simplify the complex risk stratification in Chagas disease.[30]

(iv) Deaths due to stroke were independently associated with Chagas disease. The risk of death from stroke over a 10-year period among *T. cruzi*–infected elderly was twice as that of those not infected (HR = 2.36; 95% CI 1.25, 4.44), independent of classical risk factors. Increased BNP alone, or in association with atrial fibrillation on ECG, strongly predicted death from stroke in *T. cruzi*–infected elderly. The evidence from this cohort study and from three previous hospital-based case–control studies support a causal link between *T. cruzi* infection and stroke, probably as a consequence of cardioembolism. When Bradford Hill's classic criteria for causality are applied, seven out of nine criteria are met.[31]

What are the main strengths and weaknesses?

Strengths of the Bambuí Cohort Study of Ageing include the fact that it sought to include the entire elderly population of the study area and obtained a high percentage of participation, the standardized and systematic measurement of parameters at baseline and at follow-ups, continuous measures of several outcome variables, and minimal loss of participants to follow-up. Another positive point is its multi-disciplinary scope, including epidemiology, statistics, geriatrics, gerontology, tropical medicine, psychiatry and human genomics. A promising aspect of this cohort study is the existence of storage aliquots for future use. The study has some limitations. Because of budget constraints, blood collection was performed at baseline and only 11 years later. Thus, eventual changes within this time interval will not be captured. All participants received their examination results at the baseline and follow-ups and were encouraged to seek medical attention when necessary. To avoid this becoming a source of bias, selected exposure indicators (e.g. lifestyle and treatment) have been monitored in the follow-up interviews. Change of *T. cruzi* infection status over time is unlikely for two reasons: first, as the transmission of the infection in the study area was interrupted decades ago, no incident cases are expected; second, as the benefit and safety of treating chronic *T. cruzi* infection in old age is uncertain,[32] none of the cohort participants had a history of antitrypanosomal medication upon entry into the cohort, and none received treatment during the roughly 10-year period in which patients were followed. Finally, statistical power for genomewide scanning studies is a concern, but this

might be overcome by increasing collaboration with other studies.

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

We welcome joint analyses of the cohort data. We would like interested investigators from other institutions to become collaborator by spending some time in Belo Horizonte and helping to build local capacity, but we are open to other options. The Bambuí data set includes a range of sensitive personal information about individuals. It is essential that privacy is protected and that confidentiality is maintained; we use a series of measures to ensure this. Maintenance and use of the data set are overseen by a Steering Committee and every project is considered by this committee. Researchers interested in collaborative work are invited to contact the principal investigator: Maria Fernanda Lima-Costa, lima-costa@cpqrr.fiocruz.br

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