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Prevalence of Alzheimer's disease in rural and urban areas in Cuba and factors influencing on its occurrence: epidemiological cross-sectional protocol

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ABSTRACT

Introduction According to the World Alzheimer's Report 2019, around 50 million people suffer from dementia, worldwide. Observational analysis revealed the existence of particular factors associated with the onset and progression of Alzheimer's disease (AD). There are no international homogeneous principles for the early detection and evaluation of memory impairment and possible AD. This work aimed at (1) determining the prevalence of possible AD in the elderly residing in urban and rural regions in Cuba and (2) identifying the main factors that could significantly influence on its occurrence.

Methods and analysis The study includes four neuropsychological tests (Clock Drawing Test, Mini-Mental Status Examination, Short Portable Mental Status Questionnaire, Cognitive and Non-Cognitive Alzheimer's Disease Assessment Scale) and two scales (Clinical Dementia Rating and Global Deterioration Scale). Moreover, the protocol includes a survey with demographic and socioeconomic information, educational level, occupation, health, neuropsychological status of subjects, familial pathological history, comorbidities and lifestyles. The study will comprise a total of 1092 subjects aged ≥60, of both genders, and from every ethnic group settled in rural and urban areas. Primary outcomes: prevalence of possible AD. Secondary outcomes: correlation among risk and protective factors and AD, and comparison of the performance of neuropsychological tests and scales.

Ethics and dissemination This research met the ethical codes of the Declaration of Helsinki. The Scientific Research Council of the Promoting Research Institute and the Ethics Committee of the Health Authorities approved the protocol. The proper written informed consent is also incorporated. The results of the survey will be published in scientific papers and shared with the Health Authorities of each municipality.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The protocol will include a significant diversity of factors that could influence on the prevalence and severity of Alzheimer's Disease (AD).
⇒ The study will include the suitable neuropsychological tests and scales for diagnosing possible AD.
⇒ The protocol will comprise occurrence study in rural and urban areas.
⇒ The study will not incorporate population under 60 years old; generally, the earlier prevalence of AD is associated with familial AD.
⇒ The study will not include biochemical markers of the disease.

INTRODUCTION

Dementia is a syndrome characterised by the progressive decline in memory, executive functions, language and other areas of cognition. It is usually associated with behavioural symptoms, which interfere with the normal development of the individual at familial and social environment. Alzheimer's disease (AD) is the most common of dementia. There is currently no effective treatment to prevent, stop or reverse the pathological processes of AD.[1]

According to the World Alzheimer's Report 2019, about 50 million people in the world suffer from dementia. This number will practically double every 20 years, reaching 152 million by 2050.[2] The cost of health assistance for treating dementia is estimated in US$1 trillion worldwide.[2 3]

In Latin America and the Caribbean, approximately 3.4 million people ≥60 aged are diagnosed with dementia.[4] This figure will increase to 7.6 million by 2030.[5] Thus, the estimated prevalence of AD will be around 11% of the older population in Latin America.[6] In Cuba, life expectancy is of 77 years, both female and male.[7] The number of people suffering from AD is approximately 160 000.[8] Consequently, elderly is considered a key risk factor for developing the disease and represents one of the major health problems.[9]

Several reports on population-based observational studies revealed the existence of particular factors associated with the onset and progression of AD.[9–12] The accumulation

of amyloid beta-peptide plaques and neurofibrillary tau tangles in the brain of patients has often been shown to be a trigger for AD.[13–16] Longitudinal studies and research reports show an association of AD with vascular risk, hypertension, hypercholesterolaemia, diabetes mellitus (type II), oxidative stress and genetic background.[9 17–20] Moreover, lifestyle factors such as active smoking, inadequate nutrition, alcoholism, sedentary life, low educational level and exposure to toxic elements (aluminium and silicon) are associated with AD.[9 17–20] In Cuba, a few studies have been performed concerning AD risk factors. Those studies have included variables such as hypertension, diabetes mellitus, heart failure, smoking, obesity, advanced age, sexual activity, level of education and genetic background.[21–24] Yet, the identification of protective factors (adequate nutritional habits and healthy lifestyles) to elude AD threat might prevent the occurrence of the disease.[25] There are no homogeneous criteria establishing proper tests or markers for prevalence of possible AD, thus far. Hence, there is an imperative need to select a set of possible risk factors for conducting population prevalence studies. A revision done by Quispe-Ramírez *et al*[26] identified, as risk factors for neurocognitive disorders, the necessity of elder adults of being supported to fulfil regular activities and certain social actions involving technology.

Commonly tools for performing AD neuropsychological diagnosis are: (1) Short Portable Mental Status Questionnaire (SPMSQ), a 10-question test version, which allows amending the score obtained according to the level of schooling of subjects; (2) Mini-Mental Status Examination (MMSE) for detecting cognitive impairment and exploring elements such as orientation, fixation memory, concentration and calculation, memory of evocation, perception, language and praxis and (iii) Clock Drawing Test (CDT) that permits evaluating cognitive and visuospatial skills.[27] A study done by specialists in Psychology and Medicine in Galicia (Spain) reported the MMES as the mainly functional test, followed by SPMSQ and CDT.[27] Alzheimer's Disease Assessment Scale (ADAS) is specially designed to identify stages of AD, and combined with the MMSE are frequently used, worldwide.[27] ADAS consists of two subscales: cognitive (ADAS-cog) and behavioural (ADAS-noncog). ADAS-cog includes assessment of memory, language, orientation, praxis and visual construction.[28] ADAS-noncog is based on observations or questions about behavioural symptoms. ADAS has been adapted to many languages and countries.[29–35] The mainly proficient tools for defining the stage of AD are (1) Clinical Dementia Rating (CDR) scale,[36] which explores memory, orientation, judgement, problem-solving and aspects of social life and (2) Global Deterioration Scale (GDS) scale[37] that describes seven global stages of dementia, according to the degree of cognitive and functional impairment observed.[38]

METHOD AND ANALYSIS

Objectives

Primary objective: to determine the prevalence of possible AD in elderly from urban and rural regions of Cuba.

Secondary objectives:

- To compare the performance of different neuropsychological tests and scales to establish the prevalence of AD in the Cuban population.
- To identify the main factors that could significantly influence on its occurrence.

Study design

The study is designed as a three-stage protocol. The correspondent physicians will apply the protocol in a single session at subject's places. Protocol includes four neuropsychological tests, two scales and a survey: SPMSQ[39 40]; MMSE[41 42]; CDT[43 44]; ADAS[28 34]; CDR Scale[36] and GDS.[37] In the first stage, the standard MMSE and ADAS will permit to calculate the prevalence of AD in each area, municipality and local population. In the second stage, it will be determined the correlation between SPMSQ and CDT tests, CDR and GDS scales in respect to MMSE and ADAS to define whether they are or not appropriate for the Cuban population. A third stage will include several statistical tests for analysing the influence of risk and protective factors on the already calculated prevalence of the disease.

Selection of factors for the survey

After analysing the bibliography and published reports, authors agreed on designing a protocol based on a proper selection of neuropsychological tests and scales. Thus, it will also comprise the following variables:

- Demographic and socioeconomic data (gender, age, educational level, occupation, skin colour, marital status, permanent residency, number of members living in the same house, family functionality, losing or detaching from a relative or a close friend, family relationships, past and current employment status and income level),
- Health (table 1) and neuropsychological status (table 2), sexual activity (frequency and orgasms), sleeping (hours, quantity, quality and disorders).
- Pathology of familial history.
- Lifestyles, sports, physical activity (type, frequency and intensity) and compensatory activities (hobbies, reading, writing, dance, crafts, studio/workshops, playing musical instruments, participation in activities as a volunteer, habit of watching films/documentaries/series/novels, board games, membership in cultural associations and travel).

Considering the impact of the consumption of specific food as protective factors, nutritional habits will be incorporated in the questionnaire, as well. Questions will include the frequency (daily, weekly, monthly and sporadically) and quantity of the different types of food (fish, cocoa, coconut, coconut oil, habitual eating of proteins,

Table 1 Health condition and familial pathological history

Psychiatric and neurological diseases	Vascular diseases	Immunological diseases	Genetic diseases	Metabolic diseases	Others diseases and conditions
Alzheimer disease*	Ischaemic heart disease*	Asthma*	Down's syndrome †	Type I diabetes*	Severe respiratory insufficiency*
Parkinson†	Hypertension*	Arthritis*	Autism†	Type II diabetes*	Cancer *
Schizophrenia†	Cardiac arrhythmia*			Avitaminosis (Vitamins A, B,…) *	AIDS*
*Stroke				Hyperlipidaemia†	Crohn's disease*
Dementia*				Hypercholesterolaemia†	Gingivitis*
Chronic depressive status*				Hyperthyroidism†	Rosacea*
Mental retardation†				Hypothyroidism†	Glaucoma*
Psychosis†				Osteoporosis†	Alcoholism*
Aphasia†					Smoking*
Frequent headaches*					Obesity*
Cranial trauma*					General anaesthesia‡
Hydrocephalus*					A severe blow to the head‡
Bipolar disorder†					Headache‡

*Questions concerning both, the subject and familial pathological history.
†Familial pathological history questions.
‡Questions concerning only the subject.

fruits, grains, vegetables and coffee) eaten in the last 10 years.

Personal data will be collected (general information of subjects: name, surnames, address, date of birth and ID number).

Study setting

The present protocol corresponds to a cross-sectional study including qualitative and quantitative variables.

The study will be conducted at Baracoa, located in Guantánamo province, Santa Cruz del Norte and Bejucal in Mayabeque province (figure 1).

Baracoa is the main producer of coconut and cocoa in the country. The artisanal processing and consumption of those crops are part of the nutritional traditions of that region. Baracoa has also an intense fishing activity; therefore, it constitutes a solvent and dietary source for the population. In addition, there is no significant evidence of AD prevalence in its inhabitants, thus far. Santa Cruz del Norte is a coastal region in which fish consumption is high; however, consume of coconut and cocoa is low. In contrast, the population settled in Bejucal does not have a high consumption of fish and coconut; cocoa ingestion is very low or almost null and presents a palpable incidence of AD in adult population.

Study population and sample size determination

To study the AD prevalence, the selected number of subjects will be proportionally to the demographic distribution (rural and urban areas) and gender of the population. Demographic data were collected from the last edition of the Cuban National Survey of Population and Housing in 2011.[45–47] The assent criterion for considering the compliance with the planned sample size will be 75% for each location/area/gender.

The sample size was calculated according to Morales-Vallejo (2012)[48]:

$$n = \left(\frac{N}{1+\frac{e^2(N-1)}{z^2 pq}} \right)$$

in which:
n=simple size.
N=known population size.
z=confidence level (95%), pq=variance of the population.
e=margin of error (5%).

Based on data provided by the participant family doctors, and the inclusion criteria, the calculated sample size will comprise 1095 subjects aged ≥60 (table 3).

To calculate the fraction of expected subjects to be detected with AD, it was used the closer national registered P_o value of 0.07 (160,000 subjects among 2 386 280 adults over 60 years).[8] For the proportion of subjects whose lifestyles or consumption habits favour the decrease in prevalence (P_1) a lower value of 50% in relation to P_o was taken as valid. Values (two-sided alternative hypothesis) of α=0.05, of β=0.2, $Z\alpha$=1.96 and $Z\beta$=0.84 were assumed.

Table 2 Neuropsychological status of the subject

Cognitive or behavioural symptoms	Impairment of the ability to acquire and remember new information	Deterioration of reasoning and management of complex tasks, impoverished judgement	Impairment of visuospatial capabilities	Impairment of language functions	Changes in personality, conduct, or behaviour	Neuropsychological status
Deterioration in the functional capacity at work	Decrease in the interest of executing hobbies and daily activities at home	Subject's perception of risks, without realising a possible danger	Difficulty to find visible objects, even having a good visual acuity	Dysfunction of the language tasks. Difficulty in finding the right words while speaking or forgetting words	Sudden mood swings	Sadness
Deterioration in the functional capacity to perform usual activities	Asking same questions or repetitive conversations	Inability to manage finances or confusion to get accounts	Difficulty in operating with simple utensils	Errors in speech, in spelling words or in writing	Feeling unmotivated or apathetic to do things that once caused pleasure	Nervous tenseness
Decrease in levels of functionality and performance, compared with the past behaviour of the subject	Mistakenly place personal belongings or forgetting their location	Difficulty in making decisions	Difficulty in getting dressed		Isolation or loss of empathy towards known people	Irritableness
	Unable to remembering recent or past events in personal life or daily life	Incapacity to plan complex activities			Compulsive or obsessive behaviours, physical or verbal aggression towards other people	Pessimism
	Loss in a family place				Hallucinations anxiety, phobia, depression, desire to cry for no reason	Suicidal ideas
	Fail to recall prior remembered names					Loss of auto confidence
	Difficulty to remember a fact or book, the subject just read					
	Retention of the name of the investigator					

The result of the estimation revealed that 350 subjects would be required to apply the aforementioned statistic tests. This figure is lower than the estimated for the prevalence study; for this reason, the calculated sample size of 1095 subjects will be used for both the prevalence study and the statistic correlation tests.

Physicians will execute the recruitment of subjects, in each area.

Participant selection criteria

Inclusion criteria are as follows:

- Adults aged ≥60, both genders.
- Permanent residency ≥10 years.
- Voluntariness and written consent.

Exclusion criteria are as follws:

- Prolonged length of hospital stay (≥1 year).
- Schizophrenia, mental retardation, aphasia and psychiatric treatment at psychotic level.
- Severe visual deficit, hearing impairment and motor disabilities
- Severe alcohol and psychotropic drugs dependence.

Patient recruitment and communication

Specialists from the research team will inform physicians (family doctors) and not subjects directly, about the progress of research questions and outcome measures.

Medical doctors (family doctors) look at every resident in the context of family and community and keep their medical records (customs, lifestyle, comorbidities and family situation) to mention few. Neither patients nor healthy subjects will be directly involved in the process of recruitment and management of the study. Clinical research team will notify subjects of the pertinent aspects (objectives and importance of the study, risks, personal and social benefits, relevant dates, place, commitment of not disclosing personal data and conditions of the study). Likewise, information regarding implementation of tests and surveys will be given to subjects, relatives or caregivers.

Once the selected subjects accept to participate in the survey, the clinical research team will provide them with the informed consent form. Subjects will be advised of their willingness to abandon the study whenever they

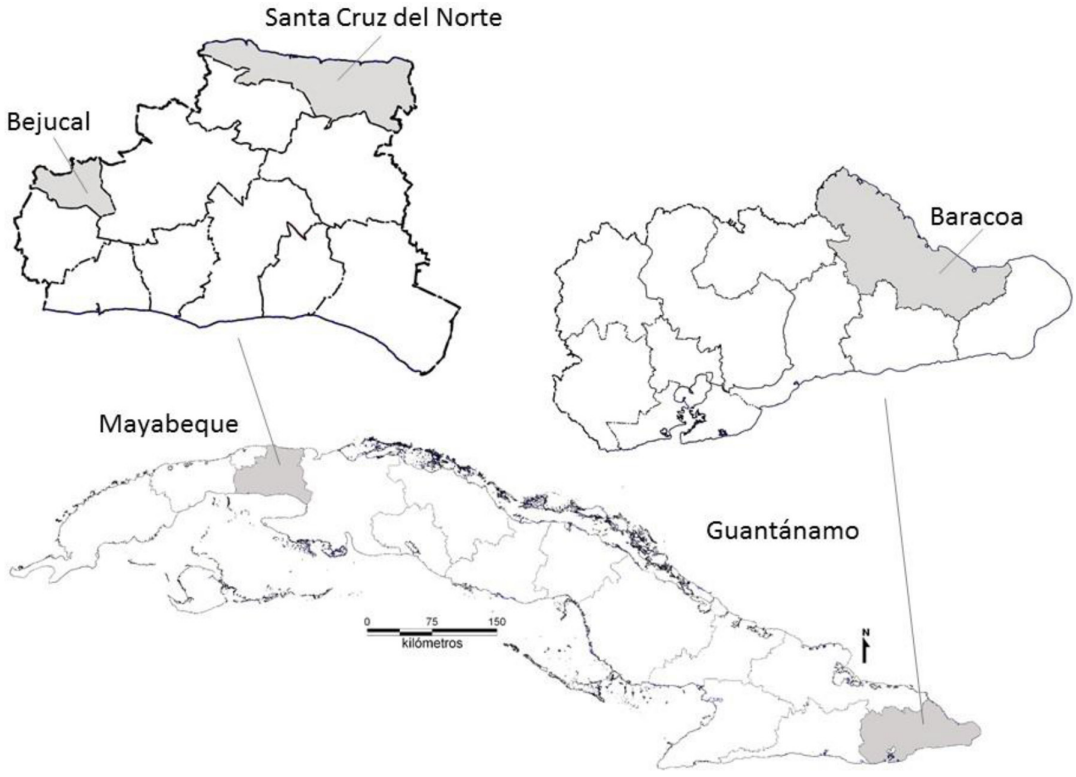

Figure 1 Location of the three selected municipalities for conducting the epidemiological study in Cuba.

consider, it, appropriate. If any of the subjects show a severe cognitive impairment or AD, a family member or caregiver will complete the informed consent.

If, derived from the results of neuropsychological tests, AD occurrence, sign of memory impairment, or other pathologies not previously declared, occurs; clinical researcher team will be obliged to share that information with physicians (family doctors); hence, they might follow the corresponding healthcare protocol established in the country.

Patient and public involvement statement

Members of the research team, experts and physicians participated in the scheme of the study. No patient intervention is included in the design, since the study will not expect any treatment. For specific questions regarding sexual relation queries, older adults of both genders were previously asked about their willingness or discomfort in answering these types of questions. Once their criteria were analysed, the designing team decided to include the corresponding additional consent.

Selection and insertion of subjects will be done at the advanced execution phase of the study.

The clinical research team will communicate the results of the study to the corresponding physician (family doctors) and they will transmit the information to subjects, family members or legally recognised caregivers.

Table 3 Sample size by locations

	Urban area		Rural area		
	Men	Women	Men	Women	Total
Baracoa	101	106	88	79	374
Bejucal	132	131	50	43	356
Santa Cruz del Norte	121	130	61	53	365
Total	354	367	199	175	1095

Outcome measures

Primary outcomes: Identification of the presence of cognitive impairment and possible AD in subjects, and prevalence of the disease in rural and urban areas applying the Spanish versions of SPMSQ,[39 40] MMSE,[41 42] CDT tests,[43 44] ADAS test,[28 34] CDR Scale[36] and GDS.[37]

Subjects will be diagnosed with AD if clinical documented evidence of the AD exists or if the subject is classified as a candidate for suffering the disease. The clinical certificate should be issued by an authorised health institute.

For exploring secondary outcomes such as comorbidities an enlarge list will be added (1) current diseases; (2) psychiatric, neurological, vascular, immunological, genetic and metabolic illnesses; (3) time frame of suffering from those diseases and indicated treatments; (4) pathology of familial history (risking factor for developing AD) (table 2) and (5) practice, frequency and intensity of performing physical activity (sports, exercises or physical labours related to the profession of subjects).

Regarding protective factors, the listing will be broaden with the inclusion of some leisure time activities of the

elderly, which could contribute to stimulating neuronal or brain activity. Risk factors like smoking (quantity, frequency and time frame), consumption of alcoholic beverages (frequency and quantity) as well as the exposure to toxic elements will be also registered.

A supplementary section of the survey will be dedicated to examine the neuropsychological status of the subjects (table 2). This section will deal with recognition of signs of deterioration symptoms of certain areas (cognition or behaviour), the ability to acquire and remember new information, reasoning and managing complex tasks, impoverished judgement, visuospatial abilities, language functions and personality changes. If subjects present evident advanced neuropsychological deterioration, their caregivers or the interviewer, should declare the physical status of the subject.

Data management and analysis plan

Descriptive statistics based on means, SD, percentages and 95% CIs will be used for describing the studied population. To determine the influence of the independent variables (age, level of schooling and consumption of certain foods, among others) on the prevalence of AD (dependent variable), different statistical test will be performed (χ^2 test, Student's t-test, Mann-Withney test, multiple logistic regression models based on the backward elimination procedure; exploratory factor analysis and multiple component analysis).

Linear and non-linear regression analysis, as well as the ROC curves (Receiver Operating Characteristic), will be used for comparing different neuropsychological tests and scales.

A portable mobile application named BioMer.apk was designed in collaboration with the Free Software Development Centre of the University of Computer Sciences in Havana City. The application included general information, results of the survey, neuropsychological tests and scales outcomes. BioMer.apk allows recording images of drawings and texts from different neuropsychological tests. Every recorded data could be exported to an Excel worksheet for further statistical analysis.

Status of the study

Physicians participating in the study did a 1-week training course on the techniques of the neuropsychological tests, the scales and survey. In the interest of validating the designed protocol, experts from the sponsoring institute, participated themselves as respondents. The procedure inquired into original questions and permitted to correct them for an improved outcome.

After this initial validation, a small group of subjects from rural areas in Baracoa, was selected to perform a pilot study. It was concluded that subjects felt comfortable at answering the questionnaire and that the survey could be completed in two hours, maximum.

The preintervention and validation phases of the study started in 2018; however, the study stopped in 2019 due to COVID-19 epidemic in Cuba. Yet, it will restart when the epidemiological situation permits a safe process and contact with older adults. The closure of the study is planned by December 2022, and data processing should be finished by March 2023.

Strengths of this study

The study includes a large number of variables (190) partly reported by different authors, as factors that influence the onset or progression of AD.[49–60] Among them, aspects such as psychoaffective relationship and family environment, sexuality,[61] sleep disorders,[62] quality of drinking water[63] highlighted among the least studied at a population scale.

To select the neuropsychological tests and scales for the protocol, the authors employed tests and scales previously validated in some Spanish-speaking countries or used in Cuba to diagnose AD in the national healthcare system. Selected tests will be of easy and quick application, and will allow collecting a wide spectrum of the cognition area of the subjects.

Comparisons between different tests and scales will allow selection of correct tests and scales for the studied population and recommend them for future population studies.

Protocol will comprise occurrence study in rural and urban areas. In Cuba, AD prevalence in rural areas has not been particularly studied and rarely analysed, worldwide.

Limitations of the study

The study will not include population aged ≤60, since the earlier prevalence of the disease, is often associated with familial AD.[64–66] Several epidemiological studies have shown that the prevalence of familial AD is typically between 2% and 10% of the overall prevalence of the disease.[64–66] Globally, studies usually used as inclusion criteria, older adults aged ≥60, and majorly of 65 years.[60 67]

Biochemical and image markers will be not considered. At population level, the position of researcher worldwide, regarding blood draws and AD are well known.[68] A large group of analysis generally correlates the amyloid-beta levels and the hyperphosphorylated tau protein in the cerebrospinal fluid. Therefore, it will be necessary to execute highly invasive procedures,[69 70] which will not justify the population epidemiological study and will not anticipate therapeutic interventions. Alternatively, it will not be practicable to perform in rural population, advanced image studies like single-photon emission CT and positron emission tomography, the right tests for determining changes in the structure and volume of different regions of the brain, related to the disease.[71 72]

Authors highlight the design of an epidemiological cross-sectional survey to identify the possible association of risk and protective factors with AD in different groups of the Cuban elderly population. Since this analysis will be no conclusive, it would be noteworthy to accomplish further studies on Cuban population.

ETHICS AND DISSEMINATION

This research followed the ethical codes of the Declaration of Helsinki. The protocol was accepted by the Scientific

Research Council from Centro Nacional de Biopreparados, as Promoting Research Institution (No. 2.12.12.17). Health Authorities and Ethic Committees of the Health Authority provided also their consent (No.12.12.17 and No.1.12.17). Subjects, caregivers or relatives will provide corresponding written informed consent.

The results will be published in scientific papers and will be also shared with the Health Authorities of each municipality. In addition, outcomes will be accessible via presentations in domestic and international scientific meetings. Authors will create guidance documents with detailed instructions for the appropriate selection of tests and scales for further studies.

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Contributors The authors' responsibilities were as follows: YLR and CRM were responsible for overall conception and design of the study and for acquisition, analysis of data for the work; MCRZ made substantial contributions to the conception or design of the work; YLR, MCRZ, JPH and CRM were responsible for drafting the manuscript; CRM and MCRZ revised the work critically for important intellectual content; CRM was responsible for the final approval of the version to be published; YLZ, MCRZ, JPH and CRM read and approved the final manuscript.

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