Neurological Disorders in Central Spain, second survey (NEDICES-2): Pilot study, difficulties and findings

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ABSTRACT

Background: The Neurological Disorders in Central Spain, second survey (NEDICES-2) is a population-

based, closed cohort study that will include over 8,000 subjects aged 55 years and older; it will also include a biobank. **Objective:** To evaluate all the major aspects of the NEDICES-2 (methods, database, screening instruments and questionnaires, as well as inter-expert rating of the neurological diagnoses) in each one of the planned areas (all of them in central Spain) and to test the possibility of obtaining biological samples from each participant. **Methods**: In this pilot study, a selection of patients and participants of the planned NEDICES-2 underwent face-to-face interviews including comprehensive questionnaire on demographics, current medications, medical conditions, and lifestyle habits; biological samples (blood, saliva, urine, and hair) were also obtained. Every participant was also examined by a neurologist. **Results:** 567 study participants were enrolled for this pilot study (196 from hospitals and 371 from primary care physicians lists). Of these 567, 310 completed all study procedures (questionnaires and the neurological evaluation). The study was time-consuming for several primary care physicians. Hence, a few primary care physicians from some areas refused to participate, which led to reconfiguration of study areas. Also, the central biobank needed to be supplemented by local biobanks at local Spanish National Health System hospitals. **Conclusion:** Population-based epidemiological surveys, such as NEDICES-2, require a pilot study to evaluate the feasibility of all aspects of a future field study (population selection, methods and instruments to be used, neurological diagnosis agreement, and data collection).

KEY WORDS

NEDICES; Dementia; Essential Tremor; Headache; Longitudinal study; Mild Cognitive Impairment; Observational study; Pilot study; Parkinson's disease; Population-based study; Stroke.

INTRODUCTION

A pilot study is usually recommended before undertaking epidemiological research in large

populations to study neurological, psychiatric, or aging-related diseases [1-9]. Surveys investigating neurological diseases are especially difficult because of the need for an expert diagnosis, since a sizable proportion of the neurological disorders do not have diagnostic biomarkers [10]. The difficulty increases when epidemiological surveys require up-front screening to obviate the workload of a two-phase survey [2]. In this type of neurological research, pilot studies prior to the field survey become mandatory.

The original *Neurological Disorders in Central Spain*, first survey (NEDICES-1) was a closed population-based study, which followed a cohort over 13 years [2, 3, 11, 12]. NEDICES has produced high-quality epidemiological research on different neurological disorders with >70 peer-reviewed publications regarding stroke, dementia, parkinsonism, tremor, and various aspects of aging and mortality. The main limitation of the NEDICES-1 was the few laboratory data we obtained from the participants. To overcome this limitation, we have established a new observational survey, the *Neurological Disorders in Central Spain*, *second survey* (NEDICES-2).

The main differences between the NEDICES-1 and NEDICES-2 are the following. First, in NEDICES-2, we selected participants by means of primary care physicians, instead of using the census as in the NEDICES-1. Currently, Spanish National Health System includes virtually all Spanish legal residents and immigrants. We used computerized data of the citizens assigned to the primary care physicians, since they perform their clinical work at Spanish National Health System centers. Second, this new cohort of participants comprises 30% subjects between 55 and 64 years old and 70% subjects over 64 years old. The younger cohort was not included in the original survey. Third, the creation of a tissue bank (biobank) of the participants. Fourth, the study areas were not the same as those of the previous NEDICES survey, although similarly located in central Spain. Finally, in NEDICES-2, the computerized registry of clinical and biological data is centralized in a specific website (http://www.imas12.es/redcap/).

The main objective of our pilot study was to evaluate all the major aspects of the NEDICES-2

survey (methods, database, screening instruments and questionnaires, as well as inter-expert rating of the neurological diagnoses) and to test the possibility of obtaining biological samples from each participant. Other important objective of this pilot study was to assess the levels of cooperation among potential participants and to identify and resolve newly-arising problems.

METHODS

NEDICES-2 DESIGN

The coordinating center (Research Institute of the University Hospital "12 Octubre" in Madrid) of NEDICES-2 designed all aspects of the survey during 2011-2012, advised by participating primary care physicians. The methods and protocols were analogous to the NEDICES-1 survey [2, 3, 11, 12].

NEDICES-2 OBJECTIVES

The NEDICES-2 survey aims to establish a population-based cohort to investigate major age-related neurological disorders (essential tremor, Parkinsonism, stroke, mild cognitive impairment [MCI], and dementia), including the risk factors and possible biomarkers for such neurological diseases. In addition, we aim to confirm the general findings of the NEDICES-1 survey with a new larger cohort, including persons in late adulthood (55-64 years-of-age) and to assess the possible changes of neurological diseases incidence over time. Finally, one important aim of this study is to obtain biological samples (blood, urine, hair and saliva).

NEDICES-2 POPULATION AND STUDY AREAS (PILOT STUDY SELECTION)

The NEDICES-2 survey aims for a baseline cohort population of approximately 8,000 participants. This number was calculated to adequately detect Parkinson's disease, which has the lowest prevalence

and incidence of all the neurological disorders studied in this research [13, 14]. We expect a similar attrition as happened in the NEDICES-1 survey [12]. The areas were selected to represent rural, semi-rural and urban populations.

The composition by age reflects the general Spanish population over 54 years old (30% in the strata of 55 to 64 years). This age composition is like other European cohorts, such as the Rotterdam study.[15]

The NEDICES-2 population will be selected from the primary care physicians lists to obtain a random group (400 to 600 subjects per primary care physicians list) representative for age (five-year strata) and sex of subjects between 55 and 84 years and of all subjects > 84 years.

The coordinating center of the NEDICES-2 set up the pilot field study and selected the study protocol (questionnaires, scales, and examinations) with few differences from the NEDICES-1 survey. Further, it also developed the telematic utilities for the survey: specific e-mail, Skype conferences, information website, and an electronic platform to collect study data with the privacy requirements. The coordinating center also conducted the pilot study.

The coordinating center selected seven areas to survey participants for the pilot study: Fuentelarreina and Comillas (central Madrid), Las Margaritas (Getafe, peripheral Madrid), Arganda del Rey (suburban Madrid, semi-rural area), Cantalejo (Segovia, rural area), Burgos county (rural area), Arévalo (Ávila, semi-rural area), and Pizarrales (Salamanca, urban area). These participants were randomly selected (choosing five out of 20) and stratified by sex and age (in 5-year age spans), to be evaluated by seven primary care physicians. The participants were considered eligible if they had lived in rural or urban areas for more than 6 months and did not anticipate a serious illness that could cause death within the next year. In addition, for this pilot study, we recruited patients from the outpatient

neurology clinics of both the University Hospital “12 de Octubre” in Madrid and the Burgos University Hospital in Burgos. These comprised patients diagnosed with the following neurological disorders: essential tremor, Parkinsonism, stroke, headache, MCI, and dementia.

QUESTIONNAIRES AND SCREENING METHODS

We administered three different types of questionnaires. First, lay interviewers (mostly students, not in medicine) administered general questionnaires, including information on the demographic and social aspects of the participants. These questionnaires also included screening questions (see below) or brief neuropsychological batteries for detecting or confirming neurological diseases, such as essential tremor,[16-18] Parkinsonism,[13, 14, 19] , stroke [20, 21], or MCI / dementia (37-item version of the Minimental State Examination, clock drawing test, 11-item version of the Pfeffer Functional Activities Questionnaire, Word Accentuation test, verbal fluency (animals and fruits), Trail-Making test, delayed late memory tests, logical memory, and nomenclature and images) [22-27] that had been used in the NEDICES-1. Second, the primary care physicians also administered a questionnaire with anthropometric data, general health status, cardiovascular risk factors, previous illnesses, clinical comorbidity,[28] and current medications. The primary care physicians took standard biochemical specimens (blood, urine) for registration and for the biobank (in some cases, hair and saliva were also included). Finally, a self-reported questionnaire was also completed by each study participant, providing personal data, professional background, education and studies, measurements of subjective health (global, age-comparative, and time-comparative self-rated health) [29], generic health-related quality of life (EuroQol) [30], Epworth sleepiness scale [31], physical activity [32], headaches [33], the Beck Depression Inventory scale [34], social relationships of participants, and information about their lifestyle (drugs, tobacco, coffee, and alcohol consumption).

Screening methods for the main neurological disorders were like those used in the NEDICES-1

survey [2, 3, 11, 12]. To assess the performance of these screening methods, a random sample of approximately 4% of those who had screened negative in NEDICES-1 was selected and contacted.[1] Of 205 subjects who were contacted, 183 were successfully scheduled for a neurological examination by a senior neurologist.[1] They all were examined, and none was found to have essential tremor, parkinsonism or stroke; however, two (1.1%, confidence interval [CI] 95% = 0.3–3.9%) of the 183 subjects were found to have "mild dementia". [1]

In NEDICES-1, for essential tremor we included a question ("have you ever suffered from tremor of the head, hands, or legs that has lasted longer than several days?").[17, 18]. Three questions we administered to screen for parkinsonism (questions about previous diagnosis of Parkinson's disease, tremor, and bradykinesia).[13, 14] Further, we also used a validated nine-item questionnaire aimed at identifying parkinsonism-related symptoms.[19] The screening instrument for stroke was a Spanish adaptation of the questionnaire used for screening in the World Health Organization (WHO) MONICA project.[35] The main screening instruments for MCI/dementia included the Spanish adaptation of a cognitive test (a 37-item version of the Mini-Mental State Examination) and an instrumental activity of daily living scale (11-item version of the Pfeffer Functional Activities Questionnaire).[22, 24] The sensitivities of both the 37-item version of the Mini-Mental State Examination and the Pfeffer FAQ scale are greater than 90%.[36]

ETHICAL ASPECTS

All the participants included in the study gave their written informed consent after full explanation of the procedure. The study, which was conducted in accordance with the principles of the Helsinki declaration of 1975, was approved by the ethical standards committee on human experimentation at the University Hospital "12 de Octubre" (Madrid). Written (signed) informed consent was obtained from all enrollees. The data collection and the biobank procedures conformed to Spanish

law.

STATISTICAL ANALYSES

Statistical analyses were performed in SPSS Version 21.0 (IBM Corp., NY, USA). All tests were two sided, and significance was accepted at the 5% level (alpha = 0.05). Continuous variables were compared using Mann–Whitney U tests because they were all non-normally distributed. The $\chi 2$ test was used to analyze categorical variables.

RESULTS

Population: Figure 1 shows the flow chart of the study. The original selected population for the pilot study was of 567 participants. Of these, 196 (34.6%) were recruited from the outpatient neurology clinics of both the University Hospital "12 de Octubre" in Madrid, which provided 168 patients with neurological diseases and 22 patients without them after a careful examination, and the Burgos University Hospital in Burgos, which provided six patients with neurological diseases. The 371 (65.4%) remaining participants were selected from the primary care physicians lists of the study areas.

Of the subjects recruited from hospitals, 26 (13.3%) refused to participate, meanwhile 170 (86.7%) were adequately evaluated (complete data and assessment by a neurologist). Of the 371 participants selected from primary care physicians lists, 31 (8.3%) were excluded due to change of primary care physician, change of address, and deaths. Of the remaining 340 who were eligible by primary care physician assessment, 54 (15.9%) were excluded due to inadequate evaluation (institutionalization, unreachable, refusals and severe diseases). The remaining 286 fulfilled or were administered the questionnaires, but 44 (15.4%) were excluded by incomplete data. Finally, 242 participants had complete data; however, only 140 (57.9%) participants were eligible for the final

analyses because neurologists could not evaluate 102 (42.1%) for several reasons.

Thus, the final sample consisted of 310 participants (190 [61.3%] with neurological diseases and 120 [38.7%] without them) who presented all the required data (three questionnaires, neurological evaluation, and biobank donation) (see table 1). Obviously, a higher proportion of participants with neurological diseases were more likely to have depression or depressive symptoms, cataracts, and score worse on screening tests for cognitive disorders (37-item version of the Minimental State Examination and 11-item version of the Pfeffer Functional Activities Questionnaire). In addition, as expected, they scored higher in the Parkinson's disease screening test and rated their health as bad/very bad. On the other hand, they were more likely to be more sedentary. Table 2 shows the final sample of participants distribution according to neurologists' diagnosis.

Table 1. Baseline demographic and a selection of clinical characteristics of the final sample of participants (N: 310).

	Without neurological diseases: **120** *(98 from hospitals + 22 from primary care physicians lists)*	*With neurological diseases:* **190** [a] *(148 from hospitals + 42 from primary care physicians lists)*	*P value*
Age	70.7 (69) ± 9.4	71.7 (73.0) ± 9.4	0.278
Sex			
Men	55 (45.8%)	86 (45.3%)	0.922
Women	65 (54.2%)	104 (54.7%)	
Years of education (years) [b]	9.9 (8.0) ± 5.6	8.4 (8.0) ± 5.2	0.523
Main non-neurologic disorders			
Diabetes	21 (18.4%)	38 (20.7%)	0.639
Arterial hypertension	62 (53.9%)	99 (53.5%)	0.946
Hypercholesterolemia	56 (48.3%)	87 (47.0%)	0.833
Heart diseases	20 (20.4%)	34 (22.2%)	0.733
Osteoarthritis	59 (51.8%)	95 (52.5%)	0.902
Cancer	18 (16.1%)	22 (12.2%)	0.352
Cataracts	30 (26.3%)	74 (41.8%)	0.007
Chronic pulmonary disease	16 (14.3%)	25 (13.7%)	0.895
Depression	17 (14.9%)	50 (27.6%)	0.011
Deafness	17 (15.2%)	57 (31.5%)	0.002
Life style variables [b]			

Sleeping hours	7.0 (7.0) ± 1.4	7.2 (7.0) ± 1.6	0.468
Ever smoker (ex-smoker plus current smoker) Ever drinker (ex-drinker	1 (11.3%)	11.0 (8.9%)	0.135
plus current drinker)	67 (57.3%)	103 (54.8%)	0.672
Physical activity			
Inactive	60 (52.2%)	130 (69.1%)	0.004
Moderately inactive	6 (5.2%)	15 (8.0%)	
Moderately active	22 (19.1%)	20 (10.6%)	
Active	27 (23.5%)	23 (12.2%)	
Self-rated health [b]			
Very good	15 (12.8%)	8 (4.2%)	0.012
Good	55 (47.0%)	72 (38.1%)	
Fair	41 (35.0%)	94 (49.7%)	
Poor	5 (4.3%)	13 (6.9%)	
Very poor	1 (0.9%)	2 (1.1%)	
Screening tests for cognitive disorders [b]			
37-item version of the Minimental State Examination (0-37, ≥25)	32.2 (33.0) ± 4.8	30.7 (32.0) ± 5.7	0.024
11-item version of the Pfeffer Functional Activities Questionnaire (0-33, ≤5	1.1 (0.0) ± 4.0	3.2 (0.0) ± 6.0	<0.001
Parkinson's disease screening test (0-9, ≤ 0) [b]	1.0 (1.0) ±1.2	2.8 (2.0) ±2.4	<0.001
Headache (yes vs. no) [b]	29 (27.4%)	57 (34.3%)	0.258
Beck Depression Inventory scale (0-63, ≤14) [b]	7.1 (6.0) ± 5.6	9.7 (9.0) ± 6.3	<0.001

Mean (median) ± standard deviation and frequency (%) are reported. [a] 15 patients had more than one disorder; [b] Data on some participants were missing; [c] Normal range, cut-off). Continuous variables were compared using Mann–Whitney U tests because they were all non-normally distributed. The $\chi 2$ test was used to analyze categorical variables.

Table 2. Final sample of participants (N: 310) distribution according to neurologists' diagnosis.

[a]

	WITHOUT NEUROLOGICAL DISEASES	**WITH NEUROLOGICAL DISEASES [a] (190)**					
		Headache	Dementia	Parkinson's disease	Stroke	Mild cognitive impairment	Essential tremor
Participants	120	37	28	35	43	23	39
Mean age (years), range	71 (55-94)	65 (50-89)	78 (62-95)	71 (54-91)	71 (55-86)	76 (62-88)	70 (48-90)
Men Women	55 (45.8%) 65 (54.2%)	11 (36.7%) 19 (63.3%)	11 (39.3%) 17 (60.7%)	21 (61.8%) 13 (38.2%)	20 (50.0%) 20 (50.0%)	12 (52.2%) 11 (47.8%)	10 (29.4%) 24 (70.6%)
Education (years)	9.9 (5.6)	9.9 (5.0)	6.1 (2.8)	9.0 (6.3)	10.0 (5.7)	6.2 (4.4)	8.0 (4.9)

15 patients had more than one disorder.

All selected areas participated in the survey (participant evaluation and acquisition of biological samples), but the quality of the information obtained and the clinical workload for the primary care physicians was quite varied, as was the biobank established in each local area. The primary care physicians of Arganda del Rey, Las Margaritas (Madrid), and Pizarrales (Salamanca) had difficulties carrying out the survey due to high clinical load and therefore refused to participate in this pilot study. These areas were then replaced by La Alamedilla (Salamanca, urban area), Calesas, (urban area, Madrid), Valladolid (urban area) and Cantalejo (rural area, Segovia).

Development of the pilot study. Each primary care physician invited selected subjects from among his/her patient list to join in the survey through a phone call or a letter. The duration of the interviews with the participants was variable (10-20 minutes). Most participants signed the informed consent for both clinical participation and donation to biobanks. The pilot study showed that the central biobank faced practical difficulties: shortage of staff, high costs, and difficulties with sample arrangements in the University Hospital “12 de Octubre” biobank. The coordinating center overcame this problem by changing the initial survey design to use local biobanks as supplements to the central biobank (except for Madrid, Ávila and Segovia).

The training of the interviewers was satisfactory. Interviewer questionnaires were digitized and sent to the central website. Most of the participants' self-report questionnaires had to be completed on paper and sent to the coordinating center in this format. Evaluations by lay interviewers lasted approximately one hour and fifteen minutes, sometimes up to three hours, with a break. Participants with possible neurological disorders received a second evaluation performed by a neurologist.

The comprehension of the questionnaires was generally adequate, with some exceptions. The Beck Depression Inventory scale [34] was difficult to understand for many participants and the coordinating center replaced it by the CES-D Scale [37] for the future field study. The 37-item version of

the Minimental State Examination, 11-item version of the Pfeffer Functional Activities Questionnaire, Word Accentuation test, verbal fluency, Trail-Making test, delayed late memory tests, logical memory, and nomenclature and images [22-25] allowed us to establish the psychometric cuts for screening for dementia, obtaining sensitivity greater than 95% with high specificity.

Once the pilot study was completed, it was decided to compile each subject's evaluations. These summary sheets were sent to each primary care physician for them to discuss with each subject, to explain the results obtained and to thank them for their collaboration.

Inter-Rater Agreement in the Clinical Diagnosis of the neurologists who will participate in the field study. Inter-Rater agreement of cognitive status and tremor disorders have been published elsewhere.[16, 38] Briefly, to assess the diagnostic agreement of cognitive status (dementia, MCI, normal cognition) among neurologists, medical histories of 30 individuals were provided to 27 neurologists (19 consultant neurologists and eight neurology residents).[38] Overall inter-rater agreement on cognitive status was κ = 0.76 (95%, CI 0.65-0.86), being slightly higher among junior neurologists (κ = 0.85, 95%, CI 0.73-0.95) than among seniors (κ = 0.71, 95%, CI 0.59-0.83) and residents (κ = 0.69, 95%, CI 0.54-0.81) but without statistical significance among groups.[38] Dementia severity showed an overall κ of 0.34, 0.44 and 0.64 for mild, moderate and severe dementia respectively.[38] Further, clinical histories and standardized video-taped neurological examinations of 26 individuals (11 ET, seven Parkinson's disease, three diagnostically unclear, four normal, one with a tremor disorder other than ET) were provided to 7 consultant neurologists, 6 neurology residents, and five neurology research fellows. For each of the 26 individuals, neurologists were asked to assign a diagnosis of "essential tremor" or "no essential tremor" using diagnostic criteria proposed by the Movement Disorders Society.[39] Overall κ was 0.61 (substantial agreement), with no differences between consultant neurologists (κ = 0.60), neurology residents (κ = 0.61), and neurology research fellows (κ = 0.66) in subgroup analyses.[16]

DISCUSSION

The pilot study is a first step in many types of epidemiological study, such as cross-sectional and longitudinal surveys [2-5, 9], case-control studies,[40] and research investigations [41]. It is unwise to establish a complex survey without an adequate pilot study, as was demonstrated by our current study.

Participants, in general, were more cooperative than expected. The main difficulties in the study were unexpected. Specifically, the study was time-consuming for primary care physicians, since they had to explain it to the participants, obtain informed consents, and complete a summary of their medical history. However, during the design of the NEDICES-2 survey, the coordinating center had erroneously considered that the three tasks could be done in ten minutes because the lay interviewer had given written information to the participant and because there was a specific website with an explanation of the study.

Primary care physicians have a heavy workload in Spain. Many participants required a lengthy explanation of the survey, despite the good explanation on the website. With the public funds that we obtained, we could pay external collaborators as interviewers, but the Spanish National Health System research policy does not permit payment to primary care physicians, even if they devote extra time beyond their working hours. All this caused three primary care physicians teams to leave this study. The coordinating center had to replace these primary care physicians study areas by others, even in other geographical areas, to overcome this problem.

Another important difficulty was obtaining the biological samples to establish the central biobank at the University Hospital “12 de Octubre” in Madrid. The pilot study showed that the only possible way to address this problem was to send all biological samples to each local Spanish National

Health System hospital laboratory (for registration and to establish a local biobank).

Otherwise, the pilot study was successful, partly because the methods were analogous to the NEDICES-1. Only a few changes in the screening questionnaires and scales were made after the pilot survey. Several tests were established for the detection of MCI and dementia.

Substantial agreement was demonstrated for the diagnosis of cognitive status (dementia, MCI and normal cognition) among neurologists of different levels of experience.[38] The agreement rate was lower in the diagnosis of dementia severity. With respect to tremor disorders, substantial agreement was also demonstrated for the diagnosis of essential tremor among neurologists of different levels of expertise.[16] However, agreement was lower than that previously reported using the Washington Heights–Inwood Genetic Study of Essential Tremor criteria.[42]

In closing, we feel that it is impossible to undertake a large and complex neuroepidemiology survey, such as NEDICES-2, without a pilot study. It is mandatory to test first the feasibility of all aspects of a future field study: population selection, methods and instruments to be used, neurological diagnosis agreement, and data collection. This pilot study revealed some serious deficiencies in the selected areas (ability of overburdened primary care physicians to collaborate) and in the biological bank configuration that could be solved by the coordinating center.

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