The NEDICES cohort of the elderly. Methodology and main neurological findings

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THE NEDICES COHORT OF THE ELDERLY. METHODOLOGY AND MAIN NEUROLOGICAL FINDINGS

Summary. Aim. To summarise the methodological aspects and main findings of the NEDICES (Neurological Disorders in Central Spain) cohort study of the elderly population, with over 5000 participants. Development. The article outlines the findings concerning the following chronic neurological diseases (CND): dementia, Parkinson's disease and Parkinsonisms, stroke and essential, or senile, tremor. The NEDICES study examined the health, mortality and a series of sociological aspects of the cohort that are not discussed here. The paper does describe, however, the objectives, methods, population and development, with the baseline (1994) and incidence (1997) cut-off points, and the main findings regarding the CND under study are discussed. Conclusions. The prevalence and incidence of the CND are comparable to those of other Spanish and European population-based studies, but with certain peculiarities, such as the fact that incidence of senile tremor is the highest of those reported in the literature and that this CND is associated with dementia. Over half the cases of Parkinson's disease were reported de novo with the study and Alzheimer's disease was associated with vascular risk factors. [REV NEUROL 2008; 46: 416-23]

Key words. Chronic neurological diseases. Cohort. Dementia. Epidemiology. Methods. Parkinsonism. Population-based study. Tremor. Stroke.

INTRODUCTION

Our knowledge of CND in the elderly (dementia, Parkinsonism, for example) can only be furthered with the help of populationbased studies, because only limited information about CND can be obtained in clinical settings. Over half the patients with cognitive impairment or Parkinsonism, especially in the early stages or in the very elderly, do not visit medical services in Spain or in other western countries [1-3]. This clearly highlights the need to conduct research among the population that eliminates the sample selection bias of clinical studies [1-3] and allows the natural history and prognosis of these conditions to be defined. Research on their risk factors (RF) is facilitated by prospective population-based studies [2,4], which allow researchers to investigate aetiological hypotheses and preventive strategies (sub-

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jects who are exposed and who are not exposed to a RF) and prevent the sample selection bias [5] that arises from limiting studies to hospital patients [1-3]. Furthermore, conducting a cohort study of CND in a particular area makes it possible to quantify them (i.e. their prevalence and incidence), which is a necessary step to be able to infer figures for the population of a country as a whole [1,3].

Population-based cohort studies usually lead to numerous reports in journals about particular aspects, and this often conditions understanding of such research work. The aim of this review is to minimise these limitations in the description of data from cohort studies by offering a summarised view of the NEDICES (Neurological Disorders in Central Spain) study of the elderly.

AIMS

This review outlines the methodological aspects and main findings of the NEDICES cohort study of the elderly, in which over 5,000 participants took part. The article sums up the findings concerning dementia, Parkinson's disease (PD) and Parkinsonisms, stroke and senile tremor. Although the NEDICES study also analyses different aspects of these CND, such as general health [6] and other medical and social characteristics of the cohort, including mortality rates, these have not been analysed in this review.

DEVELOPMENT

Aims and methods are outlined, and the main results from the NEDICES cohort are given together with a brief comment in each case.

Aims

In the initial design (in 1993), the aims were to conduct a prospective study of an elderly cohort (65 years old and above), in which state of health, lifestyle (including cardiovascular risk

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	Wave 1	Wave 2ª
General data		
DI and demographic-social data (age, sex, schooling, work, etc.)	Yes	Yes
DI of patient escort and family physician data	Yes	Yes
Interview and informed consent data	Yes	Yes
Anthropometric data (weight; height; changes in weight)	Yes	Yes
Daily physical activity (graduated, hours of sleep)	Yes	Yes
Perceived health (3 groups of questions from the NHS)	Yes	Yes
Geriatric Morale Scale questionnaire (quality of life)	No	Yes
Support and social contacts	No	Yes
Chronic disease (CD) and CVRF survey	Yes	Yes ^b
Heart attack (branched questions, maximum 13)		
Diabetes (7 questions about diagnoses, duration and therapies)		
AHT (6 questions about diagnoses, duration and therapies)		
Cholesterol (4 questions about diagnoses, duration and therapies)		
Other chronic diseases	Yes	Yes ^b
Anaemia, osteoarthritis, chronic bronchitis, cancer or tumours, cataracts and visual problems, hip fractures, osteoporosis,deafness, nervous problems and depression, circulatory problems and varicose veins, prostate disorders		
Limitations caused by CD and the most limiting CD		
ifestyle	Yes	Yes ^b
Consumption of alcohol (branched questions, maximum 8)		
Smoking (idem, maximum 9 questions)		
CND screening	Yes	Yes ^b
Dementia: MMSE-37, Pfeffer FAQ		
Stroke and TCI (4 questions; 10 if any were positive)		
Parkinsonism and tremor (3 questions)		
Depression (branched questions, maximum 21)		
Specific RF	Yes	Yes ^b
Severe traumatic head injury (branched questions, maximum 19)		
History of CND in the family (parents, siblings, children)		
Dthers		
Katz Index (if Pfeffer > 5 points)	No	Yes
Diagnosed with CND in the previous 3 years	No	Yes
Neuropsychological battery for mild cognitive impairment (Word Naming Test, Wechsler memory ^c , Set Test, IQCODE, Trail Making Test A and B, Clock Test, SEN-FIS Memory Test)	No	Yes
Medicines taken in the last week (name and dose)	Yes	Yes
		Vac
Interviewer's general observations	Yes	Yes

ties are presented; ^b All the items in the heading; ^c Reduced.

factors – CVRF) and history were the factors to be evaluated. The neurological aims were to analyse the epidemiological aspects (prevalence, incidence and RF) of several CND, including dementia, subtypes of dementia and mild cognitive impairment (MCI), PD and Parkinsonisms, stroke and transient cerebral ischaemia (TCI), and senile tremor. During the time the study was being carried out (1995-2005) a number of sub-studies were designed, including some that sought to investigate these and other neurological diseases (headaches, epilepsy); an analysis of the mortality rate of the cohort and its determining factors was also established [6-8].

Methods

The research was designed to be an observation-based, analytical (with hypotheses to be tested), prospective study to be conducted over several years of observation (initially only three years, which is the length of research projects). In other words, it was a classical prospective, closed cohort study (since it was limited to the population that was chosen *ab initio*) [2,4,9,10].

The participants in the NEDICES cohort were evaluated on general issues (health and functional capacity, among others) using the methods typically employed in a socio-medical study [11] (that is, a survey carried out by lay interviewers and answered by participants and people close to them). Possible cases of CND were submitted to an elemental biomedical assessment and were examined by neurologists with the information from the study and any other data available (reports from family doctors, hospitals or others) in order to establish their diagnosis [6-8]. The surveys (Table I) were applied to all eligible members of the cohort who were willing to participate and signed a consent document. The interviews were conducted in the nearest INSALUD health centre or in the participant's own home (in a few cases, elsewhere, for example, in an old people's home or hospital) [6-8]. Detection of the CND was performed in a two-phase process. In phase I, screening for CND was implemented at the same time as the health questionnaire, by means of specific tests [6-8] including a Spanish-language version of the MMSE from the WHO-AAD study and an instrumental activities rating scale (Pfeffer) that had previously been validated [12,13] for dementia. An adaptation of the screening used in the Italian study on ageing (ILSA) for Parkinsonism and tremor [6,14] and another adaptation of the screening for stroke and TCI from the WHO-Monica study [15] were also used. Participants who screened positively (or whose results were uncertain due to inadequate information) in phase

I went on to the diagnostic phase, which was performed by neurologists (a classical population-based study in two phases for diagnosing rare diseases) [16,17].

Population

Three areas in the centre of Spain (two urban and one rural) were chosen for the study. These areas were the district of Margaritas (Getafe), on the outskirts of Madrid; the district of Lista, in the centre of Madrid; and 38 villages in the rural area of Arévalo (Ávila) [6-8]. The eligibility conditions of the population were: inclusion in the census of the areas on 31st December 1993 and actual residence (participant's home or institutions in the area) for six months or more in 1993 in

order to avoid problems with the follow-up. All the census population of Margaritas and Arévalo (about 2,000 elderly people) and a random sample of about 2,000 elderly persons from the district of Lista were included in the study [6-8]. The NEDICES study shares these three populations with the EPICARDIAN study, which also considers another rural area (Begonte, Lugo) and analyses CVRF and cardiovascular events [18,19] by means of a biomedical study (measurement of blood pressure, glycaemic levels and other biological parameters). No mention is made of any aspects of the EPICARDIAN study in NEDICES publications or in this review.

These three areas were chosen because [6]:

- There are about 2,000 elderly people per area, which is a suitable size for evaluating the incidence of CND at three years. The minimum that was calculated for the CND with the lowest incidence, i.e. PD (confidence interval -CI- of 95% and a decrease of 15-20%/year) was 1,500 participants.
- There are computerised medical records in primary care in each area.
- The NEDICES team has a good relationship with the primary care physicians and local authorities, which lowers the chances of their being reluctant to participate in the study or to provide additional information.
- It was possible to establish a population set with three socially non-homogenous sub-populations (due to the existence of socio-economic differences), which facilitates diversification of the CVRF.
- They are populations that could be attended by a single neurological team.

Details of the location of these areas, the sex and age structure of their population (and overall), education, profession and other data were all specified [6-8]. Table II shows the composition by age and sex of the participants screened for the CND under study at the baseline cut-off point.

Implementation of the study

The study began with government and international funding (WHO-AAD study) [1,7, 20] and was approved by the ethics committees of the 'Doce de Octubre' and 'Princesa' hospitals in Madrid. A pilot study was conducted to assess the performance of the screening instruments for diagnosing the CND [6,7]. The interviewers and medical staff were also trained using different procedures [6-8] which, in the case of dementia, involved an in-

	Lista (r	Lista (n = 1566)		Arévalo (n = 1937)		Margaritas (n = 1775)	
	Male	Female	Male	Female	Male	Female	
65-69 years	216	303	258	284	265	325	
70-74 years	137	225	286	290	198	272	
75-79 years	122	170	161	187	120	198	
80-84 years	88	125	110	169	81	166	
85-89 years	55	75	58	88	38	73	
90 and over	20	30	14	32	11	28	
Total	638	928	887	1050	713	1062	

ternational diagnostic agreement study [21]. The whole cohort was divided by two cross-sectional cuts (or waves) (1994-1995 and 1997-1998) and, later, specific analyses were conducted in different diseases or age groups (1995-2006), including an analysis of mortality using the National Mortality Register.

Baseline cut-off point or first wave (prevalence of CND)

The point prevalence was taken as a measure of frequency in CND [5], on 1st May 1994. That is to say, for the participant to be considered as suffering from a CND, the disease should be present on the prevalence day. For stroke and TCI, lifetime prevalence was used, that is, the stroke or TCI must have occurred before or on the prevalence day and the subject must have survived to be included as an affected party [6-8]. The development of this wave has been described in detail [6,8]. Briefly, a letter was sent out to each eligible subject, with presentation notes from the municipal and health authorities of the area, to say that phone calls would be made to arrange interviews for the eligible participant and a person accompanying them (a close relative). They were asked to state the medication they had consumed in the last week and to bring the medical reports they had available at that time. To be able to take part in the study the citizen had to sign a consent document. The health and neurological screening questionnaire was highly structured and was read practically word for word (it consisted of more than 500 items). The average length of the interview in this phase was 40-60 minutes, although in the case of sick subjects it could take up to two hours. When an eligible subject did not answer the presentation letter or telephone call, letters were resent and further phone calls were made (up to six times) at different times and on different days. If no response was obtained then their neighbours, concierge or GP were contacted. Citizens who refused to be interviewed face-to-face were sent a shortened version of the questionnaire and a request for data to be forwarded from their GP. Participants who screened positive or uncertain for a CND were examined by the neurologists from the team in a neurological evaluation lasting 20-60 minutes (diagnostic phase, or phase II) [68].

Second cut-off point or wave (incidence cut-off point)

Several months before 1st May 1997, the 5,278 participants who had been screened in the first wave were sent reminder letters with appointments to answer a new questionnaire. The study was implemented in exactly the same way as in the case of the base-



Figure 1. Flow chart of the baseline cut-off point (1994-1995).

line cut-off point [6], although the survey was longer (about 800 items, Table I). This wave also lasted a year for most of the participants; in the cases of subjects with CND who were interviewed after the point prevalence day, the factor analysed was whether the CND was present on 1st May 1997 or not [6]. Mortality and its causes were investigated (close family and friends, family physicians, hospitals, the Community of Madrid –CM– Mortality Register, and other sources) in all the participants in the cohort.

Other later studies

A number of different studies have been conducted since 1995: caregivers of patients with dementia (1995-1999), with a research grant from the CM; analysis of CND and health in people aged ninety or over (nonagenarians) (1999-2000); MCI, behavioural aspects in Alzheimer's disease (AD) (2001); prevalence of headaches and epilepsy (2002-2003); and analysis of mortality and its causes (2006-no finished).

Main results

The flow charts for the first and second wave can be seen in

Figures 1 and 2. On observing Figure 1 and Table II, it can be deduced that the demographic aim of obtaining more than 1,500 participants per area was fulfilled. Of the participants who were considered to be eligible (n = 5,914), 5,278 persons (89.2% of eligible subjects) were screened (2,238 males and 3.040 females). The sex and age structures were similar in the three areas. Screening was performed directly with the subject on 4,503 occasions: face-to-face in the case of 4,122 participants and by letter in 381 cases; the remaining 775 citizens were screened indirectly (family physicians and relatives). A total of 2,310 persons were considered to have screened positive for one of the CND under study, either because they gave positive responses in one of the CND screening questions or because the results of the screening were uncertain or incomplete (665 participants). Altogether, 2,310 + 665= 2,975 participants were considered to have screened positive (possible cases) and were invited to take part in phase II (neurological diagnosis). In this phase 1,962 possible cases were assessed by a neurologist by means of a face-to-face interview and examination in 983 cases and, in the other 979, by a telephone call to clarify aspects concerning their screening (which was uncertain, or because they had answered a question about subjective bradykinesia positively; in this latter case, they then had to answer a phone survey about Parkinsonism [22] and, if they gave positive in this questionnaire, they were submitted to examination) [23]. In 951 cases, the information was obtained indirectly (669, from the family doctor; 167, from hospital reports; 86, from family or close friends; and 29, from the Mortality Register). It was not possible to obtain informa-

tion about all the CND under study (although data was collected on some of them) in 62 cases. Most of the data regarding the prevalence of the CND have been published (Tables III and IV) [6,23-28], and they have been included in the re-analysis of the door-to-door studies on CND carried out by the Epidemiology Unit of the Instituto Carlos III [29-31]. The prevalences of CVRF and other chronic diseases have also been published [6].

Figure 2 shows a summarised flow chart for the population that was studied at the second cut-off point (1997). In this wave there was a decrease in the number of participants. The number of non-eligible participants was 185 due to change of residence and 625 due to death before the prevalence day (1st May 1997); therefore, a little over 15% of the baseline screened population were not eligible for the second wave. The number of eligible participants also decreased: 294 could not be contacted (following letters and six phone calls or visits), 112 refused to participate, and 197 died before they could be interviewed. Therefore, 11.4% of the eligible participants did not take part (absence from participation in the pre-screening of the baseline cut-off point: 10.8%). Of the 5,278 participants in the baseline screen-

ing who were to be followed up, information was obtained about all the CND in 3,944 cases and about one or several CND in 4,177 participants (79.1% of the cohort). In general, the decrease for the study of CND was above 20% of the baseline cohort (but less than the calculated value of 10-15% per year). The incidence of the CND can be seen in Table V, except for stroke and TCI (pending detailed analysis); the rest have been published [32-34].

Other notable analyses performed in the NEDICES population have been: a sociological study of the relatives and caregivers of patients suffering from dementia, which began in 1995 with research grants from the CM [35-37]; behavioural disorders in patients with incident AD [38]; MCI [25,26, 38]; general health, dementia and Parkinsonism in nonagenarians, although it was not published in mainstream journals [6,39, 40]; prevalence of headaches and epilepsy [6,41,42]; several sub-analyses of aspects related to dementia [43,44]; sub-analyses of senile tremor and its relation to dementia [45-47]; and several other sub-studies on tremor, led by E.D. Louis, a neurologist and epidemiologist at Columbia University, which are currently being carried out [48-52].

Comments

As a population-based investigation, the NEDICES study has been satisfactory, since it has fulfilled the basic aim of achieving an adequate level of participation; in addition, it is the largest neuroepidemiological study in the elderly conducted to date in our country [29]. In the first wave, the pre-screening decrease was 10% of the eligible population, which is lower than in other Spanish studies [6,53], in the US EPESE (close to 15%) [54] and in other international studies (around 20%) [6,55], such as the widely-

acknowledged Dubbo, PAQUID, Zutphen, which come close to 30% [56-58]. Some, nevertheless, have lower decreases [59]. In the first wave, refusal was higher among the very elderly and females, as usually occurs in population-based studies [60], and this gives rise to biases [7]. It must be noted that the rate of participants with information is high in the NEDICES study, but much of this information was obtained indirectly (more than in other studies) [6,7,61].

The screened population is slightly older (9.9% of the subjects were aged 85 or above) than in other Spanish studies [7] and compared with the Spanish population as a whole (8.9% in persons aged 85 or over) in 1993 [62]. The NEDICES population therefore does not represent the Spanish elderly population, since the method employed to choose it does not allow this inference to be drawn. By areas, however, it can indicate the situation in many Spanish populations of elderly persons and, overall, many of its characteristics can be compared with the Spanish elderly population as a whole [6].



Figure 2. Flow chart of the second cut-off point (1997-1998). ^a In all the neurological diseases, but with information for some of them.

The second wave (three years after the first) saw an important decrease, since information was obtained in over 3,863 subjects for the CND (this figure varies according to the CND) [32,34], with a participation in the two phases that was slightly lower than that of the first wave. Nevertheless, the decrease is similar or lower than that of many studies on ageing [6,63], and its conditioning factors, i.e. being male, and suffering from ill health, dementia, or illiteracy (data not published), are the same as in other studies [64].

Although with limitations, socio-medical studies like NE-DICES have proved to be a reliable way of assessing health and chronic diseases in the elderly [6,65]. One important indication of quality in neuro-epidemiological studies is the method for detecting cases of CND. In NEDICES, this detection was performed using the classical two-phase method [16,17], that is, screening and diagnosis by experts [2]. This procedure is appropriate if the sensitivity of the screening instruments is known and if suitable diagnostic methods are applied [2,6,17]. Sensi-

 Table III. Prevalence of chronic neurological diseases in the NEDICES study (prevalence at the baseline cut-off point ^a, 1st May 1994).

	п	Estimated prevalence	
Dementia and cognitive impairme	nt		
Dementia (DSM-IV)	306	5.8% (CI 95% = 5.2-6.5) ^b	
Questionable dementia	83	1.6% (CI 95% = 1.3-1.9%)	
Mild cognitive impairment	194	5.1% (Cl 95% = 4.5-5.9%)	
Isolated memory loss	397	11.3% (CI 95% = 10.3-12.3%)	
Parkinsonisms	118	2.2% (CI 95% = 1.8-2.6%)	
Idiopathic Parkinsonism	81	1.5% (CI 95% = 1.2-1.8%)	
Other Parkinsonisms	37		
Essential tremor	256	4.8% (Cl 95% = 4.2-5.4%)	
Stroke and TCI	254	4.9% (Cl 95% = 4.3-5.5%)	
^a Diagnosed by neurologists; ^b Adjusted for false negatives (CI $95\% = 6-8.1\%$).			

Table IV. Prevalence of cardiovascular risk factors ^a in the NEDICES study

	Prevalence	CI 95%
Diabetes	16.6%	15.6-17.7
Arterial hypertension	43.3%	42-44.7
Hypercholesterolemia	28.7%	27.4 -30
Ischaemic heart disease	10.1%	9.3-10.9
Cerebrovascular accident	7.6%	6.9-8.4
^a Information obtained by survey.		

tivity of the screening instruments was evaluated in a pilot study that showed them to be highly efficient, but with limitations in the detection of cases of mild dementia and in their size (due to financial reasons) [7]. The CND diagnostic criteria were the international standards for those diseases and were applied by specifically trained neurologists (geriatricians in the nonagenarian studies) [6-8]. Furthermore, each CND had its own particular neurologist or diagnostic panel that reviewed all the cases that were detected and collected supplementary data (from hospital reports, family doctors or others) when the diagnosis of the case was uncertain [23-28,32-34]. In short, the design, implementation, detection and diagnosis of the CND in the NEDICES study all followed established standards.

It is difficult to summarise the main neuro-epidemiological findings. In general terms, the fact that the results on prevalence and incidence of the CND were mostly comparable to those from other Spanish (and European) studies proves the reliability of the study [6,29-31]. The studies of prevalence and incidence in dementia showed a high degree of diagnostic consistency in the mild and severe cases, although perhaps the study under-diagnosed the cases of mild dementia, even though the category of MCI with uncertain dementia was included [24]. Overall, prevalence and incidence [24,32] are similar to those of other Spanish and European studies and, as in these, AD is by far the most frequent subtype [6,29,57,66]. The strategies employed in the care of patients with dementia are an interest-

Table V. Incidence of CND (period 1994-1997).

	п	Incidence (1,000 persons/year)
Dementia and cognitive impair	rment	
Dementia (DSM-IV)	161	10.6 (Cl 95% = 8.9-12.3) ^a
Questionable dementia	50	
Parkinsonism	68	5.34 (CI 95% = 4.15-6.78) ^a
Idiopathic Parkinsonism	30	2.36 (Cl 95% = 1.59-3.37) ^a
Other Parkinsonisms	38	
Essential tremor	83	6.16 (CI 95% = 4.47-7.84) ^a
Stroke and TCI	> 109 ^b	8-11 (preliminary calculation)
^a Adjusted to the standard Euro	opean popula	ation; ^b In 262 cases in which the

^a Adjusted to the standard European population; ^b In 262 cases in which the cause of death is unknown, there are likely to be cases of stroke

ing issue, but their analysis is a complex affair [35-37]. The prevalence of MCI was carried out using statistical rather than clinical criteria [25] and pathological loss of short-term memory (retention) with prognostic significance was reported: no recall of the three words from the MMSE at five minutes [26]. In the incidence of AD, the CVRF are a RF [32]. To date, the most significant finding in the NEDICES study is the association of dementia (and frontal cognitive disorders) with senile-onset essential tremor, which was not clearly described in population-based studies [45-47] and probably suggests an association between two degenerative diseases, such as the one that may exist between the AD and PD [67,68].

Data on the prevalence and incidence of PD are similar to those from other Spanish studies, except for the one conducted by Cantalejo, where the values are markedly higher (possibly due to exhaustive searching), and show a higher risk in males than in females [23,33], as in some European studies [6]. Perhaps the most significant aspects of these studies are the large numbers of cases of incident PD detected *de novo* (over 50%) and of Parkinsonisms caused by medication, which probably reflects the frequency with which neuroleptic drugs are administered to the elderly population in Spain [23,33]. Another point that should be highlighted is the finding that over half of all nonagenarians are affected by signs of Parkinson, albeit only mildly [42].

Essential tremor is the CND that has given rise to the greatest number of studies in the NEDICES cohort [27,34,45-52]. These studies have shown a higher prevalence and incidence than those reported in previous works, as well as confirming their high rate of under-diagnosis. This indicates that, despite being the most prevalent movement disorder, little attention is paid to it. These studies outline the natural history of this CND and show that essential tremor is not altogether as benign as it was thought to be [45-52].

Strokes and TCI are the CND that have led to the fewest publications in the literature [28-30], even though the prevalence study was very thorough and showed the need for detailed population-based diagnostic research; otherwise, the false positives in the screening are not detected –see the discrepancy between the prevalence data from neurologists and from the survey (Table I)–. No significant differences were observed in the prevalence in urban and rural areas. The clear absence of differences in the prevalence and incidences of CND in the three NEDICES areas would suggest that there is a homogenous distribution of RF throughout these populations, which are close to each other but have a different social make-up. Such absences can also be interpreted as a lack of precision in the biomedical measurement of the potential RF. To some extent this absence of biomedical measurements for the RF can be seen as an important limitation of the NEDICES study.

CONCLUSIONS

The NEDICES study examined a closed, analytical cohort of elderly persons (n = 5,278 participants) in three areas in the

- 1. Bermejo-Pareja F. Enfermedades neurológicas crónicas: desde la clínica a la población. Neurología 2007; 22: 236-48.
- Tanner CM, Ross GW. Neuroepidemiology: fundamental consideration. In Nelson LM, Tanner CM, Van der Eeden SK, McGuire VM, eds. Neuroepidemiology. From principles to practice. Oxford: Oxford University Press; 2004. p. 1-22.
- Brownson RC, Regminton PL, Davis JR. Chronic disease epidemiology and control. Washington DC: American Public Health Association; 1993.
- Goldacre M. The role of cohort studies in medical research. Pharmacoepidemiol Drug Saf 2001; 10: 5-11.
- Last JM. A dictionary of epidemiology. 4 ed. Oxford: Oxford University Press; 2001.
- Bermejo FP, ed. Cohorte de ancianos NEDICES. Datos generales y de salud. Madrid: EDIMSA; 2007.
- Bermejo F, Gabriel R, Vega S, Morales JM, Rocca WA, Anderson DW, et al. Problems and issues with door-to-door, two-phase surveys: an illustration from central Spain. Neuroepidemiology 2001; 20: 225-31.
- Morales JM, Bermejo FP, Benito-León J, Rivera-Navarro J, Trincado R, Gabriel SR, et al. Methods and demographic findings of the baseline survey of the NEDICES cohort: a door-to-door survey of neurological disorders in three communities from Central. Spain. Public Health 2004; 118: 426-33.
- Fernández-Artalejo F. Estudios de cohortes. In Del Rey-Calero J, Herruzo RC, Fernández-Artalejo F, eds. Fundamentos de epidemiología clínica. Madrid: Síntesis; 1996. p. 229-62.
- Szklo M. Population-based cohort studies. Epidemiol Rev 1998; 20: 81-90.
- Elinson J. Introduction to the theme: sociomedical health indicators. Int J Health Serv 1978; 6: 385-91.
- 12. Baldereschi M, Meneghini F, Quiroga P, Albala S, Mamo J, Muscat P, et al. Cognitive versus functional screening for dementia across different countries: cross-cultural validation of the Mini-Mental State Examination (MMSE) and the Pfeffer Activities Questionnaire (PFAQ) against the standardised clinical diagnosis of dementia. Neurology 1994; 44 (Suppl 2): A365.
- Villanueva-Iza C, Bermejo-Pareja F, Berbel-García A, Trincado-Soriano R, Rivera-Navarro J. Validación de un protocolo clínico para la detección de demencia en ámbito poblacional. Rev Neurol 2003; 36: 1121-6.
- Consiglio Nazionale delle Ricerche. Studio longitudinale italiano sull'invecchiamento (ILSA). Strumenti epidemiologici. Firenze: Centro SMID; 1992.
- WHO-Monica Project. Monica manual. Geneva: World Health Organization; 1990.
- Anderson DW, Kalton G. Case-finding strategies for studying rare chronic diseases. Ital J Appl Stat 1990; 2: 309-21.
- Bermejo FP. Reflexiones sobre el cribado de enfermedades neurológicas. Neurología 2003; 18 (Suppl 2): S29-38.
- Gabriel R, Alonso MA, Bermejo FP, Muñiz JG, López IR, Suárez CF, et al. Proyecto EPICARDIAN: estudio epidemiológico sobre enfermedades y factores de riesgo cardiovasculares en ancianos españoles. Diseño, métodos y resultados preliminares. Rev Esp Geriatr Gerontol 1996; 31: 327-34.
- Gabriel R, Bermejo FP, Vega S, Muñiz J, López I, Suárez C, et al. Survey of cardiovascular disease (acute myocardial infarction and stroke) and its risk factors in the elderly population of Spain: the EPICAR-DIAN study –methods and demographic findings. CVD Prevention 1999; 2: 290-300.

centre of Spain to assess the participants' health, chronic diseases, CVRF and several CND, such as dementia, AD, MCI, PD and Parkinsonisms, stroke and TCI, and senile tremor, to name but the most important. From the aspects of this study that are discussed in this review, it can be concluded that the population-based development of the study was satisfactory in view of the acceptable level of participation. The incidence and prevalence of the diseases under study are comparable to those of other Spanish and European population-based studies, but with certain peculiarities. A previously unreported association between senile-onset tremor and dementia has also been detected in this study. At the present time, the mortality of the cohort and its determining factors are being analysed.

REFERENCES

- Amaducci L, Baldereschi M, Amato MP, Lippi A, Nencini P, Maggi S, et al. The World Health Organization cross-national research program on age associated dementias. Aging (Milano) 1991; 3: 89-96.
- Baldereschi M, Amato MP, Nencini P, Pracucci C, Lippi A, Amaducci L, et al. Cross-national interrater agreement on the clinical diagnostic criteria for dementia. Neurology 1994; 44: 239-42.
- Duarte J, Clavería LE, De Pedro-Cuesta J, Sempere AP, Coria F, Calne DB. Screening Parkinson's disease: a validated questionnaire of high specificity and sensitivity. Mov Disord 1995; 10: 643-9.
- Benito-León J, Bermejo-Pareja F, Rodríguez J, Molina JA, Gabriel R, Morales JM, et al. Prevalence of PD and other types of parkinsonism in three elderly populations of central Spain. Mov Disord 2003; 18: 267-74.
- Bermejo-Pareja F, Benito-León J, Vega J, Olazarán J, De Toledo M, Díaz-Guzmán J. Consistency of clinical diagnosis in a populationbased longitudinal study of dementia: the NEDICES study: Neuroepidemiology [submitted].
- Bermejo FP. Alteración cognitiva leve. Una revisión de la clínica y epidemiología con datos del estudio NEDICES. In García AG, Gandía L, eds. Fronteras en la enfermedad de Alzheimer. Madrid: Farmaindustria; 2002. p. 231-54.
- Olazarán J, Trincado R, Bermejo F, Benito-León J, Díaz J, Vega S. Selective memory impairment on an adapted Mini-Mental State Examination increases risk of future dementia. Int J Geriatr Psychiatry 2004; 19: 1173-80.
- Benito-León J, Bermejo-Pareja F, Morales JM, Vega S, Molina JA. Prevalence of essential tremor in three elderly populations of central Spain. Mov Disord 2003; 18: 389-94.
- 28. Díaz-Guzmán J, Bermejo-Pareja F, Benito-León J, Vega S, Gabriel R, Medrano MJ. Prevalence of stroke and transient ischemic attack in three elderly populations of central Spain. Neuroepidemiology 2008 [in press].
- 29. Del Barrio JL, De Pedro-Cuesta J, Boix R, Acosta J, Bergareche A, Bermejo-Pareja F, et al. Dementia, stroke and Parkinson's disease in Spanish populations: a review of door-to-door prevalence surveys. Neuroepidemiology 2005; 24: 179-88.
- Boix R, Del Barrio JL, Saz P, Rene R, Manubens JM, Lobo A, et al. Stroke prevalence in Spanish elderly from screening surveys. BMC Neurol 2006; 6: 36.
- 31. Del Barrio J, Medrano M, Arce A, Bergareche A, Bermejo F, Díaz J, et al. Prevalencia de factores de riesgo vascular en poblaciones españolas de 70 años y más en estudios puerta a puerta de enfermedades neurológicas. Neurologia 2007; 22: 138-46.
- Bermejo-Pareja F, Benito-León J, Vega S, Medrano MJ, Román GC. Incidence and subtypes of dementia in three elderly populations of central Spain. J Neurol Sci 2008; 264: 63-72.
- Benito-León J, Bermejo-Pareja F, Morales JM, Porta-Etessam J, Trincado R, Vega S, et al. Incidence of Parkinson disease and parkinsonism in three elderly populations of central Spain. Neurology 2004; 62: 734-41.
- Benito-León J, Bermejo-Pareja F, Louis ED. Incidence of essential tremor in three elderly populations of central Spain. Neurology 2005; 64: 1721-5.
- 35. Bermejo FP, Rivera JN, Trincado RS, Olazarán JR, Morales JM, eds. Problemas sociales y familiares de los pacientes con demencia. Datos de un estudio poblacional en Madrid. 2 ed. Madrid: Díaz de Santos; 2004.
- Rivera-Navarro J. Redes familiares en el cuidado del anciano con demencia. Análisis evolutivo de un estudio poblacional [PhD thesis]. Madrid: UCM; 1999.
- 37. Rivera-Navarro J, Bermejo-Pareja F, Franco M, Morales-González JM,

Benito-León J. Understanding care of people with dementia in Spain: cohabitation arrangements, rotation and rejection to long term care institution. J Geriatr Psychiatry 2008 [in press].

- De Toledo M, Bermejo-Pareja F, Vega-Quiroga S, Muñoz-García D. Alteraciones conductuales en la enfermedad de Alzheimer. Datos de un estudio poblacional. Rev Neurol 2004; 38: 901-5.
- Carrillo ME, Domingo V, Jiménez MT, Trincado R, Castilla JG, Sánchez-Sánchez F, et al. Estado cognitivo en una muestra poblacional de nonagenarios: datos preliminares del estudio NEDICES. Actual Neurol Neurocienc Envejec 2003; 1: 248-51.
- Domingo-García V, Bermejo-Pareja F, Carrillo E, Jiménez-López MT, Benito-León J. Mild parkinsonian signs and Parkinson's disease in a population of nonagenarians [abstract]. Neurology 2008 [in press].
- Bermejo FP, Trincado R, Castilla-Rilo JG, Sánchez-Sánchez F, Porta-Etessam J, Sepúlveda J, et al. ¿Es fiable el cribado de enfermedades neurológicas por correo? Datos preliminares del estudio NEDICES. Neurología 2003; 18: 497.
- Porta-Etessam J, Bermejo FP, Trincado R, Arroyo C, Moreno T, García-Ramos R, et al. Prevalencia de jaqueca en ancianos. Datos preliminares del estudio NEDICES. Neurología 2003; 18: 550.
- Benito-León J, Bermejo-Pareja F, Vega S. Excessive daily sleepiness in elderly people with incident dementia. A population-based study. Alzheimer Dis Assoc Disord 2006; 20 (Suppl 2): S100.
- Bermejo-Pareja F, Benito-León J, Vega S. Physical activity and risk of dementia in elderly persons: a population-based study [abstract]. Alzheimer Dis Assoc Disord 2006; 20 (Suppl 2): S100.
- Benito-León J, Louis ED, Bermejo-Pareja F, Neurological Disorders in Central Spain (NEDICES) Study Group. Population-based case-control study of cognitive function in essential tremor. Neurology 2006; 66: 69-74.
- Benito-León J, Louis ED, Bermejo-Pareja F, Neurological Disorders in Central Spain Study Group. Elderly-onset essential tremor is associated with dementia. Neurology 2006; 66: 1500-5.
- Bermejo-Pareja F, Louis ED, Benito-León J, Neurological Disorders in Central Spain (NEDICES) Study Group. Risk of incident dementia in essential tremor: a population-based study. Mov Disord 2007; 22: 1573-80.
- Louis ED, Benito-León J, Ottman R, Bermejo-Pareja F. A populationbased study of mortality in essential tremor. Neurology 2007; 69: 1982-9.
- Louis ED, Benito-León J, Bermejo-Pareja F, Neurological Disorders in Central Spain (NEDICES) Study Group. Self-reported depression and anti-depressant medication use in essential tremor: cross-sectional and prospective analyses in a population-based study. Eur J Neurol 2007; 14: 1138-46.
- Benito-León J, Louis E, Bermejo-Pareja F. Population-based case-control study of cigarette smoking and essential tremor. Mov Disord 2008 23: 246-52.
- Benito-León J, Louis ED, Bermejo-Pareja F. Reported hearing impairment in essential tremor: a population-based case-control study. Neuroepidemiology 2007; 29: 213-7.
- 52. Louis ED, Benito-León J, Bermejo-Pareja F. Population-based pros-

pective study of cigarette smoking and risk of incident essential tremor. Neurology 2008 [in press].

- Damián J, Ruigómez A, Pastor V, Martin-Moreno JM. Determinants of self assessed health among Spanish older people living at home. J Epidemiol Commun Health 1999; 53: 412-6.
- Cornoni-Huntley J, Brock DB, Ostfeldt AM, Taylor JO, Wallace RB, eds. Establish population for epidemiological studies of the elderly, resource data book. NIA. (NIH publication n.º 86-2443). Washington, DC: U.S. Government Printing Office; 1986.
- 55. Hofman A, Grobbee DE, De Jong PT, Van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. Eur J Epidemiol 1991; 7: 403-22.
- Simons LA, McCallum J, Friedlander Y, Simons J, Powell I, Heller R. Dubbo study of the elderly: sociological and cardiovascular risk factors at entry. Aust N Z J Med 1991; 21: 701-9.
- Dartigues JF, Gagnon M, Michel P, Letenneur L, Commenges D, Barberger-Gateau P, et al. Le programme de recherche PAQUID sur l'épidémiologie de la démence. Méthodes et résultat initiaux. Rev Neurol (Paris) 1991; 147: 225-30.
- Pijls LT, Feskens EJ, Kromhout D. Self-rated health, mortality, and chronic diseases in elderly men. The Zutphen Study, 1985-1990. Am J Epidemiol 1993; 138: 840-8.
- Mossey JM, Havens B, Roos NP, Shapiro E. The Manitoba longitudinal study on aging: description and methods. Gerontologist 1981; 21: 551-8.
- Anderson DW, Rocca WA, Rosario JA. Pitfalls in neuroepidemiology research. Neuroepidemiology 1998; 17: 55-62.
- Anderson DW, Rocca WA, De Rijk MC, Grigoletto F, Melcon MO, Breteler MM, et al. Case ascertainment uncertainties in prevalence surveys of Parkinson's disease. Mov Disord 1998; 13: 626-32.
- Instituto Nacional de Estadística (INE). Proyecciones de la población de España calculada a partir del censo de población de 1991. Total nacional 1990-2020. Madrid: INE; 1995.
- 63. Matthews FE, Chatfield M, Freeman C, McCracken C, Brayne C. Attrition and bias in the MRC cognitive function and ageing study: an epidemiological investigation. BMC Public Health 2004; 4: 12.
- 64. Chatfield MD, Brayne CE, Matthews FE. A systematic literature review of attrition between waves in longitudinal studies in the elderly shows a consistent pattern of dropout between differing studies. J Clin Epidemiol 2005; 58: 13-9.
- Wallace RB, Woolson RF, eds. The epidemiologic study of the elderly. New York: Oxford University Press; 1992.
- 66. Lobo A, Launer LJ, Fratiglioni L, Andersen K, Di Carlo A, Breteler MM, et al. Prevalence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 2000; 54 (Suppl 5): S4-9.
- Gibb WR, Mountjoy CQ, Mann DM, Lees AJ. A pathological study of the association between Lewy body disease and Alzheimer's disease. J Neurol Neurosurg Psychiatry 1989; 52: 701-8.
- Jellinger KA. Alpha-synuclein pathology in Parkinson's and Alzheimer's disease brain: incidence and topographic distribution –a pilot study. Acta Neuropathol 2003; 106: 191-201.

LA COHORTE DE ANCIANOS NEDICES. METODOLOGÍA Y PRINCIPALES HALLAZGOS NEUROLÓGICOS

Resumen. Objetivo. Resumir los aspectos metodológicos y principales hallazgos del estudio de cohorte poblacional de ancianos NEDICES (Neurological Disorders in Central Spain) integrada por más de 5.000 participantes. Desarrollo. Se sintetizan los hallazgos en enfermedades neurológicas crónicas (ENC): demencia, enfermedad de Parkinson y parkinsonismos, ictus y temblor senil. El estudio NEDICES investigó la salud, la mortalidad y los diversos aspectos sociológicos de la cohorte, que no se discuten. Sí se describen los objetivos, métodos, población y desarrollo con los cortes, basal (año 1994) y de incidencia (año 1997), y se comentan los principales hallazgos en las ENC investigadas. Conclusión. La prevalencia e incidencia de las ENC son análogas a las de otros estudios poblacionales españoles y europeos, aunque con peculiaridades: la incidencia de temblor senil es la más elevada de la bibliografía y esta ENC se asocia con demencia. Más de la mitad de los casos de enfermedad de Parkinson se describieron de novo con el estudio, y la enfermedad de Alzheimer se asoció con factores de riesgo vasculares. [REV NEUROL 2008; 46: 416-23]

Palabras clave. Cohorte. Demencia. Enfermedades neurológicas crónicas. Epidemiología. Estudio poblacional. Ictus. Métodos. Parkinsonismo. Temblor.