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Rates and risk factors for dementia and Alzheimer's disease

Results from EURODEM pooled analyses

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Article abstract—*Objective:* To investigate the risk of AD associated with a family history of dementia, female gender, low levels of education, smoking, and head trauma. *Background:* These putative factors have been identified in cross-sectional studies. However, those studies are prone to bias due to systematic differences between patients and control subjects regarding survival and how risk factors are recalled. *Methods:* The authors performed a pooled analysis of four European population-based prospective studies of individuals 65 years and older, with 528 incident dementia patients and 28,768 person-years of follow-up. Patients were detected by screening the total cohort with brief cognitive tests, followed by a diagnostic assessment of those who failed the screening tests. Dementia was diagnosed with the Diagnostic and Statistical Manual of Mental Disrders, 3rd ed. (revised), and AD was diagnosed according to National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria. Incident rates and relative risk (95% CI) express the association of a risk factor for dementia. *Results:* Incident rates for dementia and AD were similar across studies. The incidence of AD increased with age. At 90 years of age and older the incidence was 63.5 (95% CI, 49.7 to 81.0) per 1,000 person-years. Female gender, current smoking (more strongly in men), and low levels of education (more strongly in women) increased the risk of AD significantly. A history of head trauma with unconsciousness and family history of dementia did not increase risk significantly. *Conclusion:* Contrary to previous reports, head trauma was not a risk factor for AD, and smoking did not protect against AD. The association of family history with the risk of AD is weaker than previously estimated on the basis of cross-sectional studies. Female gender may modify the risk of AD, whether it be via biological or behavioral factors.

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Previous studies suggest that family history of dementia, female gender, low levels of education, and head trauma increase the risk of AD.[1] Smoking, on the other hand, has been reported to reduce the risk of AD.[1] However, these previous studies are based on prevalent patients and might be flawed. Information about risk factors may be systematically different between patients and control subjects. Patient data must come from a proxy, who might recall the patient's medical history differently than a proxy of a control subject or the control subject him- or herself. Also, the findings can reflect the contribution a factor makes to developing dementia as well as to surviving after the dementia starts. To date there are few, or inconsistent, reports of these risk factors derived from population-based follow-up studies that identify new patients of dementia in a cohort that is dementia free at baseline. Because the possibility is reduced for systematic differences in survival and risk factor recall between patients and control subjects, this design is preferred over one based on prevalent patients.

In 1988, investigators working on European studies formed the European Studies of Dementia (EURODEM) network to harmonize the protocols used in their newly initiated, population-based follow-up studies on incident dementing diseases.[2] We report results of analyses based on pooling the data from the studies conducted in Denmark, France, the Netherlands, and the United Kingdom. The analyses are based on 528 incident dementia patients and 28,768 person-years of follow-up.

Methods. *Study design.* The individual studies include a population-based sample of persons aged 65 years and

*See the Appendix on page 83 for a listing of group members.

†Deceased.

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Table 1 *Description of studies: Pooled European Studies of Dementia analysis of the incidence of dementia and AD*

Study	Cohort, n*	Lost to follow-up, n†	Dead, n‡	Analytical sample, n	Follow-up time, y (SD)	Person-years	Incidence of dementia§	
							Men	Women
Odense (Denmark)	3,157	13.2	6.3	2,512	2.1 (0.2)	4,944	15.6	19.4
PAQUID (France)	3,675	8.7	17.3	2,701	2.8 (0.9)	7,611	11.5	15.2
Rotterdam Study (the Netherlands)	4,710	6.4	1.5	4,401	2.1 (0.8)	9,478	10.5	17.3
MRC-ALPHA (United Kingdom)	4,792	15.3	15.3	3,320	2.0 (0.2)	6,734	10.7	18.5

* Cohort 65 years and older, excluding prevalent mild to severe cases of dementia.
† Lost to follow-up with no information on vital status or dementia status as of December 1995.
‡ Died during the follow-up period with no information on dementia status as of December 1995.
§ Incidence per 1,000 person-years standardized to the age distribution of the male and female European population reported in the World Health Organization Statistics Annual 1992.[41]

older living in the community and in nursing homes. Samples were drawn from defined geographic areas and either include all eligible individuals or individuals selected randomly within predefined strata. All studies contributed baseline data and one follow-up panel conducted after a fixed interval. The cohorts excluded the prevalent patients identified at baseline. The design of the individual studies is described briefly here. The characteristics of the follow-up are described in table 1. More detailed descriptions of the studies have been published elsewhere.[3-7]

Denmark. The Odense Study[4] (1992 to 1996) was conducted in the municipality of Odense. Persons between 65 and 85 years of age living within the municipality were selected randomly for inclusion in the study. The baseline cohort was 3,346 persons (64% response).

France. The PAQUID study[5] (1988 to 1993) was conducted in 75 parishes in the provinces of Gironde and Dordogne. The sample was selected randomly from electoral roles using a multistage procedure based on strata of age, sex, and size of geographic unit. Participants had to have been living at home at baseline to be eligible for the study. The baseline cohort was 3,777 persons (68% response).

The Netherlands. The Rotterdam study[6] (1990 to 1995) was conducted in Ommoord, a district of the municipality of Rotterdam. Although all persons aged 55 years and older living in the district were eligible for participation, our analysis was limited to persons 65 years and older. The baseline cohort starting from 65 years of age was 5,265 persons (75% response).

United Kingdom. The MRC-ALPHA study[7] (1988 to 1996) was conducted in the municipality of Liverpool. Samples were selected randomly from the general practitioner registry within equal-size strata of age (5-year bands) and sex. This general practitioner registry is essentially population based, excluding only <1% of the population living in long-term hospital facilities. The baseline cohort was 5,222 persons (87% response).

Patient assessment. Findings for dementia were conducted in two stages. The total sample was screened with brief cognitive tests, including the Mini-Mental State Examination,[8] the organic section of the Geriatric Mental State Examination,[9] and the Cambridge Examination of Mental Disorders Cognitive Test.[10] Persons who scored below a given cutoff point, chosen for high sensitivity, on one or two of the screening tests, or who were clinically suspect as judged by a clinician, were investigated in a follow-up diagnostic interview. The diagnostic phase consisted of detailed neuropsychological testing, an informant interview, and a clinical examination. Diagnoses were made in conference. If the respondent could not participate fully in the workup, medical records were used to make the diagnosis (12.8% of the patients).

For these analyses we included dementia patients of mild to severe severity diagnosed according to Diagnostic and Statistical Manual of Mental Disorders, 3rd ed. (revised) (DSM-III-R) criteria.[11] National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria[12] were used to diagnose possible and probable AD. In accordance with the criteria for possible AD we included in this category patients in whom cerebrovascular disease may contribute secondarily to the dementia.

To obtain an estimate of study differences in the application of diagnostic guidelines, the automated diagnostic data (which excluded clinical notes made by the interviewing physician) from a sample of demented and nondemented screen positives (n = 266) were reviewed by a EURODEM consensus panel. This panel included neurologists, psychiatrists, and neuroepidemiologists, each of whom had worked as a clinician at one of the participating studies. We oversampled patients indicated by the study as difficult to diagnose (22% of the sample). With the difficult patients in the sample, the kappa statistic for agreement on dementia (yes/no) between the study and the EURODEM review board diagnosis was 0.66; for AD, 0.71. Excluding the difficult patients, the kappa for agreement on dementia was 0.75 and for AD, 0.78.

Assessment of risk factors. Data regarding risk factors were collected from the participants at baseline when they were dementia free. All questions were administered by interviewers in the home of the respondents. Each study developed its own baseline interview that included questions about a core set of risk factors. The core risk factors were ascertained with questions designed to obtain the same information (i.e., Does the person have a history of head trauma that resulted in unconsciousness?). In the current analyses, risk factors were defined as follows: sex, education (number of years completed), smoking (current, former, never), history of head trauma with unconsciousness (regardless of when the trauma occurred relative to

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the onset of dementia), and self-reported family history of dementia (type unspecified) in first-degree relatives (none, one, two, or more affected relatives). Self-reported history of myocardial infarction and stroke confirmed by a physician were entered into the models as possible confounders.

Data management. Investigators from the individual studies recoded their own data into a standardized data format developed collaboratively by the data managers from the studies. Data for the entire cohort were sent to the coordinating center at Erasmus University in the Netherlands, and were checked for format and logical inconsistencies. Data were returned to the centers for correction if needed.

Statistical analysis. Incident cohorts excluded prevalent patients and those with missing data on follow-up and dementia status after baseline (nonresponders to the follow-up examination, and those who died between baseline and follow-up with unknown status at death; see table 1). Rates per 1,000 person-years (95% CIs) were estimated per 5-year age band (65 years to 90+ years) using a log–linear model that is based on the assumption that rates are constant within an age strata. Person-years for nondemented individuals were calculated as the time between baseline and follow-up. The contribution of person-years made by demented patients stopped at the time of dementia onset. To account for the fact that reliable data regarding when the dementia started is difficult to obtain, we used an iterative procedure that provides a best estimate for time of onset based on the patient's age and age-specific dementia rates.[13] Significant differences among studies in age-specific rates of dementia and AD were tested by entering into the model a product term for study site by age group (study-by-age interaction). Studies were also compared individually with each other within strata of age.

The association of a risk factor for dementia was estimated by the relative risk (RR; 95% CIs) using a standard Poisson program to estimate the measurements. Given the relatively short follow-up (mean ± SD, 2.24 ± 0.73 years), this model gives equivalent results to those based on logistic and Cox proportional hazards regression.[14] All RRs were adjusted for age (in years), the quadratic of age (in years), and study (dummy variables).[15] Depending on the model, we also adjusted for sex and education (<8 years, 8 to 11 years, and 12 years or more). Those with missing education data (n = 298) were assigned a separate value in the education variable so they could be included in the analyses. Significant study differences in risk estimates were assessed by visual inspection of study-specific risk ratios, by testing for significant differences in study estimates using interaction terms (product of the study and risk factor), and by deleting individual studies from the overall analysis to determine how the risk estimates were affected. We investigated systematically whether the relation of a risk factor for dementia was modified by sex and family history of dementia (yes/no). This was done by entering into the model a product term of the two risk factors of interest (i.e., sex by smoking).

Results. In the pooled dataset of 528 patients, 352 (65%) were subtyped with AD. The sample size and distribution of patients per 5-year age group are given in table 2. There were no consistent significant study differences in age-specific rates for dementia or AD (figure 1). The incidence of dementia and AD increased steeply with age (figures 2 and 3). At 65 years of age, the incident rate for dementia was 2.5 (95% CI, 1.6 to 4.1), and at 90+ years the rate was 85.6 (95% CI, 70.4 to 104.0). Similarly for AD, the rates were 1.2 (95% CI, 0.6 to 2.4) at 65 years of age, and 63.5 (95% CI, 49.7 to 81.0) at age 90 or older.

A reported history of dementia in two or more family members was positively but insignificantly associated with

Table 2 *Distribution of person-years and number of patients with incident dementia and AD by 5-year age strata: European Studies of Dementia*

	Dementia		AD*	
Age strata, y	Person-years	No. of patients	Person-years	No. of patients
65–69	6,352	13	6,340	7
70–74	7,778	38	7,755	21
75–79	6,529	106	6,462	63
80–84	4,538	135	4,489	97
85–89	2,390	128	2,341	89
≥90	1,181	108	1,144	75
Total	28,678	528	28,531	352

* Includes National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association probable and possible AD.[12]

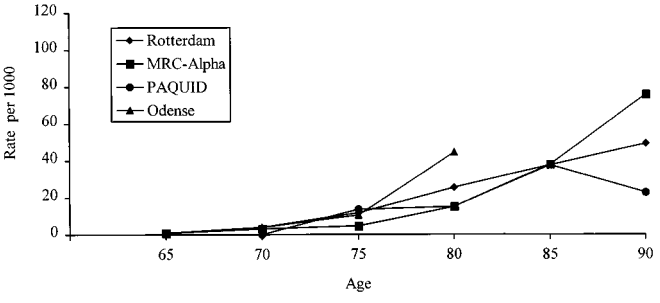

Figure 1. Incidence of AD per 1,000 person-years by age and study: European Studies of Dementia. AD includes National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association probable and possible AD.[12]

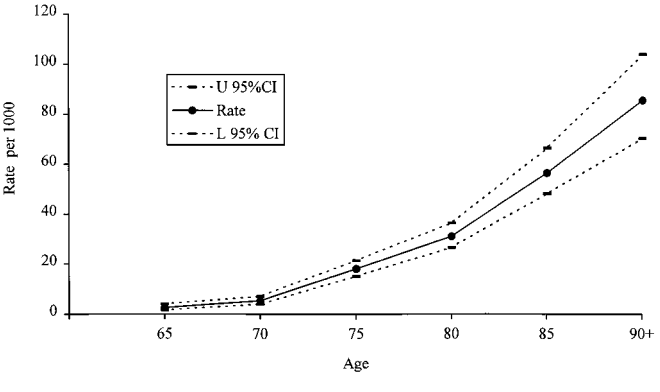

Figure 2. Age-specific incidence rate of dementia and 95% CI per 1,000 person-years by age: European Studies of Dementia pooled analyses. U = upper; L = lower.

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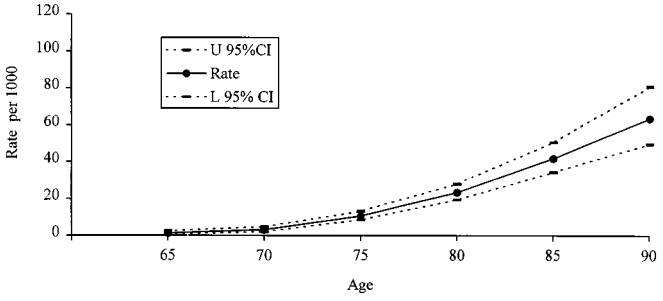

Figure 3. Age-specific incidence rate of AD and 95% CI per 1,000 person-years by age: European Studies of Dementia pooled analyses. AD includes National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association probable and possible AD.[12] U = upper; L = lower.

the risk of AD. Women had an increased risk of AD. The risk of AD increased as years of education decreased (table 3). More detailed analyses suggested that the significant association of low levels of education with AD was confined to women (compared to those with high education, women with < 8 years education: RR, 4.55; 95% CI, 1.64 to 12.57; men: RR, 1.00; 95% CI, 0.48 to 2.04; p for interaction = 0.05).

Current smoking was associated with a significantly increased risk of AD. These results did not change materially when we excluded from the AD group patients with contributing cardiovascular disease (n = 18) and those with a history of stroke not thought to contribute to the dementia (n = 15). Compared with never-smokers, the risk of AD was stronger in men who were former smokers (men: RR, 1.97; 95% CI, 0.92 to 4.22; women: RR, 1.08; 95% CI, 0.73 to 1.61; p for interaction = 0.22) and current smokers (men: RR, 3.17; 95% CI, 1.42 to 7.07; women: RR, 1.50; 95% CI, 0.94 to 2.40; p for interaction = 0.16). In addition, family history weakly modified the risk of current smokers (p for interaction = 0.17). Compared with never-smokers with no family history of dementia, current smokers without a family history had a significantly increased risk of AD of 2.28 (95% CI, 1.49 to 3.50). There was no increased risk in current smokers with a family history (RR, 1.01; 95% CI, 0.34 to 2.85).

Overall, head trauma with unconsciousness was not associated with AD, although men with head trauma did have an increased risk (RR, 1.66; 95% CI, 0.94 to 2.95). However, risk estimates for head trauma from the MRC-ALPHA study were significantly different from the other studies. When this study was removed from the analyses, the RR for AD was 0.79 (95% CI, 0.31 to 1.98), with no evidence of a modification of the risk by gender. There was also no evidence of modification of risk by family history. None of these results changed materially when self-reported myocardial infarction and stroke were entered into the model as confounding variables.

Table 3 *Risk factors for dementia and AD: Pooled European Studies of Dementia analysis on the incidence of dementia*

Risk factor	Person-years at risk	AD		All dementias	
		No. of patients	RR (95% CI)	No. of patients	RR (95% CI)
Family history of dementia*†					
0	17,099	192	1.0 (—)	272	1.0 (—)
1	3,562	32	0.88 (0.60–1.28)	45	0.88 (0.64–1.21)
2+	370	8	1.59 (0.78–3.26)	10	1.42 (0.75–2.68)
Gender‡					
Male	12,270	96	1.0 (—)	177	1.0 (—)
Female	16,498	256	1.54 (1.21–1.96)	351	1.20 (1.00–1.44)
Education§					
>11 y	2,063	13	1.0 (—)	23	1.0 (—)
8–11 y	14,945	156	1.48 (0.84–2.62)	248	1.32 (0.86–2.03)
<8 y	11,053	159	2.00 (1.11–3.60)	222	1.83 (1.17–2.88)
Smoking*¶					
Never	10,889	145	1.0 (—)	207	1.0 (—)
Former	8,757	78	1.19 (0.80–1.51)	117	1.03 (0.79–1.34)
Current	5,085	54	1.74 (1.21–2.50)	76	1.39 (1.03–1.89)
Head trauma with unconsciousness*					
No	26,102	306	1.0 (—)	450	1.0 (—)
Yes	2,493	27	1.02 (0.68–1.51)	45	1.14 (0.843–1.56)

* Controlling for age, age^2, study, sex, and education.
† No data on family history of dementia from the MRC-ALPHA Study.
‡ Controlling for age, age^2, study, and education.
§ Controlling for age, age^2, sex, and study.
¶ Data collected on a portion (n = 1,605) of the MRC-ALPHA Study.

age^2 = quadratic of age in years; RR = relative risk.

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Discussion. These collaborative analyses include the largest number of dementia patients identified in population-based follow-up studies reported to date. With this large sample we were able to investigate risk factors for AD, and whether sex and family history modified the association of these risk factors for AD. Female gender, low levels of education, and current smoking were associated with a significantly increased risk of AD. The analyses suggest gender modified the increased risk of AD associated with low education and current smoking. The education effect was significant only in women, and the smoking effect was stronger in men. The significantly increased risk in men for AD associated with head trauma with unconsciousness was due primarily to one study. Persons with a history of dementia in two or more first-degree family members had a nonsignificant increased risk for AD of 1.6.

There are several methodologic issues that need to be taken into account when interpreting these data. One set of concerns relates to patient detection. First, patients were missed in studies that did not obtain patient information on respondents lost between baseline and the follow-up investigation. This source of patient loss is minimized in these analyses because the interval was relatively short (average, 2 years). However, we cannot exclude the possibility that the loss was selective; for instance, by type of dementia or by one of the risk factors of interest. This bias probably affects all the studies in the same way, but to the degree to which individuals were lost to follow-up. Second, patients in the screen-negative strata may have been missed. Because the studies used a relatively sensitive cutoff point for screening test performance, and used more than one mechanism to identify patients, a significant underestimation of patients in the screen-negative strata is unlikely. In a community-based study[16] of AD that examined a sample of screen negatives at baseline, the investigators found the number of patients to be so low that adjustment for the presence of prevalent patients in the screen-negative sample had little effect on the estimated incidence rates. Third, the studies may have applied the diagnostic guidelines differently. However, study differences were not likely to be systematic relative to the risk factors of interest. In addition, the interrater reliability in the application of DSM-III-R criteria for dementia and the NINCDS-ADRDA criteria for AD has been found elsewhere to be good in studies based on different centers.[17] Our own measure of agreement between study diagnosis and the consensus diagnosis indicated good to excellent agreement.

Another methodologic concern is systematic bias due to the studies not using exactly worded questions to assess exposure status. The differences in wording reflect a concern that exactly worded questions may not be equally comprehensible in a multilingual and cultural context. Although we cannot exclude the possibility that different formulations lead to a different measure of exposure, the risk factors presented here were assessed with comparable questions administered under comparable conditions. Furthermore, with the exception of head trauma, there were no significant study-by-risk factor interactions, and removal of the individual studies from the analyses did not affect the overall conclusions drawn from the pooled estimates.

The rates for dementia and AD were not significantly different across studies. The incidence of AD increased steeply with age, although the incremental increase in rates is lower after 75 years of age than before this age. The rates for dementia and AD include mild to severe patients. Thus, the rates are higher than those reported for the Framingham cohort,[18] which only included moderate to severe patients. Up to age 85 years, our rates for AD are similar to those reported for the East Boston cohort[16]; after that their rates are higher (84 per 1,000) than our rates. In light of investigations concerning differences in rates of AD and vascular dementia between white and Japanese populations, it is of interest to note that our rate of AD was higher than that reported in the Hisayama Study,[19] particularly in those younger than 85 years of age. However, their report[19] does not specify whether mild patients are included in their estimates.

One important finding of these collaborative analyses is that women have a higher RR for dementia—AD in particular. Previous studies examining gender differences have been hampered by small sample size at older ages.[20] Recently, a significant difference in the risk of AD was found in the Kungsholmen Study[21] in Sweden, which has a relatively older sample than other studies. Gender may also be an important modifier of the risk of AD associated with other factors. Gender differences in risk may be due to biological differences,[22] survival differences, or cohort differences in behavior and exposures.

Family history of dementia is considered to be a marker for genetic susceptibility. Compared with the risk reported in studies based on prevalent patients, the risk of AD in our study[23] is lower. The contribution of family history to the risk of AD may be overestimated in studies of prevalent patients because informants for the patient preferentially report a family history compared with informants of control subjects. This bias is reduced in studies of incident patients when data are collected from the respondent before the onset of dementia. An overestimate of the association of family history with AD would also result if patients with a genetic susceptibility have a longer survival than patients without a susceptibility. We investigated whether family history modified any of the relations of the other variables to AD. Smoking was the only risk factor with a moderately modified effect. We were unable to investigate gene–environment interactions with more specific markers of genetic susceptibility, such as the apolipoprotein E allele.

The contribution of education to the risk of dementia and AD is controversial. Some[24] argue that

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an association reflects confounding by socioeconomic factors, or diagnostic bias due to poorer performance on neuropsychological tests by individuals with low education. Others[25] argue that education is a marker for biological capacity that modulates when a person reaches the threshold of clinical dementia. Several studies based on prevalent patients have shown a relation of low education to dementia,[26] and specifically AD.[6] Studies based on incident patients have been inconsistent. A study based on the Mayo Clinic register did not find an association of education with dementia,[27] whereas a study conducted in north Manhattan did.[28] In these studies, there was no investigation of differences by gender in the relation of education to AD. In our analyses the increased risk associated with AD was confined to women. The reasons for this are unclear.

Most previous studies on smoking have been based on prevalent patients. The results of collaborative analysis of eight case-control studies suggested that smoking may reduce the risk of AD,[29] possibly through actions related to nicotine receptors in the brain.[30] Other studies, however, failed to confirm this finding.[31] Studies based on prevalent patients are susceptible to survival bias if demented patients who smoked had a relatively higher mortality than nondemented smokers. This would produce a protective effect of smoking against AD. Our current analyses are based on incident patients. We found that former and current smoking was associated with an increased risk of AD, particularly in men. This increased risk is consistent with a contribution of smoking to silent cerebrovascular disease,[32] and with the finding that atherosclerosis is a risk factor for AD.[33] A stronger effect of smoking in men than women may reflect differences in smoking patterns. The increased risk of AD in current smokers without a family history, and not in current smokers with a family history of dementia, is consistent with studies finding an interaction between smoking and the presence of the apolipoprotein E*4 allele.[34]

Reports on the relation of AD to head trauma with unconsciousness are inconsistent. Most studies are based on prevalent patients in which they had to ask a proxy about the patient's history of head trauma. These studies have shown either no effect,[35] or an increased risk for AD only in men[36,37] or only in women with head trauma.[38] In our pooled analyses, the results across studies were also heterogeneous, with one study showing a positive association of head trauma with AD in men, and the other three showing no relation. There is also a report[39] that head trauma is only a risk factor in the presence of the apolipoprotein E*4 allele, but two other studies[37,40] have failed to find this. Because head trauma may be recalled unreliably, regardless of current cognitive state, future studies should try to collect a measure of head trauma independent from an individual's recall.

Appendix

EURODEM Incidence Research Group: list of participants and funding agencies.

Denmark: K. Andersen, A. Green, P. Kragh-Sorensen (PI), A. Lolk, and H. Nielsen; Danish Medical Research, Soster and Verner Lippert's Research Fund, Ebba and Verner Andersen's Research Fund, Institute of Clinical Research, Odense University, and The Health Insurance Fund.

France: D. Commenges, J.-F. Dartigues (PI), and L. Letenneur; Foundation de France, Sandoz Laboratories, AXA Insurance Group, Conseils Generaux de Gironde et Dordogne, CRI, MGEN, and MSA.

The Netherlands: M.M.B. Breteler, F. van Harskamp, A. Hofman (PI), and A. Ott; NESTOR program for research on the elderly (supported by the Netherlands Ministries of Health and Education), the Netherlands Heart Foundation, the Netherlands Prevention Fund, and the Municipality of Rotterdam. L.J. Launer is affiliated with the National Institute for Public Health and the Environment.

Spain/ZARADEMP: C. De-la-Camara, J.L. Dia, A. Lobo (PI), G. Marcos, P. Saz, and T. Ventura; Comision Interministerial de Ciencia y Tecnologia and Fondo de Investigacion Sanitaria.

United Kingdom/MRC-ALPHA: J.R.M. Copeland (PI), M.E. Dewey, C.F.M. McCracken, and K.C.M. Wilson. MRC-ALPHA is also a part of the MRC Study of Cognitive Function and Ageing (CFAS).

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