



Wolters Kluwer

Health

OvidSP

[Current Search Results](#)[Main Search Page](#)[Ask the Virtual Desk at the Library](#)[Help](#)[Logoff](#)

Full Text [Save Article Text](#) [Email Article Text](#) [Print Preview](#)



Wolters Kluwer

Health

Lippincott  
Williams & Wilkins

NEUROLOGY®

APOE and the risk of PD with or without dementia in a population-based study

ISSN: 0028-3878

Accession: 00006114-200003280-00018

[Email Jumpstart](#)

[Find Citing Articles](#)

[Table of Contents](#)

[About this Journal](#)

Harhangi, B. S. MD; de Rijk, M. C. MD, PhD; van Duijn, C. M. PhD; Van Broeckhoven, C.

**Author(s):** PhD; Hofman, A. MD, PhD; Breteler, M. M. B. MD, PhD

**Issue:** Volume 54(6), 28 March 2000, pp 1272-1276

**Publication**

**Type:** [Articles]

**Publisher:** Copyright © 2000 American Academy of Neurology

From the Departments of Epidemiology & Biostatistics (Drs. Harhangi, van Duijn, Hofman, and Breteler) and Neurology (Dr. de Rijk), Erasmus Medical Center Rotterdam, The Netherlands; and the Flanders Interuniversity Institute for Biotechnology (Dr. Van Broeckhoven), Born-Bunge Foundation, University of Antwerp, Belgium.

Received August 18, 1999.

Accepted in final form December 12, 1999.

**Institution(s):**

Supported in part by the "Prinses Beatrix Fonds" in the Netherlands, Biomed II, grant PL95-0664, and the Fund for Scientific Research Flanders (FWO). The Rotterdam Study is supported by the NESTOR Program for Geriatric Research in the Netherlands (Ministry of Health and Ministry of Education), the Netherlands Organization for Scientific Research (NWO) and the Municipality of Rotterdam, the Netherlands.

Address correspondence and reprint requests to Dr. Breteler, Department of Epidemiology

& Biostatistics, Erasmus Medical Center Rotterdam, P.O.Box 1738, 3000 DR, Rotterdam,  
The Netherlands; e-mail: [breteler@epib.fgg.eur.nl](mailto:breteler@epib.fgg.eur.nl)

Keywords: APOE, Parkinson's disease, Dementia, Genetics, Epidemiology.

Table of Contents:

- [▫ Association of vitamin E and C supplement use with cognitive function and dementia in elderly men.](#)
- [▫ White matter abnormalities in mobility-impaired older persons.](#)

## Links

[Abstract](#)

[Complete Reference](#)

[360 Link](#)

## Outline

- [Abstract](#)
- [Methods.](#)
  - [Study population.](#)
  - [Case ascertainment and diagnosis of PD.](#)
  - [Diagnosis of dementia.](#)
  - [APOE genotyping.](#)
  - [Data analysis.](#)
- [Results.](#)
- [Discussion.](#)
- [References](#)

## Graphics

- [Table 1](#)
- [Table 2](#)
- [Table 3](#)

Abstract 

Objective: To study the association between APOE genotype and PD with or without dementia.

Methods: The study formed part of the Rotterdam Study, a prospective, population-based cohort study on the frequency, etiology, and prognosis of chronic diseases. The cohort examined for PD consisted of 6969 independently living or institutionalized inhabitants from a suburb of Rotterdam, the Netherlands, aged 55 years or older. All participants were screened at baseline (1990 to 1993) and at follow-up (1993 to 1994) for symptoms of parkinsonism by study physicians; screen positives received a diagnostic workup by a neurologist.


Results: APOE genotyping was available for 107 PD patients (26 with and 81 without dementia) and 4805 non-PD control subjects. The presence of at least one [epsilon]2 allele significantly increased the risk of PD (OR = 1.7; 95% CI, 1.0 to 2.8). When we looked separately for demented and nondemented PD patients as compared with nonparkinsonian controls, APOE did not appear to be associated with PD without dementia, but both the [epsilon]2 and the [epsilon]4 allele increased the risk of PD with dementia (OR = 5.6; 95% CI, 2.0 to 15.2 and OR = 3.6; 95% CI, 1.3 to 9.9). The risk of dementia for [epsilon]4 allele carriers was not significantly different for persons with or without PD. However, the [epsilon]2 allele strongly increased the risk of dementia in patients with PD (interaction  $p < 0.007$ ).

Conclusions: In the elderly the APOE-[epsilon]2 allele increases the risk of PD and, in particular, the risk of PD with dementia.

---


It has been suggested that PD and AD share clinical and neuropathologic features. [1-3](#) It is known that PD patients frequently develop dementia, and AD patients frequently develop parkinsonism. Both are age-related disorders characterized by intraneuronal inclusion bodies. [4](#)

The APOE-[epsilon]4 allele has been associated with both AD [5](#) and Lewy body disease. [6,7](#) Reports on APOE genotype and PD are not consistent. Some studies have reported an association between the APOE-[epsilon]4 allele and PD or PD with dementia, whereas others have not. [8,9](#) In the majority of these studies little attention was paid to the [epsilon]2 allele and PD. However, in most of these studies, but not all, [10](#) the [epsilon]2 allele frequency was higher in PD patients [8,11-13](#) or in PD patients with dementia, [14,15](#) although this was not statistically significant. Recently, a significant association of the [epsilon]2 allele with sporadic PD was reported, although no subdivision was made between demented and nondemented PD patients. [16](#) We studied differences in the APOE genotype distribution among PD patients with and without dementia as compared with nonparkinsonian control subjects from the Rotterdam Study.

Methods. 

Study population. 

The study formed part of the Rotterdam Study, a prospective, population-based cohort study on the frequency, etiology, and prognosis of neurologic, cardiovascular, locomotor, and ophthalmologic diseases, as described previously. [17](#) Briefly, all inhabitants of a suburb of Rotterdam aged 55 years and over, including those living in homes for the elderly, were invited to participate. A total of 7,983 individuals (a 78% response rate) agreed to participate and of these, 6,969 (68%) underwent screening for parkinsonism at baseline (1990 to 1993), as described extensively elsewhere. [18](#) Informed consent was obtained from each participant and the study was approved by the Medical Ethics Committee of the Erasmus Medical Center Rotterdam, The Netherlands.

Case ascertainment and diagnosis of PD. 

All 6969 participants were interviewed about previous diagnosis of PD or antiparkinsonian drug use and screened for symptoms of parkinsonism by study physicians at the research center. All individuals who either used antiparkinsonian drugs, reported that they had PD, or had at least one possible cardinal sign of parkinsonism (resting tremor, bradykinesia, rigidity, and postural disturbances) at the screening examination received a structural diagnostic workup by a neurologist. PD was diagnosed in persons with at least two of four cardinal signs and no other apparent cause of parkinsonism. [18](#) At baseline, of 129 individuals with parkinsonism 98 had PD. The other causes of parkinsonism were: parkinsonism associated with dementia (9); drug-induced parkinsonism (3); parkinsonism related to vascular disease (1); multisystem atrophy (2); progressive supranuclear palsy (1); and other causes (15), which included parkinsonism and dementia with no clear time relationship between the two, more than one possible cause, as well as subjects in whom all causes of PD could be excluded but who had not shown any progression over more than 15 years in the course of disease and who did not respond to antiparkinsonian drugs. [18](#) At follow-up (1993 to 1994), 6,840 participants, screened for symptoms of parkinsonism at baseline, were at risk for developing parkinsonism. Participants who were demented at baseline were considered at risk for parkinsonism but not for PD. Follow-up information was available on 6,778 (99%) individuals either through complete reexamination at the research center or through our surveillance system, which continuously monitors the total cohort for incident cases of parkinsonism. Through this surveillance system, which consists of computer links to general practitioners and pharmacies' automated medical record systems, we were notified of incident cases of parkinsonism, including PD, and had access to the patients medical records. A total of 5,310 participants were completely reexamined in a similar manner to the two-phase design used at baseline. Of those who could not be reexamined, 449 had died and 558 refused screening

examinations; in 461 the screening examination was incomplete. In the follow-up period, 62 individuals with parkinsonism were identified, of whom 35 had PD, three with dementia. The other causes of parkinsonism were similar to those at baseline: parkinsonism with dementia (8 cases, of whom 6 were already demented at baseline); drug-induced parkinsonism (1); multisystem atrophy (2) progressive supranuclear palsy (1); and other causes (15), which included parkinsonism and dementia with no clear time relationship between the two (7), more than one possible cause, and subjects in whom all other causes of parkinsonism could be excluded but who did not respond to antiparkinsonian drugs (8). Neuroimaging was only performed in 20 subjects (35%) in whom the cause of parkinsonism was not obvious from physical examination alone.

In total, 133 individuals with PD were identified, of whom 107 had the APOE genotype. Of these 107 patients, 26 were diagnosed as having PD with dementia and 81 as having PD without dementia. Of the 26 PD patients with dementia, the diagnosis was obtained from general practitioners in nine and confirmed by a neurologist not affiliated to our institute in eight. Of the 81 PD patients without dementia, the diagnosis was obtained from the general practitioner in 12 and confirmed by a neurologist in 10. All other PD patients were seen in person and the diagnosis was made by neurologists affiliated with our department. In total, six of the 61 PD patients with APOE genotyping who were not demented at baseline developed dementia at follow-up.

#### Diagnosis of dementia.

A three-phase design was used, both at baseline and at follow-up, to diagnose dementia according to the American Psychiatric Association's criteria (Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised) [19](#) and has been described elsewhere. [20,21](#) Briefly, all participants were screened with a cognitive test; those who screened positive underwent further neuropsychological testing and those suspected for dementia were examined in detail and, if possible, had a MRI brain scan. Of subjects who could not be examined in person, diagnosis was obtained from the general practitioner and medical records through our surveillance system. For the diagnosis of PD with dementia, the onset of PD had to clearly precede the onset of dementia.

#### APOE genotyping.

APOE genotyping was performed on coded DNA samples from the total cohort as described previously, [22](#) without knowledge of the clinical diagnosis. PCR was performed and the amplification products were digested with Hha I, separated on an agarose gel, stained with ethidium bromide, and visualized

with ultraviolet light. The results were analyzed by three independent experts. APOE genotyping was repeated in case of discrepancies.

#### Data analysis.

We used multivariate logistic regression analysis to calculate the OR with 95% CI, to assess whether the presence of at least one [epsilon]4 allele (APOE \*4) or [epsilon]2 allele (APOE \*2) was associated with PD with or without dementia, as compared with nonparkinsonian control subjects from the Rotterdam Study. In this logistic model, PD was the dependent variable whereas APOE genotype (with dummy indicating APOE \*4, APOE \*2, and APOE 3E3) was the independent variable. The most frequent genotype APOE 3E3 was used as the reference. Additionally we used multivariate logistic regression analysis to examine the risk of dementia in PD patients as compared with nonparkinsonian control subjects, stratified by APOE genotype. In this model, dementia was the dependent variable whereas PD, APOE genotype, and the multiplicative interaction between PD and APOE were used as independent variables. To test whether our results were due to misclassification of AD as PD with dementia, we conducted similar analyses for patients with dementia with parkinsonism from the same study population. The diagnosis of dementia with parkinsonism was made for patients with at least two cardinal signs and no other apparent cause of parkinsonism except dementia, taking into account that the onset of dementia had to clearly precede the onset of parkinsonism or both were diagnosed at the same time. Moreover, to rule out the possibility of survivorship bias as an alternative explanation for our results, we used COX proportional hazard models, first to determine prospectively if the presence of an [epsilon]2 or [epsilon]4 allele increased the risk of PD, and second to determine the risk of the development of dementia during longitudinal follow-up in PD patients who were not demented at baseline. In the first analysis, PD was the dependent and APOE genotype the independent variable, whereas in the second analysis dementia was the dependent and APOE genotype the independent variable. In all analyses we adjusted for age at examination at baseline and gender and we excluded subjects with the APOE 2E4 genotype, as this genotype may obscure differences between APOE \*2 and APOE \*4.

#### Results.

The characteristics of the study population and the APOE genotype distributions are summarized in [table 1](#). After exclusion of participants with the APOE 2E4 genotype (three patients with PD and 132 nonparkinsonian participants), APOE genotype was available for analyses for 104 PD patients (22 prevalent and three incident PD with dementia and 55 prevalent and 24 incident PD without dementia) and 4673 nonparkinsonian controls. All genotype distributions were in Hardy-Weinberg

equilibrium. The crude and adjusted ORs with 95% CI for the associations between the APOE genotype with PD with and without dementia are listed in [table 2](#). Persons with at least one [epsilon]2 allele had PD significantly more often (OR = 1.7; 95% CI, 1.0 to 2.8). We found no association between the [epsilon]4 allele and PD (OR = 1.0; 95% CI, 0.6 to 1.6). For nondemented PD patients as compared with nonparkinsonian subjects, no association was found for either the [epsilon]2 allele (OR = 1.2; 95% CI, 0.7 to 2.2) or the [epsilon]4 allele (OR = 0.7; 95% CI, 0.4 to 1.2). However, the risk of PD with dementia was strongly increased by both the [epsilon]2 allele (OR = 5.6; 95% CI, 2.2 to 15.2) and the [epsilon]4 allele (OR = 3.6; 95% CI, 1.3 to 9.9). To assess whether these findings could be explained by misclassification of AD as PD with dementia, we performed similar analyses for 27 patients with dementia with parkinsonism. We found a strong association for the [epsilon]4 allele (OR = 4.1; 95% CI, 1.7 to 9.7) as expected, but no association for the [epsilon]2 allele (OR = 1.7; 0.5 to 5.6) with dementia with parkinsonism (see [table 2](#)). When we restricted ourselves to incident cases of PD, results were similar to those for the entire group of PD patients (for at least one [epsilon]2 allele, adjusted OR = 2.0; 95% CI, 0.8 to 5.2; for at least one [epsilon]4 allele, OR = 1.5; 95% CI, 0.6 to 3.6). When we looked prospectively at the risk of dementia in PD patients who were not demented at baseline, we found that the presence of at least one [epsilon]2 allele strongly increased the risk of dementia (OR = 13.5; 95% CI, 1.3 to 136.2), but we found no such relation for at least one [epsilon]4 allele (OR = 1.5; 95% CI, 0.6 to 3.7).

**Table 1** The characteristics and the distribution of the APOE genotype and alleles of the study population\*

Characteristic	All PD patients (n = 108)	PD without dementia (n = 77)	PD with dementia (n = 31)	Controls with parkinsonism (n = 107)
Mean (SD) age, y	70.4 (9.5)	70.9 (9.5)	68.3 (9.5)	68.0 (9.5)
Female sex, %	32	27	35	33
APOE genotype frequency, %				
ε2ε2	16.2 (16)	18.2 (18)	20.0 (21)	17.2 (17)
ε2ε3	38.0 (38)	38.0 (38)	41.9 (41)	37.5 (37)
ε2ε4	30.6 (30)	27.2 (27)	35.5 (35)	31.8 (31)
ε3ε3	15.8 (15)	15.8 (15)	16.1 (16)	15.8 (15)
ε3ε4	10.4 (10)	10.4 (10)	10.0 (10)	10.4 (10)
ε4ε4	1.8 (1)	1.8 (1)	1.9 (1)	1.8 (1)
APOE allele frequency, %				
ε2	30.0 (30)	29.2 (29)	31.3 (31)	29.2 (29)
ε3	69.0 (69)	70.8 (70)	68.7 (68)	70.8 (70)
ε4	1.0 (1)	1.0 (1)	1.0 (1)	1.0 (1)

Table 1. The characteristics and the distribution of the APOE genotype and alleles of the study population\* Numbers of subjects are given in parenthesis.† Numbers of alleles are given in parenthesis.

[\[Help with image viewing\]](#)  
[\[Email Jumpstart To Image\]](#)

**Table 2** The association between the APOE genotype and PD with and without dementia and dementia with parkinsonism

APOE genotype	All PD patients (n = 108)	PD without dementia (n = 77)	PD with dementia (n = 31)	Dementia with parkinsonism (n = 27)
Adjusted OR (95% CI)	1.7 (1.0-2.8)	1.2 (0.7-2.2)	5.6 (2.2-15.2)	3.6 (1.3-9.9)
Crude OR (95% CI)	1.7 (1.0-2.8)	1.2 (0.7-2.2)	5.6 (2.2-15.2)	3.6 (1.3-9.9)
Adjusted OR (95% CI)	1.7 (1.0-2.8)	1.2 (0.7-2.2)	5.6 (2.2-15.2)	3.6 (1.3-9.9)
Crude OR (95% CI)	1.7 (1.0-2.8)	1.2 (0.7-2.2)	5.6 (2.2-15.2)	3.6 (1.3-9.9)

Table 2. The association between the APOE genotype and PD with and without dementia and dementia with parkinsonism Values are expressed as OR (95% CI).\* Adjusted for age and gender.

[\[Help with image viewing\]](#)

[\[Email Jumpstart To Image\]](#)

The ORs with 95% CI for the association between PD and dementia stratified by APOE genotype are listed in [table 3](#). Overall, patients with PD had an almost three times higher risk of dementia as compared with nonparkinsonian participants. This appeared entirely due to the increased risk of dementia among PD patients with either an APOE \*4 or APOE \*2 genotype. The strength of the association between PD and dementia in the APOE \*2 stratum as compared with the APOE \*4 stratum or the APOE 3E3 stratum suggested a multiplicative interaction between PD and the APOE \*2 genotype. Adding a multiplicative interaction term for PD and the APOE genotype to the multivariate model revealed a strong interaction between the APOE \*2 genotype and PD ( $p < 0.007$ ).

Table 3. The risk of dementia in patients with PD stratified by the APOE genotype

APOE genotype	OR (95% CI)			
	APOE 2	APOE 3	APOE 4	APOE 2/3
Non-PD	1.0	1.0	1.0	1.0
PD	2.2 (1.7-2.9)	0.8 (0.5-1.2)	2.2 (1.7-2.9)	2.2 (1.7-2.9)
Adjusted*	2.2 (1.7-2.9)	0.8 (0.5-1.2)	2.2 (1.7-2.9)	2.2 (1.7-2.9)
n	100	100	100	100

\*Adjusted for age and gender.

Table 3. The risk of dementia in patients with PD stratified by the APOE genotype. Values are expressed as OR (95% CI). \* Adjusted for age and gender.

[\[Help with image viewing\]](#)

[\[Email Jumpstart To Image\]](#)

Finally, we verified the well-established association of the [epsilon]4 allele with dementia in the control population ( $n = 4763$ ). As expected, the presence of at least one [epsilon]4 allele significantly increased the risk of dementia (OR = 2.2; 95% CI, 1.7 to 2.9), whereas the [epsilon]2 allele was not associated with dementia (OR = 0.8; 95% CI, 0.5 to 1.2).

## Discussion.

In this study of the elderly, we found that carriers of the APOE-[epsilon]2 allele had a significantly increased risk of PD, in particular of PD with dementia, and that presence of at least one [epsilon]2 allele multiplied the risk for developing dementia in PD patients. The APOE-[epsilon]4 allele was not associated with PD overall, but, as expected, the [epsilon]4 allele increased the risk of dementia in PD patients in a manner similar to the way it increases the risk of dementia in the general population. No associations were found between the APOE genotype and PD without dementia.



One should consider whether our findings could result from bias, in particular misclassification, or selection or survival bias. We consider misclassification of AD or Lewy body disease as PD with dementia unlikely, as we carefully restricted the diagnosis of PD to those in whom the onset of parkinsonian signs had clearly preceded the cognitive changes in absence of other clinical features. Moreover, if misclassification had occurred, it might in part account for the associations we found for the [epsilon]4 but not for the [epsilon]2 allele. Selection bias is a potential threat in association studies. In contrast to other studies, [8,9](#) our control population was both derived from the same source population as the PD patients and based on a general, not necessarily healthy, elderly population, including institutionalized persons. This minimized the possibility of selection bias in our study. Finally, because the [epsilon]2 allele has been reported to be a genetic factor for longevity, [23](#) one should consider that our findings might be a result of selective survival. In order to rule out bias due to selective survivorship, we looked at the risk of dementia prospectively in nondemented PD patients and found that presence of the [epsilon]2 allele did increase the risk of the development of dementia in nondemented PD patients. Although the CI of the point estimate was wide, mainly due to the small sample size, these results confirmed the overall findings. Moreover, we studied survival of carriers of the [epsilon]2 allele in the Rotterdam Study, but found no association between APOE \*2 and survival (unpublished data). Hitherto, only one study reported an association between the [epsilon]2 allele and PD, but without distinguishing between PD patients with or without dementia. [16](#) Nevertheless, when we reviewed the studies that investigated APOE genotype in relation to PD, we found that in most the frequency of the [epsilon]2 allele in PD patients [8,11-13](#) or in PD patients with dementia [14,15](#) was actually increased, although this increase was not statistically significant. These other observations corroborate our view that the association we found between the [epsilon]2 allele and PD with dementia is true. However, the population screened in this survey was aged 55 years and older and our findings therefore may not generalize to younger patients with PD.

It is as yet unclear what the underlying pathologic mechanism might be. Whereas the [epsilon]4 allele occurs at an increased frequency in patients with AD, [24](#) and [beta]-amyloid plaques and neurofibrillary tangles are increased in the brains of individuals with as compared with those without the [epsilon]4 allele, [25,26](#) the [epsilon]2 allele does not increase the risk of AD. If anything, it has been suggested to play a protective role in AD and senile plaque formation. [24,27](#) Interestingly, however, a high frequency of the [epsilon]2 allele in a subset of patients with neurofibrillary tangle-predominant senile dementia was recently reported. [28](#) The authors hypothesized that this type of dementia was distinct from AD. [28](#) Moreover, the [epsilon]2 allele has been associated with argyrophilic grain disease, [29](#) and an association of the [epsilon]2 allele with cerebral amyloid angiopathy has been reported. [30](#)

The strong association of APOE \*2 with PD with dementia and not PD without dementia or dementia with parkinsonism, and the observation that the [epsilon]2 allele strongly increases the risk of dementia in nondemented PD patients suggests that PD with and without dementia have, at least partly, a different pathogenesis. Further research to elucidate a possible specific role of the [epsilon]2 allele in neurodegeneration is required.

#### References

1. Boller F, Mizutani T, Roessmann U, Gambetti P. Parkinson disease, dementia, and Alzheimer disease: clinicopathological correlations. *Ann Neurol* 1980; 7:329-335. [360 Link](#) [\[Context Link\]](#)
2. Perl DP, Olanow CW, Calne D. Alzheimer's disease and Parkinson's disease: distinct entities or extremes of a spectrum of neurodegeneration? *Ann Neurol* 1998; 44:S19-S31. [360 Link](#) [Bibliographic Links](#) [\[Context Link\]](#)
3. Brown DF, Dababo MA, Bigio EH, et al. Neuropathologic evidence that the Lewy body variant of Alzheimer disease represents coexistence of Alzheimer disease and idiopathic Parkinson disease. *J Neuropathol Exp Neurol* 1998; 57:39-46. [Ovid Full Text](#) [360 Link](#) [Bibliographic Links](#) [\[Context Link\]](#)
4. Lowe J, McDermott H, Landon M, Mayer RJ, Wilkinson KD. Ubiquitin carboxyl-terminal hydrolase (PGP 9.5) is selectively present in ubiquitinated inclusion bodies characteristic of human neurodegenerative diseases. *J Pathol* 1990; 161:153-160. [360 Link](#) [Bibliographic Links](#) [\[Context Link\]](#)
5. Strittmatter WJ, Saunders AM, Schmechel D, et al. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc Natl Acad Sci USA* 1993; 90:1977-1981. [360 Link](#) [Bibliographic Links](#) [\[Context Link\]](#)
6. Gomez-Isla T, West HL, Rebeck GW, et al. Clinical and pathological correlates of apolipoprotein E epsilon 4 in Alzheimer's disease. *Ann Neurol* 1996; 39:62-70. [360 Link](#) [Bibliographic Links](#) [\[Context Link\]](#)
7. Harrington CR, Louwagie J, Rossau R, et al. Influence of apolipoprotein E genotype on senile dementia of the Alzheimer and Lewy body types. Significance for etiological theories of Alzheimer's disease. *Am J Pathol* 1994; 145:1472-1484. [360 Link](#) [Bibliographic Links](#) [\[Context Link\]](#)

8. Whitehead AS, Bertrandy S, Finnan F, Butler A, Davey Smith G, Ben-Shlomo Y. Frequency of the apolipoprotein E epsilon 4 allele in a case-control study of early onset Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1996; 61:347-351. [360 Link](#) [Bibliographic Links](#) [\[Context Link\]](#)
9. Inzelberg R, Chapman J, Treves TA, et al. Apolipoprotein E4 in Parkinson disease and dementia: new data and meta-analysis of published studies. *Alzheimer Dis Assoc Disord* 1998; 12:45-48. [Ovid Full Text](#) [360 Link](#) [Bibliographic Links](#) [\[Context Link\]](#)
10. Marder K, Maestre G, Cote L, et al. The apolipoprotein epsilon 4 allele in Parkinson's disease with and without dementia. *Neurology* 1994; 44:1330-1331. [360 Link](#) [Bibliographic Links](#) [\[Context Link\]](#)
11. Arai H, Muramatsu T, Higuchi S, Sasaki H, Trojanowski JQ. Apolipoprotein E gene in Parkinson's disease with or without dementia. *Lancet* 1994; 344:889. [360 Link](#) [\[Context Link\]](#)
12. Benjamin R, Leake A, Edwardson JA, et al. Apolipoprotein E genes in Lewy body and Parkinson's disease. *Lancet* 1994; 343:1565. [360 Link](#) [\[Context Link\]](#)
13. Poduslo SE, Riggs D, Rolan T, Schwankhaus J. Apolipoprotein E, B alleles in Parkinson's patients. *Neurosci Lett* 1995; 194:145-147. [360 Link](#) [Full Text](#) [Bibliographic Links](#) [\[Context Link\]](#)
14. Koller WC, Glatt SL, Hubble JP, et al. Apolipoprotein E genotypes in Parkinson's disease with and without dementia. *Ann Neurol* 1995; 37:242-245. [\[Context Link\]](#)
15. Hardy J, Crook R, Prihar G, Roberts G, Raghavan R, Perry R. Senile dementia of the Lewy body type has an apolipoprotein E epsilon 4 allele frequency intermediate between controls and Alzheimer's disease. *Neurosci Lett* 1994; 182:1-2. [360 Link](#) [Full Text](#) [Bibliographic Links](#) [\[Context Link\]](#)
16. French Parkinson's Disease Genetics Study Group. Apolipoprotein E genotype in familial Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1997; 63:394-395. [360 Link](#) [Bibliographic Links](#) [\[Context Link\]](#)
17. Hofman A, Grobbee DE, de Jong PTVM, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol* 1991; 7:403-422. [360 Link](#) [Bibliographic Links](#) [\[Context Link\]](#)

18. de Rijk MC, Breteler MMB, Graveland GA, et al. Prevalence of Parkinson's disease in the elderly: the Rotterdam Study. *Neurology* 1995; 45:2143-2146. [Ovid Full Text](#) [360 Link](#) [\[Context Link\]](#)
19. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed. Revised. Washington, DC: American Psychiatric Association, 1987. [\[Context Link\]](#)
20. Ott A, Breteler MMB, van Harskamp F, et al. Prevalence of Alzheimer's disease and vascular dementia: association with education. The Rotterdam Study. *BMJ* 1995; 310:970-973. [\[Context Link\]](#)
21. Ott A, Breteler MMB, van Harskamp F, Stijnen T, Hofman A. Incidence and risk of dementia: the Rotterdam Study. *Am J Epidemiol* 1998; 147:574-580. [360 Link](#) [Bibliographic Links](#) [\[Context Link\]](#)
22. van Duijn CM, de Knijff P, Wehnert A, et al. The apolipoprotein E epsilon 2 allele is associated with an increased risk of early-onset Alzheimer's disease and a reduced survival. *Ann Neurol* 1995; 37:605-610. [360 Link](#) [Bibliographic Links](#) [\[Context Link\]](#)
23. Schachter F, Faure-Delanef L, Guenot F, et al. Genetic associations with human longevity at the APOE and ACE loci. *Nat Genet* 1994; 6:29-32. [360 Link](#) [Bibliographic Links](#) [\[Context Link\]](#)
24. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease: a meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA* 1997; 278:1349-1356. [360 Link](#) [Bibliographic Links](#) [\[Context Link\]](#)
25. Schmechel DE, Saunders AM, Strittmatter WJ, et al. Increased amyloid beta-peptide deposition in cerebral cortex as a consequence of apolipoprotein E genotype in late-onset Alzheimer disease. *Proc Natl Acad Sci USA* 1993; 90:9649-9653. [\[Context Link\]](#)
26. Nagy Z, Esiri MM, Jobst KA, et al. Influence of the apolipoprotein E genotype on amyloid deposition and neurofibrillary tangle formation in Alzheimer's disease. *Neuroscience* 1995; 69:757-761. [360 Link](#) [Full Text](#) [Bibliographic Links](#) [\[Context Link\]](#)
27. Lippa CF, Smith TW, Saunders AM, Hulette C, Pulaski-Salo D, Roses AD. Apolipoprotein E-epsilon 2, Alzheimer's disease: genotype influences pathologic phenotype. *Neurology* 1997; 48:515-519. [Ovid Full Text](#) [360 Link](#) [Bibliographic Links](#) [\[Context Link\]](#)

28. Ikeda K, Akiyama H, Arai T, et al. A subset of senile dementia with high incidence of the apolipoprotein E epsilon2 allele. Ann Neurol 1997; 41:693-695. [360 Link Bibliographic Links \[Context Link\]](#)

29. Ghebremedhin E, Schultz C, Botez G, et al. Argyrophilic grain disease is associated with apolipoprotein E epsilon2 allele. Acta Neuropathol (Berl) 1998; 96:222-224. [\[Context Link\]](#)

30. Nicoll JA, Burnett C, Love S, et al. High frequency of apolipoprotein E epsilon 2 allele in hemorrhage due to cerebral amyloid angiopathy. Ann Neurol 1997; 41:716-721. [360 Link Bibliographic Links \[Context Link\]](#)

Key words: APOE; Parkinson's disease; Dementia; Genetics; Epidemiology.

---

Copyright (c) 2000-2009 [Ovid Technologies, Inc.](#)

By accessing or using OvidSP, you agree to Ovid's [terms of use](#), conditions and all applicable laws. If you do not agree to these terms you may not use this Site.

Version: OvidSP\_UI02.01.02.102, SourceID 40419