Head injury and the risk of AD in the MIRAGE study

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Article abstract—*Objectives:* It has been suggested in some studies that head injury is a risk factor for AD, and that this risk is heightened among carriers of the *APOE*-ϵ4 allele. We examined the effects of head injury and *APOE* genotype on AD risk in a large family study. *Subjects:* A total of 2,233 probands who met criteria for probable or definite AD and their 14,668 first-degree family members (4,465 parents, 7,694 siblings, and 2,509 spouses) were ascertained at 13 centers in the United States, Canada, and Germany participating in the MIRAGE (Multi-Institutional Research in Alzheimer Genetic Epidemiology) project. Information on head injury was collected by interview of multiple informants and review of medical records. Nondemented relatives and spouses served as control subjects for this study. *Methods:* Odds of AD for head trauma with or without loss of consciousness were computed by comparing probands with unaffected spouses using conditional logistic regression analysis. To account for the unique biologic relationship between probands and their parents and siblings, odds of AD were computed using a generalized estimating equation (GEE) Poisson regression approach. GEE logistic regression was used to examine the joint effects of *APOE* genotype and head injury on the odds of AD in probands and a control group comprised of unaffected siblings and spouses. *Results:* Comparison of probands with their unaffected spouses yielded odds ratios for AD of 9.9 (95% CI, 6.5 to 15.1) for head injury with loss of consciousness and 3.1 (2.3 to 4.0) for head injury without loss of consciousness. The corresponding odds derived from the comparison of probands with their parents and sibs were 4.0 (2.9 to 5.5) for head injury with loss of consciousness and 2.0 (1.5 to 2.7) for head injury without loss of consciousness. Head injury without loss of consciousness did not significantly increase the risk of AD in spouses (OR = 1.3; 95% CI, 0.4 to 4.1). The joint effects of head injury and *APOE* genotype were evaluated in a subsample of 942 probands and 327 controls (spouses and siblings). Head injury increased the odds of AD to a greater extent among those lacking ϵ4 (OR = 3.3) than among ϵ4 heterozygotes (OR = 1.8) or homozygotes (OR = 1.3). *Conclusion:* Head injury is a risk factor for AD. The magnitude of the risk is proportional to severity and heightened among first-degree relatives of AD patients. The influence of head injury on the risk of AD appears to be greater among persons lacking *APOE*-ϵ4 compared with those having one or two ϵ4 alleles, suggesting that these risk factors may have a common biologic underpinning. **Key words:** AD—Head injury—*APOE* genotype.

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Head injury with loss of consciousness has been studied as a potential risk factor for AD. The findings from case-control studies are inconsistent. Some show that head injury has a significant or nearly significant effect on AD risk,[1-9] whereas others show no association.[10-14] Among longitudinal studies,[15-18] only one[17] reported a significantly increased risk of developing AD in persons with head injury. A reanalysis of the Rochester Epidemiology Project data suggested that head injury may reduce the time to onset of AD.[19] A recent study of 588 adults age 70 years or older indicated that the occurrence of major head injury caused by falls increased the risk of cognitive decline measured by a brief cognitive test.[20] It has been argued that the association found in case-control studies could be due to over-reporting of a history of serious head injury in cases by the informant or underreporting in control subjects.[10]

There is indirect evidence supporting the view that head injury could be a risk factor for AD. Repeated head injury as experienced by boxers can cause dementia pugilistica. Although this disorder can be distinguished clinically from AD, recent studies have revealed more similarities in pathology be-

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tween dementia pugilistica and AD than previously thought.[21] The molecular markers present in the plaques and tangles of dementia pugilistica are the same as those in AD.[22] It is well established that deposition of amyloid β-protein in the brain plays an important role in the pathogenesis of AD.[23] The deposition of amyloid β-protein also occurs in about one third of individuals dying shortly after a severe head injury, and it may be the biologic basis for the link between head injury and AD.[24]

Mayeux et al.[25] reported a synergistic interaction between head injury and *APOE*-ϵ4 on the risk of AD. In their study, head injury alone did not increase the risk, but head injury in persons with ϵ4 increased the risk 10-fold compared with those who lacked both factors. These findings support the idea that head injury increases the risk of AD only among those who are genetically susceptible,[26] and may explain the inconsistent results in previous studies, most of which did not account for ϵ4 status.

Family studies have documented that the risk of AD is higher in first-degree relatives of AD patients than in biologically unrelated individuals,[27-29] suggesting a genetic component of the disease. A family study is well suited for evaluating the interaction between an environmental factor such as head injury and genetic factors by comparing the risk of the disease associated with the factor among parents and siblings of AD patients with that among other biologically unrelated family members. For example, results showing a stronger association between head injury and AD among parents and siblings of AD patients than among spouses of AD patients would be evidence for an interaction between head injury and genetic susceptibility.

We examined the relation between head injury and AD in the Multi-Institutional Research in Alzheimer Genetic Epidemiology (MIRAGE) study. This design enabled us to address the following questions: 1) is the relation between head injury and AD due to a recall bias; 2) does head injury with loss consciousness confer a greater risk of AD than head injury without loss of consciousness; 3) do familial (genetic) factors modify the relationship between head injury and AD; and 4) does *APOE*-ϵ4 increase the susceptibility to AD due to head injury?

Methods. *Setting and subjects.* A total of 2,233 AD patients meeting the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria[30] for definite or probable AD were ascertained between 1991 and 1996 at 13 centers in the United States, Canada, and Germany. The ethnic composition of the sample was 87.2% non-Hispanic white, 2.7% African American, 2.7% Hispanic, and 7.0% other. Dementia status of the first-degree family members (parents, siblings, and spouses) was determined by assessment of information obtained from an interview with a cognitively intact family member (primary informant). This information was supplemented by multiple informants, medical records including autopsy reports, death certificates, and nursing home records. The details of the study design and the protocol for family history have been reported elsewhere.[31,32]

Data collection. A structured questionnaire administered to the primary informant (and often verified by other relatives through direct or telephone interview) was used to collect information about a variety of factors, including head injury. Head injury was defined as a broad range of injuries that led the subject to seek medical care or hospitalization. The actual primary question asked was "Has your relative ever had a head injury which required medical care (visiting a physician or seek hospital care as an outpatient or inpatient) or caused unconsciousness." For any head injury reported, a further question asked whether or not the injury resulted in loss of consciousness. The age at which head injury occurred was recorded for most probands and relatives. Disagreements among multiple informants were resolved by recontacting these informants to clarify the information, contacting additional informants, and verifying by medical records if available. A standard PCR procedure was used for *APOE* genotyping, as described previously.[33] All living subjects were eligible for *APOE* genotyping, but many of the families were lost to follow-up and recruitment of relatives for DNA studies occurred only in the last 3 years.

Data analysis. Conditional logistic regression techniques were used to analyze the effect of head injury on the odds of AD among probands and their unaffected spouses. This approach takes into account the family structure of the data set. Fifty-nine families having affected spouses were excluded from these analyses. There were more spouses than probands because of multiple mating. Odds ratios adjusted for age (age at onset for AD cases, or age of death or age at interview for control subjects) and gender were calculated from the logistic regression model to estimate the risk of AD associated with head injury. The models were also computed for subsets of families stratified by age at onset of the probands using age 65 years as the cut-off.

To investigate the contribution of family history and head injury to AD risk, cumulative risk of dementia and the age at onset distribution among first-degree relatives (parents and siblings) and spouses were estimated using a maximum likelihood procedure for survival analysis of family data.[34] Within each group (relatives and spouses), subjects were stratified by presence or absence of head injury. A Poisson regression was employed to estimate the relative risk of dementia associated with head injury in relatives taking into account gender and kinship, with the generalized estimating equation (GEE)[35] to allow for the possibility of correlation between family members. Models were estimated using the GENMOD procedure in SAS (SAS Institute, Cary, NC),[36] with the logarithm of age as the time-scale.

GEE logistic regression was used to examine the joint effects of *APOE* genotype and head injury on the odds of AD in probands and a control group composed of unaffected siblings and spouses. This method, similar to the conditional logistic regression approach, accounts for the correlated nature of family data. However, the GEE approach also permitted inclusion of AD probands lacking matched family controls. To evaluate the joint effects of *APOE* genotype and head injury on a multiplicative scale,

Table 1 *General characteristics of the study population*

Characteristics	Men	Women	Total
Probands			
Total, n	857	1,376	2,233
Head injury, n (%)	191 (22.3)	207 (15.0)	398 (17.8)
L	99 (11.6)	87 (6.3)	186 (8.3)
NL	92 (10.7)	120 (8.7)	212 (9.5)
Age at onset,* y	68.6 ± 8.9	70.6 ± 9.1	69.9 ± 9.0
Affected first-degree family members†			
Total, n	439	800	1,239
Head injury, n (%)	40 (9.1)	37 (4.6)	77 (6.2)
L	22 (5.0)	16 (2.0)	38 (3.1)
NL	18 (4.1)	21 (2.6)	39 (3.2)
Age at onset,* y	74.1 ± 9.1	76.1 ± 9.2	75.4 ± 9.2
Unaffected first-degree family members†			
Total, n	7,178	6,251	13,429
Head injury, n (%)	218 (3.0)	127 (2.0)	345 (2.6)
L	50 (0.7)	35 (0.6)	85 (0.6)
NL	168 (2.3)	92 (1.5)	260 (1.9)

* Mean ± SD.
† Parents, siblings and spouses of probands.

L = loss of consciousness; NL = no loss of consciousness.

we formed interaction terms by multiplying the individual variables. For additive interaction, three dummy variables were created to distinguish persons with both *APOE*-ϵ4 allele and head injury (AB), *APOE*-ϵ4 genotype without head injury (A), and head injury without *APOE*-ϵ4 genotype (B). Individuals lacking both factors were used as the reference group. These analyses permitted us to examine additive effects (i.e., $OR_{AB} = [OR_A + OR_B] - 1$) *and* multiplicative effects (i.e., $OR_{AB} = OR_A \times OR_B$). To formally test the interaction on the multiplicative scale, we used the *p* value from the first analysis of the interaction terms. On the additive scale we calculated Rothman's S statistic and its 95% CI to see if it included 1.[37] The *APOE*-ϵ4 homozygotes and heterozygotes were considered separately.

Results. Table 1 shows the characteristics of 2,233 probands and their 14,668 first-degree family members (4,465 parents, 7,694 siblings, and 2,509 spouses). A higher frequency of head injury was seen among both probands and affected relatives compared with unaffected relatives; the frequency of head injury was even higher among probands than affected relatives ($p < 0.001$). Men had a history of head injury more often than did women in any group. Head injury with and without loss of consciousness seemed to be equally distributed both in probands and affected relatives. However, head injury without loss of consciousness occurred more frequently than head injury with loss of consciousness in the unaffected relatives ($p = 0.04$). Probands were younger than their affected relatives at the time of onset of AD symptoms ($p < 0.001$). The mean age at onset was greater for women than men among both probands and affected relatives ($p < 0.001$). Age at onset was not different among those with and without head injury.

Probands had a history of head injury significantly more often than their unaffected spouses (table 2). Logistic regression analysis revealed that both head injury with and without loss of consciousness increased the odds of AD. However, the relation between head injury with loss of consciousness and AD (OR = 9.9) was stronger ($p < 0.001$) than that between head injury with no loss of consciousness and AD (OR = 3.1). The odds of AD associated with

Table 2 *Odds of AD associated with head injury*

Variable	Probands	Spouses	OR*	95% CI
All, n (%)				
Head injury	394 (18.1)	127 (5.2)	4.6	3.7–5.9
L	184 (8.5)	30 (1.2)	9.9	6.5–15.1
NL	210 (9.7)	97 (4.0)	3.1	2.3–4.0
No head injury	1,782 (81.9)	2,316 (94.8)	1.0	reference
Spouse as key informant, n (%)				
Head injury	145 (20.5)	55 (6.6)	2.9	2.0–4.3
L	69 (9.7)	6 (0.7)	11.9	5.0–28.8
NL	76 (10.7)	49 (5.9)	1.8	1.2–2.8
No head injury	564 (79.6)	777 (93.4)	1.0	reference
Other relatives as informants, n (%)				
Head injury	249 (17.0)	72 (4.5)	5.6	4.0–7.9
L	115 (7.8)	24 (1.5)	8.3	4.9–14.0
NL	134 (9.1)	48 (3.0)	4.2	2.7–6.4
No head injury	1,218 (83.0)	1,539 (95.5)	1.0	reference

* From conditional logistic regression model adjusted for age and gender.

L = loss of consciousness; NL = no loss of consciousness.

head injury were the same for patients with early- and late-onset AD.

Table 2 also shows the distribution of head injury among probands and their unaffected spouses according to the source of information. Spouses reported a slightly higher rate of head injury among probands and themselves than was reported by other relatives. However, spouses reported a lower rate of head injury with loss of consciousness. Increased odds of AD associated with head injury were consistent regardless of the source of information, although the relationship between head injury and AD was stronger in the group with information from other relatives than in the group with information from spouses.

Survival analysis revealed that the cumulative risk of AD by age 99 years in first-degree relatives (parents and siblings) was 41.4%. Risk of developing AD was significantly higher among relatives with head injury than among relatives without head injury at all ages after 60 years (figure, A). At age 93 years (the maximum age common to groups of relatives with and without head injury), the lifetime risk was 77.2% for those with and 40.1% for those without head injury. A similar increased risk of AD associated with head injury was also observed in spouses, although the overall risk of AD was lower (figure, B).

Table 3 shows that, in the entire sample of relatives, head injury with loss of consciousness increased the risk of dementia four times and head injury with no loss of consciousness increased the risk about two times. The effect of head injury with loss of consciousness was greater but not significantly so in male relatives (RR = 5.6) than in female relatives (RR = 3.2), whereas there was no gender difference in AD risk associated with head injury without loss of consciousness. The risks of AD associated with head injury with loss of consciousness were the same in biologic relatives and spouses. Head injury with no loss of consciousness did not significantly increase the risk of AD among spouses (RR = 1.3). Considering head injury as a whole, the risk associated with head injury among parents and siblings was similar to that among spouses, suggesting a lack of interaction between head injury and a family history.

We evaluated the joint effects of head injury and *APOE* genotype on risk of AD in a subsample of 942 probands and a comparison group of 162 unaffected spouses and 165 unaffected siblings. The mean onset age of probands with and without *APOE* genotyping was 69.8 (SD = 9.3) and 69.9 (SD = 8.9) years. The groups were also similar in terms of gender (60.0% men versus 63.0% women) and frequency of head injury (19.4% versus 16.6%). Unaffected spouses and siblings were older (69.6 ± 9.4 versus 65.8 ± 16.5%; $p < 0.001$), more likely to be women (56.0% versus 46.1%; $p < 0.001$), and more likely to have a history of head injury (10.1% versus 2.8%; $p < 0.001$) than unaffected spouses and siblings without *APOE* genotype. Among AD cases with head injury, the interval from head injury to onset of AD symptoms did not differ by *APOE*-ϵ4 status.

Table 4 shows that subjects either heterozygous for *APOE*-ϵ4 or with a head injury (but not both) had an approximately threefold risk of AD compared with subjects lacking ϵ4 and head injury. Subjects homozygous for *APOE*-ϵ4 had the highest risk: the odds of AD were 10.3 and 7.9 for subjects with and without head injury compared with those lacking both factors. Comparison of these

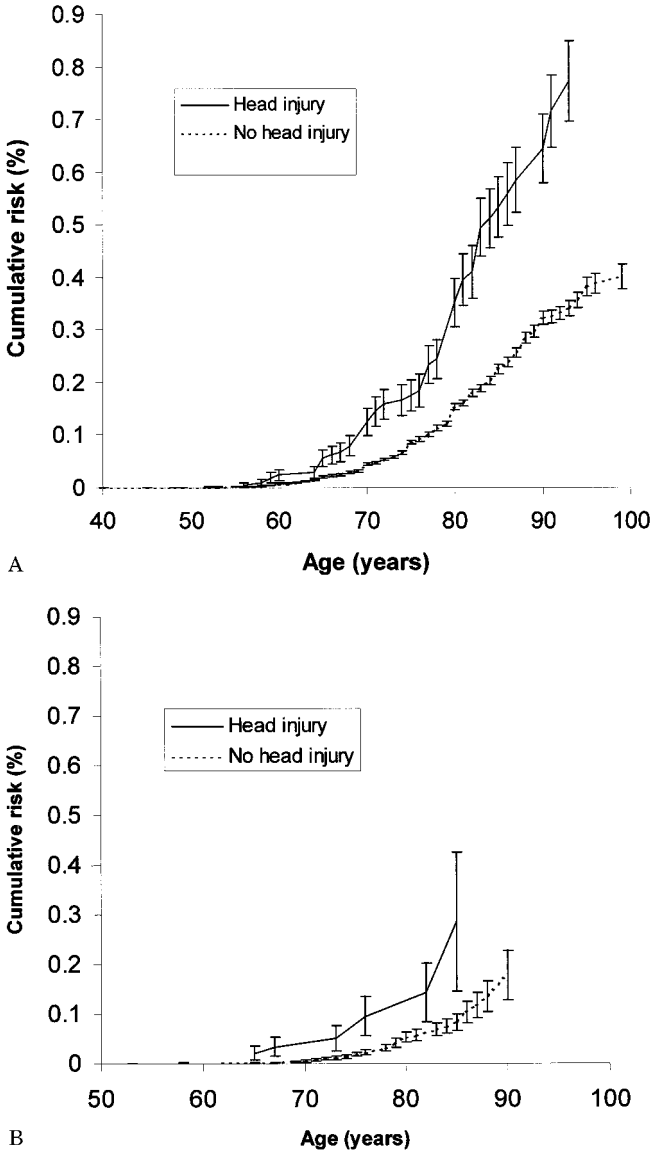

Figure. (A) The cumulative risk of AD in relation to head injury among parents and siblings of patients with AD. Vertical lines represent the 95% confidence limits for the point estimates. (B) The cumulative risk of AD in relation to head injury among spouses of patients with AD. Vertical lines represent the 95% confidence limits for the point estimates.

odds ratios within subjects with and without head injury clearly showed the dose-dependent effect of the ϵ4 allele on the risk of AD among those without head injury (table 5). Although the effect appears stronger for those without than for those with head injury, these differences were not statistically significant on either an additive or multiplicative scale. Viewed in another way, head injury increased the odds of AD to a greater extent among those lacking ϵ4 (OR = 3.3 [3.3/1.0]) than among ϵ4 homozygotes (OR = 1.3 [10.3/7.9]) or ϵ4 heterozygotes (OR = 1.8 [5.7/3.1]). Analyses that classified head injury with no loss of consciousness as negative for head injury showed a pattern of results similar to table 4 (data not shown).

We were concerned about pooling unaffected siblings and spouses because of *APOE*-ϵ4 frequency differences and

Table 3 *Head injury and the relative risk of dementia among first-degree relatives and spouses of AD probands*

Subjects		Total, n	Affected, n (%)	RR*	95% CI
First-degree relatives (parents and siblings)					
All	Head injury	287	69 (24.0)	2.7	2.2–3.3
	L	88	33 (37.5)	4.0	2.9–5.5
	NL	199	36 (18.1)	2.0	1.5–2.7
	No head injury	11,872	1,113 (9.4)	1.0	reference
Men	Head injury	166	32 (19.3)	3.0	2.2–4.2
	L	46	17 (37.0)	5.6	3.7–8.4
	NL	120	15 (12.5)	2.0	1.3–3.3
	No head injury	5,919	364 (6.2)	1.0	reference
Women	Head injury	121	37 (30.6)	2.5	1.9–3.2
	L	42	16 (38.1)	3.2	2.2–4.8
	NL	79	21 (26.7)	2.1	1.5–3.0
	No head injury	5,953	749 (12.6)	1.0	reference
Kinship					
Parents	Head injury	78	29 (37.2)	2.6	1.9–3.4
	L	22	12 (54.6)	3.7	2.5–5.7
	NL	56	17 (30.4)	2.1	1.4–3.1
	No head injury	4,387	634 (14.5)	1.0	reference
Siblings	Head injury	209	40 (19.1)	2.8	2.1–3.8
	L	66	21 (31.8)	4.5	2.9–7.0
	NL	143	19 (13.3)	2.0	1.3–3.0
	No head injury	7,485	479 (6.4)	1.0	reference
Spouses	Head injury	135	8 (5.9)	2.6	1.3–5.2
	L	35	5 (14.3)	6.1	2.6–13.9
	NL	100	3 (3.0)	1.3	0.4–4.1
	No head injury	2,374	49 (2.1)	1.0	reference

* Estimated from the general estimating equation Poisson regression adjusted for gender and kinship, if applicable.

L = loss of consciousness; NL = no loss of consciousness; RR = relative risk.

genetic influences other than ϵ4 that affect AD risk. However, evaluation of *APOE* genotype in this sample revealed that the frequency of ϵ4 alleles in siblings (21.8%) was only marginally higher than in spouses (15.7%; $p = 0.05$), and the proportions of ϵ4 carriers in these groups were not substantially different ($p = 0.08$). Although these results suggest that pooling siblings and spouses is appropriate, analyses excluding spouses from the control group yielded similar results. Specifically, compared with subjects having neither ϵ4 nor head injury, ϵ4/x subjects with head injury had odds of AD of 4.7 (1.7 to 13.5), subjects with head injury but not ϵ4 had odds of 2.7 (1.2 to 5.8), and ϵ4/x subjects with no head injury had odds of 2.9 (1.9 to 4.6).

Discussion. We examined the effect of head injury on the risk of AD in 2,233 probands and their 14,668

Table 4 *Odds of AD associated with head injury and* APOE *genotype*

Injury status	*APOE*-ε4 status*	Probands, n (%)	Spouses and siblings, n (%)	OR†	95% CI
Head injury	ε4/ε4	12 (1.3)	1 (0.3)	10.3	1.6–65.4
	ε4/x	84 (8.9)	12 (3.7)	5.7	3.1–10.5
	x/x	87 (9.2)	20 (6.1)	3.3	2.0–5.5
No head injury	ε4/ε4	123 (13.1)	12 (3.7)	7.9	4.3–14.3
	ε4/x	355 (37.7)	85 (26.0)	3.1	2.1–4.7
	x/x	281 (29.8)	197 (60.2)	1.0	reference

* x = ε2 or ε3.
† From generalized estimating equation logistic model adjusted for age and gender.

Table 5 *Odds of AD associated with* APOE *genotype according to presence of head injury*

Injury status	*APOE*-ε4 status*	OR†	95% CI
Head injury	ε4/ε4	3.1	0.4–22.3
	ε4/x	1.4	0.6–3.0
	x/x	1.0	reference
No head injury	ε4/ε4	7.1	3.9–12.7
	ε4/x	3.0	2.2–4.3
	x/x	1.0	reference

* x = ε2 or ε3.

† From generalized estimating equation logistic regression model adjusted for age and gender.

first-degree family members. Our results showed that head injury with loss of consciousness and, to a lesser extent, head injury without loss of consciousness increased the risk of AD. We also found that the risk of developing AD was significantly higher among relatives with head injury than among relatives without head injury at all ages after 60 years. Head injury with loss of consciousness also increased the risk of AD among spouses of probands. We did not find evidence for an interaction between family history and head injury, especially head injury with loss of consciousness. Our results indicate that head injury exerts a relatively greater effect on the risk of AD among persons lacking the *APOE*-ϵ4 allele compared with those having one or two ϵ4 alleles.

Compared with previous studies of head injury and AD, our investigation had several strengths. First, this sample of AD probands, first-degree relatives (parents and siblings), and spouses is to our knowledge by far the largest group studied in this manner. Although *APOE* genotype was available only in a subgroup, the sample size was sufficiently large to analyze *APOE*-ϵ4 homozygotes and heterozygotes separately. Second, we allowed for the possibility that the relationship between head injury and AD might vary according to severity of head injury. Finally, this was the first family-based study of the joint effects of head injury and *APOE* genotype on AD risk.

However, these results should be interpreted cautiously in light of several caveats associated with the study design. First, the association between head injury and AD could be simply an effect of recall bias with over-reporting of head injury in cases and under-reporting in unaffected relatives and spouses. Reporting bias is unlikely to have been a factor in the analyses involving *APOE* as these control subjects reported on themselves. The data used in the analyses that focused on risk in relatives were verified by multiple informants and medical records when available. These reports have good reliability; for example, one validation study from another dataset reported 91% agreement on head injury between subjects and their next-of-kin.[38] Moreover, even if there was a reporting bias between AD probands and relatives, our analyses examining the interaction of head injury and *APOE* genotype (see table 4) were internally consistent (i.e., probands were compared only with relatives who were interviewed directly).

Second, the frequency of head injury among control subjects (unaffected spouses and siblings) with *APOE* genotyping (10.1%) was significantly higher than among subjects who were not tested (2.8%). The reason for the discrepancy is unclear but is likely related to the fact that head injury data for those with *APOE* genotype were self-reported, whereas information about head injury for most other siblings was reported by other family members. It is noteworthy that the frequency of head injury in our genotyped control subjects was very similar to that seen in the studies of Katzman et al.[39] and Mayeux et al.[25] of head injury and *APOE* genotype, although the definitions for head injury are not the same across studies. The frequency of head injury history in control subjects was about 5% in a recent study.[5] A reporting bias, if it exists, is unlikely to influence the detection of an interaction between head injury and *APOE* genotype.

Third, our strategy of pooling unaffected siblings and spouses in analyses including *APOE* is unusual because of expected large differences in ϵ4 frequency between these groups.[40] Whereas in this sample the difference was only 6%, siblings are also more likely than spouses to have other genes in common. Nevertheless, we repeated these analyses by assigning spouses and siblings to separate control groups and found very similar patterns in terms of the interaction between ϵ4 and head injury. Finally, the diagnosis of AD among relatives was made based on information provided by the informant and review of medical records. Nonetheless, misclassification of AD among relatives could have occurred. As we noted previously,[32] this could bias the risk estimate of AD among relatives. However, this limitation would be unlikely to bias the relation between head injury and AD among relatives.

The association between head injury and AD was apparent in both men and women, although the relative risk for head injury with loss of consciousness was higher, but not significantly so, in men (RR = 5.6; 95% CL, 3.7 to 8.9) than women (RR = 3.2; 95% CL, 2.2 to 4.8). This trend is consistent with a meta-analysis of seven case-control studies showing a significant relation between head injury and AD among men but not women.[41] A recent case-control study found a similar gender effect.[5] However, one study reported an opposite effect, with a significant association only among women.[6]

In agreement with most previous studies,[41] we did not observe a difference in the age at onset between patients with and without head injury. However, one study reported that onset of AD occurred 8 years earlier in those with head injury compared to those without head injury.[42] A reanalysis of the Rochester Epidemiology Project data found that the observed time from injury to onset among 31 AD patients with

head injury during 1935 to 1984 was shorter than the expected time estimated by a life-time method based on 689 AD patents without head injury in the same cohort. Several studies have shown that head injury occurring within 10 years of onset of AD is related to a greater risk than head injury occurring beyond 10 years of onset of AD.[2,6,41] We were unable to evaluate this relationship because reliable information on age at head injury was unavailable for most relatives. However, among AD cases with head injury, the interval from head injury to onset of AD symptoms did not differ by *APOE*-ϵ4 status.

Our results suggest that severity of head injury is related to the magnitude of AD risk. Most previous studies have focused on head injury with loss of consciousness, primarily because of the possibility that head injuries without loss of consciousness would be susceptible to a greater recall bias. If that were so, one might observe a greater risk for AD among head-injured persons without than those with loss of consciousness. In contrast, we found that the risk associated with head injury with loss of consciousness was approximately double that associated with head injury without loss of consciousness. Nonetheless, even head injury without loss of consciousness significantly increased the risk of AD in parents and siblings of AD patients. Lack of this effect in spouses suggests the possibility of an interaction between head injury without loss of consciousness and family history. Alternatively, family informants may be more likely to recall a minor head injury in persons they perceive as having a greater genetic risk of AD. Notably, an interaction between head injury and a family history was not detected in two community-based studies.[3,6] A metaanalysis revealed that head injury was more likely to be related to sporadic AD than to familial AD (defined simply as a positive family history).[41]

The data in tables 4 and 5 support the idea that the effects of head injury and ϵ4 are additive (on the OR scale) but not "synergistic." Although our results suggest different risks of AD due to *APOE*-ϵ4 genotype among subjects with as compared with those without head injury, these differences are not significant, perhaps because there was an insufficient number of subjects with head injury. Our finding of a smaller effect of head injury on AD risk among ϵ4 carriers compared with noncarriers is qualitatively different from the interaction noted in previous studies.[5,25,39] Mayeux et al.[25] observed a 10-fold increase in the risk of AD among subjects with both ϵ4 and head injury, compared with a twofold increase in risk among subjects with ϵ4 alone. Head injury in the absence of ϵ4 did not increase AD risk in this community sample from northern Manhattan, composed of a substantial number of African Americans and Hispanic subjects as well as whites. In our study, there were too few African American and Hispanic patients and control subjects to examine the relationship between ϵ4 and head injury in these ethnic groups. One intriguing possibility is that the populations represented in the study by Mayeux et al.[25] are enriched for other genetic or environmental factors that promote a synergistic relationship between head injury and ϵ4. Because our findings did not confirm other studies showing synergistic effects of head injury and ϵ4 on AD risk, proposed strategies for incorporating *APOE* genotype information in counseling cognitively healthy individuals about the deleterious effects of head injury need to be carefully reevaluated.

Our results suggesting an interaction between head injury and ϵ4 are consistent with the hypothesis that head injury enhances production of amyloid plaque by increasing the expression of *APOE*.[42] There is evidence that ϵ4 is associated with deposition of amyloid β-protein following head injury.[43] A recent study of 30 boxers suggested that ϵ4 may be related to increased severity of chronic neurologic deficits in boxers sustaining traumatic brain injury.[44] Lack of evidence for synergy in even large case-control studies, including ours, might be related to a survival bias if those with both head injury and the *APOE*-ϵ4 allele would survive differently from others. A recent study reported that *APOE*-ϵ4 predicted a poor clinical outcome after brain injury,[45] although there are no data showing that AD patients with head injury and ϵ4 die early. This question can be addressed effectively by prospective studies currently in progress.

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