Enhanced Risk for Alzheimer Disease in Persons With Type 2 Diabetes and APOE ε4

The Cardiovascular Health Study Cognition Study

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Background: Diabetes and the apolipoprotein E ε4 allele (APOE ε4) increase the risk for Alzheimer disease (AD). We hypothesize that APOE ε4 may modify the risk for AD in individuals with diabetes.

Objective: To examine the joint effect of type 2 diabetes and APOE ε4 on the risk of AD, AD with vascular dementia (mixed AD), and vascular dementia without AD.

Design: The Cardiovascular Health Study (CHS) Cognition Study (1992-2000) is a prospective study designed to identify all existing and new cases of dementia among study participants. Diagnoses were made according to international criteria for dementia and subtypes. There were 2547 dementia-free participants in the CHS Cognition Study cohort with complete information on APOE ε4 and type 2 diabetes status; among these, 411 new cases of dementia developed. Risk of dementia was estimated with a Cox proportional hazard model adjusted for age and other demographic and cardiovascular risk factors.

Results: Compared with those who had neither type 2 diabetes nor APOE ε4, those with both factors had a significantly higher risk of AD (hazard ratio, 4.58; 95% confidence interval, 2.18-9.65) and mixed AD (hazard ratio, 3.89; 95% confidence interval, 1.46-10.40).

Conclusion: These data suggest that having both diabetes and APOE ε4 increases the risk of dementia, especially for AD and mixed AD.

Arch Neurol. 2008;65(1):89-93

IN ADDITION TO THE WELL-DOCUMENTED damage to large and small vessels, there are multiple neuronal and non-neuronal pathways through which diabetes-associated glycemic dysregulation can cause structural damage in the brain. Hyperglycemia can affect neuronal viability via increased oxidative stress, O-linked glycoprotein, and advanced glycation end products.1-3 Altered metabolism of glucose can also lead to less production of acetylcholine, an important neurotransmitter. Hyperglycemia may lead to hyperosmolarity and increased vasopressin, which eventually results in degeneration of hypothalamic neurons.4 There may also be a direct effect of hyperglycemia on the calcium balance in hippocampal neurons, which could lead to degeneration.5

Based on these experimental data, it is hypothesized that diabetes contributes to the pathophysiologic processes characteristic of both Alzheimer disease (AD) and vascular dementia, the 2 most common forms of dementia. The association of diabetes to AD, particularly AD mixed with vascular pathology, is a consistent finding in epidemiologic studies based on different ethnic groups.6-8 In one study of Japanese American men, an interaction was also reported between diabetes and possession of the apolipoprotein E ε4 allele (APOE ε4), a genetic susceptibility risk factor for AD.8 If this finding is replicated in other cohorts, it would strengthen the hypothesis that diabetes pathophysiology can directly or indirectly increase the risk for AD. Herein, we examine this interaction in a prospective study of white and African American men and women observed in the Cardiovascular Health Study (CHS) Cognition Study, an ancillary study to the Cardiovascular Health Study.

METHODS

STUDY POPULATION

The Cardiovascular Health Study is a 4-site longitudinal study established in 1989 to investigate risk factors for cardiovascular disease in elderly individuals. During 1989-1990, 5201 participants were randomly selected from Medicare eligibility lists in Pittsburgh, Pennsylvania, and Forsyth County, North Carolina, Washing-
ton County, Maryland, and Sacramento County, California. An additional 687 African American individuals were recruited in 1992-1993. From baseline to 1998-1999, participants were examined up to 10 times at their respective clinical centers.

In addition to measures of cardiovascular risk factors and subclinical and clinical disease, cognitive function and brain structure were also assessed. To test global cognitive function, the Modified Mini-Mental State Examination was used at baseline. Subsequently, the Modified Mini-Mental State Examination and Digit Symbol Substitution Test were administered annually until 1998. Magnetic resonance imaging (MRI) was used to assess pathologic changes in brain structure. All participants were invited to have a brain MRI in 1992-1994 and again in 1997-1999. The baseline for the CHS Cognition Study is 1992-1994 when the first MRI was acquired.

The CHS Cognition Study was initiated to identify all participants who were demented in 1992-1993 and who subsequently developed dementia through to 1999-2000. All persons in the CHS Cognition Study cohort were required to have had a clinic visit, including having taken the Modified Mini-Mental State Examination, to be part of the cohort. The study was approved by the institutional review board at each center, and an informed consent signed by all participants was obtained at entry and at specified intervals during the course of the study.

DEMENTIA CASE FINDING

A description of the dementia case–finding procedures has been published. In brief, as a part of the CHS Cognition Study, individuals who screened positive for dementia (based on cognitive testing, proxy interview, or medical history) were invited for further evaluation with a more extensive neuropsychological and neurological examination. Individuals who were deceased or refused this examination were evaluated with other methods (eg, telephone interviews with participants or their proxies, physician questionnaires, and medical records). Diagnoses made in a consensus conference were based on all prospectively obtained information on cognition collected as a part of the CHS, new data collected for the CHS Cognition Study, and other related data. The dementia criteria were based on impairment in 2 or more cognitive domains and history of normal intellectual function. Magnetic resonance imaging was used to classify different dementia types. International diagnostic guidelines, including the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer Disease and Related Disorders Association criteria for probable and possible AD and the Alzheimer Disease Diagnostic and Treatment Center's State of California criteria for probable and possible vascular dementia (VaD) with or without AD, were followed. Our analysis focuses on 3 subtypes of dementia: possible/probable AD without VaD (AD), possible/probable VaD without AD (VaD), and mixed AD for cases that met criteria for both AD and VaD. Participants with other types of dementia (ie, Parkinson dementia, dementia with Lewy bodies, or other unspecified types of dementia) were excluded from the present analysis.

DIABETES AND APOE GENOTYPE MEASURES

Blood samples were obtained early in the clinic visit after a 12-hour fast. Plasma and/or serum samples were kept frozen at −70°C and sent on dry ice to the Central Blood Analysis Laboratory, University of Vermont, Burlington. Serum chemistry analyses, including that of glucose, were conducted on the Kodak Ektachem 700 Analyzer (Eastman Kodak Corp, Rochester, New York). At the clinic visit, lasting plasma glucose and insulin levels were measured and analyzed at the CHS central laboratory. Serum insulin was assayed by solid-phase radioimmunoassay using serum-based standards (Diagnostics Products Corp, Los Angeles, California). Based on the data collected closest to the MRI acquisition date, diabetes and impaired glucose tolerance cases were defined according to American Diabetes Association criteria (fasting glucose concentration ≥126 mg/dL [to convert to mmol/L, multiply by 0.0553]) or use of hypoglycemic medication or insulin treatment. For the analysis, participants with impaired glucose tolerance were included in the nondiabetic group. Apolipoprotein E genotyping was done using the method of Hickson and Vernier only for consenting participants; the genotype was categorized as the presence or absence of the ε4 allele.

COVARIATES

The following demographic, lifestyle, and cardiovascular risk factors were considered covariates or putative confounding factors and were included in the analyses: age; race (−10% of the sample was African American); years of education (schooling completed); smoking (never, former, or current); alcohol consumption (total drinks/week); stroke prior to the date of MRI; body mass index; ankle-brachial index; depression status (closest in time to the MRI), measured with the 10-item version of the Center for Epidemiology Studies Depression Scale; total cholesterol; and blood pressure (normal: <140/90 mm Hg, borderline systolic blood pressure, 140-159 mm Hg; diastolic blood pressure, 90-95 mm Hg, or hypertension: ≥160/95 mm Hg). Our definition for hypertension also included taking antihypertensive medications for self-reported hypertension or taking antihypertensive medication but having normal blood pressure levels. Participants with borderline blood pressure measures were included in the hypertensive group for this analysis. All measurements used in this analysis were taken at the time of (or prior to) entry into the CHS Cognition Study (ie, at the time of first MRI).

STATISTICAL ANALYSIS

Our analysis is based on the 2547 participants who were examined for and found to be without dementia at the time of their MRI and had complete information on APOE genotype and diabetes status. Participants classified as having mild cognitive impairment (n=577), as defined previously, were excluded. Among the 2547 participants, 411 new cases of dementia developed, including 207 cases of AD, 132 cases of mixed AD, and 58 cases of VaD. The mean follow-up time was 5.4 years and mean age at follow-up entry and exit was 74.7 and 80.1 years, respectively. Risk of dementia and subtypes (AD, mixed AD, and VaD) was estimated using Cox proportional hazards models with age as the time scale. Age at dementia onset was calculated by adding years of follow-up from date of MRI (entry) until dementia diagnosis. Participants with neither diabetes nor APOE ε4 served as the reference group and were compared with those who had only diabetes, only APOE ε4, and those who had both.

Two models are presented: model 1 is adjusted for age, race, and years of education and model 2 is also adjusted for hypertension, total cholesterol, smoking, alcohol body mass index, depression status, ankle-brachial index, and stroke. The percentage of participants with diabetes using insulin was examined to get an estimate of diabetes severity in each diagnostic group. The statistical analysis was conducted using Stata software package, version 8 (Stata Corp, College Station, Texas).

RESULTS

There were 320 participants (12.6%) classified as having diabetes and 602 participants (23.6%) who carried the APOE ε4 allele. Compared with participants with-
out diabetes, those with diabetes had a worse cardiovascular risk profile, including a higher systolic blood pressure, total cholesterol, and body mass index, as well as a lower ankle-brachial index. The prevalence of diabetes and insulin use and the mean serum glucose level were higher in participants with incident dementia compared with those who did not have dementia (data not shown). The highest percentage of incident cases of dementia was in participants with both diabetes and APOE ε4 (Table 1). The group with both diabetes and the APOE ε4 allele had the highest incidence of dementia, and the group with none of these characteristics had the lowest (Figure). The diabetes-only group had a higher incidence of dementia than the APOE ε4–only group (P < .01).

Results from Cox proportional hazard multivariate models show that compared with those without diabetes and APOE ε4, participants with either diabetes or APOE ε4 had a higher risk of total dementia, AD, and mixed AD, but not VaD. When comparing the risk in those who had both diabetes and APOE ε4 with those who had either risk factor, the results suggest a synergistic interaction between the 2 risk factors. That is, those with only diabetes have a relative risk for AD of 1.62, those with only APOE ε4 have a risk of 2.50, and those with both have a risk of 4.99; this is a higher risk than expected if the risk factors were acting in an additive manner (ie, 2.5 + 1.62 = 4.05) (Table 2).

Of participants with diabetes, 15.4% without APOE ε4 and 17.8% with APOE ε4 used insulin (age-adjusted, P < .001); 1.6% of the group without dementia, 2.6% of the AD group, 4.1% of the mixed AD group, and 6.5% of the VaD group used insulin (P = .004). Results for AD stratified by race were similar to those from the overall analysis (hazard ratio [HR], 5.70; 95% confidence interval [CI], 1.41–23.0 vs HR, 4.91; 95% CI, 2.43–9.89 for African American and white participants, respectively) (eTable 1, available at http://www.archneurol.com). Results for mixed AD were slightly stronger in African American participants (HR, 5.89; 95% CI, 1.29–27.0 vs HR, 2.91; 95% CI, 0.88–9.64). The risk for mixed dementia among those with both diabetes and APOE ε4 was stronger in women than in men (HR, 11.5; 95% CI, 3.28–40.6 vs HR, 2.24; 95% CI, 0.64–7.76, respectively) (eTable 2, available at http://www.archneurol.com). It should be noted that the sample size in these stratified analyses is relatively small.
These data suggest that having both diabetes and the APOE ε4 allele increases the risk for AD to a greater extent than if each risk factor contributed to risk in an additive way. Similarly, the risk for mixed AD was increased in those with both diabetes and APOE ε4, but this risk was somewhat attenuated after adjusting for cardiovascular risk factors, white race, and male sex. These results are consistent with the hypothesis that APOE ε4 modifies the risk for AD in individuals with diabetes and that diabetes may directly or indirectly cause the neuronal and vessel damage.

The positive association between diabetes and the risk of AD has been reported by Luchsinger and Mayeux, and a recent report from the Framingham Study found the association only in specific subgroups that included men, those with higher systolic blood pressure, and those who had APOE ε4. The APOE ε4 allele has been shown, in various cohorts, to modify the association of cardiovascular risk factors of dementia or cognitive decline, in a previous report from the CHS cohort, Haan et al showed a significant interaction between APOE ε4 and diabetes that increased the rate of cognitive decline measured by the Modified Mini-Mental State Examination. In the present analysis, we examined whether this interaction was also important for the clinical outcome of dementia and subtypes. The pathophysiology underlying these associations is not known, but several hypotheses may be proposed that relate to the increase in the production or deposition of β-amyloid (Aβ) or the reduced clearance of the amyloid from the brain. The APOE ε4 allele stimulates Aβ deposition then binds to Aβ protein, accelerating conversion to insoluble deposits in the brain. Hyperglycemia increases the production of advanced glycation end products, which also modulate amyloid processing. Chronic cerebral hypoperfusion may also contribute to increased production of Aβ. Hypoperfusion, due to capillary distortion caused by diabetes, and other cardiovascular risk factors can lead to an energy metabolic crisis followed by an overproduction of inflammatory cytokines, oxidative stress, and neuronal deterioration, which may increase the production of the Aβ protein. Problems in clearing the amyloid may result from the large- and small-vessel damage in the brain caused by diabetes. Indeed, in an autopsy study based on the Honolulu-Asia Aging Study, investigators found that those with diabetes and APOE ε4 had a very high risk of cerebral amyloid angiopathy as well as neuritic plaques and neurofibrillary tangles; those with only diabetes had a significantly increased risk only for large infarcts.

Interestingly, we found no significant increased risk of developing VaD in participants with diabetes and/or APOE ε4. The nonsignificant association between diabetes and VaD was somewhat unexpected in light of the known association between stroke and diabetes. Issues related to diagnostic validity may lead to misclassification and less power to detect an association if one exists. However, it is more likely that there is selective mortality in those at risk for both stroke and dementia.

Hypertension is another important vascular risk factor for brain disease, such as dementia, white matter lesions, and hippocampus atrophy. Hypertension also has been reported to modify the association of diabetes with cognitive decline, brain atrophy, and dementia. In this cohort, we did not find any effect modification by hypertension of the association between dementia, diabetes, and APOE ε4; the relationship was slightly stronger in the normotensive group.

In summary, our data show that having both diabetes and APOE ε4 increases the risk of dementia, espe-
cially for AD and mixed AD, more than each risk factor alone. The 95% CIs for the risk ratios of the combined effect of diabetes and APOE ε4 overlap with those for each risk factor alone. However, higher risk in the group with the 2 risk factors has been observed in another cohort, which also had neuropathologic evidence. Therefore, additional experimental studies are warranted to examine the hypothesis that APOE ε4 modifies the risk for AD in individuals with diabetes and that diabetes may directly or indirectly cause neuronal and vessel damage. Moreover, our results, combined with those from other studies, suggest that older persons with diabetes are at an increased risk of clinically important cognitive impairment. This should be taken into account in caring for older individuals with diabetes, particularly when disease management protocols are introduced to patients.

Accepted for Publication: April 3, 2007.

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Financial Disclosure: None reported.

Funding/Sponsor: This study was supported by grant 5 R01 AG15928-02 from the National Institute on Aging; contracts N01-HC-85079 and N01-HC-85086 from the National Heart, Lung, and Blood Institute; and by the Intramural Research Program at the National Institute on Aging. Additional Information: The eTables are available at http://www.archneurol.com.

Additional Contributions: We acknowledge and thank the participating institutions and principal investigators of the CHS.

REFERENCES

### eTable 1. Risk of Dementia and Subtypes by Race

<table>
<thead>
<tr>
<th>Dementia Status</th>
<th>African American Participants</th>
<th>White Participants</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Model 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Model 2&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total Dementia (n=2547 [253 African American, 2294 White Participants])</td>
<td></td>
<td></td>
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<tr>
<td>Diabetes only</td>
<td>0.86 (0.32-2.31)</td>
<td>0.74 (0.26-2.07)</td>
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<tr>
<td>APOE ε4 only</td>
<td>1.99 (1.10-3.61)</td>
<td>2.10 (1.12-3.93)</td>
</tr>
<tr>
<td>Both&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4.20 (1.69-10.5)</td>
<td>4.06 (1.59-10.4)</td>
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<tr>
<td>AD (n=2343 [221 African American, 2122 White Participants])&lt;sup&gt;d&lt;/sup&gt;</td>
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<td></td>
</tr>
<tr>
<td>Diabetes only</td>
<td>1.65 (0.52-5.25)</td>
<td>1.76 (0.48-6.37)</td>
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<tr>
<td>APOE ε4 only</td>
<td>2.42 (0.96-6.14)</td>
<td>2.11 (0.77-5.83)</td>
</tr>
<tr>
<td>Both&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5.83 (1.54-22.0)</td>
<td>5.70 (1.41-23.0)</td>
</tr>
<tr>
<td>Mixed AD (n=2268 [209 African American, 2059 White Participants])&lt;sup&gt;d&lt;/sup&gt;</td>
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<td></td>
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<tr>
<td>Diabetes only</td>
<td>0.64 (0.07-5.49)</td>
<td>0.26 (0.02-2.74)</td>
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<tr>
<td>APOE ε4 only</td>
<td>0.91 (0.25-3.36)</td>
<td>0.76 (0.19-3.08)</td>
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<tr>
<td>Both&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8.29 (2.03-33.8)</td>
<td>5.89 (1.29-27.0)</td>
</tr>
<tr>
<td>VaD (n=2194 [200 African American, 1994 White Participants])</td>
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</tr>
<tr>
<td>Diabetes only</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>APOE ε4 only</td>
<td>5.60 (1.30-24.06)</td>
<td>6.76 (1.26-36.3)</td>
</tr>
<tr>
<td>Both&lt;sup&gt;f&lt;/sup&gt;</td>
<td>NE</td>
<td>NE</td>
</tr>
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</table>

Abbreviations: AD, Alzheimer disease; APOE ε4, ε4 allele of the apolipoprotein E genotype; NE, not estimable due to small sample size; VaD, vascular dementia.

<sup>a</sup> Adjusted for age and years of education.

<sup>b</sup> Adjusted for age, years of education, hypertension, total cholesterol, smoking, alcohol, body mass index, depression status, ankle-brachial index, and stroke.

<sup>c</sup> Cross-product between diabetes/APOE ε4 subgroups and race, P<.2. The analysis was adjusted as in model 1.

<sup>d</sup> Excluded participants with VaD and other types of dementia.

<sup>e</sup> Excluded participants with AD and other types of dementia.

<sup>f</sup> Cross-product between diabetes/APOE ε4 subgroups and race, P<.1. The analysis was adjusted as in model 1.

### eTable 2. Risk of Dementia and Subtypes by Sex

<table>
<thead>
<tr>
<th>Dementia Status</th>
<th>Men</th>
<th>Women</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Model 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Model 2&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total Dementia (n=2547 [1503 Women, 1044 Men])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes only</td>
<td>1.52 (0.95-2.42)</td>
<td>1.43 (0.89-2.30)</td>
</tr>
<tr>
<td>APOE ε4 only</td>
<td>1.55 (1.06-2.25)</td>
<td>1.59 (1.08-2.34)</td>
</tr>
<tr>
<td>Both&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3.05 (1.62-5.75)</td>
<td>2.38 (1.24-4.54)</td>
</tr>
<tr>
<td>AD (n=2343 [1394 Women, 949 Men])&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes only</td>
<td>1.85 (0.88-3.91)</td>
<td>1.87 (0.83-4.00)</td>
</tr>
<tr>
<td>APOE ε4 only</td>
<td>2.32 (1.33-4.04)</td>
<td>2.57 (1.44-4.56)</td>
</tr>
<tr>
<td>Both&lt;sup&gt;e&lt;/sup&gt;</td>
<td>4.90 (2.13-11.27)</td>
<td>4.78 (2.02-11.30)</td>
</tr>
<tr>
<td>Mixed AD (n=2268 [1332 Women, 936 Men])&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>Diabetes only</td>
<td>1.53 (0.70-3.34)</td>
<td>1.57 (0.62-3.06)</td>
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<tr>
<td>APOE ε4 only</td>
<td>1.30 (0.65-2.59)</td>
<td>1.25 (0.63-2.52)</td>
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<tr>
<td>Both&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3.52 (1.06-11.72)</td>
<td>2.19 (0.62-7.64)</td>
</tr>
<tr>
<td>VaD (n=2194 [1283 Women, 911 Men])&lt;sup&gt;f&lt;/sup&gt;</td>
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<tr>
<td>Diabetes only</td>
<td>0.89 (0.26-3.00)</td>
<td>0.80 (0.23-2.75)</td>
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<tr>
<td>APOE ε4 only</td>
<td>1.06 (0.42-2.65)</td>
<td>1.04 (0.41-2.63)</td>
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<tr>
<td>Both&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1.28 (0.17-9.71)</td>
<td>0.55 (0.07-4.45)</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; APOE ε4, ε4 allele of the apolipoprotein E genotype; NE, not estimable due to small sample size; VaD, vascular dementia.

<sup>a</sup> Adjusted for age and years of education.

<sup>b</sup> Adjusted for age, years of education, hypertension, total cholesterol, smoking, alcohol, race, body mass index, depression status, ankle-brachial index, and stroke.

<sup>c</sup> Cross-product between diabetes/APOE ε4 subgroups and sex, P>.1. The analysis was adjusted as in model 1.

<sup>d</sup> Excluded participants with VaD and other types of dementia.

<sup>e</sup> Excluded participants with AD and other types of dementia.

<sup>f</sup> Excluded participants with AD and other types of dementia.