Apolipoprotein E "4 and testosterone interact in the risk of Alzheimer’s disease in men

This item was submitted to Loughborough University’s Institutional Repository by the/an author.

Additional Information:

• This is a pre-print. This uncorrected proof was submitted to the journal, International Journal of Geriatric Psychiatry, 2002, © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Metadata Record: https://dspace.lboro.ac.uk/2134/2544

Please cite the published version.
This item was submitted to Loughborough’s Institutional Repository by the author and is made available under the following Creative Commons Licence conditions.

For the full text of this licence, please go to:

http://creativecommons.org/licenses/by-nc-nd/2.5/

For the full text of this licence, please go to:

http://creativecommons.org/licenses/by-nc-nd/2.5/
Apolipoprotein E ε4 and testosterone interact in the risk of Alzheimer’s disease in men

E. Hogervorst*, D. J. Lehmann, J. McBroom and A. D. Smith

Oxford Project To Investigate Memory and Ageing, Department of Pharmacology, Radcliffe, Infirmary, Oxford, UK

SUMMARY

The apolipoprotein E ε4 allele (APOE ε4) is a well-established risk factor for Alzheimer’s disease (AD), but the mechanisms for this association are not well understood. In addition, other risk and protecting factors are needed to explain the causality of the disease. Sex steroid hormones, such as estradiol and testosterone, are thought to exert protective mechanisms in the brain (Lee and McEwen, 2001). Lower levels of total estradiol and total testosterone in men with AD have been found (Hogervorst et al., 2001; Rasmuson et al., 2002). The current study examined relations between APOE ε4 and levels of total testosterone and total estradiol in the risk of AD in men. Copyright © 2002 John Wiley & Sons, Ltd.

SUBJECTS, METHODS AND RESULTS

We examined 116 male Caucasians from the Oxford Project To Investigate Memory and Ageing (OPTIMA). Fifty-one were autopsy confirmed CERAD AD cases (mean age at episode: 75.3 years, range: 58.8–89.5 years), 10 were diagnosed ‘probable AD’ by NINCDS/ADRDA criteria (69.8 years, range: 57.4–88.8 years) and 55 were without cognitive impairment and with CAMCOG scores ≥ 80 (73.6 years, range: 39.9–94.7 years). All had given their informed consent prior to the study (Clarke et al., 1998).

We analysed total testosterone using a competitive enzyme immunoassay (Bayer 1, Bayer Cooperation, Tarrytown, NY, USA) in non-fasting blood serum samples that had been stored at −70°C. Serum had been collected between 10 and 12 am. For total estradiol, duplicate serum samples were extracted with ether. Estradiol was then assessed by radioimmunoassay using a highly specific rabbit antiserum. SHBG levels were investigated using an immuno-enzymometric assay (IEMA). Subjects were genotyped by standard PCR methods for APOE and for the butyrylcholinesterase K variant.

Using a logistic regression model with age and SHBG as co-variables, low testosterone (odds ratio (OR) = 0.86, 95% confidence intervals (CI) 0.75–0.99) and the APOE ε4 × testosterone interaction (OR = 1.28, 95% CI = 1.07–1.54) were significantly associated with AD, which suggested that the presence of the APOE ε4 allele modified the risk of AD associated with low testosterone levels. Entering APOE ε4 by itself as a risk factor for AD, gave an OR of 7.72 (95% CI = 3.63 to 16.48, p < 0.01). In a model where estradiol replaced testosterone, neither estradiol alone nor the estradiol × APOE ε4 interaction was a significant predictor of AD.

Table 1 presents the results of analyses stratified by diagnosis. The two main results were: first, testosterone levels were lower in APOE ε4-positive controls than in those without APOE ε4; second, in men without APOE ε4, testosterone levels were lower in AD than in controls. One of the lowest testosterone levels
against the development of AD. Short-term studies gated the possibly protective effects of testosterone factor. At present, no long-term studies have investi-
spective studies are needed to resolve these issues. Pro-
not distinguish between these interpretations. Pro-
testosterone levels for other reasons. This study can-
APOE among other factors, lowers testosterone in male con-
open to various interpretations. One is that 
APOE lowers testosterone levels in controls and that AD results in a lowering of 
APOE lowers testosterone in controls and that AD results in a lowering of 

(1.6 nmol/l) was in the only control who was an 
APOE homozygote. With estradiol, levels were 
lower in APOE carriers, both in AD cases and in 
controls.

We also examined two other alleles, apolipoprotein E ε2 (APOEε2) and the butyrylcholinesterase K variant (BCHE-K). No significant association was 
found between either allele and either steroid in any 
analysis. Only a weak tendency was seen for 
APOEε2-positives to have higher steroid 
levels than those without APOEε2 (e.g. for testoster-
one: 20.2 nmol/l (n = 11) vs 16.5 nmol/l (n = 42), 
p = 0.1, t-test).

COMMENT

Table 1 illustrates two important results. First, 
APOEε4 is associated with lower testosterone levels 
in men, but only significantly so in controls. Second, 
testosterone levels are higher in controls than in AD, 
but only in men without APOEε4. These results are 
open to various interpretations. One is that APOEε4, 
among other factors, lowers testosterone in male con-
trols and low testosterone, whether or not due to 
APOEε4 status, contributes to the onset of AD. 
Another interpretation is that APOEε4 lowers testos-
sterone levels in AD cases and that AD results in a lowering of 
testosterone levels for other reasons. This study cannot 
distinguish between these interpretations. Pros-
spective studies are needed to resolve these issues.

Low testosterone is potentially a modifiable risk 
factor. At present, no long-term studies have investig-
gated the possibly protective effects of testosterone 
against the development of AD. Short-term studies 
with testosterone replacement therapy in non-
demented men have given mixed results (Wolf et al., 
1999). A possible explanation could be that, since 
APOEε4-positive controls had lower levels in the pre-
sent study than those without the allele, perhaps only 
APOEε4-positive men would profit from testosterone 
replacement therapy. Future, long-term studies should 
investigate the possibly protective effect of testoster-
one replacement therapy in APOEε4 carriers who are at risk of AD.

ACKNOWLEDGEMENTS

This work was supported by grants from The Alzhei-
mer’s Association (NIRG 00-2258), the Takayama 
Foundation, the Norman Collisson Foundation and 
Bristol-Myers Squibb. E. Hogervorst is a Margaret 
Pelly Fellow of Somerville college, Oxford.

We would like to thank Professor M. Dowsett at 
the Department of Biochemistry, Royal Marsden 
NHS Trust in London for the oestradiol assay, and 
D. Quantrill and M. Gales at the Clinical Biochemis-
try Department of the John Radcliffe Infirmary for the 
estrogen assay and SHBG assays. We would also like to 
thank the members and participants of OPTIMA for 
making this study possible.

REFERENCES

Clarke R, Smith AD, Jobst KA, Refsum H, Sutton L, Ueland PM. 
1998. Folate, vitamin B12 and serum homocysteine as candidate 
risk factors for confirmed Alzheimer’s disease. Arch Neurology 

Hogervorst E, Williams J, Budge M, Barnetson L, Combrinck M, 
Smith AD. 2001. Serum total testosterone is lower in men with 

Table 1. Sex steroid levels in AD and in controls, by APOEε4 status

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Subgroup (n)</th>
<th>APOEε4 status (n)</th>
<th>Meana</th>
<th>pb (t-test)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>AD (61)</td>
<td>With (44)</td>
<td>13.9 (±5.1)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Without (17)</td>
<td>15.0 (±4.8)a</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Controls (53)</td>
<td>With (12)</td>
<td>11.3 (±7.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Without (41)</td>
<td>19.1 (±5.4)a</td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td>AD (60)</td>
<td>With (43)</td>
<td>69.8 (±28.7)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Without (17)</td>
<td>94.9 (±28.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Controls (55)</td>
<td>With (12)</td>
<td>70.6 (±42.4)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Without (43)</td>
<td>107.8 (±34.9)</td>
<td></td>
</tr>
</tbody>
</table>

AD, Alzheimer’s disease; APOEε4, apolipoprotein E ε4; NS, not significant.

a Testosterone levels are in nmol/l and estradiol in pmol/l.
b All subgroups were normally distributed; equal variances could be and were assumed in all cases.

c Testosterone, APOEε4-negative AD cases vs APOEε4-negative controls: p = 0.009 (t-test).


Author Query Form (GPS/714)

Special Instructions: Author please write responses to queries directly on Galley proofs and then fax back. Alternatively please list responses in an e-mail.

Q1: Author: Reword as structured summary. Query to Pr. Ed—or leave as is as very shot paper?