CONFLICT OF INTEREST

The authors declare no conflict of interest.

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CSF biomarkers for Alzheimer's pathology and the effect size of *APOE* ε4

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New research and clinical criteria for Alzheimer's disease (AD) have recently been proposed, which include biomarker information on Alzheimer's plaque and tangle pathology, or AD-typical structural brain changes, as supporting or essential elements of an AD diagnosis.[1–3] In a large group of patients with both genetic and cerebrospinal fluid (CSF) biomarker data, we here show that biomarker-assisted diagnosis-making almost doubles the effect size of the association between the ε4 variant of the apolipoprotein E (*APOE*) gene and AD.

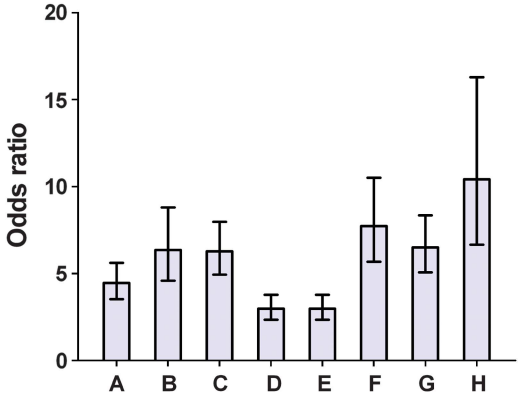

Figure 1. Odds ratios for a positive *APOE* ε4 carrier status based on (A) clinical diagnosis, comparing patients with clinical AD with dementia at inclusion or follow-up ($n=596$) versus all other diagnostic groups ($n=749$), (B) clinical diagnosis, comparing patients with clinical AD with dementia at inclusion or follow-up ($n=596$) with cognitively normal subjects ($n=251$), (C) CSF Aβ42, comparing subjects with CSF Aβ42 below ($n=779$) and above ($n=563$) 546 ng/l, (D) CSF T-tau, comparing subjects with CSF T-tau above ($n=676$) and below ($n=662$) 446 ng/l, (E) CSF P-tau, comparing subjects with CSF P-tau above ($n=497$) and below ($n=759$) 79 ng/l, (F) CSF P-tau/Aβ42 ratio, comparing subjects with CSF P-tau/Aβ42 above and below 0.15, (G) CSF biomarker signatures, comparing subjects with an AD-indicative CSF signature with regards to all three biomarkers T-tau, P-tau and Aβ42, and subjects with a normal complete profile (cut-points specified above) and (H) CSF biomarker signatures in addition to clinical diagnosis, comparing patients with clinical AD and an AD-indicative CSF biomarker signature versus cognitively normal subjects with normal CSF biomarker results (cut-points specified above). Note that columns C-G are derived without any clinical information.

We included clinically diagnosed patients with either AD dementia ($n=309$) or mild cognitive impairment (MCI) due to AD ($n=287$), cognitively normal controls ($n=251$) and patients with MCI who remained stable over at least 2 years ($n=399$) or developed dementias other than AD ($n=99$) (Table 1, Supplementary Material). All had *APOE* ε2/ε3/ε4 genotypes and results on the CSF biomarkers total tau (T-tau), phosphorylated tau (*P*-tau) and the 42-amino-acid isoform of amyloid-β (Aβ42) determined. These CSF biomarkers reflect the core elements of Alzheimer's pathology[4] and are strongly associated with AD in cross-sectional as well as longitudinal follow-up studies (Supplementary Material).[5,6]

AD dementia and MCI-AD patients were first pooled into one clinical AD group ($n=596$) and compared with all remaining categories that were designated non-AD ($n=749$). A positive *APOE* ε4 carrier status (one or two ε4 alleles) was overrepresented in the AD group and yielded an odds ratio (OR) of 4.45 (95% confidence interval (CI) 3.52–5.62) for a clinical diagnosis of AD at inclusion or follow-up (Figure 1). This OR is similar to the AlzGene meta-analysis of *APOE* (3.68, 95% CI 3.30–4.11, www.alzgene.org/meta.asp?geneID=83, November 2012 freeze). Similarly, we tested the association of *APOE* ε4 with AD, comparing the 596 AD patients with the 251 cognitively normal controls, which resulted in an OR of 6.35 (95% CI 4.59–8.80).

Disregarding the clinical diagnoses and subgrouping all subjects into amyloid-positive, defined as CSF Aβ42 $<546\,\mathrm{ng\,l^{-1}}$ ($n=779$), and amyloid-negative, defined as CSF Aβ42 $\geqslant 546\,\mathrm{ng\,l^{-1}}$ ($n=563$) (see Supplementary Material for details on cut-point determination), gave an OR for *APOE* ε4 as high as

6.27 (95% CI 4.93–7.98). Dichotomizing the material according to CSF T-tau or *P*-tau did not change the ORs as compared with clinical diagnosis only (Figure 1). Even though the OR for the ratio *P*-tau/Aβ42 (6.50 (95% CI 5.07–8.35)) was slightly higher than for Aβ42 alone, the difference was not statistically significant.

We also compared patients, again disregarding the clinical diagnoses, who had a complete CSF biomarker signature indicative of AD, that is, low Aβ42 and both high T-tau and *P*-tau ($n = 438$, see Supplementary Material for a detailed description of the signature), with subjects with a negative CSF biomarker pattern ($n = 414$). The biomarker diagnosis strengthened the association to *APOE* ε4; the OR increased from 4.45 (95% CI 3.52–5.62) in pure clinical diagnosis to 7.66 (95% CI 5.65–10.39) in patients classified on the basis of biomarker data alone.

Finally, ORs were calculated on subjects having both a clinical diagnosis and a concordant complete biomarker profile (n(AD) = 324; n(control) = 155). This approach resulted in an even stronger association of *APOE* ε4 with AD (OR 10.4, 95% CI 6.65–16.3). Similar effects were seen when comparing non-carriers with ε4 heterozygotes and homozygotes across the different diagnostic groups (Figure 1, Supplementary Material).

These results have several important implications. First, *APOE* ε4 appears as strongly associated with amyloid pathology as clinical AD. Second, clinical criteria that incorporate biomarker information on Alzheimer's pathology give a stronger association with *APOE* ε4 than clinical diagnosis alone. This is compatible with the presumed higher diagnostic accuracy of the revised clinical approach,[1–3] and has also been seen in a series of neuropathologically verified AD cases and controls.[7] Third, the approach of combining clinical with biomarker data may increase the power of genetic association studies, as well as the potential to provide insights into the mechanistic pathways through which genetic risk factors may exert their effects.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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DISCLAIMER

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

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Long-term inflammation increases risk of common mental disorder: a cohort study

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The inflammation hypothesis of depression, or more broadly, common mental disorders, proposes that chronic inflammation plays an important role in the pathophysiology of these conditions.[1,2] The hypothesis is supported by experiments of inflammatory stimuli, antidepressant trials and studies on depression-related genes and pathogen host defense,[2–5] but direct population-based evidence from long-term inflammation is scarce. Because of a lack of studies on the effects of chronically elevated inflammation, assessed over several years using repeat measurements, it has remained unclear whether the association between inflammation and common mental disorder is the consequence of acute or chronic inflammation.

This report is from the Whitehall II cohort study.[6] In our analysis of up to 4630 adults without chronic disease, we used repeat measures of inflammatory markers and mental disorder. We measured the proinflammatory cytokine interleukin 6 (IL-6) in 1992, 1997 and 2003 and common mental disorder, based on the General Health Questionnaire (GHQ), in 1997, 2003 and 2008. The IL-6 distribution was categorized as: $\leqslant 1.0\,\mathrm{pg\,ml^{-1}}$ (low), $1.1–2.0\,\mathrm{pg\,ml^{-1}}$ (intermediate) and $>2.0\,\mathrm{pg\,ml^{-1}}$ (high). Details