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/A42 (6.50 (95% CI 5.07–8.35)) was slightly higher than for A42 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 A42 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 indication on Alzheimer’s pathology give a stronger association appears as strongly associated with amyloid pathology as 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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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: < 1.0 pg ml\(^{-1}\) (low), 1.1–2.0 pg ml\(^{-1}\) (intermediate) and > 2.0 pg ml\(^{-1}\) (high). Details
of study designs, methods and the included/excluded study populations are presented in Supplementary Material, Supplementary Figures S1–S4 and Supplementary Tables S1 and S2.

Cross-sectional analysis, using data from 1997, showed IL-6 not to be associated with common mental disorder (age- and sex-adjusted odds ratio = 1.40 (95% CI 0.85–1.27), P = 0.69, Study Design A). Then we examined the cumulative 10-year risk of common mental disorder among the 2757 participants without the disorder at the first GHQ assessment in 1997. Compared to participants with low IL-6 in 1997, those with high IL-6 had a greater likelihood of common mental disorder in 2003 and/or 2008 (a total of 549 new cases) (age- and sex-adjusted odds ratio = 1.40 (1.07–1.82), P = 0.01) (Figure 1, Study Design B). Furthermore, participants with high IL-6 at both the 1992 and 1997 assessments had higher odds of a new-onset mental disorder in 2003 and/or 2008, 1.61 (1.14–2.28, P = 0.007, Figure 1), with the odds ratio being even higher, 1.75 (1.19–2.57, P = 0.004), among those who had high IL-6 in 1992, 1997 and 2003.

To further examine dose–response associations, we used the number of times a participant had IL-6 > 2 pg ml⁻¹ as the exposure (Study Design B). Results show that those demonstrating high IL-6 on 0, 1, 2 and 3 occasions had odds ratios of 1.00 (reference), 1.18 (0.94–1.47), 1.38 (1.04–1.83) and 1.56 (1.10–2.21), respectively, for a 10-year risk of common mental disorder (total N = 2757; P_{trend} = 0.002).

Multivariable adjusted results and the sensitivity analyses in Supplementary Table S3 (Study Design C) show that the association between the 5-year average level of IL-6 and subsequent 10-year risk of common mental disorder was little affected by adjustments for acute inflammation, obesity, smoking and drug treatments. The relationship between IL-6 and common mental disorder was evident in both men (odds ratio per doubling of IL-6 = 1.46 (1.19–1.78)) and women (1.34 (1.00–1.79)), and there was no statistical evidence of sex difference in this relationship (P_{sex interaction} = 0.67).

In the subgroup of participants without common mental disorder at the third inflammation measurement (2003, Study Design D), odds ratio of new common mental disorder in 2008 for high IL-6 in 1992, 1997 and 2003 was 1.42 (0.78–2.57) (details in Supplementary Material).

These findings support the hypothesis that persistently elevated levels of IL-6 contribute to the development of common mental disorder.¹² The fact that previous studies relied on a single measurement of IL-6 may partially explain the mixed findings:¹ a one-off measure does not reliably capture the chronicity of inflammation.¹ The present study has limitations: common mental disorder measured by a questionnaire is not the same as clinical diagnosis of depression or anxiety.⁹ Our data are from an occupational cohort where participants are likely to be healthier than the general population. Loss to follow-up accumulated over the extended follow-up; however, there was no evidence of major differences between the analytic sample and the sample at study recruitment.

Our findings have important clinical implications. If the observed association is causal, then targeting chronic inflammation with anti-inflammatory drugs could be useful in prevention of common mental disorder. Further studies are needed to clarify the underlying mechanisms, such as activation of the tryptophan-degrading enzyme, changes in indoleamine 2,3-dioxygenase, and abnormalities of the hypothalamic–pituitary–adrenal axis. Future investigations should also test the side effects, since anti-inflammatory strategies might increase the risk of infection and malignancy.¹⁰

CONFICT OF INTEREST
The authors declare no conflict of interest.

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