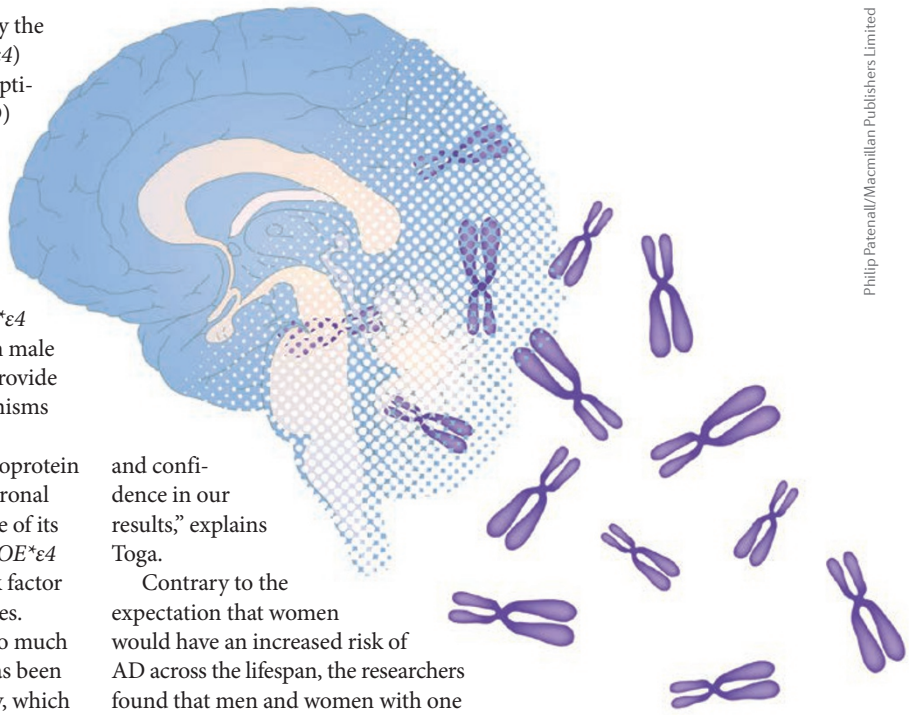
Nature Reviews Neurology | Published online 8 Sep 2017; doi:10.1038/nrneurol.2017.130

ALZHEIMER DISEASE

Revising the risk of Alzheimer disease in women



Philip Patenall/Macmillan Publishers Limited

Among individuals who carry the apolipoprotein E ε4 (*APOE*ε4*) allele, women are more susceptible to Alzheimer disease (AD) than men only between the ages of 65 and 75 years, according to a new study published in *JAMA Neurology*. The results contradict a 20-year-old belief that female carriers of *APOE*ε4* have a higher risk of AD than male carriers across all ages, and provide clues towards disease mechanisms and possible interventions.

Apolipoprotein E is a glycoprotein associated with lipid and neuronal homeostasis in the brain. One of its isoforms, encoded by the *APOE*ε4* allele, is the main genetic risk factor for late-onset AD in both sexes.

"We were surprised that so much work over the last 20 years has been dependent on one 1997 study, which reported that white females with one *APOE*ε4* allele have a higher risk over men at all ages," comments Arthur Toga, who led the new study. "Using a new big data platform, the Global Alzheimer's Association Interactive Network, we saw that we had nine times the data of the 1997 study and decided to take a second look."

Toga and colleagues analysed data from 27 independent studies on 57,979 individuals from North America and Europe between the ages of 55 and 85 years to determine how *APOE*ε4* and sex affected the risk of developing AD and mild cognitive impairment (MCI). "We were able to aggregate vast amounts of data from independent studies, affording increased statistical power and confidence in our results," explains Toga.

> "We find that women have a slightly earlier incidence of AD and MCI"

Contrary to the expectation that women would have an increased risk of AD across the lifespan, the researchers found that men and women with one copy of *APOE*ε4* had the same risk of MCI and AD between the ages of 55 and 85 years. However, compared with men, women had a higher risk of AD between the ages of 65 and 75 years, as well as an increased risk of developing MCI between the ages of 55 and 70 years.

As the pathophysiology of AD takes place over decades, the team suggests that the increased risk of AD in women between the ages of 65 and 75 years is associated with physiological events that occur 15–20 years earlier, possibly coinciding with the menopause. "We find that women have a slightly earlier incidence of AD and MCI, which may in fact be related to hormonal changes," explains Toga. "The mean start of menopause is somewhere around 51 years of age; at that point, there is a relative loss of oestrogen, which might interact with the presence of one or more copies of the *APOE*ε4* allele."

Crucially, the results could lead to the development of sex-specific biomarkers or interventions in AD. As Toga concludes, "researchers could study women 10, 15 or even 20 years before their most vulnerable period, to see if there are any detectable signals to suggest an increased risk of AD in 15 years."

Mitesh Patel

ORIGINAL ARTICLE Neu. S. C. *et al.* Apolipoprotein E genotype and sex risk factors for Alzheimer disease: a meta-analysis. *JAMA Neurol.* http://dx.doi.org/10.1001/jamaneurol.2017.2188 (2017)