

Response to: “Chronic hydroxychloroquine/chloroquine exposure for connective tissue diseases and risk of Alzheimer’s disease” by Lee

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We agree with Lee¹ that observational studies are limited by unmeasured and unknown confounding which can be best handled by a sufficiently powered randomised controlled trial. As mentioned in the discussion of our paper, we also acknowledge that Chou et al in their research on the Taiwanese National Health Insurance Research Database found that csDMARD increases the risk of Alzheimer's disease rather than providing protection.² It is interesting that both studies failed to epidemiologically capture any positive anti-inflammatory effects or suppression of microglial neurotoxicity induced by β -amyloid protein hypothesised to be triggered by these drugs. Further, as described in our paper,³ the effect of hydroxychloroquine on progression of dementia in early Alzheimer's disease has already been investigated in an 18-month randomized, placebo-controlled trial that included 168 patients with early Alzheimer's disease which showed no effect of the treatment against placebo.⁴ There are no randomised controlled trials to date that evaluate effects of these drugs on primary prevention of Alzheimer's disease. This is because such trials would have to run for several years and would need to recruit very large numbers of people in order to provide a meaningful result. In the absence of such evidence large observational studies offer the best next level of evidence on which we as clinicians can judge the effectiveness and/or safety of drugs.

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2. Chou MH, Wang JY, Lin CL, Chung WS. DMARD use is associated with a higher risk of dementia in patients with rheumatoid arthritis: A propensity score-matched case-control study. *Toxicol Appl Pharmacol.* 2017;334:217-222.
3. Fardet L, Nazareth I, Petersen I. Chronic hydroxychloroquine/chloroquine exposure for connective tissue diseases and risk of Alzheimer's disease: a population-based cohort study. *Ann Rheum Dis.* 2018 Sep 5. pii: annrheumdis-2018-214016. doi: 10.1136/annrheumdis-2018-214016
4. Van Gool WA, Weinstein HC, Scheltens P, Walstra GJ. Effect of hydroxychloroquine on progression of dementia in early Alzheimer's disease: an 18-month randomised, double-blind, placebo-controlled study. *Lancet.* 2001;358:455-60.