

## **Benzodiazepine use and risk of Alzheimer's disease: case-control study**

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*BMJ* 2014

**Objectives** To investigate the relation between the risk of Alzheimer's disease and exposure to benzodiazepines started at least five years before, considering both the dose-response relation and prodromes (anxiety, depression, insomnia) possibly linked with treatment.

**Design** Case-control study.

**Setting** The Quebec health insurance program database (RAMQ).

**Participants** 1796 people with a first diagnosis of Alzheimer's disease and followed up for at least six years before were matched with 7184 controls on sex, age group, and duration of follow-up. Both groups were randomly sampled from older people (age >66) living in the community in 2000-09.

**Main outcome measure** The association between Alzheimer's disease and benzodiazepine use started at least five years before diagnosis was assessed by using multivariable conditional logistic regression. Ever exposure to benzodiazepines was first considered and then categorised according to the cumulative dose expressed as prescribed daily doses (1-90, 91-180, >180) and the drug elimination half life.

**Results** Benzodiazepine ever use was associated with an increased risk of Alzheimer's disease (adjusted odds ratio 1.51, 95% confidence interval 1.36 to 1.69; further adjustment on anxiety, depression, and insomnia did not markedly alter this result: 1.43, 1.28 to 1.60). No association was found for a cumulative dose <91 prescribed daily doses. The strength of association increased with exposure density (1.32 (1.01 to 1.74) for 91-180 prescribed daily doses and 1.84 (1.62 to 2.08) for >180 prescribed daily doses) and with the drug half life (1.43 (1.27 to 1.61) for short acting drugs and 1.70 (1.46 to 1.98) for long acting ones).

**Conclusion** Benzodiazepine use is associated with an increased risk of Alzheimer's disease. The stronger association observed for long term exposures reinforces the suspicion of a possible direct association, even if benzodiazepine use might also be an early marker of a condition associated with an increased risk of dementia. Unwarranted long term use of these drugs should be considered as a public health concern.