

**Benzodiazepine use and risk of Alzheimer's disease: case-control study.**  
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**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 a public health concern.*

### **Abstract**

**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:** 1,796 people with a first diagnosis of Alzheimer's disease and followed up for at least six years beforehand were matched with 7,184 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:** The association between Alzheimer's disease and benzodiazepine use started at least five years before diagnosis was assessed with multivariable conditional logistic regression. Ever-exposure (at least one use during defined time) to benzodiazepines was first considered and then categorized 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 linked with an increased risk of dementia. Unwarranted long term use of these drugs should be considered a public health concern.