

**Association between metformin use and the subsequent incidence of Alzheimer's disease in patients with newly diagnosed type 2 diabetes: A population-based nested case-control study**

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## ***Abstract***

### **Objective**

To explore the risk of Alzheimer's disease (AD) in patients with type 2 diabetes mellitus (DM) who were treated with metformin.

### **Design**

Nested case-control study

### **Setting**

Population-based DM cohort in Korea (2002–2017)

### **Participants**

Among 70,499 newly diagnosed DM patients who were dementia-free at the time of DM diagnosis between 2004 and 2012 registered in the Korean National Health Insurance Service database, 1,642 AD cases were identified and matched to 8,210 controls based on age, sex, and the onset and duration of DM.

### **Main outcome measure**

The adjusted odds ratios (AOR) and 95% confidence intervals (CI) for the association of AD with metformin use were analyzed by multivariable conditional logistic regression analyses that were adjusted for comorbidities and the cardiometabolic risk profile.

### **Results**

Metformin use was significantly associated with increased odds of AD (AOR, 1.59; 95% CI, 1.30 to 1.95). The strength of the association increased with the cumulative daily defined dose per day in metformin users. The risk was greater in patients with a longer duration of DM (1.50; 95% CI, 1.15 to 1.95, for a DM duration of 5–9 years; 2.23; 95% CI, 1.43 to 3.48 for a duration greater than 10 years). Furthermore, the risk of AD was significantly higher in patients with depression (2.63; 95% CI, 1.25 to 5.55).

### **Conclusion**

Metformin use is associated with an increased risk of AD. The risk was more pronounced among patients with a longer duration of DM and those with depression. Given the large number of DM patients who are taking metformin, a double-blinded, large-scale, prospective study is needed to investigate the long-term cognitive safety of metformin.

