

## Higher daily glucose variability is associated with worse cognitive performance – The Maastricht Study

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**Background:** Type 2 diabetes is associated with an increased risk of Alzheimer's disease and vascular dementia. A better understanding of the drivers of diabetes-associated cognitive decline may provide entry points for preventive measures; daily glucose variability (GV) may be such a modifiable risk factor. We, therefore, investigated whether daily GV, assessed by continuous glucose monitoring (CGM) or oral glucose tolerance test (OGTT), is associated with cognitive performance.

**Methods:** We used cross-sectional data from The Maastricht Study, a population-based cohort enriched with type 2 diabetes. We calculated standard deviation, coefficient of variation, and time in range (TIR) in participants with >48h of CGM data (n=853), and calculated the recently validated incremental glucose peak (IGP; peak minus fasting glucose value) in participants with complete seven-point OGTT data (n=3,586). The associations of these GV indices with overall cognitive performance and individual cognitive domains (i.e., memory function, information processing speed, and executive function and attention [EFA]) were examined by use of multiple linear regression.

**Results:** Higher IGP was associated with worse overall cognitive performance, irrespective of demographics, cardiovascular risk factors, and lifestyle factors. The effect size (regression coefficient per 1mmol/L IGP [95%CI]: -0.017 [-0.028; -0.006], p=0.002) corresponded with 4 months of normal ageing. This association remained statistically significant after further adjustment for HbA<sub>1c</sub> or fasting plasma glucose. Of the individual cognitive domains, IGP was most strongly associated with EFA. This was consistent with our findings on CGM-measured indices, although only TIR was independently associated with EFA (regression coefficient per 10% TIR: 0.053 [0.001; 0.105], p=0.044).

**Conclusion:** Our results show that daily GV is an independent, clinically relevant determinant of worse cognitive performance. Future studies should explore whether therapeutic interventions that specifically target daily GV can delay or prevent cognitive decline.