A synergistic association of diabetes and AD biomarkers on cognitive decline in persons without dementia?

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Background. To improve prognostic assessment, we aimed to explore whether diabetes mellitus and Alzheimer's disease (AD) biomarkers are synergistically associated with cognitive decline in persons without dementia.

Methods. We included 1.737 persons with normal cognition (NC) and 634 with mild cognitive impairment (MCI) from 8 European memory clinic and aging cohorts as part of the PRIME project. We examined cognitive decline in MMSE (raw scores), memory (delayed recall), attention, executive functioning, and language domains (Z-scores). AD biomarkers included CSF amyloid-beta42 (data-driven cut-offs) or amyloid PET (center-specific cut-offs) as measure of amyloid positivity, CSF p-tau as measure of tau tangle positivity and CSF t-tau as measure of neurodegeneration (both center-specific cut-offs). We performed generalized linear mixed models with random intercepts and slopes, all adjusted for demographics.

Results. Mean age was 65.9 (SD=8.9) years, 54% were women, and diabetes was diagnosed in 7% of NC and 12% of MCI. Mean follow-up time was 1.8 years (range 0.5-8).

In NC, we found decline in memory and attention in persons with both diabetes and t-tau positivity. This was not shown in persons with only diabetes or only t-tau positivity. We also found this interaction between diabetes and p-tau on attention decline. When stratifying for amyloid status, we found that this was only significant in amyloid negative individuals (memory t-tau: p=0.005, attention p-tau: p=0.033, attention t-tau: p=0.039). A higher baseline language performance was found in persons with both diabetes and p-tau or t-tau positivity (p=0.011; p=0.034) compared to those with only diabetes or tau positivity. We found steeper decline in language in persons with both diabetes and amyloid positivity, compared to other groups. A similar synergism with diabetes was found for p-tau. No interaction was found for executive functioning.
In persons with MCI with both diabetes and t-tau positivity, we found higher baseline MMSE scores (p=0.041) compared to other groups. Diabetes was not associated with cognitive decline in any domain in MCI.

Conclusion. Diabetes may affect non-AD-related decline in memory and attention as well as AD-related decline in language at an early clinical stage. This may help improve prognostic procedures.