Type 2 Diabetes, Glycemia, and Brain Health: The Complexity of Causality

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For several years, based on several large-scale cohort and twin studies of people well into older age, type 2 diabetes has been recognized to be strongly associated with a two-fold increase in the risk of a "new" or incident dementia (1). The causality of this association and putative underlying pathways still remain uncertain.

Several features such as hyperglycemia, insulin resistance, inflammation, and vascular endothelial dysfunction could theoretically mediate a causal link between type 2 diabetes and dementia (2), and their putative effects may also be influenced by several modifiers (Fig. 1). It is plausible that these pathways could lead to brain injury indirectly via cerebrovascular disease, or by directly affecting the neurons (gray matter) and their connections (white matter), or both. The attractiveness of this overall causal hypothesis lies in the potential to find targeted interventions to reduce the risk of future dementia. Thus, it is important to generate strong evidence either supporting or disproving causality in the associations of type 2 diabetes and its related features with measures of brain health.

In their article in this issue of *Diabetes*, Garfield et al. (3) attempt to further clarify causality in the relationship of type 2 diabetes (and specifically its primary feature glycemia) with indicators of dementia risk (cognitive function, brain MRI) and a diagnosis of Alzheimer dementia (AD). They adopted Mendelian randomization to tackle confounding and reverse causation, which are hard to avoid in traditional cohort studies. They used the rich data collected on a large scale in the UK Biobank, a population-based study of adults at midlife (n = 349,326, aged 40–69 years), with a diabetes prevalence of ∼4% (n = 14,010) and relatively well-controlled HbA_{1c} (mean 35.5 mmol/mol, ∼5.5%). They used available outcome data in specific cognitive functions (reaction time, visual memory in all participants), brain MRI (hippocampal volume and white matter hyperintensity volume in ∼32,000 participants), and primary care recording of AD based on ICD-10 codes (746 participants). Exposures of interest were 157 independent genetic variants for diabetes explaining ∼1.5% of the sample variance in people with diabetes, and 51 single nucleotide polymorphisms for HbA_{1c} explaining 2.8% of the sample variance in HbA_{1c}. In addition, they examined reverse directionality of relationships between 43 single nucleotide polymorphisms related to reaction time and diabetes/HbA_{1c}. Their primary results showed no forward associations of either diabetes or HbA_{1c} with reaction time, visual memory, hippocampal and white matter hyperintensity volumes, and AD diagnosis. There was also no evidence for a reverse directional association between reaction time and either diabetes or HbA_{1c}. They concluded a lack of evidence to support causality of the relationships of diabetes and glycemia with the outcome measures that they used.

The conclusions should be viewed in light of certain limitations relating to the sample and measurement, and the authors acknowledge some of these in the article. Overall prevalence of diabetes in the sample was low, and with low variation in peripheral glycemia. Peripheral glycemia itself may not capture the phenomenon of brain insulin resistance. The range of cognitive tests used was small and may have lacked sufficient sensitivity to capture variation in a relatively young sample such as that in the UK Biobank. The use of more sensitive imaging markers for dementia in this scenario is therefore important. Although the authors used hippocampal volume and white matter hyperintensity volumes as reasonable intermediate measures of dementia, these measures may also be relatively insensitive in middle age. Changes in brain macrostructure are likely to become evident with impact in late old age,

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COMMENTARY
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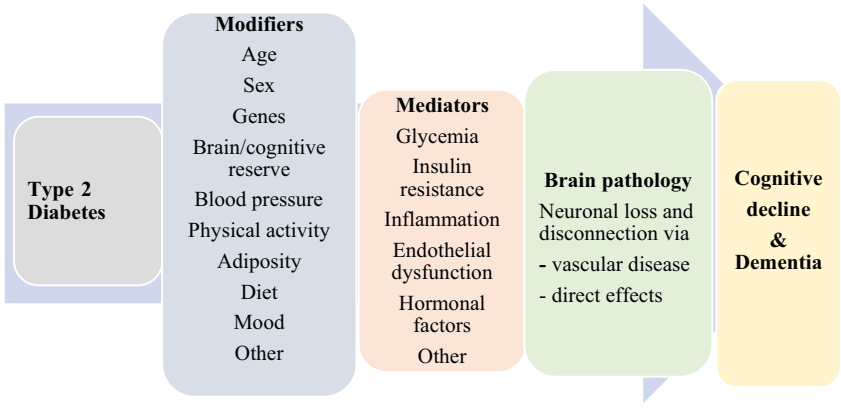

Figure 1—Potential causal pathways linking type 2 diabetes to dementia.

with brain amyloid or tau accumulation beginning earlier, and changes in white matter microstructure and brain metabolism potentially even earlier (4). Imaging modalities such as diffusion MRI, functional MRI, and positron emission tomography may be more valuable at such earlier ages (4). For example, in late middle-aged twins discordant for type 2 diabetes, substantial differences in functional MRI were found in the absence of measurable differences in several measures of cognitive tests or brain structure (5). Cognitive decline could also not be captured in the current study, as sufficient longitudinal cognitive data were not available. Finally, diagnostic accuracy of a specific diagnosis of AD is at best moderate for data reported from primary care, death records, and self-report, but somewhat better for all-cause dementia (6). The relationship between type 2 diabetes and neurodegeneration has been shown to be less likely related to amyloid-related pathways (considered essential for AD pathology) than with tau-related pathways (more nonspecific and related to multiple neurological disease processes) (7). Thus, it may have been interesting to see how the results of the study would have been affected by using a more general diagnosis of all-cause dementia to capture the broad impact of diabetes and glycemia gene variants, as has been demonstrated recently (8).

While this new Mendelian randomization study adds to the puzzle of causality in this field, it should also be viewed in context of an important issue complicating the understanding of dementia. Dementia is characterized by the presence of several cerebral pathologies that cumulatively result in neurodegeneration and expression of cognitive symptoms (9), with multiple direct or indirect causal mechanisms, each with small individual effects, acting or interacting at various stages of life, and modified by protective factors such as brain or cognitive reserve from early life (10). This may explain the paucity of evidence for cognitive benefit from trials in people with diabetes for individual targets such as glycemia (11) or blood pressure (12). It is also possible that a direct causal link does not exist between type 2 diabetes or dementia, and if this were the case, one could speculate on why there is such a consistent association between the two syndromes. The effect of diabetes may be indirect, for example, by leading to brain infarcts, which are known to lower the threshold for clinical expression of dementia (13). It is also possible that the two syndromes are merely more likely to coexist over the life span and that their association can be explained by unmeasured confounding, but this is best clarified using life-course approaches such as in birth cohorts. Nevertheless, future studies at earlier stages of life may benefit greatly from technologies that assist in the highly sensitive measurement of exposures (e.g., continuous glucose monitoring), outcomes (e.g., brain metabolism and function), and modifiers (e.g., functional imaging measures of brain reserve) while dynamically manipulating exposure states such as glycemia. Such studies would allow us to get closer to an understanding of the brain's response to diabetes-related insults and to developing ways to protect it.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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