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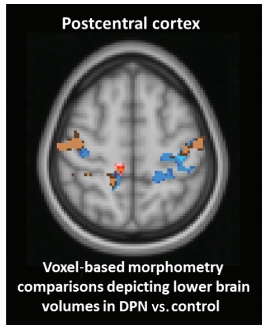
Diabetes Care®

In This Issue of *Diabetes Care*

By Max Bingham, PhD

Structural Brain Alterations Are Present in Diabetic Peripheral Neuropathy

Diabetic peripheral neuropathy (DPN) appears to be characterized by significant structural alterations in key brain regions, according to Selvarajah et al. (**p. 777**). In particular, the changes involve the somatomotor and nociceptive brain regions and are specific to whether DPN is pain-free or painful and, in this case, whether there is an irritable nociceptor phenotype or nonirritable nociceptor phenotype present. The findings come from a cross-sectional observational cohort study of 277 participants with type 1 and 2 diabetes. Fifty-seven had no DPN, 77 had painless DPN, and 77 had painful DPN. Sixty-six healthy volunteers were also included in the study. All participants then had magnetic resonance brain imaging and a series of clinical and neurophysiological assessments. They found that participants with any type of DPN (i.e., painful or painless) had significant reductions in ventrobasal thalamic nuclei volume and somatosensory/motor cortical thickness compared with controls. Somatosensory cortical thickness also correlated with measures of DPN severity. Specifically for participants with painful DPN, they found that compared with an irritable nociceptor phenotype, a nonirritable nociceptor phenotype was associated with reduced volumes of a series of brain areas. Commenting more widely, author Dinesh Selvarajah said, "In the largest neuroimaging study to date, we highlight the structural changes within the central nervous system associated with peripheral nerve damage in diabetes. We also demonstrate how these brain changes relate to the different phenotypes of clinical neuropathy seen in patients with diabetes. This is important because how the brain adapts (structural and functional neuroplasticity) to nerve injury may explain why some people report painful symptoms and others have numbness or loss of sensation. Our findings provide new mechanistic insights into the pathogenesis of diabetic neuropathy that have only been made possible by advances in magnetic resonance brain imaging. This opens up a whole new area for further research."

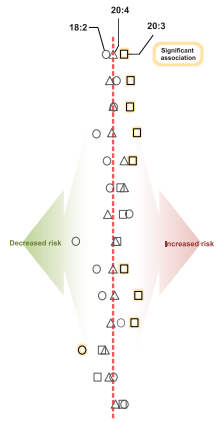


Brain alterations in key somatosensory and nociceptive regions in DPN.

Selvarajah et al. Structural brain alterations in key somatosensory and nociceptive regions in diabetic peripheral neuropathy. Diabetes Care 2023;46:777–785

Three Main Polyunsaturated Fatty Acids Are Differentially Associated With Type 2 Diabetes Risk

Polyunsaturated fatty acids (PUFAs) appear to be differentially associated with type 2 diabetes risk depending upon the type of lipid class they are found in, according to Prada et al. (**p. 836**). In addition, increased activity of delta-5 desaturase (D5D) (a key enzyme involved in PUFA conversion) was associated with reduced diabetes risk but only when present in specific lipid classes. According to the authors, the association between the different PUFAs across different lipid classes and diabetes risk has not been investigated systematically. The findings, they suggest, should provide new insights into their role in diet and metabolism and perhaps illustrate that reduced risk for diabetes associated with plasma PUFAs is not universal. The authors based their investigation on more than 26,000 individuals from the prospective European Prospective Investigation Into Cancer and Nutrition (EPIC)-Potsdam cohort. Roughly 500 were diagnosed with type 2 diabetes over a follow-up of ~6.5 years. They then established plasma levels of linoleic, dihomo-γ-linolenic, and arachidonic acids across 12 lipid classes and subclasses and a randomly drawn sample of the cohort (~1,100 participants) and evaluated their likely associations with diabetes risk. After establishing the heterogenous distribution of the fatty acids across lipid classes, they found that higher concentrations of linoleic acid were inversely associated with diabetes risk, particularly when present in lysophosphatidylcholine and monoacylglycerol classes. In contrast, higher concentrations of dihomo-γ-linolenic acid in various phospholipid, free fatty acid, and cholesteryl ester classes were associated with higher type 2 diabetes incidence. Arachidonic acid had no association with diabetes risk. While they identified reduced diabetes risk with increased D5D activity in some lipid classes, they also found that single nucleotide polymorphisms that encoded the enzyme explained relatively large variations in D5D activity in those classes. Commenting further, author Matthias B. Schulze said, "Our study indicates that a reduced D5D activity leads to the accumulation of dihomo-γ-linolenic acid in a variety of plasma lipids, which is related to increases type 2 diabetes risk."



Representative risk levels for diabetes development according to plasma levels of n-6 PUFAs (18:2, dihomo-γ-linoleic acid; 20:3, α-linolenic acid; 20:4, arachidonic acid).

Prada et al. Plasma lipidomic n-6 polyunsaturated fatty acids and type 2 diabetes risk in the EPIC-Potsdam prospective cohort study. Diabetes Care 2023;46:836–844

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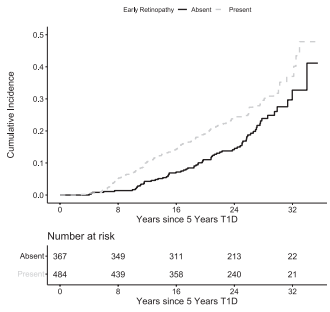
Risk for Severe Diabetic Retinopathy Is Increased With Initial Diagnosis Within First 5 Years of Type 1 Diabetes

Individuals with type 1 diabetes and any sign of retinopathy within 5 years of diagnosis appear to be at higher risk of developing more advanced diabetic retinopathy (DR) later in life, according to Malone et al. (**p. 680**). As a result, they suggest that the identification of DR at early stages should help guide therapy to reduce any potential risk of future vision loss. The findings come from further analysis of the Diabetes Control and Complications Trial (DCCT)-Epidemiology of Diabetes Interventions and Complications (EDIC) studies and specifically standardized fundus photography that looked for evidence of eye microvascular abnormalities in the context of type 1 diabetes. The longitudinal assessment used examinations at 6-month to 4-year intervals, with early-onset DR defined as onset prior to 5 years of type 1 diabetes duration. Before adjustment, they found that compared with individuals without early-onset DR ($n = 369$), those with it ($n = 484$) had increased later risks for proliferative DR, macular edema, and diabetes-related therapy. After full adjustment for a range of factors, including HbA_{1c}, only the association with proliferative DR remained significant, with a hazard ratio of 1.47 (95% CI 1.04–2.06, $P = 0.028$). Given the similarities in HbA_{1c} levels between the two groups, the authors suggest that the differences in risk and severity of DR are due to factors other than glycemia and include metabolic and genetic factors. While the analysis uses standardized data collected longitudinally over ~30 years, the authors also caution that the cohort used was largely White, meaning generalizability to other racial and ethnic backgrounds is limited, a reason (among many) for further investigation. Based on the findings, the authors propose that higher-risk patients are missed with current guidelines that recommend an initial examination within 5 years of type 1 diabetes diagnosis rather than annually.

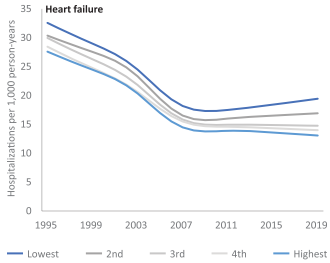


Cumulative incidence of proliferative DR according to early DR development (dotted line) and no early DR development (black). T1D, type 1 diabetes.

Malone et al. Retinopathy during the first 5 years of type 1 diabetes and subsequent risk of advanced retinopathy. Diabetes Care 2023;46:680–686

Cardiovascular Disease Rates in Individuals With Diabetes Have Fallen but Not for Those With Low Incomes

Overall hospitalization rates for a range of cardiovascular diseases among individuals with diabetes appear to have fallen between 1995 and 2019 in Ontario, Canada, according to Shah et al. (**p. 751**). However, the fall in rates largely stalled in the last decade, with the overall rate masking increasing rates for individuals with lower incomes. Using data from the entire population of Ontario with diagnosed diabetes (~1.7 million individuals), the authors calculated rates of hospitalizations for acute myocardial infarction, stroke, heart failure, and lower-extremity amputation in annual cohorts. They found that hospitalization rates for acute myocardial infarction fell over the entire study period such that in 2019 it was less than half that of 1995. Rates for stroke, heart failure, and amputations also fell but, in all cases, largely stabilized in the last decade of the study period. They also found that male individuals with diabetes had higher risks for myocardial function and amputation than female individuals. As expected, there was also an age-related gradient in cardiovascular disease risk. Stratification by income, however, revealed a growing disparity in that higher-income individuals had decreasing rates for all outcomes throughout the 2010s while lower-income individuals experienced the opposite. The design of the study precludes the assignment of any causality behind the trends, with the authors suggesting that the income-related disparity warrants further investigation. They go on to discuss many of the possible reasons for the disparity, suggesting that the 2008 global financial crisis, higher prevalence of risk factors, and the introduction of expensive new diabetes drugs are possible reasons for the worse outcomes in lower-income groups. "Our article highlights that not everyone is benefiting from the continuing improvements in diabetes care," said author Baiju R. Shah. "Even in a universal publicly funded health care system such as Canada's, lower-income individuals are actually doing worse now than they were 10 years ago. We hope that this study will alert clinicians and policymakers to the need for solutions to improve care for these highest-risk patients."



Rates of hospitalization for heart failure among people with diagnosed diabetes in 1995–2019 in Ontario, Canada, stratified by income.

Shah et al. Growing income-related disparities in cardiovascular hospitalizations among people with diabetes, 1995–2019: a population-based study. Diabetes Care 2023;46:751–756

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