In This Issue of *Diabetes Care*

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Inverse Association Between Diabetic Retinopathy and Cognition Warrants Further Investigation

Cross-sectional data in this month's issue of *Diabetes Care* appear to conflict with previous research suggesting a link between diabetic retinopathy (DR) and cognitive impairment. Previous studies have focused on the idea that diabetic microvascular complications may be a useful marker for diabetes-associated cognitive decline or even Alzheimer disease. This link is plausible because the brain is a major consumer of glucose, and a causal relationship between elevated glucose and neurological damage in tissues other than the brain has been firmly established. Results from the new report by Crosby-Nwaobi et al. (**p. 3177**) do not support this concept. The cross-sectional study examined data from the South East London Diabetic Retinopathy Study and classified subjects as having either no/mild DR or proliferative DR (PDR). The ability to distinguish severity of DR is an advantage that the new report has over some previous studies that did not have data permitting this detailed assessment. Another feature of the study is that diabetes duration was about 9 years in each DR group, a feature that limited the impact that differences in diabetes duration had on the results. Investigators administered several cognition assessments and compared performance on these tests across the two DR groups. Results showed an inverse, cross-sectional association between severity of DR and cognitive impairment. While only 5% of the PDR group had results indicating severe cognitive impairment or dementia, 12% of those with no/mild DR fit this description. The authors point out that a number of factors should be considered when interpreting their results. These include the possibility that residual confounding associated with differences in education between the groups could have influenced the findings. They also highlight the fact that patients with PDR might have been sicker and more likely to have died prior to enrollment than their counterparts with less severe disease. Survival bias may therefore have impacted the makeup of the study sample in ways that ultimately impacted the distribution of cognitive function and its association with DR. A prospective study that includes detailed assessments of both retinopathy severity and cognitive function may pick up where this study leaves off and help provide clarity on these relationships. — *Helaine E. Resnick, PhD, MPH*

Crosby-Nwaobi et al. The relationship between diabetic retinopathy and cognitive impairment. Diabetes Care 2013;36:3177–3186

Metformin Does Not Confer Protection for Patients With Breast Cancer

Data in this month's issue of *Diabetes Care* are not consistent with recent observations suggesting that metformin reduces the incidence of breast cancer. A new report by Lega et al. (**p. 3018**) builds on recent findings suggesting that metformin may be associated with a 20–30% reduction in cancer incidence. The study sought to examine whether metformin use is associated with improved survival among women with newly diagnosed breast cancer. The findings are derived from a population-based study of women in Ontario, Canada, who were eligible for care under the province's universal health plan. The investigators identified all women who were diagnosed with diabetes after age 66 years—an approach that not only resulted in a case group that was homogenous for diabetes duration but also facilitated assessment of metformin exposure because all cases were eligible for pharmacy coverage under the Ontario Drug Benefit program. Diabetes was identified by linking participants to the provincial diabetes registry, and new breast cancer cases were identified from the Ontario Cancer Registry. Breast cancer cases were identified and followed from 1 April 1997 to 30 March 2010 or death, whichever came first. The authors used variables describing any use of metformin as well as cumulative use of metformin, and they examined both all-cause mortality and breast cancer–specific mortality. The results of this new report were not indicative of associations between any metformin exposure or cumulative metformin exposure and either all-cause or breast cancer mortality. Despite the lack of statistical significance, the investigators pointed out that hazard ratios suggested a 9%

decrease in breast cancer–specific mortality with each additional year of metformin use. However, the authors emphasize that they did not have access to clinical data such as BMI and cancer stage—information that may have impacted the association between metformin use and survival. Given the increased prevalence of diabetes in older women and the accompanying increases in metformin use, it is likely that there will be continued interest in understanding the potential antitumor effects of metformin. — *Helaine E. Resnick, PhD, MPH*

Lega et al. Association between metformin therapy and mortality after breast cancer: a population-based study. Diabetes Care 2013;36:3018–3026

Sleep-Disordered Breathing Proposed as GDM Risk Factor

A report in this issue of *Diabetes Care* supports an independent role for sleep-disordered breathing (SDB) in risk of gestational diabetes mellitus (GDM). A meta-analysis by Luque-Fernandez et al. (**p. 3353**) examined data from nine studies containing data for nearly 10,000 nondiabetic pregnant women. These women also had data on habitual snoring or more detailed information on apnea-hypopnea index derived from overnight sleep monitoring. Some of the studies included in the new meta-analysis also considered BMI as a potential confounder of the association between SDB and GDM. Considering the nine studies together, the authors found that the summary odds ratio (OR) relating SDB to GDM was 2.18, an association that was statistically significant. Among the six studies that considered the role of BMI, the summary OR increased to 3.06 and was also significant. In an effort to understand how differences in methods used to assess SDB might impact results, ORs were also calculated separately for studies that used self-reported habitual snoring as a proxy for SDB and those that collected objective SDB measurements using sleep monitors. The association between habitual snoring and GDM yielded an OR of 2.45 and was significant, while the corresponding OR for SDB measured by overnight monitoring was 1.79 and did not reach statistical significance. The findings of this new report suggest a role for SDB in risk of GDM and that pregnant women with higher BMIs may be at particularly high risk. The authors suggest that consideration should be given to the potential benefits of assessing SDB during pregnancy. — *Helaine E. Resnick, PhD, MPH*

Luque-Fernandez et al. Sleep-disordered breathing and gestational diabetes mellitus: a meta-analysis of 9,795 participants enrolled in epidemiological observational studies. Diabetes Care 2013;36:3353–3360

Equivocal Results on Relationship Between Antidepressant Medications and Diabetes Risk

A systematic review in this issue of *Diabetes Care* (**p. 3337**) may raise as many questions as it answers regarding the relationship between use of antidepressant medications and the risk of developing diabetes. Marked increases in use of antidepressants have raised concerns about the potential effect of these drugs on glucose regulation. Although some antidepressant medications result in weight gain and may increase diabetes risk through this pathway, it is also possible that antidepressants may be prescribed more frequently for individuals who, as a group, are at increased diabetes risk independently of their use of these medications. These complex issues are in play against the backdrop of a profound increase in obesity that has occurred simultaneously with increases in prescribing of antidepressant medications. An additional consideration in understanding whether these medications impact glucose regulation is that different classes of antidepressants may be associated with different levels of diabetes risk. This intricate landscape creates significant challenges for identifying and quantifying the diabetes risk that is attributable specifically to use of these medications. It is therefore not surprising that the systematic review in this issue of the journal presents what the authors describe as a "confused" picture in which associations—but not causal ones—between antidepressant use and diabetes are highlighted. The new review, which is based on findings from 3 previous reviews and 22 studies, indicates that while some reports have linked antidepressants to worse glycemic control, others suggest improved control. The authors emphasize that the studies included in their analysis were of variable quality and that methodological heterogeneity across the studies—such as different definitions of diabetes and residual confounding—may impact interpretation of their data. Nonetheless, they highlight the observation that higher-quality studies tended to yield stronger evidence and that in some instances a gradient effect appeared to be present. Caution is advised regarding the potential link between antidepressants and diabetes until data from large, well-designed prospective studies are available. — *Helaine E. Resnick, PhD, MPH*

Barnard et al. Antidepressant medication as a risk factor for type 2 diabetes and impaired glucose regulation: systematic review. Diabetes Care 2013;36:3337–3345

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