

# Severe Hypoglycemia May Raise Dementia Risk

BY MIRIAM E. TUCKER

WASHINGTON — A history of severe hypoglycemic episodes was associated with an increased risk for dementia in a longitudinal cohort study involving 16,667 older patients with type 2 diabetes.

“Severe hypoglycemic episodes might be associated with a neurological consequence in a population that is already at

greater risk for dementia. ...This study also adds to the evidence base that balance of glycemic control is a critical issue, particularly for the elderly,” Rachel A. Whitmer, Ph.D., said at a press briefing. The briefing was timed to coincide with publication of the April 15th special diabetes edition of the *Journal of the American Medical Association*.

The study, which retrospectively analyzed data from the Kaiser Permanente

Northern California Diabetes Registry, identified a 2.39% increase in absolute risk of dementia per year of follow-up for patients with a history of hypoglycemia that resulted in hospitalization or an emergency department visit, compared with type 2 diabetic patients without such a history.

“Trying to aim for a very low glycemic target might not be beneficial and might even be harmful. We know that high

blood sugar isn't good, but I think the message here is also that very low levels aren't good,” added Dr. Whitmer of Kaiser Permanente's division of research.

Because the data analyses included two methods by which the hypoglycemia events were separated in time from the onset of dementia, the study supports the direction of causality that the hypoglycemia preceded the dementia, rather than the other way around. Moreover, “Our findings were independent of glycemic control as assessed by levels of [hemoglobin A<sub>1c</sub>], type of diabetes treatment, and diabetes comorbidities,” wrote Dr. Whitmer and her associates in the published report (*JAMA* 2009;301:1565-72).

The patients were all aged 55 or older on Jan. 1, 2003, with no signs of dementia at that time. A total of 11% (1,822) patients were diagnosed with dementia during a mean follow-up of 3.8 years and a median follow-up of 4.8 years, and a total of 8.8% (1,465) had at least one episode of severe hypoglycemia during 1980-2002. Of those 1,465, 68.5% had one such episode, 1% had two, and 13.5% had three or more.

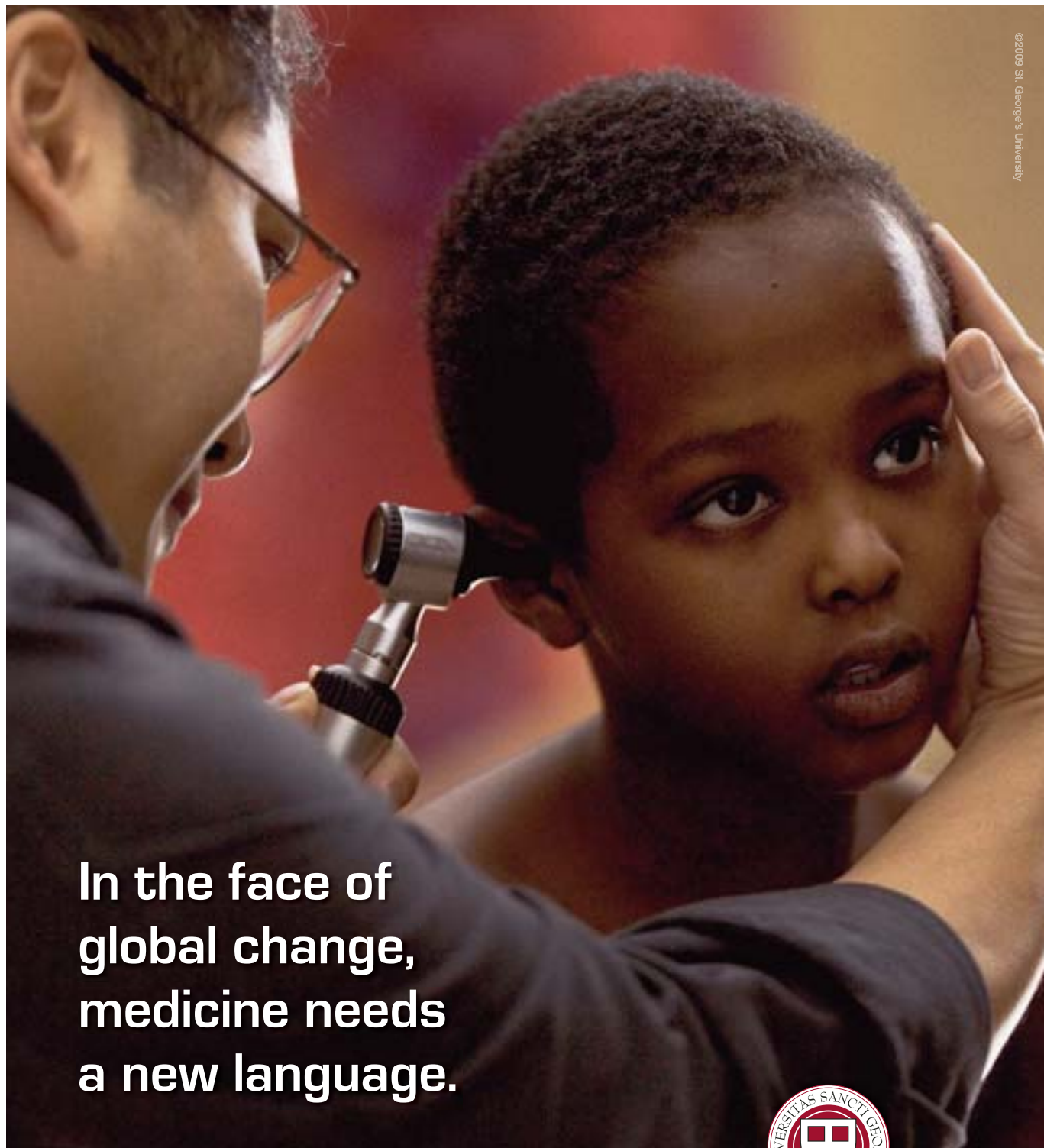
Age-adjusted incidence of dementia by frequency of severe hypoglycemic episodes was significantly higher among those with at least one episode, compared with those with no such episodes (566.8 vs. 327.6 per 10,000 person-years), with an attributable risk of 2.4% per year.

After adjustment for age, body mass index, race/ethnicity, education, sex, and diabetes duration, the hazard ratios for dementia compared with patients who had no severe hypoglycemic episodes were 1.7 for those with at least one episode, 2.2 for two or more, and 2.6 for three or more episodes. Further adjustment for diabetes-related comorbidity, HbA<sub>1c</sub> level, diabetes treatment, and years of insulin use modestly attenuated the effect but it remained “statistically significant and clinically relevant” with hazard ratios of 1.3, 1.8, and 1.9, respectively, Dr. Whitmer and her associates said.

Trends were similar when only the incident dementia cases diagnosed between Jan. 1, 2005, and Jan. 15, 2007, were considered after adjustment for all the above-mentioned factors, with hazard ratios of 1.2 for at least one severe hypoglycemia episode, 1.7 for two or more episodes, and 2.1 for three or more episodes, compared with patients who had no such episodes.

Possible mechanisms by which hypoglycemia might increase the risk of subsequent dementia in older individuals include neuronal death and/or increased platelet aggregation/fibrinogen formation. Cerebrovascular disease is another possibility, even though another analysis adjusting for acute stroke and transient cerebral ischemia in this study population did not fully account for the effect of hypoglycemia, the investigators noted.

This study was funded by the National Institutes of Health. None of the investigators disclosed any conflicts of interest. ■



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