Editors’ Note: Grabenhenrich and Roll critique the methodology and design in the study by Kerti et al. on the association between glucose metabolism and memory performance. The authors conduct additional statistical analysis to support their results. Neurology’s sometime neuromythologist and historian, William Landau, cites quotations from Parkinson’s historical monograph to comment on the article by Bohnen et al. on gait speed in Parkinson disease. The authors respond.

—Chafic Karam, MD, and Robert C. Griggs, MD

HIGHER GLUCOSE LEVELS ASSOCIATED WITH LOWER MEMORY AND REDUCED HIPPOCAMPAL MICROSTRUCTURE

Linus B. Grabenhenrich, Stephanie Roll, Berlin: Kerti et al. attempted to establish an association between glucose metabolism and memory performance. They concluded that higher blood glucose levels negatively influenced cognition. We believe that the design and methodology is inadequate to draw these conclusions.

The bivariate approaches do not consider that confounding factors might be related to both glucose metabolism and memory (e.g., age). The hippocampus as a potential mediator is stated to lose significance upon adjustment for even the most basic confounders. Presenting raw and adjusted models would allow the assessment of the role of confounders.

In addition, we could not interpret the standardized regression coefficients for sex as a dichotomous trait. Measures of precision (e.g., confidence intervals [CIs]) for associations were not reported. To translate the authors’ results to real-world quantities, we do not see how to use many significant test results without adjustment for multiple testing. We were not able to derive a meaningful adjusted measure of association between HbA1c and the presented memory tests.

The authors should provide a comprehensible magnitude adjusted for potential confounders, for example: “5 mmol/mol higher HbA1c levels were associated with an average of 1.5 (0.5–3.0) fewer words remembered in the delayed recall test.”

Author Response: Lucia Kerti, A. Veronica Witte, Ulrike Grittner, Agnes Floeel, Berlin: The authors thank Drs. Grabenhenrich and Roll for their comments. We reported significant associations of markers of glucose metabolism with memory performance in 141 older adults. In addition to bivariate analyses, we reported adjusted multiple regression models, which were controlled for confounding factors including age and sex using a stepwise selection method.

We have conducted alternative models using the “enter” method for age and sex variables and obtained similar results to those we reported, thus supporting our original conclusions. HbA1c remained significantly associated with the primary outcome (delayed recall) and the other 2 subtests of memory performance (p < 0.05). If a Bonferroni correction for multiple testing is applied, the associations between HbA1c and delayed recall and between HbA1c and learning ability remained significant. According to the regression model, a difference in HbA1c levels of 5 mmol/mol was associated with a reduction of 1.4 remembered words (95% CI 0.4–2.3) in the delayed recall task.

In our study, we outlined strengths and weaknesses of a cross-sectional design and highlighted the necessity of future longitudinal trials. A recent epidemiologic survey of glucose levels and dementia revealed that higher glucose levels may be a risk factor for dementia, even in those without diabetes.

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GAIT SPEED IN PARKINSON DISEASE CORRELATES WITH CHOLINERGIC DEGENERATION

William M. Landau, St. Louis: The authors of the article concerning gait speed in Parkinson disease (PD) seem to be unaware of a pertinent earlier clinical observation. Further quotations from that text:

As the malady proceeds the propensity to lean forward becomes invincible, and the patient is thereby forced to step on the toes and the forepart of the feet, whilst the upper part of the body is thrown so far forward as to render it difficult to avoid falling on the face. In some cases, when this state of the malady is attained, the
The patient can no longer exercise himself by walking in his usual manner, but is thrown on the toes and forepart of the feet; being at the same time, irresistibly impelled to take much quicker and shorter steps, and thereby to adopt unwillingly a running pace. In some cases it is found necessary entirely to substitute running for walking; since otherwise the patient, on proceeding only a very few paces, would inevitably fall...I think this symptom cannot be more fitly named than hastening or hurrying Scelotyrbe (Scelotyrbem festinantem, seu festiniam).

The time course of pathologic change is also pertinent.  

Author Response: Nicolaas I. Bohnen, Vikas Kotagal, Roger Albin, Martijn Muller, Ann Arbor, MI: The authors thank Dr. Landau for his comments. The passage cited from Parkinson’s historic monograph represents the earliest description of gait festination, a syndrome-specific finding seen most commonly in advanced PD.  

Our cohort consisted primarily of subjects in Hoehn & Yahr stages 1–3 (99.2%) who did not manifest significant festination at the time of study. Unlike festination, slowing of gait speed can be seen even in de novo and early PD, which likely reflects early impairments of multisystem neuronal compensatory mechanisms, and appears to signal the presence of cortical cholinergic terminal loss superimposed upon nigrostriatal dopaminergic denervation. Progressive stooping and postural impairments, seen commonly in more severe stages of PD, are likely significant contributors to festinating gait. Although more rapid sequencing of increasingly shorter steps with festination will result in higher cadence, overall gait speed may still slow.

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Gait speed in Parkinson disease correlates with cholinergic degeneration
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