Risk of mild cognitive impairment

The Olmsted County MCI Risk Score

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Early identification of disease—the earlier the better—is axiomatic in clinical practice and is key for preventing irreversible pathogenesis. This is particularly true for mild cognitive impairment (MCI), which may ultimately presage dementia.

In this issue of *Neurology*®, Pankratz et al.[1] describe development of a risk model for the progression to MCI from unimpaired cognitive performance. Using assays available in a typical clinical setting, they derived a risk score that identifies likely MCI in patients who might benefit from more invasive or more expensive diagnostic assays.

Risk scores in medical practice are useful tools for identifying—perhaps confirming—an individual patient's likely prognosis. These tools are imperfect and are rarely 100% accurate. Their utility is in summarizing in a single index clinicians' judgments that identify disease or the chance that preclinical conditions might become clinical diagnoses. The Framingham[2] risk score is perhaps the best known, although there are others for heart disease and other conditions. Over the past decade, much work has demonstrated the validity of risk scores in various demographic groups, particularly for cardiovascular conditions.[3,4]

Pankratz et al. used methods different from Framingham, reflecting contemporary medical statistics and the authors' sophistication. Although their sampling and statistical techniques are important for the credibility of their study, a deep understanding of the methods is not required to understand its implications.

Pankratz et al. recruited 70- to 89-year-old participants who were free of MCI and dementia, residing in Olmsted County, home of the Mayo Clinic. At initial and 15-month follow-up visits, they examined participants' clinical and neuropsychological status. They assigned follow-up diagnoses of MCI using established criteria such as impaired neuropsychological performance or concerns about cognitive deficits from self-reports or informants. They diagnosed dementia using *DSM-IV* criteria.

Pankratz et al. created 3 risk models starting with a basic model that included demographics and clinical measures such as body mass index, history of diabetes, and family history of dementia. In their second model, they added measures usually obtained in clinical and neurologic examinations such as gait, self- and informant-ratings on the Clinical Dementia Rating scale, and Hachinski score. In their third model, they added *APOE* genotype, not usually assessed in office examinations.

We build sequential models to examine prediction accuracy improvement after adding more predictors. It is counterintuitive: accuracy is not guaranteed to improve when there are more predictors, even though measurement error declines. Of note, the authors examined consistency with a leave-one-out cross-validation by repeatedly recomputing the risk score omitting one participant. Regrettably, as the authors acknowledge, they lacked external validation data, which might have provided more convincing evidence for replicability, but perhaps at the cost of efficiency.[5]

Model fitting is complex and technical, and the authors apply some sophisticated techniques for selecting measures for risk prediction. Briefly, they used separate-sex hazards analyses to select measures likely to predict MCI. Hazards analyses are used infrequently for predicting outcomes. Instead, the authors applied a secondary technique, penalized regression, that identifies a small number of covariates from a larger set of candidates This is different from stepwise regression methods that are notorious for capitalizing on chance, most especially because penalized regression is likely to produce replicable results.[6] This technique reduces shrinkage, the tendency for regression models to fit new data more poorly than the data from which they were derived.[7]

Pankratz et al. identified demographic and clinical measures for predicting MCI, 11 for women, 9 for men. They assigned point values for each measure, summed for a total risk score. The individual measures are unsurprising, but perhaps surprising is that this set of measures provides the best empirical prediction for MCI risk.

The point values provide a guide for relative priorities among modifiable factors. Diabetes before age 75

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has the largest, and preventing it should provide the greatest protection for future MCI. This is testable empirically, and provides a rich starting point for early prevention, as do some other modifiable factors such as alcohol problems, smoking in women, and body mass index in men.

In the "augmented clinical model," the authors identified risk factors that were previously revealed by many other groups. Age, cardiovascular risk factors, symptoms of depressive and anxiety disorders, and subjective and particularly objective memory impairment or functional impairment at baseline contribute most to the risk score.

Despite its status as the strongest genetic risk factor for developing Alzheimer disease dementia, *APOE* genotype was only moderately important when it was added to the model. It will be interesting to compare the risk factors identified in this sample with those from independent samples.

A population-based design is an important strength, but the results would be more convincing if the sample included participants who were other than Northern European ancestry, younger than 70 years, less educated, and had a broader range of comorbidities. Replications are facilitated by these results in which longitudinal data are required for follow-up status but unnecessary for follow-up diagnoses.

For medical practice, this risk score provides a tool with which to advise patients and relations about likely prognoses. For clinical research, this risk score may provide a simple and inexpensive way to identify at-risk candidates for primary prevention trials. Currently, clinicians are well advised to utilize the risk score with caution, particularly when applying it to less-educated persons with non-European origins. Various trials in other specialties demonstrated the utility of studying at-risk samples, most notably in coronary heart disease. Similar principles should apply to MCI and dementia.[8]

Pankratz et al. have shown considerable humility by neglecting to name their new risk index after their study, town, or clinic. With hopes that it will fulfill its initial promise, we renamed it for them.

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DISCLOSURE

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