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Dementia Risk Indices: A Framework for Identifying Individuals with a High Dementia Risk

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1. Introduction

There is growing consensus in the field of Alzheimer's disease (AD) research that it may be difficult to develop drugs that can reverse the neuronal damage caused by the disease once symptoms are severe enough to be diagnosable. Therefore, the goal has shifted toward identification of individuals earlier in the disease process, when symptoms are very mild, as well as identification of asymptomatic, high-risk individuals so that they can be targeted for prevention and early intervention.

In other fields, risk indices are often used to identify individuals who are asymptomatic but high-risk. Risk indices, also known as prognostic models, are tools that are used to predict the likelihood that an individual will experience a given event within a given time frame. Usually, this is accomplished by combining information from several different individual risk factors into a summary score. The prognostic accuracy of risk indices is typically assessed based on the area under the receiver operating characteristic (ROC) curve, also known as the *c* statistic [1]. The ROC curve is a graph of the true-positive rate (sensitivity) by the false-positive rate (1-specificity), and it is related to the relative probability that in all possible pairs of subjects in which one had the outcome and one didn't, the one with the outcome would receive a higher risk score. The *c* statistic may range from 0 to 1, with 0.5 reflecting predictive accuracy no better than chance and 1 reflecting perfect discrimination.

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The Framingham Heart Index is one of the most commonly used risk indices. It uses a combination of age, sex, blood pressure, cholesterol, and smoking status to identify individuals who are currently free of overt coronary heart disease but, based on their risk factor profile, have a high risk of experiencing a major coronary event within 10 years (*c* statistic, 0.79) [2,3]. Similarly, the Breast Cancer Risk Assessment Tool uses information about a woman's age, race, reproductive history, family history of breast cancer, and biopsy history to predict her risk of developing invasive breast cancer within five years (*c* statistic, 0.58) [4,5]. Risk indices also are available to predict risk of mortality [6,7], disability [8], nursing home placement [9], and diabetes [10,11], among many other conditions and disorders.

2. Dementia risk indices

Risk index methodology has only recently been applied in the context of dementia [12,13]. The first dementia risk index was a Mid-Life Dementia Risk Score that is designed to be administered to middle-aged adults (40 to 64 years) [14]. The Mid-Life Dementia Risk Score uses a combination of age, gender, education, physical inactivity and mid-life history of obesity, hypertension, and hypercholesterolemia to predict risk of dementia 20 years later with high accuracy (*c* statistic, 0.77). Inclusion of *apolipoprotein E* (*APOE*) genotype slightly improved the accuracy of the index (*c* statistic, 0.78). Given that the Mid-Life Dementia Risk Score is brief and is one of the only tools available to identify middle-aged adults with a high dementia risk, we suggest that information on mid-life vascular risk factors should be collected in all individuals included in a National Registry so that high-risk, middle-aged adults can be targeted for primary prevention efforts such as lifestyle interventions.

We have recently developed a Late-Life Dementia Risk Index [15], which is designed to be administered in older adults (65 years or older). We found that the greatest prognostic accuracy was achieved by combining information from a large number of different domains, including demographic, cognitive, lifestyle, medical, performance, genetic, cerebral magnetic resonance imaging (MRI), and carotid artery ultrasound measures (Table 1). Together, these measures predicted 6-year risk of developing dementia in older adults with very high accuracy (*c* statistic, 0.82 using the full model coefficients and 0.81 using a simplified point system).

A limitation of our original Late-Life Dementia Risk Index is that it includes several measures that would be impractical to perform in most clinical and research settings (eg, cerebral MRIs, carotid artery ultrasound, and *APOE* genotyping) due to time, feasibility, and cost constraints. Therefore, in preparation for and subsequent to the Leon Thal Symposium '09 (LTS'09), we developed an abbreviated Brief Dementia Risk Index that we propose could be used in either clinical or research settings as a practical tool to identify high-risk individuals for clinical trials and prevention efforts.

The study population and general methods used for development of the Brief Dementia Risk Index were similar to those used for our original Late-Life Dementia Risk Index [15]. Briefly, the study population was 3375 participants in the Cardiovascular Health Cognition Study [16–19] who did not have dementia at the baseline exam (1992–93). A standardized protocol was administered across the four study sites to identify subjects who had developed dementia during the 6-year follow-up period. We used stepwise logistic regression procedures to identify the combination of variables that was most predictive of 6-year dementia risk. Because our goal in the current study was to develop a brief index, we focused on examination of predictive measures that could be easily performed in a typical clinical setting without special equipment. These included demographic factors, individual

items from the Modified Mini-Mental State Exam [20] and the Center for Epidemiologic Studies-Depression Scale 10-item questionnaire [21], history of medical conditions, self-reported physical function, and lifestyle factors. A point system was developed based on the logit coefficients from the final model (1 point for coefficients < 0.9 ; 2 points for coefficients ≥ 0.9).

We found that a combination of demographic, cognitive, lifestyle, and medical factors predicted dementia risk with accuracy almost as high as our original model and comparable to other widely-used indices (c statistic, 0.77) (Table 1). The specific items included in the final Brief Dementia Risk Index were older age; recall of < 2 of 3 words presented after a brief delay; incorrectly copying a figure of two pentagons that intersect to form a diamond; incorrectly performing either of the first 2 steps of 3-step request (take piece of paper in left hand, fold in half with both hands and hand back); inability to name at least 10 four-legged animals in 30 seconds; self-reported “trouble keeping my mind on what I was doing” three or more days per week during the past month; medical history of stroke, peripheral artery disease, or coronary artery bypass surgery; low body mass index (< 18.5); and lack of current alcohol consumption. The accuracy of the index was improved by use of age as a continuous variable (c statistic, 0.78; see Table 1 footnote) or inclusion of walking speed (c statistic, 0.78; data not shown). The Table 1 footnote includes several formulas that can be used to calculate an individual's predicted 6-year dementia risk using either the model coefficients or simplified point systems for both the original and the brief indices.

It is interesting to note that many of the items identified as being predictive of dementia risk in both indices (ie, cognitive, vascular, functional, and behavioral measures) are likely to be markers of ongoing, pathological brain changes that may ultimately lead to symptomatic dementia, similar to the way in which the items in the Framingham Heart Index are markers of ongoing, pathological cardiovascular changes that may ultimately lead to a major coronary event. Thus, these indices highlight that dementia, like coronary heart disease, can be viewed as a process with multiple opportunities for intervention and prevention.

The accuracy of the original Late-Life Dementia Risk Index based on the c statistic was significantly higher than the Brief Dementia Risk Index ($P < 0.001$). However, the absolute differences in predictive accuracy using the two indices were relatively small. When we categorized subjects as having low, moderate, or high risk based on their scores, the percentages of subjects that developed dementia in each category were 4%, 23%, and 56% using the original index compared with 5%, 24%, and 52% using the brief index (Table 2). Thus, both indices had high accuracy and were able to achieve excellent separation between those with low versus high risk.

3. Next steps

We propose that a risk index approach should serve as the framework for the evaluation and comparison of different methods for identification of asymptomatic individuals with a high dementia risk. Specifically, we suggest that risk index methods should be utilized within a National Registry, if one is established, and should be incorporated into other ongoing efforts to develop strategies for identification of asymptomatic, high-risk individuals (eg, Alzheimer's Disease Neuroimaging Initiative).

How would this be accomplished? First, it would be important for the field to agree on a “core model” that would be included in all studies and against which different approaches could be compared. We suggest that the Brief Dementia Risk Index presented here could serve as this core model, given its brevity and ease of administration. The “added prognostic value” of new approaches—such as the imaging techniques, biomarkers, cognitive tests, and genetic factors discussed at LTS'09—could then be calculated by determining the increase in

c statistic associated with inclusion of the approach in the predictive model. It would be important to consider the practical as well as the statistical impact of including new measures in the model. In most clinical settings, the addition of a costly or time-consuming test probably would not be worth a small improvement in accuracy. On the other hand, if a new measure resulted in a dramatic improvement in prognostic accuracy, it would be important to incorporate it into a revised core model and, ultimately, into routine clinical and research practice. Thus, risk index methods provide a practical, flexible, and objective framework for directly comparing the predictive accuracy of different measures and combinations of measures as they are developed.

There also are several additional steps that should be taken to enhance the utility of the dementia risk indices described above and developed in the future. First, it is important to note that none of the currently published dementia risk indices—including the Brief Dementia Risk Index described here—have been validated in external study populations. Although these indices have face validity, it is important to validate them a variety of settings and study populations before they are used in routine clinical settings. In particular, it is critical to determine whether there are any meaningful differences in prognostic accuracy based on variables such as age, gender, race/ethnicity, education, or baseline level of cognitive function.

Second, although simplified point systems are useful and may be preferred by some clinicians, they also can complicate calculation of an individual's risk score if information on one or more of the variables in the index is not available. Therefore, efforts should be made to develop and validate alternative computer-based algorithms of existing dementia risk indices that can adjust for missing data.

Finally, it will be important to determine whether different risk indices should be used in different settings (eg, mid-life vs late-life; clinical vs research) or whether a single model can be developed and applied across settings (eg, by using different weights in different circumstances).

4. Conclusion

We propose that risk index methods should be utilized as the framework for development of the optimal approach for identification of asymptomatic individuals with a high dementia risk. Furthermore, we suggest that the Brief Dementia Risk Index described here could serve as the “core model” against which newer approaches are compared. One of the key strengths of risk indices is that they combine information from different risk-factor domains to maximize prognostic accuracy. In addition, they can be used to objectively-assess the added prognostic value of new measures that are added to the model. Our findings suggest that relatively simple measures can be used to identify high-risk individuals with reasonably high accuracy. However, it is possible that some of the newer techniques discussed at LTS'09 will result in substantial improvements in prognostic accuracy. Risk index methods provide a practical, flexible, and objective framework for identifying the optimal combination of measures for identification of high-risk individuals for prevention and early intervention efforts.

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References

1. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982;143:29–36. [PubMed: 7063747]
2. Kannel WB, McGee D, Gordon T. A general cardiovascular risk profile: the Framingham Study. *Am J Cardiol* 1976;38:46–51. [PubMed: 132862]
3. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837–47. [PubMed: 9603539]
4. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst* 1989;81:1879–86. [PubMed: 2593165]
5. Rockhill B, Spiegelman D, Byrne C, Hunter DJ, Colditz GA. Validation of the Gail et al. model of breast cancer risk prediction and implications for chemoprevention. *J Natl Cancer Inst* 2001;93:358–66. [PubMed: 11238697]
6. Walter LC, Brand RJ, Counsell SR, et al. Development and validation of a prognostic index for 1-year mortality in older adults after hospitalization. *JAMA* 2001;285:2987–94. [PubMed: 11410097]
7. Lee SJ, Lindquist K, Segal MR, Covinsky KE. Development and validation of a prognostic index for 4-year mortality in older adults. *JAMA* 2006;295:801–8. [PubMed: 16478903]
8. Covinsky KE, Hilton J, Lindquist K, Dudley RA. Development and validation of an index to predict activity of daily living dependence in community-dwelling elders. *Med Care* 2006;44:149–57. [PubMed: 16434914]
9. Yaffe K, Fox P, Newcomer R, et al. Patient and caregiver characteristics and nursing home placement in patients with dementia. *JAMA* 2002;287:2090–7. [PubMed: 11966383]
10. Lindstrom J, Tuomilehto J. The diabetes risk score: a practical tool to predict type 2 diabetes risk. *Diabetes Care* 2003;26:725–31. [PubMed: 12610029]
11. Schulze MB, Hoffmann K, Boeing H, et al. An accurate risk score based on anthropometric, dietary, and lifestyle factors to predict the development of type 2 diabetes. *Diabetes Care* 2007;30:510–5. [PubMed: 17327313]
12. Barnes DE, Yaffe K. Predicting dementia: role of dementia risk indices. *Future Neurology* 2009;4:555–60. [PubMed: 20161571]
13. Kivipelto M, Solomon A. Preventive neurology: on the way from knowledge to action. *Neurology* 2009;73:168–9. [PubMed: 19494247]
14. Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. *Lancet Neurol* 2006;5:735–41. [PubMed: 16914401]
15. Barnes DE, Covinsky KE, Whitmer RA, Kuller LH, Lopez OL, Yaffe K. Predicting risk of dementia in older adults: The late-life dementia risk index. *Neurology* 2009;73:173–9. [PubMed: 19439724]
16. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol* 1991;1:263–76. [PubMed: 1669507]
17. Lopez OL, Kuller LH, Fitzpatrick A, Ives D, Becker JT, Beauchamp N. Evaluation of dementia in the cardiovascular health cognition study. *Neuroepidemiology* 2003;22:1–12. [PubMed: 12566948]
18. Kuller LH, Lopez OL, Newman A, et al. Risk factors for dementia in the cardiovascular health cognition study. *Neuroepidemiology* 2003;22:13–22. [PubMed: 12566949]
19. Fitzpatrick AL, Kuller LH, Ives DG, et al. Incidence and prevalence of dementia in the Cardiovascular Health Study. *J Am Geriatr Soc* 2004;52:195–204. [PubMed: 14728627]

20. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry* 1987;48:314–8. [PubMed: 3611032]
21. Radloff LS. A self-report depression scale for research in the general population. *Applied Psychol Measure* 1977;1:385–401.

Table 1

Comparison of the original Late-Life and Brief Dementia Risk Indices *

Original Late-Life Dementia Risk Index ¹⁵			Brief Dementia Risk Index ^{**}		
Characteristic	Coeff.	Points	Characteristic	Coeff.	Points
Age 75–79 years	0.66	1	Age 75–79 years	0.84	1
Age 80–100 years	1.19	2	Age 80–100 years	1.62	2
Low 3MS	1.04	2	Delayed recall < 2 of 3 words	1.00	2
Low DSST	0.90	2	Incorrectly copying intersecting pentagons	0.68	1
≥ 1APOE ε4 allele	0.79	1	Incorrectly taking or folding paper	0.65	1
MRI white matter disease	0.61	1	Inability to name 10 four-legged animals in 30 s	0.40	1
MRI enlarged ventricles	0.38	1	Self-reported 'trouble keeping mind on things' ≥ 3 d/wk	0.64	1
Internal carotid artery thickness ≥ 2.2 mm	0.57	1	Stroke	0.56	1
Time to put on and button shirt > 45 s	0.50	1	Peripheral artery disease	0.66	1
Coronary artery bypass surgery	0.54	1	Coronary artery bypass surgery	0.56	1
BMK < 18.5	1.22	2	BMK < 18.5	0.84	1
Lack of current alcohol consumption	0.42	1	Lack of current alcohol consumption	0.46	1
Constant	−4.07	−4.03	Constant	−3.52	−3.53
c statistic	0.82	0.81	c statistic	0.77	0.77

* An individual's probability of dementia is calculated as $1 / [1 + e^{-(\alpha + \sum \beta x)}]$ where α =constant, β =coefficient, and x =variable value. This can be calculated directly from the model coefficients in Table 1 or, if using the point system, β =0.52 per point for the original index and β =0.60 per point for the brief index. For example, using the brief index, the predicted probability of developing dementia within 6 years for someone who was 75 years old; recalled 1 of 3 words presented; was unable to copy the pentagon figure correctly; did not fold the paper; named 5 four-legged animals in 30 seconds; reported trouble keeping their mind on what they were doing 5 days/week; did not have a history of stroke, peripheral artery disease, or bypass surgery; had normal BMI; and did not currently drink alcohol would be $1 / [1 + e^{-(-3.52 + 0.84 + 1.00 + 0.68 + 0.40 + 0.64 + 0.46)}] = 76\%$ using the model coefficients and $1 / [1 + e^{-(-3.53 + 0.60*8)}] = 78\%$ using the point system.

** The accuracy of the Brief Dementia Risk Index was improved slightly (c statistic=0.78) using age as a continuous variable and the following alternative model coefficients: $\beta(\text{age})=0.13$ per year, $\beta(\text{delayed recall})=1.00$, $\beta(\text{pentagons})=0.67$, $\beta(\text{paper})=0.65$, $\beta(\text{animals})=0.40$, $\beta(\text{mind on things})=0.61$, $\beta(\text{stroke})=0.50$, $\beta(\text{peripheral artery disease})=0.67$, $\beta(\text{bypass})=0.59$, $\beta(\text{low BMI})=0.84$, $\beta(\text{no alcohol})=0.46$, constant=−12.52.

Table 2

Percent who developed dementia by risk score category

Original Late-Life Dementia Risk Index			Brief Dementia Risk Index		
Score	N	No. (%) dementia	Score	N	No (%) dementia
0 – 3	1835	78 (4.2)	0 – 2	1951	104 (5.3)
4 – 7	897	205 (22.8)	3 – 5	1165	276 (23.7)
≥ 8	150	84 (56.0)	≥ 6	136	71 (52.2)