

Is the development of late-life cognitive impairment more dynamic than sexy?

Kenneth Rockwood,
MD

Correspondence & reprint
requests to Dr. Rockwood:
kenneth.rockwood@dal.ca

Neurology® 2012;78:300–301

As people age, they experience characteristic, generally subtle, changes in almost all bodily functions, including brain function.¹ Psychomotor speed slows detectably across the adult lifespan.² By age 50, many people have noticed that their memory is not as good as it was when they were younger; if it troubles them enough to seek medical evaluation, they are said to have a subjective memory complaint. Many people with a subjective memory complaint have cognitive test score abnormalities, often at a rate higher than those who are not troubled by their memory³; of these, many go on to develop dementia.

The evaluation of people with cognitive impairment who do not meet the criteria for dementia is an area of intense investigation. No group has contributed more than the Mayo Clinic investigators. They have reified criteria for mild cognitive impairment (MCI), and identified subtypes. People with MCI can be found with and without a predominant amnesic component, and further with and without impairment in other cognitive domains. Some subsequent epidemiologic reports appeared to contradict some of the initial estimates of the risk conferred by MCI. As Roberts et al.⁴ point out in this issue of *Neurology*®, discrepant estimates could be traced to many causes, epidemiologic studies sampling a different group than did the initial clinic-based MCI studies. Typically, these studies lacked sufficient data to replicate the MCI criteria, especially as subtypes began to be defined with more precision.

Against this background, the epidemiologic data from the Mayo Clinic Study of Aging are of interest to anyone concerned with how brain function changes with age. The study defined MCI and subtypes prospectively, and not from retrofitted diagnostic criteria. The data allow for the burden of MCI to be estimated and for insights from the clinic-based studies to be explored. Briefly, the authors found that

the incidence of MCI was not inconsiderable—about 64 per 1,000 in people aged 70–89 over 2–4 years, with the great majority of people assessed at least 3 times. Perhaps a bit surprisingly, given that women at any age generally accumulate more deficits than men do,⁵ the incidence of MCI and its 2 main subtypes (amnesic and nonamnesic) was higher in men. This finding would not have been obvious from other incidence investigations, but notably was present in the prevalence estimates from the Mayo Clinic study.⁶ The authors considered several factors that might confound the relationship, or at least modify the effect, especially interactions between sex and age, or education or marital status, but conclude that it is a valid finding. They also noted elements from other studies that would support a greater MCI burden among men.

Finding a difference between men and women in the incidence of MCI is not a small thing. That is because much of the interest in MCI stems from its widely confirmed status as a risk for progression to dementia. Given that women tend to have a higher risk of dementia than do men, and that even in Olmsted County, dementia incidence is similar between men and women, it is unclear how to square more men in the at-risk state not translating into more men with dementia.

In general, men tolerate deficits less well than women do—while women might have more things wrong at any age, they can live with them longer than men do; for men, deficits more often are fatal.⁵ In consequence, the risk of death might be higher for men with MCI, thereby not allowing them to live long enough to develop dementia. (It is noteworthy, however, that the incidence rates here did not much change when data from medical records were included for subjects lost to follow-up.)

A rather more optimistic possibility than differential mortality might emerge by looking at another

See page 342

From the Geriatric Medicine Research Unit, Dalhousie University and Queen Elizabeth Health Sciences Centre, Halifax; and Division of Geriatric Medicine, Department of Medicine, Dalhousie University, Halifax, Canada.

Study funding: K.R.'s research is supported by operating grants from the Canadian Institutes of Health Research (MOP-209888) and the Nova Scotia Health Research Foundation (MED2006-2086), and by a fellowship from the Alzheimer Society of Canada. K.R. receives funding from the Dalhousie Medical Research Foundation as Kathryn Allen Weldon Professor of Alzheimer Research.

Disclosure: Author disclosures are provided at the end of the editorial.

group who do not fit the usual continuous progression from no cognitive impairment to mild cognitive impairment to dementia. Intriguingly, Roberts et al. report that about one-third of people initially diagnosed with MCI were subsequently diagnosed at least once with no cognitive impairment. (The term used is “reverted to normal,” which sounds oddly pejorative, implying more regression than recovery.) The proportion of people who improved at least once is not without precedent, especially in epidemiologic studies, even when only incident cases are considered.⁷ Improvement compared with progression is an important challenge to the conventional view that MCI criteria imply a risk of dementia, but it might represent more.

Objectively verified improvement in cognition would be expected if cognitive aging represents not just relentless decline—the brain as innocent bystander—but the outcomes of a struggle between insults and repair mechanisms. Evidence for this can be seen in studies, now often advanced to therapeutics, that employ ideas like cognitive flexibility⁸ and brain plasticity.⁹ Men and women experience these effects in different ways. For example, sex modifies the protective effect of exercise on cognition.¹⁰ In women, exercise is associated more with a mortality benefit, whereas in men, the positive effect of exercise is more of a cognitive improvement. Therefore, why men have a higher incidence of MCI but a lower incidence of dementia may come about from how they express the later-life dynamics of cognition. For some men, MCI represents incomplete disease expression; alternately, they resist dementia development more. In that way, MCI in men could lend some insight into what prevented dementia might look like. Whether this explanation holds depends, as the authors propose, on further investigation of risk factors for MCI separately in men and in women.

DISCLOSURE

Dr. Rockwood serves on a Data Safety Monitoring Board for NUMC/O Plc and a scientific advisory board for Elan Corporation/Wyeth; has received a speaker honorarium from Bristol-Myers Squibb; serves on editorial advisory boards for *Neuroepidemiology*, *Journal of Gerontology—Medical Sciences*, *Alzheimer's Research & Therapy*, *BMC Medicine*, and the *Chinese Journal of Geriatrics*; serves as President & Chief Scientific Officer for and owns stock in DementiaGuide, Inc.; receives research support from Canadian Institutes of Health Research, the National Natural Science Foundation of China, and Alzheimer Society of Canada; and has served as an expert witness in legal proceedings on behalf of Eisai and Pfizer Canada.

REFERENCES

1. Fjell AM, Walhovd KB. Structural brain changes in aging: courses, causes and cognitive consequences. *Rev Neurosci* 2010;21:187–221.
2. Era P, Sainio P, Koskinen S, et al. Psychomotor speed in a random sample of 7,979 subjects aged 30 years and over. *Aging Clin Exp Res* 2011;23:135–144.
3. Roberts JL, Clare L, Woods RT. Subjective memory complaints and awareness of memory functioning in mild cognitive impairment: a systematic review. *Dement Geriatr Cogn Disord* 2009;28:95–109.
4. Roberts RO, Geda YE, Knopman DS, et al. The incidence of MCI differs by subtype and is higher in men: the Mayo Clinic Study of Aging. *Neurology* 2012;78:342–351.
5. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits: a review. *J Gerontol Med Sci* 2007;62A:722–727.
6. Petersen RC, Roberts RO, Knopman DS, et al. Prevalence of mild cognitive impairment is higher in men: The Mayo Clinic Study of Aging. *Neurology* 2010;75:889–897.
7. Fisk J, Rockwood K. Outcomes of incident mild cognitive impairment in relation to case definition. *J Neurol Neurosurg Psychiatry* 2005;76:1175–1177.
8. McDonnell MN, Smith AE, Mackintosh SF. Aerobic exercise to improve cognitive function in adults with neurological disorders: a systematic review. *Arch Phys Med Rehabil* 2011;92:1044–1052.
9. Belleville S, Clément F, Mellah S, et al. Training-related brain plasticity in subjects at risk of developing Alzheimer's disease. *Brain* 2011;134:1623–1634.
10. Fallah N, Mitnitski A, Middleton L, Rockwood K. Modeling the impact of sex on how exercise is associated with cognitive changes and death in older Canadians. *Neuroepidemiology* 2009;33:47–54.