Antihypertensive treatment and the prevention of stroke and dementia in elderly patients

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Abstract

Stroke, cognitive impairment and dementia are well-established complications of long-standing hypertension. There is a considerable time lag, usually several decades, between the onset of hypertension and the occurrence of these complications. Although antihypertensive treatment has been shown to decrease the risk of a first stroke, little evidence is available on the effects of antihypertensive treatment on the incidence of recurrent cerebrovascular events, cognitive impairment and dementia. The results of recent studies addressing this issue are discussed, along with directions for future research.

Key words: hypertension, stroke, cognitive impairment, dementia, antihypertensive treatment.

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Introduction

Hypertension increases the risk of stroke, cognitive impairment and dementia from both Alzheimer's disease (AD) and vascular dementia (VaD). Putative mechanisms include repeated ischaemic damage secondary to atheromatous lesions, arteriolar narrowing by lipohyaline deposits, and arterial spasm due to sudden elevations in blood pressure (BP). Although there is good evidence that antihypertensive treatment significantly reduces the risk of a first stroke, few data are currently available on the efficacy of antihypertensive treatment on the incidence of recurrent stroke, cognitive impairment and dementia. The results of recent studies addressing these issues and directions for future research are discussed.

Relationship between hypertension and stroke

There is a continuous, positive, linear relationship between both systolic and diastolic BP and the incidence of any subtype of ischaemic or haemorrhagic stroke, at any age and in both sexes.[2] No threshold distinguishes patients who will have a vascular event from those who will not.[2,3] In individuals with normal BP, the risk of stroke is higher in those with the highest levels of 'normal' BP.[4] Thus, the lower the blood pressure, the lower the risk of stroke. The risk of stroke doubles for every 7.5 mmHg increase in diastolic BP.[2] Isolated systolic hypertension and pulse pressure are also important risk factors for stroke in elderly subjects.[5,6]

Primary prevention of stroke

Primary prevention trials provide convincing evidence that antihypertensive treatment reduces the risk of stroke, at least in hypertensive subjects.[7-13] A meta-analysis of 14 randomised primary prevention trials showed that, for an average diastolic BP reduction of 5 to 6 mmHg, the reduction in stroke rate is 42% over a five-year period, irrespective of the severity of the hypertension.[7] A more recent meta-analysis of 18 long-term randomised trials found that both beta blockers (relative risk [RR] 0.71; 95% confidence interval [CI] 0.59–0.86) and high-dose diuretics, defined as starting doses ≥ 50 mg of chlorthalidone or hydrochlorothiazide, (RR 0.49; 95% CI 0.39–0.62) prevent stroke.[14] The reduction in stroke risk occurs soon after the treatment is started: it was already present within one year of treatment in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) and the Systolic Hypertension in the Elderly Program (SHEP).[8,10] Although a too vigorous reduction in BP could increase the vascular risk by causing a reduction in cerebral blood flow, the arterial Hypertension Optimal Treatment (HOT) trial demonstrated the benefits of lowering the systolic and diastolic BP to 140/85 mmHg or lower.[15] Below 120/70 mmHg a little further benefit was observed without additional risk.[15]

The importance of controlling isolated systolic hypertension to prevent stroke in elderly patients has been underscored in most clinical trials. For example, in SHEP, antihypertensive treatment with chlorthalidone or atenolol reduced the total incidence of stroke by 36%.[10] Similar results were obtained with nitrendipine in the Systolic Hypertension in Europe (Syst-Eur) trial,[11] which was stopped when stroke relative reduction reached 42% in the actively treated group.[11]

Most randomised clinical trials of treatment of hypertension were conducted with diuretics or beta blockers.[7,8,10] More recent-

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ly, the Heart Outcomes Prevention Evaluation (HOPE) study in high cardiovascular risk patients (who were not necessarily hypertensive) examined the effects of ramipril. It showed that angiotensin-converting enzyme inhibitors also reduce the risk of cardiovascular events.[16] In the STOP-hypertension-2 trial, a similar BP reduction was achieved in patients treated with a conventional therapy (beta blocker or hydrochlorothiazide plus amiloride) or a newer drug (enalapril, lisinopril, felodipine or isradipine), and no significant differences were found between the groups in fatal and non-fatal stroke.[17] A meta-regression analysis conducted across 27 trials, including 136,124 patients, showed that antihypertensive drugs have similar long-term efficacy and safety.[12]

Secondary prevention of stroke

There was no clear evidence until recently that reducing BP after stroke reduces the rate of recurrent stroke. A meta-analysis from nine randomised clinical trials, some of them very small, led to a barely significant estimated RR reduction of 29% (95% CI: 5–47%).[18] Although there is strong evidence that BP is a determinant of the risk of stroke among both normotensive and hypertensive subjects, there was uncertainty about the efficacy and safety of BP-lowering agents in many stroke patients.

To address this question, the Perindopril Protection against Recurrent Stroke Study (PROGRESS) included 6,105 patients who had a history of stroke or transient ischaemic attack within the past five years.[19] The subjects were randomly assigned to perindopril alone or in combination with indapamide, or to placebo. The active treatment reduced BP by 9/4 mmHg. After a four-year period, in the active treatment group the rate of recurrent stroke was reduced by 28% (95% CI 17–38%). The risk reduction was similar in normotensive and hypertensive patients. Subgroup analysis showed that the effect was significant only with combination treatment (43% RR reduction; 95% CI 30–54%). Although the effect was present in all stroke subtypes, it was greater in haemorrhagic strokes (RR reduction 50%; 95% CI 33–74%). The combination therapy prevented one recurrent stroke for 14 patients treated during a five-year period.[19]

Relationship between hypertension, cognitive function and dementia

Hypertension might predispose to cognitive impairment and dementia by several mechanisms, including regional alteration of cerebral perfusion, lacunae development, white matter lesions and progressive cortical atrophy.[20-22] Several cross-sectional observational studies support a relationship between hypertension and cognitive function, although there is some discrepancy in the results obtained. In an overview of 12 studies, four showed no correlation between BP and cognitive function,[23-26] seven showed a negative correlation between cognitive function and either systolic BP,[27] diastolic BP,[28-30] or both,[31,32] while one study showed a positive correlation in the very old.[33] Such variability might depend at least partly on the population studied and on differences between the neuropsychological methods used.[34]

Several longitudinal studies have investigated the relationship between BP, cognitive impairment and dementia. Elias *et al*. assessed cognitive function in the Framingham cohort, some 12 to 14 years after recruitment, in relation to the initial BP values. After correction for demographic variables and other cardiovascular risk factors, cognitive performance was found to be negatively correlated with the initial systolic and diastolic BP.[35] In this study most hypertensive subjects (88%) did not receive any treatment during the observation period. Similar results were obtained in the Honolulu-Asia Aging Study,[36] in which the observation period was 25 years.

Skoog *et al*. analysed the relationship between BP and dementia in subjects aged 70 years who were followed up at five-year intervals up to the age of 85 years. The subjects who developed AD and VaD at age 79 to 85 years had higher systolic and diastolic BP at the age of 70 years than those who did not.[37] Of note, in the years just preceding the onset of dementia the BP tended, paradoxically, to become lower in those with AD than in subjects with VaD. Another study in subjects aged 75–101 years showed that a lower systolic BP was associated with a worse cognitive performance.[38] The BP reduction in the pre-dementia phase could be due to brain lesions accompanying AD in prefrontal autonomic centres and central dysregulation of BP.[39] The BP reduction could also theoretically contribute to the pathogenesis of AD through periods of cerebral ischaemia.[39]

In a recent study involving middle-aged men who were followed up for 20 years, cognitive function was highest in those with an initial diastolic BP lower than 70 mmHg and lowest in subjects with a diastolic BP higher than 105 mmHg.[40] In another recent study, there was no significant linear association between BP and cognition, although an initial systolic BP above 160 mmHg was associated with a 14% higher rate of test errors compared to a group with a systolic BP between 130 and 139 mmHg.[41]

In summary, longitudinal studies support the hypothesis that mid-life hypertension predisposes to late-life cognitive decline and development of dementia. In AD the development of dementia is associated with a fall in BP whereas in VaD the BP remains high in late life.

Effects of antihypertensive treatment

Several observational studies have investigated the effect of antihypertensive treatment on cognitive function. In the Kungsholmen Project, a total of 1,301 subjects aged ≥ 75 years were followed up for three years.[42] In the subpopulation with a systolic BP higher than 160 mmHg, a diastolic BP higher than 95 mmHg, or both (n=458), 122 received diuretic therapy. Compared to untreated patients, the treated patients showed an adjusted relative risk for dementia of 0.6 (95% CI, 0.3–1.2). Although this trend was interpreted as a potential benefit from diuretic treatment, information about pharmacological treatment was only available at baseline: the duration of treatment was unknown. Moreover, a history of cardiovascular disease was present in the group not receiving treatment, unlike the treated patients.

In the Epidemiology of Vascular Ageing Study, some 1,389

subjects were assessed at baseline and after two and four years.[43] In the untreated hypertensive group, a correlation was observed between the level of BP and a subsequent decline in cognitive function (i.e. a decrement of > 4 points in the Mini Mental State Examination scale). The relative risk was 4.3 (95% CI 2.3–8.0) compared to the normotensive subjects. By comparison, in the treated group, the relative risk was 1.3 (95% CI 0.3–3.9). The results of these observational trials indicate a potential benefit from antihypertensive treatment in reducing the incidence of cognitive impairment.

Four major randomised placebo-controlled primary prevention trials have included sub-studies focusing on cognitive function and the incidence of dementia: the SHEP study,[44] the Medical Research Council (MRC) trial in older people,[45] the Syst-Eur trial,[46] and the Study on Cognition and Prognosis in the Elderly (SCOPE), which has not yet been published.

The SHEP trial involved 2,304 subjects aged ≥ 60 years with isolated systolic hypertension. They received active treatment with chlorthalidone or placebo. Psychometric tests were performed at baseline and then six-monthly for five years. Neither the evolution of cognitive dysfunction nor the incidence of dementia was significantly different between the two groups.[44]

In a subset of 2,584 participants in the MRC trial of treatment in older hypertensive patients randomised to a diuretic, beta blocker or placebo, no significant difference in test scores was detected between the different groups during a period of 54 months.[45]

The Syst-Eur trial included a side project on 2,418 subjects in whom cognitive function and incidence of vascular and degenerative dementia were assessed. Subjects were taking active treatment with nitrendipine as the primary drug or placebo.[46] The follow-up was only two years as the trial was terminated early because of significant differences in the incidence of stroke, the primary end point. The intention-to-treat analysis showed that 21 cases of dementia were observed in the placebo group versus 11 in the active treatment group. Active treatment reduced the rate of dementia by 50%, from 7.7 to 3.8 per 1,000 patient-observation years (p=0.05).[46]

After the trial ended in February 1997, randomised patients were offered active treatment for a further period of observation (3.9 years).[47] The incidence of dementia doubled during this period from 32 to 64 cases, 41 of whom had AD. Long-term antihypertensive therapy reduced the risk of dementia by 55% compared with the controls, from 7.4 to 3.3 cases per 1,000 patient-years (43 *vs.* 21 cases, p<0.001). After adjustment for sex, age, education and entry BP, the relative hazard rate associated with the use of nitrendipine was 0.38 (95% CI 0.23–0.64; p<0.001).[47]

Finally, the SCOPE trial was designed to provide outcome data on cardiovascular end points and cognitive function in 4,500 elderly hypertensive patients who were randomised to the angiotensin II receptor blocker candesartan or placebo and followed up for 4.5 years. As the placebo group ended up receiving a significant amount of antihypertensive therapy, there was only a very small difference in achieved BP. Compared with the placebo group, the change in the systolic BP in the candesartan group was -3.2 mmHg (95% CI 4.4–1.9; p<0.001) and in the diastolic BP was -1.6 mmHg (95% CI 2.2–0.9; p<0.001). There was no significant difference in cognitive function decline between the two groups.[48]

Thus, when considering the results of these four trials, nitrendipine-based therapy has emerged so far as the only antihypertensive regimen exhibiting the potential for preventing dementia, reducing its incidence by half. The beneficial effects of this regimen may be explained by nitrendipine's action on intracellular calcium. An excess of intraneuronal calcium is considered to be the prime determinant of the accumulation of neurotoxic precursors involved in the pathogenesis of neurodegenerative diseases.[49] Further studies are required to validate this hypothesis for at least two reasons. First, the Syst-Eur substudy was conducted in a relatively small sample of patients. Second, some studies investigating cognitive function have indicated that calcium channel blockers might be far from ideal when compared with other antihypertensive drug regimens.[50,51]

Interestingly, the PROGRESS trial of secondary prevention demonstrated that in patients with stroke or transient ischaemic attack (TIA) the addition of perindopril with or without indapamide significantly reduced the development of dementia by preventing stroke.[19]

New randomised controlled trials are needed to focus specifically on cognitive function and dementia, comparing the efficacy of different classes of antihypertensive agents. One such trial is being designed under the acronym DEPHY (Dementia Prevention in Hypertension) by the European Working Party on High Blood Pressure in the Elderly.

Key messages

- Hypertension increases the risk of stroke, cognitive impairment and dementia from both Alzheimer's disease and vascular dementia
- Antihypertensive treatment reduces the risk of a first stroke, at least in hypertensive patients. It also reduces the risk of recurrent stroke in hypertensive and normotensive patients
- Syst-Eur is the only study showing that antihypertensive treatment may prevent dementia. In this study, the calcium channel blocker nitrendipine was used as the active treatment
- New randomised controlled trials are needed to focus specifically on cognitive function and dementia by comparing the efficacy of different classes of antihypertensive agents

Conclusions

Unlike the studies on primary stroke prevention, the results of trials on the efficacy of antihypertensive treatment on the incidence of recurrent stroke, cognitive impairment and dementia have

been limited and largely unsatisfactory. Possible explanations are the relatively small sample size, poor choice of drugs, and crude assessment of cognitive function. More research is required in this area as several questions remain unanswered. Will benefit be obtained from universal BP reduction? Are individuals with normal BP and a high vascular risk candidates for antihypertensive treatment? What is the optimal BP level post-stroke? Are there any differences among different classes of antihypertensive drugs? Hopefully, adequate answers to all these questions will become available in the next few years.

References

1. Dickinson CJ. Why are strokes related to hypertension? Classic studies and hypotheses revisited. *J Hypertens* 2001;**19**:1515-21.
2. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke* 1991;**22**:312-18.
3. MacMahon S, Peto R, Cutler J *et al*. Blood pressure, stroke, and coronary heart disease: Part 1. Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;**335**:765-74.
4. Vasan RS, Larson MG, Leip EP *et al*. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med* 2001;**345**:1291-7.
5. Joint National Committee. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Int Med* 1997;**157**:2413-46.
6. Vaccarino V, Berger AK, Abramson J *et al*. Pulse pressure and risk of cardiovascular events in the systolic hypertension in the elderly program. *Am J Cardiol* 2001;**88**:980-6.
7. Collins R, Peto R, MacMahon S *et al*. Blood pressure, stroke and coronary heart disease: Part 2. Short-term reductions in blood pressure: overview of the unconfounded randomised drug trials in their epidemiological context. *Lancet* 1990;**335**:827-38.
8. Dahlöf B, Lindholm LH, Hansson L *et al*. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet* 1991;**338**:1281-5.
9. MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *BMJ* 1992;**304**:405-12.
10. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991;**265**:3255-64.
11. Staessen JA, Fagard R, Thijs L *et al*. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet* 1997;**350**:757-64.
12. Staessen JA, Wang JG, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. *Lancet* 2001;**358**:1305-15.
13. Tuomilehto J, Rastenyte D. Diabetes and glucose intolerance as risk factors for stroke. *J Cardiovasc Risk* 1999;**6**:241-9.
14. Psaty BM, Smith NL, Siscovick DS *et al*. Health outcomes associated with antihypertensive therapies used as first-line agents: a systematic review and meta-analysis. *JAMA* 1997;**277**:739-45.
15. Hansson L, Zanchetti A, Carruthers SG *et al*. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998;**351**:1755-62.
16. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;**342**:145-53.
17. Hansson L, Lindholm LH, Ekbom T *et al*. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity The Swedish Trial in Old Patients with Hypertension-2 study. *Lancet* 1999;**354**:1751-6.
18. The INDIANA (Individual Data Analysis of Antihypertensive intervention trials) Project Collaborators. Effect of antihypertensive treatment in patients having already suffered from stroke: gathering the evidence. *Stroke* 1997;**28**:2557-62.
19. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke of transient ischaemic attack. *Lancet* 2001;**358**:1033-41.
20. de Leeuw FE, de Groot JC, Oudkerk M *et al*. Hypertension and cerebral white matter lesions in a prospective cohort study. *Brain* 2002;**125**:765-72.
21. Goldstein IB, Bartzokis G, Guthrie D, Shapiro D. Ambulatory blood pressure and brain atrophy in the healthy elderly. *Neurology* 2002;**59**:713-19.
22. Graham DI. Morphologic changes during hypertension. *Am J Cardiol* 1989;**63**:6C-9C.
23. Farmer ME, White LR, Abbott RD, Wolz MM, Wolf PA. Blood pressure and cognitive performance: the Framingham study. *Am J Epidemiol* 1987;**126**:1103-04.
24. Scherr PA, Hebert LE, Smith IA, Evans DA. Relation of blood pressure to cognitive functions in the elderly. *Am J Epidemiol* 1991;**134**:1303-15.
25. Desmond DW, Tatemichi TK, Paik M, Stern Y. Risk factors for cerebrovascular disease as correlates to cognitive function in a stroke-free cohort. *Arch Neurol* 1993;**50**:166-70.
26. Van Boxtel MPJ, Gaillard C, Houx PJ, Buntinx F, de Leeuw PW, Jolles J. Can the blood pressure predict task performance in a healthy population sample? *J Hypertens* 1997;**15**:1069-76.
27. Seux ML, Thijs L, Forette F *et al*. Correlates of cognitive status of old patients with isolated systolic hypertension: the Syst-Eur Vascular Dementia Project. *J Hypertens* 1998;**16**:963-9.
28. Wallace RB, Lemke JH, Morris MC, Goodenberger M, Kohout F, Hinrichs JV. Relationship of free-recall memory to hypertension in the elderly: the Iowa 65+ Rural Health Study. *J Chronic Dis* 1985;**38**:475-81.
29. Gale CR, Martyn CN, Cooper C. Cognitive impairment and mortality in a cohort of elderly people. *BMJ* 1996;**312**:608-11.
30. Cacciatore F, Abete P, Ferrera N *et al*. The role of blood pressure in cognitive impairment in an elderly population. *J Hypertens* 1997;**15**:135-42.
31. Starr JM, Whalley LJ, Inch S, Schering PA. Blood pressure and cognitive function in healthy old people. *J Am Geriatr Soc* 1993;**41**:753-6.
32. Kuusisto J, Koivisto K, Mykkanen L *et al*. Essential hypertension and cognitive function: the role of hyperinsulinemia. *Hypertension* 1993;**22**:771-9.
33. Guo Z, Fratiglioni L, Winblab B, Viitanen M. Blood pressure and performance on the Mini-Mental State Examination in the very old: cross-sectional and longitudinal data from the Kungsholmen Project. *Am J Epidemiol* 1997;**145**:1106-13.
34. Seux ML, Forette F. Effects of hypertension and its treatment on mental function. *Curr Hypertens Rep* 1999;**1**:232-7.
35. Elias ME, Wolf PA, D'Agostino RB, Cobb J, White LR. Untreated blood pressure level is inversely related to cognitive functioning: the Framingham study. *Am J Epidemiol* 1993;**138**:353-64.
36. Launer J, Masaki K, Petrovich H, Foley D, Havlik RY. The association between midlife blood pressure levels and late-life cognitive function: the Honolulu-Asia Aging Study. *JAMA* 1995;**274**:1846-51.
37. Skoog I, Lernfelt B, Landahl S *et al*. 15-year longitudinal study of blood pressure and dementia. *Lancet* 1996;**347**:1141-5.
38. Waldstein SR. Hypertension and neuropsychological function: a lifespan perspective. *Exp Aging Res* 1995;**21**:321-52.
39. Skoog I. Blood pressure and dementia. In: Hansson L, Birkenhäger WH (eds.). *Assessment of Hypertensive Organ Damage*. Amsterdam, the Netherlands: Elsevier Science Inc; 1997:303-31. Birkenhäger WH, Reid JL (serial eds.). *Handbook of Hypertension*; vol 18.
40. Kilander L, Nyman H, Boberg M, Hansson L, Lithell H. Hypertension is related to cognitive impairment: a 20-year follow up of 999 men. *Hypertension* 1998;**31**:780-6.
41. Glynn RJ, Neckett LA, Hebert LE, Mossis CM, Scherr PA, Evans DA. Current and remote blood pressure and cognitive decline. *JAMA* 1999;**281**:438-45.
42. Guo Z, Fratiglioni L, Zhu L, Fastbom J, Winblad D, Viitanen M. Occurrence and progression of dementia in a community population aged 75 years and older: relationship of antihypertensive medication use. *Arch Neurol* 1999;**56**:991-6.
43. Tzourio C, Dufoil C, Ducimetière P, Alperovitch A. Cognitive decline in individuals with high blood pressure. *Neurology* 1999;**53**:1948-52.
44. Applegate WB, Pressels S, Wittes J *et al*. Impact of the treatment of iso-

lated systolic hypertension on behavioral variables: results from the Systolic Hypertension in the Elderly Program. *Arch Intern Med* 1994;**154**:2154-60.
45. Prince MJ, Bird AS, Blizard RA, Mann AH. Is the cognitive function of older patients affected by antihypertensive treatment? Results from 54 months of the Medical Research Council's treatment trial of hypertension in older adults. *BMJ* 1996;**312**:801-05.
46. Forette F, Seux ML, Staessen JA *et al*. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet* 1998;**352**:1347-51.
47. Forette F, Seux ML, Staessen JA *et al*. New evidence from the Systolic Hypertension in Europe (Syst-Eur) Study. *Arch Intern Med* 2002;**162**: 2046-52.
48. Sever P. The SCOPE Trial. *JRAAS* 2002;**3**:61-2.
49. Pascale A, Etcheberrigaray R. Calcium alterations in Alzheimer's disease: pathophysiology, models and therapeutic opportunities. *Pharmacol Res* 1999;**39**:81-8.
50. Heckbert SR, Longstreth WT, Psaty BM *et al*. The association of antihypertensive agents with MRI white matter findings and with modified Mini-Mental State Examination in older adults. *J Am Geriatr Soc* 1997;**45**:1423-33.
51. Maxwell CJ, Hogan DB, Ebly EM. Calcium-channel blockers and cognitive function in elderly people: results from the Canadian Study of Health and Aging. *CMAJ* 1999;**161**:501-66.