Published in final edited form as:

Am J Geriatr Psychiatry. 2011 January ; 19(1): 79–87. doi:10.1097/JGP.0b013e3181e043d0.

Late-life dementia predicts mortality beyond established midlife risk factors

Michal Schnaider Beeri, Ph.D.¹ and Uri Goldbourt, Ph.D.²

¹Department of Psychiatry, Mount Sinai School of Medicine, New York

²Department of Epidemiology and the Henry N. Neufeld Cardiac Research Institute, Tel Aviv University Sackler Medical Faculty, Tel Aviv, Israel

Abstract

Objectives—To compare the mortality rates of elderly demented and non-demented subjects, and the differential association of midlife risk factors with mortality according to dementia status.

Design—Prospective historical study.

Settings—Community-based.

Participants—From the 10,059 male Jewish civil servants who participated in the Israel Ischemic Heart Disease study in the 1960's, the 1,713 who were evaluated for dementia in 1999/2000 and who were unequivocally classified as demented or not demented.

Measurements—midlife sociodemographic and cardiovascular risk factors, late-life dementia, and mortality.

Results—Over a period of 6 years, 718 (42%) subjects died. Of the 307 demented subjects, 71.8% died while 35.4% of the 1407 non-demented subjects died. Multivariate survival analyses showed that compared with subjects without dementia, demented subjects had a HR for mortality of 2.27 (95% CI 1.92-2.68). Other risk factors associated with mortality were socio-economic status (.94 [.88-1.00]) higher systolic (1.16 per 20mm Hg[1.06-1.28]) and diastolic blood pressure (HR 1.15 per 10mm Hg[1.06-1.25]), and ever smoking (HR 1.38 [1.18-1.61]). Midlife total cholesterol was not associated with mortality (1.01 per 40mg/dL [.93-1.10]). None of the interactions of the risk factors with dementia was significant.

Conclusions—Dementia was associated with more than double the risk of mortality but this increased risk did not reflect exacerbation by midlife sociodemographic and cardiovascular risk factors. Our findings suggest that the dementing process itself or its consequences may go beyond well established midlife risk factors for mortality.

Keywords

Dementia; mortality; cardiovascular risk factors

Life expectancy is increasing throughout the world. One consequence is that the number of people affected by dementia is estimated to double every 20 years to 81.1 million by 2040¹. In view of the major impact of dementia on society, improvements in understanding of its causes, course, and consequences are of key importance. Individuals with dementia have

Corresponding author: Michal Schnaider Beeri, Ph.D., Mount Sinai School of Medicine, Department of Psychiatry, One Gustave Levy Place, Box 1230, New York, NY 10029, USA, Phone: 212-6598807, Fax: 212-6595626, michal.beeri@mssm.edu.

No disclosures to report.

excess mortality^{2, 3} and are two to four times more likely to die at a given age than those without dementia⁴. Several characteristics have been associated with this decreased life expectancy including increasing age and severity of dementia, male sex, , type of dementia, and genetic characteristics⁴⁻⁷ but results are inconsistent (e.g., higher mortality in women with dementia⁸). Most studies examining cause of death indicate that the primary cause in demented subjects is respiratory diseases in contrast to non-demented subjects whose primary cause of death is cancer and heart disease⁹⁻¹¹.

There is considerable uncertainty about what influences mortality in individuals with dementia shortly before death and data on characteristics and diseases that influence mortality several years or decades before death are essentially non-existent. The current report presents mortality follow-up over a 6-year period for the 1713 participants in the Israel Ischemic Heart Disease study (IIHD), who survived until 1999/2000, were examined for dementia, and were classified as unequivocally demented or non-demented. We compared demented and non-demented subjects' associations of sociodemographic and cardiovascular characteristics measured in 1963, 1965, and 1968 with risk for mortality four decades later.

Methods

Subjects

Figure 1 presents the flow of subjects. The Israel Ischemic Heart Disease (IIHD) Project (n=11,876) was chosen by stratified sampling of civil servants and municipal employees in 1963 based on 1) men aged 40 to 65 at the time of inclusion, 2) place of work limited to the three largest urban areas in Israel (Tel-Aviv, Jerusalem, and Haifa), and 3) sampling fractions aimed at obtaining numbers of study subjects from 6 geographical areas of origin (Central Europe, Eastern Europe, the Balkan countries, the Middle East, Northern Africa, and Israeli born) approximately proportional to the Israeli male population of these ages. 10,232 (86.2%) men agreed to participate. Subjects were seen upon enrollment (1963) and at two follow up visits (1965 and 1968). Subsequent analyses excluded 173 men who were not born in the six pre-defined geographical areas. According to the Israel Mortality Registry, 7136 men died by the beginning of the dementia follow-up study in 1999; another 307 died before being approached for a phone interview and 13 subjects were lost in the matching process. The remaining 2603 subjects qualified for a telephone interview, of which 2037 had phone contact (194 refused to participate and 372 were not found). The Telephone Interview for Cognitive Status-modified¹² (TICS-m) (described below) identified 799 potentially demented subjects for a home interview. Of these, 148 could not be examined (and thus were excluded from the study), 307 were demented, 175 had cognitive impairment not sufficient to meet diagnostic criteria for dementia (cognitively impaired not demented-CIND¹³), and 169 had no cognitive impairment. Of the 1238 subjects who were not identified as potentially demented by the TICS-m, 51 were examined at home for a sensitivity study of the phone interview instruments; 50 were cognitively intact and one cognitively impaired but not demented¹⁴. The remaining 1187 subjects were classified as non-demented. The present analyses included the 1713 subjects who were unequivocally demented or cognitively normal, but excluded CIND subjects (n=176).

A comparison of the characteristics of the subjects alive in 1999 to those who died since 1963 has been published¹⁵. The 2603 subjects who were alive in 1999 were younger, and taking age differences into account, were taller and had had lower BMI, total serum cholesterol, systolic and diastolic blood pressures, in the initial examinations, than the 7456 presumed dead by this time. Fewer survivors had had diabetes and fewer had smoked cigarettes in the 1960s than non survivors. More survivors were born in Eastern Europe and

fewer in the Middle East while the proportions of participants were similar in other regions, and the survivors represent higher socioeconomic status (SES).

Diagnosis of dementia

Cases of dementia were identified using a two-step procedure as described in detail elsewhere^{14, 15}. The first step was a screening interview over the phone. For the purpose of the screening phone interview, subjects were located by cross-linking the data base of the original study¹⁶ with the population registry of the Israel Ministry of Interior, using the ID number (equivalent of US social security number) as linking identifier. All identified living participants in the original cohort were phoned, reminded of their participation in the original study, and asked for consent to participate in the new assessment. The subjects who consented to participate were administered a 20 minute phone interview, including a sociodemographic questionnaire and the Hebrew version of the Modified Telephone Interview for Cognitive Status (TICS-m¹⁴). The sociodemographic questionnaire included items that were not recorded during the original study in 1963, or that might have changed with time, such as: marital status, retirement age, education, profession, leisure activities, smoking, and drinking habits.

The TICS-m is based on the Mini Mental State Exam (MMSE;¹⁷). It includes questions assessing long and short-term memory, orientation to time and place, attention, language and abstraction. The scores of the TICS-m were highly correlated with the MMSE scores in clinical studies¹⁸ and in the Hebrew version in this cohort¹⁴. Using a threshold score of 27 out of 50 TICS-m points, which corresponds approximately to an MMSE score of 24¹⁹, the sensitivity of this test was above 99% (CI 95% 91%-100%) and the specificity was 86% (CI 95% 85%-87%) for dementia¹².

The second step was a face to face interview for all subjects with a TICS-m score of 27 or lower. The aim of the second phase of the study was to ascertain the diagnosis of dementia among subjects who were identified by the TICS-m as possibly cognitively impaired. The patients were assessed at their residences by a physician. All physicians involved in this study were neurologists or psychiatrists with expertise and extensive experience in the diagnosis of dementia. Physicians were blind to the TICS-m score except for knowledge that it was under 28. The clinical assessment included the Dementia Questionnaire (DQ^{20, 21}), MMSE^{17, 22}, Global Deterioration Scale (GDS²³) and the Hachinski Ischemic Scale (HIS²⁴).

Dementia was diagnosed using the DSM-IV criteria²⁵. Subjects were classified as CIND if a memory problem was reported by both subject and informant but they had normal activities of daily living and were not demented. Thus CIND subjects did not qualify as either demented or no cognitive impairment (NCI). The present analysis compares unequivocally demented to unequivocally nondemented subjects, excluding the CIND subjects, who are heterogeneous, with some subjects early in the course of cognitive decline.

A second physician, blind to the diagnosis assigned by the physician who did the face-to-face interview, examined the data gathered from each patient and assigned an independent diagnosis. In case of disagreement between the two physicians the case was presented to a third physician for a consensus diagnosis. In five cases, the patient was approached again for this purpose.

Definition of covariates

We controlled for five potential confounders all of which have been associated with increased mortality²⁶⁻³¹. SES was represented by a five point index based on education (nine levels ranging from no formal schooling to a graduate degree) and occupation (five

levels ranging from “laborer” to “professional”)³². Smoking habits in 1963 were categorized as a dichotomy- ever and never smoked. Systolic and diastolic blood pressure (SBP and DBP, respectively) were measured in the right arm, with the subject in the recumbent position, both 30 to 45 minutes after arrival at the clinic and 15 to 30 minutes later. The second blood pressure measure in 1963 was used in this analysis. Total cholesterol measured in 1963 (by the Anderson and Keys method³³) was used in the analysis. Information was also collected in 1965 and 1968, but that was not used in order to maintain consistency of time across variables within the multivariate analysis.

Mortality information

Mortality was determined by matching the national ID number with the Israel National Population Registry which includes mortality status. Discrepancies in the original manual recording of ID were identified in close to 7% of the subjects. In most cases the discrepancy reflected the addition by the National Population Registry of a digit at the end of the ID number. Each discrepant case was examined against the Registry's microfiche; by identifying the person's name, year of birth, country of immigration and address we were able to find the correct ID for all but 7 of the 10,059 participants.

In all the Jewish communities in the small and densely populated area of Israel at that time mortality was being fully reported. The coverage of the national registry is assumed to be 100% and this should certainly hold for civil servants and municipal employees. The paucity of emigration from Israel by tenured active or state-pensioned retired, middle aged and elderly workers suggests that few were not included in the mortality registry.

Statistical Analyses

For descriptive purposes, SES is presented in its five categories. Blood pressure status is categorized as the highest of 1- SBP<120 or DBP <80; 2- SBP 121-130 or DBP 81-85; 3- SBP 131-140 or DBP 86-90; 4- SBP>140 or DBP>90. Cholesterol (1963 measure) is presented in three categories: up to 200mg/dL, between 200 and 239, and above 239. Multivariate stepwise analyses, on the continuous forms of these variables, was performed by use of the Cox proportional hazards model for the 1713 subjects who had data on both dementia and mortality statuses. Since systolic and diastolic blood pressure were highly correlated ($r=.78$) two analyses were performed, one for each. The model did not incorporate age as a covariate since we used age as the time axis. The model incorporated SES, total cholesterol, and smoking status (ever or never) in the first step; either systolic or diastolic blood pressure in the second step; dementia (yes/no) in the third step; and the interactions of dementia with each of the other predictors in the fourth step. Adjusted hazard ratios (HR) and 95% confidence intervals (CI) for each predictor were obtained from the step in which it was entered. Diabetes was not included since the number of surviving men with baseline diagnosis of diabetes was very small ($n=23$) and the estimates unstable. As a common practice at that time, anyone suffering from a stroke was granted retirement on health grounds and thus none of these employed civil servants had experienced stroke prior to 1963.

Results

Over a period of 6 years, of the 1713 subjects included in this analysis, 718 (42%) subjects died. Of the 307 demented subjects, 71.8% died while 35.4% of the 1407 non-demented subjects died. The median age at death of the demented subjects was 84.7 (95% CI 84.6-85.0, inter-quartile range-82.9 to 87.6) and for the non demented it was 85.7 (84.9-86.3, inter-quartile range-82.7 to 89.2). Table 1 presents age-adjusted rates of sociodemographic and cardiovascular risk factors by dementia and mortality status.

Increasing systolic and diastolic blood pressure, smoking and decreasing SES were associated with higher mortality while total cholesterol was not.

Table 2 presents age-adjusted mortality per 1000 person-years by sociodemographic and cardiovascular risk factors and the ratios of demented to non-demented mortality. Overall, demented were at higher risk of mortality than non-demented. The ratios were similar across the different levels of hypertension and of smoking. The ratio for the lowest SES category was smaller than for the other SES categories, consistent with less impact of dementia on mortality in this group. Similarly, the ratio for the highest cholesterol category was smaller than for the other two cholesterol categories.

Table 3 presents the results of the multivariate survival analyses. Compared with subjects without dementia, demented subjects had a HR for mortality of 2.27. Other risk factors associated with mortality were SES (.94 per SES category), higher systolic (1.16 per 20mm Hg) and diastolic blood pressure (HR 1.15 per 10mm Hg), and smoking (HR 1.38). Midlife total cholesterol was not associated with mortality. None of the interactions of the risk factors with dementia was significant, i.e. the risk factors did not show a differential association with mortality according to dementia status. Similar multivariate analyses including also area of birth (as an additional socio-demographic variable, HR for mortality in demented subjects: 2.26 (1.91-2.68)), body mass index (HR 2.25, 1.91-2.67), or percent calorie from saturated fat (as a surrogate for nutrition, HR 2.27, 1.91-2.68) left the results essentially unchanged.

Discussion

Numerous studies have examined factors predictive of long-term mortality but studies examining midlife risk factors with predictive importance for survivors several decades later are few^{34, 35}. We were unable to find studies examining associations of midlife risk factors and mortality in persons with known late-life dementia status. This study examined 6- year (2000 to 2006) mortality rate in subjects who participated in the IIHD dementia component. Consistently with other studies, mortality risk was doubled in demented subjects compared to non-demented subjects, after controlling for these sociodemographic and midlife cardiovascular risk factors. This increased rate of death is consistent with several other studies^{8, 11, 36-39} suggesting that there is a link between cognitive compromise and death that is not explained by these factors.

Identifying risk factors—especially modifiable ones—associated with length of survival in demented subjects compared to non-demented subjects would be important because they might provide insights into the disease process, especially if measured several decades before dementia assessment and death. Some studies investigating factors associated with mortality within the demented group, showed that the relationships of factors such as age, gender, and other physical disorders with mortality found among the general population disappeared or were reduced if only dementia cases were analyzed^{11, 40}. It has been argued that, whatever factors reduce life expectancy of demented individuals, they are so strong that they override other possible predictors of mortality⁴¹. However, in this study, midlife sociodemographic and cardiovascular risk factors were not only associated with mortality within the non-demented group, but had similarly strong associations within the demented group. It is possible that these discrepant results are explained by our risk factors having been collected 36 years before the mortality period, while in the other studies risk factors were measured closer to death so they might have been affected by the dementing process⁴¹. Furthermore, although not associated with differential mortality among persons with dementia, these risk factors for mortality are also associated with risk of developing dementia.

Dementia is a major cause of death in elderly men and women in the developed world^{3, 8, 38, 39, 42, 43}. Respiratory disease (primarily bronchopneumonia) is the primary cause of death of demented patients based on both death certificates and on autopsies^{5-7, 9, 10, 44}. In contrast, neoplasm and cardiovascular disease are the primary causes of death of non-demented patients^{6, 9}. Consistent with this, when severity of dementia is taken into account, mildly demented subjects have higher rates of cardiovascular causes of death than moderately or severely demented subjects⁷.

The majority of studies relating cardiovascular risk factors to dementia, evaluate dementia rates according to presence of the risk factor studied (for example diabetics vs. non-diabetics^{45, 46}). Fewer studies reverse the inference by evaluating the rates of cardiovascular risk factors according to dementia status. The latter are inconsistent with regard to prevalence of cardiovascular risk factors in demented and non-demented subjects. Some⁴⁷ found that smoking, hypertension and cholesterol are higher in demented subjects. In the IIHD¹⁵ the rates of these risk factors were similar in the two groups. Others⁴⁸ found that demented subjects have similar rates of smoking and hypertension but lower levels of cholesterol. Higher rates of diabetes and increased diabetes related markers (glucose, insulin, HbA1C) in demented subjects are relatively consistent findings⁴⁹. The inconsistency of these reported relationships suggests that it would be simplistic to interpret both dementia and cardiovascular risk factors as markers of a single underlying process affecting mortality.

Consistently with other studies of both midlife and proximal predictors of late-life mortality, SES^{26, 27, 50}, systolic and diastolic blood pressure^{29, 31}, and smoking²⁸ were associated with mortality at that age range. Midlife total cholesterol was not associated with mortality, consistent with some studies^{eg.51} but not with others^{eg.30}. The difference in average midlife total cholesterol, with survivors to age 80 having an average value lower by 7mg/dL than non-survivors in this study, is essentially identical to the difference in midlife total cholesterol observed in the Framingham study for survival to age 85³⁵. It should be noted that although Tables 1 and 2 suggest apparent mitigation of the deleterious effects of dementia on mortality in the lowest SES category and in the highest cholesterol category, these counter-intuitive patterns were not substantiated in the multivariate analysis of Table 3 that controlled for other risk factors. Furthermore, it should be noted that Table 1 presents the crude proportions of alive and dead subjects without taking into consideration the age at the beginning of the IIHD dementia follow up, which was on average 5 years later in the highest SES category (~85) compared to the lowest (~80).

Most studies have estimated associations between mortality and sociodemographic and cardiovascular characteristics relatively proximal to death. A strength of the present study is that these characteristics were collected 36 years before dementia assessment so that they are more likely to reflect disease processes rather than proximal causes of death. Another strength of our study is its representative sampling from the male Israeli civil servants population in contrast to samples from institutions or clinical settings. This study examined the relationship of late-life dementia on mortality since it was limited to subjects who had survived to late life. It considered only the 6-year mortality among the 36-year survivors of the IIHD original sample, so it may not be representative of mortality over a longer span. Since dementia was not assessed in IIHD subjects who died before 1999, its effect on mortality for earlier ages could not be evaluated. Another limitation of this study is the absence of information on either age of onset or severity of dementia both of which have been associated with mortality. Finally, the IIHD included only male participants so that generalization of these results to women must be done cautiously.

In conclusion, dementia was associated with more than double the risk of mortality but this increased risk did not reflect exacerbation by midlife sociodemographic and cardiovascular

risk factors. Our findings suggest that the dementing process itself or its consequences may go beyond well established midlife risk factors for mortality.

Acknowledgments

This study was supported by NIA grants K01 AG023515-01, RO1 AG034087, and the Graubard Fund for Dr. Beerli, P01 AG02219 and the Berkman Trust for Dr. Haroutunian, and P50 AG05138 for Dr. Sano.

Reference List

1. Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: a Delphi consensus study. *Lancet* 2005 December 17;366(9503):2112–7. [PubMed: 16360788]
2. Ewbank DC. Deaths attributable to Alzheimer's disease in the United States. *Am J Public Health* 1999 January;89(1):90–2. [PubMed: 9987474]
3. Foley DJ, Brock DB, Lanska DJ. Trends in dementia mortality from two National Mortality Followback Surveys. *Neurology* 2003 February 25;60(4):709–11. [PubMed: 12601118]
4. Dewey ME, Saz P. Dementia, cognitive impairment and mortality in persons aged 65 and over living in the community: a systematic review of the literature. *Int J Geriatr Psychiatry* 2001 August; 16(8):751–61. [PubMed: 11536341]
5. Helmer C, Joly P, Letenneur L, Commenges D, Dartigues JF. Mortality with dementia: results from a French prospective community-based cohort. *Am J Epidemiol* 2001 October 1;154(7):642–8. [PubMed: 11581098]
6. Beard CM, Kokmen E, Sigler C, Smith GE, Pettersson T, O'Brien PC. Cause of death in Alzheimer's disease. *Ann Epidemiol* 1996 May;6(3):195–200. [PubMed: 8827154]
7. Kukull WA, Brenner DE, Speck CE, et al. Causes of death associated with Alzheimer disease: variation by level of cognitive impairment before death. *J Am Geriatr Soc* 1994 July;42(7):723–6. [PubMed: 8014346]
8. Aguero-Torres H, Fratiglioni L, Guo Z, Viitanen M, Winblad B. Mortality from dementia in advanced age: a 5-year follow-up study of incident dementia cases. *J Clin Epidemiol* 1999 August; 52(8):737–43. [PubMed: 10465318]
9. Attems J, König C, Huber M, Lintner F, Jellinger KA. Cause of death in demented and non-demented elderly inpatients; an autopsy study of 308 cases. *J Alzheimers Dis* 2005 September;8(1): 57–62. [PubMed: 16155350]
10. Burns A, Jacoby R, Luthert P, Levy R. Cause of death in Alzheimer's disease. *Age Ageing* 1990 September;19(5):341–4. [PubMed: 2251969]
11. Molsa PK, Marttila RJ, Rinne UK. Survival and cause of death in Alzheimer's disease and multi-infarct dementia. *Acta Neurol Scand* 1986 August;74(2):103–7. [PubMed: 3776457]
12. Gallo JJ, Breitner JC. Alzheimer's disease in the NAS-NRC Registry of aging twin veterans, IV. Performance characteristics of a two-stage telephone screening procedure for Alzheimer's dementia. *Psychol Med* 1995 November;25(6):1211–9. [PubMed: 8637951]
13. Tuokko H, Frerichs RJ. Cognitive impairment with no dementia (CIND): longitudinal studies, the findings, and the issues. *Clin Neuropsychol* 2000 November;14(4):504–25. [PubMed: 11262720]
14. Beerli MS, Werner P, Davidson M, Schmidler J, Silverman J. Validation of the modified telephone interview for cognitive status (TICS-m) in Hebrew. *Int J Geriatr Psychiatry* 2003 May;18(5):381–6. [PubMed: 12766912]
15. Schnaider BM, Goldbourt U, Silverman JM, et al. Diabetes mellitus in midlife and the risk of dementia three decades later. *Neurology* 2004 November 23;63(10):1902–7. [PubMed: 15557509]
16. Groen JJ, Medalie JH, Neufeld HN, et al. An epidemiologic investigation of hypertension and ischemic heart disease within a defined segment of the adult male population of Israel. *Isr J Med Sci* 1968 March;4(2):177–94. [PubMed: 5650048]
17. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975 November;12(3):189–98. [PubMed: 1202204]

18. Brandt J, Folstein SE, Folstein MF. Differential cognitive impairment in Alzheimer's disease and Huntington's disease. *Ann Neurol* 1988 June;23(6):555–61. [PubMed: 2970248]
19. Ferrucci L, Del Lungo I, Guralnik JM, et al. Is the telephone interview for cognitive status a valid alternative in persons who cannot be evaluated by the Mini Mental State Examination? *Aging (Milano)* 1998 August;10(4):332–8. [PubMed: 9825025]
20. Silverman JM, Keefe RS, Mohs RC, Davis KL. A study of the reliability of the family history method in genetic studies of Alzheimer disease. *Alzheimer Dis Assoc Disord* 1989;3(4):218–23. [PubMed: 2597424]
21. Silverman JM, Breitner JC, Mohs RC, Davis KL. Reliability of the family history method in genetic studies of Alzheimer's disease and related dementias. *Am J Psychiatry* 1986 October; 143(10):1279–82. [PubMed: 3766791]
22. Werner P, Heinik J, Mendel A, Reicher B, Bleich A. Examining the reliability and validity of the Hebrew version of the Mini Mental State Examination. *Aging (Milano)* 1999 October;11(5):329–34. [PubMed: 10631883]
23. Reisberg H, Ferris SH, Sclan SG. Empirical evaluation of the global deterioration scale for staging Alzheimer's disease. *Am J Psychiatry* 1993 April;150(4):680–2. [PubMed: 8465902]
24. Wade J, Hachinski V. Revised ischemic score for diagnosing multi-infarct dementia. *J Clin Psychiatry* 1986 August;47(8):437–8. [PubMed: 3733680]
25. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th Edition. Washington: American Psychiatric Association; 1994.
26. Rask K, O'Malley E, Druss B. Impact of socioeconomic, behavioral and clinical risk factors on mortality. *J Public Health (Oxf)* 2009 June;31(2):231–8. [PubMed: 19279019]
27. Goldbourt U, Schnaider-Beerli M, Davidson M. Socioeconomic status in relationship to death of vascular disease and late-life dementia. *J Neurol Sci* 2007 June 15;257(1-2):177–81. [PubMed: 17395207]
28. Dankner R, Goldbourt U, Boyko V, Reicher-Reiss H. Predictors of cardiac and noncardiac mortality among 14,697 patients with coronary heart disease. *Am J Cardiol* 2003 January 15;91(2):121–7. [PubMed: 12521620]
29. Weitzman D, Goldbourt U. The significance of various blood pressure indices for long-term stroke, coronary heart disease, and all-cause mortality in men: the Israeli Ischemic Heart Disease study. *Stroke* 2006 February;37(2):358–63. [PubMed: 16373641]
30. Okamura T, Tanaka H, Miyamatsu N, et al. The relationship between serum total cholesterol and all-cause or cause-specific mortality in a 17.3-year study of a Japanese cohort. *Atherosclerosis* 2007 January;190(1):216–23. [PubMed: 16529754]
31. Okayama A, Kadowaki T, Okamura T, Hayakawa T, Ueshima H. Age-specific effects of systolic and diastolic blood pressures on mortality due to cardiovascular diseases among Japanese men (NIPPON DATA80). *J Hypertens* 2006 March;24(3):459–62. [PubMed: 16467648]
32. Eaton CB, Medalie JH, Flocke SA, Zyzanski SJ, Yaari S, Goldbourt U. Self-reported physical activity predicts long-term coronary heart disease and all-cause mortalities. Twenty-one-year follow-up of the Israeli Ischemic Heart Disease Study. *Arch Fam Med* 1995 April;4(4):323–9. [PubMed: 7711918]
33. Anderson JT, Keys A. Cholesterol in serum and lipoprotein fractions; its measurement and stability. *Clin Chem* 1956 June;2(3):145–59. [PubMed: 13317101]
34. Willcox BJ, He Q, Chen R, et al. Midlife risk factors and healthy survival in men. *JAMA* 2006 November 15;296(19):2343–50. [PubMed: 17105797]
35. Terry DF, Pencina MJ, Vasan RS, et al. Cardiovascular risk factors predictive for survival and morbidity-free survival in the oldest-old Framingham Heart Study participants. *J Am Geriatr Soc* 2005 November;53(11):1944–50. [PubMed: 16274376]
36. Guhne U, Matschinger H, Angermeyer MC, Riedel-Heller SG. Incident dementia cases and mortality. Results of the Leipzig Longitudinal Study of the Aged (LEILA75+). *Dement Geriatr Cogn Disord* 2006;22(3):185–93. [PubMed: 16888386]
37. Noale M, Maggi S, Minicuci N, et al. Dementia and disability: impact on mortality. The Italian Longitudinal Study on Aging. *Dement Geriatr Cogn Disord* 2003;16(1):7–14. [PubMed: 12714794]

38. Meller I, Fichter MM, Schroppel H. Mortality risk in the octo- and nonagenarians: longitudinal results of an epidemiological follow-up community study. *Eur Arch Psychiatry Clin Neurosci* 1999;249(4):180–9. [PubMed: 10449593]
39. Tsuji I, Minami Y, Li JH, et al. Dementia and physical disability as competing risks for mortality in a community-based sample of the elderly Japanese. *Tohoku J Exp Med* 1995 June;176(2):99–107. [PubMed: 7482527]
40. Molsa PK, Marttila RJ, Rinne UK. Long-term survival and predictors of mortality in Alzheimer's disease and multi-infarct dementia. *Acta Neurol Scand* 1995 March;91(3):159–64. [PubMed: 7793228]
41. Aeværsson O, Svanborg A, Skoog I. Seven-year survival rate after age 85 years: relation to Alzheimer disease and vascular dementia. *Arch Neurol* 1998 September;55(9):1226–32. [PubMed: 9740117]
42. Deaths: Final Data for 2006. National Vital Statistics Reports. 2009 Apr 17. Available at: URL: http://www.cdc.gov/NCHS/data/nvsr/nvsr57/nvsr57_14.pdf
43. Hoyert DL, Rosenberg HM. Alzheimer's disease as a cause of death in the United States. *Public Health Rep* 1997 November;112(6):497–505. [PubMed: 10822478]
44. Brunnstrom HR, Englund EM. Cause of death in patients with dementia disorders. *Eur J Neurol* 2009 April;16(4):488–92. [PubMed: 19170740]
45. Akomolafe A, Beiser A, Meigs JB, et al. Diabetes mellitus and risk of developing Alzheimer disease: results from the Framingham Study. *Arch Neurol* 2006 November;63(11):1551–5. [PubMed: 17101823]
46. Ott A, Stolk RP, van HF, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology* 1999 December 10;53(9):1937–42. [PubMed: 10599761]
47. Hayden KM, Zandi PP, Lyketsos CG, et al. Vascular risk factors for incident Alzheimer disease and vascular dementia: the Cache County study. *Alzheimer Dis Assoc Disord* 2006 April;20(2):93–100. [PubMed: 16772744]
48. Vanhanen M, Koivisto K, Moilanen L, et al. Association of metabolic syndrome with Alzheimer disease: a population-based study. *Neurology* 2006 September 12;67(5):843–7. [PubMed: 16966548]
49. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol* 2006 January;5(1):64–74. [PubMed: 16361024]
50. Gerber Y, Goldbourt U, Drory Y. Interaction between income and education in predicting long-term survival after acute myocardial infarction. *Eur J Cardiovasc Prev Rehabil* 2008 October;15(5):526–32. [PubMed: 18622301]
51. Olsen TS, Christensen RH, Kammersgaard LP, Andersen KK. Higher total serum cholesterol levels are associated with less severe strokes and lower all-cause mortality: ten-year follow-up of ischemic strokes in the Copenhagen Stroke Study. *Stroke* 2007 October;38(10):2646–51. [PubMed: 17761907]

Figure 1.
Flow of subjects

Table 1

Sample characteristics by dementia and survival status in 2006

	Demented				Non-demented				Whole Sample			
	Alive	Dead	Total	Statistic, p-value ¹	Alive	Dead	Total	Statistic, p-value ²	Alive	Dead	Total	Statistic, p-value ³
N	87	220	307	—	907	499	1406	—	994	719	1713	—
Age at censorship												
Mean (SD)	86.6 (3.8)	85.93 (4.9)	86.13 (4.7)		85.92 (3.4)	84.91 (4.4)	85.56 (3.8)		85.98 (3.44)	85.22 (4.6)	85.66 (4.0)	
SES (%)												
1-low	41.4	26.2	30.5	$\chi^2 = 7.85$	10.1	13.1	11.2	$\chi^2 = 3.63$	12.8	17.2	14.7	$\chi^2 = 10.4$
2	26.4	30.8	29.5	df=4	22.8	22.2	22.6	df=4	23.1	24.9	23.9	df=4
3	18.4	26.2	24.0	p=0.10	41.2	40.2	40.8	p=0.46	39.2	35.9	37.8	p=0.03
4	5.7	10.0	8.8		12.0	12.3	12.1		11.4	11.6	11.5	
5-high	8.0	6.8	7.1		14.0	12.1	13.3		13.4	10.5	12.2	
SBP mm Hg												
Mean (SD)	125.6 (12.4)	128.8 (14.8)	127.9 (14.2)	t=1.78 df=305 p=0.08	126.0 (14.5)	128.6 (15.3)	126.9 (14.8)	t=3.15 df=1404 p=0.002	125.9 (14.4)	128.6 (15.1)	127.1 (14.7)	t=3.74 df=1701 p=0.0002
DBP mm Hg												
Mean (SD)	79.9 (7.7)	81.3 (8.4)	80.9 (8.2)	t=1.35 df=305 p=0.18	79.8 (9.2)	81.6 (9.9)	80.4 (9.5)	t=3.42 df=1404 p=0.0007	79.8 (9.1)	81.5 (9.4)	80.5 (9.3)	t=3.84 df=1701 p=0.0001
Blood pressure status (%)												
1- SBP<120 or DBP<80	35.6	29.1	30.9	$\chi^2 = 3.88$	38.2	29.7	35.1	$\chi^2 = 14.13$	38.0	29.5	34.4	$\chi^2 = 19.21$
2- SBP 121-130 or DBP 81-85	31.0	26.8	28.0	df=3	24.9	26.3	25.4	df=3	25.4	26.4	25.8	df=3
3- SBP 131-140 or DBP 86-90	20.7	22.7	22.2	p=0.27	22.4	23.5	22.8	p=0.003	22.2	23.3	22.7	p<0.0001
4- SBP>140 or DBP>90	12.6	21.4	18.9		14.6	20.6	16.7		14.4	20.8	17.1	
Smoking (%)												
	57.5	63.8	62.0	$\chi^2 = 8.62$ df=1 p=0.13	59.1	67.1	61.9	$\chi^2 = 22.09$ df=1 p=0.001	59.0	66.8	61.9	$\chi^2 = 9.05$ df=1 p=0.003

			Demented			Non-demented			Whole Sample		
			Alive	Dead	Total	Statistic, p-value ¹	Alive	Dead	Total	Statistic, p-value ²	Statistic, p-value ³
Cholesterol mg/dL (%)											
≤200			59.8	52.0	54.2	χ ² = 5.96 df=2 p=0.051	50.2	46.5	48.9	χ ² = 1.92 df=2 p=0.38	χ ² = 1.25 df=2 p=0.54
201-239			20.7	34.4	30.5		35.2	36.6	35.7		
≥240			19.5	13.6	15.3		14.6	16.9	15.4		

¹ Comparisons of alive and dead demented subjects;

² Comparisons of alive and dead non-demented subjects;

³ Comparison of alive and dead- whole sample

Table 2
Age-adjusted mortality (per 1000 person-years) of demented and non-demented subjects
by sociodemographic and cardiovascular risk factors

	Demented	Non-demented	Ratio*
SES			
1-low	117	68	1.72
2	168	57	2.95
3	174	57	3.05
4	203	60	3.38
5-high	149	53	2.81
Blood pressure status			
1- SBP<120 or DBP<80	151	52	2.90
2- SBP 121-130 or DBP 81-85	160	65	2.46
3- SBP 131-140 or DBP 86-90	183	65	2.81
4- SBP>140 or DBP>90	213	84	2.53
Smoking			
Never	140	49	2.86
Past	166	65	2.55
Present (in 1963)	162	63	2.57
Cholesterol			
≤200	146	55	2.65
201-239	181	61	2.97
≥240	124	65	1.91

* Demented/non-demented

Table 3
Cox proportional hazard model for mortality by several midlife risk factors and late-life dementia

	Hazard Ratio	95% Confidence Interval	Wald χ^2 tests** (p-value)
Dementia	2.27	1.92-2.68	95.06 (<0.001)
SES (per category)	.94	.88-1.000	3.50 (0.062)
Systolic * (per 20mm Hg)	1.16	1.06-1.28	3.11 (0.002)
Diastolic * (per 10mm Hg)	1.15	1.06-1.25	9.67 (0.001)
Smoking (ever/never)	1.38	1.18-1.61	14.75 (<0.001)
Total cholesterol (per 40 mg/dL)	1.01	.93-1.10	0.29 (0.59)

* Since systolic and diastolic blood pressures were highly correlated, two separate multivariate survival analyses were performed, separately for systolic and diastolic blood pressure. The HRs for other variables control for SBP, and were essentially identical when controlling for DBP.

** df=1 for all Wald χ^2 tests