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Antecedents of Intact Cognition and Dementia at Age 90: A Prospective Study

George E. Vaillant, M.D.[1,*], **Olivia I Okereke, M.D. S.M.**[2], **Kenneth Mukamal, M.D.,M.P.H.**[3], and **Robert J. Waldinger, M.D.**[4]

[1]Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

[2]Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

[3]Department of Medicine, Beth Israel Deaconess Hospital, Harvard Medical School, Boston, Massachusetts, USA

[4]Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

Abstract

Objectives—To examine the possible antecedents of both dementia and sustained intact cognition at age 90 among men who underwent a prospective, multidisciplinary assessment from age 19 to 90, with little attrition.

Methods—A prospective 20-year reassessment of the 196 (out of 268) former Harvard College sophomores who survived until age 70. Begun in 1939 the Study gathered measurements of childhood environment, dominant personality traits, and objective mental and physical health over time, smoking in pack years, alcohol abuse and depression. Questionnaires were obtained every two years and physical exams every five years. Cognitive status was assessed at ages 80, 85 and 90.

Results—Despite addressing a wide variety health, behavioral and social factors over the lifespan, we observed few predictors with strong association with either intact cognition at age 90 (n = 40) or dementia (n = 44). Univariate analysis revealed seven suggestive predictors of intact cognition at age 90 or of dementia: warm childhood relationship with mother, exercise at age 60, high maternal education, young age of mother at subject's birth, low BMI, good physical health at 60, and late retirement. Only the first 3 variables: warm childhood relationship with mother, exercise at age 60, and high maternal education remained significant with logistic regression.

Conclusions—In this prospective study of long-lived, highly educated men several well-known putative predictors of AD did not distinguish those who over the next 20 years developed dementia from those with unimpaired cognition until age 90.

Correspondence to G. Vaillant. gvaillant@partners.org (mail to G. Vaillant, 151 Merrimac St (2nd Floor), Boston, Mass. USA 20014.

Keywords

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The factors leading to the development of clinical dementia remain puzzling. Of seven major factors commonly associated with Alzheimer's disease (AD): diabetes, midlife hypertension, smoking, depression, low educational attainment, cognitive inactivity, and physical inactivity (Barnes and Yaffe 2011), none have been consistently identified by prospective studies to play a causal role in AD. One reason for debate is the lack of multi-decade studies. Shorter, decade-long prospective studies (Bennett et al 2005, Albert et al 1995, Kawas et al 2000) can produce unreliable solutions, which may confuse association with cause. For example, are depression and diminished physical and intellectual activity causes of dementia or are they premonitory symptoms?

A second reason for debate is the absence of autopsy examination. Most of these seven risk factors for AD, compellingly documented in the review by Barnes and Yaffe, have a known causal effect on small vessel disease. To claim causal attribution of these risk factors to AD arises from the fact that clinical dementia correlates only modestly with autopsy evidence of either AD or small vessel pathology alone (MRC CFAS 2001, Schneider et al 2007, Riley et al 2002). Rather, dementia is much more likely to occur when small vessel disease *and* amyloid plaques and tau tangles occur together making an either/or diagnosis uncertain. This suggests that the alleged predictors of AD may actually be predicting dementia partially due to small vessel disease (de la Torre, 2013). In addition, longitudinal studies like the Nun Study (Snowdon 1997) and the Rush Memory and Aging Project (Bennett et al 2005) have provided dramatic case studies reflecting discrepancies between Braak Staging of AD neuropathology and severity of dementia.

Our study uses 70 years of prospectively collected longitudinal data to examine the environmental predictors of sustained intact cognition and of dementia by age 90. The value of our study lies in the fact that due to high education (76% attended graduate school) and social class, our sample is unusually long-lived and had less than the expected number of risk factors for early vascular disease. (U.S. Census data reveals that the 30% survival at 90 of the original 268 men in our Study was roughly 10 times the expected proportion for white men born in 1920. (National Vital Statistics Reports 2007). When the Study members were contrasted to an Inner City comparison group (Vaillant 2002), both vascular risk factors and mortality (10 years difference) differed significantly. The Inner City men manifested diabetes, a BMI > 29, and heavy smoking (40+ pack-years) three times more frequently than our Study sample and a diastolic blood pressure at age 50 >89 mm hg twice as often.

The present report is of the 196 College men (out of an original cohort of 268) who survived until age 70—when the first Study members developed dementia—and who have been followed prospectively every two years from adolescence until death or age 90 (Vaillant 2002, Vaillant 2012). First, the Study provides a means of addressing many of the cart/horse temporality directionality questions related to the environmental contributions to dementia. Second, because of the cohort's relatively low prevalence of vascular risk factors, it is possible to question whether these are not risk factors for vascular dementia rather than AD.

Third, the long follow-up permits examination of childhood risk factors for dementia. Admittedly, due to its small numbers and selected cohort, our study will only be hypothesis generating.

METHODS

Subjects

The Study of Adult Development (Vaillant 1977) originally consisted of 268 Caucasian sophomore males at Harvard University (born circa 1920) drawn from the graduating classes of 1940–1944. Selection criteria included the absence of known physical and mental illness and a satisfactory scholastic admission record. Fifty percent of the men were on scholarship and/or had to work during college.

During college an interdisciplinary team of physiologists, internists, psychiatrists, psychologists and physical anthropologists assessed the men. The students' parents were interviewed, and extensive family, social and medical histories were obtained. Most of the surviving men were re-interviewed at approximately ages 25, 30, 50, 65 and 85 years. Two-thirds of the men obtained graduate degrees and most have worked as physicians, lawyers, university professors or business executives.

Since age 25, the men have been asked to complete questionnaires every two years and since age 45 complete records of their physical examinations have been obtained every five years until the present and interviews on most about every 15 years. All men who survived to age 70 and who were still active in the study (n = 196) were included.

MEASURES

A. Antecedent Variables (Age 0–20)

Parental Social Class—This was estimated by the 5-point classification devised by Hollingshead and Redlich (1958).

Head Circumference—Measured by a physical anthropologist circa age 19.

Intelligence Quotient (IQ)—IQ was extrapolated from the Army Alpha for Verbal Ability (Wells, Woods, 1946). (Range 110 to >150)

Warmth of Childhood excluding relationship with Mother (Age 0–18 years)—Two research assistants, blind to data gathered after age 20, separately reviewed 10–20 hours of social history gathered from the participants and their families. They rated the men on five subscales, described in detail elsewhere (Vaillant, 1974, 1995). A high score on the sum of four of these subscales reflected familial cohesion, good relations with father, good relations with siblings, and the rater's global assessment of childhood (range: 5–20). Inter-rater reliability was 0.71.

Mother/Child Relationship (the fifth subscale)—1 = not encouraging self-esteem (distant, hostile mother or upbringing overly punitive, overprotective, or mother absent, or seductive. 3 = rater neutral. 5 = warm, nurturing, encouraging of autonomy, helping boy develop initiative.

B. Antecedent Variables (Age 20–60)

Smoking—The men's smoking history was obtained from biennial questionnaires from age 22 to 47 and was summarized in pack/years (Vaillant et al, 1995).

Alcohol Abuse and Dependence (Age 20–60)—Medical and psychiatric records, interviews and biennial questionnaires were reviewed. Alcohol problems were assessed on 20 to 60 occasions. Four or more lifetime problems were usually classified as alcohol abuse (Vaillant et al 1991). DSM-III criteria (American Psychiatric Association 1980) were used to create a three-point scale: 1 = No or rare problems, 2 = Alcohol abuse, 3 = Alcohol dependence.

Depressive Disorder (Age 20–50) (Vaillant et al, 1996)—A psychiatrist, blinded to other ratings, reviewed the complete records (from college until age 50) of the then active members (n = 223) for nine correlates of depression not explicable due to concurrent alcoholism. All men with 3 or more future DSM-III indicators of depression (n = 19) were classified as having probable major depressive disorder; the mean age of onset was 34 ± 8 yr. The mean number of indicators was 5.9 ± 1.6 among the depressed men contrasted with 0.10 ± 0.38 indicators for the remaining 204 men. (The DSM-III was not yet published.

Retirement—This was estimated by the sum of retirement status from age 60–70. 1 = Fully employed for all of the decade; 3 = Fully or partly employed for much of the decade; 6 = fully retired for most of the decade.

Social Supports (Age 50–70) (Vaillant et al, 1998)—After reviewing 11 biennial questionnaires and all interview data, an independent rater assigned social support ratings. The rating is based on 6 items; score: range 14 = best; 0 = worst. The 6 items were: warm marriage (doubled), Close Adult Sibling Relationships, Close to Kids, Use of Confidantes, Regular Recreation with Friends, Other Contact with Friends. Interclass correlations computed for 3 raters on 30 cases was .92.

Years of Education—This ranged from 14 (college dropout) to 20 (Ph.D. or M.D.)

Objective Physical Health—Every 5 years since age 45 each man's health status (using data from physical examination, blood chemistries, EKG, and chest x-ray) has been rated by an internist blinded to other data. 1 = physical health excellent; 2 = minor irreversible problems (e.g., glaucoma, gout); 3 = life shortening irreversible illness without permanent disability (e.g. diabetes, myocardial infarction); 4 = chronic illness with significant disability (e.g. multiple sclerosis); 5 = deceased (Vaillant, 1979). Death certificates were obtained for all the deceased men, except for three who died abroad.

Body mass index at age 50—This was calculated from age 50 self-reported height and physician reported weight as kg/m^2.

Exercise (Age 45–60) (Schnurr et al 1990)—Exercise between age 45 and 60 (reported on multiple questionnaires and interviews), were rated on a 1 to 3 scale defined as 1 ("heavy") = > 2000 kcal/wk, 2 = 500–2000 kcal/wk, 3 (little) = < 500 kcal/week (using the tables provided in the Harvard Sports Code) (Taylor 1979).

Midlife Hypertension—A diastolic BP > 89 mm Hg at age 50, from the objective physical exam.

Ancestral Longevity—In order to control for adventitious death, longevity was calculated by taking the average age at death of oldest maternal and oldest paternal first-degree relative (range 67.5 to 97.5) (Vaillant 1991).

C. Outcome Measures

Intact Cognition—This was determined using the Telephone Interview for Cognitive Status (TICS) (Brandt et al 1988). This eleven-item interview was administered by telephone to all surviving College men within an average of 7 months of their birthday at age 80, age 85, and age 90. The 5 men born in 1923 were tested at age 89. Men severely disabled from dementia were not tested. The TICS includes a range of cognitive domains, including orientation, registration, short-term recall, concentration, serial subtraction, and language. Scores range from 0 to 41. Our arbitrary cut-points were based on 10 years of prospective follow-up. A score of 33–31 suggested MCI (Mild Cognitive Impairment); in our sample a score, below 31 suggested dementia. (Eventually, all men but one receiving a TICS score<31 progressed by corroborating information to severe dementia and/or death. The exception, a man with a TICS score of 28 at age 85, was diagnosed with a reversible brain pathology and attained a TICS of 33 at age 90. Three very ill men who died within 12 months of receiving a TICS score <31 were excluded to minimize the possibility that the apparent dementia merely reflected terminal illness.) Patience and, sometimes, visual presentation were used to overcome problems in hearing.

The TICS has been shown to have good test-retest reliability as well as adequate specificity and sensitivity for dementia (Carpenter et al, 1995). The TICS is highly correlated ($r = 0.94$) with the Mini-Mental State Examination (MMSE) (Folstein et al 1975).

To diagnose dementia, in addition to the arbitrary TICS score of <31, we also relied on our in depth knowledge of each man—compensation for the small sample. Clinical evidence for dementia included systematic review of information from relatives, psychosocial course after 70, results from the physical exams conducted every five years, and death certificates.

Since 1992 this project has been reviewed and approved annually by the Brigham and Women's Hospital and, more recently, by Partners' IRB.

STATISTICAL METHODS

Variables were examined in their continuous and dichotomized forms. Because many of our continuous variables were not normally distributed, Spearman's rho (two tailed) was used as the statistical test of correlation in univariate analyses. Mean values were imputed to the few cases with missing values. Although Spearman correlations are unorthodox for binary variables (Table 3), our *p* values did not differ significantly from chi-square (Fisher's Exact Test) and Wilcoxon Tests.

RESULTS

Of the 268 men in the original sample, 31 (12%) were excluded due to early death (before 45) or withdrawal from the Study. Although usually included in most Study reports, 41 additional men (15%) were excluded because they died before age 70 when the Study members became at risk for dementia. The 72 men excluded from this Study were no different from the 196 men included in the Study – in terms of IQ, social class, obesity, or the maternal variables to be discussed later. The excluded men manifested significantly less exercise, education, and long-lived ancestors and more depression and vascular risk factors.

Thirteen men (5%) not receiving the TICS were included due to clear dementia before 80 (confirmed either by family and/or physician (85%), and/or by death certificate (85%). By age ninety, 31 additional men were classified demented by TICS, and confirmed by family report and/or by medical exam making a total of 44 (23%) cases of dementia.

At age 80 142 men received telephone cognitive testing (TICS) as did the surviving men at age 85 and 90. By age 90 96 (49%) men had died (including 41 men, untested by the TICS who died before 80 without any evidence of dementia by history or physical exam, death certificate or questionnaire). Fourteen men developed dementia between 70 and 79; 29 (twice as many) developed dementia between 80 and 89. (Of the 34 out of 44 men with dementia who have died, an average of 5 years elapsed between diagnosis and death.) Only seven (16%) of the 44 men have suffered with identified dementia for more than 7 years before death.

At age 90, besides the 96 dead and the 44 men with dementia, 40 men (20%) were still alive with a TICS >33 at 90 and the remaining 16 (8%) of the original 196 men survived but with a TICS of 33–31) classified as MCI. As of this writing (2013) 6 of these 16 are already dead, and 4 became demented at an average of 2 years after their 90th birthday.

Table 1 illustrates that the TICS, despite its relative simplicity and inherent limitations, performed very well over the long term. Over a ten-year period, a score above 33 remained very stable until the onset in a few men of frank dementia. In contrast, a score of 31–33, similar to current assessments of amnestic mild cognitive impairment (MCI) (Cook et al 2009, Petersen et al 2009), was related to progression to incipient dementia. Only 4 of the 58 men scoring 36 or above at age 80 were demented ten years later. Only 5 of the 34 men scoring less than 34 at age 80 were alive; 2 of these 5 still had MCI and 3 suffered from dementia.

Table 2 performs three tasks. First, it examines the correlates of relative physical health at age 70 among the 196 survivors. Second, it examines the correlates of dementia. In this column, the Barnes and Yaffe's 7 putative predictors of AD (with the exception of exercise) are clearly insignificant. (Diabetes before age 70 was too rare to be included.) Finally, Table 3 contrasts the 44 men who suffered dementia before 90 (scored 0) with their 40 peers who survived until 90 with a TICS > 33 (scored 1). In our long-lived, relati men with relatively few vascular risk factors, most of the 7 risk factors listed in the introduction played a minor role in distinguishing the men with intact cognition at 90 from those with dementia. However, the 14 men who from clinical course and death certificate were suspected of “multi-infarct dementia” had three times as many vascular risk factors as the 17 men with dementia clinically suspected to be due to Parkinson’s disease or AD. Contrary to findings from shorter prospective studies, in our multi-decade study small head circumference (Mortimer et al, 2001), poor social supports, and no volunteer activities did not appear to be major risk factors for dementia.

Table 3 employs logistic regression to examine the variables leading to sustained intact cognition rather than dementia. The positive effect of exercise on late life cognition has received wide attention (Lautenschlager et al 2008, Ahiskog et al 2011) and was confirmed in our data. The importance of early maternal factors to sustained cognition is more surprising.

DISCUSSION

Without postmortem data, it seemed fruitless to try to divide men with vascular dementia from AD. However, concomitant vascular pathology is often critical in catalyzing existing AD neuropathology into clinical dementia. Much of the variance leading to AD per se can be ascribed to genetic factors (Plomin et al 1994, Pedersen et al 2004, Bird 2005).

In our highly educated cohort, the dementia rate—14 per 1,000 person-years (age 76–85) was about half of the EURODEM multi-study rate at age 76–85 (Launer et al 1999). At age 85 the prevalence of 25% was roughly equal to the average prevalence of 22% reported by Misiak et al (2013) for multiple countries. As of this writing, at age 92–96 only 10 (19%) of the 54 surviving men (out of 196) whose status is known appear to suffer from dementia.

An interesting finding of this prospective study was that in the absence of dementia, which *is* age dependent, advancing age per se may be less important than many believe as a cause of late life cognitive decline in individuals without dementia, multiple vascular risk factors or depression (Jacquimin-Gadda et al 1997). In our study, between age 80 and 90 the mean TICS score of the 40 men still cognitively intact (only 8 of whom had even a single vascular risk factor) declined by just 0.65 points (2 times the standard error of the mean), but still an only barely significant decline. In other words, without risk factors the human brain in its ninth decade may not be destined to lose significant function. Admittedly, those who survive until age 90 may also be blessed with unusual cognitive reserve.

While poor social network/support has been postulated as a cause of AD (Bennett et al 2006, Fratiglioni et al 2000), our longer-term data found social supports correlated with vascular risk factors (rho .30, p< .001) (not in table) but not with dementia. In short, while exploratory, our results suggest that vascular risk factors, especially alcoholism and smoking, may lead to both low social supports and to vascular disease, and hence poor social supports may not be a primary cause of dementia.

In our study depression before age 50 (a frequently cited contributor to dementia) (Wilson et al 2008, Jorn 2001) was significantly correlated with vascular risk factors (rho .19, p = .016), but not with dementia 20 to 40 years later. On the other hand, convincing studies have indicated that depression in the elderly, not vascular disease, may be a prime cause of cognitive impairment. (Alexopoulos et al 1997, Barnes et al 2006). Previous studies linking depression to dementia are supported by well-designed meta-analyses of existing literature (Ownby et al 2006, Diniz et al 2013). However, these positive studies depression was not ruled out as a cause of dementia—as in our Study—by two decades or more of separation between diagnosis of the two disorders. In addition, our study is not alone in failing to observe a significant correlation between depression and dementia (Jorn 2001). Finally, we observed that depression was positively correlated (Rho .25, p<. 001) with vascular risk factors, a potent cause of vascular dementia

To date, almost none of the cognitive aging literature has focused on emotional and relational aspects of early childhood environments. Yet, some studies have estimated that 50% of cognitive reserve is determined by childhood intelligence levels (Plassman et al 1995) and strongly influenced by the quality of emotional, nutritional, and relational inputs (Bennett et al 2003). Thus, an intriguing finding of the current study is its apparent link between late-life cognitive reserve and excellent childhood relations with mother (Crandell, Hobson 1999, Dreary et al 2000, Whalley et al 2004, Fritsch et al 2007) and maternal education. That this relationship is not a false positive is supported by the fact that in this study warm mothering, *but not fathering*, significantly predicted a number of other key variables associated with superior cognition and achievement: I.Q., being in *Who's Who in America*, high midlife income, and remaining employed at age 70 (Vaillant 2012). Warm maternal, but not paternal, relationship correlates positively with the TICS at age 80 (rho .23, p<.01) and at 85 (rho .19, p<.05).

Our elite sample has significant limitations including limited measurements and statistical methods that are inherent in any research carried out over the many decades of this study. Ideally, the neuropsychological testing should have been more extensive (for example, the TICS does not cover executive problem-solving and judgment impairments), and our use of early retirement as an index of cognitive inactivity leaves much to be desired. Our small n was inadequate to control for false negatives. The elegant study from the Rush Alzheimer Disease Center (Wilson et al 2007) on the basis of an average of three years of prospective investigation offers support to the argument that cognitive inactivity is a cause rather than a result of incipient AD. The fact that we found education and IQ non-significant in part reflects the truncated range of these variables in our study

Our study also has important strengths. First, recent research and Table 2 suggest that the TICS can, especially over a ten-year span, reliably detect MCI with its negative prognostic consequences. With respect to sensitivity to dementia, the TICS was only minimally affected by the men’s intelligence. Second, although in sociological studies heterogeneity of sample is a necessity, in biological studies homogeneity of sample may be advantageous insofar as it eliminates potential confounds such as race, gender, and educational background. Third, the person-years under observation are far greater than the sample size would suggest. For example, the extended life expectancy of this privileged sample meant that 60% of our sample, rather than the expected 20%, survived past their eightieth birthday, significantly multiplying the number of person-years at risk for dementia. Finally, since it is the first prospective biosocial study of its length, our study should offer future investigators useful leads.

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TABLE 1

A TEN-YEAR FOLLOW-UP OF THE 142 MEN WHO WERE ADMINISTERED THE TICS AT AGE 80

TICS AT 80	**DEMENTED BY 90 n = 31**	**TICS at 90 31 – 33 n = 16**	**TICS at 90 34 – 38 n = 48**	**NOT DEMENTED BUT DEAD BY 90 n= 57**	**TOTAL TICS AT 80[a] n = 142**
TICS 34–41	13 (12%)[a]	14 (13%)	40 (37%)	41 (38%)	108 (100%)
TICS 31–33 (MCI)	12 (44.5%)	3 (11%)	0 (0%)	12 (44.5%)	27 (100%)
DEMENTIA	6 (85.5%)	0 (0%)	0 (0%)	1 (14%) [b]	7 (100%)

[a]. Percentages above are row percentages, not column percentages.

[b]. Although this man scored a TICS of 30 at age 80 he was classified non-demented because there was no clinical evidence of dementia and his TICS at 85 was 33.

TABLE 2

PREDICTORS OF POOR HEALTH AT 70 AND INTACT COGNITION AT 90

	POOR HEALTH AT AGE 70 N = 196	DEMENTED BY AGE 90 N == 196	INTACT COGNITION (1) OR DEMENTIA (0) AT AGE 90 N = 84
A. Predictors of Sustained Cognition and/or Dementia			
Adequate Vision	−.10	−.11	.19
Warm Relations w/Mother < 20	−.01	−.18*	.33**
Mother's Education	−.03	−.15*	.24*
Mother's Age at Birth	−.02	.10	−.20
Excellent Health Age 60	−.38***	.01	.26*
No Exercise age 45–60	−.13	−.18*	−.32**
B. Major Risk Factors for Dementia (Barnes and Yaffe 2001)			
Midlife Hypertension	.12	−.01	−.10
Years of Education	−.04	−.02	.08
Pack-Years of Smoking	.17*	.01	−.02
Body Mass Index	.27**	.06	−.21*
Major Depression	.29***	.02	−.10
C. Other Putative Predictors of Dementia			
Volunteer Activities Age 65 (n = 130)	−.23**	−.14	.04
Good Social Supports (50–70)	−.28***	.01	.12
Alcohol Abuse	.28***	.00	−.14
Early Retirement	.18*	.16*	−.26*
Ancestral Longevity	−.01	−.03	.16
Warm Childhood (mother excluded)	−.04	−.04	.12
Verbal IQ	.02	.01	.08
Head Circumference	−.05	−.04	.02
Father's Education	−.06	.00	.09
Parental Social Class	−.04	.00	.13

* p<.05

** p<.01

*** p<.001

Spearman rho was the statistic used.

Table 3

Distinction between dementia and intact cognition at age 90 years affected putative risk or protective factors

Variable	Odds ratio	95% Wald confidence limits	
Warm mother (yes/no)	5.06	1.29	19.8
Exercise at ages 45–60 years (none/some)	8.02	1.59	40.4
Mother's education (years)	1.98	1.16	3.39
Mother's age at birth (years)	0.27	0.06	1.13
Impaired eyesight at age 80 years (yes/no)	0.54	0.11	2.78
Diastolic blood pressure at age 50 years (10-mmHg intervals)	1.00	0.54	2.01
Years of education	0.75	0.54	1.06
Smoking at age 47 years (pack-years)	1.07	0.67	1.70
Body mass index (kg/m^2)	0.77	0.58	1.03
Major depression (yes/no)	1.05	0.59	1.87