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# Midlife cardiovascular risk factors and risk of dementia in late life

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**Abstract—Objective:** To evaluate if midlife cardiovascular risk factors are associated with risk of late-life dementia in a large, diverse cohort. **Method:** The authors conducted a retrospective cohort study of 8,845 participants of a health maintenance organization who underwent health evaluations from 1964 to 1973 when they were between the ages of 40 and 44. Midlife cardiovascular risk factors included total cholesterol, diabetes, hypertension, and smoking. Diagnoses of dementia were ascertained by medical records from January 1994 to April 2003. **Results:** The authors identified 721 participants (8.2%) with dementia. Smoking, hypertension, high cholesterol, and diabetes at midlife were each associated with a 20 to 40% increase in risk of dementia (fully adjusted Cox proportional hazards model: HR 1.24, 95% CI 1.04 to 1.48 for hypertension, HR 1.26, 95% CI 1.08 to 1.47 for smoking, HR 1.42, 95% CI 1.22 to 1.66 for high cholesterol, and HR 1.46, 95% CI 1.19 to 1.79 for diabetes). A composite cardiovascular risk score was created using all four risk factors and was associated with dementia in a dose-dependent fashion. Compared with participants having no risk factors, the risk for dementia increased from 1.27 for having one risk factor to 2.37 for having all four risk factors (fully adjusted model: HR 2.37, 95% CI 1.10 to 5.10). **Conclusion:** The presence of multiple cardiovascular risk factors at midlife substantially increases risk of late-life dementia in a dose dependent manner.

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Although neurodegenerative processes are thought to start several years before clinically identifiable signs of dementia emerge, few studies have examined risk factors in middle age for late-life dementia. Recent evidence suggests that traditional risk factors for cardiovascular disease in old age are also important risk factors for dementia.<sup>1,2</sup> While the association between some of these factors, such as diabetes, has been inconsistent, others such as high cholesterol and hypertension have shown a consistent association with both increased risk of Alzheimer disease (AD) and vascular dementia.<sup>1,3–6</sup> Whether these risk factors in midlife are prospectively associated with risk of dementia in old age has not been thoroughly investigated.

Defining whether risk factors in midlife are associated with risk of dementia in late life is important because neurodegeneration associated with dementia may start many years before clinically identifiable symptoms emerge. Midlife risk factors may also provide a more accurate estimation of the length of exposure to a certain risk factor by complementing information on late-life risk factors. While several studies have reported an association between individual risk factors and dementia, these were primarily conducted in a single cohort of Japanese American men,<sup>2,3,7–10</sup> with the exception of one study from Finland.<sup>11</sup> Yet there are major differences in prevalence of cardiovascular risk factors as well as types of dementia in Japanese men that hamper gen-

eralizability to other ethnic groups and women.<sup>12</sup> We sought to determine the predictive value of cardiovascular risk factors (e.g., high cholesterol, diabetes, hypertension, and smoking) in midlife on risk of developing dementia in a large multiethnic cohort of men and women followed up for an average of 27 years, all with equal access to medical care.

**Methods. Study population.** We conducted a retrospective cohort study of members of the Kaiser Permanente Medical Care Program of Northern California who participated in voluntary periodic multiphasic health checkups (MHC) in San Francisco and Oakland, CA, between 1964 and 1973 when the participants were ages 40 to 44 years. If members attended more than one MHC during this interval, data from the first visit were evaluated. In order to determine the effect of midlife risk factors only, our analytic cohort consisted of participants ages 40 to 44 who were also still members of the health plan in 1994 when computerized outpatient diagnoses of dementia became available. Nine participants with missing data for sex were excluded, 1,700 with missing smoking information were excluded, and 814 with missing cholesterol information were excluded. This resulted in a cohort of 8,845 people.

Kaiser Permanente of Northern California is a nonprofit, group-practice health integrated delivery system that covers more than one fourth of the population in the geographic areas served. Kaiser Permanente members are representative of the sociodemographics of the local population.<sup>13</sup>

**Determinants of midlife cardiovascular risk factors.** At the MHC, participants were interviewed and information on demographics, lifestyle, and medical history was collected including questions on medical conditions, medication use, and smoking history.<sup>14</sup> Systolic and diastolic blood pressure, weight, and height were measured according to standard procedures<sup>15</sup> and body mass index was calculated (kg/m<sup>2</sup>). Blood was drawn for total serum cholesterol and levels were measured with an Auto-analyzer

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(Technicon Co., White Plains, NY) from 1964 to 1968, with an Autochemist (AGA Corp, Stockholm, Sweden) from 1969 to 1972, and with an Auto-Analyzer (model SMA-12, Technicon, CO) in 1973.<sup>14,16</sup> High cholesterol was defined as a total serum cholesterol  $\geq 240$  mg/dL. The participants were considered to have hypertension if they had one of the following: self-report of physician-diagnosed hypertension, use of antihypertensive medication, systolic blood pressure  $\geq 140$  mm Hg, or diastolic blood pressure  $\geq 90$  mm Hg. Diabetes was defined by self report of physician-diagnosed diabetes, use of insulin or oral hypoglycemic agents, a fasting glucose (last food eaten in  $\geq 8$  hours) of  $\geq 140$  mg/dL, or a nonfasting (last food eaten in  $\leq 4$  hours) glucose of  $\geq 200$  mg/dL. If the participants had no mention of a self report of hypertension or diabetes, no mention of medications taken for these diseases, and no laboratory or hematologic evidence of these diseases, it was assumed that the participants did not have these risk factors. Smoking was defined as never or ever smoked. The MHC study was approved by the Internal Review Board of Kaiser Permanente.

**Diagnosis of dementia.** Dementia diagnoses were ascertained through electronic medical records from a database that contains diagnoses from all outpatient encounters at Kaiser Permanente medical centers and clinics. The database, which was implemented in all facilities in 1994, utilizes over 50 different optically scannable medical specialty-specific forms. The appropriate form is generated at time of registration and contains a list for the most commonly used diagnoses and procedures (ICD-9-CM and CPT4 codes). The form is completed by the treating clinician.

Dementia diagnoses included dementia, memory impairment, AD, vascular dementia, and dementia not otherwise specified (ICD codes 2900.0, 7809.3, 3310.0, 29040.1, 2900.1). We ascertained dementia diagnoses from January 1994 to April 2003 when the MHC participants would have been 61 to 83 years of age. The criteria for diagnosing dementia did not change during the ascertainment period and no chart validation of the dementia diagnosis was conducted. Mortality information was available on our cohort through the end of 2000 using the California Automated Mortality Linkage System, which has a sensitivity of 0.97 compared to the National Death Index.<sup>17</sup> From January 1, 2000, to December 31, 2002, mortality information was available using a weighted linkage system incorporating matches by social security number, name, date of birth, and home address to Social Security Death Data. From January 1, 2003, to April 3, 2003, mortality information was not yet available.

**Statistical analysis.** All analyses were done using SAS version 8.0 (SAS Institute, Cary, NC).  $\chi^2$  tests and *t* tests were used to determine if demographic characteristics and cardiovascular risk factors at the time of the MHC were significantly different by presence of late-life dementia. Cox proportional hazards models were used to identify independent predictors of risk of late-life dementia over a 9-year follow-up period, from January 1, 1994, to April 3, 2003. Person-years were calculated from onset of dementia ascertainment, January 1, 1994. Participants were censored according to date of dementia diagnosis, date of death, date of end of Kaiser membership, or end of follow-up, April 3, 2003. Two proportional hazard models were generated for each cardiovascular risk factor: an unadjusted model and a model adjusted for age at time of MHC examination, age at start of dementia ascertainment (age in 1994), education, race, and sex. For each cardiovascular risk factor, the referent group was those with absence of disease with the exception of smoking, where never smoked was the referent group. Age at time of the MHC examination, as well as age in 1994, were entered in the model as continuous variables. One and a half percent of the cohort was missing for the education variable ( $n = 143$ ). Thus, education was categorized as high school, trade school, college, or unknown, with grade school as the referent group. Race was entered as black, Asian, or other, with Caucasian as the referent group.

A composite cardiovascular disease risk score was created incorporating presence of hypertension, diabetes, high cholesterol, and smoking at midlife based on a modified version of the Framingham Cardiovascular Risk Score.<sup>18</sup> Participants with no cardiovascular risk factors at midlife were assigned a score of zero (the referent group), while those with the presence of any one risk factor were assigned a score of one, with a maximum score of four. To determine whether the association between midlife cardiovascular risk factors and risk of dementia varied by sex or race, we

**Table 1** Demographic characteristics of the participants at mid-life by dementia status

Characteristics	Diagnosis of dementia		<i>p</i> Value
	No, n = 8,124	Yes, n = 721	
Age at MHC exam, y	41.97 (1.42)	42.25 (1.39)	<0.0001
Age in 1994, y	68.37 (2.64)	69.32 (2.43)	<0.0001
Age at end of follow-up, y	76.59 (3.34)	74.86 (3.41)	<0.0001
			Age-adjusted <i>p</i> value
Female	4,341 (53.4)	410 (56.9)	
Male	3,783 (46.6)	311 (43.1)	0.0843
Race			
White	5,952 (73.6)	499 (69.2)	
Black	1,285 (15.9)	165 (22.9)	
Asian	511 (6.3)	31 (4.3)	
Other	360 (4.4)	26 (3.6)	0.1021
Education			
Grade school	1,093 (13.5)	132 (18.3)	
High school	2,766 (34.1)	240 (33.3)	
Trade school	529 (6.5)	45 (6.2)	
College	3,606 (44.4)	291 (40.4)	
Unknown	130 (1.6)	13 (1.8)	0.0501
Marital status			
Married	6,646 (81.8)	543 (75.3)	
Never married	412 (5.1)	35 (4.9)	
Divorced/widowed/ separated	754 (9.3)	95 (13.2)	
Unknown	312 (3.8)	48 (6.7)	0.0753
Mortality during follow-up	1,434 (17.7)	200 (27.7)	<0.0001

Mean (SD) for continuous variables; *p* values were calculated using a *t*-test. N (column %) for categorical variables; *p* values were calculated using logistic regression adjusted for age in midlife (age at time of MHC examination).

MHC = multiphasic health checkups.

entered a cross-product interaction term for each cardiovascular risk factor and the composite score for both sex and race (e.g., women  $\times$  hypertension) to the fully adjusted models.

**Results.** Fifty-four percent of the cohort were women and 27% were of non-white ethnicity (table 1). At the time of the MHC examination, the participants had a mean age of 42 years, 81% were married, while more than 40% had attended at least some college. Average time to dementia diagnosis, death, or end of follow-up from time of MHC examination was 26.67 years for the cohort. Eighteen percent of the cohort (1,634 participants) had died by the end of 2002. The participants had a mean age of 68.5 at onset of dementia ascertainment in 1994, and average person-years was 7.9.

From January 1, 1994, through April 3, 2003, there

**Table 2** Midlife cardiovascular risk factors by dementia status

Risk factors	Dementia diagnosis, n (%)*		Age-adjusted p value†
	No, n = 8,124	Yes, n = 721	
Diabetes	889 (10.9)	115 (16.0)	<0.0001
Hypertension	1,553 (19.1)	160 (22.2)	0.0649
High cholesterol	2,578 (31.7)	266 (36.9)	0.0107
Smoking	4,831 (59.5)	454 (63.0)	0.0531
Cardiovascular composite scale			
0	1,732 (21.3)	120 (16.6)	
1	3,573 (44.0)	293 (40.6)	
2	2,227 (27.4)	229 (31.8)	
3	544 (6.7)	72 (10.0)	
4	48 (0.6)	7 (1.0)	<0.0001

\* Percents shown are column percents.

† p Values were calculated using a logistic regression model, adjusted for age in midlife.

were 721 participants who were diagnosed with dementia (8.2% of the cohort). Mean age at initial recorded diagnosis was 74.5 years (range, 66 to 82). There was no significant sex difference in odds of dementia; however, those with a grade-school education were significantly more likely to be diagnosed with dementia (see table 1).

At midlife the prevalence of diabetes was 11%, of high cholesterol was 32%, of having ever smoked was 60%, and hypertension was 19%. Compared to those not diagnosed with dementia, participants diagnosed with dementia were more likely to have smoked, and to have had hypertension, diabetes, or high cholesterol at midlife (table 2).

All of the cardiovascular risk factors at midlife were significantly associated with a 20% to 40% increased risk of dementia in late life (table 3). Those with hypertension were 24% more likely to have dementia (fully adjusted model, HR = 1.24, 95% CI 1.04 to 1.48), those with diabetes were 46% more likely to have dementia (fully adjusted model, HR = 1.46, 95% CI 1.19 to 1.79), and those with high cholesterol were 42% more likely to have dementia (fully adjusted model, HR = 1.42, 95% CI 1.22 to 1.66). Participants who reported ever smoking at midlife were 26% more likely to have dementia (fully adjusted model, HR = 1.26, 95% CI 1.08 to 1.47). Adjustments for age at MHC examination, age at time of dementia ascertainment, education, race, and sex did not weaken the magnitude of the effect, compared to the unadjusted models (see table 3).

The cardiovascular composite score was associated with risk of late-life dementia in a dose dependent fashion (see table 3). Compared to those with no cardiovascular risk factors, those with a score of one were 27% more likely to be diagnosed with dementia (fully adjusted model, HR = 1.27, 95% CI 1.02 to 1.58). However, those with a score of two were 70% more likely to be diagnosed with dementia (fully adjusted model, HR = 1.69, 95% CI 1.34 to 2.12, see table 3), while those with a score of three were more than twice as likely to be diagnosed with dementia (fully ad-

**Table 3** Cox proportional hazards models of cardiovascular risk factors at midlife and risk of dementia

Risk factors	Unadjusted HR (95% CI)	Adjusted for age at mid- life exam, age at start of case ascertainment, race, education, and sex, HR (95% CI)
Cardiovascular composite score		
1	1.23 (1.00–1.52)	1.27 (1.02–1.58)
2	1.59 (1.28–1.98)	1.69 (1.34–2.12)
3	2.19 (1.63–2.93)	2.31 (1.71–3.11)
4	2.61 (1.22–5.60)	2.37 (1.10–5.10)
Risk factors		
Hypertension	1.26 (1.06–1.50)	1.24 (1.04–1.48)
Diabetes	1.64 (1.34–2.00)	1.46 (1.19–1.79)
High cholesterol	1.29 (1.11–1.50)	1.42 (1.22–1.66)
Smoking	1.22 (1.05–1.42)	1.26 (1.08–1.47)

justed model, HR = 2.31, 95% CI 1.71 to 3.11). Those with the presence of four cardiovascular risk factors at midlife had a 2.37 greater risk of being diagnosed with dementia (fully adjusted model, HR = 2.37, CI, 1.10 to 5.10). There were no race or sex interactions in the association between any of the cardiovascular risk factors and diagnosis of dementia ( $p > 0.20$  for all interaction terms).

**Discussion.** Our results suggest that the presence of multiple cardiovascular risk factors at midlife independent of age, race, sex, and education substantially increases risk of dementia in old age. Those with all four risk factors at midlife had a more than twofold greater risk of dementia than those with no risk factors. Individual cardiovascular risk factors including smoking, hypertension, high cholesterol, and diabetes were each associated with a 20 to 40% increased risk of developing dementia. These results are similar with findings from other studies examining this in both midlife<sup>13,19-21</sup> and late life.<sup>13,22-29</sup> Testing of interaction terms by race and sex showed that effects were not statistically different for men and women or by race/ethnic group.

Diabetes was most strongly associated with risk of dementia, and this may be due to the cumulative effects of both microvascular and macrovascular changes in the brain.<sup>30</sup> While a large number of studies have found that diabetes in late life is associated with an increased risk of dementia,<sup>31-34</sup> future studies are needed to determine if improving glycemic control among diabetics may lower risk of dementia. High cholesterol was also strongly associated with risk of dementia and this may be due to increased production of  $\beta$ -amyloid or presence of apolipoprotein E type 4 allele.<sup>35</sup> A number of observational studies have shown that use of cholesterol lowering drugs such as statins reduces risk of cognitive impairment and dementia, and clinical trials are currently under way.<sup>29,36,37</sup> Recent studies have found that treatment

of hypertension in late life reduces cognitive impairment and risk of dementia.<sup>38,39</sup> In light of these intervention data, the present findings suggest that earlier treatment may have an even greater benefit in lowering risk of cognitive impairment by virtue of the cumulative effect of longer exposure to therapy.

Although neuropathologic findings have suggested that smoking may lower risk of AD via the effects of nicotine on senile plaque formation,<sup>40</sup> prospective studies in older participants have suggested that smoking is associated with an increased risk of both dementia and AD.<sup>41</sup> Our finding of an increased risk of dementia due to midlife smoking is consistent with findings from the Honolulu-Asia Aging Study<sup>42</sup> but not with a study conducted in Japan which found no association.<sup>43</sup>

Pathologic studies in humans show that high density lipids measured in late life, as well as midlife blood pressure, are positively associated with number of neuritic plaques and neurofibrillary tangles in the brains of AD patients.<sup>44,45</sup> There is also evidence that the neurodegeneration associated with AD starts in middle age.<sup>46</sup> While we did not have the ability to determine subtypes of dementia, it is very likely that the majority of our dementia cases are AD. If indeed AD has a vascular etiology, identification and treatment of cardiovascular risk factors at midlife may lower risk of dementia.

Strengths of our study include our longitudinal design, the comprehensive nature of the health examination at midlife, a long follow-up period, and our multiethnic representative sample including both men and women with equal access to medical care. Also, because these risk factors were measured in people between the ages of 40 and 44, it is highly unlikely that there was subclinical dementia present at the time of cardiovascular risk factor assessment; thus the temporality of the associations is clear.

There are a number of limitations to our study. We did not have the ability to determine subtypes of dementia since most of our diagnoses were made by primary care physicians. Since our dementia diagnoses were obtained electronically from chart diagnoses, which may be insensitive, it is likely that a portion of our sample had dementia that was not diagnosed. It is also likely that we missed some dementia cases in participants who died prior to 1994, the onset of dementia ascertainment. However, this would tend to bias our results toward an underestimation of the true effect of midlife cardiovascular risk factors on dementia. Although our definition of cardiovascular risk factors included a combination of clinical and laboratory values, we also included self-report of physician diagnoses, medication use, or smoking as part of the definition of having a cardiovascular risk factor. This may have resulted in some misclassification of the presence of cardiovascular risk factors. However, this also would have tended to reduce the strength of associations with dementia. Finally, due to the design of our study it was only

possible to assess dementia status in those who were still Kaiser members at the time of dementia ascertainment. Post hoc analyses revealed no significant differences in any of the midlife cardiovascular risk factors by health plan membership status in 1994. Our findings suggest that earlier treatment of cardiovascular disease may lower risk of dementia. Future studies are needed to elucidate the mechanisms due to the implications for earlier prevention.

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