Rates and risk factors for progression to incident dementia vary by age in a population cohort

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ABSTRACT

Objective: To estimate rate of progression from normal cognition or mild impairment to dementia, and to identify potential risk and protective factors for incident dementia, based on age at dementia onset in a prospective study of a population-based cohort (n = 1,982) aged 65 years and older.

Methods: Following the cohort annually for up to 5 years, we estimated incidence of dementia (Clinical Dementia Rating ≥1) among individuals previously normal or mildly impaired (Clinical Dementia Rating 0 or 0.5). In the whole cohort, and also stratified by median onset age, we examined several vascular, metabolic, and inflammatory variables as potential risk factors for developing dementia, using interval-censored survival models.

Results: Based on 67 incident cases of dementia, incidence rate (per 1,000 person-years) was 10.0 overall, 5.8 in those with median onset age of 87 years or younger, and 31.5 in those with onset age after 87 years. Adjusting for demographics, the risk of incident dementia with onset age of 87 years or younger (n = 33) was significantly increased by baseline smoking, stroke, low systolic blood pressure, and *APOE*4* genotype, and reduced by current alcohol use. Among those with dementia with onset after 87 years (n = 34), no risk or protective factor was significant.

Conclusion: Risk and protective factors were only found for incident dementia with onset before the median onset age of 87 years, and not for those with later onset. Either unexplored risk factors explain the continued increase in incidence with age, or unknown protective factors are allowing some individuals to delay onset into very old age. ***Neurology*® 2015;84:72–80**

GLOSSARY

BMI = body mass index; **CDR** = Clinical Dementia Rating; **CI** = confidence interval; **DBP** = diastolic blood pressure; **HDL** = high-density lipoprotein; **HR** = hazard ratio; **MCI** = mild cognitive impairment; **MYHAT** = Monongahela-Youghiogheny Healthy Aging Team; **SBP** = systolic blood pressure.

It is well established that the incidence of dementia increases with age.[1–3] As life expectancy increases across the world,[4] it remains unclear whether the incidence rate continues to increase or levels off in very old age.[5–7] A critical question is whether the same risk and protective factors identified for dementia developing in the eighth and ninth decades continue to influence risk into the tenth decade. The relatively few studies to date have yielded sparse and inconsistent results.[8–15]

Over 5 years in a population-based cohort of older adults, we identified incident cases of dementia and estimated age-specific incidence rates. We also examined risk and protective factors for dementia among individuals with onset before and after the median dementia onset age in our cohort.

METHODS

Study site and population. Our study cohort, named the Monongahela-Youghiogheny Healthy Aging Team (MYHAT), is an age-stratified random population sample drawn from the publicly available voter registration lists for a small-town region of Pennsylvania (United States).[16]

Standard protocol approvals, registrations, and consents. As previously reported, we recruited participants from the local community. For assessment protocols, we received standard institutional review board approval from the University of Pittsburgh. The study population included those 65 and older and living in the study area. We excluded individuals already living in long-term

Supplemental data at Neurology.org

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institutions. Those with severe illness, vision or hearing impairments, or cognitive disabilities were also ineligible.[16] All 2,036 participants provided written informed consent during the baseline recruitment within 2005 and 2006. Because the project was designed to study mild impairment, we screened out those who, at study entry, exhibited substantial impairment by scoring <21 of 30 on the age- and education-corrected Mini-Mental State Examination (figure e-1 on the *Neurology*® Web site at Neurology.org). The remaining 1,982 individuals were representative of older adults in the targeted communities, with age range 65 to 99 years and mean (SD) age of 77.6 (7.4) years; 61.0% were women, 94.7% were of mixed European descent, and high school graduation was the median educational level.[16]

Assessments. At baseline (wave 1) and at each annual data collection wave, we assessed cognitively driven everyday functioning to rate participants on the Clinical Dementia Rating (CDR) scale,[17] disregarding any previous years' classifications. Independent of neuropsychological test scores, we designated as normal and mildly impaired those participants who received CDRs of 0 and 0.5, respectively.[18] All individuals rated as CDR <1 at any wave were included in the analyses to determine their rate of progression to dementia. We estimated the onset date of dementia as the midpoint between the wave at which the individual was first rated as CDR ≥1 and the preceding wave.[19] For participants classified as incident cases, we used data collected until the wave when they were thus classified. For noncases, we used data collected until their last observed wave (up to wave 6, fifth follow-up wave) (table 1).

Potential baseline vascular risk factors. ***History.*** Participants self-reported their history of ever-diagnosed cerebrovascular and cardiovascular disease, hypercholesterolemia, body weight,[20] and current (previous year) and past smoking and alcohol consumption (table 2).[21] We lacked medical record information to confirm self-report, and neuroimaging data to identify unreported infarcts[22]; however, self-reported health history is standard in population surveys and sufficiently reliable in individuals without dementia.[23,24]

Examination. The physical examination protocol at each wave included measurement of systolic blood pressure (SBP) and diastolic blood pressure (DBP) in mm Hg, and height. SBP and DBP were categorized into tertiles (SBP 90–126, 127–138, 139–200; DBP 48–70, 71–78, 79–110). We calculated body mass index (BMI) as weight/height^2, which we also categorized as tertiles (14.0–24.9, 24.9–29.9, 29.9–54.0).

Laboratory tests. At wave 1, we requested all participants, with specific informed consent, to provide nonfasting blood samples. This specimen was only drawn once per participant, at either wave 1 or wave 2; we treated all assays as baseline. We performed *APOE* genotyping and assayed total cholesterol and high-density lipoprotein (HDL) cholesterol, calculating low-density lipoprotein cholesterol as (total cholesterol − HDL); ApoA1 (lipoprotein for HDL cholesterol); ApoB (lipoprotein for low-density lipoprotein cholesterol), categorizing the lipoprotein levels by tertile (ApoA1: 16–128, 129–146, 147–217; ApoB: 17–84, 85–103, 104–195); cystatin C; HbA1c (glycosylated hemoglobin); homocysteine; and C-reactive protein.[21]

Tracking and attrition. We contacted participants by telephone every 3 months between annual assessments. We excluded from these analyses the early dropouts who were lost to follow-up after baseline, thus contributing no follow-up data. The later dropouts (after at least one follow-up assessment), due to death or illness, were designated as informative dropouts, while dropouts for other reasons (e.g., relocation) were designated as random dropouts (table 1).

Statistical analyses. As noted, we used the midpoint between 2 waves as the estimated date of onset for calculating incidence rate per 1,000 person-years. For each participant, we computed person-years of follow-up as the time from when they were first classified as normal or mild cognitive impairment (MCI) until estimated onset of dementia or the date of last follow-up (either time of dropout or censoring at wave 6). We compared early dropouts and the informative dropouts with random dropouts and those who continued to participate, using Wilcoxon rank sum tests for continuous variables and χ^2 tests for categorical variables.

Risk/protective factor models. For the risk factor models, rather than time to estimated midpoint onset date, we used Weibull interval-censored survival regression models. These models assumed that the first wave at which the participant was rated as CDR ≥1 and its preceding wave were, respectively, the right and left bounds of the interval during which dementia onset occurred. We examined several potential risk factors for incidence of/progression to dementia over 5 years (table 2). For each factor, we assessed individual effects with and without adjustment for demographics (age, sex, and education). To determine whether risk and protective factors were constant regardless of onset age, we refit 2 interval-censored models: time from first classification as normal or MCI to dementia, censored at the median onset age

Table 1 Participant status over 5 years of follow-up

Baseline CDR	Wave 1	Early dropout	Sufficient data	CDR remained unchanged	Reverted to normal	Incident MCI	Incident dementia	Later dropout	
								Random	Informative
0 (normal)	1,413	154	1,259	968	—	287	12[a]	220[b]	258[c]
0.5 (MCI)	546	104	442	221	166	—	55	88[d]	142[e]
≥1 (dementia)	23	—	—	—	—	—	—	—	—
Total	1,982	258	1,701	1,189	166	287	67	308	400

Abbreviations: CDR = Clinical Dementia Rating; MCI = mild cognitive impairment.
[a] Four cases progressed directly from 0 to ≥1, and 8 cases progressed from 0 through 0.5 to ≥1, so these 8 cases were first incident MCI and then incident dementia.
[b] One subject progressed to CDR ≥1 before dropout.
[c] Six subjects progressed to CDR ≥1 before dropout.
[d] Eight subjects progressed to CDR ≥1 before dropout.
[e] Thirty-two subjects progressed to CDR ≥1 before dropout.

Table 2 Characteristics of those who progressed and did not progress to dementia, in the cohort by dementia onset age

			≤87 y			>87 y		
	No. (%)	Mean (SD)	Not progressed (n = 1,499)	Progressed (n = 33)	*p* Value	Not progressed (n = 425)	Progressed (n = 34)	*p* Value
Variable								
Age, y	1,701	77.4 (7.3)	76.0 (6.4)	79.4 (4.4)	0.0033	86.0 (3.2)	87.5 (3.2)	0.0057
65–74	602 (35.4%)	—	—	—	—	—	—	—
75–84	789 (46.4%)	—	—	—	—	—	—	—
85+	310 (18.2%)	—	—	—	—	—	—	—
Female	1,060 (62.3%)	—	925 (61.7%)	20 (60.6%)	0.8975	274 (64.5%)	21 (61.8%)	0.7514
Education ≥HS	1,478 (86.9%)	—	1,337 (89.2%)	29 (87.9%)	0.7757	327 (76.9%)	20 (58.8%)	0.0179
Smoking	113 (6.7%)	—	104 (7.0%)	5 (15.6%)	0.0724	9 (2.1%)	1 (2.9%)	0.5405
Alcohol	1,129 (66.4%)	—	1,029 (68.7%)	14 (42.4%)	0.0014	249 (58.6%)	19 (55.9%)	0.7581
Self-reported health history								
Stroke	75 (4.4%)	—	60 (4.0%)	4 (12.1%)	0.0458	19 (4.5%)	2 (5.9%)	0.6628
Heart attack	243 (14.3%)	—	210 (14.0%)	5 (15.2%)	0.8007	76 (17.9%)	3 (8.8%)	0.1781
CHF	152 (9.0%)	—	125 (8.4%)	3 (9.1%)	0.7525	41 (9.7%)	3 (8.8%)	1.0000
Hypercholesterolemia	1,039 (61.3%)	—	935 (62.5%)	14 (43.8%)	0.0305	242 (57.3%)	16 (47.1%)	0.2443
Diabetes	370 (21.8%)	—	322 (21.5%)	11 (33.3%)	0.1030	82 (19.3%)	5 (14.7%)	0.5113
Hypertension	1,099 (64.7%)	—	968 (64.7%)	19 (57.6%)	0.4000	284 (67.0%)	22 (64.7%)	0.7863
Examination								
SBP, mm Hg	1,691	133.3 (15.1)	133.1 (15.0)	131.8 (15.8)	0.2830	135.2 (15.6)	135.7 (12.7)	0.9089
≤126	575 (34.0%)	—	505 (33.9%)	17 (51.5%)	0.0804	128 (30.3%)	6 (17.7%)	0.0295
127–138	565 (33.4%)	—	505 (33.9%)	10 (30.3%)		131 (31.0%)	18 (52.9%)	
≥139	551 (32.6%)	—	480 (32.2%)	6 (18.2%)		163 (38.6%)	10 (29.4%)	
DBP, mm Hg	1,690	74.3 (9.4)	74.6 (9.4)	72.2 (7.8)	0.0706	72.5 (9.5)	72.9 (8.3)	0.8014
≤70	664 (39.29%)	—	558 (37.5%)	19 (57.6%)	0.0486	209 (49.5%)	15 (44.1%)	0.8260
71–78	470 (27.81%)	—	425 (28.5%)	8 (24.2%)		98 (23.2%)	9 (26.5%)	
≥79	556 (32.9%)	—	506 (34.0%)	6 (18.2%)		115 (27.3%)	10 (29.4%)	
BMI, kg/m^2								
14–24.9	501 (30.0%)	—	413 (28.1%)	12 (36.4%)	0.3840	168 (40.1%)	18 (54.6%)	0.2604
24.9–29.9	643 (38.5%)	—	565 (38.4%)	9 (27.3%)		159 (37.9%)	9 (27.3%)	
≥29.9	525 (31.5%)	—	492 (33.5%)	12 (36.4%)		92 (22.0%)	6 (18.2%)	
Test results								
*APOE**4	330 (21.0%)	—	298 (21.6%)	14 (45.2%)	0.0017	66 (16.7%)	5 (17.9%)	0.7973
Total cholesterol	898	193.2 (44.5)	193.9 (43.8)	178.1 (35.3)	0.1349	190.6 (48.6)	190.6 (57.5)	0.6413
HDL	898	48.0 (14.8)	48.0 (15.0)	42.4 (10.6)	0.1159	48.4 (14.4)	49.6 (10.2)	0.5035
LDL	898	145.2 (42.7)	145.9 (41.7)	135.7 (30.9)	0.3831	142.2 (47.7)	141.0 (57.5)	0.6566
ApoA1	891	138.4 (21.9)	138.8 (22.1)	129.0 (19.6)	0.0292	137.2 (22.1)	138.5 (21.1)	0.9052
≤128	303 (34.0%)	—	258 (33.1%)	11 (55.0%)	0.0427	81 (37.0%)	5 (38.5%)	0.9999
129–146	293 (32.9%)	—	252 (32.3%)	7 (35.0%)		75 (34.2%)	4 (30.8%)	
≥147	295 (33.1%)	—	270 (34.6%)	2 (10.0%)		63 (28.8%)	4 (30.8%)	
ApoB	891	94.7 (23.8)	95.1 (23.4)	91.0 (18.1)	0.5973	92.4 (26.1)	88.8 (26.6)	0.4761
≤84	311 (34.9%)	—	264 (33.9%)	5 (25.0%)	0.2976	94 (42.9%)	5 (38.5%)	0.0691
85–103	292 (32.8%)	—	260 (33.3%)	10 (50.0%)		58 (26.5%)	7 (53.9%)	
≥104	288 (32.3%)	—	256 (32.8%)	5 (25.0%)		67 (30.6%)	1 (7.7%)	

Continued

Table 2 Continued

	No. (%)	Mean (SD)	≤87 y: Not progressed (n = 1,499)	≤87 y: Progressed (n = 33)	≤87 y: p Value	>87 y: Not progressed (n = 425)	>87 y: Progressed (n = 34)	>87 y: p Value
Cystatin C	891	1.1 (0.4)	1.1 (0.3)	1.2 (0.3)	0.2736	1.3 (0.4)	1.2 (0.3)	0.1796
HbA1c	845	6.4 (1.0)	6.4 (1.0)	6.3 (0.5)	0.9619	6.4 (0.9)	6.2 (0.6)	0.4773
Homocysteine	888	12.8 (7.2)	12.7 (7.5)	12.8 (3.6)	0.3209	14.5 (9.3)	14.0 (5.2)	0.5832
C-reactive protein	891	3.9 (7.1)	3.9 (7.2)	4.5 (10.5)	0.4768	3.6 (5.3)	2.0 (1.1)	0.7887

Abbreviations: ApoA1 = lipoprotein for high-density lipoprotein cholesterol; ApoB = lipoprotein for low-density lipoprotein cholesterol; BMI = body mass index; CHF = congestive heart failure; DBP = diastolic blood pressure; HbA1c = glycosylated hemoglobin; HDL = high-density lipoprotein; HS = high school; LDL = low-density lipoprotein; SBP = systolic blood pressure.
Data are n (%) or mean (SD). Alcohol consumption = during past year; frequency = 13.8% daily, 11.7% daily to weekly, 8.5% weekly, 11.1% less than weekly, 54.8% once a month or less; quantity = 1 drink 70.7%, 2–3 drinks 26.9%, 4–5 drinks 1.9%.

of 87; and time from age 87 to dementia (truncating those who developed dementia or dropped out before age 87).

Joint models. In post hoc analyses, we adjusted the risk factor models for attrition using joint modeling of incidence and informative dropout. These models account for a given risk factor competing to predict both incidence and attrition, so that attrition associated with that factor before the median onset age could prevent that factor from increasing risk of incidence after that age.[25]

We repeated the above analyses restricting the incident cases to those who had progressed from CDR 0.5 to CDR ≥1, i.e., excluding 4 incident cases who had appeared to progress directly from normal to dementia without being observed as CDR 0.5. For these analyses, we used history and examination variables at the wave when participants were first classified as CDR 0.5, and computed the person-years of follow-up as the time from that wave to when they were first classified as CDR ≥1, or the date of last follow-up.

All analyses were performed using SAS version 9.3, including the NLMIXED procedure for joint modeling.[26]

RESULTS Among the 1,982 participants who underwent the full assessment at baseline (wave 1), 546 (27.5%) were mildly impaired (CDR 0.5), 23 (1.2%) had at least mild dementia (CDR ≥1), and 1,413 (71.3%) were normal (CDR 0). After eliminating those with baseline dementia, and early dropouts who were only assessed at baseline, we had 1,701 participants (1,259 normal and 442 mildly impaired) to follow for potential incident dementia (figure e-1); of those who were normal at baseline, 287 were rated as mildly impaired at some point during follow-up. By the end of wave 6, we identified 67 incident cases of dementia. Of these incident cases, 55 progressed from baseline CDR 0.5 to CDR ≥1; 8 cases progressed first from baseline CDR 0 to CDR 0.5, and then to CDR ≥1. Four cases progressed directly from CDR 0 to CDR ≥1 (table 1).

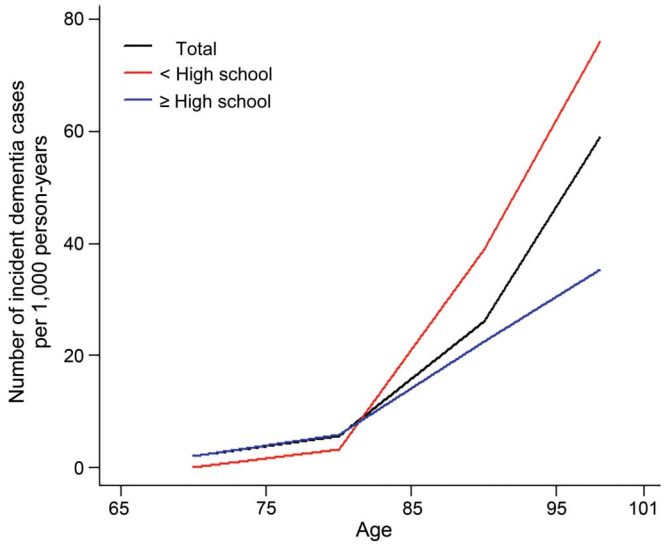
Incidence and age at onset. The mean (SD) and median age at onset of dementia were 86.5 (6.0) years and 87 years, respectively. Table 2 presents characteristics of participants who progressed and did not progress to dementia, by median dementia onset age (≤87 and >87 years); 33 individuals experienced dementia onset at or before age 87, and 34 after age 87; these numbers were reduced to 32 and 31 after excluding the 4 cases who appeared to progress directly from normal to dementia.

Based on a total of 6,730.73 person-years of follow-up, the incidence rate of dementia (CDR ≥1) per 1,000 person-years was 10.0 overall, 5.8 with onset age at 87 years or younger, and 31.5 with onset age after 87 years. Age-specific incidence rate increased exponentially with age. Incidence rate was higher among those with less than high school education (21.7/1,000 person-years) than those with high school or greater education 8.3/1,000 person-years) (figure 1). Incidence was similar in men (10.5/1,000 person-years) and women (9.6/1,000 person-years).

The early dropouts (baseline data only) and the informative dropouts (dropped out later because of death or illness), compared with random dropouts and those who continued to participate, were significantly older, more likely to be male, less likely to have high school or greater education, less likely to currently use alcohol, more likely to report stroke, heart attack, and heart failure, to have lower SBP and DBP, lower total cholesterol, ApoA1, and ApoB, and higher cystatin C, homocysteine, and C-reactive protein ($p < 0.05$).

Risk and protective factors for progression from normal or mild impairment to dementia. In a univariable interval-censored model, the risk of incidence (progression) increased with age and was about 7 times higher for those aged 75 to 84 years and 20 times higher for those aged 85 years or older than for 65- to 74-year-old participants. Risk was increased by having less than high school education, *APOE*4* (at least one *E*4* allele), and stroke history. Risk was decreased by reported hypercholesterolemia,

Figure 1 Incidence rates for progression from normal or mild impairment to dementia



BMI ≥24.9, ApoA1 ≥147, and current alcohol consumption (table e-1). After adjusting for demographics, current smoking and ApoB (the middle tertile 85–103 compared with the lowest tertile ≤84) became significant risk factors, *APOE*4* remained a significant risk factor, while BMI 24.9–29.9 and reported hypercholesterolemia were significant protective factors (table e-2).

For dementia onset at age 87 years or younger, the unadjusted model showed risk increased by greater age (19% increase per year), stroke history, and *APOE*4*; risk was reduced by ApoA1 ≥147, DBP ≥79 mm Hg, reported hypercholesterolemia, and current alcohol consumption (table e-2). After adjustment for demographics, only *APOE*4*, stroke, and alcohol consumption remained significant, SBP ≥139 mm Hg became a significant protective factor, and current smoking became a significant risk factor.

Several additional factors reached borderline significance (p values between 0.05 and 0.1) in the younger-onset group. In unadjusted models, current smoking increased risk, while SBP ≥139 mm Hg and total cholesterol reduced risk. In the demographically adjusted models, reported diabetes increased risk, while ApoA1, the highest tertile of DBP, and reported hypercholesterolemia reduced risk (table 3).

For dementia with onset after 87 years, education greater than high school showed a borderline protective effect ($p = 0.099$). SBP between 127 and 138 mm Hg showed a borderline hazard effect in both the unadjusted and adjusted models ($p = 0.0549$ and 0.0648, respectively). No other significant risk or protective factors were detected in either the unadjusted or the adjusted models (table e-2 and table 3).

When we refit the risk factor models restricted to 63 cases who progressed from CDR 0.5 to dementia, no substantive changes were seen in the results. After adjustment for demographics, the middle tertile of ApoB decreased to borderline significant ($p = 0.06$) and BMI 24.9–29.9 became nonsignificant (data not shown).

Adjustment for informative attrition. Of the 1,701 participants in the longitudinal analyses, over 5 years, 278 participants (16.3%) died, and 122 (7.2%) dropped out because of illness (informative attrition); a further 308 (18.1%) relocated or dropped out for other reasons (random attrition).

In the post hoc joint models, adjusting for informative dropout, risk of dementia incidence was increased with borderline significance by smoking (hazard ratio [HR]: 2.81, confidence interval [CI]: 0.86–9.14, $p = 0.09$), *APOE*4* genotype (HR: 2.28, CI: 0.96–5.42, $p = 0.06$), ApoA1 (highest tertile compared with lowest tertile) (HR: 0.40, CI: 0.13–1.17, $p = 0.095$), and ApoB (middle tertile compared with lower) (HR: 2.42, CI: 0.89–6.60, $p = 0.09$). Among those with dementia onset at age 87 years or younger, smoking (HR: 3.79, CI: 1.08–13.22, $p = 0.04$) significantly increased risk of incident dementia. *APOE*4* (HR: 2.39, CI: 0.87–6.53, $p = 0.09$) increased risk with borderline significance; ApoA1 (highest tertile compared with lowest) (HR: 0.18, CI: 0.03–1.04, $p = 0.06$) decreased risk with borderline significance. As in the previous models, no risk or protective factors were found among those with dementia onset age after 87. Thus, selective attrition (competing risks) does not explain why no risk factors could be found in the later-onset group.

Refitting the joint models excluding the 4 cases who progressed directly from CDR 0 to ≥1, smoking became a significant risk factor (HR: 5.23, CI: 1.62–16.92, $p = 0.01$) and ApoA1 became a significant protective factor (HR: 0.76, CI: 0.70–0.84, $p < 0.0001$), while HDL (HR: 0.91, CI: 0.82–1.01, $p = 0.09$) was a borderline significant protective factor.

DISCUSSION In the MYHAT population-based cohort of older adults followed for 5 years, the incidence of dementia (and progression from mild impairment to dementia) increased exponentially with age, was elevated in those with less than high school education, but not different between men and women. In the Leisure World 90+ Study cohort, dementia prevalence continued to double every 5 years of age in women but not men[27]; dementia incidence increased with age and was the same in both sexes.[7] In the Swedish population-based Kungsholmen study, incidence continued to increase

Table 3 Risk factors for progression to dementia adjusted for demographics, overall and by age at dementia onset (see table e-2 for unadjusted data)

	Overall	Onset age ≤87 y	Onset age >87 y
	Hazard ratio (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Smoking	2.58 (1.08–6.17)[a]	3.79 (1.33–10.75)[a]	1.50 (0.20–11.06)
Alcohol	0.56 (0.34–0.94)[a]	0.34 (0.16–0.75)[b]	1.04 (0.52–2.11)
Self-reported health history			
Stroke	2.14 (0.91–5.06)	3.82 (1.25–11.65)[a]	1.19 (0.28–5.01)
Heart attack	0.64 (0.30–1.37)	1.04 (0.39–2.72)	0.39 (0.12–1.34)
CHF	1.00 (0.43–2.33)	1.19 (0.36–3.92)	0.82 (0.25–2.73)
Hypercholesterolemia	0.57 (0.35–0.95)[a]	0.50 (0.24–1.04)	0.72 (0.36–1.43)
Diabetes	1.17 (0.67–2.07)	1.98 (0.93–4.23)	0.64 (0.25–1.68)
Hypertension	0.82 (0.50–1.35)	0.72 (0.35–1.44)	0.89 (0.43–1.82)
Examination			
SBP, mm Hg	0.997 (0.98–1.01)	0.99 (0.97–1.02)	1.00 (0.98–1.02)
127–138[c]	1.08 (0.62–1.87)	0.55 (0.25–1.23)	2.51 (0.94–6.65)
≥139[c]	0.60 (0.31–1.15)	0.35 (0.13–0.95)[a]	1.18 (0.43–3.27)
DBP, mm Hg	0.99 (0.97–1.02)	0.98 (0.95–1.02)	1.01 (0.97–1.05)
71–78[d]	0.84 (0.47–1.52)	0.63 (0.27–1.46)	1.32 (0.57–3.06)
≥79[d]	0.78 (0.42–1.43)	0.43 (0.16–1.13)	1.59 (0.70–3.61)
BMI, kg/m^2			
24.9–29.9[e]	0.46 (0.25–0.84)[a]	0.50 (0.20–1.21)	0.48 (0.21–1.10)
≥29.9[e]	0.73 (0.40–1.33)	0.91 (0.41–2.05)	0.67 (0.25–1.76)
Test results			
*APOE**4	2.25 (1.25–4.05)[b]	2.85 (1.28–6.33)[a]	1.76 (0.65–4.77)
Total cholesterol	0.996 (0.99–1.00)	0.99 (0.98–1.00)	1.00 (0.99–1.01)
HDL	0.99 (0.96–1.02)	0.97 (0.94–1.01)	1.01 (0.97–1.05)
LDL	0.997 (0.99–1.01)	0.99 (0.98–1.01)	1.00 (0.99–1.01)
ApoA1	0.99 (0.97–1.01)	0.98 (0.96–1.003)	1.01 (0.98–1.03)
129–146[f]	0.67 (0.30–1.47)	0.64 (0.24–1.72)	0.75 (0.20–2.84)
≥147[f]	0.43 (0.16–1.19)	0.19 (0.03–1.03)	1.23 (0.31–4.86)
ApoB	0.99 (0.98–1.01)	0.99 (0.97–1.01)	0.99 (0.97–1.02)
85–103[g]	2.41 (1.04–5.58)[a]	2.28 (0.74–7.07)	2.76 (0.79–9.68)
≥104[g]	0.75 (0.27–2.11)	1.14 (0.32–4.00)	0.29 (0.03–2.72)
Cystatin C	0.83 (0.28–2.43)	1.32 (0.37–4.72)	0.30 (0.04–2.03)
HbA1c	0.78 (0.51–1.19)	0.86 (0.53–1.41)	0.58 (0.23–1.49)
Homocysteine	1.00 (0.96–1.04)	1.00 (0.94–1.07)	1.00 (0.93–1.06)
CRP	0.998 (0.94–1.06)	1.01 (0.96–1.06)	0.87 (0.65–1.17)

Abbreviations: ApoA1 = lipoprotein for high-density lipoprotein cholesterol; ApoB = lipoprotein for low-density lipoprotein cholesterol; BMI = body mass index; CHF = congestive heart failure; CI = confidence interval; CRP = C-reactive protein; DBP = diastolic blood pressure; HbA1c = glycosylated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SBP = systolic blood pressure.
[a] p Values <0.05.
[b] p Values <0.01.
[c] Reference group: SBP ≤126 mm Hg.
[d] Reference group: DBP ≤70 mm Hg.
[e] Reference group: BMI 14–24.9.
[f] Reference group: ApoA1 ≤128.
[g] Reference group: ApoB ≤84.

with age, especially in women.[1] In the all-volunteer Bronx Aging Study, incidence rose more slowly with age.[3] Our cohort's median age at onset of dementia was 87 years, which is older than typically seen in clinical settings, suggesting that the older half of incident dementia cases in the community rarely seek services for dementia or participate in clinical dementia research. Population-based studies are critically needed to complement clinical studies by revealing the full spectrum of dementia across the community.

We have previously reported several vascular, inflammatory, and metabolic risk factors for incidence of MCI[21] and for cognitive decline.[21,25] Examining the same factors in relation to incident dementia, we found that smoking, stroke, and *APOE*4* significantly increased the risk of dementia up until the median onset age, while lower blood pressure and current alcohol use showed a significant protective effect. These risk and protective factors are consistent with the literature.[21,25,28] The protective mechanism of light to moderate alcohol consumption[29] has been attributed to improved cardiovascular health,[30] but could also be a healthy survivor effect.[31] The borderline protective effects of higher DBP, cholesterol, and body mass are consistent with studies showing that these factors increase risk when present in midlife but that the effects reverse in later life.[28] Potentially, lower blood pressure may increase risk through hypoperfusion. Declining cholesterol is known to precede dementia[32] and multiple mechanisms have been proposed.[33] Of note, neither these nor any other factors influenced the risk of dementia after age 87.

In the MYHAT cohort, we previously reported that stroke was associated with baseline cognitive impairment,[25] incident CDR of 0.5, and incident nonamnestic MCI,[21] while *APOE*4* was associated with accelerated decline in language, memory, and executive functions.[25] We also previously found a consistent protective effect for current alcohol consumption against incident MCI and cognitive decline.[21,25] To our knowledge, earlier studies have not compared risk factors for later- and earlier-onset cases of dementia within the same cohort. The few studies focused on the oldest old have shown sparse and inconsistent risk factor associations. For example, in different studies, *APOE*4* was associated with Alzheimer disease pathology,[8] cognitive decline,[9] and neither cognitive decline nor dementia.[10] Hypertension was associated with nonamnestic MCI[12] and with cognitive decline but not dementia.[15] Reported hypercholesterolemia was protective against both cognitive decline and dementia[15]; HDL cholesterol was associated with lower risks of cognitive impairment and dementia, independent of heart disease.[11] The known association between metabolic syndrome and cognitive decline did not hold up in the oldest old.[13]

Risk factors may be elusive in the oldest old because of the heterogeneity of cognitive impairment and dementia in this group. A population-based neuroimaging study showed that in the very old, atrophy parameters overlapped considerably between elderly who were normal and those with dementia.[34] Several neuropathology studies suggest an apparent increasing dissociation between dementia and Alzheimer disease pathology, or even any specific pathology, with increasing age.[35–37]

To address the possibility of limited power to detect small effects in the older group, we stratified the cohort by median onset age to equalize number of incident cases across the groups, and yet found significant risk effects only in the younger group. Nonetheless, our data are based on 67 incident cases detected over 5 years; because overall power can be an issue, we have reported our borderline significant results as well.

The same factors that increase risk of dementia also increase the risk of illness and mortality, so that individuals with those factors who have not yet developed dementia can die or drop out of the study before they can be observed to develop dementia. This competing-risks explanation was not borne out by jointly modeling attrition and dementia. These are not cohort effects because we examined age at onset regardless of when individuals were born or of their age at study entry.

Because the risk of dementia continues to rise steeply with age, there must be either other unexplored risk factors or protective factors that allow these individuals to delay dementia onset into very old age. The protective effect we observed of at least high school education suggests that cognitive reserve has a role.[38] It would be consistent with the Women's Health Initiative study finding that higher educational attainment was associated with a delay in the diagnosis of dementia/MCI in the face of a growing neuropathologic load (based on MRI studies).[39]

While our study cohort is representative of the underlying population, our results should be replicated in larger cohorts with longer follow-up, and in populations with different racial/ethnic backgrounds. Neuroimaging data to identify unreported infarctions and white matter disease would be useful where feasible at the population level. Given the aging of the world's population, our finding that established risk and protective factors appear to lose their impact in the oldest old deserves further investigation.

AUTHOR CONTRIBUTIONS

Dr. Ganguli was responsible for study supervision, concept, and design, acquisition of funding and data, interpretation of data, writing of the

manuscript. Dr. Lee was responsible for statistical analyses under the supervision of Dr. Chang, interpretation of the data, and critical revision of the manuscript for important intellectual content. Dr. Hughes was responsible for study coordination, creation of analytic datasets, interpretation of the data, and critical revision of the manuscript for important intellectual content. Dr. Snitz was responsible for neuropsychological input, interpretation of the data, and critical revision of the manuscript for important intellectual content. Dr. McDade was responsible for neurologic input, interpretation of the data, and critical revision of the manuscript for important intellectual content. Dr. Chang was responsible for statistical analysis, supervision of Dr. Lee, interpretation of the data, and critical revision of the manuscript for important intellectual content.

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