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The effect of risk factors on cognitive impairment

A lifetable approach of the U.S. Health and Retirement Survey

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Introduction

In a rapidly ageing society the concern of decline of memory and other cognitive functioning is a major health problem. Cognitive impairment is a major cause of disability and care dependence. The prevalence of dementia increases exponentially with age. In the absence of effective prevention or treatment, the increase in the numbers of people with dementia will come about as a simple consequence of an increase in the size of the population most at risk, those at middle and old age.
There is a large literature on the relationship between behavioral risk factors and cognitive decline, but the conclusions are often conflicting. In this paper we use a large longitudinal dataset and demographic life table methods to estimate life years lived with cognitive impairment (CI). As risk factors we consider overweight or obesity, smoking and education.

Cognitive decline can be the result of different kinds of cognitive impairment. The largest part is the result of Alzheimer's disease (35% at 90+), followed by cardiovascular dementia, Parkinson's disease dementia and other dementias. Little is known about the development of dementia and how the risk factors have an influence. There is however a large literature finding associations between BMI, smoking or education and cognitive decline. Several studies have found an increased risk of dementia for overweight or obese people compared to those of normal weight.(Kivipelto 2005; Rosengren 2005; Whitmer 2005) The literature about smoking as a risk factor for cognitive impairment is ambivalent. In the early 90's, van Duijn et al. reported that nicotine would decrease the risk of Alzheimer's disease.(van Duijn 1991) The Rotterdam Study found a doubling of the risk of dementia and Alzheimer's disease for smokers.(Ott 1998) These results were contradicted by a prospective study among male British doctors.(Doll 2000) A study of Juan et al suggests that both smoking status and amount of smoking is associated with dementia.(Juan 2004)
Several studies have elicited a substantially higher prevalence of dementia in subjects with low educational attainment. It is possible that higher education may simply reduce the chance of detecting cognitive decline.(Stern 1994) Others found no significant risk of low education for the incidence of dementia of Alzheimer's disease.(Cobb 1995)

We use the longitudinal US Health and Retirement Survey to estimate age-specific transition probabilities to cognitive impairment and translate. We use multi-state life tables to estimate the incidence and duration of CI, dependent on the risk factors BMI, smoking and education.

Data and study population

We used data from the RAND Health and Retirement Survey (HRS) data file containing the HRS and the Asset and Health Dynamics Among the Oldest Old (AHEAD) which began in 1992 and 1993, respectively, and were merged in 1998. More information is available elsewhere (http://hrsonline.isr.umich.edu/). The HRS and AHEAD surveys include a nationally representative sample of initially non-institutionalized persons born in 1931–1941 (HRS, aged 51–61 in 1992) and in 1923 or earlier (AHEAD, aged 70 and older in 1993). Sampled persons were re-interviewed biannually. We used data from 7 waves from 1992 to 2004. Response was on average 86% (HRS) and 90% (AHEAD). We selected white non-Hispanic men and women. Data on vital status and month and year of death are obtained through the mortality register (the National Death Index) and exit interviews.

Cognitive impairment (CI)

To measure cognitive impairment (CI) the AHEAD93 and HRS98 used identical tools to measure cognitive functioning, a modified version of the TICS (The Telephone Interview Cognitive Screen) instrument, a to a telephone interview adapted version of the MMSE (mini mental state examination).(Brandt 1988) (Folstein, Robins et al. 1983)There were six tasks yielding a maximum of 35 points, with higher scores implying better functioning. The tasks included immediate and delayed recall test; a serial seven subtraction test; a counting backwards test; an object naming test and recall of date, the president and the vice-president.
HRS 1992 and HRS 1994 included limited questions to test cognitive functioning and is therefore not comparable.

Herzog and Wallace suggested that a cutoff of 8 (out of 35) identifies a percentage of the population with severe cognitive impairment.(Herzog 1997) We adopted this suggestion but also explored the sensitivity of our analysis to this definition setting the cut points at 7 and 9. Because of possible erratic answering to the TICS questions, we used a cutoff of 10 to define recovery of CI.

Proxy-respondents
When a proxy represented the respondent (about 10% of the sample in each wave), a different tool was used to assess cognitive functioning. Each proxy was asked: "How would you rate the respondent's memory at the present time?" and "How would you rate the respondent in making judgments and decisions?" Respondent's who's memory and judgment were assessed as poor were considered to have CI. Our definitions and cut points were based on prior studies using HRS data.(Suthers 2003; Langa 2008)
In 2004, the judgment question has not been asked. Therefore we solely used the poor memory to define CI by proxy for this year. In the 2002 data, 80% of proxies responding poor memory also answered poor judgment.

Independent variables used as covariates
Exposures are BMI, smoking and levels of education. Self-reported weight and height at baseline are used to calculate BMI (kg/m2), classified as low normal weight (18.5-22.9), high normal weight (23-24.9), overweight (25-29.9), mildly obese (30-34.9) and severely obese (35+). We split normal weight in two classes, defined by BMI 23, because previous analyses suggested important heterogeneity at middle age. We excluded underweight (BMI < 18.5), not being part of our study of normal and excess weight. We use the first length and weight reported. Smoking status is included as 'never smoked', 'stopped smoking' and 'currently smoking' based on the first reported information on smoking status. We distinguish three groups of educational attainment: Less than high-school or General Educational Development (GED), High-School graduate, and College graduate and above.

Methods
We estimated Cox proportional hazard model for proportional hazard ratios for BMI, smoking and education. Age is used as the timescale for the baseline hazard. The Cox model accounts for left truncation and right censoring. In order to describe the burden of mortality and cognitive decline of BMI, smoking and education we defined multistate life tables by the estimated transition rates. We estimated the hazard rates of transitions to death and CI by age for each determinant of interest and for males and females. The transition rates are smoothed using Poisson regression assuming Gompertz baseline hazard. To translate the rates in annual probabilities we assume the rates to be constant in the 1- year intervals. The main outcomes are life expectancy measures at age $x \geq 55$ total life expectancy, CI-free life expectancy or years to live free from cognitive impairment and life expectancy with CI or years to live with cognitive

impairment. Confidence intervals for the multistate lifetable outcomes were calculated using bootstrapping with 100 replicates.

Results

The total HRS sample includes 30207 respondents, of which 13092 males and 17115 females. We selected the white non-hispanic population (22355) who participated at least 2 waves (18559) and were observed at age 55 or over (17795). Table 1 shows the characteristics of the study population. For the analyses, we also excluded the underweight (BMI<18.5) resulting in a sample of 17342, 7763 males and 9579 females.

Table 1: distribution of sample characteristics at entry into the survey

		Males	Females
Total		7804	9863
Education	Low education	2198	2635
	Medium education	3772	5806
	High education	1834	1422
Smoking	Never smoked	2012	5082
	Stopped smoking	4163	2953
	Currently smoking	1629	1828
BMI	BMI < 18.5	41	284
	BMI 18.5-23	1008	2712
	BMI 23-25	1465	1806
	BMI 25-30	3809	3215
	BMI 30-35	1162	1278
	BMI 35+	319	568
Age at Entry	[55,65]	4655	5186
	(65,75]	2004	2704
	(75,85]	957	1550
	(85,95]	185	397
	(95,105]	3	26
Cognitive Impaired at first survey	[55,65]	7	7
	(65,75]	25	21
	(75,85]	31	53
	(85,95]	6	32
	(95,105]	1	8

Incidence and recovery

Following the definitions described above, 515 men and 820 women experienced the onset of CI during observation, of which respectively 45% and 47% was reported by a proxy. A total of 252 individuals experienced recovery, equaling 23% and 16% for males and females respectively. Relapse to impairment after recovery during the study follow-up was rare (N=15). On average, it took 2.5 years to fall back to cognitive impairment after recovery. We assume this relapse was just a temporary upheaval and consider these individuals as never recovered from cognitive impairment.

Table 2: Population size, exposures and events by age and sex.

Population at entry into the survey			Mean follow-up until CI or death/censoring		Onset of first cognitive decline		Mean follow-up until death/ censoring		Death incidence	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
[55,60]	3684	4423	8.01	7.74	128	111	8.08	7.78	392	250
(60,65]	960	652	9.68	9.82	38	20	9.76	9.86	204	77
(65,70]	510	845	7.58	7.28	29	36	7.69	7.40	145	114
(70,75]	1482	1782	6.95	7.55	126	143	7.16	7.75	476	386
(75,80]	572	872	7.36	7.92	73	179	7.62	8.41	315	331
(80,85]	371	607	6.53	6.60	82	175	7.14	7.47	247	374
(85,90]	151	282	5.04	5.55	30	105	5.48	6.48	125	216
(90,95]	30	93	4.34	4.63	8	37	5.06	5.65	28	79
(95,105]	3	23	4.83	2.64	1	14	5.67	4.32	2	19
Total	7763	9579	7.80	7.65	515	820	7.94	7.85	1934	1846

Proportional hazard analysis

A Cox hazard regression model shows the proportional hazard ratios for transitions to death and to CI by BMI, smoking status and levels of education. (table 3)

The effects of the risk factors on recovery from cognitive impairment to healthy were not significant and are therefore not shown. The analyses show that BMI has no effect on becoming cognitively impaired or on survival once impaired. Smoking seems to increase the risk to CI although this is not significant for males. Higher education clearly protects against cognitive decline for both males and females. The mortality risks of higher educated individuals once cognitively impaired tend to be higher compared to the lower educated, although this is only significant for medium educated females.

As a way of sensitivity analysis we redid the analysis using 7 and 9 as cutoff point TICS scores for defining CI, which did not result in significant differences. When using the 9 point score as threshold, highly educated men with CI face a significantly increased mortality risk of 58%.

Table 3: Cox proportional hazard ratios by risk factor status (95% confidence intervals), adjusted for each other. Significant ratios are printed in bold.

Males					Females		
Healthy to Death							
bmi1	**1.199**	1.039	1.383		0.980	0.858	1.120
bmi3	0.898	0.796	1.013		0.887	0.777	1.014
bmi4	1.087	0.923	1.281		0.991	0.829	1.184
bmi5	**1.362**	1.039	1.785		**1.594**	1.271	1.999
smo2	**1.373**	1.214	1.552		**1.261**	1.130	1.406
smo3	**2.469**	2.136	2.854		**2.204**	1.918	2.533
edu2	0.915	0.828	1.010		**0.784**	0.709	0.867
edu3	**0.643**	0.558	0.740		**0.695**	0.585	0.827
Healthy to CI							
bmi1	1.136	0.847	1.524		1.028	0.834	1.268
bmi3	0.855	0.668	1.095		0.921	0.746	1.137

bmi4	1.067	0.768	1.482		1.039	0.787	1.372
bmi5	0.984	0.537	1.803		1.135	0.749	1.720
smo2	0.959	0.764	1.204		1.043	0.877	1.241
smo3	1.332	0.997	1.780		**1.415**	1.108	1.807
edu2	**0.53**	0.432	0.650		**0.738**	0.631	0.864
edu3	**0.365**	0.270	0.495		**0.543**	0.405	0.728
CI to death							
bmi1	1.052	0.708	1.563		0.926	0.706	1.216
bmi3	0.812	0.567	1.161		0.906	0.670	1.226
bmi4	0.926	0.549	1.562		1.195	0.800	1.785
bmi5	0.834	0.391	1.781		1.127	0.609	2.086
smo2	**1.482**	1.068	2.055		**1.364**	1.062	1.753
smo3	1.4	0.903	2.171		1.328	0.850	2.076
edu2	1.184	0.881	1.591		**1.394**	1.118	1.740
edu3	1.557	0.986	2.458		1.303	0.871	1.951

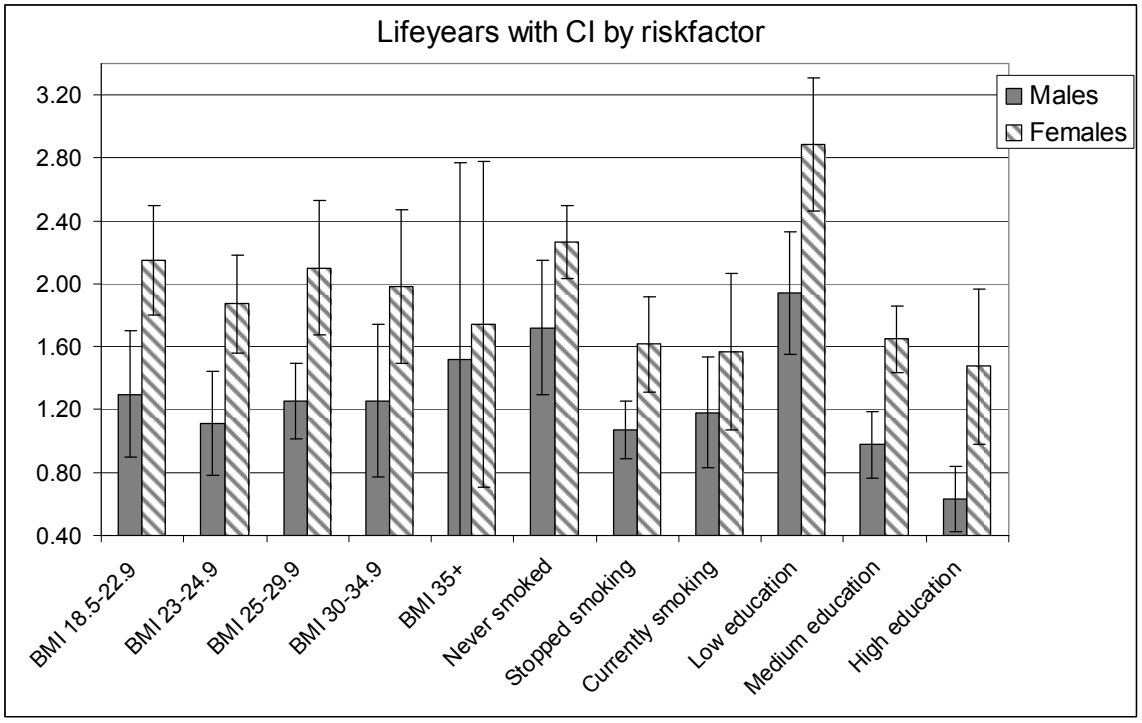
Cognitively impaired life expectancy

Translating age, sex and risk factor-specific transition rates (univariate) into life expectancies at age 55 gives the stratified life expectancy with and without cognitive impairment for each risk group. The actual life expectancy of the total unselected white American population in 2003 was 24.6 for men and 28.1 for women at age 55.(Centers for Disease Control and Prevention 2006) The comparable life expectancy of our study population was respectively 25.1 and 29.6 years (excluding underweight individuals).

Since the Cox analysis did not show any significant effect of the risk factors on recovery and because the number of recovered stratified by risk factor becomes very small, we excluded this state from the multistate life table analysis.

On average males spend 1.2 [1.1,1.4] years and females 2.0 [1.8,2.2] years with CI. The number of years lived with CI varies among risk factors, as shown in figure 1.

Figure 1: Lifeyears with CI by riskfactor, error bars are 95% confidence intervals.

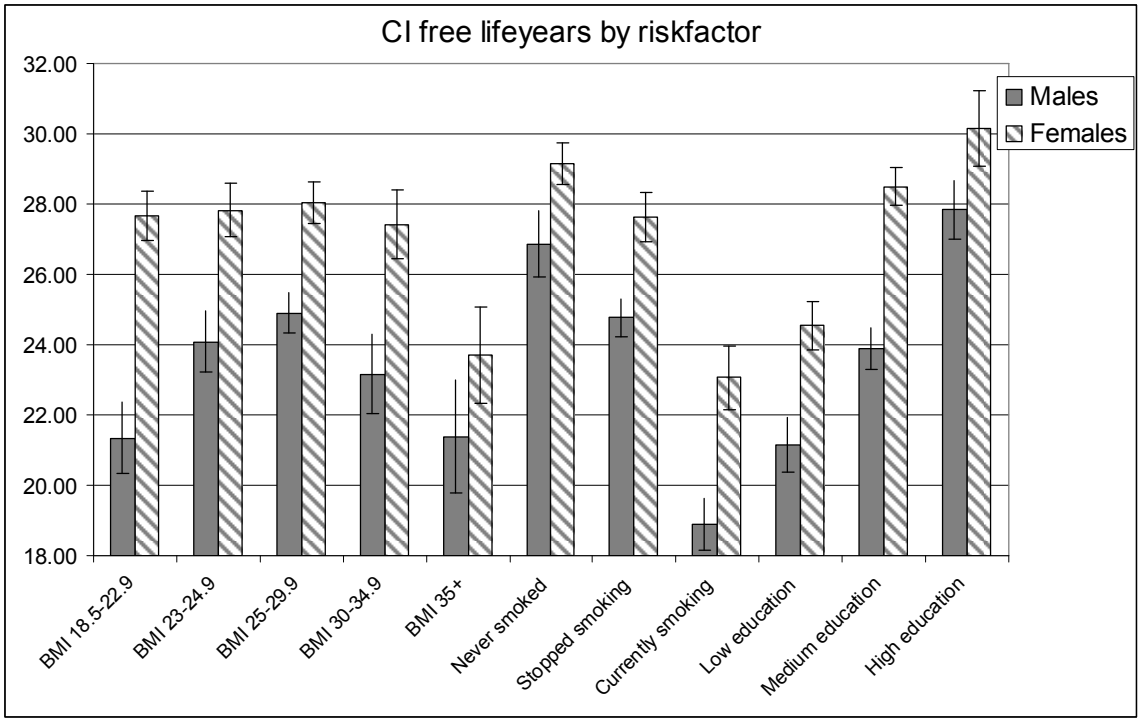


The results show that BMI has virtually no effect on years lived with CI. Smoking however does seem to shorten the cognitive impaired lifespan, although the difference is not significant for current smokers. When we combine ever and current smokers and compare their CI lifespan with never smokers, the former live 0.6 years less with CI ([-1.1,-0.2] for males and [-0.9,-0.3] for females). Education is the most influencing risk factor to predict CI. Highly educated men live on average 0.6 [0.4,0.8] years with CI, 1.3 [0.9,1.8] years shorter than lowly educated men. For women, high education predicts 1.5 [1.0,2.0] years with CI, saving 1.4 [0.8,2.1] years compared to low education.

Paradoxically, factors that prolong lifespan also increase the average period lived with CI. The longest CI free lifespan is obtained for never-smokers and highly educated individuals having a BMI between 23 and 30. The CI free life expectancy of this optimal group is 29.5 for males and 31.2 for females. Shortest lifespan with CI is funnily enough obtained for (former-) smokers with a high education: males 0.56 and females 1.23 years.

When we express the CI life expectancy as percentage of total life expectancy, males live on average 4.9% [4.3,5.5]of their life after age 55 with CI and females 6.9% [6.2,7.5]. Only education has a significant impact on this share ranging from 8.4% [6.8,10.0] and 2.2% [1.5,2.9] for respectively low and high education men and from 10.5% [9.1,12.0] to 4.7% [3.1,6.2] for women.

Figure 2: CI-free life expectancy by risk factor. Error bars are 95% confidence intervals.



Lifetime probability of CI

Another interesting measure that can be derived from the lifetable is the lifetime probability of CI. Women, by living longer, have a higher chance (0.36 [0.34,0.39]) to experience CI at some point in their life compared to men (0.23 [0.21,0.25]). BMI does not have a significant effect on the lifetime probability of CI. Smoking, by shortening life does lower the lifetime probability of CI: 0.29 [0.25,0.33] for never smoking men and 0.19 [0.15,0.23] for currently smoking men and respectively 0.41 [0.39,0.43] and 0.23 [0.18,0.28] for women. High education, as we have seen before, both increases life expectancy and decreases CI incidence. These two effects result in a lower lifetime probability of CI for the higher educated (0.21 [0.15,0.26] males, 0.30 [0.24,0.36] females) compared to lower educated individuals (0.30 [0.27,0.32] males, 0.39 [0.36,0.42] females).

Discussion

From the large longitudinal HRS survey of white non-Hispanic Americans aged 55 and over we find that male sex, smoking and education lower lifeyears lived with cognitive impairment. Women and non-smokers live more years with CI than men, simply because they live longer. The same holds for never-smokers compared to (former) smokers. We did not find any effect of BMI on the incidence of CI, however, confounding by weight loss induced by senescence and cognitive decline, is a major problem. Smoking might increase the risk of CI, but this is largely offset by the elevated mortality of smokers, shortening lifespan with CI. High education increases total lifespan, but increases lifespan free of cognitive decline even more, shortening life with cognitive impairment.

The estimated lifespan with CI is comparable with the results of other studies, like the 1980 cohort of the Kaiser Permanente Medical Care Program of North California.(Sauvaget 1999) Suthers et al using AHEAD data show lower estimates for total, CI-free and CI life expectancy at age 70, although the confidence intervals for the latter overlap.(Suthers 2003) The difference is

mainly due to higher mortality in Suthers' analyses, which can be explained by the earlier observation (1993) and including blacks, Hispanics and underweight individuals in their sample. Evidence on the effect of body weight on CI is conflicting. A systematic review on the association between BMI and dementia suggests increased BMI as a likely independent risk factor for dementia. Our results did not confirm this. The relation between BMI and CI might be complex as losing weight is associated with the onset of dementia.(Stewart 2005) The disentanglement of the intimate relationships of BMI, weigh loss and CI is beyond the scope of this study.
The relation between smoking and cognitive impairment is complex. Nicotin might enhance cerebral functioning, but the effects are disputed.(Lopez-Arrieta, Rodriguez et al. 2000; Swan and Lessov-Schlaggar 2007) Smoking surely promotes vascular disease and related dementias.(Swan and Lessov-Schlaggar 2007) Consistent with a meta-analysis of prospective studies of smoking as risk factor for CI,(Anstey, Sanden et al. 2007) we found an increased risk of CI for smokers compared to never smokers.
Our findings on the effect of education are in line with the so-called cognitive reserve hypothesis.(Stern 1995; Stern 2006) This hypothesis suggests that brains of higher educated individuals can sustain greater damage before reaching the critical threshold of CI. However, having reached later a higher level of organic damage means a more advanced stage of brain disease, resulting in an increased dementia related mortality risk.(Witthaus, Ott et al. 1999) The HRS data support this hypothesis. A higher education was related to a decreased risk of cognitive decline but an increased risk of mortality once cognitively impaired. Other known causal factors related to the onset of dementia are high blood pressure, high alcohol consumption and the presence of the APOE4 allele, but the data did not support these.

The HRS survey is a social study, not providing a clinical diagnosis of dementia. The definition of CI and scores used are comparable to the MMSE, a much used screening tool, and have shown good correlation with dementia in prior studies.(Langa 2001) One of the disadvantages of the HRS data is that the measures for CI differ for self- and proxy respondents. The combining of these unequal measures is used in most studies.(Suthers 2003) Another shortcoming is that all covariates are based on self-reports. It is known that self-reported BMI tends to be underreported by 1 BMI point.(Visscher, Viet et al. 2006) However, for epidemiological studies, this is sufficient.(McAdams 2007) Finally a remark on the timeframe of the study. We used the HRS data from 1993 to 2004 representing a recent experience of a middle- and old aged cohort. Declining CI prevalence, as suggested by Langa et al.(Langa 2008) has not been taken into account in the analysis.

As Olshansky put it "Few topics in the world of science are as interesting and personal as the question of how much time will pass between our birth and death, and the status of our health along the way."(Olshansky 2008) Cognitive impairment is a major cause of disability and care dependence and nearly all people fear loss of cognition and the ability for selfcare. Ageing and life extension of the baby boom cohorts will cause numbers of demented people to increase rapidly. While smoking increases the age adjusted incidence of dementia, less smoking paradoxically increases the duration of life with dementia, by the same principle of life extension. However, the Flynn effect describes secular increases in intelligence that parallel increases in life expectancy.(Dickens and Flynn 2001) As raising levels of intelligence and education postpone incidence of dementia more than death, even if we may live longer with cognitive impairment, we gain more life years free of cognitive impairment.

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