

# Cigarette Smoking and Dementia

## *Potential Selection Bias in the Elderly*

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**Abstract:** We conducted a systematic review of published prospective studies that estimated the association between smoking and the incidence of Alzheimer disease and dementia. The relative rate for smokers versus nonsmokers ranged from 0.27 to 2.72 for Alzheimer disease (12 studies) and from 0.38 to 1.42 for dementia (6 studies). The minimum age at entry (range: 55–75 years) explained much of the between-study heterogeneity in relative rates. We conjecture that selection bias due to censoring by death may be the main explanation for the reversal of the relative rate with increasing age.

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The article by Euser et al<sup>1</sup> in this issue of *EPIDEMIOLOGY* shows that study participants with complete follow-up are healthier and have better age-specific cognitive scores than those with incomplete follow-up. A well-known potential consequence of these differences is selection bias: when the analysis is restricted to individuals with complete follow-up (eg, those not too ill to participate), it is possible to find an exposure-outcome association that is not due to the causal effect of the exposure on the outcome.<sup>2</sup> An extreme case of “incomplete follow-up” for nonfatal outcomes is death; hence censoring by death may introduce selection bias. In studies of old people, this selection bias may be large because the death rate is high and death is often affected by the exposure.<sup>3</sup> Here we provide some empirical support for selection bias due to censoring by death in epidemiologic studies of the effect of cigarette smoking on risk of dementia.

We conducted a systematic review of published prospective cohort studies that estimated the association between smoking and the incidence of Alzheimer disease or dementia. We searched PubMed using the following query: “(smok\* OR tobacco OR cigar\*) AND (cognit\* OR Alzheimer OR dementi\*) AND (cohort\* OR follow-up OR incidenc\* OR

prospective OR epidemiolog\*).” We excluded studies that relied exclusively on death certificates to ascertain the dementia diagnosis.<sup>4,5</sup>

Table 1 summarizes the characteristics of the 12 studies that met our criteria.<sup>6–17</sup> The relative rate (RR) for smokers versus nonsmokers ranged from 0.27 to 2.72 for Alzheimer disease (12 studies) and from 0.38 to 1.42 for dementia (6 studies). We hypothesized that part of this between-study heterogeneity could be explained by the between-study differences in minimum age at entry (range: 55–75 years).

Figure 1 plots the log RR of Alzheimer disease versus the minimum age at baseline. The weighted average RR was 1.71 for studies with minimum age at baseline 55–64 years (2 studies), 1.17 for 65–74 years (7 studies), and 0.52 for 75 or more years (3 studies). The results did not materially change when we restricted the analysis to studies in which the rate ratio estimate was adjusted for age and sex. Figure 2 plots the log rate ratio of dementia versus the minimum age at baseline. The weighted average RR was 1.42 for studies with minimum age at baseline 55–64 years (1 study), 1.26 for 65–74 years (2 studies), and 0.72 for 75 years or more (3 studies).

Our findings can receive at least 2 interpretations that are not mutually exclusive. First, the effect of cigarette smoking on the risk of dementia is modified by age: smoking harmful at younger ages, beneficial at older ages. Second, the effect of cigarette smoking is harmful overall but appears beneficial at older ages because of selection bias, eg, most smokers who are susceptible to developing dementia due to their smoking do so by age 75, and thus the group of 75-year-olds without dementia at baseline is depleted of susceptible smokers. The data from these observational studies, or even from hypothetical randomized experiments of cigarette smoking, cannot conclusively rule out either of these interpretations. However, it is interesting that similar differences of age-specific estimates have been previously reported for the association of body mass index<sup>18</sup> and high blood pressure<sup>19</sup> with mortality. All these “bad” exposures—smoking, obesity, high blood pressure—are apparently associated with a reduction (or even reversal) of the RR with increasing age. Although it is biologically conceivable that the effect of each of these exposures is dramatically affected by age, a simpler explanation may be that much of the variation in age-specific RRs is due to selection bias by death.

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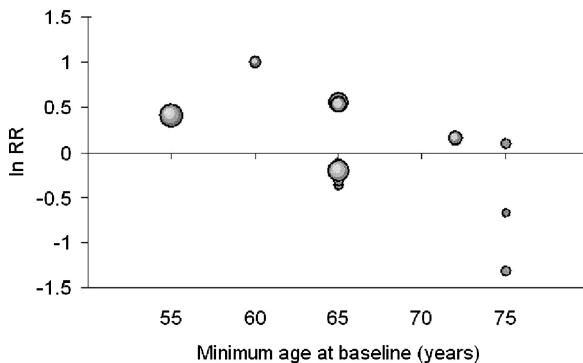
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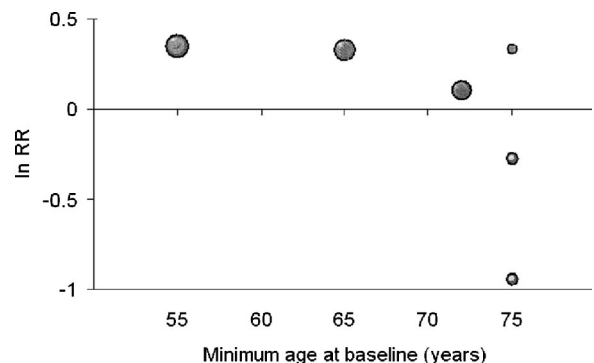
**TABLE 1.** Details of Prospective Studies on the Association of Cigarette Smoking With Alzheimer Disease or Dementia

| Author                        | Year of Publication | Location                         | No. Participants | No. Cases              | Age at Baseline (yrs) | Maximum Follow-up | RR (95% CI) for Smoking   |   |
|-------------------------------|---------------------|----------------------------------|------------------|------------------------|-----------------------|-------------------|---|---|
|                               |                     |                                  |                  |                        |                       |                   | Alzheimer Disease   | Dementia  |
| Hebert et al <sup>6</sup>     | 1992                | Boston, MA, USA                  | 513              | 76 AD                  | 65+                   | 4.7 yr            | Ever vs. never: 0.7 (0.3–1.4)   | —   |
| Juan et al <sup>7</sup>       | 2004                | Chongqing, China                 | 2,820            | 121 dementia<br>84 AD  | 60+                   | 2 yr              | Current vs. never: 2.72 (1.63–5.42)<br>Past vs. never: 1.53 (0.65–1.42) | —   |
| Katzman et al <sup>8</sup>    | 1989                | Bronx, NY, USA                   | 434              | 56 dementia<br>32 AD   | 75–85                 | 45 mo             | Ever vs. never: 0.27 (0.13–0.57)  | Ever vs. never: 0.39 (0.23–0.69)  |
| Launer et al <sup>9</sup>     | 1999                | UK, Netherlands, Denmark, France | 16,334           | 400 dementia<br>277 AD | 65+                   | 2 yr              | Current vs. never: 1.74 (1.21–2.50)<br>Past vs. never: 1.19 (0.80–1.51) | Current vs. never: 1.39 (1.03–1.89)<br>Past vs. never: 1.03 (0.79–1.34) |
| Lindsay et al <sup>10</sup>   | 2002                | Canada                           | 6,434            | 194 AD                 | 65+                   | 5 yr              | Smoking vs. nonsmoking: 0.82 (0.57–1.17)                                | —   |
| Merchant et al <sup>11</sup>  | 1999                | Manhattan, NY, USA               | 1,062            | 142 AD                 | 65+                   | 2 yr              | Current vs. never: 0.83 (0.60–1.16)<br>Past vs. never: 0.7 (0.5–1.1)    | —   |
| Piguat et al <sup>12</sup>    | 2003                | Sydney, Australia                | 377              | 63 dementia<br>21 AD   | 75–98                 | 6 yr              | Smoking vs. nonsmoking: 0.51 (0.21–1.21)                                | Smoking vs. nonsmoking: 0.76 (0.45–1.26)                                |
| Reitz et al <sup>13</sup>     | 2007                | Rotterdam, Netherlands           | 6,868            | 706 dementia<br>555 AD | 55+                   | 14 yr             | Current vs. never: 1.51 (1.10–2.08)<br>Past vs. never: 1.17 (0.90–1.52) | Current vs. never: 1.42 (1.07–1.89)<br>Past vs. never: 1.17 (0.92–1.48) |
| Tyas et al <sup>14</sup>      | 2001                | Manitoba, Canada                 | 1,355            | 36 AD                  | 65–93                 | 5 yr              | Smoking vs. nonsmoking: 0.90 (0.37–2.21)                                | —   |
| Tyas et al <sup>15</sup>      | 2003                | Hawaii, USA                      | 3,232            | 297 dementia<br>113 AD | 72–91                 | 3 yr              | Current vs. never: 1.17 (0.69–1.98)<br>Past vs. never: 0.93 (0.58–1.50) | Current vs. never: 1.11 (0.79–1.55)<br>Past vs. never: 0.80 (0.58–1.10) |
| Wang et al <sup>16</sup>      | 1999                | Stockholm, Sweden                | 343              | 46 dementia<br>34 AD   | 75–101                | 3 yr              | Ever vs. never: 1.1 (0.5–2.4)   | Ever vs. never: 1.4 (0.8–2.7)   |
| Yoshitake et al <sup>17</sup> | 1995                | Hisayama, Japan                  | 828              | 42 AD                  | 65–98                 | 7 yr              | Ever vs. never: 0.73 (0.34–1.57)  | —   |

AD indicates Alzheimer disease; CI, confidence interval.



**FIGURE 1.** Log RR of Alzheimer disease by the minimum age at baseline in the study. The area of the circle is proportional to the precision (1/variance) of the log RR estimate.



**FIGURE 2.** Log RR of dementia by the minimum age at baseline in the study. The area of the circle is proportional to the precision (1/variance) of the log RR estimate.

Like Euser et al,<sup>1</sup> we have provided another example of potentially large selection bias in studies of old people, which has implications for study design, comparison of estimates among studies, and biologic interpretation of the results. As the number of epidemiologic studies of aging-related conditions increases, readers should beware of age-specific estimates of RR. Selection bias due to censoring by competing risks may be near.

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### REFERENCES

- Euser SM, Schram MT, Hofman A, et al. Measuring cognitive function with age: The influence of selection by health and survival. *Epidemiology*. 2008;19:440–447.
- Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. *Epidemiology*. 2004;15:615–625.
- Greenland S. Quantifying biases in causal models: classical confounding vs collider-stratification bias. *Epidemiology*. 2003;14:300–306.
- Doll R, Peto R, Boreham J, et al. Smoking and dementia in male British doctors: prospective study. *BMJ*. 2000;320:1097–1102.
- Hirayama T. Large cohort study on the relation between cigarette smoking and senile dementia without cerebrovascular lesions. *Tob Control*. 1992;1:176–179.
- Hebert LE, Scherr PA, Beckett LA, et al. Relation of smoking and alcohol consumption to incident Alzheimer's disease. *Am J Epidemiol*. 1992;135:347–355.
- Juan D, Zhou DHD, Li J, et al. A 2-year follow-up study of cigarette smoking and risk of dementia. *Eur J Neurol*. 2004;11:277–282.
- Katzman R, Aronson M, Fuld P, et al. Development of dementing illnesses in an 80-year-old volunteer cohort. *Ann Neurol*. 1989;25:317–324.
- Launer LJ, Andersen K, Dewey ME, et al. Rates and risk factors for dementia and Alzheimer's disease: results from the EURODEM pooled analysis. *Neurology*. 1999;52:78–84.
- Lindsay J, Laurin D, Verreault R, et al. Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. *Am J Epidemiol*. 2002;156:445–453.
- Merchant C, Tang M-X, Albert S, et al. The influence of smoking on the risk of Alzheimer's disease. *Neurology*. 1999;52:1408–1412.
- Piguet O, Grayson DA, Creasey H, et al. Vascular risk factors, cognition and dementia incidence over 6 years in the Sydney Older Persons Study. *Neuroepidemiology*. 2003;22:165–171.
- Reitz C, den Heijer T, van Duijn C, et al. Relation between smoking and risk of dementia and Alzheimer disease: the Rotterdam Study. *Neurology*. 2007;69:998–1005.
- Tyas SL, Manfreda J, Strain LA, et al. Risk factor for Alzheimer's disease: a population-based, longitudinal study in Manitoba, Canada. *Int J Epidemiol*. 2001;30:590–597.
- Tyas SL, White LR, Petrovitch H, et al. Mid-life smoking and late-life dementia: the Honolulu-Asia Aging Study. *Neurobiol Aging*. 2003;24:589–596.
- Wang H-X, Fratiglioni L, Frisoni GB, et al. Smoking and the occurrence of Alzheimer's disease: cross-sectional and longitudinal data in a population-based study. *Am J Epidemiol*. 1999;149:640–644.
- Yoshitake T, Kiyohara Y, Kato I, et al. Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama study. *Neurology*. 1995;45:1161–1168.
- Stevens J, Cai J, Pamuk ER, et al. The effect of age on the association between body-mass index and mortality. *N Engl J Med*. 1998;338:1–7.
- Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903–1913.