Combined impact of smoking and heavy alcohol use on cognitive decline in early old age: Whitehall II prospective cohort study.

Gareth Hagger-Johnson, Séverine Sabia, Eric John Brunner, Martin Shipley, Martin Bobak, Michael Marmot, Mika Kivimaki, Archana Singh-Manoux

To cite this version:


HAL Id: inserm-01153653
https://www.hal.inserm.fr/inserm-01153653
Submitted on 20 May 2015

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.
Combined impact of smoking and heavy alcohol use on cognitive decline in early old age: Whitehall II prospective cohort study

Gareth Hagger-Johnson, Séverine Sabia, Eric John Brunner, Martin Shipley, Martin Bobak, Michael Marmot, Mika Kivimaki and Archana Singh-Manoux

Background
Identifying modifiable risk factors for cognitive decline may inform prevention of dementia.

Aims
To examine the combined impact of cigarette smoking and heavy alcohol consumption on cognitive decline from midlife.

Method
Prospective cohort study (Whitehall II cohort) with three clinical examinations in 1997/99, 2002/04 and 2007/09. Participants were 6473 adults (72% men), mean age 55.76 years (s.d. = 6.02) in 1997/99. Four cognitive tests, assessed three times over 10 years, combined into a global z-score (mean 0, s.d. = 1).

Results
Age-related decline in the global cognitive score was faster in individuals who were smoking heavy drinkers than in non-smoking moderate alcohol drinkers (reference group). The interaction term (P = 0.04) suggested that the combined effects of smoking and alcohol consumption were greater than their individual effects. Adjusting for age, gender, education and chronic diseases, 10-year decline in global cognition was \(-0.42\) z-scores (95% CI \(-0.45\) to \(-0.39\)) for the reference group. In individuals who were heavy alcohol drinkers who also smoked the decline was \(-0.57\) z-scores (95% CI \(-0.67\) to \(-0.48\)); 36% faster than the reference group.

Conclusions
Individuals who were smokers who drank alcohol heavily had a 36% faster cognitive decline, equivalent to an age-effect of 2 extra years over 10-year follow-up, compared with individuals who were non-smoking moderate drinkers.

Declaration of interest
None.

Cognitive decline refers to a wide continuum of changes in cognitive function across the life course, including both age-related decline and pathological decline.1 Poor cognitive status, even in the absence of clinical dementia, is perhaps the single most disabling condition in old age. Dementia is a syndrome characterised by impairment of multiple cognitive capacities that are severe enough to interfere with daily functioning. It is often preceded by mild cognitive impairment, defined as ‘cognitive impairment short of dementia’ or ‘a transitional state between normal cognition and dementia’.2 It is estimated that pathological changes that lead to dementia start as early as several decades before clinical diagnosis.3,4 An effective cure for dementia remains elusive and given high and rising treatment and care costs, knowledge about early modifiable risk factors may be important from a public health perspective. Importantly, unhealthy behaviours may accelerate cognitive decline and be amenable to low-cost intervention at a population level.5 In the UK, cigarette smoking and heavy alcohol consumption remain prevalent, including among older adults.6 Several studies have found an association between smoking and cognitive decline7–9 and dementia.10 Earlier studies apparently suggesting a protective effect of smoking11,12 were later attributed to selection bias.13 Evidence concerning alcohol use as a risk factor for cognitive decline and dementia is also mixed. There may be non-linear associations between alcohol and cognitive outcomes. For example, a meta-analysis found lower risk of dementia in people who were moderate (for example up to 14 units per week for women and up to 21 units per week for men) but not heavy drinkers compared with non-drinkers.13 Smoking and heavier alcohol consumption often co-occur14 and their combined effect on cognition may be larger than the sum of their individual effects. In combination they have been associated with greater risk of all-cause mortality in an occupational cohort in West Scotland15 and with aerodigestive cancer risk in a meta-analytic study.16 To date few studies have examined the combined effect of smoking and alcohol use on cognitive decline. In two early cross-sectional studies of community-dwelling older adults in the USA (age 60–84), one found no greater combined effect17 and the other found general cognitive function to be 6% lower among those who smoked and drank alcohol heavily compared with all other groups.18 An earlier study of older adults in the USA (age 65 and older) found no separate effects but did not test for a possible interaction.19 A later study in Finland found more frequent (vs. never or infrequent) alcohol use in midlife was associated with better cognitive performance 21 years later (at age 65–79), which was stronger among non-smokers.20

The evidence from studies on older populations on the combined effect of alcohol and smoking on the risk of cognitive function,17,18,20 cognitive decline,19,21 or later Alzheimer’s disease12,22 is inconsistent. An added complication is that older smokers are a selected population.7 As cognitive decline is evident in midlife,7 the aim of our study was to examine whether cigarette smoking and alcohol consumption interact to accelerate cognitive decline in the transition from midlife to early old age.

Method
Study population
The Whitehall II cohort was established in 1985/88 among 10 308 British civil servants.23 All civil servants aged 35–55 years in 20 London-based departments were invited to participate by letter, and 73% agreed (67% men). Cognitive testing was introduced in 1997/99 (the baseline for our analysis) during a clinical
The longitudinal association between individuals who were smokers was classified as current smoker, ex-smoker or never smoker. Women and men smoked at a rate of 20 cigarettes per day at the same time, to evaluate their impact on cognitive outcomes. We used latent growth curve models to examine both the cross-sectional and longitudinal associations. The cognitive tests comprised four cognitive tests and were administered at three clinical examinations over 10 years (1997/99, 2002/04 and 2007/09). We repeated the models after excluding participants who were very heavy drinkers ( >20 cigarettes per day) at the same time, to evaluate their impact on cognitive outcomes. We used latent growth curve models to examine both the cross-sectional and longitudinal associations. The cognitive tests comprised four cognitive tests and were administered at three clinical examinations over 10 years (1997/99, 2002/04 and 2007/09). We repeated the models after excluding participants who were very heavy drinkers ( >20 cigarettes per day) at the same time, to evaluate their impact on cognitive outcomes. We used latent growth curve models to examine both the cross-sectional and longitudinal associations. The cognitive tests comprised four cognitive tests and were administered at three clinical examinations over 10 years (1997/99, 2002/04 and 2007/09). We repeated the models after excluding participants who were very heavy drinkers ( >20 cigarettes per day) at the same time, to evaluate their impact on cognitive outcomes. We used latent growth curve models to examine both the cross-sectional and longitudinal associations. The cognitive tests comprised four cognitive tests and were administered at three clinical examinations over 10 years (1997/99, 2002/04 and 2007/09). We repeated the models after excluding participants who were very heavy drinkers ( >20 cigarettes per day) at the same time, to evaluate their impact on cognitive outcomes.
Results

The analytic sample comprised 6473 participants (4635 men) with data on cigarette smoking, alcohol units, covariates and global cognition for at least one examination. Of the analytic sample, 68.4% had three waves of cognitive data and 19.3% had two waves. Compared with the Whitehall II study population at recruitment (1985/88, n = 10 308) those excluded were slightly older (mean 44.8 v. 44.2 years in 1985–88, P < 0.001), more likely to be female (41.1% v. 28.4%, P < 0.001), more likely to smoke (24.7% v. 14.8%, P < 0.001) and less likely to drink alcohol heavily (14.6% v. 16.3%, P < 0.001). Table 1 presents characteristics of the participants included in the analysis, showing that individuals who were current smokers were more likely to drink alcohol heavily.

Growth curve models to estimate the combined effect of alcohol consumption and smoking status at baseline (1997/99) on global cognitive score over follow-up (2002/04 and 2007/09) were fitted with adjustment for age, gender, prevalent chronic disease and educational attainment. These models showed a significant interaction between smoking status and alcohol consumption, both for the intercept (cognitive function at baseline, $\chi^2(4) = 20.83$, $P < 0.001$) and the slope (cognitive decline over 10 years, $\chi^2(4) = 9.99$, $P < 0.04$).

In order to estimate the combined effect of each alcohol × smoking status group, the model was re-parameterised and fitted using eight dummy variables that compared each alcohol × smoking status group with the largest group used as the reference group (never smoker, moderate alcohol drinker). This enabled estimation of the cognitive outcomes in each group in terms of cognition function in 1997/99 (intercept) and cognitive decline during the follow-up (slope). Table 2 shows the estimated mean intercept and slope for each alcohol × smoking status group (coefficients for the alternative parameterisation are shown in online Table DS1, and for all groups in online Table DS2). Compared with those who were never smokers and consumed a moderate amount of alcohol, participants reporting no alcohol consumption in the previous 7 days generally had worse cognitive function at baseline. Moderate drinkers who were current smokers also had a significantly lower baseline cognitive function. In general, estimated cognitive function at baseline was higher as alcohol consumption increased.

In analysis of cognitive decline (expressed as the change in cognitive function over 10 years), only one group differed significantly from the reference group of never smokers and moderate alcohol users. In individuals who were current smokers and who were also heavy drinkers, cognitive decline was 36% faster than the reference group. Cognitive decline in this group was equivalent to an age effect of 12 years ($-0.153/ -0.013 = 12$), 2 years faster than in those who were non-smoking moderate drinkers (an age effect of 2 extra years over 10-year follow-up). Figure 1 shows both the baseline cognitive function (intercept) and the cognitive decline trajectory (slope) for the ‘current smoker, heavy drinker’ group compared with the total sample.

Among those reporting alcohol consumption, we observed a linear dose–response association between log alcohol units and 10-year cognitive decline among the male smokers group ($B_{slope} = -0.12$, 95% CI $-0.20$ to $-0.04$, $P = 0.004$). Cognitive decline was faster as the number of alcohol units increased (online Fig. DS1).

Among males who were heavy alcohol drinkers, cigarette smoking (v. never smoking) was associated with significantly

![Fig. 1 Cognitive decline in the 'current smoker, heavy alcohol drinker' group compared with the total sample.](image-url)
faster cognitive decline ($B_{\text{slope}} = -0.22$, 95% CI $-0.35$ to $-0.10$, $P = 0.001$), consistent with the results from the interaction models. Among these men there was little evidence for a dose–response association between the number of cigarettes smoked and cognitive decline: 1–10 cigarettes per day ($B_{\text{slope}} = -0.14$, 95% CI $-0.28$ to 0.01, $P = 0.06$); 11–20 cigarettes per day ($B_{\text{slope}} = -0.32$, 95% CI $-0.53$ to $-0.10$, $P = 0.01$); $\geq 21$ cigarettes per day ($B_{\text{slope}} = -0.15$, 95% CI $-0.37$ to 0.08, $P = 0.21$) (online Fig. DS2).

Results from sensitivity analyses are summarised in Table 3. These did not influence the conclusions drawn from the main analysis materially. For the ‘non-smoker, 0 alcohol units per week’ group, effect sizes were similar for non-drinkers and occasional drinkers (17% v. 19% faster than the reference group respectively).

### Discussion

This study of over 6000 adults aged 45–69 years at the start of cognitive testing examined cigarette smoking and alcohol consumption as predictors of cognitive decline assessed three times over 10 years. The combined effect of cigarette smoking and heavy alcohol consumption accelerated cognitive decline over the 10-year follow-up period. Cognitive decline was 36% faster in those who reported both cigarette smoking and drinking alcohol above the recommended limits at baseline, this effect was equivalent to an age effect of an additional 2 years over 10-year follow-up. The pattern was strongest for tests requiring executive function; that is reasoning, semantic and phonemic fluency.

### Strengths and limitations

The large sample size, long follow-up period and multiple waves of cognitive assessment strengthen confidence in the results. Several known confounding factors were controlled for in the analysis. Combining four tests into a single measure of global cognition can reduce measurement error. There are some limitations to our study. First, participants reporting 0 alcohol units per week in the past 7 days were a heterogeneous group comprising occasional drinkers, lifetime abstainers, those with existing morbidity (including ‘sick quitters’) and those not drinking alcohol for other reasons. ‘Sick quitters’ may account partly for the significantly higher levels of chronic disease observed in those reporting 0 alcohol units per week (online Table DS3). It is also possible that symptoms of prodromal cognitive decline may have motivated participants to stop drinking alcohol. This makes it difficult to determine any protective effect of non-drinking, because this group contains some previously heavy drinkers and a high prevalence of chronic disease. However, effect sizes were similar among occasional and non-drinkers. Second, because all participants were white collar workers, results may not generalise to manual occupations or to the unemployed. However, the cohort covers a wide socioeconomic range, with a tenfold difference in full-time salary between the highest and lowest occupational grade.

### Comparison to other studies

Previous studies evaluating the combined impact of cigarette smoking and alcohol use on risk of cognitive decline or dementia have focused on older adults, often with smaller sample sizes and have tended to be cross-sectional or case-control studies of Alzheimer’s disease, although these studies did not distinguish moderate from heavy alcohol drinkers. We studied longitudinally the

---

**Table 2**

<table>
<thead>
<tr>
<th>Total sample</th>
<th>Never smoker</th>
<th>Current smoker</th>
<th>Ex-smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10</td>
<td>0.10</td>
<td>0.42</td>
<td>b**</td>
</tr>
<tr>
<td>(0.07 to 0.12)</td>
<td>(0.07 to 0.12)</td>
<td>(0.47 to 0.42)</td>
<td>b**</td>
</tr>
</tbody>
</table>

---

b** $P < 0.01$; a. Estimated means are adjusted for age, gender, education and chronic disease; intercept centred at age 55, male, with no chronic disease and having higher secondary level education.
combined effect of both behaviours from midlife to early old age on both cognitive function and decline.

There is now consistent evidence to suggest that studies based on elderly people have selection bias because of the greater mortality among smokers, producing a selected group of older smokers. Although our study followed participants from midlife, we found some evidence for a healthy survivor effect over follow-up. It is therefore likely that we underestimated the combined effect of smoking and heavy alcohol drinking on cognitive decline, owing to greater mortality among smokers and heavy alcohol drinkers. The findings presented here extend our previous report that smoking in men is associated with faster cognitive decline over 10 years (online Table DS4).9

**Meaning of the study**

It is important to know whether the effects of smoking and alcohol use combine to increase risk of cognitive decline in early old age, since this may offer opportunities for prevention. Strategies designed to encourage adults to stop smoking could be implemented sequentially with other behaviour change interventions, such as using smoking cessation to begin discussions about other risky behaviours. Preventable risk factors that co-occur could potentially offer a double dividend, since removal of either risk factor can remove the excess risk associated with the risk factor and the excess risk associated with the interaction. However, the particularly strong combined effect we demonstrate here should not detract from concerns about the separate impact of unhealthy behaviours, particularly smoking, but additionally shows the importance of looking at how the effects of behaviours may combine. Future research should identify reasons why combining these two behaviours accelerates cognitive decline. Studies could look at cumulative damage to aerodigestive or vascular pathways and any subsequent association with cognitive decline. In terms of public health recommendations, guidelines already exist about smoking and drinking alcohol within recommended levels but these could be modified to emphasise excess risk from combined behaviours.

**Implications**

From a public health perspective, the increasing burden associated with cognitive ageing could be reduced if lifestyle risk factors can be modified. We concur with Anttila et al.8 that people should not drink more heavily in the belief that alcohol is a protective factor against cognitive decline. Our findings, assuming the observed associations are causal, show that alcohol use and cigarette smoking do not appear to ‘cancel each other out’. Their combined effect appears to accelerate cognitive decline. Individuals who smoke should stop or cut down, and avoid heavy alcohol drinking, consistent with existing advice. Adults should additionally be advised however, not to combine these two unhealthy behaviours, particularly from midlife onwards.


### Table DS1

Association between alcohol consumption and smoking status on global cognition: beta coefficients\(^a\), 95% confidence intervals and \(p\) values for a model containing interaction terms between exposures.

<table>
<thead>
<tr>
<th>N = 6473</th>
<th>Model including interaction terms between exposures(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intercepts</td>
</tr>
<tr>
<td></td>
<td>B (95% CI)</td>
</tr>
<tr>
<td><strong>Main effects</strong></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>-0.26 (-0.37, -0.15)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>0.03 (-0.02, 0.09)</td>
</tr>
<tr>
<td>0 alcohol units/week</td>
<td>-0.47 (-0.57, -0.38)</td>
</tr>
<tr>
<td>Heavy drinker</td>
<td>0.09 (0.01, 0.16)</td>
</tr>
<tr>
<td><strong>Interaction terms</strong></td>
<td></td>
</tr>
<tr>
<td>Current smoker*Heavy drinker</td>
<td>0.17 (-0.01, 0.34)</td>
</tr>
<tr>
<td>Current smoker*0 alcohol units/week</td>
<td>0.48 (0.24, 0.72)</td>
</tr>
<tr>
<td>Ex-smoker*Heavy drinker</td>
<td>0.07 (-0.04, 0.17)</td>
</tr>
<tr>
<td>Ex-smoker*0 alcohol units/week</td>
<td>0.18 (0.03, 0.33)</td>
</tr>
<tr>
<td>Current smoker*female</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\)Coefficients are adjusted for age, sex, education and chronic disease. Results are equivalent to online Table DS2. Reference categories are ‘never smoker’ and ‘moderate drinker’.
**Table DS2** Association between alcohol consumption and smoking status on global cognition: beta coefficients, 95% confidence intervals and p values for a model using eight dummy variables

<table>
<thead>
<tr>
<th>N = 6473</th>
<th>Intercepts</th>
<th>Slopes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nine groups (eight dummy variables)</strong></td>
<td><strong>B (95% CI)</strong></td>
<td><strong>p</strong></td>
</tr>
<tr>
<td>Never smoker, 0 alcohol units/week</td>
<td>-0.47 (-0.57, -0.38)</td>
<td>.00</td>
</tr>
<tr>
<td>Ex-smoker, 0 alcohol units/week</td>
<td>-0.26 (-0.38, -0.14)</td>
<td>.00</td>
</tr>
<tr>
<td>Current smoker, 0 alcohol units/week</td>
<td>-0.26 (-0.46, -0.06)</td>
<td>.01</td>
</tr>
<tr>
<td>Never smoker, moderate drinker</td>
<td>(reference group)</td>
<td>(reference group)</td>
</tr>
<tr>
<td>Ex-smoker, moderate drinker</td>
<td>0.03 (-0.02, 0.09)</td>
<td>.27</td>
</tr>
<tr>
<td>Current smoker, moderate drinker</td>
<td>-0.26 (-0.37, -0.15)</td>
<td>.00</td>
</tr>
<tr>
<td>Never smoker, heavy drinker</td>
<td>0.09 (0.01, 0.16)</td>
<td>.04</td>
</tr>
<tr>
<td>Ex-smoker, heavy drinker</td>
<td>0.18 (0.11, 0.25)</td>
<td>.00</td>
</tr>
<tr>
<td>Current smoker, heavy drinker</td>
<td>-0.01 (-0.13, 0.11)</td>
<td>.88</td>
</tr>
</tbody>
</table>

*Coefficients are adjusted for age, sex, education and chronic disease. The model is a reparameterization of the model shown in online Table DS1.*
### Table DS3

Prevalence of chronic disease in the study population according to cigarette smoking status and alcohol drinking level

<table>
<thead>
<tr>
<th>Total N = 6473</th>
<th>Never smoker (N = 3192)</th>
<th>Ex-smoker (N = 2647)</th>
<th>Current smoker (N = 634)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic disease(^a) (N positive, prevalence (%))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 alcohol units/week (N = 994)</td>
<td>174 (29.1)</td>
<td>75 (26.5)</td>
<td>36 (31.6)</td>
</tr>
<tr>
<td>1-14/1-21 alcohol units/week (N = 3911)</td>
<td>395 (19.4)</td>
<td>375 (23.9)</td>
<td>74 (23.8)</td>
</tr>
<tr>
<td>&gt;14/&gt;21 alcohol units/week (N = 1568)</td>
<td>103 (18.3)</td>
<td>147 (18.4)</td>
<td>43 (20.6)</td>
</tr>
<tr>
<td>(p^b)</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

\(^a\) Chronic disease are defined as physician diagnosed cancer, coronary heart disease (CHD), stroke (excluding transient ischaemic attack) or diabetes.

\(^b\) P value for linear trend according to chronic disease status, from 0 alcohol units/week, to 1-14/1-21 units/week, to >14/>21 units/week (Mantel-Haenszel test).
Table DS4 Beta coefficients, 95% confidence intervals and p values for a model containing main effects only^a

<table>
<thead>
<tr>
<th>N = 6473</th>
<th>Model including main effects only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>Slopes</td>
</tr>
<tr>
<td>B (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Current smoker (vs. never smoker)</td>
<td>-0.13 (-0.21, -0.04)</td>
</tr>
<tr>
<td>Ex-smoker (vs. never smoker)</td>
<td>0.07 (0.03, 0.12)</td>
</tr>
<tr>
<td>0 alcohol units/week (vs. moderate drinker)</td>
<td>-0.37 (-0.44, -0.30)</td>
</tr>
<tr>
<td>Heavy drinker (vs. moderate drinker)</td>
<td>0.13 (0.08, 0.18)</td>
</tr>
</tbody>
</table>

^a Coefficients are adjusted for age, sex, education and chronic disease.
**Fig. DS1** Estimated cognitive trajectories in male current cigarette smokers reporting $\geq 1$ unit of alcohol/week, according to alcohol units drunk weekly.

Figure DS1. Nested sample of 416 male cigarette smokers. Adjusted for exposed (reporting $\geq 1$ unit of alcohol/week) vs. unexposed (0 units of alcohol/week), additionally estimating the linear effect among the exposed: solid line = 30 alcohol units/week, dashed line = 20 alcohol units/week, dotted line = 10 alcohol units/week.
**Fig. DS2** Estimated cognitive trajectories in male heavy alcohol drinkers, according to number of cigarettes smoked daily (grouped).

Figure DS2. Nested sample of male heavy alcohol drinkers (N = 1286). Intercepts (cognitive function at baseline) for cigarette smoking groups do not differ significantly from the intercept for non-smokers. Group membership: light grey line = 0 cigarettes/day (N = 1123, 87.3%), medium grey line = 1-10 cigarettes/day (N = 51, 4.0%), dark grey line = 11-20 cigarettes/day (N = 45, 3.5%), black line = 21+cigarettes/day (N = 67, 5.2%).
Combined impact of smoking and heavy alcohol use on cognitive decline in early old age: Whitehall II prospective cohort study
Gareth Hagger-Johnson, Séverine Sabia, Eric John Brunner, Martin Shipley, Martin Bobak, Michael Marmot, Mika Kivimaki and Archana Singh-Manoux

BJP 2013, 203:120-125.
Access the most recent version at DOI: 10.1192/bjp.bp.112.122960

Supplementary Material
Supplementary material can be found at:
http://bjp.rcpsych.org/content/suppl/2013/06/24/bjp.bp.112.122960.DC1.html

References
This article cites 32 articles, 7 of which you can access for free at:
http://bjp.rcpsych.org/content/203/2/120#BIBL

Reprints/permissions
To obtain reprints or permission to reproduce material from this paper, please write to permissions@rcpsych.ac.uk

You can respond to this article at
http://bjprcpsych.org/letters/submit/bjprcpsych;203/2/120

Downloaded from
http://bjp.rcpsych.org/ on May 20, 2015
Published by The Royal College of Psychiatrists

To subscribe to The British Journal of Psychiatry go to:
http://bjp.rcpsych.org/site/subscriptions/