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## Original Contribution

# Health Behaviors From Early to Late Midlife as Predictors of Cognitive Function

## The Whitehall II Study

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The authors examined associations of health behaviors over a 17-year period, separately and in combination, with cognition in late midlife in 5,123 men and women from the Whitehall II study (United Kingdom). Health behaviors were assessed in early midlife (mean age = 44 years; phase 1, 1985–1988), in midlife (mean age = 56 years; phase 5, 1997–1999), and in late midlife (mean age = 61 years; phase 7, 2002–2004). A score of the number of unhealthy behaviors (smoking, alcohol abstinence, low physical activity, and low fruit and vegetable consumption) was defined as ranging from 0 to 4. Poor (defined as scores in the worst sex-specific quintile) executive function and memory in late midlife (phase 7) were analyzed as outcomes. Compared with those with no unhealthy behaviors, those with 3–4 unhealthy behaviors at phase 1 (odds ratio (OR) = 1.84, 95% confidence interval (CI): 1.27, 2.65), phase 5 (OR = 2.38, 95% CI: 1.76, 3.22), and phase 7 (OR = 2.76, 95% CI: 2.04, 3.73) were more likely to have poor executive function. A similar association was observed for memory. The odds of poor executive function and memory were the greater the more times the participant reported unhealthy behaviors over the 3 phases. This study suggests that both the number of unhealthy behaviors and their duration are associated with subsequent cognitive function in later life.

cognition; health behavior; longitudinal studies; middle aged

Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation.

In developed countries, dementia prevalence is about 1.5% at age 65 years, and it doubles every 4 years to reach more than 30% at 80 years of age (1). There is growing evidence of an association between health behaviors and cognitive aging. Smoking (2, 3), alcohol abstinence (4–9), lack of physical activity (10–13), and poor dietary behavior (14–16) have all been found to be associated with cognitive decline and dementia. The core hypothesis linking health behaviors to cognitive aging involves cerebro- and cardiovascular diseases as mediators (17, 18), and their association with cognitive impairment is well established (19). The extent to which health behaviors are related to cognitive outcomes is of substantial public health relevance, especially because health behaviors are potentially modifiable.

Although prospective studies have shown individual health behaviors to be associated with cognition (2, 6, 11, 15), their combined impact on cognition remains unexplored. Risk factors for dementia are hypothesized to involve effects over many years, making the investigation into cumulated exposures to unhealthy behaviors crucial to understanding their associations with cognitive aging (20, 21). Increasingly, midlife risk factors are seen to be important for dementia and poor cognitive status at older ages (19, 20, 22, 23). Research on the relation between health behaviors and cognitive aging among the elderly is complicated, as preclinical dementia itself modifies behaviors (24). This has led to studies that examine risk factors for cognitive outcomes at earlier ages, knowing that mild

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cognitive impairment has been shown to progress to clinically diagnosed dementia at an accelerated rate (25–27).

The objective of the present study is to assess the association of individual health behaviors and their combination with poor cognition in late midlife. We used health behaviors assessed 3 times over a 17-year period to examine whether unhealthy behaviors, separately and in combination with others, are associated with poorer executive function and memory and whether the risk associated with unhealthy behaviors accumulates over the adult lifecourse.

## MATERIALS AND METHODS

### Study population

The target population for the Whitehall II study was all London-based office staff, aged 35–55 years, working in 20 civil service departments (28). The baseline examination (phase 1) took place during 1985–1988 ($n = 10{,}308$; 67% men) and involved a clinical examination and a self-administered questionnaire that included sections on lifestyle factors. Subsequent phases of data collection have alternated between postal questionnaire alone (phases 2 (1988–1990), 4 (1995–1996), 6 (2001), and 8 (2006)) and postal questionnaire accompanied by a clinical examination (phases 3 (1991–1993), 5 (1997–1999), and 7 (2002–2004)). Phase 7 included cognitive testing for the entire cohort. Participants gave written consent to participate in the study, and the University College London ethics committee approved the study.

### Measures of health behaviors

Data on health behaviors were drawn from questionnaires in early midlife (phase 1: mean age = 44.1 (standard deviation (SD), 6.0) years); midlife (phase 5: mean age = 55.6 (SD, 6.0) years); and late midlife (phase 7: mean age = 61.1 (SD, 6.0) years).

*Smoking status.* At each of 3 phases, smoking status was assessed by using questions on current smoking; high risk was defined as being a ''current'' smoker.

*Alcohol consumption.* Consumption of alcohol was assessed via questions on the number of alcoholic drinks (''measures'' of spirits, ''glasses'' of wine, and ''pints'' of beer) consumed in the last 7 days, converted to number of units of alcohol with each unit corresponding to 8 g of ethanol (4). A standard measure of spirits and a glass of wine was considered to contain 8 g (1 unit) of alcohol and a pint of beer, 16 g (2 units) of alcohol. Alcohol consumption was categorized as follows: no alcohol, 1–14 units, and 15 or more units of alcohol per week. After preliminary analyses, the high-risk category was defined as ''abstinence from alcohol'' (4, 29). In this cohort, heavy alcohol use ($\geq$42 units per week, corresponding to 6 or more drinks per day) was rare (at phase 1, $n = 166$ (3.2%)).

*Physical activity.* At phase 1, participants were asked about the frequency and duration of their participation in mildly energetic (e.g., weeding, general housework, bicycle repair), moderately energetic (e.g., dancing, cycling, leisurely swimming), and vigorous (e.g., running, hard swimming, playing squash) physical activity. Examples for each level of physical activity were provided in order to allow similar interpretation of the items by the participants. At phases 5 and 7, the questionnaire was modified to include 20 items on frequency and duration of participation in different physical activities (e.g., walking, cycling, sports) that were used to compute hours per week of each intensity level. ''Low risk'' was defined at each of the 3 phases as more than 2.5 hours per week of moderate physical activity *or* more than 1 hour per week of vigorous physical activity (30).

*Dietary behavior.* Dietary behavior was assessed by using a measure of frequency of fruit and vegetable consumption with the question, ''How often do you eat fresh fruits or vegetables?''; responses were on an 8-point scale, ranging from ''seldom or never'' to ''2 or more times a day.'' The ''low-risk category'' was defined as eating fruits and vegetables 2 or more times a day.

### Cognitive function

Executive function was derived from 3 measures: a measure of reasoning and 2 measures of verbal fluency. The Alice Heim 4-I (AH4-I) test was used to assess reasoning. This test is composed of a series of 65 verbal and mathematical reasoning items of increasing difficulty (31). It tests inductive reasoning, measuring the ability to identify patterns and infer principles and rules. Participants had 10 minutes to do this section. We used 2 measures of verbal fluency: phonemic and semantic (32). Phonemic fluency was assessed via ''S'' words, and semantic fluency was assessed via ''animal'' words. Subjects were asked to recall in writing as many words beginning with ''S'' and as many animal names as they could. One minute was allowed for each test.

Memory was assessed by using a test of short-term verbal memory that included a 20-word free recall test. Participants were presented a list of 20 words with 1 or 2 syllables each at 2-second intervals and then had 2 minutes to recall in writing as many of the words in any order that they could.

### Covariates

The sociodemographic variables used were age, sex, and socioeconomic position. This last variable was assessed by using the 6-level civil service employment grade at phases 1, 5, and 7. Employment grade in the Whitehall II study is a comprehensive marker of socioeconomic position and is related to salary, social status, and level of responsibility (28).

### Statistical methods

A composite score of executive function was created by using the reasoning, phonemic, and semantic fluency scores. In order to take into account the correlation among these scores, a principal component analysis was used, and the first factor was retained to define score in executive function (33). This factor accounted for 70.6% of the variance; factor loadings were 0.57 for reasoning, 0.57 for phonemic fluency, and 0.59 for semantic fluency.

As in previous studies of this cohort (3, 4, 12), ''poor cognition'' was defined as cognitive scores in the lowest sex-specific quintile. As the executive function score was a continuous variable, cutoffs for poor executive function in men and women were chosen to have exactly 20% of the population under these cutoffs. The memory score was a discrete variable; we defined ''poor memory'' as scores lower than 5 out of 20 corresponding to 15.1% of men and 17.1% of women. We examined the association between health behaviors and the dichotomized measures of cognition using logistic regression. First, we analyzed individual health behaviors at phase 1 (long-term association), then at phase 5 (short-term association), and finally at phase 7 (cross-sectional association) with poor executive function and memory at phase 7. All analyses were adjusted for measures of age, sex, and socioeconomic position drawn from the same phase as the health behaviors.

For the next step of the analyses, we created a score of unhealthy behaviors at study phases 1, 5, and 7. This score was the sum of unhealthy behaviors, ranging from 0 (all healthy behaviors) to 4 (current smoking, alcohol abstinence, low physical activity, and low fruit and vegetable consumption). We then examined the long-term, short-term, and cross-sectional associations between these scores and poor executive function and memory using 2 models: one including the number of unhealthy behaviors and the other including all possible combinations of unhealthy behaviors. In each case, the reference group was those with no unhealthy behavior. The second model was used to visually check the homogeneity of estimates of the impact of combinations of unhealthy behaviors on cognition, some of these combinations being too small for formal testing.

Finally, in order to examine whether the risk associated with unhealthy behaviors accumulated over the midlife, we created a score representing the number of times a person reported each unhealthy behavior throughout the follow-up, with scores ranging from 0 (no unhealthy behavior at phase 1, 5, or 7) to 3 (reporting the unhealthy behavior at all 3 study phases). We then calculated a summary cumulative score of unhealthy behaviors by adding the individual cumulative scores for each of the 4 unhealthy behaviors. This score ranged from 0 (none of the 4 unhealthy behaviors at phase 1, 5, or 7) to 12 (all 4 unhealthy behaviors at the 3 study phases) and was categorized into 4 groups, 0–2, 3–5, 6–8, 9–12, to allow enough numbers in each group. All analyses were performed by using SAS, version 9.1, software (SAS Institute, Inc., Cary, North Carolina).

## RESULTS

### Sample description and missing data

Of the 10,308 participants at phase 1, 6,327 participated in cognitive testing at phase 7. Data on health behaviors, cognitive function, and all covariates were available for 5,123 respondents. Compared with participants not included in the present study, this group was younger (61.1 years vs. 61.7 years), composed of fewer women (27.9% vs. 38.2%), and composed of fewer participants from the low-socioeconomic position group (12.8% vs. 32.5%) ($P < 0.0001$). Participants included in the analysis reported here were also more likely at phase 1 to be nonsmokers (86.4% vs. 76.7%), alcohol consumers (86.0% vs. 77.3%), more physically active (53.1% vs. 45.6%), and to eat more fruits and vegetables (19.0% vs. 14.1% ate fruits or vegetables at least 2 or more times per day) ($P < 0.0001$).

In Table 1, baseline socioeconomic characteristics and cognitive scores at phase 7 are presented as a function of the number of unhealthy behaviors at phase 1. There was no evidence that the association between the score of unhealthy behaviors at the 3 study phases and the 2 cognitive outcomes differed by sex ($P_{\text{interaction}} > 0.22$). Thus, all analyses combine men and women.

### Association between each health behavior and poor cognition

Table 2 presents the association between each health behavior at phase 1 (long-term association), phase 5 (short-term association), and phase 7 (cross-sectional association) and poor executive function and memory at phase 7. At each phase, in analyses adjusted for age, sex, and socioeconomic position, current smokers were more likely to be in the lowest quintile of executive function and of memory (odds ratios between 1.21 and 1.34). Compared with moderate alcohol consumption (1–14 units/week), alcohol abstinence at the 3 study phases was associated with a higher risk of poor executive function (for alcohol abstinence at phases 1, 5, and 7: odds ratio (OR) = 1.33, 95% confidence interval (CI): 1.07, 1.64; OR = 1.71, 95% CI: 1.39, 2.10; OR = 1.65, 95% CI: 1.35, 2.02, respectively). Alcohol abstinence at phases 5 and 7 was also associated with poor memory. As no increase in risk was found among participants who consumed more than 14 units per week, we have used alcohol abstinence rather than excessive alcohol consumption as the marker of unhealthy behavior in further analyses. Those reporting low levels of physical activity at phases 5 and 7 were at higher risk of poor executive function (OR = 1.19) compared with those undertaking high levels of physical activity. This association was also evident cross-sectionally for low physical activity and poor memory at phase 7 (OR = 1.28, 95% CI: 1.09, 1.50). Finally, those consuming fruits and vegetables less than 2 times per day had a higher risk of poor executive function, with a stronger association seen with measures of behavior proximal to cognitive assessment (for fruit and vegetable consumption at phases 1, 5, and 7: OR = 1.32, 95% CI: 1.06, 1.64; OR = 1.60, 95% CI: 1.36, 1.89; OR = 1.85, 95% CI: 1.56, 2.19, respectively). This measure of dietary behavior was also associated with poor memory, although these associations were weaker.

### Combination of health behaviors and poor cognition

Results on the association between combination of health behaviors and poor executive function and memory are presented in Tables 3 and 4, respectively. The proportion of the study population with no unhealthy behaviors was 8.4% at the mean age of 44 years (phase 1) and 22.0% at the mean age of 61 years (phase 7). Individuals with a greater number

**Table 1.** Sociodemographic Characteristics of Participants at Baseline ($n = 5,123$) as a Function of Score of Unhealthy Behaviors, Whitehall II Study, United Kingdom, 1985–1988

| | No. of Unhealthy Behaviors at Phase 1[a] | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | | | 1 | | | 2 | | | 3 | | | 4 | | |
| | Mean (SD) | No. | % | Mean (SD) | No. | % | Mean (SD) | No. | % | Mean (SD) | No. | % | Mean (SD) | No. | % |
| Total subjects by no. of unhealthy behaviors | | 433 | 8.4 | | 2,100 | 41.0 | | 1,962 | 38.3 | | 574 | 11.2 | | 54 | 1.1 |
| Sociodemographic variables | | | | | | | | | | | | | | | |
| Age, years | 43.9 (5.8) | | | 44.0 (6.0) | | | 44.2 (6.0) | | | 44.0 (6.0) | | | 45.2 (5.9) | | |
| Female sex | | 131 | 30.3 | | 442 | 21.1 | | 567 | 28.9 | | 262 | 45.6 | | 29 | 53.7 |
| Low employment grade | | 39 | 9.0 | | 156 | 7.4 | | 256 | 13.1 | | 183 | 31.9 | | 20 | 37.0 |
| Cognitive scores | | | | | | | | | | | | | | | |
| Memory (range, 0–20) | 7.2 (2.3) | | | 6.9 (2.4) | | | 6.8 (2.4) | | | 6.5 (2.5) | | | 6.1 (2.3) | | |
| AH4-I test (range, 0–65) | 46.7 (9.5) | | | 45.9 (9.6) | | | 44.5 (10.7) | | | 39.1 (11.7) | | | 37.5 (12.9) | | |
| Semantic fluency (range, 0–34) | 16.6 (3.9) | | | 16.2 (6.1) | | | 15.7 (4.0) | | | 14.6 (4.0) | | | 14.4 (4.3) | | |
| Phonemic fluency (range, 0–33) | 16.5 (3.8) | | | 16.0 (3.8) | | | 15.7 (3.7) | | | 14.6 (3.9) | | | 14.4 (3.6) | | |
| Poor cognitive function | | | | | | | | | | | | | | | |
| Poor executive function | | 54 | 12.5 | | 370 | 17.6 | | 397 | 20.2 | | 185 | 32.2 | | 18 | 33.3 |
| Poor memory (score, <5) | | 50 | 11.6 | | 308 | 14.7 | | 305 | 15.6 | | 123 | 21.4 | | 15 | 27.8 |

Abbreviations: AH4-I, Alice Heim 4-I; SD, standard deviation.

[a] Unhealthy behaviors correspond to the following: current smoking, alcohol abstinence, low physical activity, and eating fruits or vegetables less than 2 times per day.

of unhealthy behaviors had a greater risk of poor executive function, irrespective of the phase at which health behaviors were assessed (for poor executive function: all $P_{\text{trend}} \leq 0.002$). Compared with participants with no unhealthy behaviors, those with 3 or 4 unhealthy behaviors, whether at phase 1 (OR = 1.84, 95% CI: 1.27, 2.65), phase 5 (OR = 2.38, 95% CI: 1.76, 3.22), or phase 7 (OR = 2.76, 95% CI: 2.04, 3.73), were more likely to have poor executive function. The association with poor memory (Table 4) was evident particularly with the more recent measures of health behaviors ($P_{\text{trend}} = 0.07$, 0.0004, and <0.0001 for phases 1, 5, and 7, respectively). Those with 3–4 unhealthy behaviors at phase 1 (OR = 1.50, 95% CI: 1.04, 2.17), phase 5 (OR = 1.59, 95% CI: 1.16, 2.19), and phase 7 (OR = 2.03, 95% CI: 1.49, 2.76) had greater odds of poor memory.

Tables 3 and 4 also show the results aimed at exploring whether the associations between the number of unhealthy behaviors (when they total 1, 2, or 3–4 out of the 4 unhealthy behaviors) and cognition are driven by specific combinations of unhealthy behaviors. Participants with only 1 unhealthy behavior were essentially those with poor dietary behavior; for example, out of the 2,100 participants with 1 unhealthy behavior at phase 1, 1,666 ate fruits or vegetables less that 2 times per day. The 2 out of 4 unhealthy behaviors category was composed essentially of those physically inactive and with poor dietary behavior. The representations in Tables 3 and 4 appear to suggest that no particular combination of unhealthy behaviors drives the association between the number of unhealthy behaviors (when they total 1, 2, or 3–4 out of the 4 unhealthy behaviors) and poor executive function (Table 3) and memory (Table 4). Thus, despite the greater prevalence of poor dietary behavior and physical inactivity, the impact of all combinations of unhealthy behaviors is similar.

### Cumulative risk over time

The association of cumulative exposure to unhealthy behaviors over time and poor cognition is presented in Table 5. Participants with greater exposure across midlife to smoking had greater odds of poor executive function and memory (for both, $P = 0.03$). Similar associations were found for alcohol abstinence (for executive function, $P < 0.0001$; for memory, $P = 0.01$), low physical activity ($P = 0.06$ and $P = 0.03$), and poor dietary behavior ($P < 0.0001$ and $P = 0.02$). The combined impact of unhealthy behaviors over time, reflected in the cumulative score, was strong; compared with those with 0–2 unhealthy behaviors over the follow-up, participants with a total of 9–12 unhealthy behaviors had greater odds of poor executive function

**Table 2.** Association Between Individual Health Behaviors Through the Follow-up With Poor Executive Function and Memory at Phase 7, Whitehall II Study, United Kingdom, 1985–2004 ($n = 5{,}123$)[a]

| | Long-Term Association (Health Behaviors at Phase 1) | | | | Short-Term Association (Health Behaviors at Phase 5) | | | | Cross-sectional Association (Health Behaviors at Phase 7) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | % | Odds Ratio | 95% Confidence Interval | No. | % | Odds Ratio | 95% Confidence Interval | No. | % | Odds Ratio | 95% Confidence Interval |
| Executive function | | | | | | | | | | | | |
| Current smoking | | | | | | | | | | | | |
| No | 4,428 | 86.4 | 1 | | 4,670 | 91.2 | 1 | | 4,742 | 92.6 | 1 | |
| Yes | 695 | 13.6 | 1.27 | 1.03, 1.56* | 453 | 8.9 | 1.30 | 1.01, 1.67* | 381 | 7.4 | 1.29 | 0.98, 1.69 |
| Alcohol consumption, units/week | | | | | | | | | | | | |
| 0 | 715 | 14.0 | 1.33 | 1.07, 1.64* | 726 | 14.2 | 1.71 | 1.39, 2.10* | 774 | 15.1 | 1.65 | 1.35, 2.02* |
| 1–14 | 3,081 | 60.1 | 1 | | 2,608 | 50.9 | 1 | | 2,738 | 53.4 | 1 | |
| ≥15 | 1,327 | 25.9 | 0.85 | 0.70, 1.04 | 1,789 | 34.9 | 0.92 | 0.76, 1.10 | 1,611 | 31.5 | 0.88 | 0.73, 1.06 |
| Physical activity[b] | | | | | | | | | | | | |
| Low | 2,402 | 46.9 | 1 | | 2,293 | 44.8 | 1 | | 2,242 | 43.8 | 1 | |
| High | 2,721 | 53.1 | 0.95 | 0.81, 1.11 | 2,830 | 55.2 | 1.19 | 1.01, 1.39* | 2,881 | 56.2 | 1.19 | 1.02, 1.39* |
| Consumption of fruits and vegetables | | | | | | | | | | | | |
| <2 times a day | 4,150 | 81.0 | 1.32 | 1.06, 1.64* | 3,044 | 59.4 | 1.60 | 1.36, 1.89* | 2,964 | 57.9 | 1.85 | 1.56, 2.19* |
| ≥2 times a day | 973 | 19.0 | 1 | | 2,079 | 40.6 | 1 | | 2,159 | 42.1 | 1 | |
| Memory | | | | | | | | | | | | |
| Current smoking | | | | | | | | | | | | |
| No | 4,428 | 86.4 | 1 | | 4,670 | 91.2 | 1 | | 4,742 | 92.6 | 1 | |
| Yes | 695 | 13.6 | 1.29 | 1.04, 1.60* | 453 | 8.9 | 1.21 | 0.93, 1.57 | 381 | 7.4 | 1.34 | 1.01, 1.78* |
| Alcohol consumption, units/week | | | | | | | | | | | | |
| 0 | 715 | 14.0 | 1.06 | 0.85, 1.33 | 726 | 14.2 | 1.34 | 1.08, 1.66* | 7,742 | 15.1 | 1.40 | 1.13, 1.73* |
| 1–14 | 3,081 | 60.1 | 1 | | 2,608 | 50.9 | 1 | | 738 | 53.4 | 1 | |
| ≥15 | 1,327 | 25.9 | 1.02 | 0.83, 1.23 | 1,789 | 4.9 | 0.96 | 0.80, 1.16 | 1,611 | 31.5 | 1.02 | 0.85, 1.24 |
| Physical activity[b] | | | | | | | | | | | | |
| Low | 2,402 | 46.9 | 1 | | 2,293 | 44.8 | 1 | | 2,242 | 43.8 | 1 | |
| High | 2,721 | 53.1 | 1.09 | 0.93, 1.28 | 2,830 | 55.2 | 1.04 | 0.89, 1.23 | 2,881 | 56.2 | 1.28 | 1.09, 1.50* |
| Consumption of fruits and vegetables | | | | | | | | | | | | |
| <2 times a day | 4,150 | 81.0 | 1.01 | 0.82, 1.24 | 3,044 | 59.4 | 1.35 | 1.14, 1.59* | 2,964 | 57.9 | 1.21 | 1.02, 1.43* |
| ≥2 times a day | 973 | 19.0 | 1 | | 2,079 | 40.6 | 1 | | 2,159 | 42.1 | 1 | |

* $P < 0.05$.

[a] Each model is adjusted for age, sex, and socioeconomic position at the corresponding phase.

[b] High physical activity corresponds to 2.5 hours or more per week of moderate activity or 1 hour or more of vigorous activity.

(OR = 2.87, 95% CI: 1.90, 4.32) and memory (OR = 2.01, 95% CI: 1.32, 3.08).

### Sensitivity analysis

A longitudinal cohort inevitably results in nonresponse over time. The analysis reported on here comprises complete cases with behavioral data and covariates from phases 1, 5, and 7 and cognitive data from phase 7 ($n = 5{,}123$). We repeated the analysis on phase 1 health behaviors using all available data ($n = 6{,}161$). These results showed slightly stronger associations between individual and combined health behaviors and poor cognition (results not shown).

## DISCUSSION

Data from a large British occupational cohort show that each of the 4 unhealthy behaviors examined—smoking, alcohol abstinence, low physical activity, poor dietary behavior—at any of the 3 measures over the 17-year follow-up was associated with poor executive function and memory in late midlife. Results suggest greater risk of poor

**Table 3.** Association Between Combination of Health Behaviors Through the Follow-up and Poor Executive Function at Phase 7, Whitehall II Study, United Kingdom, 1985–2004 ($n = 5,123$)

| No. of Unhealthy Behaviors[a] (Combinations) | Long-Term Association (Health Behaviors at Phase 1) | | | Short-Term Association (Health Behaviors at Phase 5) | | | Cross-sectional Association (Health Behaviors at Phase 7) | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. | Odds Ratio | 95% Confidence Interval | No. | Odds Ratio | 95% Confidence Interval | No. | Odds Ratio | 95% Confidence Interval |
| No unhealthy behaviors | 433 | 1 | | 1,074 | 1 | | 1,129 | 1 | |
| All with 1 unhealthy behavior[b] | 2,100 | 1.34 | 0.96, 1.87 | 2,103 | 1.38 | 1.09, 1.74 | 2,135 | 1.30 | 1.03, 1.64 |
| 1 (No alcohol)[c] | 72 | 2.17 | 1.10, 4.26 | 128 | 1.89 | 1.16, 3.08 | 139 | 1.35 | 0.83, 2.21 |
| 1 (Low physical activity)[c] | 336 | 0.94 | 0.59, 1.52 | 649 | 1.04 | 0.75, 1.43 | 669 | 0.90 | 0.65, 1.26 |
| 1 (<2 fruits/vegetables)[c] | 1,666 | 1.38 | 0.99, 1.95 | 1,271 | 1.49 | 1.16, 1.91 | 1,281 | 1.54 | 1.20, 1.96 |
| 1 (Current smoking)[c] | 26 | 1.44 | 0.48, 4.28 | 55 | 1.22 | 0.54, 2.78 | 46 | 0.51 | 0.15, 1.72 |
| All with 2 unhealthy behaviors[b] | 1,962 | 1.38 | 0.99, 1.93 | 1,465 | 1.83 | 1.43, 2.33 | 1,388 | 1.71 | 1.34, 2.19 |
| 2 (No alcohol and no physical activity)[c] | 70 | 1.04 | 0.49, 2.19 | 127 | 1.69 | 1.01, 2.82 | 139 | 1.32 | 0.79, 2.21 |
| 2 (No alcohol and <2 fruits/vegetables)[c] | 215 | 1.93 | 1.23, 3.03 | 149 | 2.96 | 1.96, 4.48 | 158 | 2.30 | 1.52, 3.47 |
| 2 (Low physical activity and <2 fruits/vegetables)[c] | 1,368 | 1.25 | 0.89, 1.77 | 1,014 | 1.71 | 1.32, 2.22 | 961 | 1.79 | 1.38, 2.31 |
| 2 (Current smoking and no alcohol)[c] | 4 | | | 6 | | | 7 | | |
| 2 (Current smoking and no physical activity)[c] | 29 | 2.20 | 0.76, 6.38 | 37 | 2.27 | 0.95, 5.39 | 21 | 0.34 | 0.07, 1.69 |
| 2 (Current smoking and <2 fruits/vegetables)[c] | 276 | 1.58 | 1.02, 2.45 | 132 | 1.96 | 1.21, 3.16 | 102 | 2.24 | 1.34, 3.74 |
| All with 3–4 unhealthy behaviors[b] | 628 | 1.84 | 1.27, 2.65 | 481 | 2.38 | 1.76, 3.22 | 471 | 2.76 | 2.04, 3.73 |
| 3 (All unhealthy except smoking)[c] | 268 | 1.91 | 1.25, 2.93 | 258 | 2.73 | 1.92, 3.88 | 266 | 3.55 | 2.52, 5.00 |
| 3 (All unhealthy except fruits/vegetables)[c] | 3 | | | 3 | | | 9 | | |
| 3 (All unhealthy except physical activity)[c] | 29 | 2.19 | 0.90, 5.38 | 15 | 1.02 | 0.27, 3.87 | 19 | 3.60 | 1.28, 10.1 |
| 3 (All unhealthy except alcohol)[c] | 274 | 1.85 | 1.20, 2.85 | 165 | 1.94 | 1.25, 3.02 | 140 | 2.04 | 1.27, 3.27 |
| 4 (All unhealthy behaviors)[c] | 54 | 1.50 | 0.74, 3.06 | 40 | 5.12 | 2.46, 10.70 | 37 | 3.34 | 1.58, 7.07 |

[a] Unhealthy behaviors correspond to the following: current smoking, alcohol abstinence, low physical activity, and eating fruits or vegetables less than 2 times a day.

[b] Results from a model with number of unhealthy behaviors included in the model, with the category "no healthy behaviors" as reference. All analyses were adjusted for age, sex, and socioeconomic position (at the corresponding phase).

[c] Results from a model with all combinations included in the model, with the category "no healthy behaviors" as reference.

executive function and memory with increase in the number of unhealthy behaviors. Furthermore, greater exposure from early to late midlife to individual or a combination of unhealthy behaviors was found to be associated with a greater risk of poor cognitive function in a dose-response manner.

Although there is some evidence showing that different health behaviors tend to cluster (34, 35), they have been studied for their combined impact on health only recently. Research suggests that the combined impact of unhealthy behaviors leads to a 3-fold to 4-fold increase in risk of mortality (29, 36–38), a 7-fold increase in risk of coronary heart disease in men (39), and a 3-fold increase in risk of ischemic stroke in women (40) compared with those with no unhealthy behaviors. Given these results, our findings are important because this is the first time that the association between a combination of health behaviors and cognitive function has been demonstrated. These results are in agreement with previous research showing greater risk of poor cognition in current smokers (2, 3), alcohol abstainers (4–9), the physically inactive (10–13), and those with poor dietary behavior (14–16) when these have been examined separately. Our results suggest the importance of the combined impact of health behaviors for cognitive outcomes. In addition to the number of unhealthy behaviors, we examined their combinations, but there was no evidence to suggest that any particular combination of unhealthy behaviors drives the association. Thus, a simple summary score of unhealthy behaviors might be enough to assess association with cognitive outcomes.

Our results add to the previous evidence showing that health behaviors across the adult lifecourse may influence cognitive function at older ages (2, 7, 10, 14). These findings support the idea that midlife risk factors have a role in the development of cognitive impairment in later life (19, 23).

**Table 4.** Association Between Combination of Health Behaviors Through the Follow-up and Poor Memory at Phase 7, Whitehall II Study, United Kingdom, 1985–2004 ($n = 5,123$)

| No. of Unhealthy Behaviors[a] (Combinations) | Long-Term Association (Health Behaviors at Phase 1) | | | Short-Term Association (Health Behaviors at Phase 5) | | | Cross-sectional Association (Health Behaviors at Phase 7) | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. | Odds Ratio | 95% Confidence Interval | No. | Odds Ratio | 95% Confidence Interval | No. | Odds Ratio | 95% Confidence Interval |
| No unhealthy behaviors | 433 | 1 | | 1,074 | 1 | | 1,129 | 1 | |
| All with 1 unhealthy behavior[b] | 2,100 | 1.23 | 0.89, 1.71 | 2,103 | 1.40 | 1.11, 1.76 | 2,135 | 1.28 | 1.02, 1.61 |
| 1 (No alcohol)[c] | 72 | 1.36 | 0.66, 2.77 | 128 | 1.47 | 0.88, 2.46 | 139 | 1.66 | 1.04, 2.68 |
| 1 (Low physical activity)[c] | 336 | 1.44 | 0.94, 2.22 | 649 | 1.26 | 0.93, 1.72 | 669 | 1.34 | 0.99, 1.81 |
| 1 (<2 fruits/vegetables)[c] | 1,666 | 1.19 | 0.85, 1.67 | 1,271 | 1.52 | 1.18, 1.95 | 1,281 | 1.23 | 0.95, 1.58 |
| 1 (Current smoking)[c] | 26 | 0.83 | 0.23, 3.01 | 55 | 0.90 | 0.35, 2.33 | 46 | 1.75 | 0.79, 3.90 |
| All with 2 unhealthy behaviors[b] | 1,962 | 1.21 | 0.87, 1.68 | 1,465 | 1.61 | 1.26, 2.06 | 1,388 | 1.47 | 1.15, 1.88 |
| 2 (No alcohol and no physical activity)[c] | 70 | 1.63 | 0.82, 3.23 | 127 | 2.01 | 1.23, 3.28 | 139 | 1.39 | 0.83, 2.32 |
| 2 (No alcohol and <2 fruits/vegetables)[c] | 215 | 1.15 | 0.71, 1.86 | 149 | 2.45 | 1.61, 3.72 | 158 | 1.77 | 1.15, 2.72 |
| 2 (Low physical activity and <2 fruits/vegetables)[c] | 1,368 | 1.12 | 0.80, 1.58 | 1,014 | 1.41 | 1.07, 1.84 | 961 | 1.48 | 1.14, 1.93 |
| 2 (Current smoking and no alcohol)[c] | 4 | | | 6 | | | 7 | | |
| 2 (Current smoking and no physical activity)[c] | 29 | 1.98 | 0.73, 5.33 | 37 | 1.66 | 0.66, 4.22 | 21 | 1.72 | 0.54, 5.45 |
| 2 (Current smoking and <2 fruits/vegetables)[c] | 276 | 1.56 | 1.00, 2.42 | 132 | 2.24 | 1.39, 3.59 | 102 | 1.35 | 0.74, 2.46 |
| All with 3-4 unhealthy behaviors[b] | 628 | 1.50 | 1.04, 2.17 | 481 | 1.59 | 1.16, 2.19 | 471 | 2.03 | 1.49, 2.76 |
| 3 (All unhealthy except smoking)[c] | 268 | 1.40 | 0.90, 2.17 | 258 | 1.65 | 1.13, 2.41 | 266 | 2.21 | 1.55, 3.15 |
| 3 (All unhealthy except fruits/vegetables)[c] | 3 | | | 3 | | | 9 | | |
| 3 (All unhealthy except physical activity)[c] | 29 | 0.68 | 0.22, 2.10 | 15 | 1.48 | 0.40, 5.46 | 19 | 1.76 | 0.55, 5.63 |
| 3 (All unhealthy except alcohol)[c] | 274 | 1.70 | 1.10, 2.60 | 165 | 1.67 | 1.05, 2.67 | 140 | 2.45 | 1.54, 3.90 |
| 4 (All unhealthy behaviors)[c] | 54 | 1.75 | 0.86, 3.52 | 40 | 1.73 | 0.79, 3.78 | 37 | 1.12 | 0.44, 2.83 |

[a] Unhealthy behaviors correspond to the following: current smoking, alcohol abstinence, low physical activity, and eating fruits or vegetables less than 2 times a day.

[b] Results from a model with number of unhealthy behaviors included in the model, with the category "no healthy behaviors" as reference. All analyses were adjusted for age, sex, and socioeconomic position (at the corresponding phase).

[c] Results from a model with all combinations included in the model, with the category "no healthy behaviors" as reference.

Moreover, repeated measures of health behaviors allowed us to assess the association of cumulative exposure to unhealthy behaviors, separately and in combination, over midlife with cognition in late midlife. A greater risk of poor cognition was found with greater exposure to each of the health behaviors, as well as for combinations of health behaviors, suggesting that, not only the number of unhealthy behaviors but also the period of exposure should be taken into account in risk assessment.

It is increasingly clear that dementia has a long preclinical phase leading to increasing calls to examine the association between risk factors and cognitive outcomes many years before the clinical diagnosis of dementia (21, 22). Research suggests that individuals with mild cognitive impairment progress to clinically diagnosed dementia at an accelerated rate (25–27), spurring research into cognition earlier in the lifecourse. In these studies, there is no clinical cutoff to define cognitive deficit, and 3 methods are commonly used to denote poor performance: either scores below 1.5 standard deviation from the mean (41) or scores in the worst decile (42) or worst quintile (43). In the present study, we use the third definition with the objective of assessing the association with midlife poor cognition specific to the population studied.

In this study, 2 specific cognitive domains, executive function and memory, were found to be associated with health behaviors. Executive function, an umbrella term for various complex cognitive processes involved in achieving a particular goal (44), has been shown to be particularly strongly affected in vascular dementia (45). We assessed executive function using measures of reasoning and verbal fluency, as these tasks require the combination of different cognitive abilities such as memory, attention, and speed of information processing (31, 32). Health behaviors are

**Table 5.** Cumulative Effect of Health Behaviors Over Midlife (From Phase 1 to Phase 7) and Poor Executive Function and Memory at Phase 7, Whitehall II Study, United Kingdom, 1985–2004 ($n = 5,123$)[a]

| | No. | % | Executive Function | | Memory | |
|---|---|---|---|---|---|---|
| | | | Odds Ratio | 95% Confidence Interval | Odds Ratio | 95% Confidence Interval |
| Current smoking[b] | | | | | | |
| 0 | 4,337 | 84.7 | 1 | | 1 | |
| 1 | 339 | 6.6 | 1.08 | 0.81, 1.46 | 1.28 | 0.96, 1.71 |
| 2 | 151 | 2.9 | 1.42 | 0.95, 2.14 | 0.99 | 0.63, 1.56 |
| 3 | 296 | 5.8 | 1.29 | 0.94, 1.75 | 1.39 | 1.02, 1.90* |
| $P_{trend}$ | | | | 0.03 | | 0.03 |
| Alcohol abstinence[b] | | | | | | |
| 0 | 3,839 | 74.9 | 1 | | 1 | |
| 1 | 645 | 12.6 | 1.44 | 1.16, 1.80* | 1.21 | 0.96, 1.53 |
| 2 | 347 | 6.8 | 1.57 | 1.19, 2.08* | 1.36 | 1.02, 1.81* |
| 3 | 292 | 5.7 | 2.02 | 1.51, 2.71* | 1.32 | 0.97, 1.80 |
| $P_{trend}$ | | | | <0.0001 | | 0.01 |
| Low physical activity[b] | | | | | | |
| 0 | 1,380 | 26.9 | 1 | | 1 | |
| 1 | 1,484 | 29.0 | 0.94 | 0.76, 1.16 | 1.14 | 0.92, 1.42 |
| 2 | 1,324 | 25.8 | 1.09 | 0.86, 1.38 | 1.23 | 0.98, 1.55 |
| 3 | 935 | 18.3 | 1.19 | 0.96, 1.48 | 1.29 | 1.01, 1.65* |
| $P_{trend}$ | | | | 0.06 | | 0.03 |
| Eating fruits and vegetables <2 times a day[b] | | | | | | |
| 0 | 609 | 11.9 | 1 | | 1 | |
| 1 | 1,125 | 22.0 | 1.42 | 1.00, 2.03* | 1.17 | 0.85, 1.61 |
| 2 | 1,134 | 22.1 | 2.02 | 1.43, 2.84* | 1.35 | 0.99, 1.85 |
| 3 | 2,255 | 44.0 | 2.38 | 1.72, 3.29* | 1.38 | 1.03, 1.86* |
| $P_{trend}$ | | | | <0.0001 | | 0.02 |
| Cumulative score of unhealthy behaviors[b] | | | | | | |
| 0–2 | 1,222 | 23.9 | 1 | | 1 | |
| 3–5 | 2,708 | 52.9 | 1.58 | 1.27, 1.98* | 1.51 | 1.21, 1.88* |
| 6–8 | 1,022 | 19.9 | 2.52 | 1.96, 3.24* | 1.64 | 1.27, 2.13* |
| 9–12 | 171 | 3.3 | 2.87 | 1.90, 4.32* | 2.01 | 1.32, 3.08* |
| $P_{trend}$ | | | | <0.0001 | | <0.0001 |

* $P < 0.05$.

[a] Number of times a participant reported an unhealthy behavior out of the time points (phases 1, 5, and 7).

[b] Each model is adjusted for age, sex, and socioeconomic position at phase 1.

important risk factors for vascular diseases (46) and could influence executive function via the vascular pathway. In our data, there was also an association between health behaviors and memory, although it was less consistent. This difference could be explained by the fact that memory is likely to be less influenced by vascular risk factors (hypertension, cholesterol, diabetes) (47–49). Another explanation could be better measurement precision for executive function as the score was made up of 3 tests compared with the single measure of memory.

The specific strengths of this study include a detailed prospective assessment of health behaviors over a 17-year period and adjustments for socioeconomic position, an important confounder that is associated with both health behaviors and cognition. However, at least 5 limitations for this study are noteworthy. First, although the sample covered a wide socioeconomic range, with annual full-time salaries ranging from £4,995 to £150,000 (1 British pound = 1.62900 US dollars), data are from white-collar civil servants and cannot be assumed to be representative of the

general population. Second, during the 17-year follow-up, 50% of the baseline population was lost to follow-up, and baseline data suggest that these subjects were more likely to have unhealthy behaviors. Sensitivity analysis using phase 1 health behaviors suggests that the association between health behaviors and cognition could be underestimated in this study. Third, a U-shaped relation between alcohol consumption and cognition has been reported previously (50). In our study, no higher risk was found in those who consumed more than 14 units per week. However, few participants of the Whitehall II study are heavy drinkers, and our data are best not used to pursue this further (4). Fourth, the measure of physical activity changed between phase 1 and phase 5, which could explain the lack of association with physical activity at phase 1. Finally, the World Health Organization diet recommendation advises persons to eat at least 400 g of fruits and vegetables per day (51), but we had only a measure of frequency of fruit and vegetable consumption and not the amount consumed.

In conclusion, our results show a prospective, cross-sectional, and cumulative association of smoking, alcohol abstinence, low physical activity level, and consumption of fruits and vegetables less than 2 times a day with poor cognitive function. Furthermore, we found that a greater number of these unhealthy behaviors were associated with a higher risk of poor cognition, particularly evident in executive function, and that this risk accumulated over the midlife. All these health behaviors are modifiable, and our results suggest that the promotion of a healthy lifestyle at all ages is important for cognitive outcomes.

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