Cigarette Smoking and Cognitive Decline in Midlife: Evidence From a Prospective Birth Cohort Study

Marcus Richards, PhD, Martin J. Jarvis, DSc, Neil Thompson, BSc, and Michael E.J. Wadsworth, PhD

Objectives. The authors investigated the effects of cigarette smoking on midlife cognitive performance.

Methods. Multiple regression was used to test the association between cigarette smoking and changes in cognitive test scores among male and female members of the British 1946 birth cohort aged between 43 and 53 years.

Results. Smoking was associated with faster declines in verbal memory and with slower visual search speeds. These effects were largely accounted for by individuals who smoked more than 20 cigarettes per day and were independent of sex, socioeconomic status, previous (adolescent) cognitive ability, and a range of health indicators.

Conclusions. The present results show that heavy smoking is associated with cognitive impairment and decline in midlife. Smokers who survive into later life may be at risk of clinically significant cognitive declines. (*Am J Public Health.* 2003;93:994–998)

Population-based evidence of an effect of smoking on cognitive function has been inconclusive, with most longitudinal studies reporting weak or null associations,[1–5] although at least 2 investigations have indicated increased risks of cognitive decline.[6,7] One difficulty is that most studies have been conducted among postretirement populations, in which observed associations may be attenuated by smokers' relatively low rates of survival into old age.[8] An exception is a recent cross-sectional study of predominantly middle-aged participants that showed reduced psychomotor speed and cognitive flexibility among current smokers relative to individuals who had never smoked.[9]

In the present study, we investigated the association between smoking and cognitive function in midlife among the British 1946 birth cohort, controlling for socioeconomic status and a range of health indicators, including maternal smoking, respiratory and cardiovascular disease, forced expiratory volume in 1 second (FEV_1), blood pressure, affective disturbances, and potential alcohol abuse. Because data had been gathered previously on cohort members' cognitive functioning in adolescence, we also were able to control for the possibility that smoking initiation in adolescence is mediated by cognitive ability.

METHODS

1946 Birth Cohort

The participants comprised the study population of the Medical Research Council (MRC) National Survey of Health and Development (NSHD), also known as the British 1946 birth cohort, initially consisting of 5362 children of nonmanual and agricultural workers and a random sample of 1 in 4 manual workers selected from all single and legitimate births that occurred in England, Scotland, and Wales during a designated week in March 1946.[10] The cohort was followed up 21 times between birth and age 53 years, and information was collected on sociodemographic characteristics and medical, cognitive, and psychological functioning via interviews and examinations.

The most recent follow-up (n=3035) occurred in 1999, when the participants were aged 53 years. In 1989, the cohort was shown to comprise a representative sample of the UK population legitimately and singly born in the immediate postwar era.[11] Exceptions were overrepresentations among nonresponders of individuals who had never married, those at the lowest education levels, those in manual-occupational social class, and those with psychiatric disturbances.

Smoking Frequency

Interview-based prospective information on cigarette smoking frequency at ages 36, 43, and 53 years was obtained by research nurses. At each age, frequency was categorized as 0, 1 to 20, or more than 20 cigarettes smoked per day.

Cognitive Measures

Measures of verbal memory and measures of speed and concentration were repeated at ages 43 and 53 years. Verbal memory was assessed with a 15-item word-learning task devised by the NSHD. Each word was shown for 2 seconds. When all 15 words had been shown, the cohort member was asked to write down as many of the words as possible. The total number of words correctly recalled over 3 identical trials was summed to provide an overall score (maximum: 45).

Speed and concentration were assessed with a visual search task in which participants were required to cross out the letters *P* and *W,* randomly embedded within a page of other letters, as quickly as possible within 1 minute. Scores were computed as total number of letters searched (maximum: 600) minus number of targets missed. Both tests were administered by research nurses.

Background Variables

Potential confounding variables were sex, educational attainment (in tables, categorized as none, vocational only, ordinary secondary, advanced secondary, higher), occupational social class (in tables, categorized as I, II, III: manual, III: nonmanual, IV, V), previous (adolescent) cognitive ability, and a range of health indicators. Previous cognitive ability was represented as summed verbal and nonverbal ability scores, reading comprehension, and mathematical ability[12] at age 15 years from tests administered by the NHSD.

Several health indicators were considered. Early life indicators were maternal smoking, based on recall of the survey member at age

53 years; low birthweight (2.5 kg or less), obtained from medical records; and occurrence of lower respiratory disease in infancy, as reported by respondents' mothers. Indicators at age 53 years were (1) self-reported bronchitis, angina, heart attack, abnormal blood pressure, stroke, and cancer and (2) measured FEV_1, adjusted for adult height, systolic and diastolic blood pressure levels, and resting pulse. Affective disturbances, assessed with the General Health Questionnaire,[13] and potential alcohol abuse, defined by at least 2 positive item scores on the CAGE alcohol abuse screen,[14] also were assessed at the 53-year follow-up.

Statistical Analyses

We investigated the associations between smoking and verbal memory and visual search speed using linear regression models. First, we assessed the association between smoking at age 43 years and both cognitive outcomes at age 43 years. Second, to examine whether smoking at age 43 years was associated with rates of change in cognition between ages 43 and 53 years, we conducted analyses using cognitive scores at age 53 years, adjusting for corresponding scores at age 43 years. To investigate the possible effect of an additional 10 years of smoking, we repeated these models, using smoking at age 53 years instead of age 43 years. We adjusted all of the regression models for sex, educational attainment, occupational social class (all entered as categorical variables), and cognitive ability at age 15 years. We then adjusted the models for each of the study health indicators in turn.

RESULTS

Sample Size

The study sample comprised the 1941 (of 3035) participants interviewed at age 53 years who had complete data with regard to smoking at age 36, 43, and 53 years; memory and visual search test results at age 43 and 53 years; cognitive ability at age 15 years; educational level; and adult occupational social class. Those with missing memory scores at age 53 years had lower mean cognitive scores at age 15 years than did those with available scores, as well as lower levels of education ($P<.001$ in both cases).

Smoking Patterns at Age 36 to Age 53 Years

A trend toward reduction and cessation is evident. The frequency of non-smoking was 1352 (69.7%) at 36 years, 1420 (73.2%) at 43 years, and 1516 (78.1%) at 53 years. For those smoking 1-20 cigarettes per day these figures were 455 (23.4%) at 36 years, 386 (19.9%) at 43 years, and 338 (17.4%) at 53 years. For those smoking more than 20 per day these figures were 134 (6.9%) at 36 years, 135 (7.0%) at 43 years, and 87 (4.5%) at 53 years. On the other hand, consistent levels of exposure to cigarettes over time within each smoking frequency category were observed, with non-smokers at 53 years having smoked a mean (SD) of 2.32 (6.48) cigarettes at 36 years, and 1.56 (5.62) at 43 years. It can be seen that cigarette consumption at age 53 years reflected consistent levels of exposure to cigarettes over the previous 17 years.

Smoking at Age 43 Years and Memory

Table 1 shows beta coefficients representing mean respondent differences in memory scores at age 43 years and mean declines in memory between ages 43 and 53 years, after control for sex, educational attainment, occupational social class, and previous cognitive ability. Beta coefficients for these control variables are shown as well. There was no association between smoking at age 43 years and memory at age 43 years. However, smoking at age 43 years was associated with a more rapid decline in memory from 43 to 53 years.

TABLE 1—Beta Coefficients Representing Mean Differences in Memory Scores at Age 43 Years and Changes in Memory Scores From 43 to 53 Years, by Smoking Frequency at 43 Years

	Memory Score at 43 Years, β (95% CI)	P	Change in Memory Score From 43 to 53 Years,[a] β (95% CI)	P
Smoking Frequency (cigarettes per day) at 43 y (reference: 0)				
1–20	–0.08 (–0.65, 0.50)	.80	–0.05 (–0.56, 0.46)	.84
>20	–0.19 (–1.08, 0.71)	.68	–1.10 (–1.89, –0.30)	.007
P for trend		.57		.02
Sex (reference: male)	2.16 (1.65, 2.68)	<.001	1.08 (0.62, 1.55)	<.001
Educational qualifications (reference: none)				
Vocational only	–0.21 (–1.09, 0.68)	.65	–0.37 (–1.15, 0.42)	.36
Ordinary secondary	1.47 (0.78, 2.16)	<.001	0.96 (0.34, 1.57)	.002
Advanced secondary	2.00 (1.27, 2.72)	<.001	1.05 (0.40, 1.70)	.002
Higher	3.56 (2.49, 4.64)	<.001	1.07 (0.10, 2.04)	.03
P for trend		<.001		.002
Adult social class (reference: I)				
II	0.73 (–0.27, 1.72)	.15	0.03 (–0.86, 0.91)	.95
III: nonmanual	0.84 (–0.30, 1.97)	.15	0.52 (–0.49, 1.52)	.31
III: manual	–0.52 (–1.66, 0.63)	.38	–0.79 (–1.81, 0.22)	.13
IV	–0.75 (–1.99, 0.49)	.24	–0.02 (–1.12, 1.09)	.98
V	–1.88 (–3.57, –0.20)	.03	–0.72 (–2.22, 0.78)	.34
P for trend		<.001		.13
Cognitive ability at 15 years	0.07[b] (0.06, 0.08)	<.001	0.05[b] (0.04, 0.06)	<.001

Note. All coefficients were adjusted for sex, educational attainment, occupational social class, and previous cognitive ability. CI = confidence interval.
[a]Memory score at age 53 years after adjustment for memory score at age 43 years.
[b]Per-item increase in cognitive score.

TABLE 2—Beta Coefficients Representing Mean Differences in Visual Search Speed at 43 Years and Changes in Search Speed From Ages 43 to 53 Years, by Smoking Frequency at 43 Years

	Visual Search Score at 43 Years, β (95% CI)	*P*	Change in Search Score From 43 to 53 Years,[a] β (95% CI)	*P*
Smoking Frequency (cigarettes per day) at 43 y (reference: 0)				
1–20	–7.80 (–16.12, 0.51)	.07	–3.81 (–11.03, 3.41)	.30
>20	–14.79 (–27.83, –1.75)	.03	–9.08 (–20.40, 2.24)	.12
P for trend		.007		.08
Female	21.36 (13.91, 28.80)	<.001	9.35 (2.84, 15.85)	.005
Educational qualifications (reference: none)				
Vocational only	–7.15 (–20.03, 5.74)	.28	–2.74 (–13.92, 8.44)	.63
Ordinary secondary	5.22 (–4.77, 15.21)	.31	–2.89 (–11.56, 5.78)	.51
Advanced secondary	3.21 (–7.38, 13.79)	.55	–1.86 (–11.05, 7.32)	.69
Higher	18.52 (2.84, 34.20)	.02	–0.30 (–13.92, 13.32)	.97
P for trend		.11		.82
Adult social class (reference: I)				
II	–10.39 (–24.89, 4.17)	.15	1.34 (–11.25, 13.92)	.84
III: nonmanual	–8.66 (–25.14, 7.81)	.28	0.32 (–13.98, 14.61)	.97
III: manual	–13.30 (–29.95, 3.36)	.11	–3.46 (–17.91, 11.00)	.64
IV	–18.52 (–36.58, –0.46)	.04	6.34 (–9.34, 22.02)	.43
V	–19.93 (–44.52, 4.66)	.10	–5.16 (–26.50, 16.18)	.64
P for trend		.04		.98
Cognitive ability at 15 years	0.18[b] (0.03, 0.32)	.02	0.32[b] (0.20, 0.45)	<.001

Note. All coefficients were adjusted for sex, educational attainment, occupational social class, and previous cognitive ability. CI = confidence interval.
[a]Search score at age 53 years after adjustment for search score at 43 years.
[b]Per-item increase in cognitive score.

Although a test for trend was significant at the 5% level for memory decline, this effect was accounted for by individuals who smoked more than 20 cigarettes per day. Sex × Smoking interactions were not significant at the 5% level for memory decline. Strong associations between previous cognitive ability, educational attainment, and memory were evident, along with an advantage among female respondents on this measure and a lack of association involving adult social class over and above educational attainment.

Smoking at Age 43 Years and Timed Visual Search

Table 2 shows a model, identical to that presented in Table 3, for timed visual search. Smoking was associated with slower search speeds at age 43 years. Although inspection of the coefficients suggests a dose–response effect, supported by a trend test significant at the 5% level, this effect was again largely accounted for by individuals who smoked more than 20 cigarettes per day. There was no association between smoking and change in search speed from 43 to 53 years. Sex × Smoking interactions were not significant at the 5% level for this measure. As with memory, associations between previous cognitive ability and search speed were evident, as was a female advantage on this measure; however, the contributions of educational attainment and adult social class were far less pronounced than for memory.

Smoking at Age 53 Years and Cognition

Table 3 presents models similar to those shown in Tables 3 and 4, but based on smoking at age 53 years. Data for the background variables are not shown, because these data were similar to those for smoking at age 43 years. As with smoking at age 43 years, there was no association between smoking at age 53 years and memory at age 43 years. However, smoking at age 53 years was associated with a more rapid decline in memory from 43 to 53 years. Although the trend test was significant at the 5% level for memory decline, this effect was once again accounted for by individuals who smoked more than 20 cigarettes per day. Those smoking at this rate

TABLE 3—Beta Coefficients Representing Mean Differences in Cognitive Scores at Age 43 Years and Changes in Cognitive Scores Between Ages 43 and 53 Years, by Smoking Frequency at Age 53 Years

	Memory Score				Visual Search Score			
Smoking Frequency	43 Years, β (95% CI)	*P*	Change From 43 to 53 Years,[a] β (95% CI)	*P*	43 Years, β (95% CI)	*P*	Change From 43 to 53 Years,[a] β (95% CI)	*P*
Cigarettes per day at age 53 y (reference: 0)								
1–20	–0.05 (–0.65, 0.55)	.87	–0.38 (–0.91, 0.16)	.16	–5.68 (–14.38, 3.02)	.20	–5.82 (–13.39, 1.74)	.13
>20	0.25 (–0.84, 1.35)	.65	–2.00 (–2.96, –1.03)	<.001	–31.06 (–46.93, –15.19)	<.001	–10.77 (–24.62, 3.08)	.13
P for trend		.91		<.001		<.001		.04

Note. All coefficients were adjusted for sex, educational attainment, occupational social class, and previous cognitive ability. CI = confidence interval.
[a]Memory score at age 53 years after adjustment for memory score at age 43 years.
[b]Per-item increase in cognitive score.

at age 53 years showed a mean decline 2 words (4.4% of the maximum score) greater than those not smoking at this age. Sex × Smoking interactions were not significant at the 5% level for this measure.

As with smoking at age 43 years, smoking at age 53 years was associated with slower search speed at age 43 years, an effect again largely accounted for by participants who smoked more than 20 cigarettes per day. There was no association between smoking and change in search speed from 43 to 53 years. Because the effect of smoking on search speed decline was confined to men, the Sex × Smoking interaction was significant at the 5% level for this measure ($P=.01$).

Control for Health Indicators

The association between smoking at age 53 years and change in search speed from 43 to 53 years was slightly reduced after additional adjustment for FEV_1 and low birthweight, although it should be noted that this association was already of relatively low magnitude before this adjustment. When adjusted in turn, none of the other health indicators modified the associations between smoking and cognition to any notable extent. In each case, the effect of smoking more than 20 cigarettes per day at age 53 years on search speed at age 43 years and the effect on change in memory from 43 to 53 years remained significant at the .001 level.

Smoking Cessation and Cognitive Functioning

To investigate whether the effects of smoking on cognition were modified by smoking cessation, we reclassified participants into those who did not smoke at age 36, 43, or 53 years; those who were smoking at age 36 years only; those who were smoking at age 36 and 43 years only; and those who were smoking at all 3 ages. In the case of 127 of the participants, irregular smoking patterns could not be classified in this way. Cigarette consumption was relatively light in this group (means of 8.8 [SD=8.58], 9.05 [SD=9.88], and 2.90 [SD=6.92] cigarettes smoked per day at age 53, 43, and 36 years, respectively).

Table 4 shows that participants who smoked at all 3 ages had significantly lower scores, and exhibited significantly greater declines, on both cognitive tests at age 53 years compared with those smoking at none of these ages. This effect was almost certainly accounted for by individuals who smoked more than 20 cigarettes per day, because most of these participants were classified with those who smoked at all 3 ages. There was, in addition, a trend toward a slowing of memory decline among those who stopped smoking (particularly those who did not smoke at age 43 and 53 years) relative to those who had never smoked. Participants who stopped smoking had slower visual search speeds than did those who had never smoked, but this effect was relatively weak. As before, all analyses were adjusted for sex, educational attainment, occupational social class, and cognitive ability at age 15 years.

TABLE 4—Beta Coefficients Representing Mean Differences in Cognitive Scores for Participants Who Stopped Smoking After Age 36 Years, Those Who Stopped Smoking After Age 43 Years, and Those Still Smoking at Age 53 Years, Relative to Participants Not Smoking at Any of These Ages

Smoking Pattern, 36–53 Years	Cognitive Score at 53 Years, β (95% CI)	*P*	Change in Cognitive Score From 43 to 53 Years,[a] β (95% CI)	*P*
Memory				
Never smoked	Reference		Reference	
Stopped after 36 y	0.91 (−0.03, 1.85)	.06	0.80 (−0.03, 1.63)	.06
Stopped after 43 y	0.42 (−0.55, 1.39)	.40	0.60 (−0.25, 1.46)	.17
Still smoking at 53 y	−0.69 (−1.32, −0.06)	.03	−0.68 (−1.23, −0.12)	.02
P for trend		.09		.07
Visual search				
Never smoked	Reference		Reference	
Stopped after 36 y	−5.30 (−18.72, 8.12)	.44	−11.80 (−23.70, 0.10)	.05
Stopped after 43 y	−7.96 (−21.79, 5.86)	.26	−2.84 (−15.09, 9.41)	.65
Still smoking at 53 y	−11.97 (−20.93, −3.00)	.009	−7.78 (−15.72, −0.17)	.06
P for trend		.005		.04

Note. All coefficients were adjusted for sex, educational attainment, occupational social class, and previous cognitive ability. CI = confidence interval.
[a]Represented by cognitive score at age 53 years adjusted for cognitive score at 43 years.

DISCUSSION

In this prospective population-based study, cigarette smoking was associated with faster declines in verbal memory between ages 43 and 53 years. These results are consistent with those from a recent study by Kalmijn et al.,[9] in which smoking was associated with reduced cross-sectional performance on a test of speed and concentration in this age range, although not with changes in this measure. These effects were largely accounted for by individuals who smoked more than 20 cigarettes per day and were independent of sex, socioeconomic status, previous cognitive ability, and a range of health indicators, including respiratory and cardiovascular disease, FEV_1, blood pressure, affective disturbances, and potential alcohol abuse.

We should highlight several potential limitations of this study. First, smoking measures were self-reported, and measures of cotinine were not available to quantify inhaled doses. Second, there was a disproportionate loss to follow-up among participants at lower cognitive ability levels, limiting the generalizability of the results and possibly leading to underestimations of the true effect of smoking on cognition. However, we have no reason to believe that this loss to follow-up had any impact on the patterns of associations themselves. This limitation is balanced, furthermore, by the relatively young age of the participants, among whom premature death from smoking was unlikely to have reached a level that would cause significant survival bias.

Third, participants were required to abstain from smoking during their interviews. It is therefore possible that some smokers were in a state of incipient nicotine withdrawal during cognitive testing (approximately 90 minutes into the interview), which could have led to reductions in performance.[15]

With these limitations in mind, we must ask: What is the nature of the association between smoking and cognitive impairment in this population? The inability of the physical health indicators (e.g., cardiovascular and respiratory functioning) to explain the association between smoking and cognition raises the possibility of a direct effect of smoking on the central nervous system. In this regard, smoking was identified as a risk factor for perfusional decline, cerebral atrophy, and leukoaraiosis in a sample of individuals at increased risk of cognitive decline[16] whose mean age (59 years) was similar to that of the NSHD cohort.

A second possibility concerns the role of nutrition. Smokers have been found to have lower intakes of antioxidant vitamins and higher levels of triglycerides, fibrinogen, and serum cholesterol compared with nonsmokers.[17] The implications of such findings for the cognitive functioning of the NSHD cohort will be a matter for detailed investigation.

Two further aspects of our results deserve attention. First, the association between smoking and memory was not observed at age 43 years but emerged as a change in functioning between ages 43 and 53 years. This finding implies a possible temporal window of action in terms of smoking effects on central nervous system processes underlying memory. The effect of smoking on psychomotor speed was already evident by age 43 years, however, and thus such a window for this area of functioning cannot be inferred from the results of the present study.

Second, the association between smoking and memory observed at age 53 years was far stronger than that observed at age 43 years. This finding represents either the effect of a further 10 years of smoking exposure or an uncontrolled characteristic of the subgroup that persisted in smoking heavily throughout midlife.

What are the public health implications of this study? Peto et al. have estimated that in developed countries, tobacco use causes approximately 30% of all mortality among individuals between ages 35 and 69 years, making it the largest single cause of premature death in the industrialized world.[8] Because memory impairment has been shown to predict dementia,[18,19] our results suggest that even if smokers survive into later life, they may be at high risk of clinically significant cognitive decline. Continued follow-up of the NSHD cohort will determine this risk with greater precision. ■

About the Authors

Marcus Richards, Neil Thompson, and Michael E.J. Wadsworth are with the Medical Research Council, National Survey of Health and Development, University College London, London, England. Martin J. Jarvis is with the Cancer Research UK Health Behaviour Unit, University College London.

Requests for reprints should be sent to Marcus Richards, PhD, MRC National Survey of Health and Development, Royal Free and University College London Medical School, University College London, Department of Epidemiology and Public Health, 1-19 Torrington Pl, London WC1E 6BT, England (e-mail: m.richards@ucl.ac.uk).

This article was accepted January 12, 2003.

Contributors

M. Richards initiated the core study ideas, and M.J. Jarvis, N. Thompson, and M.E.J. Wadsworth helped to develop these ideas. M. Richards designed and performed the statistical analysis. The article was written jointly by all authors.

Human Participant Protection

Ethical clearance for this research was obtained from multicenter and local research ethics committees across the United Kingdom. Informed consent was obtained from all participants.

References

1. Herbert LE, Scherr PA, Beckett LA, et al. Relation of smoking and low-to-moderate alcohol consumption to change in cognitive function: a longitudinal study in a defined community of older persons. *Am J Epidemiol.* 1993;137:881–891.

2. Ford AB, Mefrouche Z, Friedland RP, Debanne SM. Smoking and cognitive impairment: a population-based study. *J Am Geriatr Soc.* 1996;44:905–909.

3. Edelstein SL, Kritz-Silverstein D, Barrett-Connor E. Prospective association of smoking and alcohol use with cognitive function in an elderly cohort. *J Womens Health.* 1998;7:1271–1281.

4. Wang H-X, Fratiglioni L, Frisoni GB, Vitanen M, Winblad B. 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.

5. Doll R, Peto R, Boreham J, Sutherland I. Smoking and dementia in male British doctors: a prospective study. *BMJ.* 2000;320:1097–1102.

6. Launer LJ, Andersen K, Dewey ME, et al. Rates and risk factors for dementia and Alzheimer's disease: results from EURODEM pooled analyses. *Neurology.* 1999;52:78–84.

7. Cervilla JA, Prince M, Mann A. Smoking, drinking, and incident cognitive impairment: a cohort community based study included in the Gospel Oak project. *J Neurol Neurosurg Psychiatry.* 2000;68:622–626.

8. Peto R, Lopez AD, Boreham J, Thun M, Heath C. Mortality from tobacco in developed countries: indirect estimation from national vital statistics. *Lancet.* 1992;339:1268–1278.

9. Kalmijn S, van Boxtel MPJ, Verschuren MWM, Jolles J, Launer LJ. Cigarette smoking and alcohol consumption in relation to cognitive performance in middle age. *Am J Epidemiol.* 2002;156:936–944.

10. Wadsworth MEJ. *The Imprint of Time: Childhood, History and Adult Life.* Oxford, England: Clarendon Press; 1991.

11. Wadsworth MEJ, Mann SL, Rodgers B, Kuh DL, Hilder WS, Yusuf EJ. Loss and representativeness in a 43 year follow-up of a national birth cohort. *J Epidemiol Community Health.* 1992;46:300–304.

12. Pigeon DA. Details of the fifteen years tests. In: Douglas JWB, Ross JM, Simpson HR, eds. *All Our Future.* London, England: Davies; 1968:194–197.

13. Goldberg DP, Hillier VF. A scaled version of the General Health Questionnaire. *Psychol Med.* 1979;9:139–145.

14. Ewing JA. Detecting alcoholism: the CAGE questionnaire. *JAMA.* 1984;252:1905–1907.

15. Waters AJ, Sutton SR. Direct and indirect effects of nicotine/smoking on cognition in humans. *Addict Behav.* 2000;25:29–43.

16. Meyer JS, Rauch GM, Crawford K, et al. Risk factors accelerating cerebral degenerative changes, cognitive decline and dementia. *Int J Geriatr Psychiatry.* 1999;14:1050–1061.

17. Woodward M, Bolton-Smith C, Tunstall-Pedoe H. Deficient health knowledge, diet, and other lifestyles in smokers: is a multifactorial approach required? *Prev Med.* 1994;23:354–361.

18. Masur DM, Sliwinski M, Lipton RB, Blau AD, Crystal HA. Neuropsychological prediction of dementia and the absence of dementia in healthy elderly persons. *Neurology.* 1994;44:1427–1432.

19. Jacobs DM, Sano M, Dooneief G, Marder K, Bell KL, Stern Y. Neuropsychological detection and characterization of preclinical Alzheimer's disease. *Neurology.* 1995;45:957–962.