Objectively measured secondhand tobacco smoke and cognitive impairment in disability-free older adults

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Abstract

Previous studies have suggested that exposure to secondhand smoke (SHS) may be associated with greater risk of cognitive impairment. However, no longitudinal study has examined the association of serum cotinine (as objective measure of SHS exposure) and cognitive function in older adults. We used data from 2087 non-smoking adults aged≥65years participating in the ENRICA-2 cohort and free from limitations in Instrumental Activities of Daily Living. Cognitive function was assessed through the Mini-Mental State Examination (MMSE), the Digit Span Backwards subtest(DSBT), the Luria´s motor series subtest from the Frontal Assessment Battery, the Trail Making Test A (TMT-A), the Free and Cued Selective Reminding Test(FCSRT), and the Categorical Verbal Fluency Test (CFT) of the 7 minutes test. Cross-sectional analyses were performed using multivariable logistic and ordered logistic models, while analyses on changes in cognition over time used multivariable repeated-measures mixed-effects models. Compared to the unexposed, those in the highest exposure group (≥0.161ng/ml) were more likely to have cognitive impairment (MMSE<24) (odds ratio[OR]:1.64;95% confidence interval[CI]:1.04-2.60) and lower DSBT scores (OR:1.25;95%CI:1.00-1.57), as well as a non-significant higher odds of a lower score in the Luria test (OR:1.23;95%CI:0.92-1.64) or episodic memory impairment (FCSRT<12, OR:1.38;95%CI:0.90-2.11). In longitudinal analyses, those with baseline cotinine ≥0.161ng/ml showed an increased risk of cognitive impairment (MMSE<24,OR:2.23;95%CI:1.14-4.33; p-trend across cotinine categories=0.028) and decreased DSBT (OR:1.23;95%CI:1.01-1.51; p-trend across cotinine categories=0.046). Findings show an increased risk of global cognitive impairment and declines in working memory performance in older adults exposed to SHS. More efforts are needed to protect older adults from SHS in areas not covered by smoke-free legislation.

Keywords: Cotinine, involuntary tobacco smoke, memory, cognition, cohort study.

Introduction

Ageing entails structural and functional changes in the brain that correlate with declines in fluid cognitive abilities, such as reasoning, speed of processing, episodic memory, working memory, inhibition, or executive function (1). Although the initial loss of cognitive function can be clinically undetectable, the progressive loss of mental abilities in older adults can lead to a decrease in quality of life (2), a loss of autonomy and independence (3), and an increased risk of dementia and death (4). The prevalence of cognitive impairment is around 19% worldwide (5). The World Health Organization projects that, by 2050, 139 million adults globally will have dementia (6).

It is now clear that the pace of cognitive ageing can be modified throughout the lifespan. Among the factors that increase the rate of decline seen with normal aging are a lower number of years of education, unhealthy lifestyles such as poor diet and physical inactivity during lifetime, or biological cardiovascular risk factors like hypertension and diabetes (7,8). Some studies have suggested that exposure to certain environmental factors, such as air pollutants or toxic and trace metals, may also increase the risk of accelerated cognitive decline and dementia in late life (9).

Secondhand tobacco smoke (SHS) is the combination of smoke from the burning end of a cigarette and the smoke breathed out by smokers. It is an established risk factor for lung cancer, heart disease, and stroke in nonsmoking adults (10), with suggestive evidence that it may cause asthma, chronic obstructive pulmonary disease, atherosclerosis, and cancer of the paranasal sinus, pharynx, larynx and breast (10). Although in most developed countries, exposure to SHS has been reduced, tobacco laws prohibiting smoking in workplaces and leisure spaces do not influence tobacco consumption in the home environment, the major living space of older adults. Only in Europe, around three out of

five smokers allow smoking in their homes, with the burden attributable to SHS in 2017 estimated as 30,000 deaths and 712,000 daily-adjusted life years (DALYs), which account for both the years of potential life lost due to premature death and the years of productive life lost due to disability compared to a standardized life expectancy (11). Worldwide these figures amount to 603,000 deaths and 10.9 million DALYs (12).

Smoking is a potential risk factor of accelerated cognitive decline and dementia (7), with experimental models proving the atherothrombotic and oxidative effects of cigarette smoking in cerebral vessels, and human studies showing increased oxidative stress biomarkers in cerebrospinal fluid (13,14) as well as a reduced gray and white matter density in subjects with a history of smoking (15). Brain regions affected by smoking include the anterior frontal regions, the subcortical nuclei, the hippocampus or the commissural white matter (16–19). Regarding SHS, a few studies have suggested that it may also accelerate cognitive decline and increase the risk of dementia in old age (20–23). However, most of the investigations are cross-sectional and, thus, may have a high risk of reverse causation (i.e. older adults with cognitive impairments and dementia being less likely to live independently of a caregiver that smokes), and survival and reporting biases. Moreover, none of the few prospective studies so far have used objective measures of SHS. In this context, the present report evaluates for the first time the prospective association between objectively measured exposure to SHS, assessed by serum cotinine concentrations, and changes in cognitive function in disability-free older adults living in the community.

Methods

Study design and participants

The ENRICA-2 cohort was established between 2015 and 2017 with 3,273 individuals selected by sex- and district-stratified random sampling of all community-dwelling individuals aged ≥65 years, holding a national healthcare card and living in the city of Madrid (Spain) or four surrounding large towns (24). At baseline (2015-2017) and follow-up (2019), information on socio-demographic, lifestyle, self-rated health and morbidity was collected using a computer-assisted telephone interview. Also, two home visits were conducted in order to collect biological samples and perform a physical exam and cognitive assessment.

From the initial sample of 3,273 subjects, we excluded self-reporting active smokers (n=307), those with serum cotinine concentrations over 10 ng/ml (n=40), those who did not provide a blood sample (n=626) or had missing values on important confounders (n=40), and those with IADL limitations (n=173), leading to an analytical cross-sectional sample of 2,087 participants. In prospective analyses we further excluded 615 individuals who were lost to follow-up, 18 who died, 194 who did not perform a cognitive examination, and 10 with missing information on potential confounders, leading to 1,250 participants.

The Clinical Research Ethics Committee of the *La Paz* University Hospital in Madrid approved the study (Protocol #HULP-PI 1793). All participants provided written informed consent. All participants provided verbal informed consent during the phone interview and written informed consent during the first home visit.

Study Variables

Exposure assessment.

At baseline, serum cotinine was measured by high performance liquid chromatography and tandem mass spectrometry detection at Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain. The limit of quantification (LOQ) was 0.05 ng/ml, and serum cotinine concentrations below the LOQ were replaced by the LOQ divided by the square root of 2. Participants self-reporting being active smokers (n=307) and those who had serum cotinine concentrations over 10 ng/ml regardless of the self-reported information (n=40) were classified as active smokers and excluded from the analyses. Non- active smokers with cotinine concentrations between 0.05 and 9.9 ng/ml regardless of self-reporting not being exposed were classified as exposed, while non-active smokers who reported not being exposed to SHS and with cotinine levels below 0.05 ng/ml were classified as unexposed.

Cognitive function.

At baseline and follow-up, global cognitive function was measured with the Mini-Mental State Examination (MMSE) validated for Spain (25). This tool includes items about orientation (time and place), registration, attention and calculation, recall, language, repetition and reading, and visual-spatial skills. Scoring ranges from 0 to 30, with higher scores indicating better cognitive function. Individuals who scored between 21 and 24, between 11 and 20, or below 11 were deemed to have mild, moderate or severe cognitive impairment, respectively.

In addition to global cognition, performance on specific cognitive functions was evaluated with the following screening tools: 1- The Digit Span Backwards subtest (DSBT) from the Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV) (26). Digit Span was calculated as the sum of the longest string of three to seven digits repeated without error under backward conditions. The final score ranged from 1 to 7, with lower

scores indicating worse working memory performance; 2- The Luria´s motor series subtest from the Spanish version of the Frontal Assessment Battery (FAB) (27,28). Participants had to repeat three times the Luria "fist–edge–palm" series, and scored from 0 to 3, with lower values indicating greater impairment in motor programming; 3-The Trail Making Test A (TMT-A) (29). Participants had to draw lines to connect numbers 1 to 25 in ascending order, and the time invested to connect the trail was recorded. Higher scores in the TMT-A reveal greater impairment on visual attention and task switching and individuals with scores greater than 78 seconds were considered cognitively impaired for this test (29); 4- The Free and Cued Selective Reminding Test (FCSRT) from the Spanish version of the 7 minute screening neurocognitive battery (7MS) (30). The final score ranged 1 to 16 and was obtained by summing the number of items freely recalled plus the number of items named during cued recall. Individuals with values ≤12 were considered to have impaired episodic memory (31); 5- The Categorical Verbal Fluency Test (CFT) of the Spanish version of the 7MS (30). The score ranged from 0 to 35 according to the total number of words that the individual was able to produce, with lower scores indicating worse function. Individuals with values ≤10 were considered to have impaired semantic memory (31).

Other variables

At baseline and follow-up, information was collected on sociodemographic characteristics including sex, age, education level (< high school, high school, > high school), cohabitation, and having a paid carer to help in meal preparation or in daily home activities. Information on recreational physical activity was collected using the EPIC-cohort questionnaire validated in Spain (32). The assigned metabolic equivalents of tasks (METs) for each activity were 2.5 for walking (commuting, shopping, or leisure time) and 4.0 for cycling (commuting or leisure time) and playing sports. Weight and height

were measured in standard conditions and the body mass index (BMI) calculated as the weight (kg) divided by the squared height (m). Cardiovascular disease (CVD) was defined as a self-reported medical diagnosis of coronary heart disease, congestive heart failure, heart attack or stroke. A history of hypertension was based on a self-reported physician diagnosis, current use of anti-hypertensive medication, or the average of three causal blood pressure readings ≥140/90 mmHg taken under standardized conditions. Fasting serum glucose was measured with colorimetric enzymatic methods using Atellica Solution® (Siemens Healthineers) and definition of type 2 diabetes mellitus was based on a self-reported physician diagnosis, fasting glucose ≥126 mg/dL, or current use of anti-diabetic medication. Depression was ascertained with the 10-item Geriatric Depression Scale (GDS-10 ≥5) (33), a self-report of clinically diagnosed depression, or being on anti-depressant medication. Limitations in instrumental activities of daily living (IADL) were assessed with the Lawton and Brody Scale (34).

Statistical analyses

We first evaluated the cross-sectional association between baseline serum cotinine concentrations and presence of cognitive impairment using either logistic, ordered logistic or linear regression models as appropriate. With this purpose, we classified individuals with cotinine concentrations below 0.05 ng/ml as unexposed and categorized exposed participants according to tertiles of serum cotinine distribution. Additionally, because cotinine concentrations were highly skewed, we run regression models on log-transformed serum cotinine. Models were progressively adjusted for age, sex, educational level, cohabitation, and having or not a paid carer to help in meal preparation or in daily home activities (Model 1); recreational physical activity, past active tobacco smoke (never, former), and BMI (Model 2); and prevalence of cardiovascular disease, hypertension, diabetes, cancer and depression (Model 3).

In a second step, we evaluated the prospective association between baseline serum cotinine concentrations and changes in cognitive function using either mixed-effects logistic, ordered logistic or linear regression models, as appropriate, with robust standard error estimates to account for within-participant correlations induced by repeated measures. Results for panel level variance and intraclass correlation coefficients are shown in Supplementary Table 1. We adjusted these models for both time-varying (i.e. age, cohabitation, having a paid carer, recreational physical activity, tobacco smoke, body mass index, and comorbidities) and time-constant (i.e. sex, educational level) covariates.

To evaluate the consistency of our findings, we used likelihood-ratio tests to compare models with and without cross-product interaction terms for log-transformed cotinine concentrations and indicator variables for baseline age, sex, education, past smoking status, BMI, hypertension, CVD, cancer, diabetes and depression. All the analyses were performed using Stata software version 14.0.

Results

At baseline, 139 (6.69%) and 6 (0.29%) participants presented mild or moderate cognitive impairment as assessed with the MMSE, respectively. Also, a total of 298 (14.5%) individuals presented TMT-A time score > 78 seconds, 173 (8.3%) an FCSRT score < 12, and 221 (10.6%) a CFT score < 10. The mean (SD) DSBT and Luria scores were 4.72 (1.04) and 2.67 (0.70), respectively.

The median (interquartile range) concentration of serum cotinine was 0.055 (IQR: 0.035-0.113) ng/ml, with less than 1% of participants showing concentrations ≥3 ng/ml. Participants with lower education, former smokers, and those with overweight and obesity or a diagnosis of diabetes were more likely to be exposed to SHS (**Table 1**). In fully-adjusted baseline models (**Table 2**), participants in the highest category of SHS

exposure (≥ 0.161 ng/ml) showed a 64% higher odds (95%confidence interval [CI]: 1.04-2.60) of cognitive impairment (MMSE <24), and a 25% higher odds (ordered logistic 95%CI: 1.00-1.57) of a lower DSBT score, compared to the unexposed. Also, participants in the highest category of SHS showed a non-significant higher odds of a lower Luria test score. No significant association was observed between levels of SHS exposure and results in the TMT-ACFT, or FCSRT tests.

During a mean (SD) follow-up of 2.6 (0.52) years, 60 participants developed a MMSE <24, 314 a TMT-A score > 78, 80 a FCSRT score < 12 and 288 a CFT score < 10. The mean (SD) changes in the DSBT and Luria scores were -1.00 (2.48) and -0.24 (1.13), respectively. Compared to the unexposed to SHS, those in the highest category of baseline cotinine showed an increased risk of cognitive impairment (MMSE <24, OR: 2.23; 95%CI: 1.14-4.33; p-trend across cotinine categories=0.028) or decreased DSBT (OR:1.23; 95%CI:1.01-1.51; p-trend across cotinine categories=0.046) (**Table 3**). No significant associations were observed for the other cognitive tests.

In sensitivity analyses, the effects of SHS on cognition were similar when modeling the scores of the tests as continuous (Supplementary Tables 2 and 3). Moreover, most effects were consistent in strata defined by age, sex, education, smoking status, BMI and comorbidities (Supplementary Figures 1 and 2). However, in both cross-sectional and prospective analyses, SHS exposure was associated with reduced Luria scores in obese participants (p-interaction 0.05 and <0.01, respectively), and with reduced FCSRT scores in former smokers (p-interaction 0.02 and 0.03, respectively).

Discussion

In this study of community-dwelling older adults, exposure to SHS, as measured by serum cotinine, was associated with a higher risk of global cognitive impairment and

lowered performance in working memory. Results were consistent in former and never smokers, independent of socioeconomic and lifestyle factors, and chronic morbidities.

Previous studies in children have shown reduced vocabulary and reasoning skills, as well as more general cognitive and intellectual deficits, in those exposed to SHS, compared to the non-exposed (35). Moreover, higher cotinine levels in non-smoking children and adolescents have been associated with reductions in reading and mathematics performance and with worse visual and spatial abilities (35). For older adults, the evidence is scarce and mostly based on cross-sectional studies (36–42) and a few longitudinal investigations using self-reported SHS (21–23,43). Among the cross-sectional studies, two based on data from never-smoking older adults participating in the Annui cohort study (n=1,081) (38) and in the Four province study (n=2,692) (37), both of which assessed cognition with the Automated Geriatric Examination for Computer Assisted Taxonomy, found that those exposed to SHS at higher intensity or during longer periods of time presented a higher prevalence of cognitive impairment (38), and, when the exposure occurred at home, a higher prevalence of dementia (37). Additionally, two cross-sectional studies with objective SHS, one based on 2452 non-smoking older adults from the National Health And Nutrition Examination Survey (NHANES) (36) and the other on 4,809 non-smoking adults aged ≥50 years from the English Longitudinal Study of Ageing (ELSA) (39), found that participants, particularly never smokers, with higher cotinine levels had worst executive function (36) and higher prevalence of cognitive impairments, as measured summing the standardized scores of six different neuropsychological tests (39). In prospective studies with self-reported SHS exposure, it was associated with a 2-year increased risk of cognitive impairment defined as low MMSE among Chinese older adults (23); exposure to more than 25 years (vs < 25) of passive smoking was associated with a 6-year increased risk of dementia

among non-smokers from the Cardiovascular Health Cognition Study having >25% carotid stenosis (43); while more than 40 years of passive smoking (vs non-exposure) was associated with a 2-year faster decline in episodic memory evaluated with an immediate and delayed word recall assessment (22), and also with a 4-year faster decline in overall cognition, episodic memory and visuospatial ability (21), among women aged ≥50 years from the China Health and Retirement Longitudinal Study (CHARLS). Taken together, and despite the difficulties in direct comparisons between studies because of the wide variety of measurements used to evaluate cognition and of differences in the magnitude of neurocognitive dysfunction among populations, the evidence points out to a detrimental effect of SHS on cognition. Plausible mechanisms for this relationship include the potential direct central nervous damage of neurotoxicants such as lead contained in SHS (44), as well as the direct and indirect effects of SHS on the nervous (45), cardiovascular (45) and musculoskeletal (46) systems through its pro-atherothrombotic, oxidative and proinflammatory effects. Moreover, previous studies in older adults with a history of cigarette smoking have shown thinner cortex in large areas of the medial and lateral frontal cortex, as well as regions of the medial and lateral temporal and parietal cortices compared to never smokers (47,48).

Results are also coherent with the effects caused by active tobacco smoking in cognition. Previous studies of middle-aged and older adults have shown positive associations between active chronic smoking, global cognitive decline and reductions in executive function, general intellectual abilities, learning and memory processing speed, auditory verbal memory, and working memory (16). As examples, in a multicenter European cohort with 17,610 persons aged ≥65 years and followed for 2.3 years, current smokers showed higher rates of decline in the MMSE compared to never smokers, with

a dose-response trend observed between the number of pack-years smoked and the rate of cognitive decline (49). In the Whitehall II cohort study, with 5,099 men and 2,137 women aged 44-59 years at baseline, male current smokers showed greater 10-year declines in global cognition and executive function than never smokers (50). On the other hand, in the Atherosclerosis Risk in Communities Study, with 14,000 middle-aged participants, current smoking was associated with poorer performance on the Delayed Word Recall in women, but not men, and with poorer scores in the Digit Symbol Subtest of the Wechsler Adult Intelligence Scale-Revised in both sexes (50).Finally, a recent study on a large sample of 33,293 smokers from the UK Biobank also showed poorer DSBT in smokers compared to controls, which was mediated by an older-appearing brain (51).

Compared to previous research, the present study has important strengths. First, it is the first prospective study to evaluate the association between SHS and cognition using an objective measure of environmental tobacco smoke. Second, it accounts for a wide array of potentially important confounders including demographic factors and health conditions and used several statistical models with different adjustment levels yielding consistent results. Also, because we excluded participants with cotinine concentrations greater than 10 ng/mL and participants with IADL limitations we reduced the potential of misclassification of smoking status and reverse causality. Among the limitations, the tests used in the analyses did not evaluate all cognitive domains. Also, we used a single measurement of cotinine, which only reflects exposure over the previous 1-2 days and is an imperfect surrogate of long-term exposure. Lastly, (vs non-exposure) Lastly, due to the small proportion of participants heavily exposed to SHS (with concentrations close to 10ng/mL), results may not apply to higher cotinine concentrations. Moreover, we did not adjust our analyses for important social-related variables such as social support or

loneliness, which are also known predictors of cognitive decline, and could not account for the smoking behavior of household members. Lastly, our study sample came from an urban and mass area (Madrid) and that could affect the generalization of the study results. Moreover, as in other ageing cohorts, losses to follow-up may have resulted in a lost of representativeness of the cohort over time.

In conclusion, our findings suggest that exposure to SHS in old age may contribute to accelerate cognitive decline. At present, 35% of non-smoking older adults around the world are exposed to SHS(52); these high population figures and the subsequent risk of cognitive deficit suggest more efforts are needed to protect them, especially in areas not covered by smoke-free legislation.

Acknowledgments and authorship: EGE conceived the study. EGE, RO, JRB and FRA collected information on study participants. JAP and RPO handled the laboratory determinations. EGE performed statistical analyses. EGE drafted the initial manuscript. All authors reviewed the manuscript for important intellectual content, read and approved the final manuscript.

All authors have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Conflicts of interest: The authors declare they have nothing to disclose.

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Tables

Table 1. Distribution of participant´s characteristics by serum cotinine concentrations (n=2087)

	Unexposed	Exposed Tertiles (T) of Cotinine, ng/ml			
	Ref. (<0.05)	**T1 (0.05-0.082)**	**T2 (0.083-0.16)**	**T3 (0.16-9.9)**	**p-value***
n (%)	964 (46.19)	394 (18.88)	369 (17.68)	360 (17.25)	
Age, years, %					0.49
<69	35.79	39.09	36.59	37.22	
70-74	40.87	41.37	37.40	39.44	
≥75	23.34	19.54	26.02	23.33	
Sex, %					0.59
Male	46.06%	48.22%	50.14%	47.22%	
Female	53.94%	51.78%	49.86%	52.78%	
Educational level, %					0.05
<High School	59.34%	61.68%	59.08%	68.89%	
High School	20.54%	18.53%	21.95%	17.22%	
>High School	20.12%	19.80%	18.97%	13.89%	
Cohabitation, %					
No	78.32%	77.41%	73.44%	78.89%	0.24
Yes	21.68%	22.34%	26.56%	21.11%	
Having a paid carer , %					
No	34.13%	33.25%	32.79%	35.56%	0.87
Yes	65.87%	66.75%	67.21%	64.44%	
Tobacco smoke, %					0.02
Former	39.42%	42.64%	46.34%	47.50%	
Never	60.58%	57.36%	53.66%	52.50%	
Physical activity (tertiles), %					0.12
Lowest	36.10%	31.98%	34.42%	39.44%	
Second	31.74%	28.93%	29.81%	26.11%	
Highest	32.16%	39.09%	35.77%	34.44%	
Body mass index, kg/m^2, %					<0.01
<25	30.29%	27.16%	23.31%	17.22%	
25-30	46.47%	47.72%	50.68%	51.94%	
≥30	23.24%	25.13%	26.02%	30.83%	
Hypertension, %					0.44
No	33.92%	32.49%	34.15%	29.44%	
Yes	66.08%	67.51%	65.85%	70.56%	
Cardiovascular disease, %					0.69
No	96.58%	96.70%	97.83%	96.67%	
Yes	3.42%	3.30%	2.17%	3.33%	
Cancer, %					0.05
No	96.68%	98.22%	95.12%	98.06%	
Yes	3.32%	1.78%	4.88%	1.94%	
Diabetes, %					0.02
No	81.85%	84.26%	80.76%	75.56%	
Yes	18.15%	15.74%	19.24%	24.44%	
Depression, GDS score, %					0.41
<5	94.92%	96.44%	96.47%	92.78%	
≥5	5.08%	3.55%	3.52%	5.28%	

GDS: Geriatric Depression Scale.
* p-values derived from chi-square tests.

Table 2. Cross-sectional association between serum cotinine concentrations (ng/ml), and measures of cognitive function among non-smokers. Results are from logistic and ordered logistic regression models and expressed as Odds Ratios (OR) and their 95% confidence intervals (95%CI).

	Serum cotinine						
	Unexposed	Exposed, cotinine tertiles (ng/ml)					
	Ref. (<0.05)	T1 (0.050-0.082)	T2 (0.083-0.160)	T3 (≥0.161)	*p-trend	Per doubling increase in serum cotinine	**pseudo-R^2
GENERAL COGNITION							
MMSE <24							
n/total	55/960	24/389	29/369	35/359		143/2077	
Model 1, OR† (95%CI)	1.00	1.11 (0.66-1.83)	1.46 (0.91-2.36)	**1.70 (1.08-2.67)**	**0.033**	**1.12 (1.01-1.25)**	0.085
Model 2, OR† (95%CI)	1.00	1.10 (0.66-1.82)	1.43 (0.88-2.32)	**1.62 (1.03-2.57)**	**0.050**	**1.11 (1.00-1.24)**	0.094
Model 3, OR† (95%CI)	1.00	1.12 (0.67-1.87)	1.51 (0.93-2.45)	1.64 (1.04-2.60)	0.060	**1.11 (1.00-1.24)**	0.100
WORKING MEMORY							
DSBT (7-1)							
n	959	390	369	357		2075	
Model 1, OR†† (95%CI)	1.00	0.95 (0.77-1.19)	**1.37 (1.10-1.70)**	**1.29 (1.03-1.60)**	**0.039**	**1.08 (1.03-1.14)**	0.100
Model 2, OR†† (95%CI)	1.00	0.95 (0.76-1.18)	**1.33 (1.07-1.66)**	**1.23 (1.00-1.54)**	0.088	**1.07 (1.02-1.13)**	0.114
Model 3, OR†† (95%CI)	1.00	0.95 (0.77-1.19)	**1.35 (1.08-1.68)**	**1.25 (1.00-1.57)**	0.073	**1.08 (1.02-1.14)**	0.214
MOTOR PROGRAMMING							
"Luria" test (3-0)							
n	960	390	369	357		2076	
Model 1, OR†† (95%CI)	1.00	0.86 (0.64-1.17)	0.84 (0.62-1.15)	1.28 (0.97-1.70)	**0.029**	1.06 (0.99-1.14)	0.005
Model 2, OR†† (95%CI)	1.00	0.86 (0.63-1.15)	0.82 (0.60-1.13)	1.24 (0.93-1.65)	**0.047**	1.05 (0.98-1.12)	0.006
Model 3, OR†† (95%CI)	1.00	0.85 (0.63-1.16)	0.85 (0.62-1.16)	1.23 (0.92-1.64)	0.061	1.05 (0.98-1.13)	0.010
VISUOPERCEPTUAL ABILITIES							
TMT-A >78							
n/total	137/952	55/386	51/364	55/351		298/2053	
Model 1, OR† (95%CI)	1.00	1.01 (0.71-1.43)	0.98 (0.69-1.41)	1.05 (0.74-1.49)	0.778	1.02 (0.94-1.10)	0.079
Model 2, OR† (95%CI)	1.00	1.01 (0.71-1.43)	0.96 (0.67-1.38)	0.99 (0.69-1.41)	0.969	1.00 (0.92-1.09)	0.085
Model 3, OR† (95%CI)	1.00	1.00 (0.70-1.44)	1.00 (0.70-1.45)	0.97 (0.68-1.40)	0.856	1.00 (0.92-1.09)	0.094
EPISODIC MEMORY							
FCSRT <12							
n	75/964	25/394	37/369	36/360		173/2086	
Model 1, OR† (95%CI)	1.00	0.81 (0.51-1.30)	1.31 (0.86-1.98)	1.34 (0.88-2.04)	0.139	1.09 (0.99-1.20)	0.014
Model 2, OR† (95%CI)	1.00	0.82 (0.51-1.32)	1.32 (0.87-2.00)	1.36 (0.89-2.08)	0.130	**1.10 (1.00-1.21)**	0.021
Model 3, OR† (95%CI)	1.00	0.81 (0.50-1.30)	1.32 (0.87-2.02)	1.38 (0.90-2.11)	0.117	**1.10 (1.00-1.21)**	0.027
SEMANTIC MEMORY							
CFT <10							
n	101/960	40/392	40/368	40/357		221/2077	
Model 1, OR† (95%CI)	1.00	1.00 (0.67-1.48)	1.08 (0.73-1.61)	1.01 (0.68-1.50)	0.997	1.01 (0.92-1.11)	0.081
Model 2, OR† (95%CI)	1.00	1.00 (0.67-1.49)	1.09 (0.73-1.63)	1.00 (0.67-1.50)	0.960	1.01 (0.92-1.11)	0.091
Model 3, OR† (95%CI)	1.00	1.00 (0.67-1.48)	1.09 (0.73-1.63)	1.00 (0.67-1.50)	0.960	1.01 (0.92-1.11)	0.095

OR: Odds Ratios; 95%CI: 95% confidence interval; MMSE: Mini Mental Examination; DSBT: Digital Span Backward Test; FCSRT: Free and Cued selective reminding test; CFT: Categorical Fluency Test

Model 1 adjusted for sex, age and education level. Model 2 further adjusted for body mass index (kg/m^2), recreational physical activity (METS-h/week) and past tobacco smoke (former, never).

Model 3 further adjusted for chronic morbidities (hypertension, cardiovascular disease, diabetes, cancer and depression).

*p values for trend across cotinine categories were obtained by including the medians corresponding to each category of the cotinine distribution (0.035, 0.060, 0.114, 0.845 ng/ml) as continuous variables in the regression models. †OR obtained from logistic regression models †† OR obtained from ordered logistic regression models.** McFadden´s R2

Table 3. Prospective association between baseline serum cotinine concentrations (ng/ml), and changes in measures of cognitive function among non-smokers. Results are from logistic and ordered logistic repeated-measures mixed-effects models and expressed as Odds Ratios (OR) and their 95% confidence intervals (95%CI).

	Serum cotinine						
	Unexposed	Exposed, cotinine tertiles (ng/ml)					
	Ref. (<0.05)	T1 (0.050-0.082)	T2 (0.083-0.160)	T3 (≥0.161)	*p-trend	Per doubling increase in serum cotinine	**pseudo-R^2
GENERAL COGNITION							
MMSE <24							
n/total	18/547	14/233	11/205	**17/194**		60/1179	
Model 1, OR† (95%CI)	1.00	1.33 (0.68-2.62)	1.50 (0.73-3.06)	**2.43 (1.26-4.71)**	**0.013**	**1.19 (1.01-1.32)**	0.064
Model 2, OR† (95%CI)	1.00	1.34 (0.69-2.67)	1.47 (0.72-3.03)	**2.21 (1.14-4.27)**	**0.029**	1.16 (0.99-1.37)	0.073
Model 3, OR† (95%CI)	1.00	1.33 (0.67-2.64	1.42 (0.68-2.98)	**2.23 (1.14-4.33)**	**0.028**	1.15 (0.98-1.36)	0.189
WORKING MEMORY							
DSBT (7-1)	574	245	218	209		1246	
n							
Model 1, OR†† (95%CI)	1.00	1.01 (0.83-1.22)	**1.22 (1.00-1.49)**	**1.26 (1.04-1.53)**	**0.026**	**1.05 (1.00-1.10)**	0.013
Model 2, OR†† (95%CI)	1.00	1.01 (0.83-1.23)	**1.22 (1.00-1.48)**	**1.23 (1.01-1.50)**	**0.050**	1.05 (0.99-1.10)	0.016
Model 3, OR†† (95%CI)	1.00	0.99 (0.81-1.21)	1.20 (0.99-1.47)	**1.23 (1.01-1.51)**	**0.046**	1.04 (0.99-1.10)	0.026
MOTOR PROGRAMMING							
"Luria" test (3-0)	574	245	218	209		1246	
n							
Model 1, OR†† (95%CI)	1.00	1.03 (0.80-1.31)	0.96 (0.73-1.24)	1.04 (0.81-1.34)	0.737	1.02 (0.96-1.08)	0.021
Model 2, OR†† (95%CI)	1.00	1.02 (0.80-1.32)	0.96 (0.74-1.25)	1.05 (0.82-1.36)	0.680	1.02 (0.96-1.08)	0.024
Model 3, OR†† (95%CI)	1.00	1.03 (0.80-1.32)	0.96 (0.73-1.24)	1.06 (0.82-1.37)	0.618	1.03 (0.97-1.09)	0.037
VISUOPERCEPTUAL ABILITIES							
TMT-A >78							
n/total	147/495	58/205	59/191	50/181		314/1072	
Model 1, OR† (95%CI)	1.00	1.05 (0.72-1.52)	1.01 (0.68-1.49)	1.22 (0.81-1.82)	0.344	1.03 (0.94-1.13)	0.113
Model 2, OR† (95%CI)	1.00	1.04 (0.71-1.51)	1.03 (0.69-1.52)	1.24 (0.83-1.87)	0.291	1.03 (0.94-1.14)	0.115
Model 3, OR† (95%CI)	1.00	1.05 (0.71-1.54)	1.02 (0.69-1.52)	1.23 (0.82-1.86)	0.320	1.03 (0.94-1.14)	0.137
EPISODIC MEMORY							
FCSRT <12							
n/total	38/531	15/232	15/198	12/190		**80/1151**	
Model 1, OR† (95%CI)	1.00	0.85 (0.50-1.47)	1.26 (0.74-2.13)	1.12 (0.66-1.89)	0.645	1.03 (0.90-1.17)	0.011
Model 2, OR† (95%CI)	1.00	0.89 (0.52-1.54)	1.32 (0.77-2.25)	1.10 (0.64-1.90)	0.747	1.03 (0.90-1.16)	0.026
Model 3, OR† (95%CI)	1.00	0.85 (0.48-1.49)	1.22 (0.70-2.13)	1.09 (0.63-1.89)	0.729	1.02 (0.89-1.16)	0.043
SEMANTIC MEMORY							
CFT <10							
n/total	131/533	51/230	62/199	44/191		288/1153	
Model 1, OR† (95%CI)	1.00	0.87 (0.62-1.24)	**1.41 (1.01-1.97)**	1.04 (0.72-1.51)	0.906	1.05 (0.96-1.15)	0.113
Model 2, OR† (95%CI)	1.00	0.90 (0.63-1.27)	**1.41 (1.00-1.96)**	0.99 (0.68-1.44)	0.853	1.04 (0.95-1.14)	0.123

Model 3, OR† (95%CI)	1.00	0.87 (0.61-1.24)	**1.40 (1.00-1.97)**	1.01 (0.69-1.46)	0.945	1.04 (0.95-1.14)	0.134

OR: Odds Ratios; 95%CI: 95% confidence interval; MMSE: Mini Mental Examination; DSBT: Digital Span Backward Test; FCSRT: Free and Cued selective reminding test; CFT: Categorical Fluency Test

Model 1 adjusted for sex, age, civil status and education level. Model 2 further adjusted for body mass index (kg/m^2), recreational physical activity (METS-h/week) and past tobacco smoke (former, never). Model 3 further adjusted for chronic morbidities (hypertension, cardiovascular disease, diabetes, cancer and depression).

*p values for trend across cotinine categories were obtained by including the medians corresponding to each category of the cotinine distribution (0.035, 0.060, 0.114, 0.845 ng/ml) as continuous variables in the regression models. †OR obtained from logistic random-intercept models †† OR obtained from -multilevel mixed-effects ordered logistic regression.** McFadden´s R2