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Secondhand tobacco smoke and functional impairments in older adults living in the community

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Implications section

This manuscript offers a comprehensive examination of secondhand smoke exposure and a broad range of functional limitations in older adults. Results show that:

1- Never smokers who had been exposed to higher cumulative doses of SHS in adulthood show worse physical function
2- Exposure to SHS during old age, as measured with cotinine concentrations, is associated with accelerated short-term functional declines
3- The effects of SHS are stronger among older adults with previous diagnosed chronic morbidities
4- Results suggest that more efforts are needed to protect older adults from passive smoking, especially to those with chronic conditions because of their potential greater vulnerability to the effects of SHS.

Abstract

Background/aim: Secondhand tobacco smoke (SHS) is a risk factor of coronary heart disease, lung cancer and stroke. Recent evidence suggests that SHS may increase the risk of functional limitations. However, no comprehensive examination has been made of the potential association of both serum cotinine (as objective measure of SHS exposure) and self-reported SHS with broad functional limitations assessment in older adults, where functional limitations are burdensome and challenging.

Methods: We examined 2258 community dwelling non-smoking older adults aged ≥65 years from the Seniors-Enrica-2 cohort (Spain). At baseline (2017) and follow-up (2019) grip strength was measured with Jamar dynamometer, lower-extremity performance evaluated with the Short Physical Performance Battery (SPPB), overall physical function using the Spanish version of the physical component summary (PCS) of the 12-Item Short-Form Health questionnaire, frailty with a Deficits Accumulation Index (DAI), and mobility limitations with the Rosow and Breslau scale. Baseline exposure to SHS was assessed by serum cotinine concentrations, while past exposure was self-reported. Cross-sectional analyses were performed using linear and logistic regression models, while analyses on changes in grip strength, SPPB, PCS and DAI used repeated measures models with robust standard error estimates to account for within-participant correlations induced by repeated measures.

Results: Participant's median (interquartile range) concentration of serum cotinine was 0.079 (0.035-0.175) ng/ml, with <1% of participants showing concentrations ≥3 ng/ml. After adjustment for potential confounders, and compared to the unexposed, those in the highest exposure group (≥0.239 ng/ml) showed lower mean difference in grip strength values (MD: -1.05 kg; 95%CI: -1.80, -0.31) and higher DAI scores (MD: 1.52; 95%CI:

0.38, 2.66). In models of self-reported past exposure, never smokers who had lived with ≥2 smokers or had been exposed to higher cumulative doses of SHS showed lower baseline SPPB values, higher DAI scores and higher prevalence of mobility limitations. In prospective analyses, those in the highest quartile of baseline cotinine, showed deleterious changes in the SPPB [-0.24 (-0.46, -0.02)] and DAI [1.28 (0.00, 2.55)], and higher risk of mobility limitations [HR:1.64; 95%CI: 1.01, 2.68].

Conclusions. Findings show consistent, prospective association of serum cotinine and lifetime self-reported passive smoking with higher accumulation of health deficits and mobility limitations, and lower physical performance, in older adults living in the community. Results suggest that exposure to SHS during old age may accelerate functional decline, especially in those with chronic morbidities, where stronger associations were observed.

Background

Exposure to secondhand tobacco smoke (SHS) is a serious public health concern. In non-smoking adults, passive smoking is a known risk factor for lung cancer, heart disease and stroke (1), with suggestive evidence that it may also cause asthma, chronic obstructive pulmonary disease, atherosclerosis, and cancers of the paranasal sinus, pharynx, larynx and breast (1). According to worldwide estimates of the Tobacco Atlas, approximately 33% of non-smoking women and 20% of non-smoking men are currently exposed to SHS, with an estimated attributable 1 million deaths in 2020.

In line with what is observed for active smoking (2–7), four cross-sectional studies, all based on the US National Health and Nutrition Examination Study (8–10), have suggested that passive smoking may increase the risk of functional limitations, particularly among older adults. Specifically, these studies have shown average reductions in gait speed of 0.02 m/s (8) and 0.34 kg reduction in grip strength (9) per one unit increase in log-transformed blood cotinine levels; as well as a higher prevalence of frailty with increased serum cotinine concentrations in non-smoking older adults (10). Consistently, the only published longitudinal analysis that has addressed the link between SHS and physical function, based on data from the English Longitudinal Study of Ageing, recently showed a positive association between baseline salivary cotinine concentrations in older adults and a lower baseline and follow-up performance on tests of gait speed and grip strength, as well as a lower probability to complete a balance´s chair test (11).

The aim of the present study is to provide further, comprehensive insight into the currently limited epidemiological data on passive smoking and functional impairments, by evaluating both the cross-sectional and longitudinal associations between objectively

quantified exposure to SHS assessed by serum cotinine concentrations and lifetime self-reported exposure to SHS, and a wide array of validated measures of physical performance in a general population of non-smoking older adults, where functional limitations are burdensome and challenging.

Methods

Study design and participants

The Seniors-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 and older, holding a national healthcare card and living in the city of Madrid (Spain) or four surrounding large towns (12).

At baseline (2017), 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 examination. From the initial sample of 3,273 participants, 86.5% (n=2831), 85.4% (n=2795), and 79.7% (n=2610), agreed to the physical exam, completed the diet history and provided blood samples, respectively. At follow-up (2019), data collection was done using the same protocols as at baseline.

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.

Study Variables

Exposure assessment.

At baseline, exposure to SHS was assessed by serum cotinine and self-reported data:

1- Serum cotinine was measured by high performance liquid chromatography and tandem mass spectrometry detection at Hospital del Mar Medical Research
2- 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 were excluded from the analyses,. Non active smokers who self-reported being exposed to SHS at home or leisure time, as well as those with cotinine concentrations between 0.05 and 9.9 ng/ml regardless of self-reporting not being exposed were classified as exposed (n=1806), while non active smokers who self-reported not being exposed to SHS and with cotinine levels below 0.05 ng/ml were classified as unexposed.
3- Past exposure to SHS was estimated as the self-reported number of smokers at home, as well as the number of pack-years of exposure at home or work.

Outcome assessment.

At baseline and follow-up, grip strength was measured as the highest of two consecutive measures with a Jamar dynamometer, while lower-extremity performance was assessed with the Short Physical Performance Battery (SPPB), which combines balance testing, walking speed and a *sit-to-stand* test (13). 1) Balance testing included a side-by-side, a semitandem and a tandem stand. Participants were first asked to stand with their feet together, and if were able to stand for 10 seconds in this position were tested in the semitandem stand position (i.e. with the heel of one foot placed to the side of the big toe

of the other foot). Those who were able to stand for 10 seconds in the semitandem were then tested in the full-tandem stand (i.e. with the heel of one foot placed in front of the toes of the other foot). A score of 0 in the balancing test indicates the inability to stand in any of the positions, while a score of 4 indicates a full-tandem stand for 10 seconds. 2) Gait speed was calculated as the walking distance (3 m) divided by the time to complete the test in seconds. In this test, 0 points indicated the inability to perform the walk, and 4 being in the fastest quartile of walking speed according to sex and height. 3) Finally, the sit-to stand test consisted in standing up and sitting down from a chair five times repeatedly, with arms crossed across the chest. A score of 0 was given if a participant was unable to perform the five chair stands, while scores of 1, 2, 3, or 4 were assigned to participants who completed five chair stands in ≥16.7, 13.7-16.6, 11.2-13.6, and ≤11.1 seconds, respectively. The total SPPB score was calculated by the sum of the components, with a range from 0 to 12 (best performance).

Overall physical function was evaluated using the Spanish version of the physical component summary (PCS) of the 12-Item Short-Form Health questionnaire. The PCS assesses general health, physical functioning, role functioning difficulties caused by physical problems, and bodily pain, and uses Likert scales to analyze the intensity or frequency of each response (14). PCS scores were standardized to the national norm with a mean of 50.0 and a standard deviation of 10.0. A zero score in PCS indicates the lowest level of health, and a score of 100 indicates the highest level.

Frailty was defined according to a Rockwood's Deficit Accumulation Index (DAI) (15,16), calculated using a total of 52 health deficits, including impairments in physical and cognitive functioning, self-reported health and vitality problems, mental health conditions, as well as morbidity, polypharmacy, and health services use. The DAI summarizes age-related vulnerability, so the more health deficits (symptoms, signs,

diseases, or disabilities) an individual has, the higher the risk of death, institutionalization, health service use, or further deficit accumulation.

Finally, mobility limitations were evaluated at baseline and follow-up with three questions from the Rosow and Breslau scale (17): “How much difficulty do you experience…”1) “…picking up or carrying a shopping bag?”, 2) “…climbing one flight of stairs?”, 3) “…walking a few hundred meters?”. Individuals who answered “some difficulty", "much difficulty", or "unable to do" to any of these three questions were considered as having mobility limitations.

Other variables

At baseline and follow-up, information was collected on sociodemographic characteristics including sex, age, civil status (single, married, divorced or widowed), and social class of the main earner at home based on the last profession performed and coded according to the National Classification of Occupations in Spain (RD 1591/2010). Information on recreational physical activity was collected using the EPIC-cohort questionnaire validated in Spain (18). 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 a causal blood pressure reading ≥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) (19), a self-report of clinically diagnosed depression, or being on anti-depressant medication.

Statistical analyses

As shown in **Supplementary Figure 1**, 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), and those who did not provide a blood sample (n=626), did not perform a physical examination (n=2) or had missing values in important confounders (n=40). In prospective analyses we further excluded 688 individuals who were lost to follow-up, 27 who died, 5 who did not perform a physical examination, and 32 with missing information in potential confounders.

We first evaluated the association between baseline serum cotinine concentrations and the prevalence of functional limitations using either linear or logistic 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 quartiles of serum cotinine distribution. Additionally, because cotinine concentrations were highly skewed, we run regression models on log-transformed serum cotinine. Similarly, we assessed the association between self-reported past exposure to SHS and prevalence of functional limitations at baseline. In both cases, models were progressively adjusted for age, sex, civil status and social class (Model 1); recreational physical activity, past active tobacco smoke (never, former), and body mass index (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 physical function using linear mixed models with robust standard error estimates to account for within-participant correlations induced by repeated measures. We adjusted these models for both time-varying (i.e. age, civil status, recreational physical activity, body mass index, and comorbidities) and time-constant (i.e. sex, educational level and social class) covariates. Additionally, we evaluated the prospective association between baseline serum cotinine and incidence of mobility limitations using Cox proportional hazard models with age as time scale and individual starting follow-up times treated as staggered entries.

To evaluate the consistency of our findings, we used likelihood-ratio tests to compare models with and without cross-product interaction terms for cotinine concentrations and indicator variables for age, sex, past smoking status, civil status, social class, BMI, hypertension, CVD, diabetes, and cancer.

Results

In total, only 8% of study participants self-reported being exposed to SHS but 53% showed serum cotinine levels above the LOQ. The median (interquartile range) concentrations of serum cotinine was 0.079 (IQR: 0.035-0.175) ng/ml, with less than 1% of participants showing concentrations ≥3 ng/ml.

Divorced and widowed participants showed higher cotinine concentrations, while former smokers, individuals with a BMI < 25 kg/m^2, and non-diabetics were less likely to show cotinine concentrations above the LOQ (please, see **Table 1**). Age and sex-adjusted mean (standard error [SE]) grip strength, SPPB, PCS, and DAI scores among those below and

above the LOQ were, respectively, 27.8 (0.13) and 26.8 (0.42) kg; 9.9 (0.04) and 9.4 (0.12) points; 46.4 (0.61) and 45.7 (0.33) points; and 14.9 (0.20) and 18.7 (0.67) deficits. The age and ex-adjusted prevalence (SE) of mobility limitations in the abovementioned groups were, respectively, 25.4 (0.02) and 27.7 (0.01).

In fully-adjusted models of serum cotinine and baseline functional impairments (**Table 2**), and compared to the unexposed, participants in the highest quartile of cotinine (≥ 0.239 ng/ml) showed lower mean grip strength values (mean difference [MD]:-1.05 kg; 95% confidence interval [CI]: -1.80, -0.31) and higher DAI scores (MD: 1.52; 95%CI: 0.38, 2.66), some trend towards lower SPPB (MD: -0.19; 95%CI: -0.40, 0.01) and PCS scores (MD:-0.77; 95%CI: -2.09, 0.55), and a non-significant increased odds of mobility limitations (odds ratio [OR]: 1.26; 95%CI: 0.90, 1.76).

In models of self-reported past exposure, never smokers who had lived with ≥2 smokers showed higher DAI values than those who had lived with no smokers. Also, in analyses limited to never smokers who self-reported their past intensity of exposure at home and work (n=509), a 20 pack-year increase in SHS exposure was associated with a -0.19 (95%CI: -0.32, -0.06) points reduction in baseline SPPB scores, a 0.64 (95%CI: 0.00, 1.29) points increase in the DAI, and a higher prevalence of baseline mobility limitations (OR: 1.30; 95%CI: 1.08, 1.57) (**Table 3**).

During a mean follow-up of 2.6 years (standard deviation: 0.52), grip strength, SPPB and PCS scores decreased, on average, -2.07 kgs, 0.04 and -0.81 points, respectively. During this same period, participants gained, on average, 2.90 health deficits, and 139 participants developed mobility limitations. Compared to the unexposed, those in the highest quartile of baseline cotinine showed significant deleterious changes in the SPPB [-0.24 (-0.46, -0.02)] and DAI [1.28 (0.00, 2.55)], no significant changes in the PCS [-

0.88 (-2.15, 0.40)], a higher risk of mobility limitations [HR:1.64; 95%CI: 1.01, 2.68], and a tendency towards lower grip strength [-0.86 (-1.79, 0.06)] (**Table 4**).

In sensitivity analyses, the effects of passive smoking over grip strength, the SPPB and DAI tended to be stronger among participants with hypertension, diabetes or CVD **(Supplementary Figure 2)**, and were mostly consistent in strata defined by age, sex, social class, civil status smoking status and BMI.

Discussion

In this study of community-dwelling older adults, exposure to SHS, measured by serum cotinine and lifetime self-reported exposure, was modestly inversely related to several measures of physical capacity. Most associations were independent of sex, age, past smoking status, civil status or social class and remained consistent after 2.6 years of follow-up The effects tended to be stronger among participants with chronic morbidities, particularly hypertension, CVD or diabetes, which may reflect the increased risk of functional decline in individuals with previous chronic disease (20).

There is in vitro evidence that cigarette smoke induces skeletal muscle damage through atrophy of oxidative muscle fibers, impaired synthesis of muscle proteins, and over-expression of atrophy related genes (21–23). Studies in mice have also observed increased muscular oxidative stress and systemic inflammation after exposure to cigarette smoke (24,25). In humans, a study comparing skeletal muscle properties and fatigue resistance of 45 non-smokers and 40 smokers showed that smokers suffered from greater peripheral muscle fatigue than non-smokers (26); while a longitudinal study with 963 men and women aged >30 years from the *Mini-Finland health examination survey*, followed for up to 22 years found that persistent tobacco use during follow-up was associated with accelerated grip strength declines (7). In the same line, a meta-analysis of 12 cross-

sectional and case-control studies with a total of 22,515 participants showed a positive association between self-reported active smoking and sarcopenia (4). Also, in a study based on 26, 692 European older adults in 9 British cohorts, a group of researchers used mendelian randomization to explore the causal nature between smoking and functional measures at older ages, and found lower walk speeds in current than never smokers (3).

Although not directly comparable, the present findings support those of the few previous studies on SHS and physical function. .For example, we here show a consistent although weaker association with grip strength than the described in our previous NHANES report (9), based on 5,390 non-smoking participants aged 30 years and older with median (IQR) serum cotinine concentrations of 0.015 ng/mL (0.011-0.36). Also, results from NHANES had previously shown a dose-response relationship between cotinine concentrations and slow walking speed, a component of the SPPB, in older adults (8). We now present the first evidence for an association between cotinine exposure and lower SPPB scores, which is more clinically relevant than the evidence for gait speed because the SPPB is a better predictor of future hospitalizations and mortality than gait speed alone (27). Unfortunately, due to the very low number of cases, we could not compare our results to those of our previous NHANES study in which we found a link between SHS and frailty as per the Fried criteria in a sample of 2059 non-smoking older adults (10). Still, we could illustrate a dose-response relationship between cotinine and DAI scores, which also summarize age-related physical vulnerability. Additionally, we provide for the first time some evidence for an association between SHS, lower PCS scores, and increased risk of mobility limitations.

Among the limitations of our study is the relatively short follow-up period, which does not preclude reverse causation. However, and although limited by the small sample size, results using self-reported information on lifetime past cumulative exposure in never

smokers, showed consistent findings. Cotinine has the advantage of capturing all forms of exposure to SHS, some of which can be missed by self-report, but a single measurement of this biomarker only reflects exposure over the previous 1-2 days and is an imperfect surrogate of long-term exposure. Another limitation is that, despite we have adjusted for many relevant confounders, we cannot rule out some residual confounding. It is encouraging, though, to see how adjustment for different socio-demographic, lifestyle and health-related variables modified the point estimates minimally. Finally, due to the small proportion of participants heavily exposed to SHS (with concentrations close to 10ng/mL), results may be hard to interpret at higher cotinine concentrations.

Our study also has strengths. First, we used several validated measures of physical function in older adults. Second, physical performance tests were conducted by trained staff under standardized conditions. Third, results were consistent in former and never smokers, as well as in analyses of self-reported information among never smokers, reducing the risk of confounding by long-term smoking in former smokers.

In conclusion, results suggest that exposure to SHS during old age may accelerate functional decline. Further prospective research with repeated cotinine measures should confirm these results in other populations. In the meanwhile, more efforts are needed to protect older adults from passive smoking, especially to those with chronic conditions because of their potential greater vulnerability to the effects of SHS.

Table 1. Distribution of participant´s characteristics by serum cotinine concentrations (n=2258)

		Unexposed	**Exposed**				
		Quartiles of Cotinine, ng/ml					
		Ref. (<0.05)	**Q1 (0.05-0.071)**	**Q2 (0.072-0.11)**	**Q3 (0.112-0.23)**	**Q4 (≥0.239)**	**p-value***
n (%)		1051 (46.6)	305 (13.5)	326 (14.4)	277 (12.3)	299 (13.2)	
Age (years)							0.282
<69		357 (44.6)	115 (14.4)	117 (14.6)	104 (12.9)	108 (13.5)	
70-74		420 (47.5)	131 (14.8)	117 (13.2)	103 (11.7)	113 (12.8)	
≥75		274 (47.8)	59 (10.3)	92 (16.06)	70 (12.2)	78 (13.6)	
Sex							0.701
Male		463 (45.1)	144 (14.0)	157 (15.3)	126 (12.3)	137 (13.3)	
Female		588 (47.8)	161 (13.1)	169 (13.7)	151 (12.3)	162 (13.2)	
Civil status							**<0.001**
Single		73 (50.0)	14 (9.6)	26 (17.8)	20 (13.7)	13 (8.9)	
Married		729 (48.7)	218 (14.6)	205 (13.7)	168 (11.2)	177 (11.8)	
Divorced		53 (35.6)	23 (15.4)	23 (15.4)	26 (17.5)	24 (16.1)	
Widowed		196 (42.1)	50 (10.7)	72 (15.5)	63 (13.5)	85 (18.2)	
Social class							0.299
I		111 (46.4)	40 (16.7)	42 (17.6)	19 (7.95)	27 (11.3)	
II		143 (49.3)	39 (13.5)	43 (14.8)	37 (12.8)	28 (9.7)	
III		259 (47.5)	72 (13.2)	77 (14.1)	61 (11.2)	76 (13.9)	
IV		454 (46.2)	122 (12.4)	135 (13.8)	129 (13.1)	142 (14.5)	
V		84 (41.6)	32 (15.8)	29 (14.4)	31 (15.4)	26 (12.9)	
Tobacco smoke							**0.004**
Never		391 (42.13)	127 (13.7)	145 (15.6)	120 (12.9)	145 (15.6)	
Former		660 (49.6)	178 (13.4)	181 (13.6)	157 (11.8)	154 (11.6)	
Physical activity (tertiles)							0.062
First		406 (47.2)	105 (12.2)	110 (12.8)	111 (12.9)	128 (14.9)	
Second		322 (49.3)	87 (13.3)	92 (14.1)	81 (12.4)	71 (10.9)	
Third		323 (43.4)	113 (15.2)	124 (16.6)	85 (11.4)	100 (13.4)	
Body mass index (kg/m2)							**<0.001**
<25		314 (53.9)	85 (14.6)	83 (14.3)	49 (8.4)	51 (8.8)	
25-30		482 (44.9)	139 (12.9)	172 (16.0)	135 (12.6)	144 (13.4)	
≥30		255 (42.2)	81 (13.4)	71 (11.8)	93 (15.4)	104 (17.2)	
Hypertension							0.089
No		361 (49.1)	101 (13.7)	104 (14.1)	93 (12.6)	77 (10.5)	
Yes		690 (45.3)	204 (13.4)	222 (14.6)	184 (12.1)	222 (14.6)	
Cardiovascular disease							0.954
No		1015 (46.6)	295 (13.5)	312 (14.3)	267 (12.3)	289 (13.3)	
Yes		36 (45.0)	10 (12.5)	14 (17.5)	10 (12.5)	10 (12.5)	
Cancer							0.390
No		1014 (46.3)	300 (13.7)	313 (14.3)	270 (12.3)	291 (13.3)	
Yes		37 (52.9)	5 (7.1)	13 (18.6)	7 (10.0)	8 (11.43)	
Diabetes							**0.003**
No		854 (47.3)	252 (14.0)	264 (14.6)	223 (12.3)	214 (11.8)	
Yes		197 (43.7)	53 (11.8)	62 (13.8)	54 (12.0)	85 (18.9)	
Depression, GDS score							0.934
<5		984 (46.2)	293 (13.8)	311 (14.6)	261 (12.3)	279 (13.11)	
≥5		67 (51.54)	12 (9.23)	15 (11.54)	16 (12.3)	20 (15.4)	

GDS: Geriatric Depression Scale. Q: Quartile

* p-values derived from chi-square tests.

Table 2. Cross-sectional association between serum cotinine concentrations (ng/ml), and measures of physical function among non-smokers

	Serum cotinine						
	Unexposed	**Exposed, cotinine quartiles (ng/ml)**					
	Ref. (<0.05)	**Q1 (0.050-0.071)**	**Q2 (0.072-0.110)**	**Q3 (0.112-0.230)**	**Q4 (≥0.239)**	**[a]p-trend**	**Per log-2 transformed serum cotinine**
Grip strength (kg)							
n	1048	300	326	277	299		2250
Model 1, MD (95%CI)	1.00	-0.01 (-0.75, 0.73)	0.06 (-0.66, 0.78)	0.19 (-0.58, 0.96)	**-1.02 (-1.77, -0.28)**	0.006	**-0.17 (-0.33, -0.01)**
Model 2, MD (95%CI)	1.00	-0.08 (-0.83, 0.65)	-0.07 (-0.78, 0.65)	0.18 (-0.59, 0.93)	**-1.06 (-1.81, -0.31)**	0.005	**-0.18 (-0.34, -0.02)**
Model 3, MD (95%CI)	1.00	-0.15 (-0.89, 0.59)	-0.05 (-0.61, 0.91)	0.15 (-0.61, 0.91)	**-1.05 (-1.80 -0.31)**	0.005	**-0.17 (-0.33, -0.01)**
SPPB							
n	1040	300	326	277	297		2240
Model 1, MD (95%CI)	1.00	**0.33 (0.12, 0.54)**	0.10 (-0.11, 0.31)	0.12 (-0.10, 0.34)	**-0.28 (-0.50, -0.07)**	0.001	**-0.07 (-0.11, -0.02)**
Model 2, MD (95%CI)	1.00	**0.32 (0.12, 0.53)**	0.08 (-0.13, 0.28)	0.20 (-0.01, 0.42)	**-0.20 (-0.42, 0.00)**	0.029	**-0.05 (-0.09, -0.00)**
Model 3, MD (95%CI)	1.00	**0.29 (0.09, 0.49)**	0.07 (-0.12, 0.27)	0.19 (-0.02, 0.40)	-0.19 (-0.40, 0.01)	0.032	**-0.04 (-0.08, 0.00)**
PCS							
n	1031	302	325	275	285		2218
Model 1, MD (95%CI)	1.00	0.67 (-0.70, 2.04)	0.86 (-0.47, 2.19)	-0.51 (-1.94, 0.91)	**-1.45 (-2.85, -0.04)**	0.030	**-0.35 (-0.65, -0.05)**
Model 2, MD (95%CI)	1.00	0.43 (-0.91, 1.77)	0.59 (-0.71, 1.89)	-0.37 (-1.77, 1.02)	-1.34 (-2.82, 0.04)	0.020	**-0.33 (-0.62, -0.03)**
Model 3, MD (95%CI)	1.00	0.33 (-0.94, 1.61)	0.67 (-1.34, 1.91)	-0.01 (-1.34, 1.32)	-0.77 (-2.09, 0.55)	0.130	-0.21 (-0.50, 0.08)
DAI							
n	1051	305	326	277	299		2258
Model 1, MD (95%CI)	1.00	-1.10 (-2.28, 0.06)	-0.69 (-1.83, 0.45)	0.08 (-1.13, 1.30)	**1.67 (0.48, 2.85)**	0.001	**0.43 (0.18, 0.68)**
Model 2, MD (95%CI)	1.00	-0.82 (-1.95, 0.31)	-0.36 (1.46, 0.74)	-0.06 (-1.23, 1.10)	**1.52 (0.38, 2.66)**	0.003	**0.39 (0.15, 0.64)**
Mobility limitations							
nº cases/total	292/1040	73/303	75/326	79/276	100/287		619/2232
Model 1, OR (95%CI)	1.00	0.88 (0.63, 1.20)	0.78 (0.57, 1.05)	1.01 (0.74, 1.38)	**1.41 (1.04, 1.90)**	0.009	**1.08 (1.01, 1.15)**
Model 2, OR (95%CI)	1.00	0.90 (0.65, 1.25)	0.83 (0.60, 1.15)	0.87 (0.62, 1.21)	1.26 (0.91, 1.74)	0.183	1.05 (0.98, 1.13)
Model 3, OR (95%CI)	1.00	0.92 (0.66, 1.30)	0.82 (0.58, 1.15)	0.89 (0.63, 1.26)	1.26 (0.90, 1.76)	0.169	1.05 (0.97, 1.13)

MD: Mean difference; OR: Odds Ratios; 95%CI: 95% confidence interval; SPPB: Short Physical Performance Battery; PCS: physical component summary of the 12-Item Short-Form Health questionnaire; DAI: Deficit Accumulation Index

Model 1 adjusted for sex, age, civil status and social class. Model 2 further adjusted for body mass index (kg/m^2), recreational physical activity (METS-h/week) and tobacco smoke (former, never). Model 3 further adjusted for chronic morbidities (hypertension, cardiovascular disease, diabetes, cancer and depression). Models for DAI were not adjusted for BMI or chronic morbidities because these conditions are included in the outcome definition.

[a]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, 0.088, 0.150 and 0.550 ng/ml) as continuous variables in the regression models.

Table 3. Association of self-reported past number of smokers at home and cumulative exposure to tobacco with measures of physical function among never-smokers who self-report having been exposed to secondhand tobacco smoke in the past.

	Past nº of smokers at home 0	1	≥2	Cumulative exposure Per 20 pack-years
Grip strength (kg)				
n	624	530	160	507
Model 1, MD (95%CI)	Ref.	-0.03 (-0.79, 0.65)	-0.86 (-1.85, 0.13)	-0.15 (-0.55, 0.25)
Model 2, MD (95%CI)	Ref.	0.03 (-0.64, 0.70)	-0.81 (-1.79, 0.17)	-0.10 (-0.50, 0.31)
Model 3, MD (95%CI)	Ref.	-0.01 (-0.65, 0.68)	-0.79 (-1.77, 0.19)	-0.09 (-0.50, 0.31)
SPPB				
n	619	529	**159**	505
Model 1, MD (95%CI)	Ref.	-0.09 (-0.31, 0.12)	**-0.30 (-0.62, -0.00)**	**-0.24 (-0.39, -0.10)**
Model 2, MD (95%CI)	Ref.	-0.04 (-0.24, 0.16)	-0.28 (-0.58, 0.02)	**-0.19 (-0.33, -0.06)**
Model 3, MD (95%CI)	Ref.	-0.05 (-2.45, 0.15)	-0.26 (-0.55, 0.03)	**-0.19 (-0.32, -0.06)**
PCS				
n	613	519	157	499
Model 1, MD (95%CI)	Ref.	-0.02 (-1.37, 1.33)	**-2.07 (-4.05, -0.09)**	-0.57 (-1.49, 0.35)
Model 2, MD (95%CI)	Ref.	0.33 (-0.96, 1.62)	**-1.82 (-3.71, 0.00)**	-0.23 (-1.10, 0.64)
Model 3, MD (95%CI)	Ref.	0.27 (-0.99, 1.54)	-1.75 (-3.60, 0.11)	-0.21 (-1.07, 0.66)
DAI				
n	627	533	160	509
Model 1, MD (95%CI)	Ref.	0.44 (-0.72, 1.61)	**1.79 (0.08, 3.51)**	**1.06 (0.33, 1.80)**
Model 2, MD (95%CI)	Ref.	0.01 (-1.05, 1.03)	**1.49 (0.00, 3.02)**	**0.64 (0.00, 1.29)**
Mobility limitations				
nº cases/total	176/619	186/522	71/159	189/499
Model 1, OR (95%CI)	Ref.	0.95 (0.72, 1.25)	1.30 (0.88, 1.91)	**1.34 (1.12, 1.60)**
Model 2, OR (95%CI)	Ref.	0.81 (0.60, 1.09)	1.22 (0.81, 1.85)	**1.27 (1.06, 1.54)**
Model 3, OR (95%CI)	Ref.	0.81 (0.59, 1.10)	1.20 (0.78, 1.84)	**1.30 (1.08, 1.57)**

MD: Mean difference; OR: Odds Ratios; 95%CI: 95% confidence interval; SPPB: Short Physical Performance Battery; PCS: physical component summary of the 12-Item Short-Form Health questionnaire; DAI: Deficit Accumulation Index

Model 1 adjusted for sex, age, civil status and social class. Model 2 further adjusted for BMI, and physical activity. Model 3 further adjusted for number of chronic morbidities (hypertension, cardiovascular disease, diabetes, cancer and depression). Models for DAI were not adjusted for BMI or chronic morbidities because these conditions are included in the DAI definition.

Table 4. Prospective association between baseline serum cotinine concentrations (ng/ml), changes in measures of physical function during follow-up, and risk of mobility limitations among non-smokers

	Serum cotinine						
	Unexposed	**Exposed, cotinine quartiles (ng/ml)**					
	Ref. (≤0.05)	**Q1 (0.050-0.071)**	**Q2 (0.072-0.110)**	**Q3 (0.112-0.230)**	**Q4 (≥0.239)**	**p-trend[a]**	**Per log-2 transformed serum cotinine**
n (%)	693 (46.0)	219 (14.5)	216 (14.3)	188 (12.5)	190 (12.6)		1506
Grip strength (kg)							
n	605	191	192	160	165		1313
Model 1, MC (95%CI)	Ref.	0.55 (-0.41, 1.52)	0.06 (-0.81, 0.92)	0.19 (-0.70, 1.09)	-0.83 (-1.75, 0.10)	**0.036**	-0.16 (-0.37, 0.06)
Model 2, MC (95%CI)	Ref.	0.46 (-0.52, 1.43)	-0.05 (-0.92, 0.82)	0.16 (-0.73, 1.05)	-0.82 (-1.75, 0.10)	**0.044**	-0.16 (-0.37. 0.05)
Model 3, MC (95%CI)	Ref.	0.49 (-0.48, 1.45)	-0.01 (-0.88, 0.85)	0.15 (-0.75, 1.04)	-0.86 (-1.79, 0.06)	**0.034**	-0.16 (-0.38, 0.05)
SPPB							
n	601	191	192	159	164		1307
Model 1, MC (95%CI)	Ref.	0.09 (-0.12, 0.29)	0.05 (-0.16, 0.25)	0.03 (-0.18, 0.24)	**-0.34 (-0.58, -0.10)**	**0.002**	**-0.07 (-0.12, -0.02)**
Model 2, MC (95%CI)	Ref.	0.09 (-0.11, 0.29)	0.05 (-0.15, 0.25)	0.08 (-0.11, 0.28)	**-0.26 (-0.49, -0.03)**	**0.014**	**-0.05 (-0.10. -0.01)**
Model 3, MC (95%CI)	Ref.	0.08 (-0.10, 0.27)	0.05 (-0.14, 0.25)	0.10 (-0.09, 0.28)	**-0.24 (-0.46, -0.02)**	**0.013**	**-0.05 (-0.09, -0.00)**
PCS							
n	684	217	216	187	184		1488
Model 1, MC (95%CI)	Ref.	0.77 (-0.62, 2.15)	0.82 (-0.57, 2.21)	-0.03 (-1.57, 1.52)	**-1.49 (-2.94, -0.04)**	**0.014**	-0.30 (-0.63, 0.02)
Model 2, MC (95%CI)	Ref.	0.46 (-0.87, 1.80)	0.58 (-0.80, 1.95)	0.01 (-1.51, 1.56)	-1.25 (-2.64, 0.13)	0.104	-0.25 (-0.56, 0.06)
Model 3, MC (95%CI)	Ref.	0.71 (-0.56, 1.98)	0.88 (-0.42, 2.18)	0.29 (-1.09, 1.67)	-0.88 (-2.15, 0.40)	0.063	-0.14 (-0.43, 0.14)
DAI							
n	693	219	216	188	190		1506
Model 1, MC (95%CI)	Ref.	-0.72 (-1.88, 0.45)	-0.69 (-1.88, 0.49)	-0.24 (-1.55, 1.08)	**1.56 (0.20, 2.91)**	**0.007**	**0.35 (0.04, 0.65)**
Model 2, MC (95%CI)	Ref.	-0.39 (-1.51, 0.72)	-0.45 (-1.61, 0.72)	-0.30 (-1.59, 0.99)	**1.28 (0.00, 2.55)**	**0.220**	**0.28 (0.00, 0.57)**
Mobility limitations							
nº cases/total	59/462	14/170	24/166	18/142	24/128		139/1127
Model 1, HR (95%CI)	Ref.	0.77 (0.43, 1.38)	1.24 (0.72, 2.08)	1.22 (0.72, 2.08)	**1.74 (1.08, 2.81)**	**0.016**	**1.12 (1.01, 1.24)**
Model 2, HR (95%CI)	Ref.	0.79 (0.44, 1.42)	1.19 (0.74, 1.93)	1.06 (0.61, 1.82)	1.60 (0.99, 2.60)	**0.042**	1.10 (0.99, 1.22)
Model 3, HR (95%CI)	Ref.	0.82 (0.45, 1.47)	1.21 (0.75, 1.96)	1.07 (0.62, 1.84)	**1.64 (1.01, 2.68)**	**0.036**	1.10 (0.99, 1.23)

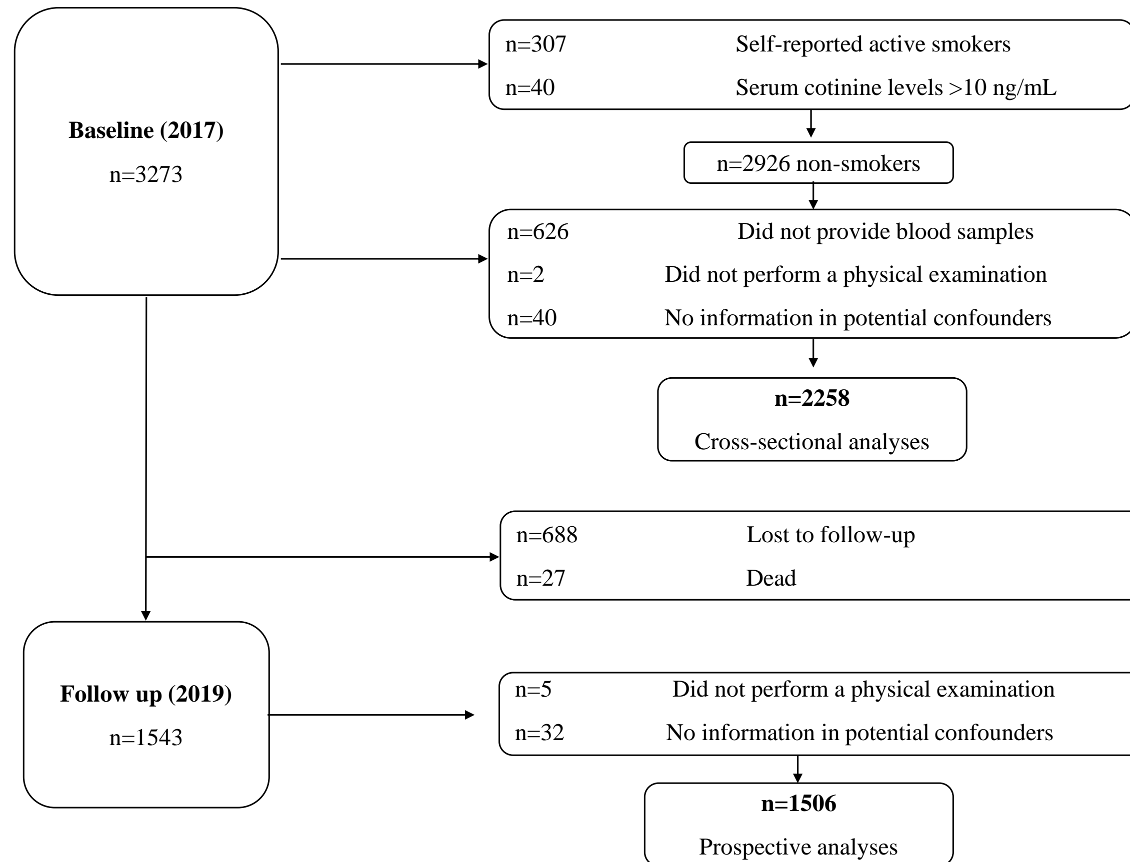
MC: Mean changes; HR: Hazard Ratios; 95%CI: 95% confidence interval; SPPB: Short Physical Performance Battery; PCS: physical component summary of the 12-Item Short-Form Health questionnaire; DAI: Deficit Accumulation Index

Model 1 adjusted for sex, age, civil status and social class. Model 2 further adjusted for changes in tobacco smoke, BMI, and physical activity. Model 3 further adjusted for changes in chronic morbidities (hypertension, cardiovascular disease, diabetes, cancer and depression). Models for DAI were not adjusted for BMI or chronic morbidities because these conditions are included in the DAI definition.

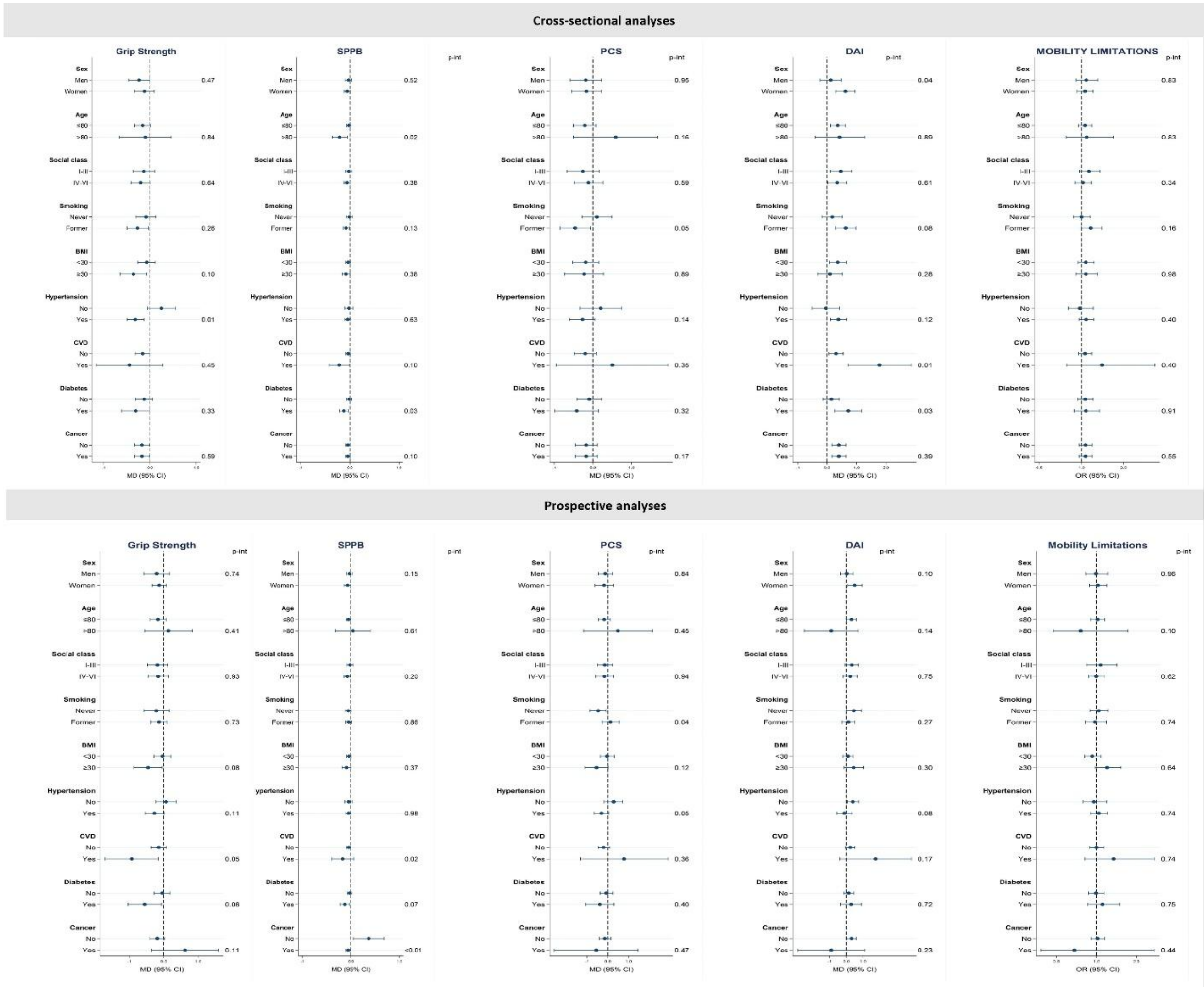
[a]p values for trend across cotinine categories were obtained by including the medians corresponding to each category of the cotinine distribution (0.035, 0.06, 0.088, 0.150 and 0.550 ng/ml) as continuous variables in the regression model

Supplementary material:

Supplementary Figure 1. Flow Chart of the included participants in the analysis



Supplementary Figure 2: Cross-sectional and prospective associations between log-2 transformed serum cotinine concentrations and measures of physical performance in older adults.



SPPB (Short Physical Performance Battery), PCS (physical component summary of the 12-Item Short-Form Health questionnaire) and DAI (Deficit Accumulation Index) scores . Data in cross-sectional analyses are mean differences and their 95% confidence intervals for grip strength, SPPB, PCS and DAI scores; and odds ratios and their 95% confidence intervals for mobility limitations. Data in prospective analyses are mean changes and their 95% confidence intervals for grip strength, SPPB, PCS and DAI scores; and hazard ratios and their 95% confidence intervals for mobility limitations.

Short running title: Secondhand smoke and physical function

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Authors' contributions: 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. OC and 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.

Data availability statement: Data are available upon request to the corresponding author

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