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

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Implications section

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

1- Non-smokers who had been exposed to higher cumulative doses of SHS in adulthood show worse physical function than non-exposed.
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 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: There has been no comprehensive examination of the potential association of SHS with broad functional limitation assessment in older adults, where functional limitations are burdensome and challenging.

Methods: We examined 2258 community dwelling non-smoking older adults from the Seniors-Enrica-2-cohort. At baseline (2017) and follow-up (2019) grip strength was measured with a Jamar dynamometer, lower-extremity performance with the Short Physical Performance Battery (SPPB), overall physical function using the physical component summary (PCS) of the Spanish version of the SF-12, frailty with a Deficits Accumulation Index (DAI), and mobility limitations with the Rosow-Breslau scale. Baseline exposure to SHS was assessed by serum cotinine, and past exposure was self-reported. Cross-sectional analyses were performed using linear and logistic regression models, whereas functional performance changes were examined using repeated measures models with robust standard error estimates.

Results: Overall, the median (IQR) serum cotinine concentration was 0.079(0.035-0.175)ng/ml, with 20 participants presenting concentrations ≥3ng/ml. Compared to the unexposed, fully adjusted models showed that the highest exposure group (≥0.239ng/ml) presented lower grip strength (mean difference:-1.05kg; 95%CI:-1.80,-0.31) and higher DAI scores (1.52; 95%CI:0.38,2.66) at baseline. Similarly, in models of self-reported past exposure, never smokers who had lived with ≥2 smokers or been exposed to higher SHS cumulative doses 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 presented harmful SPPB [-0.24 (-0.46,-0.02)] and DAI [1.28

(0.00,2.55)] changes, and higher risk of mobility limitations [hazard ratio:1.64; 95%CI:1.01,2.68] than the unexposed.

Conclusions:SHS exposure over the life-course and during old age may accelerate functional decline

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); evidence also suggesting that it may 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 Spain, the parliament passed legislation aiming to control tobacco consumption in public places in 2005 (law 28/2005). This new legislation restricted tobacco smoking in health centers, educational institutions, workplaces, and some recreation venues. Five years later, law 28/2005 was amended by law 42/2010 which mandated a ban on smoking in all indoor public places, workplaces, and open spaces adjacent to education centers, health care centers, and children's playgrounds. Unfortunately, these laws did not contemplate private settings (i.e., cars and homes), and around 15-20% of the adult population is still exposed to SHS (Encuesta Nacional de Salud, 2017).

Similarlty to what is known regarding 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 increases 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 a 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 cross-sectional and longitudinal associations between objectively quantified and lifetime self-reported exposure to SHS, and physical performance among 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 (all people residing in Spain are entitled to free healthcare), and living either in the City of Madrid (Spain) or in one of the four large (>100,000 inhabitants) surrounding municipalities, namely, Alcalá de Henares, Getafe, Alcorcón and Torrejón de Ardoz (12).

At baseline (2017), information on socio-demographic, lifestyle, self-rated health and morbidity was collected using a computer-assisted telephone interview. Additionally, two home visits were conducted to collect biological samples and perform a physical examination. From the initial sample of 3,273 participants, 86.5% (n=2831) agreed to

the physical exam, 85.4% (n=2795) completed the diet history, and 79.7% (n=2610), provided blood samples. The 2019 follow-up collected data using the same protocols as the 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 levels 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 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 reporting being active smokers (n=307) and those who had serum cotinine concentrations over 10 ng/ml regardless of self-reported smoking status (n=40), were classified as active smokers and were excluded from the analyses. Non active smokers who reported being exposed to SHS at home or during leisure time, as well as those with cotinine concentrations between 0.05 and 9.9 ng/ml, regardless of self-reporting exposure status (n=1806). Finally, non-active smokers who reported no SHS exposure and presented cotinine levels below 0.05 ng/ml were classified as unexposed.

2- Exposure to SHS during adulthood was estimated using information on the presence and number of smokers at home, the years of exposure, and the number of cigarettes smoked by the different household members. For this purpose, questions were formulated following previous recommendations by a panel of experts (13). Cumulative exposure to SHS was expressed in pack-years, calculated as the "average number of cigarette/days smoked by household smokers divided by 20" multiplied by the "number of years cohabiting with those smokers. Additionally, participants who reported having lived with at least one smoker during adulthood were asked about the average number of cohabiting smokers.

Outcome assessment.

At baseline and follow-up, grip strength was measured as the highest of two consecutive measures with a Jamar dynamometer. Lower-extremity performance was assessed with the Short Physical Performance Battery (SPPB), which combines balance testing, gait speed and a sit-to-stand test (14). More specifically, balance testing included a side-by-side, a semitandem and a tandem stand. Participants were first asked to stand with their feet together (side-by-side); those 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). Again, those able to stand for 10 seconds in the semitandem position 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 these positions, whereas a score of 4 indicates a full-tandem stand for 10 seconds. Gait speed was calculated as the walking distance (3 m) divided by the time (in seconds) to cover said distance. In this test, 0 points indicated the inability to perform the walk at all, and a score of 4 indicates a walking speed within the fastest quartile

according to sex and height. 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 all five chair stands, whereas scores of 1, 2, 3, or 4 were assigned to participants who completed the 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 its components, with scores ranging 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 using Likert scales to analyze the intensity or frequency of each response (15). PCS scores were standardized to the national norm with a mean of 50.0 and a standard deviation of 10.0. A PCS score of 0 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) (16,17). The DAI is 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 health service use, further deficit accumulation, institutionalization or death.

Finally, mobility limitations were evaluated at baseline and follow-up with three questions from the Rosow and Breslau scale (18): "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, marital status (single, married, divorced or widowed), and social class of the main household earner based on their last occupation 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 (19). 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 the self-report of a physician diagnosis, current use of anti-hypertensive medication, or a casual blood pressure reading ≥140/90 mmHg taken under standardized conditions during the baseline examination. 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 (20). Depression was ascertained with the 10-item Geriatric Depression Scale (GDS-10) (21), 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-reported active smokers (9.4%, n=307), those with serum cotinine concentrations over 10 ng/ml (1.2%, n=40). Additionally, we excluded those who did not provide a blood sample (19.1%, n=626), did not undergo a physical examination (0.06%, n=2), or had missing values in potential confounders (1.2%, n=40) such as: hypertension (0.55%, n=18), social class (0.49%, n=16), BMI (0.15%, n=5), or cancer (0.03%, n=1). In prospective analyses we further excluded 688 individuals who were lost to follow-up, 27 who died, 5 who did not undergo 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. For 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, marital status and social class (Model 1); recreational physical activity, past active smoking status (never, former), and BMI (Model 2); and prevalence of cardiovascular disease, hypertension, diabetes, cancer and/or depression (Model 3).

In a second step, we evaluated the prospective association between baseline serum cotinine concentrations and changes in physical function. We used 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, marital 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, marital 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 (0.035-0.175) ng/ml, with only 20 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 (**Table 1**). Sex- and age-adjusted mean (standard error) values of the study outcomes for those below and above the LOQ, respectively, were: 27.8 (0.13) and 26.8 (0.42) kg for grip strength; 9.9 (0.04) and 9.4 (0.12) for the SPPB; 46.4 (0.61) and 45.7 (0.33) for the PCS; and 14.9 (0.20) and 18.7 (0.67) deficits for the DAI. The age- and sex-adjusted prevalence (standard error) of mobility limitations in the aformentioned 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:-1.05 kg; 95% confidence interval [CI]: -1.80, -0.31) and higher DAI scores (mean difference: 1.52; 95%CI: 0.38, 2.66), some trend towards lower SPPB (mean difference: -0.19; 95%CI: -0.40, 0.01) and PCS scores (mean difference:-0.77; 95%CI: -2.09, 0.55), and a non-significant increased odds of mobility limitations (odds ratio: 1.26; 95%CI: 0.90, 1.76).

During a mean follow-up of 2.6 years (range: 1.6-3.9 years), grip strength, SPPB and PCS scores decreased, on average, -2.07 kgs, 0.04 and -0.81 points, respectively. During this same period, participants accumulated 2.90 health deficits on average, and 139 of them developed mobility limitations. Compared to the unexposed, those in the highest quartile of baseline cotinine showed significant harmful changes in the SPPB [-0.24 (-0.46, -0.02)] and the 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 trend towards lower grip strength [-0.86 (-1.79, 0.06)] (**Table 3**).

In models of self-reported past exposure, never smokers who had lived with ≥2 smokers showed higher DAI values than those who had not lived with any smokers. Also, in analyses limited to never smokers for whom we had self-reported data on the intensity of past SHS exposure both at home and at 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) point increase in the DAI, and a higher prevalence of baseline mobility limitations (OR: 1.30; 95%CI: 1.08, 1.57) (**Supplementary Table 1**).

In sensitivity analyses, the effects of SHS exposure over grip strength, the SPPB, and the DAI tended to be more substantial among participants with hypertension, diabetes, or CVD **(Supplementary Figures 2 and 3)**, and were mostly consistent across age, sex, social class, marital status, smoking status, and BMI strata. Finally, adjustment for residential traffic density (calculated by estimating total vehicle miles traveled per square mile within the residence´s 500-foot radius area) did not modify the results.

Discussion

In this sample of community-dwelling older adults, serum cotinine and lifetime SHS exposure were modestly inversely related to several measures of physical capacity. Most associations were independent of sex, age, past smoking status, marital status, or social class and remained consistent after 2.6 years of follow-up. The impacts 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 (22).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 (23–25). Studies in mice have also observed increased muscular oxidative stress and systemic inflammation after exposure to cigarette smoke (26,27). 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 (28). Also, 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). Similarly, 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). Lastly, 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 that active smokers had slower walking speeds than never smokers (3).

Although not directly comparable, our findings support those of the few previous studies on SHS exposure and physical function. For example, in this study we show a consistent, though weaker, association with grip strength than the one described in our previous NHANES report (9). A report, based on 5,390 non-smoking participants aged 30 years and older with a median (interquartile range) 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 in older adults (8). As far as we are aware of, our results are the first evidence of an association between cotinine exposure and lower SPPB scores. This association 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 (29). 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 exposure 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. Finally, for the first time, as far as we know, we provide evidence for an association between SHS exposure, lower PCS scores, and an 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 though 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 SHS exposure, some of which can be missed by self-report. Unfortunately, a single measurement of this biomarker only reflects exposure over the previous 1-2 days and is an imperfect surrogate of long-term exposure. However, self-reported information may be an inaccurate measurement of past exposure, leading in turn to biased estimates. Another limitation is that, despite having adjusted for many relevant confounders, we did not have information on other sources of indoor air pollution, and we cannot rule out some residual confounding. Also, we did not have data on on time since diagnosis of the studied chronic morbidities. It is encouraging, however, seeing 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 over the life-course and 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 SHS, particularly those with chronic diseases, which themselves increase the risk of functional limitations and may

be aggravated by this exposure. Because older people are one of the segments of the population that spend more time at home and have great vulnerability to environmental exposures, we should start to consider legislation to limit SHS exposure in private homes, particularly addressed to carers and visitors.

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)							0.339
<71		535 (45.7)	175 (14.9)	164 (14.0)	141 (12.0)	156 (13.3)	
≥71		516 (47.5)	130 (12.0)	162 (14.9)	136 (12.5)	143 (13.1)	
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)	
Marital 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								
n° 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, marital 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. 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							
n° 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, marital 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

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.

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