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Exposure to second hand smoke and 10-year (2002-2012) incidence of cardiovascular disease in never smokers: the ATTICA cohort study

Running title: SHS exposure and 10-year CVD risk

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HIGHLIGHTS

- Smoking bans reduce second hand smoke (SHS) exposure and lead to improved health outcomes.
- The study quantified the association of SHS exposure on 10-year CVD risk in never smokers in Greece.
- SHS incurred a 2-fold elevated 10-year CVD risk, following adjustment for confounding effects.
- SHS induced 32% excess risk of 10-year CVD events in never smokers, with highest rates in the workplace.
- Effective implementation of national smoking bans is mandated to prevent SHS attributable CVD.

POTENTIAL CONFLICTS OF INTEREST

The authors have no potential conflicts to declare.

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ABSTRACT

Background: Despite WHO Framework Convention of Tobacco Control (FCTC) adoption, effective implementation of national smoking bans remains pending in several countries. This study quantified the association of second hand smoke (SHS) exposure and 10-year cardiovascular disease (CVD) among never smokers in such settings.

Methods: In 2001-2002, a sample of 1,514 males and 1,528 females (18-89 years old) were randomly selected in Greece. Frequency and duration of SHS exposure (i.e. exposure extending >30 minutes/day) within the home and/or workplace were assessed by interview. Following a 10-year follow-up period (2002-2012), incidence of non-fatal and fatal CVD (ICD-10) was evaluated among $n=2,020$ participants. The analytic study sample consisted of all never smokers ($n=910$).

Results: Despite national smoking ban implementation (2009), 44.6% ($n=406$) of never smokers reported SHS exposure. While SHS exposed never smokers exhibited a more favorable profile of CVD-related risk factors at baseline, they subsequently developed similar 10-year CVD incidence rates, at a younger mean age ($p=0.001$), to their non-exposed counterparts. Following adjustment for several lifestyle and clinical factors, SHS exposed never smokers exhibited a two-fold elevated 10-year CVD risk (adj. HR: 2.04, 95% CI: 1.43-2.92), particularly among women (adj. HR: 2.45, 95% CI: 1.45-4.06). SHS exposure accounted for 32% excess Population Attributable Risk (PAR) for 10-year CVD events in never smokers, with highest rates (PAR: 52%) being among those exposed in the workplace.

Conclusion: The prevention of SHS associated CVD and related healthcare costs mandates additional strategies for securing the effective implementation of comprehensive WHO FCTC based national smoking bans.

INTRODUCTION

One third of adult never smokers are exposed to second hand smoke (SHS) [1], one of the most frequent indoor air pollutants worldwide [2]. SHS exposure detrimentally impacts cardiovascular health, attributing 2.8 million ischemic heart disease cases globally [2]. Recent meta-analyses reveal that SHS exposure increases cardiovascular disease (CVD) risk by 23% [3], including ischemic and coronary heart disease risk by 25-30% [4-6]. SHS impacts CVD risk in a curvilinear dose-effect relationship, exhibiting detrimental effects even at low exposure levels due to elevated side stream smoke toxicity and non-smoker's low tolerance levels to transient exposure [7]. The underlying pathophysiology entails the effects of nicotinic stimulus on both the sympathetic system and vascular oxidative stress. Hence, the CVD effects of SHS are similar to light active smoking [8, 9]. However, limited evidence exists regarding its long-term effects upon fatal and non-fatal CVD [5, 10].

To diminish SHS exposure, national smoke-free bans are increasingly adopted. Such bans protect non-smokers from adverse SHS effects and facilitate smokers to quit smoking, while concomitantly deterring associated healthcare costs. The implementation of even partial smoke-free bans is associated with beneficial health impacts regarding myocardial infarction among passive smokers [11], whereas when fully implemented as national smoke-free bans a 17% reduction in hospital admission rates for acute coronary syndrome [5] and myocardial infarction [12], as well as related healthcare costs [13] is observed. While WHO Framework Convention on Tobacco Control (FCTC) policy measures have been realized during the past decade in numerous countries, the effective implementation of smoking bans remains suboptimal in several regions [14]. Specifically, in countries such as Greece, where smoking prevalence rates in 2002 were 50% [15], despite the adoption of smoke-free legislation in 2009, implementation remains feeble and persisting smoking rates at 40% remain one of the highest in Europe [16]. Furthermore, SHS exposure among never smokers in Greece remains similar

to those reported in 2002 [15], persisting at 40%, 51%, and 67% at work, home, and restaurants, respectively [17]. Elucidating the long-term effects of SHS on CVD risk may facilitate concerted public health actions for improving the effective implementation of smoke-free bans, whilst concomitantly deterring CVD and its related healthcare costs [18, 19].

The present prospective cohort study aimed to quantify the association of SHS exposure upon 10-year non-fatal and fatal CVD risk in a Greek population-based sample.

METHODS

Study design

The ATTICA Study [20] is a population-based, prospective cohort study implemented in Attica, Greece, consisting of 78% urban and 22% rural municipalities. Random, multistage sampling based on age and gender distributions of the reference population (defined by the Hellenic National Statistical Service Census Survey of 2001) was applied. Sampling procedures entailed enrolment of one participant per household. Persons with a history of cardiovascular or atherosclerotic disease were excluded from sampling. Of 4,056 eligible participants, 3,042 were enrolled (75% participation rate, including 1,514 men (mean age \pm standard deviation (SD) 46 ± 13 y; range 18-87 y) and 1,528 women (aged 45 ± 13 y; range: 18–89 y)). The study sample did not differ from the general population with respect to age and gender. All participants were interviewed by trained personnel (including cardiologists, nutritionists, and nurse practitioners) who used a standardized questionnaire.

Baseline measurements

Socio-demographic characteristics

Baseline measurements were collected upon enrolment in 2001-2002. On-site interviews included a questionnaire regarding demographic characteristics (e.g., age, gender, marital status, financial status, and years of education completed, as proxy of socioeconomic status).

Years of education completed and mean annual income during years prior to baseline examination were used to assess socioeconomic status (SES) defined as being low, moderate, or high [20].

Smoking status and SHS exposure

Never smokers had never smoked, current smokers smoked ≥ 1 cigarette/day, and former smokers had ceased smoking ≥ 1 year prior to enrolment. SHS exposure was evaluated based on responses to the following: "Are you currently exposed to tobacco smoke from other people for ≥ 30 minutes / day?". SHS exposure was evaluated separately for the workplace, home or other venues, including public facilities and/or restaurants. Responses were categorized into two levels: no SHS exposure or SHS exposure (≥ 30 minutes per day). To deter reporting bias, participants' responses were compared with relatives' and/or accompanying persons' reports, rendering high concordance [21].

Lifestyle assessment

As previously detailed [20], dietary habits were assessed based on a validated semi-quantitative food-frequency questionnaire [22], including average intake (per week or day) of several food items during the past year. The Mediterranean diet score was used (range 0-55) to depict adherence to the Mediterranean diet [23, 24].

The International Physical Activity Questionnaire (IPAQ) [25] was used as an index of weekly energy expenditure using frequency (times/week), duration (in minutes/time) and intensity of physical activity (in expended calories/time). Physical activity was leisure-time activity of a certain intensity and duration, at least once/week during the past year, ranging from <4 Kcal/min - >7 Kcal/min expended calories.

Anthropometric measurements and clinical assessment

Body mass index (BMI) was expressed as weight (kg) divided by standing height (m^2), with obesity being BMI >29.9 kg/ m^2 . Waist (in cm) and hip (in cm) circumferences were measured

using standard procedures. Subjects' arterial blood pressure (BP) was measured in a sitting position at the end of the physical examination, following ≥ 30 minutes at rest. BP was assessed blindly by a trained cardiologist three times, from participants' right arm which was relaxed and well supported by a table, with an angle of 45° from the trunk (ELKA aneroid manometric sphygmometer, Von Schlieben Co, West Germany). Systolic BP (SBP) was determined by the first perception of sound (tapping quality), while diastolic BP (DBP) by phase V when repetitive sounds become fully muffled. Hypertensive participants had mean systolic/diastolic BP $\geq 140/90$ mmHg or received antihypertensive medication [26].

Blood samples were collected from the antecubital vein between 8 to 10 AM, in a sitting position after 12 hours of fasting and alcohol abstinence. Blood lipids (i.e., serum total cholesterol, HDL-cholesterol and triglycerides) were measured with a Technicon automatic analyzer RA-1000 and Technicon reagents, according to manufacturer instructions (*Dade Behring, Marburg, Germany*); serum total cholesterol was measured using cholesterol esterase and cholesterol oxidase in a colorimetric procedure. Hypercholesterolemia was defined as total cholesterol levels ≥ 200 mg/dl or the use of lipids lowering agents (NCEP ATPIII [27]). LDL cholesterol was calculated using the Friedewald formula: {total cholesterol} – {HDL cholesterol} – $1/5$ (triglycerides) (only in people who had triglycerides levels lower than 250 mg/dl). The intra and inter-assay coefficients of variation of cholesterol levels did not exceed 9%, triglycerides 4% and HDL 4%. Blood glucose levels (in mg/dl) were measured with a Beckman Glucose Analyzer (Beckman Instruments, Fullerton, CA, USA). Diabetes mellitus was defined as fasting blood sugar >125 mg/dl or administration of antidiabetic drugs. High sensitivity C- reactive protein, fibrinogen, and homocysteine levels were measured by Behring BNII automatic analyzer (*Dade Behring, Marburg, Germany*). High sensitivity IL-6 plasma levels were measured by enzyme-linked immunosorbent assays (R&D systems Inc, Minneapolis, Minnesota).

Follow-up assessment

Follow-up assessments were conducted 10 years following baseline (median years to follow-up: 8.41 years; interquartile range (IQR): 5.0-10.0 years). Of the baseline population (N=3,042), 10-year follow-up assessment was achieved in 2,583 participants (85% participation rate; of those lost to follow-up, $n=224$ had missing/incorrect contact information and $n=235$ declined). Among never smokers, 10-year follow-up assessment was achieved in 87% of participants (13% loss to follow-up rate, $n=85$ had missing/incorrect contact information and $n=75$ declined). Complete CVD assessment was achieved in 2,020 participants, of which 910 were never smokers and constitute the analytic sample. Follow-up examination included retrieval of detailed information from participants' medical records. Participants without accurate records were evaluated by interview, including assessment of vital status (death from any cause or CVD) or development of coronary heart disease (including myocardial infarction, angina pectoris, other identified forms of ischemia (WHO-ICD coding 410-414.9, 427.2, 427.6), heart failure of different types, and chronic arrhythmias (WHO-ICD coding 400.0-404.9, 427.0 -427.5, 427.9) or stroke (WHO-ICD coding 430-438)).

Statistical analysis

Continuous variables are presented as mean \pm standard deviation (SD) and categorical variables as absolute and relative frequencies (n, %). The normality of distributions of continuous variables was assessed with P-P plots. The Student's t-test, chi-squared test, and Likelihood Ratio test were applied to compare normally distributed continuous, categorical, and ordinal variables between groups, respectively [28]. To account for differing ages at baseline, the effect of SHS exposure (as well as potential interactive effects of demographic, dietary, lifestyle, and clinical characteristics) upon 10-year CVD incidence (outcome variable) was evaluated with age-scaled Cox proportional hazard models and corresponding Hazard Ratios (HR, and 95% Confidence Intervals, CI) in the overall study population and by gender. The proportionality

assumption was assessed graphically. Adjusted population attributable risks (PARs) were calculated based on 45% SHS prevalence rate [21]. Analyses were conducted with STATA v.15 and based on two-sided tests (STATA Hellas, M.Psarros & Assoc., Greece).

RESULTS

Baseline exposure to SHS and 10-year CVD incidence in never smokers

Never smokers retained in the final analytic sample (n=910) did not differ from those lost to follow-up with respect to gender (p=0.97), age (p=0.85), and/or SHS exposure (p=0.88). At baseline, 44.6% (n=406) of never smokers were exposed to SHS. Among those exposed, 99.4% (350/352) reported exposure in the workplace, while 37.0% (133/359) in their homes or other venues, including public facilities and/or restaurants. Exposed never smokers were of younger mean age and more often male. As compared to their non-exposed counterparts, at baseline SHS exposed never smokers had a more favorable clinical profile regarding established CVD-related risk factors, including lower mean levels of BMI, SBP, total serum cholesterol, LDL, fibrinogen and IL-6 levels (all p's<0.05). They did not differ from their non-exposed counterparts with regard to the concomitant presence of hypertension and in fact less often had hypercholesterolemia. Despite these favorable profiles, SHS exposed individuals subsequently exhibited similar incidence rates of 10-year combined (n=137) (including fatal (n=23; 16.8%) or non-fatal (n=114; 83.2%) CVD (SHS exposed vs non-exposed: 16.7% (n=68) vs 13.7% (n=69); p=0.200), most notably at a younger age (namely approximately 7 years earlier) (mean age \pm SD: 58.4 \pm 13.4 years vs 65.6 \pm 11.6; p=0.001) (*Table 2*).

Baseline SHS exposed never smokers who subsequently developed 10-year CVD had higher mean BMI and lower adherence to the Mediterranean Diet. They were approximately five-fold (HR: 4.93; 95% CI: 2.78-8.77) more likely to have hypertension at baseline. Furthermore, this group was in excess of six-fold (HR: 6.62; 95% CI: 3.09-14.21) and 70%

(HR: 1.70; 95% CI: 1.00-2.90) more likely to have diabetes and hypercholesterolemia. Finally, exposed individuals with 10-year CVD had higher mean levels of fibrinogen and IL-6 at baseline (all p's <0.0001) as compared to their CVD-event free counterparts (*Table 2*).

SHS exposure and 10-year incidence of CVD

To account for differing ages at baseline, multivariate age-scaled Cox proportional hazard models were applied to evaluate the effect of SHS exposure upon 10-year CVD in both the overall study population and according to gender (*Table 3*). SHS was associated with a two-fold elevated 10-year CVD risk (Adj. HR: 2.04, 95% CI: 1.43-2.92) even after adjusting for various clinical (e.g., hypertension, hypercholesterolemia, and diabetes) and lifestyle (e.g. adherence to the Mediterranean Diet and physical activity) variables, with females exhibiting higher risk (Adj. HR: 2.45, 95% CI: 1.48-4.08) than males (Adj. HR: 1.97, 1.13-3.46).

Population Attributable Risk of SHS exposure on 10-year CVD incidence

Following adjustment for several clinical and lifestyle factors, SHS exposure accounted for 32% excess risk (i.e., Population Attributable Risk, PAR) of 10-year fatal and non-fatal CVD events in never smokers (*Table 4*). Based on 45% SHS exposure prevalence rate in Greece, it is estimated that 320 of 1000 CVD cases among never smokers could have been deterred had SHS exposure been avoided. Corresponding 10-year CVD PAR rates among female and male never smokers were 39% and 30%, respectively. Hence, 300 and 390 of 1000 male and female CVD cases, respectively, could have been evaded had exposure been avoided. PAR rates were highest among those exposed in the workplace; 590 male and 500 female of 1,000 cases could have been deterred if exposure were avoided.

DISCUSSION

Smoking bans lead to SHS reduction and subsequent improved health outcomes [14], including cardiovascular health [29], and attributable healthcare costs [30]. The study aimed to quantify

the association of SHS exposure upon 10-year non-fatal and fatal CVD risk among never smokers in Greece, where the effective implementation of a national smoking ban remains pending despite long-standing WHO FCTC based legislation. Despite the smoking ban, SHS exposure rates among never smokers approximated 45%. While SHS exposed persons exhibited a more favorable profile of CVD-related risk factors at baseline, they subsequently developed 10-year CVD incidence rates comparable to their exposed counterparts, however at a younger age. Following adjustment for confounding factors, SHS exposure incurred a two-fold elevated 10-year CVD risk in never smokers, with highest rates observed in females. SHS exposure accounted for 32% excess risk of 10-year CVD events in never smokers, with highest rates (52%) regarding workplace exposure. Finally, at the population level, SHS exposure accounts for 39% and 30% excess risk for 10-year CVD events among female and male never smokers, respectively. These findings highlight the need for further public health actions against SHS exposure in a country where several, albeit apparently unsuccessful, tobacco control measures have been implemented recently.

Even limited levels of SHS exposure are associated with 25-30% increased CVD risk [4-6]. Compared to non-exposed never smokers and following adjustment for potential confounding factors, middle-aged never smokers with ≥ 25 h/week SHS exposure at home displayed 7.86 fold elevated risk of peripheral arterial disease [31]. A recent meta-analysis conducted among 23 prospective and 17 case-control studies revealed that the pooled relative risk (RR) for CVD (n=38 studies) in never smokers exposed to SHS, as compared to their non-exposed counterparts, is 1.23 (95% CI: 1.16-1.31) [3]. The corresponding pooled risk rate for all-cause mortality (n=12 studies) is 1.18 (95% CI: 1.10-1.27) [3], including a 5% increased risk of death from coronary heart disease [32], which is notably augmented at 15% in women [33]. SHS appears to induce vascular dysfunction by a multitude of mechanisms entailing proinflammatory and prothrombotic cascades, including the enhanced aggregation of platelets,

increased adherence of macrophages, acceleration of lipid peroxidation, and damage in endothelial cells [2, 4, 34-36]. Interference of SHS with the production of nitric oxide permits enhanced adhesion of inflammatory cells to the endothelium [29], further propagating atherosclerotic processes. Ultimately, the combinatory effects of tissue remodeling, prothrombotic processes, and augmented inflammatory response contribute to the manifestation of arteriosclerotic vessels [36] and consequent onset of CVD.

The study findings reveal that, following adjustments for potential confounding effects, SHS exposed never smokers remained approximately two-fold more likely to develop 10-year fatal and non-fatal CVD. These findings are slightly higher than recent meta-analytic findings showing that, never smokers aged ≥ 50 years have a 1.23 (95% CI: 1.16-1.31) increased risk of CVD [3]. Disparities with our findings may be attributed to inherent differences regarding the age distribution of populations investigated and SHS exposure being assessed solely within the home. Even so, given the age-scaled statistical modelling procedures employed, our findings add to the existing knowledge base a quantifiable association between SHS exposure and 10-year CVD risk. Furthermore, previous work revealed that CVD risk factors include age, male gender, and adherence to the Mediterranean diet [20], and were subsequently incorporated in all models. As Hazard Ratios remained relatively stable as covariates were added to the models, the observed association is unlikely due to unobserved confounding. To the best of our knowledge, similar investigations have not been documented to date in smoke-free ban settings.

SHS exposure accounted for 39% and 30% excess risk for 10-year CVD in female and male never smokers, respectively. A significant interaction between gender and ETS in relation to 10-year CVD was not documented (HR:0.97; 95% CI:0.97-2.31). In regions such as France characterized by high smoking prevalence rates, SHS exposure rates has decreased over time in both men and women [37]. However, women report higher rates of SHS exposure at home

[38]. Also, exposed women have a 15% augmented attributable mortality rate due to heart disease [33]. Our findings corroborate that a gender disparities exist between SHS exposure and subsequent CVD risk. Additionally, our findings reveal that 320 and 520 of 1000 10-year CVD incident cases could have been avoided if SHS exposure been deterred overall and in the workplace, respectively. These findings are in agreement with previous reports [39, 40]. In an attempt to explore the paths by which SHS may affect CVD risk, we revealed that when introducing various demographic, lifestyle, clinical and/or biochemical factors, the effect size measure of SHS on 10-year CVD risk was mediated, but still remained significantly associated, with an approximately two-fold elevated risk of 10-year CVD. Hence, it is speculated that in never smokers SHS exposure is an independent risk factor for 10-year CVD risk, propagating the disease at a younger age.

Country-wide smoking bans are decisive in improving cardiovascular health and reducing attributable healthcare costs [30], particularly in settings such as Greece which has one of the highest tobacco consumption rates in Europe [21] and is concomitantly challenged by financial austerity measures. However, effective implementation of bans often remains poor, likely due to enforcement-related difficulties [14]. The most recent WHO Global Tobacco Adult Survey underlines the necessity for overturning feeble implementation rates of smoke free bans in countries such as Greece [21], where despite rising tobacco cessation rates, SHS remains elevated. Specifically, the Greek Parliament adopted the WHO FCTC in 2005, a smoke-free law in 2010 (Law 3868/2010), and national smoking ban in 2011 [21]. Nevertheless, SHS exposure at the population level remains at 90%, with rates among never smokers being 40.0%, 51.1%, and 67.1% in workplaces, homes, and restaurants. Based on persistently high SHS exposure rates alone, it is evident that implementation of the existing smoke-free ban in public and/or workplaces remains inadequate [17]. Hence, more effective

implementation, monitoring and evaluation of smoke-free bans are needed to diminish SHS exposure and attributable CVD risk.

For the potential of the WHO FCTC to be achieved in such settings, challenges (including ineffective implementation of guidelines and insufficient capacity and/or financial support) need to be addressed and progress must be escalated in related policy domains [14], preferably through horizontal policy actions and engagement of multidisciplinary stakeholders. To this effect, the study findings may enhance the evidence base necessary for developing horizontal policy actions, including i.e. concerted actions regarding FCTC Article 8 (e.g. protection from SHS exposure), Article 20 (e.g. research that addresses the consequences of SHS), and Article 22 (e.g., facilitation of the transfer of knowledge related to tobacco control). Given that particularly children are often additionally exposed to third-hand smoke pollutants and toxicants [41], further actions are mandated. Specifically, since evidence arising from preliminary animal studies regarding the CVD-related health impacts of third-hand smoke are limited albeit alarming [42, 43], future epidemiologic investigations may facilitate risk assessment and inform current smoking bans by evaluating both the differential and cumulative risks of second- and third- hand smoke exposure upon CVD outcomes.

Strengths and Limitations

The study strengths include the prospective cohort study design applied in a representative randomly selected population-based sample from the most densely populated urban district of Greece. Length of follow-up assessment extended 10 years, allowing for sufficient time to evaluate CVD outcomes whilst avoiding bias due to disease latency. The study limitations include that SHS exposure was based on self-report prone to a misclassification bias. Due to the study design employed, external validation of SHS exposure by external validation methods such as cotinine levels or confirmation by bystanders was not feasible. However, the observed SHS exposure rates agree with other similar reports [17], albeit both unconfirmed via

biomarkers, such as cotinine levels. In addition, while adherence to the Mediterranean Diet (MedDietScore) was measured, complete dietary analysis for nutrient components was not assessed. However, due to the extended follow-up period, dietary patterns likely more accurately predict CVD risk as they provide insights regarding how comprehensive nutritional intake affects disease risk. Finally, potential treatment effects for other underlying diseases (e.g., hypertension, hypercholesterolemia, and diabetes mellitus) upon CVD risk were not assessed. Even so, treatment effects would likely bias findings towards the null hypothesis and hence the effects observed are likely an underestimation of true effects.

Conclusions

The prevention of SHS associated CVD, as well as respective healthcare costs, mandates the adoption of additional concerted strategies for achieving effective national smoking bans and comprehensive tobacco control programs, especially among populations with persistent high rates of smoking habits.

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AUTHOR CONTRIBUTIONS

Elena Critselis: Formal analysis; Writing - original draft, review & editing. **Demosthenes B Panagiotakos:** Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Writing – original draft, review & editing; Supervision. **Ekavi N Georgousopoulou:** Investigation; Data curation; Methodology; Project administration. Writing - review & editing. **Paraskevi Katsaounou:** Investigation; Methodology; Resources; Writing - review & editing. **Christina Chrysohoou:** Conceptualization; Investigation; Methodology; Resources; Writing - review & editing. **Christos Pitsavos:** Conceptualization; Funding acquisition; Investigation; Methodology; Writing - review & editing.

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Table 1. Baseline characteristics of the ATTICA study participants who were never smokers, according to the frequency of exposure to second hand smoke (SHS) (n=910)

	Overall (n=910)	Without SHS exposure (n=504)	With SHS exposure (n=406)	<i>p</i>
Age of participants (years)	46.2 ± 15.4	48.6 ± 15.7	43.1 ± 14.5	<0.0001
Male gender, %	344 (37.8)	176 (34.9)	168 (41.4)	0.046
Socioeconomic status				0.316
<i>Low, %</i>	91 (17.3)	32 (20.8)	59 (15.9)	
<i>Medium, %</i>	247 (47.0)	66 (42.9)	181 (48.8)	
<i>High, %</i>	187 (35.6)	56 (36.4)	131 (35.3)	
Body Mass Index (Kg/m ²)	26.2 ± 4.5	26.4 ± 4.6	25.8 ± 4.4	0.046
Obesity, %	160 (17.9)	94 (19.0)	66 (16.5)	0.334
Physical inactivity	501 (55.1)	270 (53.6)	231 (56.9)	0.316
MedDietScore (range 0 to 55)	26.0 ± 7.0	25.7 ± 6.8	26.4 ± 7.1	0.113
Ethanol intake (g/day)	10.2 ± 12.7	13.0 ± 13.6	8.1 ± 11.6	<0.0001
Systolic Blood Pressure (mm Hg)	123.9 ± 19.3	126.0 ± 19.0	121.2 ± 19.2	<0.0001
Diastolic Blood Pressure (mm Hg)	79.1 ± 12.0	79.4 ± 11.8	78.7 ± 12.3	0.443
Hypertension, %	281 (33.2)	162 (34.3)	119 (31.7)	0.427
Total serum cholesterol (mg/dL)	193.6 ± 40.8	198.0 ± 41.1	188.0 ± 39.9	<0.0001
Hypercholesterolemia, %	367 (40.3)	230 (45.6)	137 (33.7)	<0.0001
Fasting blood glucose (mg/dL)	92.4 ± 21.2	92.2 ± 18.8	92.6 ± 23.8	0.793
Diabetes Mellitus, %	71 (7.8)	40 (7.9)	31 (7.6)	0.866

High Density Lipoprotein (mg/dL)	51.3 ± 13.2	50.8 ± 12.5	52.0 ± 13.9	0.177
Low Density Lipoprotein (mg/dL)	121.7 ± 36.3	125.3 ± 35.4	116.7 ± 36.9	0.002
Fibrinogen (mg/dL)	313.9 ± 73.2	319.7 ± 73.0	306.0 ± 72.9	0.012
Homocysteine (µmol/L)	11.7 ± 5.7	12.0 ± 5.0	11.4 ± 6.2	0.216
C-reactive protein (mg/dL)*	0.9 (1.8)	1.0 (1.8)	0.9 (1.7)	0.749
IL-6 (pg/ml)*	1.4 (0.4)	1.4 (0.4)	1.3 (0.4)	0.016

Continuous variables are presented as mean±standard deviation (M±SD), and categorical variables as absolute and relative frequencies (*n*(%)). P-values referring to differences between CVD-events and CVD-free events during the 10-year follow-up, derived using either the Student's t-test or the Pearson chi-square test for the continuous and the categorical characteristics, respectively. Differences between groups regarding ordinal variables were compared with the Likelihood Ratio test. *Expressed as median (interquartile range, IQR).

Table 2. Baseline characteristics of the ATTICA study's participants who were never smokers in relation to the 10-year fatal or non-fatal incidence of CVD, according to exposure to second hand smoke (SHS) (n=910)

	Status at 10-year follow-up among those without SHS exposure (n=504)			Status at 10-year follow-up among those with SHS exposure (n=406)		
	CVD event free (n=435)	CVD events (n=69)	<i>p</i>	CVD event free (n=338)	CVD events (n=68)	<i>p</i>
Age of participants (years)	45.9 ± 14.5	65.6 ± 11.6	<0.0001	40.1 ± 12.6	58.4 ± 13.4	<0.0001
Male gender, %	151 (34.7)	25 (36.2)	0.806	135 (39.9)	33 (48.5)	0.189
Socioeconomic status			<0.0001			<0.0001
<i>Low, %</i>	26 (17.8)	6 (75.0)		37 (11.7)	22 (40.7)	
<i>Medium, %</i>	64 (43.8)	2 (25.0)		160 (50.5)	21 (38.9)	
<i>High, %</i>	56 (38.4)	0 (0.0)		120 (37.9)	11 (20.4)	
Body Mass Index (Kg/m ²)	26.2 ± 4.5	28.0 ± 5.0	0.002	25.5 ± 4.4	27.6 ± 4.2	<0.0001
Obesity, %	75 (17.6)	19 (27.9)	0.043	50 (15.0)	16 (24.2)	0.064
Physical inactivity	234 (53.8)	36 (52.2)	0.802	195 (57.7)	36 (52.9)	0.470
MedDietScore (range 0 to 55)	26.2 ± 6.5	22.1 ± 7.8	<0.0001	27.1 ± 6.9	22.8 ± 7.2	<0.0001
Ethanol intake (g/day)	12.1 ± 13.3	21.8 ± 13.5	0.010	7.7 ± 11.8	10.9 ± 10.2	0.187
Systolic Blood Pressure (mm Hg)	124.4 ± 18.2	136.1 ± 22.0	<0.0001	118.3 ± 17.0	136.6 ± 22.7	<0.0001

Diastolic Blood Pressure (mm Hg)	79.2 ± 11.7	80.2 ± 12.3	0.530	77.6 ± 11.8	85.0 ± 13.3	<0.0001
Hypertension, %	128 (31.3)	34 (54.0)	<0.0001	80 (25.6)	39 (62.9)	<0.0001
Total serum cholesterol (mg/dL)	197.6 ± 42.4	200.6 ± 31.5	0.577	184.2 ± 37.6	208.2 ± 45.4	<0.0001
Hypercholesterolemia, %	193 (44.4)	37 (53.6)	0.152	107 (31.7)	30 (44.1)	0.047
Fasting blood glucose (mg/dL)	90.7 ± 15.7	102.1 ± 30.8	<0.0001	90.4 ± 21.6	104.0 ± 30.6	<0.0001
Diabetes Mellitus, %	21 (4.8)	19 (27.5)	<0.0001	15 (4.4)	16 (23.5)	<0.0001
HDL-cholesterol (mg/dL)	51.3 ± 12.7	47.4 ± 10.9	0.026	52.6 ± 14.1	48.8 ± 12.4	0.054
LDL-cholesterol (mg/dL)	125.2 ± 36.0	125.8 ± 32.1	0.902	113.6 ± 35.2	135.2 ± 41.5	<0.0001
Fibrinogen (mg/dL)	315.2 ± 69.2	347.5 ± 89.2	0.002	298.8 ± 69.1	349.2 ± 80.5	<0.0001
Homocysteine (µmol/L)	11.8 ± 4.6	12.9 ± 7.1	0.229	11.2 ± 6.5	12.3 ± 4.0	0.289
C-reactive protein (mg/L)*	0.9 (1.7)	1.4 (1.8)	0.134	0.9 (1.5)	1.3 (2.3)	0.104
IL-6 (pg/ml) *	1.3 (0.4)	1.7 (0.3)	<0.0001	1.3 (0.4)	1.6 (0.6)	<0.0001

Continuous variables are presented as mean±standard deviation (M±SD), and categorical variables as absolute and relative frequencies (n(%)). P-values referring to differences between CVD-events and CVD-free events during the 10-year follow-up, derived using either the Student's t-test or the Pearson chi-square test for the continuous and the categorical characteristics, respectively. Differences between groups regarding ordinal variables were compared with the Likelihood Ratio test. *Expressed as median (interquartile range, IQR).

Table 3. Multivariate age-scaled Cox Proportional Hazards models that evaluated the association between SHS on 10-year CVD risk among ATTICA Study never smokers, taking into account the effect of various clinical and lifestyle factors. Results are presented as Adjusted Hazard Ratios (Adj. HR) and 95% Confidence Intervals (CI).

	Model 1	Model 2	Model 3
	Adj. HR (95% CI)	Adj. HR (95% CI)	Adj. HR (95% CI)
All never smokers			
<i>SHS exposure (Y/N)</i>	2.14 (1.52-3.00)	2.03 (1.42-2.90)	2.04 (1.43, 2.92)
<i>Hypertension (Y/N)</i>		1.23 (0.86-1.78)	1.18 (0.81-1.73)
<i>Hypercholesterolemia (Y/N)</i>		1.18 (0.82-1.69)	1.19 (0.82-1.71)
<i>Diabetes (Y/N)</i>		1.08 (0.71-1.63)	1.08 (0.71-1.65)
<i>MedDietScore (per 1/55)</i>			1.01 (0.98-1.04)
<i>Physically active (Y/N)</i>			1.26 (0.88-1.80)
Male never smokers			
<i>SHS exposure (Y/N)</i>	2.02 (1.20-3.40)	2.05 (1.17-3.57)	1.97 (1.13-3.46)
<i>Hypertension (Y/N)</i>		1.43 (0.78-2.61)	1.39 (0.75-2.56)
<i>Hypercholesterolemia (Y/N)</i>		1.32 (0.74-2.33)	1.39 (0.77-2.49)
<i>Diabetes (Y/N)</i>		0.68 (0.36-1.29)	0.66 (0.34-1.27)
<i>MedDietScore (per 1/55)</i>			1.02 (0.98-1.06)
<i>Physically active (Y/N)</i>			1.16 (0.66-2.06)
Female never smokers			
<i>SHS exposure (Y/N)</i>	2.22 (1.40-3.51)	2.30 (1.40-3.77)	2.45 (1.48-4.08)
<i>Hypertension (Y/N)</i>		1.33 (0.81-2.16)	1.28 (0.77-2.11)
<i>Hypercholesterolemia (Y/N)</i>		1.02 (0.63-1.67)	1.04 (0.62-1.73)
<i>Diabetes (Y/N)</i>		1.57 (0.87-2.83)	1.66 (0.90-3.06)
<i>MedDietScore (per 1/55)</i>			1.01 (0.97-1.05)
<i>Physically active (Y/N)</i>			1.49 (0.91-2.44)

Table 4. Age- scaled adjusted Cox proportional hazard ratios and corresponding population attributable risks (PAR) for 10-year fatal or non-fatal incidence of CVD (outcome) among never smoker participants in the ATTICA study, according to gender

	Adjusted Hazard Ratio (95% Confidence Interval)	Adjusted Population Attributable Risk (%)
All never smokers		
Overall SHS exposure	2.04 (1.43-2.92)	32
<i>SHS exposure at home, restaurants, and other venues</i>	1.47 (0.85-2.54)	17
<i>SHS exposure at the workplace</i>	3.43 (1.53-7.72)	52
Male never smokers		
Overall SHS exposure	1.97 (1.13-3.46)	30
<i>SHS exposure at home, restaurants, and other venues</i>	2.19 (0.83-5.78)	35
<i>SHS exposure at the workplace</i>	4.21 (1.20-14.77)	59
Female never smokers		
Overall SHS exposure	2.45 (1.48-4.08)	39
<i>SHS exposure at home, restaurants, and other venues</i>	1.40 (0.67-2.95)	15
<i>SHS exposure at the workplace</i>	3.24 (1.04-10.07)	50

Adjusted Hazard Ratios (Adj. HR) according to age, clinical (including hypertension, hypercholesterolemia), and type 2 diabetes mellitus) and lifestyle (including MedDiet Score and physical activity levels) characteristics.