Title page

Impact of second-hand smoke exposure followed by cigarette smoking quitting on subsequent risk of coronary heart disease: Evidence from the population-based cohort of Tehran Lipid and Glucose Study (TLGS)

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Running Title: second-hand smoke exposure followed by cigarette smoking quitting and CHD risk

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Abstract

OBJECTIVS: Cigarette smoking with its various phenotypes is an established, strong, and modifiable risk factor for coronary heart disease (CHD). Little research has been conducted on the effect of former smokers who have quitted smoking but are exposed to others' cigarette smoke (former & secondhand smokers) on CHD risk. Limitations of published data have left this important question.

METHODS: A prospective population-based cohort (TLGS) was conducted (n=20069) with median follow-up time of 14.6 years. A subset of 8050 participants ≥30 years old (first CHD events as study outcome) were considered. Participants were categorized as never, former, current, secondhand, and former & secondhand smokers. Data on smoking intensity (cigarettes/day) were also collected. Cox proportional hazards regression model was applied to estimate the risk of CHD taking into account the main potential confounders.

RESULTS: The mean (SD) age of individuals was 46.10 (11.38) years that experienced 1118 first CHD events (most CHD cases in former smokers) during follow-up. The risk of CHD was higher in current, former & secondhand, former, and secondhand smokers (HR: 1.99, 95% CI: 1.65-2.39; HR: 1.55, 95% CI: 1.15-2.08; HR: 1.39, 95% CI: 1.12-1.72; HR: 1.27, 95% CI: 1.07-1.51) respectively than never smokers. The risk of CHD increased with rising the smoking intensity (as a better proposed smoking phenotype) indicating a dose-response pattern.

CONCLUSIONS: The risk of CHD in former & secondhand smokers was an interesting and remarkable finding which need to further research to establish and approve in future studies to transfer to health policy makers.

KEY WORDS: Smoking, Coronary heart disease, TLGS, Cohort

INTRODUCTION

Despite remarkable advances in the treatment of cardiovascular disease (CVD) and in particular coronary heart disease (CHD), but, this disease and its clinical consequences continue to be the leading cause of morbidity and mortality in the worldwide [1-3]. Based on the available evidence, CHD is a major concern for global health and also a main barrier to achieving to Sustainable Development Goals [1, 4]. CHD was found to be the main cause of death in Iran and it is projected that years of life lost owing to this disease will increase dramatically in the coming years [5, 6].

In general, 1.4 billion adults worldwide smoke, which 1.12 billion are men and 279 million are women [7]. Although the prevalence of current smokers has decreased over time in several countries, the global absolute number of smokers has increased owing to population growth [8]. Cigarette smoking is an established, strong, and modifiable risk factor for coronary heart disease [9-11]. A relatively large number of observational studies in recent years focused on association between cigarette smoking and CVD, MI, CHD, and stroke [12-15]. A set of studies have exactly addressed smoking behaviors as simple dichotomous (smoker/nonsmoker) variable while a few prospective cohort studies attempted to investigate various phenotypes of cigarette smoking such as smoking status (never, former, and current smoker), pack/years, duration, age of onset smoking at various age groups and communities [16, 17]. Based on the Framingham cohort study findings, former heavy smokers have significantly elevated cardiovascular disease risk beyond 5 years after cessation compared to never smokers [18]. A recently published systematic review and meta-analysis indicated that smoking only about one cigarette per day carries a risk of developing coronary heart disease and stroke much greater than expected [9].

Although our knowledge based in relation to risk of coronary heart disease owing to cigarette smoking (current and former vs. never smokers) has expanded over the last decade, comparatively little research has been conducted on secondhand smokers and former smokers who have quitted smoking but are still expose to others' cigarette smoke. Limitations of published data leave important question about the magnitude and effect size of CHD risk in individuals who expose to others' cigarette smoke after cigarette smoking quitting/cessation.

In an attempt to fill this evidence gap, the present study set out to explore the influence of smoking status (former, current, secondhand, and in particular with focus on second-hand exposure followed by cigarette smoking quitting compared to never smoking) as well as smoking intensity (as proposed appropriate measure of cigarette smoking) on subsequent risk of coronary heart disease.

MATERIALS AND METHODS

Study Design

Tehran Lipid and Glucose Study (TLGS) is an open-ended prospective population-based cohort project of a representative sample of dwellers in Tehran (the capital city of Iran), in the eligible age (≥3 years) at the time of recruitment. This study was originated in March 1999 to Dec 2001, follow up and data collection was planned to be accomplished in 3-years intervals. Briefly, 15005 individuals participated in the first examination and 3550 individuals were added in the second examination. New born children of families were added to the study population after they completed three years of age during the follow-ups. Study population includes 20069 individuals and to date, the median follow-up time of this cohort is 14.66 years [interquartile range (IQR) 10.45–16.22]. The details of TLGS cohort study have been described elsewhere [19-21]. The study has been approved by the ethics committee of the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Written Informed consent was obtained from all participants.

Study sample

A subset of 8050 participants from the TLGS cohort was considered. Included individuals restricted to those were 30 years and older. Furthermore, participants who had positive history of cardiovascular disease (prevalent cases) at baseline examination, missing values for either coronary heart disease or smoking status, and subjects who participated in only one phase of the study were excluded (Figure 1).

Exposure; Cigarette Smoking Status

People's cigarette smoking status was determined based on self-reported smoking behaviors. Collected data on history of current and preceding smoking habits were used to categorization of individuals as never, secondhand, former/ex, former & secondhand, and current smoker. Participants were considered as ever smoker if have smoked more than 100 cigarettes in their lifetime, someone who has not smoked cigarettes at all or smoked ≤ 100 cigarettes in his/her lifetime and does not currently smoke was grouped as never smoker. Ever smokers were assigned into two groups; participant who has smoked greater than 100 cigarettes in his/her lifetime and has smoked in the last 28 days was considered as current smoker and ever smokers who have smoked greater than 100 cigarettes in their lifetime but have quitted smoking were considered as former/ex-smoker . Secondhand smoker (or environmental tobacco

smoke, ETS) was who never smoker but are exposed to smoke of cigarette at home or job environment. Individuals who are exposed to others' cigarette smoke despite quitting smoking hereinafter referred to briefly as "former & secondhand smokers". Age at starting cigarette smoking (categorized to ≤ 17 and >17 years old), smoking intensity (number of cigarettes used per day), and history of smoking cessation (years) were also collected.

Outcome assessment

All participants of the TLGS are followed up for any medical event during preceding year by telephone call. They are asked for any medical conditions by a trained nurse. Study outcome was the first CHD events in the present study. In order to gather outcome data, all participants have followed up annually for fatal or non-fatal CHD (definite myocardial infarction (MI), probable MI, unstable angina pectoris, angiography proven CHD and unstable angina pectoris, angiography proven CHD and CHD death, which are comparable with ICD-10 criteria. Each participant is under continuous follow-up for any CHD event leading to hospitalization or death, confirmed by an outcome committee (Cohort Outcome Panel) consisted of principal investigator, internist, endocrinologist, cardiologist, epidemiologist and physician who collected outcome data [22, 23].

Covariates

Potential covariates in the present study were Age, sex, Body Mass Index (BMI), HDL-Cholesterol (mg/dl), LDL-Cholesterol (mg/dl), history of type 2 diabetes mellitus (T2DM), systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), and education level (less than high school, high school and Diploma, more than high school/Academic level). Details of anthropometrics, clinical, and laboratories measurements have been described elsewhere [22, 24].

Statistical Analysis

The Cox proportional hazard regression model was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for CHD incidence after assessing and confirming the proportionality hazard assumptions statistically and graphically. Multivariable Cox model was used to estimate age, sex, education level, and aforementioned potential confounders adjusted HRs for CHD risk separated by smoking status (never, former, current, secondhand, and formers who exposed to secondhand smoke). Hazard ratios were estimated in 4 models in tandem with the

increase in the number of covariates. Model 1: smoking status alone; model 2: age as a covariate; model 3: age and sex; model 4: model 3 plus education level, BMI, history of T2DM, SBP, DBP, HDL and LDL-Cholesterol.

Since smoking intensity (cigarette per day) has been proposed as preferred measure of smoking phenotype for modeling cardiovascular outcomes (17), we estimated crude and fully adjusted HRs for CHD risk stratified by smoking intensity (≤10, 10-20, and ≥20 cigarettes per day). All statistical analyses were carried out using Stata14.0 (Stata Corp., College Station, TX, USA) and SPSS 16.0 (SPSS Inc, Chicago, Illinois). All statistical tests were two tailed with significance level of $\alpha<0.05$. Missing values was relatively low (minimum for sex with 0.2% and maximum for education level with 5.1%) for all variables.

Ethics statement

The study has been approved by the Shahid Beheshti University of medical Sciences Ethic Committee (Code: IR.SBMU.PHNS.REC.1396.144). Written Informed consent was obtained from all participants.

RESULTS

Eligible participants for this study were 8050 individuals aged ≥ 30 years. More of them were female (54%) with a mean (SD) age of 46.10 (11.38) years. During a 14.66 years median follow-up, participants experienced 1118 first coronary heart disease events. Occurrence of first CHD was more in male compared with female (8.2% vs. 5.6%). 61% CHD cases occurred before the age of 65 years. Less than 15% of study population had history of type 2 diabetes mellitus and both sex were overweight (mean BMI; 27.5±4.6). One quarter of the participants reported positive history of cigarette smoking (25.4%) that only 3.4% of them were female. Among those who reported no history of cigarette smoking, 22.2% were exposed to secondhand smoke that was more for the females. Considerable of ever smokers (36.6%) had initiated cigarette smoking in adolescence. Baseline participant characteristics are shown in Table 1.

Distribution of the first CHD events and all study covariates separated by cigarette smoking status has been presented in Table 2. Findings indicated that the most CHD cases were in former, former & secondhand, current, never, and secondhand smokers (24.3%, 20.0%, 17.4%, 12.2%, and 11.6%) respectively. In the case of the smoking intensity, only 9.4% of current smokers reported that they smoke ≥20 cigarette per day. About 70% of former & secondhand smokers had quit smoking more than 5 years ago.

Based on both crude and multivariable adjusted model, exposure to cigarette smoking regardless of being active or passive was associated with significantly increased risk of CHD compared to never smoking (Table 3). Surprisingly, association between cigarette smoking and CHD was higher in former smokers (HR; 2.26, 95% CI; 1.85-2.75) than current smokers (HR; 1.58, 95% CI; 1.35-1.86) in crude model (Table 3 and Figure 2(A)). The remarkable finding in the present study was the important and significant risk of CHD in former & secondhand smokers (HR; 1.86, 95% CI; 1.41-2.44). After adjusting for age as main covariate, the association in former smokers and current smokers were changed meaningfully so that the risk of CHD increased in current smokers (HR; 2.07, 95% CI; 1.76-2.43) while decreased in former smokers (HR; 1.56, 95% CI; 1.28–1.91).

It is interesting to note that in the case of former & secondhand smokers, the observed considerable association remained almost unchanged (HR; 1.82, 95% CI; 1.38-2.39). In other words, in individuals who are still exposed to others' cigarette smoke despite quitting smoking, the risk of CHD is 1.8 times more than never smokers. After controlling for age, sex, education level, BMI, history of T2DM, SBP, DBP, HDL and LDL-Cholesterol, the risk of CHD was higher in current smokers, former & secondhand smokers, former smokers, and secondhand smokers (HR: 1.99, 95% CI: 1.65-2.39; HR: 1.55, 95% CI: 1.15-2.08; HR: 1.39, 95% CI: 1.12-1.72; HR: 1.27, 95% CI: 1.07-1.51) respectively than never smokers (Table 3 and Figure 2(B)).

As illustrated in full adjusted model in table 3, the risk of CHD in males was 1.57 times more than females (HR: 1.57, 95%CI: 1.35-1.84). Different levels of education had not effect on CHD incidence however, it seems that education years >12 (more than high school) have significantly borderline protective role on CHD nearly 20% (HR: 0.78, 95% CI: 0.59-1.01).

When smoking status (study exposure) replaced with smoking intensity as another phenotype of cigarette smoking, an evidence of a significant dose-response pattern between increasing the number of cigarette per day and risk of CHD was observed. To sum up, in both crude and full adjusted models the risk of coronary heart disease increased with rising the smoking intensity (cigarette per day <10, HR: 1.65, 95% CI: 1.32-2.06; cigarette per day 10-19, HR: 2.22, 95% CI: 1.75-2.80; and cigarette per day ≥20, HR: 2.38, 95% CI: 1.58-3.58) (Table 4).

DISCUSSION

In this large population based prospective cohort from Iran with remarkable median follow-up, the risk for incident first coronary heart disease was higher in current, former & secondhand, former, and secondhand smokers (99%, 55% 39%, and 27%) respectively than in never smokers independent of other CHD risk factors. It is worth mentioning that the risk of CHD event in participants who have quitted smoking but are exposing to others' cigarette smoke at home or job was 1.55 times relative to never smokers while the risk was 1.39 times in those who have positive history of cigarette smoking (former smokers) and 1.27 times in never smokers who exposed to others' cigarette smoke (secondhand smokers). As to the another study aim which dealt with the influence of smoking intensity (cigarette per day) on incidence of coronary heart disease, the findings of data analysis indicated that considerable risk of coronary heart disease comes from cigarette smoking even in the light form (1-10 cigarettes per day). Strictly speaking, CHD event may be said to have occurred 65% higher in light smokers compared with who have no history of cigarette smoking. This window of hazard for incident coronary heart disease was more for those who smoked more than 10 cigarettes per day (more than twice than never smokers). This is a key message for smokers who suppose that light smoking is associated with less risk or is harmless.

Our results are consistent with previously conducted large cohort studies form various societies [17, 18, 25-30] and offer more evidence to support the association between smoking status and risk of CHD. In Framingham heart cohort study with 8770 participants mean aged 42.2 ±11.8 years, risk of cardiovascular disease was meaningfully high (75%) in current than never smokers while former smokers, regardless of intensity were not at increased risk [18], suggesting that risk may drop because of the considerable time they quit smoking. The relative risk of CVD event for never smokers exposed to secondhand smoke (secondhand smokers) in comparison with those unexposed (never smokers) was 1.23 (95% CI 1.16-1.31) in a systematic review conducted on 38 large observational studies [31]. The point is that the observed association between secondhand smoke exposure and cardiovascular disease was distinctly stronger among Chinese than in the Americans [31].

It is widely suppose that quitting smoking is associated with a significant reduction in risk of death among patients with CHD. It can be stated that irrespective of age, sex, index cardiac event, country, and initiating study year, this mortality risk reduction seems to be consistent [32].

It is even believed that the risk of sudden cardiac death in smokers who quit smoking more than 20 years will be equivalent to that of never smokers [33]. On the other hand, those who have positive history of cigarette smoking are

less sensitive to others' cigarette smoke (secondhand smoke). Studies conducted on environmental tobacco smoke/secondhand smoke suggest that its effects on risks of coronary heart disease are more than would be expected based on associations in current smokers who exposed to higher doses of cigarette smoke [34]. There are some who argue that current smokers may have adaptive responses that lead to lower increases in CHD risk at high levels of exposure compared to the increases in risks experienced by light secondhand smokers [35, 36]. Available evidence suggest that cardiovascular system, platelet and endothelial function [37-39], atherosclerosis and arterial stiffness [40, 41], oxidative stress [42], inflammation [43, 44], and increased infarct size is too much sensitive to the toxins in secondhand smoke. The effects of even short-term exposure (minutes to hours) to secondhand smoke are nearly as large (on average 80% to 90%) as current smoking [45].

The current analysis confirmed findings mentioned above and provides sufficient evidence for the association between secondhand smoke exposure and risk of coronary heart disease event. In addition, we observed as a notable finding that the risk of CHD in individuals who are exposed to others' cigarette smoke after smoking cessation (former & secondhand smokers) was greater than the secondhand smokers and former smokers respectively and was getting close to the current smokers. However this group as a class of smoking status had not been examined in other studies which seem to have been neglected. Since this is an important issue, further research should be done to establish this finding.

In the context of smoking intensity, our findings also confirmed the results obtained from the research conducted in recent years [17, 27-29, 46, 47]. It means that the average baseline smoking intensity (cigarette per day) was significantly associated with incidence of CHD as a reflection of dose-response pattern. Slight inconsistencies in the size of the risk among studies may be attributed to diversity in study participants, or may be due to residual confounding and/or interaction with other baseline factors including physical activity, nutritional and genetic factors [48].

Strengths of the present study include the large population based prospective cohort with considerable sample size and more than 14 years follow-up. Track and frequent follow-up of participants as well as in-person assessment of smoking histories resulted in a comprehensive picture of study exposure. Because almost the main potential covariates related to the CHD were considered, the estimated hazard ratios can be claimed are valid and accurate. Modeling of smoking history in the context of coronary heart disease was performed using two distinct phenotypes

of cigarette smoking (smoking status as a common phenotype and smoking intensity as a better proposed alternative).

The present study has several sources for uncertainty. Although smoking histories information was obtained in-person, recorded data on duration of smoking cessation and history of other types of tobacco smoking were not very reliable. Furthermore, a recall bias may have happened about smoking initiation and exact date to quit smoking. Our analysis might have underestimated the true hazard ratio because of the social stigma of cigarette smoking in Iranian women, leading to underreporting of cigarette smoking in female participants. Finally, there is the probability of residual confounding in our models despite carefully adjustment for main confounders.

Findings of this large population-based prospective cohort indicated that current, former & secondhand, former, and secondhand smoking increase risk of incident coronary heart disease respectively compared to never smokers. Furthermore, an evidence of a significant dose-response pattern between increasing the number of cigarette per day (smoking intensity) and risk of CHD was observed. The risk of CHD in individuals who were exposed to others' cigarette smoke after smoking cessation was an interesting and remarkable finding. This study has raised this important issue, which needs further exploration. Efforts should be made to transfer this message to health policy makers and governments to improve effective tobacco control and anti-smoking strategies, especially in communities where prevalence of smoking is increasing but smoking-free laws in public environments and political commitment are not available, provided that the message is approved by future studies.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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AUTHOR CONTRIBUTIONS

HS, MS, and MSD conceived the idea and designed the study. HS, SK, MSD, AAM, and MA were involved in planning and supervised the work. SK and MS performed the analysis, drafted the manuscript and designed the figures. HS and AAM aided in interpreting the results and revised the manuscript. All authors reviewed, discussed the results and commented on the manuscript.

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Table 1 Distribution of baseline characteristics of the cohort (TLGS; 1999-2018)

Characteristics	Male N=3709	Female N=4341	Total N=8050
Age, mean (SD), years	47.76 (12.82)	46.10 (11.38)	46.89 (12.11)
Incident CHD-1st, N (%)	663 (8.20)	455 (5.60)	1118 (13.80)
Education Level			
Not graduated	326 (9.30)	375 (9.10)	702 (9.20)
Less than high school (≤ 9 years)	1378 (39.20)	2100 (51.11)	3482 (45.61)
High School (10-12 years)	1156 (32.90)	1170 (28.50)	2329 (30.50)
More than high school (>12 years)	655 (18.60)	467 (1.40)	1127 (14.81)
History of Cigarette Smoking (%)			
No history	1933 (24.10)	4057 (50.50)	6003 (74.60)
Positive history	1770 (22.00)	275 (3.40)	2047 (25.40)
Smoking Status N (%)			
Never smoking	1263 (15.70)	2938 (36.60)	4212 (52.30)
Former/ex-smoking	674 (8.40)	109 (1.40)	783 (9.70)
Current smoking	1096 (13.60)	166 (2.10)	1264 (15.70)
Second-hand smoking	670 (8.30)	1119 (13.90)	1791 (22.2)
Age at starting smoking mean (SD) years	20.65 (10.23)	26.07(13.53)	21.50 (10.98)
≤ 17 N (%)	599 (33.60)	47 (2.60)	647 (36.20)
> 17 N (%)	952 (53.40)	185 (10.40)	1138 (63.80)
History of Noncigarette forms of tobacco N (%)			
No history	2699 (73.30)	3987 (49.80)	6700 (83.50)
Positive history	983 (12.30)	336 (4.20)	1320 (16.50)
History of T2 Diabetes N (%)			
No Diabetes	2376 (64.50)	2622 (62.00)	4229 (63.20)
Pre-Diabetes	830 (22.54)	974 (23.03)	1804 (22.80)
Diabetes	476 (12.96)	633 (14.97)	1109 (14.00)
Cigarettes/Day, median	10 (5-20)	12 (5-20)	8 (5-11)
Smoking Cessation, years	11 (5-20)	11 (4.5-20)	13 (5-22.5)
SBP, mean (SD), (mm Hg)	121.26 (18.61)	121.05 (20.29)	121.14 (19.53)
DBP, mean (SD), (mm Hg)	78.32 (11.04)	78.65 (10.91)	78.50 (10.97)
LDL-C, (mg/dl)	132.05 (36.17)	139.57 (39.89)	136.08 (38.40)
HDL-C, (mg/dl)	37.84 (9.29)	44.60 (11.16)	41.47 (10.87)
Non-HDL, (mg/dl)	173.11 (41.92)	177.61 (47.71)	175.65 (45.35)
Body Mass Index, (kg/m ^{2})	26.29 (3.96)	28.53 (4.79)	27.49 (4.56)

Table 2 Description of baseline cohort characteristics separated by cigarette smoking status (TLGS; 1999-2018)

Characteristics/Covariates	Never Smoking N= 4212	Former Smoking N= 498	Current Smoking N= 1264	Secondhand N= 1791	Former & Secondhand N= 285
Age, mean (SD), years	47.49 (12.37)	54.25 (12.84)	44.85 (10.76)	44.66 (11.05)	48.32 (12.77)
Coronary Heart Disease (%)	512 (12.20)	121 (24.30)	220 (17.40)	208 (11.60)	57 (20.00)
Sex/ Male (%)	1263 (30.10)	420 (84.30)	1096 (86.80)	670 (37.50)	254 (89.10)
Education Level					
Not graduated (%)	354 (8.80)	50 (10.50)	109 (9.10)	164 (9.80)	26 (9.50)
Less than high school (≤ 9 years) (%)	1969 (49.00)	224 (47.30)	454 (37.80)	727 (43.40)	108 (39.60)
High School (10-12 years) (%)	1146 (28.50)	121 (25.50)	454 (37.80)	513 (30.60)	95 (34.80)
More than high school (>12 years) (%)	549 (13.70)	79 (16.70)	184 (15.30)	271 (16.20)	44 (16.10)
Age at starting smoking (years)					
≤17	NA	102 (26.45)	502 (40.51)	NA	47 (27.32)
>17	NA	276 (73.54)	737 (59.48)	NA	125 (72.67)
Intensity (Cigarettes per Day)					
< 10	NA	77 (88.50)	576 (46.50)	NA	44(86.30)
10-19	NA	9 (10.30)	548 (44.22)	NA	6 (11.80)
≥ 20	NA	1 (1.10)	116 (9.40)	NA	1 (2.00)
History of Smoking Cessation, years					
<5	NA	105 (21.40)	0	NA	83 (29.60)
5-9	NA	90 (18.40)	0	NA	52 (18.60)
10-14	NA	77 (15.70)	0	NA	45 (16.10)
15-24	NA	129 (26.30)	0	NA	55 (19.60)
≥25	NA	89 (18.20)	0	NA	45 (16.10)
Body Mass Index (Kg/m2)					
<18.5	31 (0.700)	4 (0.80)	40 (3.20)	12 (0.70)	5 (1.80)
18.5-24.9	1056 (25.20)	157 (31.60)	491 (39.00)	455 (25.50)	92 (32.30)
25-29.9	1844 (43.90)	230 (46.30)	533 (42.30)	792 (44.40)	133 (46.70)
≥30	1267 (30.20)	106 (21.30)	196 (15.60)	524 (29.40)	55 (19.30)
History of T2 Diabetes N (%)					
No Diabetes	2514 (61.40)	258 (53.30)	877 (71.80)	1145 (66.50)	169 (61.00)
Pre-Diabetes	987 (24.10)	134 (27.70)	118 (9.70)	222 (12.70)	47 (17.00)
Diabetes	591 (14.40)	92 (19.00)	226 (18.50)	381 (21.80)	61 (22.00)

Blood Pressure, mean (SD), mm Hg					
SBP	122.72 (20.01)	126.20 (20.20)	115.31 (17.13)	119.87 (18.97)	119.86 (18.97)
DBP	79.47 (10.96)	79.22 (10.99)	74.94 (10.38)	78.51 (10.63)	78.51 (10.63)
LDL-C, (mg/dl)	43.09 (10.92)	39.43 (9.56)	37.37 (9.69)	41.63 (11.17)	132.66 (36.18)
HDL-C, (mg/dl)	138.81 (39.59)	140.28 (37.99)	131.07 (36.31)	132.66 (36.18)	41.63 (11.17)

Table 3. Multivariable adjusted risk of CHD separated by cigarette smoking status

Variables	No. of People	No. of CHD	Model 1	Model 2	Model 3	Model 4
			HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Smoking status						
never smoker	4212	512	1	1	1	1
former smoker	498	121	2.26 (1.85-2.75)	1.56 (1.28-1.91)	1.37 (1.112-1.69)	1.39 (1.12-1.72)
current smoker	1264	220	1.58 (1.35-1.86)	2.07 (1.76-2.43)	1.76 (1.48-2.09)	1.99 (1.65-2.39)
secondhand smoker	1791	208	1.02 (0.87-1.20)	1.27 (1.07-1.49)	1.24 (1.05-1.46)	1.27 (1.07-1.51)
former & secondhand smoker	285	57	1.86 (1.41-2.44)	1.82 (1.38-2.39)	1.58 (1.19-2.09)	1.55 (1.15-2.08)
Age, mean **(**years)	-	-	-	1.07 (1.06-1.07)	1.06 (1.06-1.07)	1.05 (1.05-1.06)
Gender						
female	4341	455	-	-	1	1
male	3709	663	-	-	1.37 (1.19-1.57)	1.57 (1.35-1.84)
Education						
Not graduated	326	113	-	-	-	1
<=9	1378	547	-	-	-	0.92 (0.76-1.15)
10-12	1156	262				0.88 (0.70-1.11)
>12	655	134	-	-	-	0.78 (0.59-1.01)
T2DM						
normal	2376	468	-	-	-	1
prediabetes	830	292	-	-	-	1.21 (1.04-1.42)
diabetes	476	327	-	-	-	1.91 (1.99-2.72)
BMI, kg/m^2	-	-	-	-	-	1.01 (0.99-1.01)
SBP, mmHg	-	-	-	-	-	1.01 (1.004-1.01)
DBP, mmHg	-	-	-	-	-	1.01 (1.00-1.01)
LDL-cholesterol, mg/dl	-	-	-	-	-	1.01 (1.005-1.01)
HDL-cholesterol, mg/dl	-	-	-	-	-	0.98 (0.98-0.99)

Model 1; crude model (smoking status alone)
Model 2; adjusted for age
Model 3; adjusted for age and sex
Model 4; adjusted for age, sex, education level, T2DM, BMI, SBP, DBP, LDL and HDL-Cholesterol

Table 4. Multivariable adjusted risk of CHD separated by smoking intensity (Cigarette per day)

Variables	No. of people	No. of CHD	Model 1	Model 2	Model 3	Model 4
			HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Smoking intensity						
never smoker	6003	720	1	1	1	1
< 10, cigarettes per day	830	124	1.36 (1.11-1.66)	1.71 (1.40-2.10)	1.52 (1.23-1.89)	1.65 (1.32-2.06)
10 - 19	455	96	1.76 (1.43-2.15)	2.18 (1.78-2.68)	1.87 (1.50-2.33)	2.22 (1.75-2.80)
≥ 20	88	24	2.31 (1.58-2.37)	2.74 (1.87-3.99)	2.31 (1.56-3.41)	2.38 (1.58-3.58)
Age, mean (years)	-	-		1.07 (1.06-1.07)	1.07 (1.06-1.07)	1.06 (1.05-1.06)
Gender						
female	4341	455	-	-	1	1
male	3709	663	-	-	1.32 (1.14-1.52)	1.46 (1.24-1.72)
Education						
Not graduated	326	113	-	-	-	1
<=9, years	1378	547	-	-	-	0.88 (0.70-1.11)
10-12	1156	262				0.86 (0.67-1.10)
>12	655	134	-	-	-	0.75 (0.56-0.99)
T2DM						
normal	2376	468	-	-	-	1
prediabetes	830	292	-	-	-	1.25 (1.06-1.47)
diabetes	476	327	-	-	-	2.48 (2.10-2.94)
BMI, kg/m^2	-	-	-	-	-	1.02 (1.00-1.03)
SBP, mmHg	-	-	-	-	-	1.01 (1.005-1.01)
DBP, mmHg	-	-	-	-	-	1.02 (1.00-1.02)
LDL-cholesterol, mg/dl	-	-	-	-	-	1.01 (1.005-1.01)
HDL-cholesterol, mg/dl	-	-	-	-	-	0.98 (0.97-0.99)

Model 1; crude model (smoking status alone)
Model 2; adjusted for age
Model 3; adjusted for age and sex
Model 4; adjusted for age, sex, education level, T2DM, BMI, SBP, DBP, LDL and HDL-Cholesterol

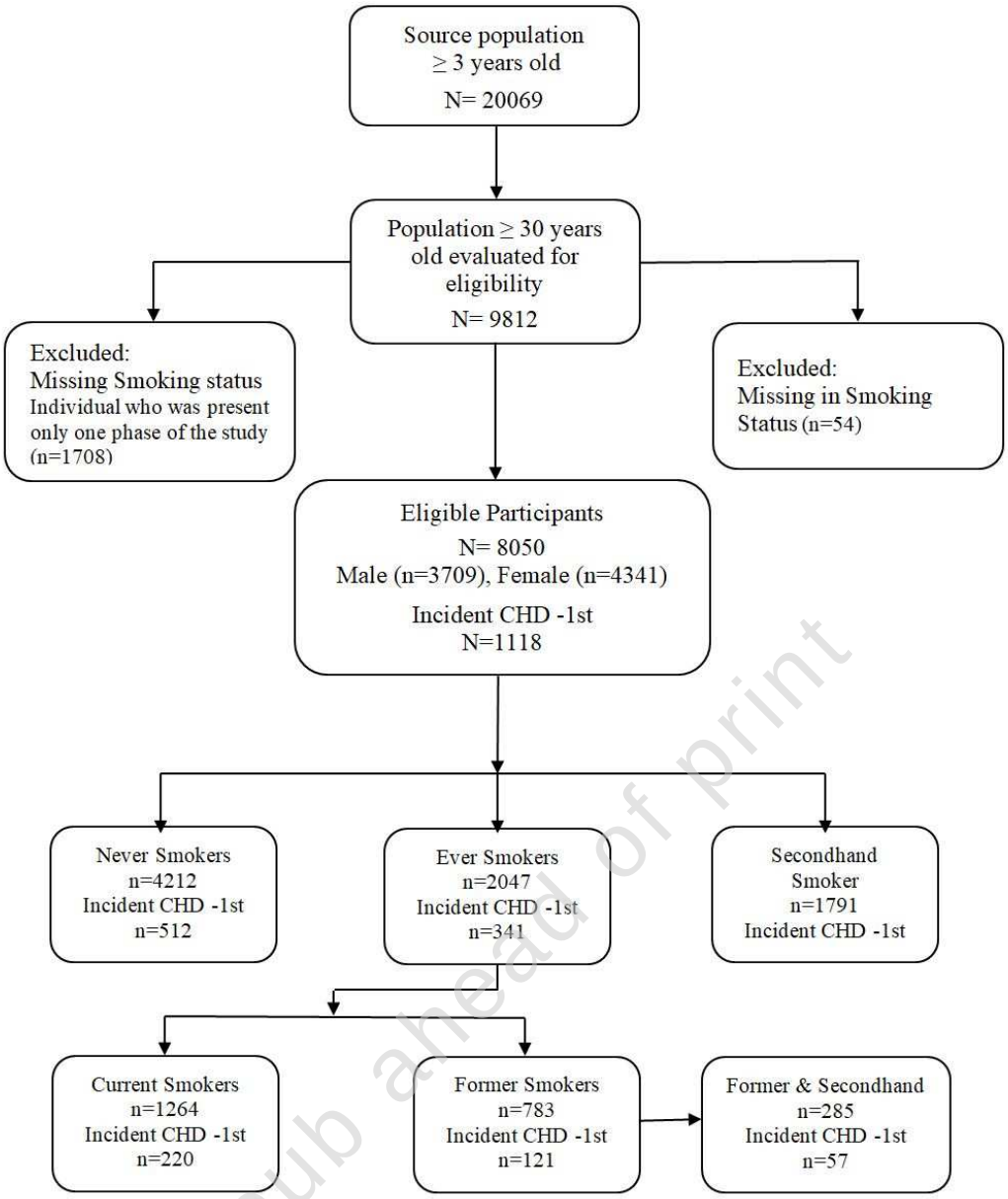

Figure 1 Flow diagram of study design and participants in the TLGS cohort (1999-2018)

Figures

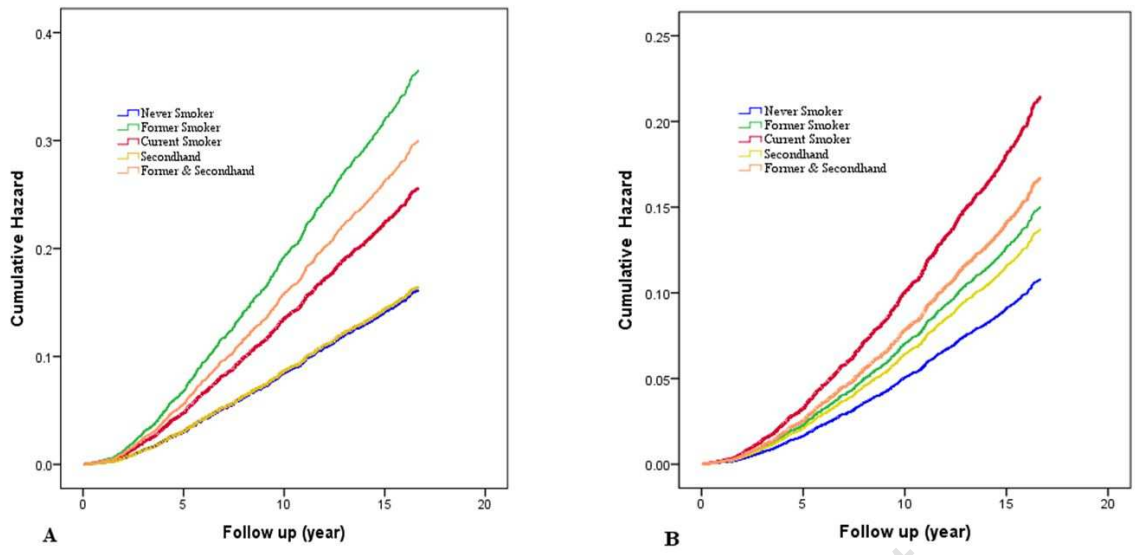

Figure 2 Risk of CHD based on crude (A) and multivariable fully adjusted model (B) by cigarette smoking status

Figure 2