Original Article

Combined Effect of Smoking and Obesity on Coronary Heart Disease Mortality in Male Veterans: A 30-year Cohort Study*

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Abstract

Objective Evidence is lacking regarding the combined effects of smoking and obesity on mortality from coronary heart disease in male veterans. This study aimed to explore the combined effect of smoking and obesity on coronary heart disease mortality in male veterans in China.

Methods A cohort of 1,268 male veterans from 22 veteran centers in Xi'an (Shaanxi Province, China) were followed up once every 2 years from February 1, 1987 to October 30, 2016. The endpoint was death from any cause. The hazard ratio (*HR*) of each risk factor and the 95% confidence interval (*CI*) were calculated using a multivariate Cox proportional hazard model.

Results The total follow-up was 24394.21 person-years; each subject was followed up for a mean duration of 19.24 years. By the end of the study, of the 1,268 veterans, 889 had died, 363 were alive, and 16 were lost to follow-up. Cox regression analysis results revealed that current smoking (*HR*: 1.552, 95% *CI*: 1.074–2.243), obesity (*HR*: 1.625, 95% *CI*: 1.024–2.581), and the combined effect of the two factors (*HR*: 2.828, 95% *CI*: 1.520–5.262) were associated with coronary heart disease mortality.

Conclusion Our results suggest that obese veterans who smoke might be an important target population for coronary heart disease mortality control.

Key words: Smoking; Obesity; Coronary heart disease; Combined effect; Cohort study

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INTRODUCTION

Evidence is lacking regarding the combined effects of smoking and obesity on mortality due to coronary heart disease (CHD) in male veterans. This is the first veteran cohort study in Chinese military. Cardiovascular disease (CVD) is a leading cause of death globally, contributing to more than 17 million deaths in 2017, of which mortality from CHD is the most prevalent[1]. The morbidity of CHD in the United States is high, with 300,000 to 400,000 sudden cardiac death cases per year. In China, CHD has been shown to be a main threat to human health[2]. The morbidity of CHD in China was relatively lower than that in Western countries; however, due to the huge population base, was

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about 23 million CHD cases were reported in China in 2016[3].

Apart from the proven risk factors (age, diabetes mellitus, and insulin resistance), some blood parameters, for example, Apolipoprotein B, apolipoprotein AI, apolipoprotein B/apolipoprotein AI[4], lipoprotein A[5], high fibrinogen acidosis[6], neopterin[7], and adiponectin[8], are also associated with CHD. Other independent risk factors include ankle arm index[9], depression[10], and left ventricular hypertrophy[11]. Among those, smoking is one of the major traditional risk factors for coronary heart disease. Doll and Hill first studied the association between smoking and mortality due to relevant diseases[12]. Their study, which established smoking as an independent risk factor for death, also became a classical cohort epidemiological study because of the high-quality experimental design. Cigarette smoking plays an important role in the onset of acute coronary thrombosis, which causes the majority of sudden cardiac deaths and myocardial infarctions[13]. The mechanism involved includes vascular inflammation, platelet coagulation, vascular dysfunction, and oxidation of low-density lipoprotein cholesterol[14,15]. Epidemiological, animal, and clinical evidence showed that smoking was not only an independent factor for CHD, but also has combined effect with other factors such as high blood pressure and high cholesterol[16]. In addition, with obesity, there is a higher risk of CHD. Several studies have examined the risk of mortality associated with obesity in nonsmokers[17,18]. However, only limited data on the magnitude of CHD mortality risk about overweight individuals, who are also former or current smokers, exist.

Currently, evidence of most cohort studies only focused on single factor effect, while evidence on the combined effect of multi-factors is lacking. Additionally, some case control studies with in-hospital patients, are not representative of the general population[19]. Therefore, the present study aimed to clarify the combined effect of smoking and obesity on CHD mortality risk based on a cohort data collected from 1987 to 2016.

MATERIALS AND METHODS

Study Design and Participants

Ethics approval was obtained from the ethics committee of Xijing Hospital (Xi'an, Shaanxi Province, China). All experiments and study procedures were performed in accordance with the relevant guidelines and regulations, including any relevant details. Informed consent was obtained from each participant. Veterans were recruited from 22 veteran centers in Xi'an (Shaanxi Province, China) from February 1, 1987 to October 30, 2016. The inclusion criteria were male sex, age ≥ 55 years, registered veterans, able to complete the investigations and tests during the study duration, and provision of voluntary informed consent.

Data Collection

Each subject was surveyed by trained interviewers (professional clinicians at the veteran centers) for information on age, lifestyle (smoking, drinking, sport activities), and medical history (CHD, hypertension, cerebral stroke, diabetes). The subjects' physiological parameters, including height, weight, blood pressure, serum cholesterol (enzymatic assay) and triglyceride (acetylacetone assay) were also recorded. Body mass index (BMI), calculated as weight divided height squared (kg/m^2), was further categorized into underweight (< 18.5 kg/m^2), normal weight (18.5 to 24.0 kg/m^2), overweight (24.0 to 28.0 kg/m^2), or obesity (fat) (≥ 28.0 kg/m^2). Negative affairs in this study included divorce, widowhood, childlessness, social reduction, psychosomatic disorders, and property loss. Past medical history included CHD, hypertension, stroke, and diabetes mellitus.

According to the published 1997 World Health Organization (WHO) criteria, smoking is defined as the consumption of at least one cigarette per day and a smoking history of longer than 1 year. Current smokers were defined as those who were currently smoking while former smokers were defined as those that have discontinued smoking for at least 2 years at the time of the baseline survey. Smoking index (SI) = number of cigarettes per day × duration of smoking. Hypertension was diagnosed as systolic blood pressure of at least 18.7 kPa (140 mmHg) or diastolic blood pressure of at least 12 kPa (90 mmHg) without any anti-hypertension medication. The cause of death was determined from the death certificates or medical records (from a hospital that is at least at municipal level) and was verified by two senior clinicians at Xijing Hospital (Xi'an, Shaanxi Province, China). All deaths were encoded following the WHO International Classification of Diseases (10th version).

Statistical Analysis

All information was blindly input into the Foxbase database by two staff separately to check for errors. After cleaning, the data were then

converted and analyzed using Statistical Analysis System (SAS 9.3; SAS Institute Inc., NC, USA). Age (years) was categorized into '< 60', '60–64', '65–69', and '≥ 70'. The hazard ratio (*HR*) of each factor and the 95% confidence interval (95% *CI*) were calculated using a multivariate Cox proportional hazard model and the proportional hazard assumptions were checked using Schoenfeld residuals. To present much stronger association between potential risk factors and CHD deaths, continuous variables were first entered into the multivariate analysis model. After that, important categorical risk factors (age, smoking index, BMI, and systolic blood pressure) were analyzed to further explore correlations. Significant variables with a *P* value of ≤ 0.05 in univariate analysis were then entered into the multivariate model. However, based on previous evidence, duration of smoking years, alcohol intake, exercise, negative affairs, and total cholesterol were retained in the model regardless of their univariate results. The log-rank statistic was used to compare Kaplan-Meier curves. All statistical analyses were performed using SPSS 23.0 software (Authorization No.6b4543b2xxxxf3c69a68). All *P* values were two-sided and statistical significance was defined as $P < 0.05$.

RESULTS

Baseline Characteristics of the Study Population

During the 24,394.21 person-years of follow-up, 889 deaths, including 192 (21.60%) CHD deaths, were recorded. The adjusted death rate was 3,644 per 100,000 person-years over an observed mean person-years of 19.24. At baseline, the subjects in this cohort study were all older than 50 years, with a mean age of 62.55 ± 5.19 years. In addition, 363 alive and 16 lost-to-follow-up participants were registered.

Association of Risk Factors with CHD Death

As shown in Table 1, using a Cox proportional hazard model, the results showed that in the univariate analysis, age, BMI, systolic blood pressure, diastolic blood pressure, triglyceride, duration of smoking year, history of hypertension, and diabetes were associated with CHD death. The *HR* (95% *CI*) for these factors were 1.122 (1.092–1.152), 1.096 (1.045–1.150), 1.022 (1.015–1.030), 1.020 (1.007–1.033), 1.002 (1.000–1.004), 1.010 (1.001–1.018), 2.664 (1.988–3.570), and 2.736 (1.701–4.403), respectively. After adjusting for age (years), systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, alcohol intake, exercise, negative affairs, and past medical history (of CHD, hypertension, cerebral vascular sclerosis, and DM), the *HR* (95% *CI*) for BMI and duration of smoking in years were 1.051 (1.000–1.104) and 1.009 (1.000–1.017), respectively.

Table 2 shows the multivariate results of the categorical variables. Individuals aged ≥ 60 years had a significantly increased risk of mortality compared to those aged ≤ 59 years at baseline (60–64 years, adjusted *HR* [a*HR*]: 2.072, 95% *CI*: 1.393–3.082; 65–69 years, a*HR*: 3.627, 95% *CI*: 2.338–5.628; and ≥ 70 years, a*HR*: 5.787, 95% *CI*: 3.312–10.111). In addition, risk factors associated with CHD mortality were *smoking status with current smokers* (a*HR*: 1.552, 95% *CI*: 1.074–2.243), and BMI ≥ 28 kg/m^2 (a*HR*: 1.625, 95% *CI*: 1.024–2.581). The adjusted factors included age, systolic pressure, BMI, total cholesterol, triglyceride, smoking status, alcohol intake, exercise, negative affairs, and past medical history.

Combined Effect of Smoking and BMI on CHD Death

Figure 1A presents the Kaplan-Meier survival curves stratified by baseline BMI. Compared with normal BMI subjects, obese subjects (a*HR*: 1.603, 95% *CI*: 1.012–2.538) had significantly increased risk of mortality at baseline, after adjusting for age, systolic blood pressure, total cholesterol, triglyceride, smoking index, alcohol intake history, exercise, negative affairs, and past medical history. Figure 1B shows the cumulative survival for CHD with the combined effect of smoking and obesity. Compared with normal BMI and nonsmoking subjects, the *HR* and 95% *CI* of the overweight and obesity nonsmokers was 1.936 (1.053–3.561), while those of smokers with overweight and obesity was 2.828 (1.520–5.262) (Table 3 and Table 4).

DISCUSSION

This cohort study is the first reported veteran cohort study in Chinese military. There is lack of evidence regarding the combined effects of smoking and obesity on CHD mortality in male veterans. There is now an urgent need to identify approach by which male veterans can give up smoking and for weight control management by the military health care personnel, especially because of deaths from CHD.

In this prospective cohort study conducted in male veterans in China, we observed that obese

subjects with heavy smoking history had significantly increased risk of CHD death. This risk was found to be 183% higher among them than among the nonsmoking and normal weight subjects.

In accordance with the well-established evidence on the relationship between obesity and CHD mortality, our findings confirm that CHD mortality was higher in veterans with higher BMI. Notably, when BMI was entered into the multivariate analysis model as a categorical variable, it was found to be an independent predictor of CHD mortality. With the increasing living standards, more and more people are becoming obese[20,21], and most studies have reported the association between obesity and CHD[22–25]. The American Heart Association and the National Institutes of Health have identified obesity as the strongest risk factor for CHD. A meta-analysis[26] showed that compared with those of normal weight, the relative risks (RRs) of *overweight* men and women were 1.097 (95% *CI*, 1.001–1.201) and 1.159 (95% *CI*, 1.088–1.235), while the RRs of obese men and women were 1.624 (95% *CI*, 1.459–1.806) and 1.508 (95% *CI*, 1.362–1.67), respectively. According to the UK biobank[23],

Table 1. Risk factors for CHD-related deaths at baseline

Variables	Univariate analysis		Multivariate analysis	
	HR (95% *CI*)	*P* value	a*HR* (95% *CI*)	*P* value
Age (years)	1.122 (1.092–1.152)	< 0.0001	1.108 (1.076–1.142)	< 0.0001
Body mass index (kg/m^2)	1.096 (1.045–1.150)	0.0002	1.051 (1.000–1.104)	0.0491
Systolic pressure (mmHg)	1.022 (1.015–1.030)	< 0.0001	1.012 (1.000–1.024)	0.0472
Diastolic pressure (mmHg)	1.020 (1.007–1.033)	0.0028	0.997 (0.978–1.017)	0.7812
Total cholesterol (mg/dL)	1.002 (0.999–1.005)	0.1925	1.001 (0.997–1.004)	0.7140
Triglyceride (mg/dL)	1.002 (1.000–1.004)	0.0412	1.001 (0.999–1.003)	0.3739
Alcohol intake	1.005 (0.746–1.355)	0.9718	0.902 (0.661–1.231)	0.5157
Exercise	0.756 (0.535–1.068)	0.1125	0.811 (0.570–1.154)	0.2441
Negative affairs	1.312 (0.894–1.926)	0.1655	0.981 (0.661–1.458)	0.9262
Smoking related factors				
Duration of smoking (years)	1.010 (1.001–1.018)	0.0285	1.009 (1.000–1.017)	0.0574
Duration of quitting smoking (years)	0.998 (0.995–1.001)	0.2024		
Cigarettes per day	1.006 (0.991–1.021)	0.4378		
Smoking Index	1.000 (1.000–1.001)	0.0862		
Family history (Yes/No)				
Hypertension	1.202 (0.764–1.892)	0.4254		
Stroke	1.202 (0.764–1.892)	0.4254		
CHD	1.410 (0.904–2.199)	0.1294		
Past medical history (Yes/No)				
CHD	1.857 (1.386–2.488)	< 0.0001	1.071 (0.771–1.487)	0.6818
Stroke	1.671 (0.533–5.235)	0.3783		
Hypertension	2.664 (1.988–3.570)	< 0.0001	1.711 (1.192–2.456)	0.0036
Cerebral vascular sclerosis (CVS)	2.114 (1.481–3.018)	< 0.0001	1.314 (0.891–1.937)	0.1677
Hyperlipidemia (HLP)	0.864 (0.356–2.101)	0.7475		
Diabetes Mellitus (DM)	2.736 (1.701–4.403)	< 0.0001	2.126 (1.301–3.475)	0.0026

Note. Adjusted for age (years), body mass index, systolic pressure, diastolic pressure, total cholesterol, triglyceride, alcohol intake, exercise, negative affairs, duration of smoking years, and past medical history (of coronary heart disease [CHD], hypertension, cerebral vascular sclerosis [CVS], diabetes mellitus [DM]). *HR*, hazard ratio; *CI*, confidence interval; a*HR*, adjusted hazard ratio.

Mendelian randomization analyses support a causal association between higher BMI and mortality from CHD (*HR*: 1.12; 95% *CI*: 1.00–1.25). Importantly, veterans differ from other populations of patients in several other respects. One of the most prominent differences is the need to meet the selection criteria at the time of enlistment. Subjects who had certain preexisting health problems would have been excluded during the recruitment. In addition, volunteering individuals who qualify for military service may be more likely to be physical fit or have other health attributes than those not volunteering

Table 2. Multivariate analysis for risk factors of mortality from CHD at baseline

Item	Number of deaths/ total number	Observed person year/ total observed person year	*HR*	95% *CI*	*P* value
Age (years)					
< 60	39/402	744.9/9314.58	Reference		
60–64	77/473	1352.8/9248.83	2.072	1.393–3.082	0.0003
65–69	52/250	894.5/4108.92	3.627	2.338–5.628	< 0.0001
≥ 70	24/143	244.1/1721.87	5.787	3.312–10.111	< 0.0001
Smoking status					
Never smokers	59/388	1070.5/7982.74	Reference		
Former smokers	66/461	1165.9/8653.68	0.904	0.622–1.314	0.5966
Current smokers	67/419	1000.0/7757.80	1.552	1.074–2.243	0.0192
BMI (kg/m^2)					
< 18.5	2/39	6.0/590.60	0.648	0.156–2.684	0.5497
18.5–24.0	61/511	1086.7/10056.88	Reference		
24.0–28.0	100/587	1643.9/11309.57	1.339	0.966–1.858	0.0798
≥ 28.0	29/131	499.9/2437.16	1.625	1.024–2.581	0.0395
Systolic pressure (mmHg)					
< 120	37/300	667.5/6243.15	Reference		
120–129	43/381	782.1/7718.01	0.696	0.443–1.094	0.1160
130–139	33/207	520.9/3778.99	1.078	0.661–1.759	0.7636
≥ 140	79/380	1265.9/6654.06	1.221	0.785–1.899	0.3767

Note. Adjusted for age, systolic blood pressure, body mass index (BMI), total cholesterol, triglyceride, smoking status, alcohol intake, exercise, negative affairs, past medical history (of coronary heart disease [CHD], hypertension, stroke, diabetes mellitus [DM]). *HR*, hazard ratio; *CI*, confidence interval.

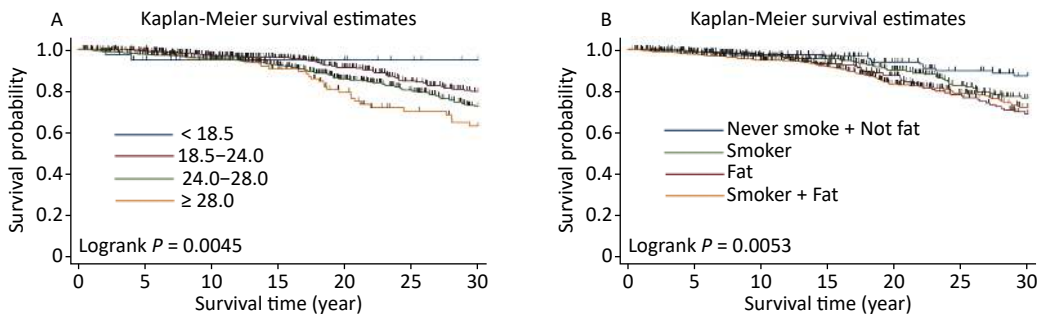

Figure 1. Comparison of the cumulative survival rates of the different body mass index (BMI) categories, for different smoker, fat, or the combined smoker and fat groups. (A) Comparison of the cumulative survival rates of the different BMI groups; (B) Comparison of the cumulative survival rates of the different smoker, fat, or the combined smoker and fat groups.

for military service. Therefore, at baseline, in our study, the subjects seemed to be much healthier than the general population to some extent, which implies the need for caution when interpreting our findings.

Smoking was observed to be an independent risk factor for CHD mortality in our study, and it seemed that higher mortality appears to be confined to the current smoker subgroup. This finding is in agreement with those of previous prospective studies[27–29]. In 2017, smoking was the leading risk factor for the burden of disease in China[30], and it is considered an important modifiable factor that can be prevented, to decrease mortality. Additionally, with increasing rates of smoking, passive smoking is becoming an increasingly severe social problem in China. However, our study had no information on passive smoking. The effect of passive smoking on CHD mortality needs further studies.

Although there are more studies on the independent effects of risk factors, there is less evidence on the multiple effects of multiple risk factors. Smoking and obesity are independent risk factors for CHD. This study investigated the combined effect of smoking and obesity on CHD mortality. In this study, the association of the combined effect of BMI and smoking on CHD mortality was found. In terms of the present study results, there is another issue worth mentioning. The estimated *HR* of the combined effects was higher than that of either BMI or smoking. Evaluation of the combined effects of BMI and smoking are of particular importance because it provides insights on the potential mechanism of the individual change in risk in relation to the values of conventional risk factors and convey the clinical importance. The potential reasons for these may be that the combination of the two risk factors, resulted in significantly high point estimates (*HR*) with wide *CI*s. However, the interaction effect on the extent of effect of these risk factors, for example, the effect of the severity of smoking and the change in BMI trend, deserved to be further explored. As traditional risk factors for CHD, BMI and smoking were simple to assess, and might improve the identification of high-risk CHD patients for a more intensive secondary

Table 3. Effect of BMI of CHD related death at baseline

BMI (kg/m^2)	< 18.5	18.5–24.0	24.0–28.0	≥ 28.0
< 18.5	1	1.670 (0.399–6.989)	2.094 (0.503–8.724)	2.677 (0.614–11.671)
18.5–24.0		1	1.254 (0.905–1.737)	1.603 (1.012–2.538)
24.0–28.0			1	1.278 (0.835–1.956)
≥ 28.0				1

Note. Adjusted for age, systolic pressure, total cholesterol, triglyceride, smoking index, alcohol intake, exercise, negative affairs, past medical history (of coronary heart disease [CHD], hypertension, stroke, diabetes mellitus [DM]). BMI, body mass index.

Table 4. Combined effect of smoking and obesity of CHD related death at baseline (*HR* and 95% *CI*)

Smoking and fat	Never smoker + not fat	Never smoker + fat	Former smoker + not fat	Former smoker + fat	Current smoker + not fat	Current smoker + fat
Never smoker + not fat	1	1.936 (1.053–3.561)	1.451 (0.736–2.861)	1.435 (0.769–2.678)	1.853 (0.959–3.579)	2.828 (1.520–5.262)
Never smoker + fat		1	0.750 (0.445–1.263)	0.741 (0.479–1.148)	0.957 (0.582–1.575)	1.461 (0.936–2.279)
Former smoker + not fat			1	0.989 (0.591–1.655)	1.277 (0.723–2.254)	1.949 (1.150–3.302)
Former smoker + fat				1	1.291 (0.780–2.138)	1.971 (1.262–3.078)
Current smoker + not fat					1	1.527 (0.923–2.524)
Current smoker + fat						1

Note. Adjusted for age, systolic pressure, total cholesterol, triglyceride, alcohol intake, exercise, negative affairs, past medical history (of coronary heart disease [CHD], hypertension, stroke, diabetes mellitus [DM]), fat refers to body mass index (BMI) > 28.0.

prevention treatment.

Several limitations in our study should be considered. First, the subjects in our study were all males (all of whom had prior military service and heavy exercise experience); therefore, the results should be considered population-specific. Therefore, our results may not apply to more general populations. Second, although BMI is the most commonly used factor to identify obesity status, it is not the optimal index. Other indexes (waist to hip ratio and lean body weight) are suggested to be superior. Furthermore, our analysis only included the baseline BMI measurements. We did not examine the influence of changes in body habitus during the follow-up. We also only had the baseline data on cardiorespiratory fitness, and other exposure variables. Therefore, we do not know if changes in any of these variables occurred during the follow-up or how they might have influenced the results. Third, the present study did not investigate possible inequality in the uptake of treatments for CHD, which might have affected the direction of the associations of potential risk factors with CHD mortality. Finally, smoking status was self-reported; this approach to measurement was sometimes questioned under the assumption that smokers tend to underestimate the amount smoked or even deny smoking.

CONCLUSIONS

Our results suggest that obese veterans who smoke might be an important target population for coronary heart disease mortality control. Thus, we conclude that more attention should be paid to the prevention of the combined risk factors in the management of CHD. Efficient interventions on smoking and obesity could have significant result on CHD death; further study is needed to provide stronger evidence.

CONFLICTS OF INTEREST

None.

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