

The Effect of Total Cholesterol on Myocardial Infarction in Chinese Male Hypertension Population¹

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Objective Total cholesterol (TC) is an important risk factor for myocardial infarction (MI), but the effect of TC on MI in Chinese male hypertension population has not been well documented. We conducted a prospective cohort study to determine the incidence and relative risk for MI across a wide range of TC levels in Chinese male hypertension population. **Methods** A cohort of 5 298 male employees aged 18-74 years recruited from Capital Steel and Iron Company in Beijing of China in 1974-1980 was followed up for an average of 20.84 years. A total of 122 incident MI cases were identified during the period of follow-up. **Results** The incidence of MI among participants with elevated TC and those with desirable TC in male non-hypertension population was 137.20 and 63.81 per 100 000 person-years, respectively; and the corresponding incidence in male hypertension population was 279.80 and 130.96 per 100 000 person-years, respectively. After adjustment for important covariables, 10.38%, 16.71%, and 23.80% of MI cases were attributable to hypertension, elevated TC, and hypertension plus elevated TC, respectively. In male hypertension population, the multivariate adjusted hazard ratios of MI were 1.21, 2.39, 3.38, and 3.95 for participants with TC level of 5.17-5.68, 5.69-6.20, 6.21-6.71, and ≥ 6.72 mmol/L, compared with those with TC < 5.17 mmol/L. The corresponding population attributable risks were 2.92%, 9.20%, 8.87%, and 9.84%, respectively. **Conclusion** Elevated TC is an important independent risk factor of MI both in male non-hypertension and hypertension populations. There is a linear association between TC level and MI incidence in Chinese male hypertension population.

Key words: Hypertension; Cholesterol; Myocardial infarction; Cohort studies

INTRODUCTION

Cardiovascular disease is already the leading cause of mortality in China, and coronary heart disease (CHD) is the 4th leading cause of death^[1-3]. It is estimated that there were 12.3 million CHD events and 5.2 million CHD deaths in China in 2000-2009. It is predicted that 3.4 million excess CHD events and 1.4 million excess CHD deaths will occur in the decade 2010-2020 and 7.8 million excess CHD events (a 69% increase) and 3.4 million excess CHD deaths (a 64% increase) in the decade 2020-2029 as compared with in 2000-2009^[4].

Elevated total cholesterol (TC) and hypertension are two most important modifiable risk factors for myocardial infarction (MI)^[5-11]. They co-exist more often than would be expected by chance alone^[12], and they increase the risk of MI. But the effect of TC on MI in Chinese male hypertension population has not

been well documented. We conducted a prospective cohort study in China to determine the incidence and relative risk for MI across a wide range of TC levels in male hypertension population; to compare the risk of TC level on MI in them with that in male non-hypertension population.

MATERIALS AND METHODS

Study Population

Subjects were selected from the male employees in Capital Steel and Iron Company (CSIC). Seven representative factories (of the 21 factories in CSIC) located within 15 kilometers from the city center, were included for study. The total number of male employees aged 18-74 years in these 7 factories was 7 933. These employees were invited to participate in a health check in 1974, 1979, and 1980, respectively.

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In total, 5 298 male employees attended this health check, of whom 5 270 were free of CHD. Final follow-up was conducted in 2001, and loss to follow-up was 312 participants. There were 122 incident MI cases identified during the period of follow-up.

Baseline Examination

All baseline data were obtained using a standard questionnaire by trained research staff. Demographic data and other risk factors, such as life style, medical history, height, weight, blood pressure, serum TC, and electrocardiogram, were collected according to the same protocol.

Blood pressure was measured in the right arm using a standard mercury sphygmomanometer on a single occasion after participants had been seated at least 5 minutes. Serum TC was also determined on the same single occasion, from an 8 hours fasting venous blood sample, using the enzyme reagent method. A smoker was defined as anyone who smoked not less than 1 cigarette per day on average, and lasted for 1 year at least. An alcohol drinker was defined as anyone who drank at least once a week in the past 1 year. Body mass index (BMI) was calculated as weight (kg)/height (m)².

Follow-up Data Collection

The follow-up survey was carried out in 1982, 1987, 1993, and 2001, respectively. During the follow-up period, trained research staff administered a standard questionnaire to get the information on the incidence and death for cardiovascular disease by way of face to face or telephone interviews. If participants moved, their relatives or colleagues were contacted for information, and hospital records were checked. If participants reported CHD, their hospital records were checked by doctors from the Fuwai Hospital (a tertiary care referral center) or the company hospital. MI cases were identified according to WHO standards, including 2 of the following 3: Electrocardiogram changes, elevated cardiac enzyme levels (creatinase), and typical chest pain. Death certificates were also obtained for all fatalities to confirm cause of death. An end-point assessment committee at the Fuwai Hospital reviewed all of the incidence and death records to determine the final end-point events.

Statistical Analysis

Study participants were grouped according to

their baseline blood pressure level (non-hypertension: systolic blood pressure (SBP) <140 mmHg and diastolic blood pressure (DBP) <90 mmHg; and hypertension: SBP \geq 140 mmHg and/or DBP \geq 90 mmHg)^[13]. In each blood pressure group, study participants were grouped into 2 categories: desirable TC and elevated TC (baseline TC <5.17 mmol/L, TC \geq 5.17 mmol/L)^[14]. No administration of antihypertensive or cholesterol-lowering medications was considered, because they were seldom used in employees in CSIC in the 1970s. This analysis was performed with the 4 521 individuals that had serum cholesterol measurements available and no CHD in baseline. For descriptive statistics of the baseline characteristics, continuous variables were compared using Student *t* test; categorical variables were compared using chi-square test. Person-years of follow-up for each study participant were calculated from the date of the baseline examination until the date of occurrence of MI. Cumulative incidence of MI was calculated by the combined categories of blood pressure and TC level using the Kaplan-Meier method with differences across categories assessed using the log-rank test^[15-16]. In participants with hypertension, five categories (baseline TC level <5.17, 5.17-5.68, 5.69-6.20, 6.21-6.71, and \geq 6.72 mmol/L) were created to allow a detailed examination of the association between TC and incidence of MI across a wide range of TC levels.

Cox proportional hazards models were used to adjust for baseline variables, and compute hazard ratios (HR) estimating the relative risk (RR) of MI associated with level of TC. The presence of a linear association was tested using the median TC in each of the categories as a continuous variable in the Cox proportional hazards models^[17]. The population attributable risk (PAR) was used to estimate the proportion of MI explained by TC level. The formula of PAR was expressed as $PAR = P(RR-1) / [P(RR-1) + 1]$. Where P was the proportion exposed in the entire cohort^[18]. Statistical analysis was performed using SPSS, (Version 12.0).

RESULTS

Baseline characteristics of the study participants are presented in Table 1. In male non-hypertension population, participants with elevated TC were older, and more likely to have a higher BMI and SBP level, to drink alcohol than those with desirable TC ($P < 0.05$). In male hypertension population, participants with elevated TC were more likely to have a higher BMI than those with desirable TC ($P < 0.05$).

TABLE 1

Baseline Characteristics among 4 521 Male Employees in Capital Steel and Iron Company

Baseline Characteristics	Non-hypertension			Hypertension		
	Desirable TC (n=2 159)	Elevated TC (n=898)	P Values	Desirable TC (n=873)	Elevated TC (n=591)	P Values
Age (year)	43.30±8.29	45.05±6.84	<0.001	47.26±7.00	47.95±6.87	0.061
BMI (kg/m ²)	22.49±2.41	23.06±2.56	<0.001	23.99±2.92	24.64±2.83	<0.001
TC (mmol/L)	4.25±0.59	5.90±0.70	<0.001	4.34±0.61	5.93±0.73	<0.001
SBP (mmHg)	113.45±10.41	114.45±10.44	0.015	142.63±16.92	143.74±17.19	0.221
DBP (mmHg)	74.49±6.65	75.00±6.82	0.054	94.30±8.59	94.37±9.85	0.888
Smoking (%)	75.41	75.20	0.901	71.70	67.01	0.057
Drinking (%)	44.66	49.94	0.008	49.30	54.00	0.079

Note. TC, total cholesterol. BMI, body mass index. SBP, systolic blood pressure. DBP, diastolic blood pressure. All data are means± standard deviation or proportion.

During an average follow-up of 20.84 years (103 927 person-years of observation), 122 incident MI cases (117.39 cases per 100 000 person-years) were identified. In male non-hypertension population, the incidence of MI was 137.20 per 100 000 person-years among participants with elevated TC, and 63.81 per 100 000 person-years among those with desirable TC. The corresponding incidence was 279.80 and 130.96 per 100 000 person-years in male hypertension population, respectively.

The cumulative incidence of MI at the end of follow-up was 2.02%, 3.31%, 3.06%, and 8.23% among participants with non-hypertension and desirable TC, non-hypertension and elevated TC, hypertension and desirable TC, and hypertension and elevated TC, respectively ($P<0.001$; Fig. 1).

Multivariate adjusted HRs and PARs of MI incidence by combined categories of blood pressure and TC level are presented in Table 2. Compared with participants with non-hypertension and desirable TC, the multivariate adjusted HRs of MI incidence were 2.01 (1.17-3.45), 1.60 (0.89-2.90), and 3.39 (1.98-5.81) for those with non-hypertension and elevated TC, hypertension and desirable TC, hypertension and elevated TC. 10.38%, 16.71%, and

23.80% of MI cases were attributable to hypertension, elevated TC, and hypertension plus elevated TC, respectively.

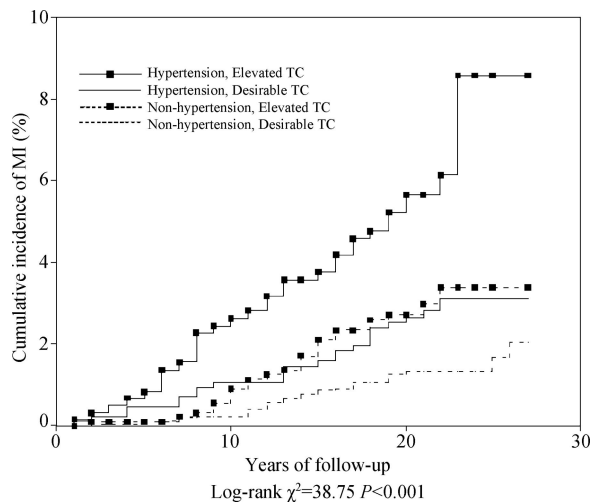


FIG. 1. Cumulative incidence of myocardial infarction (MI) among Male Employees in Capital Steel and Iron Company who had different total cholesterol (TC) and blood pressure level.

TABLE 2

HR and PAR of MI Associated with Level of Blood Pressure and TC in Male Employees in Capital Steel and Iron Company

Blood Pressure Level	TC Level	Multivariate Adjusted HR* (95% Confidence Interval)	P Values	P (%)	PAR (%)
Non-hypertension	Desirable TC	1.00 (Reference)	-	-	-
	Elevated TC	2.01 (1.17-3.45)	0.011	19.86	16.71
Hypertension	Desirable TC	1.60 (0.89-2.90)	0.118	19.31	10.38
	Elevated TC	3.39 (1.98-5.81)	<0.000	13.07	23.80

Note. HR, hazard ratio. PAR, population attributable risk. MI, myocardial infarction. TC, total cholesterol. *Adjusted for age, BMI, and smoking.

Multivariate adjusted HRs and PARs of MI incidence by detailed TC categories in male hypertension population are presented in Table 3. After multivariate adjustment for age, BMI, SBP, and smoking, significant and positive association was observed between TC levels and MI incidence in male hypertension population (P for trend <0.001). The multivariate adjusted HRs of MI incidence were

1.21 (0.55-2.67), 2.39 (1.05-5.47), 3.38 (1.43-8.03), and 3.95 (1.72-9.03) for participants with TC level of 5.17-5.68, 5.69-6.20, 6.21-6.71, and ≥ 6.72 mmol/L, compared with those with TC <5.17 mmol/L in them. The corresponding PARs were 2.92%, 9.20%, 8.89%, and 9.84%. The multivariate adjusted PARs of MI incidence approached to 9% in categories of TC not less than 5.69 mmol/L.

TABLE 3

HR and PAR of MI Associated with Level of TC in Hypertension Category in Male Employees in Capital Steel and Iron Company

TC Level (mmol/L)	Multivariate Adjusted HR* (95% Confidence Interval)	P Values	P (%)	PAR (%)
<5.17	1.00 (Reference)	-	-	-
5.17-5.68	1.21 (0.55-2.67)	0.638	14.30	2.92
5.69-6.20	2.39 (1.05-5.47)	0.039	7.29	9.20
6.21-6.71	3.38 (1.43-8.03)	0.006	4.09	8.87
≥ 6.72	3.95 (1.72-9.03)	0.001	3.70	9.84
P for Trend	<0.001			

Note. HR, hazard ratio. PAR, population attributable risk. MI, myocardial infarction. TC, total cholesterol. *Adjusted for age, BMI, SBP, and smoking.

DISCUSSION

As shown by previous reports of this cohort^[19-20] and other studies^[5, 12, 21], elevated blood pressure and TC level were important risk factors for MI. They always acted together, and increased the risk of MI.

Our study in this cohort demonstrated that elevated TC and hypertension were important independent risk factors for MI. The incidence of MI among participants with single elevated TC (137.20 per 100 000 person-years) or single hypertension (130.96 per 100 000 person-years) was higher than among those with non-hypertension and desirable TC (63.81 per 100 000 person-years), and the incidence among those with elevated TC plus hypertension (279.80 per 100 000 person-years) was much higher than among any other three categories. The cumulative hazard curves showed that, both in male non-hypertension and hypertension populations, the cumulative incidence of MI among participants with elevated TC was much higher than those with desirable TC. 16.71% of incident MI cases could be explained by elevated TC, 10.38% could be explained by hypertension, and 23.80% could be explained by hypertension plus elevated TC.

Our study observed a strong, significant and linear association between TC levels and MI incidence in male hypertension population. 2.92, 9.20, 8.87, and 9.84% of incident MI cases could be explained by TC level of 5.17-5.68, 5.69-6.20, 6.21-6.71, and ≥ 6.72 mmol/L in this population. It

indicated that higher TC level was associated with an increased risk for MI incidence in them. Lowering TC to a desirable level in male hypertension population could decrease 30.83% of incidence of MI, as much as 31.4% in Glazer's report^[22]. When TC level was more than 5.69 mmol/L among them, the HR and PAR were increasing rapidly. It suggested that 5.69 mmol/L might be a cutoff of TC level for MI incidence in male hypertension population in China. In other words, TC level should be lowering to less than 5.69 mmol/L in male hypertension population, which could decrease 27.91% of incidence of MI.

This prospective study was conducted during period of 1974 to 2001, in a large sample of male employees in CSIC, with a high follow-up rate. Standard protocols and instruments along with strict training processes for data collection and a rigorous quality assurance program were used to ensure that the data we collected were of high quality. For these reasons, this study provides reliable information on the effect of risk factors on MI in male employees in CSIC.

The present study has several limitations. Firstly, the information on antihypertensive or cholesterol-lowering treatment at baseline and during the follow-up period was not collected. Therefore, its impact on MI incidence could not be examined. However, the percentages of treatment and control of hypertension and elevated TC was very low in China during the period from 1974 to 2001^[23-26]. The effect

of antihypertensive or cholesterol-lowering treatment on MI incidence in the population should be little. Secondly, baseline blood pressure was based on a single measurement, which would cause non-differential bias. Third, this population was an occupational population, and may not represent the general population, especially with regard to comparisons with other studies. However, the prevalence of these classical risk factors was similar to other studies in China.

Our findings have important public health implications. Elevated TC was an important independent risk of MI both in male non-hypertension and hypertension populations. We observed a strong, independent, and linear relationship between TC level and MI incidence in male hypertension population. Reduction of TC level to a desirable level in this population should be considered an important approach to the prevention of MI incidence. Strategies that aim to prevent MI incidence in China need to incorporate the prevention, treatment, and control of elevated TC, especially, in male hypertension population.

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