Unique and Varied Contributions of Traditional CVD Risk Factors: A Systematic Literature Review of CAD Risk Factors in China

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Abstract: This study is the first systematic review of risk factors for stroke in China and supports the importance of current public health initiatives to manage the risk factors appropriately to reduce risk of stroke in high risk patients. Additionally, this study has been co-authored by prominent Chinese and US physicians and researchers with expertise in cardiovascular disease, neurologic disorders, epidemiology, and real world data. While there have been several systematic reviews of real world associations of risk factors for coronary artery disease, none focus specifically on the population of China, where there is growing evidence that such risk factors are poorly treated or uncontrolled, especially in rural areas.

Background: To better understand the impact of traditional cardiovascular risk factors on risk of coronary artery disease (CAD) in China, a systematic review of all Chinese observational studies published in either English or Chinese in MEDLINE and EMBASE over the last 5 years was performed and the association between any of 5 traditional risk factors (ie, hypertension, diabetes, elevated lipid levels, obesity, and smoking) and the risk of CAD was studied.

Methods and results: The study found a consistent relationship between lipid levels and CAD. Higher low-density lipoprotein cholesterol values were associated with greater risk of CAD, with an odds ratio as high as 3.31. Other factors found to be significant contributors to the risk of CAD included hypertension (crude odds ratio range of 1.40–5.11), diabetes (1.50–5.97), and smoking (1.37–5.19). An association between obesity and CAD in China was observed, but the evidence supporting this was considered weak due to the paucity of studies found as part of this review.

Conclusions: This review provides a systematic summary of CAD risk factors in China and demonstrates the important differences that exist in CAD risk factors between countries and regions. Approaches to reduce CAD globally must take into account the unique risk factors that drive CAD in each country and region as is demonstrated by these findings.

Keywords: coronary disease, risk factors, smoking, diabetes, hypertension, dyslipidemia

Clinical Medicine Insights: Cardiology 2013:7 59–86
doi: 10.4137/CMC.S10225

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Introduction
Worldwide, over 7 million people each year die from coronary artery disease (CAD), a condition where plaque builds up in the blood vessels supplying the heart. Evidence supports an association between CAD trends with major cardiovascular risk factors. Major modifiable risk factors include high blood pressure, diabetes, obesity, metabolic syndrome, abnormal lipids, tobacco use, and physical inactivity. The prevention and control of major risk factors of CAD among the developed nations has contributed to a significant reduction in CAD mortality rates.

Contrary to trends in developed nations, China has experienced a considerable increase in the prevalence of CAD over the past several decades. CAD has climbed from the fifth most common heart disease in 1948–1957 to the most common in 1980–1989, where it has remained to this day. CAD is reported as one of the leading causes of death in China, where it contributes to 51.4% of the mortality attributed to cardiovascular disease (CVD) in urban areas and 32.8% in rural areas. It is projected that from 1990 to 2020, CAD is likely to have reached 72.7 million men and 72.1 million women in the general Chinese population, with CVD mortality likely to increase by 108% in men and 79% in women.

China is also not experiencing a decrease in these risk factors, especially in diabetes and smoking. Hypertension, diabetes, obesity, dyslipidemia, and hypercholesterolemia are rising rapidly in the Chinese population and an estimated 28.1% of adults and 52.9% of males were current smokers in 2010, contributing to China as the world’s largest consumer and producer of tobacco products. Hypertension, diabetes, abnormal lipid conditions, obesity, and smoking are all major risk factors of CAD.

Given the potential economic, social, and public health burden of CAD on China’s large population, effective primary and secondary prevention strategies for risk factors can greatly reduce the risk of CAD. However, the impact of each of these risk factors in the Chinese population is unknown, and most models linking these traditional risk factors to CAD have been derived from studies on largely Caucasian populations including whether there might be geographic variation of the impact of these traditional risk factors. Regarded as a leading developing economy with an estimated population of 1.3 billion people, a careful examination of this epidemic increase in China will benefit the future prevention of the disease worldwide and contribute to a stronger understanding of the relationship between cardiovascular risk factors and CAD within the Chinese population. We performed a systematic review of the literature to assess the impact of hypertension, diabetes, abnormal lipid conditions, obesity, and smoking on the risk of CAD in China.

Methods
The literature search was performed in MEDLINE (via PubMed) and EMBASE for all observational studies published in either English or Chinese in the last 5 years (2006–2011) on the association between any of the 5 risk factors (ie, hypertension, diabetes, abnormal lipid conditions, obesity, and smoking) and the risk of CAD in the general population of China. Chinese literature databases Wanfang Data and Chinese National Knowledge Infrastructure (CNKI) were also searched but with no significant yield. The main search terms used were as follows: “coronary artery disease” [Mesh], “China,” “incidence” [MeSH Terms], “prevalence” [MeSH Terms], “epidemiology” [MeSH Terms], “observational,” “community-based,” and “cross-section.”

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Figure 1. Attrition diagram.
Notes: Rounded corners = Accepted articles at each stage. Squared corners = Rejected articles.
Procedures for the review followed established methods used in the science of systematic review research.\textsuperscript{15,16}

The initial search yielded 196 abstracts. We manually reviewed the abstracts of the articles to exclude study types such as abstracts, case reports, letters, commentaries, editorials, reviews, meta-analyses and clinical trials, studies not on population from mainland China, and studies with no apparent outcomes of interest. If an article did not have an abstract, the article was still retrieved if the title suggested the full text would include the outcomes of interest. Forty-two articles were selected for detailed evaluation. The full text was reviewed to identify only observational studies reporting the association of any of the 5 risk factors and risk of CAD. Seventeen publications met these criteria and were selected for review (Table 1). The article attrition diagram lists the number of articles excluded at each step and the reason for exclusion.

Both study-level and patient-level information from each article were reviewed. Study-level information included publication language, patient population characteristics, geographic region of China, study design (prospective/retrospective cohort, survey or case control), and characteristics such as study period and length of follow-up. Information on distinctive sample characteristics, sample size, baseline demographics, and comorbidities was reviewed for each cohort patient population if reported, such as CAD patients versus non-CAD patients. Main outcomes of interest included any reported association between the 5 risk factors (hypertension, abnormal lipid conditions, obesity, diabetes, and smoking) and CAD, such as odds ratios (OR) or relative risks (RR). Only half of the articles reported adjusted hazard ratios or relative risks. For those that did not, we calculated crude odds ratios from the counts available.

Review was performed by 1 investigator and checked by another who reviewed the extracted data for consistency and accuracy. Data discrepancies were resolved by consensus of the 2 investigators. Articles published in Chinese were translated into English by a native Chinese speaker with fluency in English. Translation was validated by a second native speaker. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.\textsuperscript{17}

**Results**

Of the 17 articles identified and reviewed for reported association between any of the 5 risk factors and risk of CAD, 12 were published in English and 5 in Chinese. Most studies (70.6\%) reported on multiple risk factors. The review included 8 cohort studies (7 prospective, 1 retrospective), most of which examined consecutive patients referred for coronary angiography with suspected or confirmed CAD. Sample sizes ranged from 237 to 3,513 patients (mean: 843). There were 6 case-control studies with sample sizes ranging from 384 to 1,127 (mean: 664). Three of the larger studies were survey studies. One specifically targeted retired military men over age 55 and had a sample size of 1,268. Another, Liu et al.,\textsuperscript{18} included 3,223 inpatients diagnosed with acute coronary syndrome (ACS) from 64 hospitals representative of China. The third, Wang et al.,\textsuperscript{19} surveyed 30,378 individuals among the general Chinese population across 11 provinces. With regard to geographic coverage, only 1 study\textsuperscript{18} was found to be representative of both urban and rural China. The other 16 focused on major cities (Beijing, Shanghai, Nanjing, Shenyang, and Xi’an) or provincial areas (Shandong, Jiangshu, and Zhejiang provinces).

Association between hypertension and CAD was reported in 13 studies (Table 2A). Association between abnormal lipid conditions and CAD was reported in 12 studies (Table 2B). Seven studies reported the association between obesity and CAD (Table 2C). Associations between CAD and diabetes, and between CAD and smoking were reported each in 14 studies (Tables 2D–E). One study reported association with a composite risk factor (Table 2F).

**Hypertension and risk of CAD**

Thirteen studies were selected for review on the association between hypertension and CAD. The association ranged between 1.40 and 5.11 for crude ORs and between 1.68 and 2.47 for adjusted relative ratios. Seven studies had crude ORs derived from the available prevalence of hypertension in the CAD group versus non-CAD group. Four studies reported crude ORs between 1.40 and 1.94, while 3 others\textsuperscript{20–22} reported much higher crude ratios of 5.11, 4.69, and 3.46. Adjusted RR ratios ranged between 1.28 and 2.47. Cui et al\textsuperscript{23} did not report the magnitude of the association, but found the risk association among women to be significant while that among men to
Table 1. Systematic literature review of risk factors of coronary artery disease (CAD) in China.

| Author, year | Citation | Publication language | Region | Patient population |
|--------------|----------|----------------------|--------|--------------------|
| Su G, 2011   | Su G, Mi S, Tao H, et al. Association of glycemic variability and the presence and severity of coronary artery disease in patients with type 2 diabetes. *Cardiovascular Diabetology.* 2011;10:19. | English | Beijing | Consecutive T2DM patients with chest pain referred to coronary angiography |
| Sai XY, 2007 | Sai XY, He Y, Men K, et al. All-cause mortality and risk factors in a cohort of retired military male veterans, Xi’an, China: an 18-year follow up study. *BMC Public Health.* 2007;7:290. | English | Xi’an | Retired military men aged 55 or older from 22 military retirement centers in Xi’an |
| Hu DY, 2006  | Hu DY, Pan CY, Yu JM. The relationship between coronary artery disease and abnormal glucose regulation in China: The China Heart Survey. *European Heart Journal.* 2006;27(21):2573–9. | English | Seven cities | Patients admitted to hospital cardiovascular wards, T1DM excluded |
| Chen ZW, 2011| Chen ZW, Qian JY, Jian Y, et al. Prevalence and severity of coronary artery disease in diabetic patients with aortic valve calcification. *Acta Cardiol.* 2011;66(1):15–20. | English | Shanghai | Consecutive patients with chest pain or chest distress referred for coronary angiography |
| Zhang K, 2010| Zhang K, Wang YY, Liu QJ, et al. Two single nucleotide polymorphisms in ALOX15 are associated with risk of coronary artery disease in a Chinese Han population. *Heart Vessels.* 2010;25(5):368–3. | English | Shandong province | Subjects consecutively recruited from hospital inpatients who underwent coronary angiography. History of other diseases were excluded |
| Han Y, 2010  | Han Y, Xu W, Zhang W, Liu N, Ji Y. T-786C polymorphism in the endothelial nitric oxide synthase gene is associated with increased risk of coronary artery disease in a Chinese population. *Heart Vessels.* 2010;25(5):368–3. | English | Jianshu province | Chinese Han subjects, CAD confirmed by angiography and healthy controls |
| Xu H, 2008   | Xu H, Hou X, Wang N, et al. Gender-specific effect of estrogen receptor-1 gene polymorphisms in coronary artery disease and its angiographic severity in Chinese population. *Clin Chim Acta.* 2008;395(1–2):130–3. | English | Nanjing | Angiographically defined CAD patients and controls in hospital |
| Tang NP, 2008| Tang NP, Wang LS, Yang L, et al. Genetic variant in glutathione peroxidase 1 gene is associated with an increased risk of coronary artery disease in a Chinese population. *Clin Chim Acta.* 2008;395(1–2):89–93. | English | Jiangsu province | Consecutive CAD inpatients admitted for angina pectoris or other symptoms/signs of cardiovascular diseases and controls |
| Cui, 2007    | Cui HB, Wang SH, Wang DQ, et al. Modified classic risk factors for coronary artery disease in Chinese Han population. *Chin Med Sci J.* 2007;22(4):216–23. | English | Xi’an, Shanxi, Lanzhou, Ningbo, Shiyian | Angiographically assessed consecutive subjects from Chinese coronary collaborative group presenting at five hospitals with coronary angiography |
| Ni M, 2007   | Ni M, Zhang XH, Jiang SL, Zhang Y. Homocysteinemia as an independent risk factor in the Chinese population at a high risk of coronary artery disease. *Am J Cardiol.* 2007;100(3):455–8. | English | Shandong province | Consecutive patients undergoing coronary angiography |
Systematic literature review of CAD risk factors in China

| Sample size | Risk factors                               | Study design   | Study length      | Risk of CAD                                      |
|-------------|--------------------------------------------|----------------|-------------------|-------------------------------------------------|
| 344 (CAD: 252; non CAD: 92) | Hypertension, lipids, obesity, diabetes, smoking | Prospective cohort | NR                |                                                 |
| 1268        | Smoking                                    | Survey         | 1987–2005/18 years | CHD adjusted mortality rates: 421 per 100,000 person years |
| 3513        | Smoking, obesity, hypertension, hyperlipidemia, diabetes | Prospective cohort | Jun–Aug 2005       |                                                 |
| 325 (CAD: 222; non-CAD: 103) | Diabetes, Hypertension                      | Prospective cohort | Jun–Dec 2007      |                                                 |
| 1127 (CAD: 519; control 608) | Hypertension, lipids, obesity, diabetes, smoking | Case control | 2006–2008         |                                                 |
| 622 (CAD 312; control 310) | Hypertension, lipids, smoking               | Case-control    | NR                |                                                 |
| 384 (CAD 210; control 174) | Hypertension, lipids, BMI, diabetes, smoking | Case control | NR                |                                                 |
| 530 (CAD 265; control 265) | Hypertension, lipids, obesity, diabetes, smoking | Case control | NR                |                                                 |
| 762 (CAD 423; control 339) | Hypertension, lipids, diabetes, smoking | Prospective cohort | NR                |                                                 |
| 237 (CAD:138; control 99) | Hypertension, lipids, obesity, smoking, diabetes | Prospective cohort | NR                |                                                 |

(Continued)
### Table 1. (Continued)

| Author, year | Citation | Publication language | Region | Patient population |
|--------------|----------|----------------------|--------|--------------------|
| Han Y, 2007 | Han Y, Yang Y, Zhang X, Yan C, Xi S, Kang J. Relationship of the CAG repeat polymorphism of the MEF2A gene and coronary artery disease in a Chinese population. *Clin Chem Lab Med.* 2007;45(8):987–92. | English | Shenyang | Coronary angiography patients and healthy controls, Han Chinese |
| Jin Z, 2006 | Jin Z, Zhang Y, Chen J, et al. Study of the correlation between blood lipid levels and the severity of coronary atherosclerosis in a Chinese population sample. *Acta Cardiol.* 2006;61(6):603–6. | English | Zhejiang | Patients with coronary artery atherosclerosis verified by coronary angiography |
| Liu, 2008 | Liu J, Zhao D, Liu Q, et al. Study on the prevalence of diabetes mellitus among acute coronary syndrome inpatients in a multiprovincial study in China. Zhonghua Liu Xing Bing Xue Za Zhi = Zhonghua Liuxingbingxue Za Zhi. 2008;29(6):526–9. | Chinese | 64 hospitals representative of China | Inpatients diagnosed with acute coronary syndrome (ACS) |
| Wang, 2007 | Wang Y, Huang JY, Cao YF, et al. Risk factors for type 2 diabetes mellitus in middle-aged and elderly populations of Shanghai rural areas: A nested case-control study. *Journal of Clinical Rehabsilitative Tissue Engineering Research.* 2007;11(52):10433–6. | Chinese | Shanghai | Diabetes patients and control |
| Li, 2007 | Li BL, Li L, Hou XL, et al. Prevalence of coronary artery disease in patients with rheumatic heart disease in China. *National Medical Journal of China.* 2007;87(47):3313–6. | Chinese | Shanghai | Patients with rheumatic heart disease aged > 40 who were scheduled for valve surgery |
| Wang, 2006 | Wang W, Zhao D, Sun JY, et al. Risk factors comparison in Chinese patients developing acute coronary syndrome, ischemic or hemorrhagic stroke: a multi-provincial cohort study. *Zhonghua Xin Xue Guan Bing Za Zhi [Chinese Journal of Cardiovascular Diseases].* 2006;34(12):1133–7. | Chinese | 11 provinces | Chinese population aged 35–64 |
| Li, 2006 | Li X, Gao X, Zhang B, Gu Q, Ren LM, Gao J. Glucose metabolism status and angiographic features of coronary artery in patients undergoing their first coronary angiography: study of 553 cases. *Zhonghua Yi Xue Za Zhi.* 2006;86(24):1689–92. | Chinese | NR | Inpatients with suspected or confirmed CAD |

be insignificant. Chen et al.²⁴ reported differential ratios among diabetic and non-diabetic populations. The adjusted ORs among diabetics were found to be higher than that among non-diabetics (1.85 vs. 1.28).

There were 6 case-control studies, 6 cohort studies, and 1 survey. The case-control studies generally reported higher ORs compared to the cohort studies (mean 3.8 vs. 1.55).

The largest crude ORs and adjusted RR ratios were both found in Han et al.²⁵ The study was a case-control study that recruited 378 CAD patients and 348 healthy controls from Northern Hospital in Shenyang.
| Sample size | Risk factors | Study design | Study length | Risk of CAD |
|-------------|--------------|--------------|--------------|-------------|
| 726 (CAD 378; control 348) | Hypertension, diabetes, hyperlipidemia, smoking | Case control | 2003–2006 | 71 (10.91%) |
| 363 | Lipids | Prospective cohort | Jan–Dec 2004 | Male: 17.94%, Female 4.86% (P < 0.01) |
| 3223 | Diabetes | Survey | March 2006–May 2006 | Age: 40–59, 6.39% 60–69 |
| 597 (type 2 diabetes: 199 non diabetes 398) | Diabetes | Case control | 2003 and 2005 | 21.47% (P < 0.01) ≥ 70 22.22% (P < 0.01) |
| 651: CAD 71 non CAD 580 | Diabetes mellitus, hypertension, smoking, dyslipidemia | Retrospective cohort | Sep 2001–Apr 2006 | Overall: 114 per 100,000 person-year |
| 30,378 (ACS stroke) | Hypertension, smoking, diabetes, high TC, low HDL-C, obesity | Survey | 1992–2003/6.6 years | 35–44: 53 per 100,000 person-year |
| 553: CAD 388 non CAD 165 | Hypertension, smoking, TC, TG, HDL-C, LDL-C, diabetes | Prospective cohort | Aug 2004–Oct 2005 | 45–54: 106 per 100,000 person-year |
| 597 (type 2 diabetes: 199 non diabetes 398) | Diabetes | Case control | 2003 and 2005 | 55–64: 249 per 100,000 person-year |

### Lipid profile and risk of CAD

Twelve studies were selected for review on the association between lipid conditions and risk of CAD. Three studies reported the association between hyperlipidemia and risk of CAD, 2 between dyslipidemia and risk of CAD, and 10 between values on total cholesterol (TC), triglyceride (TG), LDL cholesterol (LDL-C) and HDL cholesterol levels (HDL-C), and risk of CAD.

For the association between hyperlipidemia and the risk of CAD, significant crude and adjusted odds ratios were reported in only 1 case-control study conducted in Shenyang,\(^2\) where the crude OR was reported as 2.77 and adjusted OR as 2.63 (95% confidence interval...
Table 2A. Association between hypertension and risk of CAD.

| Author, year | Study design | Number of patients | Age                  | Gender (M:F) | Treatment history |
|--------------|--------------|--------------------|----------------------|--------------|-------------------|
| Han Y, 2007  | Case-control | 726 (CAD 376; control 348) | Mean: 57.2 (10.5)  | 492:234 CAD: 284:94 Control: 210:138 |
| Cui, 2007    | Prospective cohort | 762 (CAD 423; control 339) | Mean: 60 (10) Range 17–81 | 481:281 CAD: 261:162 Control: 220:119 100%: lipid-lowering agents |
| Han Y, 2010  | Case-control | 622 (CAD 312; control 310) | Mean: 61.96 (10.71) | 209:103 CAD: 209:103 Control: 184:126 P = 0.096 |
| Ni M, 2007   | Case-control | 237 (CAD:138; control 99) | Mean: 54.18 (9.25) Range 35–70 | 163:74 CAD: 108:30 Control: 55:44 P < 0.01 |
| Su G, 2011   | Prospective cohort | 344 (CAD: 252; non CAD: 92) | CAD: mean: 65 (9) | 165:87 CAD: 108:27 Non CAD: 48:44 100%: lipid-lowering agents |
| Tang NP, 2008 | Case-control | 530 (CAD 265; control 265) | CAD: 64 (56–71) Control: 64 (55–71) | CAD: 194:71 NS |
| Xu H, 2008   | Case-control | 384 (CAD 210; control 174) | CAD: 56 (7.3) Non CAD: 55 (8.6) | 201:183 CAD: 116:94 Control: 85:89 |
| Zhang K, 2010 | Case-control | 1127 (CAD: 519; control 608) | CAD: 61.285 (10.755) Control: 60.3777 (10.730) P = 0.16 | 362:157 CAD: 201:107 Control: 401:207 |
| Chen ZW, 2011 | Prospective cohort | 325 (CAD: 222; non-CAD: 103) | 63.4 (9.7) Diabetic: 66.2 (8.1) Non diabetic: 62.2 (10.2) P < 0.01 | 218:107 Diabetic 61:43 Non diabetic: 157:64 P = 0.027 |
### Table 2A.

| Definition of risk factor | Crude OR  | Adjusted association | Adjusted model configuration |
|--------------------------|-----------|----------------------|------------------------------|
| Being treated for hypertension | 5.11 (P = 0.002) | OR (95% CI): 2.47 (2.20–2.78) (P = 0.00) | Logistic: age, gender, hypertension, diabetes mellitus, hyperlipidemia, smoking |
| According to Joint National Committee (JNC) VI guideline | NR | Women: 95% significant association with hypertension | |
| | NR | Men: No significant association with hypertension | |
| | 1.94 (P < 0.01) | | |
| Systolic and diastolic BP ≥ 140/90 mmHg or use of antihypertensive treatment | 4.69 (P < 0.01) | OR: 1.857 (95% CI: 0.969, 3.557, P = 0.062) | Logistic: smoking, male, older age, MAGE (mean amplitude of glycemic excursions), hs-CRP, hyperlipidemia, hypertension, renal insufficiency |
| Systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or treatment with oral anti-hypertension drugs | 1.52 (NS) | | |
| Resting systolic blood pressure N140 mmHg and/or diastolic blood pressure N90 mmHg or in the presence of active treatment with antihypertensive agents | 3.46 (P < 0.001) | OR: 1.676 (95% CI: 1.165–2.788); P = 0.014 | Logistic: diabetes, hypertension, high LDL levels and genotype |
| NR | Health control cohort had zero patients with hypertension. (OR can’t be calculated.) % of patients with hypertension: 63% in the CAD vs. 0% in the non CAD | | |
| Systolic pressure > 140 mmHg or diastolic pressure > 90 mmHg or being treated with antihypertensive medication | | Diabetic: OR: 1.846 (P = 0.389) | Logistic regression: aortic valve calcification (AVC), sex, age, hypertension, smoking, serum level of fibrinogen, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, apoprotein |
| | | Non diabetic: OR: 1.280 (P = 0.638) | |

(Continued)
Table 2A. (Continued)

| Author, year | Study design | Number of patients | Age | Gender (M:F) | Treatment history |
|--------------|--------------|--------------------|-----|--------------|-------------------|
| Hu DY, 2006  | Prospective cohort | 3513 (CAD: 3513) | 69 (65–77) | 2341:1172 |                   |
| Li, 2007     | Retrospective cohort | 651: CAD 71 non CAD 580 | Mean: 56 (8) | 301:350 | CAD: 54:17         |
|              |               |                    | Range: 42–75 | Non-CAD: 247:333 | Non-CAD: 247:333 |
| Li, 2006     | Prospective cohort | 553: CAD 388: non-CAD 165 | Mean: 60.1 (9.7) | CAD: 82.6% |                   |
|              |               |                    | Mean: 61.4 (9.7) | 301:350 | Non-CAD: 63.9%     |
|              |               |                    | Non CAD: 57.2 (8.8) | P = 0.00 |                   |
| Wang, 2006   | Survey | 30,378 (ACS 227 stroke 582 non CVD 29,569) | Mean: 46.89 | ASC: male 70.5% |                   |
|              |               |                    |ASC: 52.4 (7.9) | Non CVD: male 53.2% |                   |

[CI]: 2.32–2.99). The criteria for defining hyperlipidemia were not provided in this study. For the association between dyslipidemia and the risk of CAD, significance was found in 2 of 3 studies reviewed. Ni et al22 reported the crude ORs to be 3.71 for a case-control study conducted in Shandong province. The study population consisted of 138 CAD patients and 99 controls, where the CAD patient cohort was significantly older (55.3 vs. 52.7, P = 0.03) and had a higher percentage of male patients (78.3% vs. 55.6%, P < 0.01) than the control cohort. Dyslipidemia was defined as total cholesterol ≥ 5.2 mmol/L, LDL ≥ 3.4 mmol/L, triglycerides ≥ 1.7 mmol/L or HDL ≥ 1.03 mmol/L. Tang et al23 reported the crude OR to be 2.76. This study had a similar study design as Ni et al,22 where 265 patients were selected each for a CAD cohort and healthy control cohort. However, Tang et al22 found no significant difference in baseline patient characteristics. Dyslipidemia in this study was defined as total cholesterol ≥ 6.2 mmol/L or on drugs.

For the association between total cholesterol (TC), triglycerides (TG), HDL-C, LDL-C, and risk of CAD, 7 studies compared values of lipoprotein profile between CAD patients and the healthy controls. Su et al26 found the difference in the lipid conditions reported between the 2 cohorts to be generally insignificant. Two studies25,27 found CAD patients had slightly lower TC values than healthy controls (P < 0.01); 2 studies22,28 found CAD patients had significantly higher values; and 1 study29 found the difference to be insignificant. For reported TG values, 2 studies22,27 found CAD patients to have significantly higher values than their comparative healthy controls, although 3 studies22,25,27–29 found the difference to be insignificant. Comparison on HDL-C and LDL-C values is more consistent between studies. All 5 studies22,25,27–29 reported significantly lower HDL-C values than non-CAD patients. Wang et al19 reported a crude OR of 1.75 and adjusted RR of 1.39 for low HDL-C among CAD patients, and Cui et al23 reported the adjusted risk among men to be higher at 2.80 (95% CI: 1.50–4.20). For LDL-C values, 4 studies22,27–29 found significantly higher levels among CAD patients, but 1 study25 found the opposite. This is consistent with the adjusted RR reported in Xu et al,29 where LDL-C is associated with an OR of 3.31 for risk of CAD.

Jin et al30 reported the association between the severity of CAD and lipoprotein profiles. Severity was positively correlated with the number of coronary arteries diseased. Among the lipid conditions examined, which include TG, TC, HDL-C, LDL-C, and non-HDL-C, only LDL-C was found to be consistently related to the progression of the disease. Patients in more severe disease conditions were found to have significantly higher LDL-C values. Chen et al34 reported differential
adjusted association among diabetic and non-diabetic patients. Among diabetic patients, the association between TC, TG, and LDL-C and risk of CAD were statistically insignificant, while among non-diabetic patients, the association between TG, HDL-C, and risk of CAD were not significant. The remaining significant ORs were relatively small except for LDL-C, where non-diabetic patients had an OR of 3.59.

### Diabetes and risk of CAD
Fourteen studies were reviewed for the association between diabetes and risk of CAD. While for 2 studies\(^22,24\) the association was found to be insignificant, the rest of the reviewed studies reported relatively high association between diabetes and risk of CAD. For crude OR, the association ranged between 1.50 and 5.97. Two studies\(^19,29\) reported similar crude ORs of 1.50 and 1.53, respectively. However, study designs differed considerably between the two. Xu et al\(^29\) employed a case-control setting in Nanjing where 210 CAD patients and 174 controls were enrolled in the hospital; Wang et al\(^9\) employed data from the Chinese Multi-Provincial Cohort Study (CMCS), where 227 acute coronary syndrome patients and 29,569 non-CAD patients were surveyed across 11 provinces in China. Three studies\(^20,28,31\) reported the crude ORs between 2.08 and 3.02. Li et al\(^28\) and Ni et al\(^20\) performed similar studies where consecutive patients were enrolled as comparative cohorts and patients characteristics differed in terms of age and gender distribution. Han et al\(^25\) reported a crude OR of 3.83, and the definition of diabetes used included both type 1 and type 2 diabetes. The upper bound of crude OR at 5.97 was reported in Li et al\(^9\) which was a retrospective cohort study conducted in Shanghai Second Military Medical University Hospital. The study enrolled 71 CAD patients and 580 non-CAD patients, and patient characteristics seemed to have different mean of age and gender distribution, but no statistical significance on the difference was reported.

Four studies reported adjusted RR ratios of diabetes on risk of CAD. Wang et al\(^19\), a multi-provincial cohort study, reported a risk ratio of 1.19; Han et al\(^25\), which included both type 1 and type 2 diabetes, reported the ratio to be 3.28 (95% CI: 2.60–4.14); and Xu et al\(^29\), a case-control study in Nanjing reported the ratio to be 4.38 (95% CI: 2.54–7.76). Cui et al\(^23\), a prospective cohort study conducted in 5 cities, reported significant association between diabetes and risk of CAD, but the risk ratio was not represented. Both crude and adjusted ORs indicated that diabetes is a significant contributor to the risk of CAD.

### Obesity and risk of CAD
Seven studies were reviewed for the association between obesity or body mass index (BMI)
| Author, year | Study design | Number of patients | Age | Gender (M:F) | Treatment history |
|-------------|--------------|--------------------|-----|--------------|-------------------|
| Han Y, 2007 | Case-control | 726 (CAD 378; control 348) | Mean: 57.2 (10.5) Range: 29–89 CAD: mean: 57.7 (10.7) Control: 55.6 (10.4) | 492:234 CAD: 284:94 Control: 210:138 |  |
| Cui, 2007   | Prospective cohort | 762 (CAD 423; control 339) | Mean: 60 (10) Range: 17–81 | 481:281 CAD: 261:162 Control: 220:119 | 100%: lipid-lowering agents |
| Han Y, 2010 | Case-control | 622 (CAD 312; control 310) | Mean: 61.96 (10.71) | 209:103 CAD: 209:103 Control: 184:126 |  |
| Ni M, 2007  | Case-control | 237 (CAD:138; control 99) | Mean: 54.18 (9.25) Range: 35–70 CAD: 55.28 (9.03) Control: 52.65 (9.39) | 163:74 CAD: 108:30 Control: 55:44 |  |

Jin Z, 2006 Prospective cohort 363 NR NR
Tab. 2B. Association between lipids and risk of CAD.

| Author, year | Study design | n (number of patients) | Age | Gender (M:F) | Treatment history | Definition of risk factor | Crude OR (95% CI) | Adjusted association (OR (95% CI)) | Adjusted model configuration |
|--------------|--------------|------------------------|-----|--------------|--------------------|--------------------------|-------------------|-----------------------------------|-------------------------------|
| Han Y, 2007  | Case-control | 726 (CAD 378; control 348) | Mean: 57.2 (10.5) | Range: 29–89 | CAD: mean: 57.7 (10.7) | Control: 55.6 (10.4) | 492:234 | 2.77 (P < 0.01) | 2.63 (2.32–2.99) (P = 0.00) | Logistic: age, gender, hypertension, diabetes mellitus, hyperlipidemia, smoking |
| Cui, 2007    | Prospective cohort | 762 (CAD 423; control 339) | Mean: 60 (10) | Range: 17–81 | 481:281 | CAD: 261:162 | Control: 220:119 | 100%: lipid-lowering agents | Low HDL-C (men): RR = 2.8 (95% CI: 1.5–4.2) LDL, TC, TG (men): 95% significant association LDL/HDL: 95% significant association |
| Han Y, 2010  | Case-control | 622 (CAD 312; control 310) | Mean: 61.96 (10.71) | CAD: 61.96 (10.71) | Control: 60.54 (10.18) | P = 0.09 | 209:103 | 209:103 | P = 0.056 | TC, TG, HDL, LDL values |
| Jìn Z, 2006  | Prospective cohort | NR NR | TC, TG, HDL-C, LDL-C, non-HDL-C values | TG (mmol/l): Group I 1.91 (1.20) vs. group II 1.73 (0.88) vs. group III 1.86 (1.40) vs. group IV 1.48 (0.60) | TC (mmol/l): Group I 4.38 (1.19) vs. non CAD 4.84 (1.09) (P < 0.01) | HDL-C (mmol/l): Group I 1.21 (0.39) vs. group II 1.30 (0.34) vs. group III 1.28 (0.38) vs. group IV 1.20 (0.27) | LDL-C (mmol/l): Group I 2.30 (0.77) vs. group II 2.64 (0.84) (P < 0.01) vs. group III 2.74 (1.23) (P < 0.01) vs. group IV 2.91 (0.68) (P < 0.01) | Non-HDL-C (mmol/l): Group I 3.17 (0.91) vs. group II 3.43 (0.94) (P < 0.05) vs. group III 3.59 (1.41) (P < 0.05) vs. group IV 3.58 (0.75) (P < 0.05) | *Group according to the number of coronary arteries diseased |
| Ni M, 2007   | Case-control | 237 (CAD:138; control 99) | Mean: 54.18 (9.25) | Range: 35–70 | CAD: 55.28 (9.03) | Control: 52.65 (9.39) | 163:74 | 3.71 (P < 0.001) |  | |

Dyslipidemia: Total cholesterol level 5.2 mmol/L (200 mg/dL), LDL cholesterol level 3.4 mmol/L (130 mg/dL), triglyceride level 1.7 mmol/L (150 mg/dL), or HDL cholesterol level 1.03 mmol/L (40 mg/dL)
### Table 2B. (Continued)

| Author, year | Study design | Number of patients | Age | Gender (M:F) | Treatment history |
|--------------|--------------|--------------------|-----|--------------|-------------------|
| Su G, 2011   | Prospective cohort | 344 (CAD: 252; non CAD: 92) | CAD: mean: 65 (9) Non CAD: 61 (9) | CAD: 165:87 Non CAD: 48:44 | Oral anti-hyperglycemic CAD: 45.7% Non CAD: 44.0% Not significant Insulin CAD: 35.9% Non CAD: 40.9% Not significant Statins CAD: 61.9% Non CAD: 69.4% Not significant |
| Tang NP, 2008 | Case-control | 530 (CAD 265; control 265) | CAD: 64 (56–71) Control: 64 (55–71) | CAD: 194:71 Non CAD: 194:71 NS |
| Xu H, 2008   | Case-control | 384 (CAD 210; control 174) | CAD: 56 (7.3) Non CAD: 55 (8.6) | 201:183 CAD: 116:94 Control: 85:89 |
| Zhang K, 2010| Case-control | 1127 (CAD: 519; control 608) | CAD: 61.285 (10.755) Control: 60.3777 (10.730) $P = 0.16$ | CAD: 362:157 Control: 401:207 |
| Chen ZW, 2011| Prospective cohort | 325 (CAD: 222; non-CAD: 103) | 63.4 (9.7) Diabetic: 66.2 (8.1) Non diabetic: 62.2 (10.2) $P < 0.01$ | 218:107 Diabetic: 61.43 Non diabetic: 157:64 $P = 0.027$ |
| Study | Design | Number (CAD: non-CAD) | Age | Gender (M:F) | Treatment History | Definition of risk factor | Crude OR | Adjusted association | Adjusted model configuration |
|-------|--------|-----------------------|-----|--------------|-------------------|--------------------------|----------|---------------------|-------------------------------|
| Su G, 2011 | Prospective cohort | 344 (252:92) | CAD: mean 65 (9) vs. non CAD: 61 (9) | CAD: 165:87 vs. non CAD: 48:44 | | Hyperlipidemia: diagnosed according to guideline of the National Cholesterol Education Program (ATP III). TC, LDL-C, HDL-C, TG values | Hyperlipidemia: OR: 1.44 (NS) | Hyperlipidemia: OR: 1.425 (95% CI: 0.817, 2.486, P = 0.212) | Logistic: smoking, male, older age, MAGE (mean amplitude of glycemic excursions), hs-CRP, hyperlipidemia, hypertension, renal insufficiency |
| Tang NP, 2008 | Case-control | 530 (265:265) | CAD: 64 (56–71) vs. Control: 64 (55–71) | CAD: 194:71 vs. Non CAD: 194:71 | NS | Dyslipidemia: total cholesterol level of 6.2 mmol/l or on drugs TC, TG, HDL-C, LDL-C values | Dyslipidemia: 2.76 (P < 0.01) | Dyslipidemia: TC (mmol/l): CAD 4.11 vs. non CAD 3.95 (3.48–4.71) vs. non CAD 3.95 (3.31–4.54) (P = 0.036) | Logistic: diabetes, hypertension, high LDL levels and genotype |
| Xu H, 2008 | Case-control | 384 (210:174) | CAD: 56 (7.3) vs. Non CAD: 55 (8.6) | CAD: 201:183 vs. Control: 85:89 | | TC, TG, HDL-C, LDL-C values | TC (mg/dL): CAD 194 (8.6) vs. non CAD 186 (10.2) (NS) | TC (mmol/l): CAD 119 (17.7) vs. non CAD 99.2 (16.4) (P = 0.003) | Logistic regression: aortic valve calcification (AVC), sex, age, hypertension, smoking, serum level of fibrinogen, total cholesterol, triglyceride, high-density lipoprotein |
| Zhang K, 2010 | Case-control | 1127 (519:608) | CAD: 61.285 (10.755) vs. Control: 60.3777 (10.730) (P = 0.16) | CAD: 362:157 vs. Control: 401:207 | | TC, TG, HDL-C, LDL-C values | TC (mmol/l): CAD 4.71 vs. non CAD 4.78 (0.67) (P = 0.066) | TC (mmol/l): CAD 119 (17.7) vs. non CAD 99.2 (16.4) (P = 0.003) | Logistic regression: aortic valve calcification (AVC), sex, age, hypertension, smoking, serum level of fibrinogen, total cholesterol, triglyceride, high-density lipoprotein |
| Chen ZW, 2011 | Prospective cohort | 325 (222:103) | Diabetic: 66.2 (8.1) vs. Non diabetic: 62.2 (10.2) (P = 0.01) | Diabetic: 218:107 vs. Non diabetic: 157:64 (P = 0.027) | | TC, TG, HDL-C, LDL-C values | TC (mmol/l): Diabetic: OR: 2.543 (P = 0.504) vs. Non diabetic: OR: 0.172 (P = 0.043) | TC (mmol/l): Diabetic: OR: 2.543 (P = 0.504) vs. Non diabetic: OR: 0.172 (P = 0.043) | Logistic regression: aortic valve calcification (AVC), sex, age, hypertension, smoking, serum level of fibrinogen, total cholesterol, triglyceride, high-density lipoprotein |
Table 2B. (Continued)

| Author, year | Study design | Number of patients | Age | Gender (M:F) | Treatment history |
|--------------|--------------|--------------------|-----|--------------|-------------------|
| Li, 2006     | Prospective cohort | 553: CAD 388 non CAD 165 | Mean: 60.1 (9.7) CAD: 61.4 (9.7) Non CAD: 57.2 (8.8) P = 0.00 | CAD: 82.6% Non CAD: 63.9% |
| Wang, 2006   | Survey       | 30,378 (ACS 227 stroke 582 non CVD 29,569) | Mean: 46.89 ASC: 52.4 (7.9) Non CVD: 46.7 (8.0) | ASC: male 70.5% Non CVD: male 53.2% |

and risk of CAD. Two studies\textsuperscript{19,20} defined obesity as $\geq 28 \text{ kg/m}^2$ and $\geq 30 \text{ kg/m}^2$ and reported statistically significant crude ORs to be 2.05 and 1.68, respectively. Only 1 study\textsuperscript{19} reported adjusted RR of 1.29. Four studies\textsuperscript{22,26,27,29} used BMI as a surrogate for obesity and reported the difference in BMI between CAD patients and non-CAD patients. Three of these studies\textsuperscript{22,27,29} found CAD patients had significantly higher levels of BMI, while 1 study\textsuperscript{26} found the difference in BMI between CAD and non-CAD groups to be statistically insignificant.

Smoking and risk of CAD
Fourteen studies were reviewed for the association between smoking and risk of CAD. The definition of smoking applied varied between studies, which included former smokers, current smokers, or ever smokers. Ever smokers included former smokers and current smokers. Thus reported crude ORs ranged widely, between 1.37 and 5.19. For the studies that provided the categories of smokers included, current smokers had crude ORs reported of 3.06,\textsuperscript{20} 2.02,\textsuperscript{21} and 1.69\textsuperscript{19}; while ever smokers had crude ORs reported of 1.42\textsuperscript{21} and 1.37.\textsuperscript{21} Seven studies did not refine the definition of smoking status used in the study. However, except for 1 study,\textsuperscript{20} the rest found smoking to be a significant factor to the risk of CAD. The highest crude association was reported in Zhang et al\textsuperscript{27} at 5.19, which had 519 CAD patients and 608 controls comparable in demographic characteristics at baseline.

Adjusted risk ratios ranged between 1.23 and 3.83. Current smokers had adjusted OR of 3.83 (95% CI: 1.08–13.68)\textsuperscript{20} and 1.75,\textsuperscript{19} while men had a RR of 2.40 (95% CI: 1.60–3.30).\textsuperscript{21} Ever smokers had adjusted OR of 1.23 (95% CI: 1.09–1.39). One study\textsuperscript{21} reported the risk ratio for CAD mortality. Former smokers had a risk ratio of 0.68 for CAD when compared to never smokers, while current smokers had a risk ratio of 1.81. When stratified by diabetic and non-diabetic populations, the adjusted RR ratios were not significant.\textsuperscript{24}

Composite risk factor and CAD
One study, in addition to reporting on the association of the risk factors of interest, also reported an
null
Table 2C. Association between obesity and risk of CAD.

| Author, year | Study design     | Number of patients | Age       | Gender (M:F)                |
|--------------|------------------|--------------------|-----------|----------------------------|
| Ni M, 2007   | Case-control     | 237 (CAD:138; control 99) | Mean: 54.18 (9.25) | CAD: 108:30 |
|              |                  | Range: 35–70       | Control: 52.65 (9.39) | Control: 55:44 |
|              |                  | CAD: 55.28(9.03)   | P = 0.031 | NS |
| Su G, 2011   | Prospective cohort | 344 (CAD: 252; non CAD: 92) | CAD: mean: 65 (9) | CAD: 165:87 |
|              |                  | Non CAD: 61(9)     | Control: 55:44 | Non CAD: 48:44 |
| Tang NP, 2008 | Case-control     | 530 (CAD 265; control 265) | CAD: 64 (56–71) | CAD: 194:71 non |
|              |                  | Control: 64 (55–71) |               | CAD: 194:71 NS |
| Xu H, 2008   | Case-control     | 384 (CAD 210; control 174) | CAD: 56 (7.3) | 201:183 |
|              |                  | Non CAD: 55 (8.6)  |                     | CAD: 116:94 |
|              |                  |                   | Control: 85:89 | Control: 362:157 |
| Zhang K, 2010 | Case-control     | 1127 (CAD: 519; control 608) | CAD: 61.285 (10.755) | CAD: 60:3777 (10.730) |
|              |                  | Control: 60.3777 (10.730) | P = 0.16  | Control: 401:207 |
| Hu DY, 2006  | Prospective cohort | 3513 (CAD: 3513) | 69 (65–77) | 2341:1172 |
| Wang, 2006   | Survey           | 30,378 (ACS 227 stroke 582 non CVD 29,569) | Mean: 46.89 | ASC: male 70.5% |
|              |                  | ASC: 52.4 (7.9)    | Non CVD: 46.7 (8.0) | Non CVD: male 53.2% |

the highest crude ORs and adjusted RR ratios for hypertension, diabetes, smoking, and hyperlipidemia in CAD patients, suggesting that the population of Northern China may be at greater risk for stroke than the Chinese population as a whole. Such geographic variation was also found in the United States, and this was largely suspected to be because areas with higher CAD prevalence were frequently characterized as rural and poor. However, while differences in measurement were in part based on geography, studies were mostly regional in scope and lacked comparison across different areas of the country. Well-designed epidemiological studies are needed to better estimate the impact of individual and overall risk factors on reduction and prevention of CAD in China.

Gender and age differences in CAD mortality and prevalence were widely reported in the articles included in this review, and gender played a significant role in the differentiation of prevention and reduction of CAD. CAD mortality rates increased by 50% in men and 21% in women when adjusted for age. This systematic review also confirmed previous findings that in China, hypertension among women was found to be significant, while hypertension among men was found not to be significant. Prevalence also seemed to differ by age group with the likelihood of having diabetes among CAD patients increasing with age. This observation is supported by a meta-analyses of 41 cohort studies conducted from Asia, Australia, and New Zealand that
| Treatment history | Definition of risk factor | Crude OR | Adjusted association | Adjusted model configuration |
|-------------------|--------------------------|----------|----------------------|-----------------------------|
| BMI ≥ 30 km/m²    | 2.05 (P = 0.032)         |          |                      | BMI not statistically different between CAD and non-CAD groups |

**Table 2.** Association between obesity and risk of CAD.

- **Author, year**
  - Ni M, 2007
  - Su G, 2011
  - Tang NP, 2008
  - Xu H, 2008
  - Zhang K, 2010
  - Hu DY, 2006
  - Wang, 2006

- **Study design**
  - Case-control
  - Prospective cohort
  - Survey

- **Number of patients**
  - Ni M: 237 (CAD: 138; control 99)
  - Su G: 344 (CAD: 252; non CAD: 92)
  - Tang NP: 530 (CAD 265; control 265)
  - Xu H: 384 (CAD 210; control 174)
  - Zhang K: 1127 (CAD: 519; control 608)
  - Hu DY: 3513
  - Wang: 30,378 (ACS 2272 stroke 582 non CV 29,569)

- **Age**
  - Mean: 54.18 (9.25) Range: 35–70
  - CAD: mean: 65 (9)
  - Non CAD: 61(9)
  - CAD: 64 (56–71)
  - Control: 64 (55–71)
  - CAD: 56 (7.3)
  - Non CAD: 55 (8.6)
  - 61.285 (10.755)

- **Gender (M:F)**
  - CAD: 108:30
  - Control: 55:44

- **Treatment history**
  - Oral anti-hyperglycemic: CAD: 45.7%
  - Non CAD: 44.0%
  - Not significant
  - Insulin: CAD: 35.9%
  - Non CAD: 40.9%
  - Not significant
  - Statins: CAD: 61.9%
  - Non CAD: 69.4%
  - Not significant

- **Definition of risk factor**
  - BMI ≥ 30 km/m²

- **BMI (kg/m²)**
  - CAD: Median: 24.2
  - Quartiles: 22.1–26.4
  - CAD: 25.1 (3.3)
  - Non CAD 23.8 (3.6)
  - (P < 0.001)
  - BMI: CAD 24.6 (4.2)
  - Non CAD 23.6 (6.1)
  - (P = 0.056)

- **BMI (kg/m²) vs. non CAD**
  - BMI: CAD 26.0 (13.6)
  - Non CAD 24.3
  - (13.3) (P < 0.001)

- **BMI ≥ 28 kg/m²**
  - 1.68 (P < 0.001)

- **RR: 1.290**

**Cox regression:** age, gender, Blood pressure, TC, smoking, low HDL-C, diabetes, obesity

found higher CAD risk among stratified age groups, particularly amongst women.33

When looking at other countries such as the United States35,36 and France,37 CAD has declined significantly due to treatments and changes in diet,38 the addition of health and nutrition programs, and promoting healthy eating and physical activity via marketing.19 A study conducted in Singapore38 suggested changes in diet to address incidence of CAD. Additionally, Wang et al11 advised that preparations be made in the health care infrastructure to accommodate the growing need for treatment of CAD and related chronic disease. Additionally, antihypertensives and statins have proved an effective treatment for preventing coronary events and death from coronary heart disease, especially for preventing secondary coronary events. Three large trials in the United States39,40 and Scandinavia41 demonstrated that statin treatment reduced coronary events by 23%–34% and reduced CAD mortality by 20%–42%. Antihypertensive medication use in China is only 28.2% even among those aware of their hypertensive condition. Increasing antihypertensive medication use, therefore, has the potential to greatly impact hypertension-related CAD mortality.

Meta-analyses were considered, but differences represented in these studies in terms of study design (eg, case-control vs. cohort, blinding vs. non-blinding) patient population, and outcome measurement can have large effects on results.42 These problems were exacerbated in the current dataset by heterogeneity in
### Table 2D. Association between diabetes and risk of CAD.

| Author, year | Study design | Number of patients | Age | Gender (M:F) | Treatment history |
|--------------|--------------|--------------------|-----|--------------|-------------------|
| Han Y, 2007  | Case-control | 726 (CAD 378; control 348) | Mean: 57.2 (10.5) | 492:234 | CAD: 284:94 |
|              |              | Range: 29–89       |     |              | Control: 210:138  |
|              |              | CAD: mean: 57.7 (10.7) |     |              |                   |
|              |              | Control: 55.6 (10.4) |     |              |                   |
| Cui, 2007    | Prospective cohort | 762 (CAD 423; control 339) | Mean: 60 (10); Range: 17–81 | 481:281 | CAD: 261:162 |
|              |              |                   |     |              | Control: 220:119  |
| Ni M, 2007   | Case-control | 237 (CAD:138; control 99) | Mean: 54.18 (9.25) | 163:74 | CAD: 108:30 |
|              |              | Range: 35–70       |     |              | Control: 55:44    |
|              |              | CAD: 55.28 (9.03)  |     |              |                   |
|              |              | Control: 52.65 (9.39) | P = 0.031 |              |                   |
| Su G, 2011   | Prospective cohort | 344 (CAD: 252; non CAD: 92) | CAD: mean: 65 (9) | 165:87 | Oral anti-hyperglycemic |
|              |              | Non CAD: 61 (9)     |     |              | CAD: 48:44        |
| Tang NP, 2008| Case-control | 530 (CAD 265; control 265) | CAD: 64 (56–71) | 194:71 | CAD: 194:71 |
|              |              | Control: 64 (55–71) |     |              | NS                |
| Xu H, 2008   | Case-control | 384 (CAD 210; control 174) | CAD: 56 (7.3) | 201:183 | CAD: 116:94 |
|              |              | Non CAD: 55 (8.6)  |     |              | Control: 85:89   |
| Zhang K, 2010| Case-control | 1127 (CAD: 519; control 608) | CAD: 61.285 (10.755) | 362:157 | CAD: 401:207 |
|              |              | Control: 60.3777 (10.730) P = 0.16 |     |              |                   |
|              |              | 63.4 (9.7)         |     |              |                   |
| Chen ZW, 2011| Prospective cohort | 325 (CAD: 222; non-CAD: 103) | 218:107 | Diabetic: 61.43 |
|              |              | Diabetic: 66.2 (8.1) |     |              | Non diabetic: 157.64 |
|              |              | Non diabetic: 62.2 (10.2) | P < 0.01 |              |                   |
|              |              | 69 (65–77)         |     |              |                   |
| Hu DY, 2006  | Prospective cohort | 3513 (CAD: 3513) | Mean: 56 (8) | 301:350 | CAD: 54:17 |
|              | Retrospective cohort | 651: CAD 71 non CAD 580 | Range: 42–75 |              | Non CAD: 247:333 |
| Li, 2007     | Prospective cohort | 553: CAD 388 Non CAD 165 | Mean: 60.1 (9.7) | 82.6%  | Non CAD: 63.9% |
|              |              | Range: 61.4 (9.7)  |     |              | P = 0.00         |
|              |              | Control: 57.2 (8.8) |     |              |                   |
| Li, 2006     | Prospective cohort | 597 (Type 2 Diabetes: 199 non diabetes 398) | Range: 40–85 | Diabetes: 76:123 |
| Wang, 2007   | Survey       | 30,378 (ACS 227 stroke 582 non CVD 29,569) | Mean: 46.89 | Non diabetes: | 152:246 |
| Wang, 2006   | Survey       | 1127 | ASC: 52.4 (7.9) | ASC: male 70.5% |
|              |              | Range: 40–85       |     |              | Non CVD: male 53.2% |
| Definition of risk factor                                                                 | Crude OR | Adjusted association                      | Adjusted model configuration                                                                 |
|----------------------------------------------------------------------------------------|----------|------------------------------------------|-----------------------------------------------------------------------------------------------|
| Type 1 and type 2                                                                       | 3.83 (P < 0.01) | OR (95% CI): 3.28 (2.60–4.14) (P = 0.00) | Logistic: age, gender, hypertension, diabetes mellitus, hyperlipidemia, smoking                  |
| Self-reported or oral glucose tolerance and insulin level assayed                         | NR       | 95% significant association with diabetes |                                                                                               |
|                                                                                         | 3.02 (P = 0.005) |                                          |                                                                                               |
| Diagnosed according to the American Diabetes Association criteria                       | Duration of diabetes (months): CAD: 78 (77) |                                          |                                                                                               |
|                                                                                         | No CAD: 58 (68) |                                          |                                                                                               |
|                                                                                         | P = 0.022   |                                          |                                                                                               |
| Fasting blood glucose ≥ 7.8 mmol/l or a diagnosis of diabetes needing diet or antidiabetic drug therapy | NR       | 1.47 (NS)                                |                                                                                               |
|                                                                                         | 1.50 (P = 0.02) | OR: 4.381 (95% CI: 2.536–7.764); P < 0.001 | Logistic: diabetes, hypertension, high LDL levels and genotype                                  |
|                                                                                         | 22% of CAD patients had diabetes, 0% in non CAD patients. (P = 1.00) |                                          |                                                                                               |
| 1999 WHO diagnostic criteria                                                             | 1.50 (P = 0.31) |                                          |                                                                                               |
| Type 2 diabetes only: ≥ 7.0 or ≥11.1 mmol/L on FPG test                                  | 52.9% CAD patients had diabetes |                                          |                                                                                               |
|                                                                                         | 5.97 (P < 0.01) |                                          |                                                                                               |
| History of DM and Newly diagnosed                                                       | 2.97 (P < 0.05) |                                          |                                                                                               |
| 1999 WHO and International Diabetes Association criteria                                  | 2.08 (1.16–3.74) | (P < 0.01)                   | Cox regression: age, gender, blood pressure, TC, smoking, low HDL-C, diabetes, obesity             |
| Fasting blood glucose ≥ 7 mmol/L or previous diagnosis by physicians                     | 1.53 (P < 0.001) | RR: 1.191                               |                                                                                               |

(Continued)
Table 2D. (Continued)

| Author, year | Study design | Number of patients | Age | Gender (M:F) | Treatment history |
|--------------|--------------|--------------------|-----|--------------|-------------------|
| Liu, 2008    | Survey       | 3223 (ACS history 27.1%) | 65 (11) | 2183:1040 |                    |

Table 2E. Association between smoking and risk of CAD.

| Author, year | Study design | Number of patients | Age | Gender (M:F) | Treatment history |
|--------------|--------------|--------------------|-----|--------------|-------------------|
| Han Y, 2007  | Case-control | 726 (CAD 378; control 348) | Mean: 57.2 (10.5) Range: 29–89 CAD: mean: 57.7 (10.7) Control: 55.6 (10.4) | 492:234 | CAD: 284:94 Control: 210:138 |
| Cui, 2007    | Prospective cohort | 762 (CAD 423; control 339) | Mean: 60 (10); range 17–81 | 481:281 | CAD: 261:162 Control: 220:119 209:103 CAD: 209:103 Control: 184:126 P = 0.056 100%: lipid-lowering agents |
| Han Y, 2010  | Case-control | 622 (CAD 312; control 310) | Mean: 61.96 (10.71) CAD: 61.96 (10.71) Control: 60.54 (10.18) P = 0.09 | 163:74 | CAD: 108:30 Control: 55:44 P < 0.01 |
| Ni M, 2007   | Case-control | 237 (CAD:138; control 99) | Mean: 54.18 (9.25) Range: 35–70 CAD: 55.28 (9.03) Control: 52.65 (9.39) P = 0.031 | | |
| Sai XY, 2007 | Cross-sectional survey | 1268 | Mean: 62.95 (5.18) Never smoker: 62.52 (5.20) Ever smoker: 63.13 (5.16) | 1268:0 | |
| Su G, 2011   | Prospective cohort | 344 (CAD: 252; non CAD: 92) | CAD: mean: 65 (9) Non CAD: 61 (9) | CAD: 165:87 | Non CAD: 48:44 Oral anti-hyperglycemic CAD: 45.7% Non CAD: 44.0% Not significant Insulin CAD: 35.9% Non CAD: 40.9% Not significant Statins CAD: 61.9% Non CAD: 69.4% Not significant |
### Definition of risk factor

| Definition of risk factor | Crude OR | Adjusted association | Adjusted model configuration |
|--------------------------|----------|----------------------|-----------------------------|
| History of DM or newly diagnosed | 22.6% | | |
| By gender | | | |
| Female: 26.3% | | | |
| Male: 20.8% \( P < 0.01 \) | | | |
| By age | | | |
| \(< 45 \): 10.4% | | | |
| 45 – 20.2% | | | |
| 55 – 23.2% | | | |
| 65 – 23.8% | | | |
| \( \geq 75 \): 25.2% | | | |

### Definition of risk factor

| Definition of risk factor | Crude OR | Adjusted association | Adjusted model configuration |
|--------------------------|----------|----------------------|-----------------------------|
| Past and present (former smoker + current smoker) | 1.42 \( (P < 0.01) \) | OR (95% CI): 1.23 \( (1.09–1.39) \) \( P = 0.00 \) | Logistic: age, gender, hypertension, diabetes mellitus, hyperlipidemia, smoking |
| Smoked at least one cigarette per day in at least one year | | Men: \( RR = 2.4 \) (95% CI: 1.6–3.3) | |
| NR | 0.41 \( (P < 0.01) \) | | |
| Current smoker | 3.06 \( (P < 0.001) \) | OR (95% CI): 3.83 \( (1.08–13.68) \) \( P = 0.038 \) | Logistic: age, male, gender, CAD family history, smoking, obesity, dyslipidemia, diabetes mellitus, hypertension, systolic BP, diastolic BP, fasting glucose, total cholesterol, triglycerides, LDL-C, HDL-C, hs—CRP, homocysteine |
| Ever vs. never (ever-smoker: one who had smoked at least one cigarette daily for one year or more) | Ever smoker: 1.37 | CHD mortality: former smoker HR 0.681 \( (95\% \text{ CI}: 0.376–1.233) \) Current smoker HR 1.805 \( (95\% \text{ CI}: 1.022–3.188) \) | |
| Former smoker: those who had stopped for at least 2 years. Current smoker: ever-smokers who were smoking at baseline | 2.17 \( (P = 0.007) \) | OR: 2.492 \( (95\% \text{ CI}: 1.315, 4.720, P = 0.005) \) | Logistic: smoking, male, older age, MAGE (mean amplitude of glycemic excursions), hs-CRP, hyperlipidemia, hypertension, renal insufficiency |

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(Continued)
Table 2E. (Continued)

| Author, year | Study design | Number of patients | Age | Gender (M:F) | Treatment history |
|--------------|--------------|--------------------|-----|-------------|------------------|
| Tang NP, 2008 | Case-control | 530 (CAD 265; control 265) | CAD: 64 (56–71) | CAD: 194:71 Non | 201:183 |
| Xu H, 2008 | Case-control | 384 (CAD 210; control 174) | CAD: 56 (7.3) | CAD: 116:94 Control: 85:89 |
| Zhang K, 2010 | Case-control | 1127 (CAD: 519; control 608) | CAD: 61.285 (10.755) | CAD: 362:157 |
| Chen ZW, 2011 | Prospective cohort | 325 (CAD: 222; non-CAD: 103) | Diabetic: 66.2 (8.1) | Non diabetic: 62.2 (10.2) |
| Hu DY, 2006 | Prospective cohort | 3513 (CAD: 3513) | 69 (65–77) | 218:107 Diabetic: 61:43 Non diabetic: 157:64 |
| Li, 2007 | Retrospective cohort | 651: CAD 71 non CAD 580 | Mean: 56 (8) | CAD: 54:17 |
| Li, 2006 | Prospective cohort | 553: CAD 388 non CAD 165 | Mean: 60.1 (9.7) | CAD: 63 (9) |
| Wang, 2006 | Survey | 30,378 (ACS 227 stroke CVD 29,569) | Mean: 46.89 | 301:350 ASC: male 70.5% Non CVD: male 53.2% |

the statistical methods employed when examining relationships between comorbidities and outcomes. For instance, in the 23 hypertension studies, there were:

1. Differences in definition of hypertension (eg, ≥140/90 vs. ≥160/95)
2. Differences in the type of stroke (ischemic vs. total vs. hemorrhagic vs. stroke mortality, with several different types of ischemic stroke)
3. Differences in patient population (eg, some studies are on the general population, some on only diabetics, some only on patients with atrial fibrillation (AF), some only on elderly patients)
4. Differences in how relationships are measured (some analyses given a crude OR/RR, others adjust for multiple factors)
5. Differences in factors controlled for in multivariate analyses (some control for age and duration of diabetes, while some control for 10 or more variables such as familial stroke history, ie, variables which may be endogenous to risk, thus resulting in a lower than expected hazard ratio between the variables of interest)
6. Differences in study design (prospective cohort vs. retrospective cohort vs. survey vs. case-control)

Given this host of differences, we concluded that while meta-analysis was statistically viable, the results would not be interpretable without digging down into very small subsets of studies.

Another weakness of the data extracted is that fewer than half of the articles reported adjusted hazard ratios
| Definition of risk factor                     | Crude OR       | Adjusted association          | Adjusted model configuration                      |
|----------------------------------------------|----------------|------------------------------|--------------------------------------------------|
| ≥10 cigarettes/d                             | 2.02 (P < 0.001) |                              |                                                  |
| NR                                           | 1.53 (NS)      |                              |                                                  |
|                                              | 5.19 (P < 0.001)|                              |                                                  |
| NR                                           |                | Diabetic: OR: 2.941 (P = 0.199) | Logistic regression: aortic valve calcification (AVC), sex, age, hypertension, smoking, serum level of fibrinogen, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, apoprotein |
|                                              |                | Non diabetic: OR: 1.603 (P = 0.256) |                                                  |
|                                              |                | 50% of CAD were never smokers, 30% former smokers, 20% current smokers | 3.89 (P < 0.01) |
|                                              |                |                              |                                                  |
|                                              |                | 3.30 (P = 0.00)               |                                                  |

| Currently smoking and ≥1 cigarette per day   | 1.69 (P < 0.001) | RR: 1.750                    | Cox regression: age, gender, blood pressure, TC, smoking, low HDL-C, diabetes, obesity |

or RRs. Much of the discussion relies on crude ORs extracted from the reported frequencies. This dependence on crude ORs ignores the role of other important risk factors for CAD such as age and gender. Though a strong association was found in this review between lipid levels and risk of CAD, evidence relating these 5 risk factors to CAD has largely gone unexamined in the Chinese population. As noted earlier, the lack of quality data makes difficult comparisons between the different regions of China, both geographic and economic. More large epidemiologic studies relating CAD to its risk factors, especially nationwide studies, would go a long way towards clarifying the effects these 5 conditions have on incidence of CAD in China. The need for large, regional studies is made more important by the fact that China has experienced a considerable increase in the prevalence of CAD in recent decades, and understanding the contribution of the leading 5 risk factors to CAD in China is a critical first step toward future prevention of this disease.

Regardless of the quantity or quality of research in this area, this review found that all 5 of the risk factors examined—hypertension, smoking, diabetes, obesity, and, in particular, low LDL-C levels—were associated with CAD in China. Hypertension, diabetes, and smoking were associated with CAD, with crude ORs ranging from 1.37 to 5.97. While few ORs or RR ratios were calculated, high LDL-C levels were consistently associated with CAD, and to a somewhat lesser extent, so were low HDL-C levels. While the connection between obesity and CAD deserves additional study due to a paucity of existing research within the subject
population, studies in this review did find that obesity was positively associated with CAD in China, and this matches results of similar studies conducted in Western populations. Addressing these 5 risk factors through drug treatment as well as diet and lifestyle changes has led to reduced risk of CAD in countries such as the United States. Given that the prevalence of these risk factors in China, especially smoking, is comparatively greater than these other populations, we suspect that treating the risk factors discussed in this review will lead to dramatic and positive effects in the risk of CAD in China. Therefore, we recommend that the Chinese health care system accommodate the increased need for treatment of CAD and its related chronic diseases, in particular the risk factors hypertension, smoking, diabetes, obesity, and elevated lipid levels.

**Acknowledgements**

Medical writing and editorial support to prepare this manuscript under the direction of the authors was provided by Dylan Boyd of United BioSource Corporation and funded by Pfizer Inc.

**Author Contributions**

Conceived and designed the experiments: JF, HJM, SS. Analyzed the data: DB, SS. Wrote the first draft of the manuscript: DB, SS. Contributed to the writing of the manuscript: SS. Jointly developed the structure and arguments for the paper: Made critical revisions and approved final version: JF, YH, LJ, DZ, DH. All authors reviewed and approved of the final manuscript.

**Funding**

This study was sponsored by Pfizer Inc, Emerging Markets Outcomes Research and Epidemiology. The principal investigators and co-investigators had full access to the data and were responsible for the study protocol, study progress, analysis, study reporting, and decision to publish the paper. Pfizer Inc, had the opportunity to comment on the manuscript before submission.

**Competing Interests**

Prof. Yong Huo, Prof. Linong Ji, Prof. Dong Zhao, and Prof. Dayi Hu have no conflicts of interest. Dr. JoAnne Foody is a Pfizer Inc, consultant. Dylan Boyd is an employee of United BioSource Corporation. Dr. Hai Jin Meng is an employee of Pfizer, Ltd, Dr. Susan Shiff is a Pfizer Inc, medical employee and is also an owner of Pfizer stock.
Disclosures and Ethics
As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent expert peer review. The reviewers reported no competing interests.

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