Gallstone Disease and the Risk of Ischemic Heart Disease

Jun Lv, Lu Qi, Canqing Yu, Yu Guo, Zheng Bian, Yiping Chen, Ling Yang, Jie Shen, Shanqing Wang, Mingqiang Li, Yongmei Liu, Libo Zhang, Junshi Chen, Zhengming Chen, Liming Li; on behalf of the China Kadoorie Biobank Collaborative Group*

Objective—Gallstone disease (GSD) is related to multiple cardiovascular risk factors; the present study was to prospectively examine the association between GSD and ischemic heart disease (IHD).

Approach and Results—We examined the association of GSD with IHD among 199,292 men and 288,081 women aged 30–79 years in the China Kadoorie Biobank study. Participants with cancer, heart disease, and stroke at baseline were excluded. Cox proportional hazards regression model was used to estimate the association of GSD with IHD. The prevalence of self-reported GSD was 3.7% in men and 7.3% in women at baseline. During 3,431,124 person-years of follow-up between 2004 and 2013 (median, 7.2 years), we documented 10,245 incident IHD cases in men and 14,714 in women. As compared with men without GSD at baseline, the multivariate-adjusted hazard ratio for IHD was 1.11 (95% confidence interval, 1.02–1.22) for men with GSD; the respective hazard ratio was 1.27 (95% confidence interval, 1.20–1.34) in women and 1.23 (95% confidence interval, 1.17–1.28) in the whole cohort. The sex difference in IHD risk associated with GSD was statistically significant (P=0.009 for interaction with sex). In addition, we found that the association between GSD and IHD was stronger in nonhypertensive than in hypertensive women (P<0.001 for interaction).

Conclusions—In this large prospective study, the presence of GSD was associated with an increased risk of incident IHD, independent of other risk factors of cardiovascular disease. Our findings suggest novel prevention strategy to mitigate heart disease through improvement of gastrointestinal health. (Arterioscler Thromb Vasc Biol. 2015;35:2232-2237. DOI: 10.1161/ATVBHA.115.306043.)

Key Words: cardiovascular disease ■ Chinese ■ ischemic heart diseases ■ longitudinal cohort study ■ risk factor

Gallstone disease (GSD), a condition with crystalline deposits in the gallbladder, is one of the most common and costly gastrointestinal disorders resulting in hospital admission in developed countries.1 To a relatively lower degree, GSD is also a common health problem in Asian populations, such as Chinese;2 and the prevalence has been increasing along with growing adoption of western lifestyle and epidemic of obesity.3

See accompanying editorial on page 2073

Patients with GSD have higher prevalence of cardiovascular risk factors, such as obesity, type 2 diabetes mellitus, dyslipidemia, hyperinsulinemia, and sedentary lifestyle.1 In addition, a recent study linked gut microbiota dysbiosis with the presence of cholesterol gallstone.4 Emerging evidence has implicated gut microbiota as a novel factor for cardiovascular disease (CVD).5,6 Several previous studies have related presence of GSD with an increased CVD risk, including outcomes of coronary heart disease, stroke, and CVD mortality.7-13 However, these studies were largely limited by cross-sectional design or small sample size. Prospective investigations on the relation between GSD and CVD risk in large cohorts are sparse.

Therefore, we aimed to prospectively examine the association between a history of GSD and the risk of incident ischemic heart disease (IHD) in a large cohort of 0.5 million of adult Chinese—the China Kadoorie Biobank study.14,15 In addition, we particularly assessed potential interactions between GSD and conventional CVD risk factors.

Materials and Methods

Materials and Methods are available in the online-only Data Supplement.
Results

At baseline, 5.8% of 487,373 participants reported the presence of GSD (men 3.7%; women 7.3%). Age- and site-adjusted baseline characteristics according to the presence of GSD are presented in Table 1. Compared with participants without GSD, those with GSD were older, more likely to be urban residents, less likely to smoke tobacco and drink alcohol, less physically active, and had higher body mass index, waist circumference, and prevalence of diabetes mellitus, chronic hepatitis/cirrhosis, and peptic ulcer (Table 1). Women with GSD had an earlier age at the first diagnosis and longer duration than men with GSD.

During a median follow-up of 7.2 years (interquartile range, 1.91 years; total person-years, 3,431,124), we documented 10,245 incident IHD cases in men (1034 [10.1%] fatal and 9,211 [89.9%] nonfatal) and 14,714 in women (767 [5.2%] fatal and 13,947 [94.8%] nonfatal). Incidence rates according to the presence of GSD were 7.1 and 9.8 deaths per 1000 person-years for participants without and with GSD, respectively. Figure 1 presents the Nelson–Aalen curves of the cumulative hazard of IHD according to the presence of GSD. The cumulative incidence of IHD was statistically significantly higher in participants with GSD than in those without GSD (log-rank test, P<0.001). In age-adjusted analyses, the presence of GSD was significantly associated with an increased risk of incident IHD. Further adjustment for other potential confounders, especially body mass index, hypertension, diabetes mellitus, and several lifestyle risk factors, did not substantially attenuate these associations (Table 2). As compared with men without GSD at baseline, the multivariate-adjusted hazard ratio (HR) for IHD was 1.11 (95% confidence interval [CI], 1.02–1.22) for men with GSD; the respective HR was 1.27 (95% CI, 1.20–1.34) in women and 1.23 (95% CI, 1.17–1.28) in the whole cohort. We found that the association between GSD and IHD was significantly stronger in women than in men (P=0.009 for interaction with sex). These associations were not materially changed in sensitivity analyses with additional adjustment for the presence of digestive system diseases, replacement of body mass index by waist circumference, or exclusion of patients with diabetes mellitus (Table 2).

We further performed stratified analyses according to the duration of GSD from the first diagnosis to the baseline. Similar associations were observed among participants with different durations of GSD in the whole cohort. Notably, the association of GSD with incident IHD appeared to be stronger in women than in men among those who reported their duration of GSD since the first diagnosis >10 years (Table 3).

We also analyzed the associations between GSD and incident IHD according to other potential baseline risk factors; the positive associations were generally similar across subgroups stratified according to age, smoking status, alcohol consumption, level of physical activity, body mass index, abdominal obesity measured by waist circumference, and the presence of diabetes mellitus (all P values for interaction >0.05; Figure 2; Table I in the online-only Data Supplement). Statistically significant difference across strata was observed for the presence of hypertension in women (P<0.001 for interaction) but not in men (P=0.216 for interaction), with a stronger association in nonhypertensive than in hypertensive women.

Discussion

In this large prospective study with >3.4 million person-years of follow-up, we found that presence of GSD was associated with a significantly increased risk of incident IHD, and such association was independent of traditional cardiovascular risk factors. The association was stronger in women than in men and was stronger in nonhypertensive than in hypertensive women.

Our findings are consistent with the results from 4 previous smaller prospective studies. In those studies, a history of GSD was associated with an increased risk of coronary heart disease (odds ratio =1.75; 95% CI, 1.13–2.69) among men in the Framingham Heart Study,9 CVD mortality (HR=1.4; 95% CI, 1.2–1.7) in a general US population from the third US National Health and Nutrition Examination Survey,10 CVD, including myocardial infarction and stroke (HR=1.24; 95% CI, 1.02–1.50), in the German arm of the European Prospective Investigation into Cancer and Nutrition (EPIC),11 and coronary heart disease (HR=1.42; 95% CI, 1.28–1.58) in a Taiwan population identified from the Taiwan National Health Insurance Research Database (NHIRD).12 In addition, in a retrospective cohort study based on Taiwan NHIRD, persons with GSD were also found to have an increased risk of developing ischemic (HR=1.28; 95% CI, 1.25–1.31) and hemorrhagic stroke (HR=1.33; 95% CI, 1.25–1.41).13

Several potential mechanisms may account for the association between GSD and cardiovascular risk. Presence of GSD has been related to a variety of cardiovascular risk factors, such as obesity,16,17 hyperinsulinemia,18,19 insulin resistance,20 diabetes mellitus,19,21 and metabolic syndrome.22 However, in our study, the association of GSD with IHD risk remained significant after adjustment for obesity, hypertension, diabetes mellitus, and common lifestyle risk factors, suggesting other mechanisms might also be involved.

In a recent study, it was found that GSD was related to gut microbiota dysbiosis,4 probably through disturbed secretion of bile acids that play a key role in regulating abundance or metabolism of gut microbiota.23 Gut microbiota has recently emerged as a novel risk factor for CVD, and several studies have associated gut microbiota–related metabolites, such as trimethylamine-N-oxide and L-carnitine, with risk of CVD and mortality.6,24 In addition, abundance of gut microbiota has been related to elevated levels of CVD risk factors, including inflammation and dyslipidemia, through metabolic endotoxemia.25,26 We assume that the association between GSD and IHD might be at least partly through affecting gut microbiota metabolism; our findings would motivate further investigation on this hypothesis.

In our study, the risk for incident IHD associated with GSD differed by sex and was stronger in women than in men. Estrogen has been suggested to be an important risk factor for the formation of cholesterol gallstones, leading to observations that cholesterol gallstones are more common in women than in men, and such sex difference begins from puberty and continues through the childbearing years.27 Sustained effect of estrogen on gallstone
formation may also account for a potentially more important etiologic role of GSD in the development of IHD in women than in men. This result was different from the findings from previous studies, which reported either no sex difference\textsuperscript{10–12} or stronger association in men.\textsuperscript{9} The discrepant observations may be partly explained by population diversity. In addition, the previous studies were largely small in size and might have been underpowered to detect such sex difference. How sex may affect the association between GSD and IHD warrants further investigations.

In addition, we observed statistically significant interaction between GSD and hypertension on IHD risk, and stronger association was observed in nonhypertensive than in hypertensive women. GSD and hypertension may partially share common pathogenic mechanisms that contribute to the increased risk of IHD. It is possible that hypertensive patients were already at a high risk of IHD, and GSD status added only modestly deleterious effect on the relative scale. However, it is notable that the absolute risk associated with hypertension among women with GSD was much greater than that without hypertension. In addition, antihypertensive therapy or lifestyle modifications among hypertensive patients may play an antagonistic role on the pathways involved in the development of IHD among women with both conditions. Further study is needed to clarify the possible biological mechanisms underlying differential effects of GSD on IHD by hypertension. No interaction was observed between GSD and hypertension on

### Table 1. Baseline Characteristics of 487373 Participants According to the Presence of Gallstone Disease

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Men With GSD</th>
<th>Men Without GSD</th>
<th>P Value</th>
<th>Women With GSD</th>
<th>Women Without GSD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>7436</td>
<td>191856</td>
<td>...</td>
<td>20909</td>
<td>267172</td>
<td>...</td>
</tr>
<tr>
<td>Age, y</td>
<td>53.9</td>
<td>51.8</td>
<td>&lt;0.001</td>
<td>53.3</td>
<td>50.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urban area, %</td>
<td>55.8</td>
<td>42.1</td>
<td>&lt;0.001</td>
<td>45.4</td>
<td>43.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Currently married, %</td>
<td>94.5</td>
<td>92.9</td>
<td>&lt;0.001</td>
<td>89.9</td>
<td>89.4</td>
<td>0.016</td>
</tr>
<tr>
<td>Middle school and above, %</td>
<td>62.8</td>
<td>57.6</td>
<td>&lt;0.001</td>
<td>46.7</td>
<td>43.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current regular smoker, %</td>
<td>57.7</td>
<td>62.3</td>
<td>&lt;0.001</td>
<td>2.3</td>
<td>2.3</td>
<td>0.789</td>
</tr>
<tr>
<td>Current regular drinker, %</td>
<td>28.3</td>
<td>34.2</td>
<td>&lt;0.001</td>
<td>1.8</td>
<td>2.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Physical activity, MET h/d</td>
<td>21.1</td>
<td>22.7</td>
<td>&lt;0.001</td>
<td>19.8</td>
<td>20.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Average weekly consumption, day*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red meat</td>
<td>4.0</td>
<td>3.9</td>
<td>0.089</td>
<td>3.4</td>
<td>3.5</td>
<td>0.177</td>
</tr>
<tr>
<td>Fresh vegetables</td>
<td>6.9</td>
<td>6.8</td>
<td>0.048</td>
<td>6.85</td>
<td>6.83</td>
<td>0.016</td>
</tr>
<tr>
<td>Fresh fruits</td>
<td>2.4</td>
<td>2.1</td>
<td>&lt;0.001</td>
<td>2.8</td>
<td>2.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>23.9</td>
<td>23.4</td>
<td>&lt;0.001</td>
<td>24.2</td>
<td>23.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WC, cm</td>
<td>83.5</td>
<td>81.8</td>
<td>&lt;0.001</td>
<td>80.0</td>
<td>78.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prevalence of, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>34.5</td>
<td>36.0</td>
<td>0.007</td>
<td>31.3</td>
<td>32.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6.5</td>
<td>5.0</td>
<td>&lt;0.001</td>
<td>6.6</td>
<td>5.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic hepatitis/cirrhosis</td>
<td>4.4</td>
<td>1.6</td>
<td>&lt;0.001</td>
<td>1.4</td>
<td>0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>8.5</td>
<td>5.1</td>
<td>&lt;0.001</td>
<td>5.3</td>
<td>2.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postmenopausal, %</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>51.7</td>
<td>50.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history of heart attack, %</td>
<td>6.8</td>
<td>6.7</td>
<td>0.745</td>
<td>6.7</td>
<td>5.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Characteristics of GSD†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at the first diagnosis, y</td>
<td>45.3</td>
<td>…</td>
<td>…</td>
<td>44.3</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Duration since the first diagnosis, y</td>
<td>8.2</td>
<td>9.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The results are presented as adjusted means or percentages. All variables are adjusted for age and survey sites, as appropriate. BMI indicates body mass index; GSD, gallstone disease; MET, metabolic equivalent task; and WC, waist circumference.

*The average weekly consumptions of red meat, fresh vegetables, and fruits were calculated by assigning participants the midpoint of their consumption category.

†There were statistically significant differences in both the age at the first diagnosis and the duration since the first diagnosis between men and women (P<0.001).

![Figure 1. Nelson–Aalen cumulative hazard for incident ischemic heart disease according to the presence of gallstone disease (GSD). Log-rank test, P<0.001.](https://example.com/figure1.png)
IHD risk in men, probably partly because of less important etiologic role of GSD in men than in women.

Our study had several strengths. To our knowledge, this was thus far the largest prospective study assessing time-dependent association between GSD and incident IHD. We carefully controlled for a wide range of established and potential confounders associated with CVD. We excluded participants with a history of CVD at baseline to minimize the influence of possible reverse causation. However, our results need to be interpreted in the context of a few limitations. First, one of the main limitations was that the study relied on self-reporting of the presence of GSD, potentially leading to misclassification of exposures. However, previous smaller prospective studies using GSD diagnosed by gallbladder ultrasonography or based on medical records showed similar findings. In addition, in a prospective study design, measurement errors with regard to GSD may be nondifferential, and the association is more likely to be biased toward the null. Second, we did not collect specific information on the subtypes of gallstone. However, because most gallstones in the Chinese population have been of the cholesterol type since the early 1990s, we expected that lack of such information might only have minor impact on the results. Our data were also not able to identify the severity of GSD, such as asymptomatic, symptomatic, or having performed cholecystectomy. This could limit our in-depth analysis to explore this association of interest to a further extent. Third, although we have carefully adjusted for a broad range of known or potential risk factors, residual confounding by other unmeasured or unknown factors, such as dyslipidemia and hyperinsulinemia, was still possible. For example, if dyslipidemia confounds the observed association between GSD and IHD but was not controlled for, it would have potentially led to an overestimation of observed association and biased our results away from the null value.

### Table 2. Hazard Ratios (95% CIs) for Association Between Gallstone Disease and Incident Ischemic Heart Disease

<table>
<thead>
<tr>
<th></th>
<th>Without GSD</th>
<th>With GSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>23,017/3,233,478</td>
<td>19,421/197,646</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.00</td>
<td>1.26 (1.21–1.32)</td>
</tr>
<tr>
<td>Sensitivity analyses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 4</td>
<td>1.00</td>
<td>1.22 (1.17–1.28)</td>
</tr>
<tr>
<td>Model 5</td>
<td>1.00</td>
<td>1.11 (1.01–1.22)</td>
</tr>
<tr>
<td>Model 6</td>
<td>1.00</td>
<td>1.12 (1.01–1.24)</td>
</tr>
</tbody>
</table>

Model 1 was adjusted for age. Model 2 additionally included sex (for whole cohort only); level of education; marital status; alcohol consumption; smoking status; physical activity; intake frequencies of red meat, fresh fruits, and vegetables; prevalent hypertension; prevalent diabetes mellitus; family history of heart attack; menopausal status (for women only). Model 3 additionally included body mass index (BMI). On the basis of model 3, model 4 additionally included the histories of digestive system diseases, including chronic hepatitis/cirrhosis and peptic ulcer; model 5 replaced BMI with WC; and model 6 excluded diabetic patients from the analyses. CI denotes confidence interval; GSD, gallstone disease; and WC, waist circumference.

### Table 3. Hazard Ratios (95% CIs) for Association Between Gallstone Disease and Incident Ischemic Heart Disease According to the Duration (Years) Since the First Diagnosis

<table>
<thead>
<tr>
<th>Duration</th>
<th>Without GSD</th>
<th>With GSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case/person-years</td>
<td>HR (95% CI)</td>
<td>Case/person-Years</td>
</tr>
<tr>
<td>Total</td>
<td>23,017/3,233,478</td>
<td>523/54,333 (1.22 (1.12–1.34))</td>
</tr>
<tr>
<td>0–</td>
<td>1.00</td>
<td>696/38,367 (1.21 (1.13–1.31))</td>
</tr>
<tr>
<td>10–</td>
<td>1.00</td>
<td>723/69,235 (1.25 (1.16–1.34))</td>
</tr>
<tr>
<td>Men</td>
<td>9772/1,337,533</td>
<td>142/15,293 (1.16 (0.98–1.37))</td>
</tr>
<tr>
<td>0–</td>
<td>1.00</td>
<td>184/19,358 (1.20 (1.04–1.39))</td>
</tr>
<tr>
<td>10–</td>
<td>1.00</td>
<td>147/16,325 (0.99 (0.84–1.16))</td>
</tr>
<tr>
<td>Women</td>
<td>13,245/1,895,946</td>
<td>381/39,041 (1.24 (1.12–1.38))</td>
</tr>
<tr>
<td>0–</td>
<td>1.00</td>
<td>512/54,510 (1.22 (1.12–1.33))</td>
</tr>
<tr>
<td>10–</td>
<td>1.00</td>
<td>576/52,910 (1.35 (1.24–1.46))</td>
</tr>
</tbody>
</table>

The multivariate models were adjusted for the following baseline factors: age; sex (for whole cohort only); level of education; marital status; alcohol consumption; smoking status; level of physical activity; intake frequencies of red meat, fresh fruits, and vegetables; prevalent hypertension; prevalent diabetes mellitus; family history of heart attack; menopausal status (for women only); and body mass index. CI denotes confidence intervals; and GSD, gallstone disease.
Conclusions
In summary, in thus far the largest prospective cohort of the Chinese population, we observed that the presence of GSD was associated with an increased risk of incident IHD. Our findings lend further support to the potential role of GSD in affecting cardiovascular risk and suggest novel prevention strategy to mitigate heart disease through improvement of gastrointestinal health. Additional studies are warranted to confirm the association and to elucidate the potential biological mechanism.

Appendix

China Kadoorie Biobank Collaborative Group
1. International Steering Committee: Liming Li (PI), Junshi Chen, Rory Collins, Richard Peto, Zhengming Chen (PI).
2. Study Coordinating Centers
International Co-ordinating Center, Oxford: Zhengming Chen, Garry Lancaster, Xiaoming Yang, Alex Williams, Margaret Smith, Ling Yang, Yumei Chang, Iona Millwood, Yiping Chen, Sarah Lewington.
National Co-ordinating Center, Beijing: Yu Guo, Jun Lv, Zheng Bian, Canqing Yu, Can Hou, Lei Guo, Bingyang Han, Shuzhen Qu, Ge Chen.
Regional Co-ordinating Centers, 10 areas in China:
Licang CDC: Silu Lv, Junzheng Wang, Wei Hou.
Heilongjiang Provincial CDC: Jiuyuan Yin, Shumei Liu, Zhigang Pang, Xue Zhou, Huijun Wang.
Nangang CDC: Liqiu Yang, Bo Yu, Yanjie Li, Jing Qi, Huaiyi Mu, Qin’ai Xu, Meiling Dou.
Hainan Provincial CDC: Jianwei Du, Shanshan Wang, Ximin Hu, Hongmei Wang, Jinyan Chen, Yan Fu, Zhenwang Fu, Xiaohuan Wang, Hua Dong.
Meilan CDC: Min Weng, Xiangyang Zheng, Yijun Li, Huimei Li.
Jiangsu Provincial CDC: Xianping Wu, Ningmei Zhang, Xiaofang Chen, Xuefeng Tang.
Pengzhou CDC: Guojin Luo, Jianguo Li, Xiaofang Chen, Jian Wang, Jiaqiu Liu, Qiang Sun.
Gansu Provincial CDC: Pengfei Ge, Xiaolan Ren, Caixia Dong.
Hunan Provincial CDC: Youping Xiong, Weifang Jia, Xianzhi Li, Libo Zhang, Zhe Qiu.

Acknowledgments
The chief acknowledgment is to the participants, the project staff, and the China National Center for Disease Control and Prevention (CDC).
and its regional offices for access to death and disease registries. The Chinese National Health Insurance scheme provides electronic linkage to all hospital treatment.

Sources of Funding
This work was supported by grants (81390544 and 81390541) from the National Natural Science Foundation of China; by a grant (2011BAI09B01) from the National Key Technologies Research and Development Program in the 12th Five-year Plan, Chinese Ministry of Science and Technology; by a grant (08815812/09/Z) from the Wellcome Trust in the United Kingdom; by a grant from the Kadoorie Charitable Foundation in Hong Kong. Dr Qi is supported by National Institute of Health grants from the National Heart, Lung, and Blood Institute (HL071981, HL034594, and HL126024), the National Institute of Diabetes and Digestive and Kidney Diseases (DK019718, DK100383, and DK078616), the Boston Obesity Nutrition Research Center (DK46200), and United States-Israel Binational Science Foundation Grant 2011036. Dr Qi was a recipient of the American Heart Association grants (HL071981, HL034594, and HL126024), the National Institute of Health grants from the National Heart, Lung, and Blood Institute (HL071981, HL034594, and HL126024), the National Institute of Diabetes and Digestive and Kidney Diseases (DK019718, DK100383, and DK078616), the Boston Obesity Nutrition Research Center (DK46200), and United States-Israel Binational Science Foundation Grant 2011036. Dr Qi was a recipient of the American Heart Association Scientist Development Award (0730094N). The funders had no role in the study design, data collection, data analysis and interpretation, writing of the report, or the decision to submit the article for publication.

Disclosures
None.

References

Significance
Gallstone disease is one of the most common and costly gastrointestinal disorders resulting in hospital admission. Gallstone disease is related to multiple cardiovascular risk factors; however, prospective investigations on the relation between gallstone disease and cardiovascular risk in large cohorts are sparse. In this study, the presence of gallstone disease was independently associated with an increased risk of incident ischemic heart disease. Our findings suggest novel prevention strategy to mitigate heart disease through improvement of gastrointestinal health.
Gallstone Disease and the Risk of Ischemic Heart Disease

Jun Lv, Lu Qi, Canqing Yu, Yu Guo, Zheng Bian, Yiping Chen, Ling Yang, Jie Shen, Shanqing Wang, Mingqiang Li, Yongmei Liu, Libo Zhang, Junshi Chen, Zhengming Chen and Liming Li on behalf of the China Kadoorie Biobank Collaborative Group*

Arterioscler Thromb Vasc Biol. 2015;35:2232-2237; originally published online August 13, 2015;
doi: 10.1161/ATVBAHA.115.306043

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/35/10/2232

Data Supplement (unedited) at:
http://atvb.ahajournals.org/content/suppl/2015/08/13/ATVBAHA.115.306043.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/
Material and Methods

Study population

The CKB is a prospective cohort study of over 0.5 million adults from ten geographically diverse areas across China; participants were enrolled between 2004 and 2008 and followed up ever since for morbidities and mortality. Further details of the CKB study design and the characteristics of the study participants have been described elsewhere.1, 2 Briefly, a total of 512,891 adults aged 30–79 years had valid baseline data including completed questionnaire, physical measurements, and a written informed consent form. The CKB study was approved by the Ethical Review Committee of the Chinese Center for Disease Control and Prevention (Beijing, China) and the Oxford Tropical Research Ethics Committee, University of Oxford (UK).

We excluded 2,577 persons with cancer, 15,472 persons with heart disease, and 8,884 persons with stroke at baseline based on self-reported medical history, 2 persons with incomplete data of body mass index (BMI) measurement, as well as 3 persons recorded with an implausible censoring date for loss to follow-up. The final analyses included 199,292 men and 288,081 women.

Assessment of exposure

At baseline survey, trained interviewers administered a standardized questionnaire using a laptop-based direct data-entry system, with built-in functions to prevent logical errors and missing items. The participants were asked if they had ever been diagnosed with GSD, with or without cholecystitis complication, by a doctor, and their age at the first diagnosis.

Assessment of covariates

Covariates were obtained from the baseline questionnaire including socio-demographic characteristics (age, sex, level of education, and marital status), lifestyle behaviors (alcohol consumption, smoking status, physical activity, and intakes of red meat, fresh fruits, and vegetables), personal health and medical history (hypertension, diabetes, chronic hepatitis/cirrhosis, peptic ulcer, and menopausal status for women only), and family medical history. A participant was considered as having a family history of heart attack if they reported at least one first-degree relative with the condition. The daily level of physical activity was calculated by multiplying the metabolic equivalent tasks (METs) value for a particular type of physical activity by hours spent on that activity per day and summing the MET-hours for all activities. Habitual dietary intake in the past year was assessed by a qualitative food frequency questionnaire. At baseline, body weight, height, waist circumference (WC), and blood
pressure were measured by trained staff using calibrated instruments. BMI was calculated as measured weight in kilograms divided by the square of measured height in meters. A stepwise on-site testing of plasma glucose level was undertaken using the SureStep Plus meter (LifeScan, Milpitas, CA, USA). Prevalent hypertension was defined as measured SBP ≥ 140 mmHg, measured diastolic blood pressure (DBP) ≥ 90 mmHg, self-reported diagnosis of hypertension, or self-reported use of antihypertensive medication at baseline. Prevalent diabetes was defined as measured fasting blood glucose ≥ 7.0 mmol/L, measured random blood glucose ≥ 11.1 mmol/L, or self-reported diagnosis of diabetes.

**Ascertainment of incident IHD**

Incident IHD cases were identified by means of linkage with local disease and death registries, with the recently established national health insurance system, and by active follow-up (i.e., visiting local communities or directly contacting participants). The 10th revision of the International Classification of Diseases (ICD-10) was used to code all incident IHD cases by trained staff “blinded” to baseline information. IHD was defined as ICD-10 I20-I25. Fatal IHD event was defined as death with IHD as the underlying cause. Patients who survived a first IHD for more than 28 days and who died thereafter during follow-up were included in the nonfatal group.

The verification process of ascertained incident IHD cases has been formally started since 2014. The medical records of IHD cases are retrieved and reviewed. The diagnosis is adjudicated centrally by qualified cardiovascular specialists blinded to study assay. By March 2015, of 6,528 incident IHD cases reported since baseline and whose medical records have been retrieved, the diagnosis of IHD was confirmed in 5,608 (85.9%) cases.

**Statistical analyses**

Baseline characteristics were adjusted for age and survey site and compared between participants with and without GSD using analysis of covariance for continuous variables and logistic regression for categorical variables. Person-years were measured from the recruitment date at baseline to the date of incident IHD diagnosis, loss to follow-up, or December 31, 2013, whichever came first. Participants with and without GSD were compared descriptively with respect to incident IHD through Nelson-Aalen cumulative hazard curves. Cox proportional hazards regression model was used to estimate the hazard ratio (HR) and the 95% confidence interval (CI) of GSD and incident IHD risk, with age as the underlying time scale. The group-specific effect of ten survey sites on the hazard function was accounted for by stratifying on the survey site variable in the Cox model.

Three multivariate models were fitted with different levels of adjustment.
for baseline factors. Model 1 included age (continuous, serving as the underlying timescale). Model 2 additionally included sex (male or female; for whole cohort only); level of education (no formal school, primary school, middle school, high school, college, or university or above); marital status (married, widowed, divorced/separated, or never married); alcohol consumption (non-drinker, occasional drinker, ex-drinker, or current regular drinker); smoking status (never smoker, occasional smoker, ex-smoker, or current regular smoker); physical activity in MET-hours per day (continuous); intake frequencies of red meat, fresh fruits, and vegetables (daily, 4-6 days/week, 1-3 days/week, monthly, or rarely or never); prevalent hypertension and diabetes at baseline (presence or absence); family history of heart attack (presence, absence, or unknown); menopausal status (premenopausal, perimenopausal, or postmenopausal; for women only). Model 3 additionally included BMI (continuous). Further, three additional sensitivity analyses were performed on the basis of model 3: (1) additionally included the histories of digestive system diseases including chronic hepatitis/cirrhosis and peptic ulcer; (2) replaced BMI with WC; and (3) excluded diabetic patients from the analyses.

Subgroup analyses were conducted separately among participants who reported different years since the first diagnosis of GSD (<3, 3–9, or ≥10 years), all as compared with those without GSD at baseline. We also examined associations between GSD and incident IHD among pre-specified baseline subgroups based on the following: age (<50, 50–59, or ≥60 years); smoking status (current regular smoker or not); alcohol consumption (current regular drinker or not); level of physical activity (categorized using tertile cut-offs); BMI (<24.0, 24.0–27.9, or ≥28.0 kg/m²); abdominal obesity (presence or absence); prevalent hypertension (presence or absence); and prevalent diabetes (presence or absence). Abdominal obesity was defined as WC ≥ 90 cm in men and ≥ 80 cm in women. Tests for interaction were performed by means of likelihood-ratio tests, which involved comparing models with and without cross-product terms between the baseline stratifying variable and GSD status.

The statistical analyses were performed with Stata (version 13.1, StataCorp, College Station, TX, USA). All P values were two sided, and statistical significance was defined as P<0.05.

References


<table>
<thead>
<tr>
<th></th>
<th>Case/person-years</th>
<th>HR (95% CI)</th>
<th>P value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 50 year</td>
<td>5,084/1,577,415</td>
<td>1.00</td>
<td>310/73,468</td>
</tr>
<tr>
<td>50 to &lt; 60 year</td>
<td>7,216/984,925</td>
<td>1.00</td>
<td>676/70,089</td>
</tr>
<tr>
<td>≥ 60 year</td>
<td>10,717/671,139</td>
<td>1.00</td>
<td>956/54,089</td>
</tr>
<tr>
<td>Not current regular smoker</td>
<td>16,746/2,355,163</td>
<td>1.00</td>
<td>1,610/163,999</td>
</tr>
<tr>
<td>Current regular smoker</td>
<td>6,271/878,315</td>
<td>1.00</td>
<td>332/33,647</td>
</tr>
<tr>
<td>Not current regular drinker</td>
<td>20,015/2,732,850</td>
<td>1.00</td>
<td>1,769/178,299</td>
</tr>
<tr>
<td>Current regular drinker</td>
<td>3,002/500,628</td>
<td>1.00</td>
<td>173/19,347</td>
</tr>
<tr>
<td>MET 0-</td>
<td>10,929/989,631</td>
<td>1.00</td>
<td>998/64,930</td>
</tr>
<tr>
<td>MET 12.29-</td>
<td>6,770/1,098,927</td>
<td>1.00</td>
<td>567/70,791</td>
</tr>
<tr>
<td>MET 25.31-</td>
<td>5,318/1,144,921</td>
<td>1.00</td>
<td>377/61,925</td>
</tr>
<tr>
<td>BMI &lt; 24.0</td>
<td>11,702/1,855,976</td>
<td>1.00</td>
<td>879/100,513</td>
</tr>
<tr>
<td>BMI 24.0 to &lt; 28.0</td>
<td>8,018/1,055,266</td>
<td>1.00</td>
<td>710/71,735</td>
</tr>
<tr>
<td>BMI ≥ 28.0</td>
<td>3,297/322,236</td>
<td>1.00</td>
<td>353/25,398</td>
</tr>
<tr>
<td>Non-abdominal obesity</td>
<td>12,696/2,166,037</td>
<td>1.00</td>
<td>867/111,232</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>10,321/1,067,441</td>
<td>1.00</td>
<td>1,075/86,414</td>
</tr>
<tr>
<td>No hypertension</td>
<td>10,765/2,170,637</td>
<td>1.00</td>
<td>998/128,217</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12,252/1,067,441</td>
<td>1.00</td>
<td>944/69,429</td>
</tr>
<tr>
<td>No diabetes</td>
<td>20,582/3,074,937</td>
<td>1.00</td>
<td>1,700/183,687</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2,435/158,541</td>
<td>1.00</td>
<td>140/16,035</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 50 year</td>
<td>2,027/614,600</td>
<td>1.00</td>
<td>84/19,100</td>
</tr>
<tr>
<td>50 to &lt; 60 year</td>
<td>2,758/407,986</td>
<td>1.00</td>
<td>132/16,913</td>
</tr>
<tr>
<td>≥ 60 year</td>
<td>4,987/314,947</td>
<td>1.00</td>
<td>257/14,985</td>
</tr>
<tr>
<td>Not current regular smoker</td>
<td>4,008/499,710</td>
<td>1.00</td>
<td>215/22,240</td>
</tr>
<tr>
<td>Current regular smoker</td>
<td>5,764/837,822</td>
<td>1.00</td>
<td>258/28,758</td>
</tr>
<tr>
<td>Not current regular drinker</td>
<td>7,049/876,503</td>
<td>1.00</td>
<td>333/34,963</td>
</tr>
<tr>
<td>Current regular drinker</td>
<td>2,723/461,030</td>
<td>1.00</td>
<td>140/16,035</td>
</tr>
<tr>
<td>MET 0-</td>
<td>4,454/384,482</td>
<td>1.00</td>
<td>249/17,439</td>
</tr>
<tr>
<td>MET 12.29-</td>
<td>2,790/411,948</td>
<td>1.00</td>
<td>128/16,607</td>
</tr>
<tr>
<td>MET 25.31-</td>
<td>2,528/541,102</td>
<td>1.00</td>
<td>96/16,952</td>
</tr>
<tr>
<td>BMI &lt;24.0</td>
<td>5,394/792,038</td>
<td>1.00</td>
<td>215/25,701</td>
</tr>
<tr>
<td>BMI 24.0 to &lt; 28.0</td>
<td>3,267/431,488</td>
<td>1.00</td>
<td>179/19,336</td>
</tr>
<tr>
<td>BMI ≥ 28.0</td>
<td>1,111/114,006</td>
<td>1.00</td>
<td>79/5,962</td>
</tr>
<tr>
<td>Non-abdominal obesity</td>
<td>6,972/1,064,288</td>
<td>1.00</td>
<td>284/36,902</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>2,800/273,245</td>
<td>1.00</td>
<td>189/14,096</td>
</tr>
<tr>
<td>No hypertension</td>
<td>4,411/869,682</td>
<td>1.00</td>
<td>199/32,549</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5,361/467,851</td>
<td>1.00</td>
<td>274/18,449</td>
</tr>
<tr>
<td>No diabetes</td>
<td>8,817/1,275,379</td>
<td>1.00</td>
<td>408/47,292</td>
</tr>
<tr>
<td></td>
<td>Case/person-years</td>
<td>HR</td>
<td>Case/person-years</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>-------------------</td>
<td>-----</td>
<td>-------------------</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>955/62,154</td>
<td>1.00</td>
<td>65/3,706</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;50 year</td>
<td>3,057/962,815</td>
<td>1.00</td>
<td>226/54,368</td>
</tr>
<tr>
<td>50 to &lt; 60 year</td>
<td>4,458/576,939</td>
<td>1.00</td>
<td>544/53,176</td>
</tr>
<tr>
<td>≥ 60 year</td>
<td>5,730/356,192</td>
<td>1.00</td>
<td>699/39,104</td>
</tr>
<tr>
<td><strong>Not current regular smoker</strong></td>
<td>12,738/1,855,453</td>
<td>1.00</td>
<td>1,395/141,759</td>
</tr>
<tr>
<td><strong>Current regular smoker</strong></td>
<td>507/40,493</td>
<td>1.00</td>
<td>74/4,889</td>
</tr>
<tr>
<td><strong>Not current regular drinker</strong></td>
<td>12,966/1,856,347</td>
<td>1.00</td>
<td>1,436/143,336</td>
</tr>
<tr>
<td><strong>Current regular drinker</strong></td>
<td>279/39,598</td>
<td>1.00</td>
<td>33/3,312</td>
</tr>
<tr>
<td><strong>MET 0</strong></td>
<td>6,475/605,149</td>
<td>1.00</td>
<td>749/47,490</td>
</tr>
<tr>
<td><strong>MET 12.29</strong></td>
<td>3,980/686,979</td>
<td>1.00</td>
<td>439/54,183</td>
</tr>
<tr>
<td><strong>MET 25.31</strong></td>
<td>2,790/603,818</td>
<td>1.00</td>
<td>281/44,974</td>
</tr>
<tr>
<td><strong>BMI &lt;24.0</strong></td>
<td>6,308/1,063,938</td>
<td>1.00</td>
<td>664/74,812</td>
</tr>
<tr>
<td><strong>BMI 24.0 to &lt; 28.0</strong></td>
<td>4,751/623,778</td>
<td>1.00</td>
<td>531/52,399</td>
</tr>
<tr>
<td><strong>BMI ≥ 28.0</strong></td>
<td>2,186/208,230</td>
<td>1.00</td>
<td>274/19,437</td>
</tr>
<tr>
<td><strong>Non-abdominal obesity</strong></td>
<td>5,724/1,101,749</td>
<td>1.00</td>
<td>583/74,329</td>
</tr>
<tr>
<td><strong>Abdominal obesity</strong></td>
<td>7,521/794,196</td>
<td>1.00</td>
<td>886/72,319</td>
</tr>
<tr>
<td><strong>No hypertension</strong></td>
<td>6,354/1,300,955</td>
<td>1.00</td>
<td>799/95,668</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>6,891/594,991</td>
<td>1.00</td>
<td>670/50,980</td>
</tr>
<tr>
<td><strong>No diabetes</strong></td>
<td>11,765/1,799,558</td>
<td>1.00</td>
<td>1,292/136,395</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>1,480/96,388</td>
<td>1.00</td>
<td>177/10,253</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CI, confidence interval; MET, metabolic equivalent tasks hours per day (MET-hr/day); BMI, body mass index (kg/m²). Multivariate models were adjusted for: age, gender (for whole cohort only), education, marital status, alcohol consumption, smoking status, physical activity, intake frequencies of red meat, fresh fruits, and vegetables, prevalent hypertension, prevalent diabetes, family history of heart attack, menopausal status (for women only), and body mass index.