Association between Metabolic syndrome/its components and gallstones in Urban Han Chinese: A Longitudinal Cohort Study

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Abstract

Background: Currently, few researches based on cohort studies had investigated the relationship between metabolic syndrome and GSD. The objective of this study was to explore the relationship between MS/its components and gallstone disease (GSD) and to evaluate the value of MS as early markers for predicting the risk of GSD in a large scale longitudinal cohort in Urban Han Chinese population.

Method: A total of 18134 participants who were free of GSD at their baseline year were included in our study between January 2005 and January 2010. The baseline characteristics of the cohort were compared by MS status at baseline, GSD status after follow-up. Cox proportional hazards models was used to examine the association between metabolic syndrome / its components and incident GSD.

Result: During the 54367 person-years’ follow-up, 828 (4.02%) new cases of gallstone diseases occurred, leading a total incidence density of 15.3 per 1,000 person-years. with 24.46 per 1,000 person-years in MS group and 13.74 per 1,000 person-years in non-MS group. The age and gender adjusted HR of MS for GSD were 1.43 (1.2, 1.69). All the components of MS were positively associated with GSD, and the HRs (95%CI) were 1.33 (1.15, 1.54) for overweight, 1.76(1.51, 2.06) for high blood pressure, 1.4 (1.16, 1.7) for hyperglycemia and 1.31 (1.14, 1.51) for dyslipideima. It was also found that the risk of GSD increase with metabolic syndrome components.

Conclusion: Our study indicated that MS / its components were associated with gallstone disease in urban Han Chinese population, and people who have metabolic syndrome or its components should take measures to prevent the occurrence of GSD.

Keywords: Gallstone disease (GSD), Metabolic Syndrome (MS), cohort study, incidence
Gallstone disease (GSD) is one of the most common and costly gastro-intestinal disorders, representing a major health burden world-wide [1, 2], which is more prevalent in Americans and Europeans than in Africans and Asians [3]. Nowadays, along with the socio-economic conditions, the incidence of gallstone is also on the rise in the Asian population [3]. According to several report, the prevalence of GSD in Chinese population ranges from 4.3% to 12.1% [4-7]. Gallstones are likely to result from a complex interaction of genetic and environmental factors [8]. Epidemiological studies have identified that the risk-factors for cholesterol gallstones include age (>40), gender(female), obesity, diabetes, hyperlipidemia, rapid appetite loss, hepatitis C, cirrhosis, and high calorie, high cholesterol, high carbohydrate, low-fiber diets [1, 3].

Metabolic syndrome (MS) refers to a cluster of risk factors—obesity, hypertension, hyperglycemia, and dyslipidemia —that is considered to be a clinical predictor of cardiovascular disease [9] [10]. In the last two decades, the prevalence of MS has been growing gradually in urban Chinese population along with the increasingly sedentary lifestyles and diets changes [11-13]. It has been noted in various cross-sectional studies that MS [7, 14-16] as well as its components, including obesity [17], diabetes [18-21], dyslipidemia [22] are associated with gallstone disease. However, to our best knowledge, few research based on cohort study has investigated these relationships. Due to the inherent limitation of cross-sectional studies, temporal relationship between MS and gallstone disease could not be established and long-term effect of MS / its components on GSD risk remains unclear.

We therefore conducted a large scale longitudinal cohort study in urban Han Chinese population to investigate the association between MS / its components and GSD incident and to evaluate the value of MS for predicting GSD risk.

Materials and Methods
Study Population

We conducted a large scale longitudinal cohort study in Urban Han Chinese population from 2005 to 2011 based on the routine health check-up system in Centers for Health Management of Shandong Provincial Qianfoshan Hospital and of Shandong Provincial Hospital. A total of 21267 asymptomatic subjects who went to the check-up center for routine physical examination for at least twice included in our longitudinal cohort study between 2005 and 2008. Among these participants, 677 subjects who had gallstones at their baseline year or had a previous history of gallstone disease or cholecystectomy were excluded. Ultimately, 20590 subjects were eligible for this study. The total follow-up period was 54367 person years and the average follow-up period was 2.76 (standard deviation, 1.22) person years.

This study was approved by the Ethics Committee of School of Public Health, Shandong University, and all participants gave informed written consent before the investigation was performed.

Measurements

All participants underwent a general health questionnaire, physical examination, abdomen ultrasonography, and laboratory examination after an overnight fasting of at least 12 hours at each health check-up. Lifestyle information about diet habits, smoking habits, alcohol intake and physical exercise were obtained by a health questionnaire. Height and weight of the participants were measured wearing light clothing without shoes. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared (kg/m2). Blood pressure was measured on the right arm in a sitting position after a 5min rest. Laboratory examinations included fasting plasma glucose (FPG), triglycerides(TG), total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), uric acid, blood urea nitrogen (BUN), serum creatinine (CREA), gamma-glutamyltransferase (GGT), serum albumin (ALB), serum globulins (GLO), white blood count (WBC), hemoglobin (Hb), hematokrit (HCT), mean corpuscular volume(MCV), mean
corpuscular hemoglobin (MCH), red blood cell distribution width (RDW), platelet distribution width (PDW), mean platelet volume (MPV), thrombocytocrit (PCT), etc. Moreover, all participants accepted abdominal B-ultrasonography examination. Additionally, lifestyle behaviors, including smoking, alcohol intake and physical activity, were surveyed by a questionnaire on health-related behavior. Ultrasonography of the abdomen was conducted by ultrasonographers using a scanner equipped with a 3.5-MHz transducer.

**Definition and variable assignment**

GSD was diagnosed based on the results of abdominal ultrasound (US) conducted by an experienced radiologist (one or several echogenic, distally shadowing, possibly movable structures in the gallbladder).

According to the criteria recommended by the Chinese Medical Association Diabetes Branch (CDS) designed for Chinese, a participant was claimed to have MS if he or she had at least three of the following four medical conditions: (1) overweight or obesity, BMI $\geq 25.0$ Kg/M$^2$; (2) hypertension, systolic/diastolic blood pressure $\geq 140/90$ mmHg or previous diagnosed as hypertension; (3) dyslipidemia, fasting triglycerides (TG) $\geq 1.7$ mmol/L (110 mg/dl), or fasting high-density (HDL) $< 0.9$ mmol/L (35 mg/dl); (4) hyperglycemia, fasting blood-glucose (FPG) $\geq 6.1$ mmol/L (110 mg/dl), or 2h Postmeal Glucose (PG) $\geq 7.8$ mmol/L (140 mg/dl), or previous diagnosis.

**Data analysis**

To handle missing values, multiple imputations were performed. Considering that the variables in our analysis were continuously distributed with arbitrary missingness patterns, a multivariate normal distribution model was assumed and Markov chain Monte Carlo (MCMC) method was chosen according to the MI Procedure of SAS 9.2. Most of the imputed variables had less than 10% missing values.

Baseline characteristics were described and their differences between MS and non-MS groups,
as well as between participants who developed GSD during the follow-up and those who did not were compared. Continuous variables were expressed as mean ± standard deviation (SD) and compared by t-tests, while categorical variables were summarized as frequency (percentage %) and compared using Chi-square test. The person years were calculated as the sum of follow-up times from the baseline to the occurrence time of GSD or the last health check-up. The Cox proportional-hazards model was used to calculate the adjusted and unadjusted hazard ratios (HRs) and 95% confident for predicting GSD risk by baseline MS/its components. The crude incidence of GSD in subjects with and without MS/its components were computed. A p value <0.05 was considered significant.

All statistical analysis was performed in SAS 9.2.

**Results**

During the 54367 person-years’ follow-up, 828 (4.02%) new cases of gallstone diseases occurred, leading to a total incidence density of 15.3 per 1,000 person-years, with 16.5 per 1,000 person-years in males and 13.05 per 1,000 person-years in females. At baseline examination, study subjects ranged in age from 20 to 80, and the mean age ± SD was 43.8±13.3 years (44.7±13.4 in males, and 42.2±13.0 in females).

Table 1 and Table S1 show the baseline characteristic of subjects with and without metabolic syndrome. The baseline prevalence of metabolic syndrome was 11.6% (2,839 cases), which was significantly higher in male (17.99%) than in female (6.32%). Those who had MS at their baseline were generally older and had a higher prevalence of fatty liver. With the exception of MCV, RDW, RDW-SD, PDW and PCT, the values for other parameters were significantly higher in subjects with, as compared to without, metabolic syndrome.

The baseline characteristic grouped by development of GSD during follow up was shown in Table S2 (listed in Supplementary material). In contrast to those without GSD, those with incident
GSD were older, and had a higher prevalence of obesity, hypertension, hyperglycemia and dyslipidemia, fatty liver and gallbladder polyps. The statistically significant differences between the two groups were also observed in GLO, A/G, BUN, CREA, MCH, WBC and MPV.

Table 2 shows the crude GSD incidence rates per 1000 person year and HRs (95%CI) of metabolic syndrome, its components and different numbers of MS components for prediction GSD. The GSD event rate was much higher in the MS exposed group compared with MS free group (24.46 per 1,000 person-years verses 13.74 per 1,000 person-years). The HR (95%CI) was 1.43(1.2, 1.69) for MS predicting GSD in the age and gender adjusted model. Considering the individual components of MS independently, all these factors were positively related with GSD, the age and gender adjusted HRs (95%CI) were 1.33(1.15, 1.54) for overweight, 1.76(1.51, 2.06) for high blood pressure, 1.4(1.16, 1.7) for hyperglycemia and 1.31(1.14, 1.51) for dyslipidemia. And moreover, we can see that the risk of GSD increase with the number of metabolic syndrome components. The HRs increase from 1.76 (1.43, 2.17) for one MS component to 3.23 (2.31, 4.51) for four MS components, with the absence of MS components as reference. Although the strength of all these associations above were weakened after adjusting other potential confounding factors, HRs still remained statistically significant.

Subgroup analysis was conducted for female and male population respectively (shown in Supplementary material Table S3 and Table S4). In the age-adjusted model, HR (95% CI) for MS predicting MetS were 1.78(1.25, 2.53) in females and 1.32(1.09, 1.60) in males. After adjusting other potential confounding factors, HR (95% CI) decreased to 1.35(1.03, 1.97) in females and 1.23(1.01, 1.50) males. Of the individual components of MS, factors independently associated with GSD in male were hypertension, hyperglycemia, and obesity, while in female were hypertension, and dyslipidemia.

Discussion
In our cohort study, 828 (4.02%) new cases of GSD occurred during 54,367 person years’ follow-up between 2005 and 2010, and the incidence of GSD in MS patients was obviously higher than that in non-MS group. The Cox proportional hazards models demonstrated that MS and all its components are associated with GSD after adjusting for the potential confounding factors. Additionally, there was a significant dose-response relationship between the number of metabolic syndrome components and the risk of biliary stones, which indicated that the presence of multiple components may have an additive effect on the risk of gallstones, and that the severity of metabolic syndrome exacerbates the development of stones.

The gender difference for the association between MS and gallstone disease was observed in our study. The baseline prevalence of MS in males (2377/13,180, 17.99%) was much higher than that in females (468/7,410, 6.32%) in our population. However, we found the incidence of GSD in women (15.9 per 1,000 person-years) was similar to that in men (16.3 per 1,000 person-years). As a result, the HR (95% CI) of MS for GSD were higher in female 1.88(1.25, 2.53) than in male 1.32(1.09, 1.60). Similar result was found in a cross sectional study from China [7], in which the OR of MS for GSD was higher in women than in men. This suggested that the females with MS are at higher risk of GSD in future than males. Therefore, more attention should be paid to the female population with MS.

For the components of metabolic syndrome, our findings confirm conclusions drawn from previous studies [7, 15, 20, 26-29]. Among the all components of metabolic syndrome, factor with the highest HR (95% CI) was high blood pressure in both males and females. Although the association between high blood pressure and gallstones had been documented in various studies [7, 26, 30, 31], the underlying mechanism remains unclear. Some scholars attributed this association to the effect of insulin resistance in metabolic syndrome. Our findings suggested that people should pay more attention to their blood pressure for the prevention of GSD.
Obesity has long been recognized as an important risk factor for gallstone disease. The mechanism might be increased hepatic secretion of hepatic cholesterol [32][33, 34]. However, a study which examined the susceptibility to cholesterol gallstone formation in three polygenic and five monogenic strains of overweight mice found that, while some murine models of obesity increased cholesterol gallstone susceptibility, the others decreased. They suggested that cholesterol gallstone formation in overweight mice is not simply a direct consequence of obesity, but rather, certain obesity genes impact cholesterol gallstone risk while others have no effect[35]. This might explain why only modestly increased risk of GSD among overweight patients was found in our study.

Hyperglycemia was also proved to be an independent risk factor for gallstone disease in our study, which is well documented in previous studies [15, 36-38]. The possible mechanism of the association between hyperglycemia and gallstone might be: fasting hyperinsulinemia and diabetic neuropathy inhibits bile secretion from the liver and disturbs gallbladder contraction and thus induce cholesterol supersaturation and gallbladder hypomotility[37, 39, 40] [41, 42]; the mechanism of gallbladder hypomotility has been attributed to cholecystokinin and Na-K pump regulation by insulin.

There’s still no conclusive evidence about the association between gallstone disease and dyslipidemia. High triglyceride and low HDL-C were considered to be risk factors for the development of gallstones in many studies [22, 26, 28, 43, 44], while a study in western China found that total cholesterol, low HDL-C, and high LDL-C levels were negatively associated with the risk of gallstone disease in both genders [29]. In our longitudinal cohort study, dyslipidemia, which was defined as high triglyceride or low HDL-C in our criterion, significantly increased the risk of GSD. Large scale case-control studies had indicated that long term use of statin, which can depress cholesterol synthesis, was associated with a reduced risk of gallstone disease followed by
cholecystectomy [45, 46]. And this effect is largely independent of hypercholesterolemia. This suggested that dyslipidemia might not associate with the gallstone directly, but through the abnormal metabolism of lipids in patients, and that statin, which can treat hypercholesterolemia to prevent cardiovascular disease, might also help prevent GSD.

Although the mechanism of the relationship between MS and GSD remains unclear, there’s evidence showed that hepatic insulin resistance can directly promote the formation of cholesterol gallstone, through at least two distinct mechanism[47][48]: 1) The disinhibition of the forkhead transcription factor FoxO1, which would lead to an increased expression of the biliary cholesterol transporters Abcg5 and Abcg8, can result in an increase in biliary cholesterol secretion. 2) it can also decrease the expression of the bile acid synthetic enzymes, particularly Cyp7b1, and produces partial resistance to the farnesoid X receptor (FXR), leading to a lithogenic bile salt profile [47]. Since that insulin resistance plays a centre role in the pathogenesis of metabolic syndrome [49], it is clear that the insulin resistance provides the critical link between metabolic syndrome and increased metabolic syndrome susceptibility.

Gallstone formation is a result of the complex interaction of genetic and environmental factors [8]. It is speculated that “thrifty” genes, which can promote more efficient calorie utilization and storage in the form of adipose tissues, might produce a predisposition for obesity, diabetes mellitus as well as gallstone formation when interact.[50] The result in our study that MS /its components are associated with gallstone just supports this speculation. Since lifestyle changes can help prevent MS, it is anticipated that lifestyle changes reduce the risk of gallstones.

In conclusion, metabolic syndrome / its components were associated with GSD in urban Chinese population, and the risk of GSD increased with the number of MS components. So we suggest that people who are diagnosed as MS, especially those with higher blood pressure should go for routine abdominal ultrasongraphy, initiate blood pressure control and change their lifestyle as
early as possible so as to prevent the development of gallstones.

A major limitation of the present study was that the use of health check-up population for middle-to-upper class urban Han Chinese can be subject to selection bias. Further investigation which can represent general population is preferable. Due to the disadvantage of our routine health check-up database, some factors that might play an important role in the development of gallstone disease, such as family history, birth parity, oral contraceptive use, estrogen replacement therapy, statine usage insulin level and waist-circumference, were not collected in detail. And owing to the absence of waist-circumference, the diagnostic criteria of MS in our study just based the China Diabetes Federation, rather than international Standard criteria.

Competing interests

The authors declare that they have no competing interests.

Authors Contribution

Lu Wang performed the statistical analysis and drafted the manuscript. Chengqi Zhang and Fang Tang participated in coordination and data collection of the study. Dongzhi Zhang and Haiyan Lin participated in the data collection. Jia Liu and Shuo Wu participated in the study design and data cleaning. Fuzhong Xue conceived of the study, and participated in its design and coordination. All authors read and approved the final manuscript.

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References


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### Tables

#### Table 1

Baseline characteristics of participants grouped by MS status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Non-MS</th>
<th>MS</th>
<th>Total</th>
<th>Statistics*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>17751</td>
<td>2839</td>
<td>20590</td>
<td></td>
<td></td>
</tr>
<tr>
<td>age (years)</td>
<td>42.61±12.92</td>
<td>51.25±13.14</td>
<td>43.8±13.3</td>
<td>-33.01</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>10809(%60.89)</td>
<td>2371(%83.52)</td>
<td>13180</td>
<td>543.7641</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>female</td>
<td>6942(%39.11)</td>
<td>468(%16.48)</td>
<td>7410</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.07±3.23</td>
<td>28.15±3.43</td>
<td>24.64±3.55</td>
<td>-61.85</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>119.89±16.72</td>
<td>143.95±17.65</td>
<td>123.22±18.79</td>
<td>-70.6</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>72.32±10.68</td>
<td>85.84±11.89</td>
<td>74.20±11.82</td>
<td>-61.58</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>FPG (mmol/l)</td>
<td>5.03±0.88</td>
<td>6.26±1.77</td>
<td>5.20±1.13</td>
<td>-58.15</td>
<td>&lt;.0001</td>
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<tr>
<td>CHOL (mmol/l)</td>
<td>5.01±0.93</td>
<td>5.47±1.04</td>
<td>5.07±0.96</td>
<td>-24.34</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>1.40±1.11</td>
<td>2.76±1.89</td>
<td>1.60±1.34</td>
<td>-53.25</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td>1.32±0.31</td>
<td>1.17±0.45</td>
<td>1.30±0.34</td>
<td>22.27</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>LDL-C (mmol/l)</td>
<td>2.88±0.72</td>
<td>3.22±0.83</td>
<td>2.93±0.75</td>
<td>-22.55</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Fatty liver (%)</td>
<td>3854(%21.71)</td>
<td>1626(%57.27)</td>
<td>5480</td>
<td>1584.812</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gallbladder polyps (%)</td>
<td>851(%4.79)</td>
<td>145(%5.11)</td>
<td>996</td>
<td>0.522</td>
<td>0.47</td>
</tr>
<tr>
<td>High calorie diet (%)</td>
<td>11667(%65.73)</td>
<td>2038(%71.79)</td>
<td>13705</td>
<td>40.3833</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Alcohol drinking (%)</td>
<td>3729(%21.01)</td>
<td>999(%35.19)</td>
<td>4728</td>
<td>278.2492</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>3427(%19.31)</td>
<td>815(%35.19)</td>
<td>4242</td>
<td>132.2478</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Regular exercise (%)</td>
<td>5455(%30.73)</td>
<td>1075(%37.87)</td>
<td>6530</td>
<td>57.5317</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

*Statistics by t-test for continuous variables and Chi-square test for categorical variables.

The abbreviations of the variables: BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; FPG = fasting blood-glucose; CHOL = cholesterol; TG = triglycerides; LDL = low-density lipoprotein; HDL = high-density lipoprotein
<table>
<thead>
<tr>
<th>No of events</th>
<th>Person-Years</th>
<th>Event rate</th>
<th>HR(95%CI)</th>
<th>HR(95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>20590</td>
<td>828(4.02%)</td>
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<td>Overweight</td>
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<td>No</td>
<td>11719</td>
<td>374(3.19%)</td>
<td>30457</td>
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</tr>
<tr>
<td>Yes</td>
<td>8871</td>
<td>454(5.12%)</td>
<td>23910</td>
<td>18.99</td>
</tr>
<tr>
<td>Hypertension</td>
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<tr>
<td>No</td>
<td>15591</td>
<td>468(3%)</td>
<td>40612</td>
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</tr>
<tr>
<td>Yes</td>
<td>4999</td>
<td>360(7.2%)</td>
<td>13755</td>
<td>26.17</td>
</tr>
<tr>
<td>hyperglycemia</td>
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</tr>
<tr>
<td>No</td>
<td>18330</td>
<td>692(3.78%)</td>
<td>48752</td>
<td>14.19</td>
</tr>
<tr>
<td>Yes</td>
<td>2260</td>
<td>136(6.02%)</td>
<td>5615</td>
<td>24.22</td>
</tr>
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<td>Dyslipidemia</td>
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<tr>
<td>No</td>
<td>12696</td>
<td>452(3.56%)</td>
<td>33973</td>
<td>13.3</td>
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<tr>
<td>Yes</td>
<td>7894</td>
<td>376(4.76%)</td>
<td>20394</td>
<td>18.44</td>
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<td>MS</td>
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</tr>
<tr>
<td>No</td>
<td>17751</td>
<td>643(3.62%)</td>
<td>46804</td>
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<tr>
<td>Yes</td>
<td>2839</td>
<td>185(6.52%)</td>
<td>7563</td>
<td>24.46</td>
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<td>MS components</td>
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</tr>
<tr>
<td>0</td>
<td>7438</td>
<td>161(2.16%)</td>
<td>19521</td>
<td>8.25</td>
</tr>
<tr>
<td>1</td>
<td>5700</td>
<td>242(4.25%)</td>
<td>15022</td>
<td>16.11</td>
</tr>
<tr>
<td>2</td>
<td>4613</td>
<td>240(5.2%)</td>
<td>12261</td>
<td>19.57</td>
</tr>
<tr>
<td>3</td>
<td>2258</td>
<td>136(6.02%)</td>
<td>6122</td>
<td>22.21</td>
</tr>
<tr>
<td>4</td>
<td>581</td>
<td>49(8.43%)</td>
<td>1441</td>
<td>34</td>
</tr>
</tbody>
</table>
a: (per 1000 person-year)
b: adjusted for age and gender
c: adjusted for age, gender and other potential confounding including: fatty liver, A/G, BUN, CREA, MCH, WBC and MPV.
Additional file 1:

Tables:

Table 21: Baseline characteristics of participants grouped by MS status at baseline

Table S2: Baseline characteristics of participants grouped by GSD status after follow-up

Table S3: Crude GSD incidence rates and HRs (95%CI) for metabolic syndrome in females

Table S4: Crude GSD incidence rates and HRs (95%CI) for metabolic syndrome in males
Additional files provided with this submission:

Additional file 1: Additional file 1.doc, 152K
http://www.biomedcentral.com/imedia/1786150588130494/supp1.doc