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).[3] 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).[2] 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/m^2); 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

1. Chen Z, Lee L, Chen J, Collins R, Wu F, Guo Y, Linksted P, Peto R. Cohort profile: the Kadoorie Study of Chronic Disease in China (KSCDC). *Int J Epidemiol*. 2005;34:1243-1249
2. Chen Z, Chen J, Collins R, Guo Y, Peto R, Wu F, Li L, China Kadoorie Biobank collaborative group. China Kadoorie Biobank of 0.5 million people: survey methods, baseline characteristics and long-term follow-up.

Int J Epidemiol. 2011;40:1652-1666
3. Bragg F, Li L, Smith M, Guo Y, Chen Y, Millwood I, Bian Z, Walters R, Chen J, Yang L, Collins R, Peto R, Lu Y, Yu B, Xie X, Lei Y, Luo G, Chen Z, China Kadoorie Biobank Collaborative G. Associations of blood glucose and prevalent diabetes with risk of cardiovascular disease in 500 000 adult chinese: the China Kadoorie Niobank. *Diabet Med*. 2014;31:540-551