The Online-only Data Supplement

MATERIALS AND METHODS

Study Populations

The Nurses' Health Study (NHS) began in 1976 with the enrollment of 121,700 female nurses aged 30 to 55 years who completed an initial questionnaire on medications, lifestyle, and medical history. The Nurses' Health Study II (NHS II) began in 1989, enrolling 116,430 female nurses aged 25 to 42 years. The Health Professionals Follow-up Study (HPFS) began in 1986 with the enrollment of 51,529 male health professionals (including dentists, optometrists, osteopaths, pharmacists, podiatrists, and veterinarians) aged 40 to 75 years. For the current study, the baseline year was the first year for which detailed information was available on gallstone disease, lifestyle, dietary habits, and physical activity: 1980 for NHS, 1989 for NHS II, and 1986 for HPFS. History of gallstone disease, CHD, and other medical conditions has been updated every two years until the end of follow-up: June 2010 for NHS, June 2011 for NHS II, and January 2010 for HPFS. Participants with a baseline self-reported history of myocardial infarction (MI), coronary revascularization, or cancer were excluded from the analysis.

The study protocol was approved by the institutional review boards of Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health, with informed consent indicated by return of the baseline questionnaire.

Assessment of Gallstone Disease

The exposure of interest was a history of gallstone disease, including unremoved gallstones and cholecystectomy. In NHS, biennial questionnaires were used to assess the occurrence and date of cholecystectomy. Previously, we randomly selected 50 nurses who self-reported cholecystectomy, and 43 who agreed to requests for additional information reiterated their earlier report. Cholecystectomy was confirmed in all 36 nurses for whom medical records were available.[1]

For NHS II and HPFS, at baseline and in each biennial follow-up questionnaire, participants reported whether they had cholecystectomy or had received a diagnosis of gallstones from a physician. The participants were also asked whether their gallstone disease was symptomatic and whether the diagnosis had been confirmed by radiography or ultrasonography. To verify self-reports of gallstone disease including symptomatic unremoved gallstones and cholecystectomy, we previously reviewed a random sample of 441 medical records of men who reported having gallstone disease or cholecystectomy; of these, 99% (all but 5) confirmed the diagnosis.[2]

Assessment of CHD

The primary outcome was total CHD, defined as a composite of nonfatal or fatal MI, or coronary revascularization procedure (coronary artery bypass grafting surgery or percutaneous transluminal coronary angioplasty).[3] Secondary outcomes were nonfatal

or fatal MI, and coronary revascularization, examined separately. We defined fatal MI as documented fatal MI or fatal CHD determined by deaths identified from state death certificates or the National Death Index or reported by the participant's next of kin or the postal system. Fatal and nonfatal MI events were confirmed through medical record review and required characteristic symptoms with either diagnostic electrocardiographic changes or positive myocardial enzymes; revascularization was self-reported but has been found to be virtually 100% specific in the HPFS.[4]

Assessment of Covariates

The covariates considered in the current study were traditional CHD risk factors: age (months, continuous); race (white/nonwhite); family history of MI (yes/no); marital status (married/not married); smoking status (never smoked, past smoker, current smoker); body mass index (BMI, calculated as weight in kilograms divided by height in meters squared; continuous); physical activity (metabolic equivalent task hours/d in quintiles); diabetes (yes/no); hypertension (yes/no); hypercholesterolemia (yes/no); regular use of aspirin (yes/no); daily intake of alcohol (0, 0.1–5.0, 5.0–9.9, 10.0–14.9, ≥15.0 g/d), daily intake of the energy-adjusted dietary cholesterol (g/d in quintiles), 2010 Alternate Healthy Eating Index (AHEI score in quintiles), and daily energy intake (kcal/d in quintiles). In women from NHS and NHS II, menopausal status (yes/no), postmenopausal hormone uses (yes/no), and uses of oral contraceptive pills (yes/no) were also considered as covariates. Detailed information on cigarette smoking, physical activity, and several lifestyle factors and health outcomes were updated every 2 years. Marital status and status with respect to a family history of MI were assessed periodically. Dietary information was collected from validated food-frequency questionnaires approximately every 4 years in each cohort.[5, 6] Diet quality was assessed using the 2010 AHEI (higher scores indicating a healthier diet),[7] which predicts cardiovascular disease risk well in our cohorts.[8]

Statistical Analysis

We used Cox proportional hazards models to calculate the crude, age- and multivariable-adjusted hazard ratios (HRs) and 95% CIs for the risk of incident CHD in participants with a history of gallstone disease compared with those without. We used updated information on unremoved gallstones or cholecystectomy history, and updated information on covariates for each 2-year follow-up period in multivariable-adjusted models. Person-time was calculated from the date of return of the baseline questionnaire (1980 for NHS, 1989 for NHS II, and 1986 for HPFS) to the date of incident CHD, death, or end of follow-up (June 1, 2010 for NHS, June 1, 2011 for NHS II, and January 31, 2010 for HPFS), whichever came first. The proportional-hazards assumption was evaluated with a likelihood-ratio test comparing the model with and without an interaction term between time period and the status of gallstone disease; there was no evidence suggesting that the proportional-hazards assumption was violated (NHS: P=0.53; NHS II: P=0.62; and HPFS: P=0.49 in the multivariate model).

To minimize possible reverse causation, we also conducted several sensitivity analyses: 1) we conducted 4-year-lagged analyses by starting the follow-up period four years after the assessment of gallstone disease; and 2) we analyzed the association

between gallstone disease reported at baseline and incident CHD, without updating information for exposures or covariates across the follow-up period.

To minimize possible residual confounding, we conducted the following analyses: 1) we repeated the above analysis among (a) participants with normal blood lipid levels, (b) those not taking lipid-lowering medication, and (c) those who were not obese. The baseline years for analyses among participants not taking lipid-lowering medication were 1990 for NHS, 1998 for NHS II, and 1986 for HPFS, because information on lipid medications was collected biennially beginning with these questionnaires. 2) We included history of kidney stones as a covariate in the fully adjusted model, because previous publications have shown that kidney stones are related to both gallstone disease and CHD.[3, 9]

In addition, we repeated our analyses after stratifying by age, BMI, physical activity, current smoking status, moderate alcohol intake, AHEI, and disease status of diabetes, hypertension, and hyperlipidemia. Effect modification by the above factors was assessed using the multiplicative interaction term between gallstone disease and the effect modifier, added to the multivariable model which included both main effect variables.

Finally, we repeated the above analyses in secondary analyses that either limited the exposure to history of cholecystectomy alone, or assessed the secondary outcomes when defined separately as nonfatal or fatal MI, or as coronary revascularization.

Analyses were carried out with SAS software, version 9.3 (SAS Institute), at a two-tailed alpha level of 0.05.

We conducted a meta-analysis to combine our new results from the 3 cohorts with previously published reports from other prospective cohort studies. We conducted a systematic review in accordance with PRISMA guidelines.[10] We systematically searched PUBMED (up to October 26, 2015) and EMBASE (up to October 26, 2015) for published studies that examined gallstone disease in relation to risk of coronary heart disease, using the following search protocol and related extensions to filter information: ((((“heart disease”[Title/Abstract]) OR cardiovascular diseases[Title/Abstract])) AND (((cholecystectomy[Title/Abstract]) OR gallstone[Title/Abstract]) OR cholelithiasis[Title/Abstract]). The keywords were combined using the Boolean operators “AND” and “OR”. No restrictions in the search strategy were inserted. Additionally, we hand-searched the reference lists of all identified publications. Articles were considered for inclusion in the systematic review if: the investigators reported data from an original, peer-reviewed study (i.e., not review articles or conference abstracts); the report was of a prospective study done in adults without CHD at baseline; and the investigators reported risk estimates of CHD by gallstone disease status. We assessed eligible articles first by screening titles or abstracts, followed by full-text review. One author (Y.Z.) assessed study eligibility and extracted the data, and another (M.X.) independently double-checked the data.

We extracted the following information using a predesigned collection form: study characteristics (study name, authors, publication year, journal, study location, follow-up

length, number of participants, and number of incident cases of CHD), participant characteristics (mean age or age range, sex, and ethnic origin), CHD outcome assessment methods (self-report, medical record, or clinical examination), and analysis strategy (statistical models and covariates included in the models).

For one prospective study that used odds ratio to present results,[11] we converted the reported adjusted odds ratio to approximate relative risk,[12, 13] and for the other studies, fully-adjusted relative risks presented were extracted and analyzed as the common measure of association across studies. We pooled relative risks using inverse-variance-weighted random-effects models that incorporated both a within-study and an additive between-studies component of variance,[14] and produced forest plots. We calculated heterogeneity of study results using the I^2 statistic.[15] Publication bias was assessed by use of the Egger's test and visual inspection of funnel plots.[16] Analyses were carried out with Stata 12.0 (StataCorp, College Station, TX) at a two-tailed alpha level of 0.05.

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