

Gallstones, Body Mass Index, C-Reactive Protein, and Gallbladder Cancer: Mendelian Randomization Analysis of Chilean and European Genotype Data

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Abstract

Background and Aims: Gallbladder cancer (GBC) is a neglected disease with substantial geographical variability: Chile shows the highest incidence worldwide, while GBC is relatively rare in Europe. Here, we investigate the causal effects of risk factors considered in current GBC prevention programs as well as C-reactive protein (CRP) level as a marker of chronic inflammation. **Approach and Results:** We applied two-sample Mendelian randomization (MR) using publicly available data and our own data from a retrospective Chilean and a prospective European study. Causality was assessed by inverse variance weighted (IVW), MR-Egger regression, and weighted median estimates complemented with sensitivity analyses on potential heterogeneity and pleiotropy, two-step MR, and mediation analysis. We found evidence for a causal effect of gallstone disease on GBC risk in Chileans ($P = 9 \times 10^{-5}$) and Europeans ($P = 9 \times 10^{-5}$). A genetically elevated body mass index (BMI) increased GBC risk in Chileans ($P = 0.03$), while higher CRP concentrations increased GBC risk in Europeans ($P = 4.1 \times 10^{-6}$). European results suggest causal effects of BMI on gallstone disease ($P = 0.008$); public Chilean data were not, however, available to enable assessment of the mediation effects among causal GBC risk factors. **Conclusions:** Two risk factors considered in the current Chilean program for GBC prevention are causally linked to

GBC risk: gallstones and BMI. For Europeans, BMI showed a causal effect on gallstone risk, which was itself causally linked to GBC risk.