Title

Genetic Susceptibility to Nonalcoholic Fatty Liver Disease and Risk for Pancreatic Cancer: Mendelian Randomization.

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Genetic susceptibility to nonalcoholic fatty liver disease and risk for pancreatic cancer: Mendelian randomization

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Abstract

Background: There are conflicting data on whether nonalcoholic fatty liver disease (NAFLD) is associated with susceptibility to pancreatic cancer (PC). Using Mendelian randomization (MR), we investigated the relationship between genetic predisposition to NAFLD and risk for PC.

Methods: Data from genome-wide association studies within the Pancreatic Cancer Cohort Consortium (PanScan; cases n=5090, controls n=8733) and the Pancreatic Cancer Case Control Consortium (PanC4; cases n=4,163, controls n=3,792) were analyzed. We used data on 68 genetic variants with four different MR methods (inverse variance weighting [IVW], MR-Egger, simple median, and penalized weighted median) separately to predict genetic heritability of NAFLD. We then assessed the relationship between each of the four MR methods and PC risk, using logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for PC risk factors, including obesity and diabetes.

Results: No association was found between genetically predicted NAFLD and PC risk in the PanScan or PanC4 samples (e.g., PanScan, IVW OR=1.04, 95% CI: 0.88–1.22, MR-Egger OR=0.89, 95% CI: 0.65–1.21; PanC4, IVW OR=1.07, 95% CI: 0.90–1.27, MR-Egger OR=0.93, 95% CI: 0.67–1.28). None of the four MR methods indicated an association between genetically predicted NAFLD and PC risk in either sample.

Conclusion: Genetic predisposition to NAFLD is not associated with PC risk.

Impact: Given the close relationship between NAFLD and metabolic conditions, it is plausible that any association between NAFLD and PC might reflect host metabolic perturbations (e.g., obesity, diabetes, or metabolic syndrome) and does not necessarily reflect a causal relationship between NAFLD and PC.

Keywords

pancreatic cancer; nonalcoholic fatty liver disease; NAFLD; susceptibility; risk; cancer

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Conflict of Interest: The authors declare no potential conflicts of interest related to this work.

Introduction

Nonalcoholic fatty liver disease (NAFLD), a rapidly growing public health problem, affects ~30% of Americans (1). NAFLD is a spectrum of conditions ranging from simple steatosis (fatty liver) to nonalcoholic steatohepatitis to liver fibrosis and cirrhosis, and is considered a hepatic manifestation of metabolic abnormalities (1). NAFLD has been associated with a higher risk of pancreatic cancer (PC)(2), but the reported association between NAFLD and PC is not entirely consistent due partly to different definitions of NAFLD across studies (e.g., based on International Classification of Disease codes, laboratory values of liver function, or hepatic imaging) and small numbers of PC cases (n=24 to 72) included in these studies (2,3). There is also the possibility that NAFLD may not be an independent risk factor for PC, but rather a reflection of underlying metabolic abnormalities, such as obesity and diabetes, which are known risk factors for PC.

Genetic factors explain up to 50% of individual variability in the risk of NAFLD (4) and may be a more robust means of exploring the temporal relationship between NAFLD and PC. Mendelian randomization (MR) allows for combining multiple genetic variants previously associated with NAFLD in genome-wide association studies (GWASs) to infer the causal relationship between NAFLD and PC. Using MR, we tested the hypothesis that inherited genetic predisposition to NAFLD is causally related to PC.

Materials and Methods

Data were obtained from the Pancreatic Cancer Cohort Consortium (PanScan) and the Pancreatic Cancer Case Control Consortium (PanC4). To maximize statistical power, data from the three PanScan GWAS series (PanScan I, II, III) were combined (cases n=5090, controls n=8733) and analyzed separately from PanC4 (cases n=4163, controls n=3792). Details of the two consortia, including genetic data quality control checks have been published (5). All participants were of European ancestry.

For MR analyses, we identified 77 single-nucleotide polymorphisms (SNPs) associated with NAFLD, defined as chronically elevated serum alanine aminotransferase (cALT) in GWAS ($p < 5 \times 10^{-8}$)(6). Of the 77 SNPs, 22 were validated by imaging-defined NAFLD, 36 were validated by biopsy-confirmed NAFLD, and 17 were directionally concordant and nominally significant with both imaging and biopsy data (6). In this study, we used the following sets of instrumental variables for analyses: (a) 77 cALT-defined NAFLD SNPs, (b) 22 imaging-defined NAFLD SNPs, (c) 36 biopsy-confirmed NAFLD SNPs, and (d) 17 directionally concordant and nominally significant SNPs with both imaging and biopsy data. From these we excluded duplicate SNPs in linkage disequilibrium (retaining the SNP with the largest effect size) and palindromic SNPs with MAF >0.42. Imputed SNPs were restricted to those with $r^2 \geq 0.3$. Final sets of SNPs used for each analysis are shown in Supplementary Tables S1-S8. Alleles were converted to reflect increased risk of NAFLD. We calculated weighted genetic risk scores (GRS) using the formula:

$$GRS = \sum_{j=1}^{n} w_j G_{ij}$$

where w_j represents the weighted coefficient of the j^{th} SNP and G_{ij} represents the number of risk alleles for the j^{th} SNP of the i^{th} participant (G_{ij} = 0, 1, 2). β-estimates from the published GWAS were used to calculate the weighted coefficients (w_j)(6). Four MR methods were used for each analysis: (i) inverse variance weighting, (ii) MR-Egger, (iii) simple median, and (iv) penalized weighted median (7). Logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) modeling the weighted GRS as exposure and PC as outcome in minimally adjusted models, adjusting for age, sex, and top five principal components, and fully adjusted models with additional adjustment for diabetes, obesity, and cigarette smoking.

Data Availability

The data may be made available to researchers upon request to the Pancreatic Cancer Cohort Consortium (PanScan) and the Pancreatic Cancer Case Control Consortium (PanC4).

Results

Descriptive characteristics of the participants are presented in Supplementary Tables S9-S10. During initial evaluation of individual SNPs, only one NAFLD-related SNP was associated with PC, *ABO*-rs687621, p-value=1.15×10^{-17} for PanScan and 1.31×10^{-13} for PanC4 (Supplementary Tables S1-S2, S5-S6). The MR analyses did not show an association between genetically predicted NAFLD and risk of PC in the fully adjusted (Figures 1–2) or minimally adjusted (Supplementary Figures S1-S2) models.

Discussion

To our knowledge, this is the first study to examine the relationship between genetic predisposition to NAFLD and risk of PC. We did not find an association between NAFLD heritability and PC risk. Although some non-genetic studies have reported an association between NAFLD and PC, those studies were limited by small numbers of PC cases. In addition to using data from two consortia, we employed four different MR approaches to evaluate the relationship between NAFLD and PC, with each producing null results. Our findings thus suggest that the reported association between NAFLD and PC likely reflects the presence of metabolic perturbations among PC cases. This is supported by data indicating that a majority (~75%) of individuals with NAFLD have a concurrent diagnosis of diabetes (8), a well-established risk factor for PC. A limitation of our study is that all participants were of European ancestry and the findings cannot be generalized to individuals from other ethnicities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

cALT	chronically elevated serum alanine aminotransferase
CI	confidence interval

GRS	genetic risk scores
GWAS	genome-wide association study
IVW	inverse variance weighting
MR	Mendelian randomization
NAFLD	nonalcoholic fatty liver disease
OR	odds ratio
PanC4	Pancreatic Cancer Case Control Consortium
PanScan	Pancreatic Cancer Cohort Consortium
PC	pancreatic cancer

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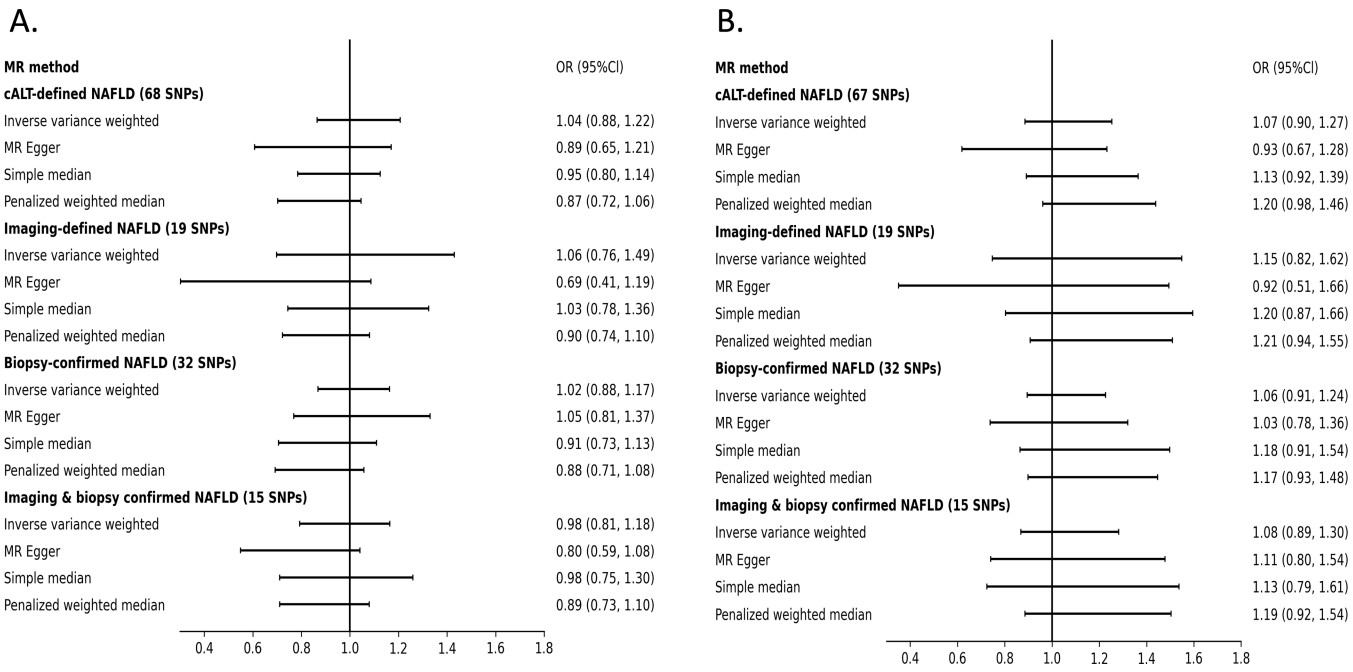

Figure 1: Results from Mendelian randomization analyses.

The first plot (**A**) shows results for the PanScan cohort derived from logistic regression analyses using four different instrumental variables (polymorphism sets) with four different Mendelian randomization methods to assess the relationship between genetic heritability of NAFLD and PC risk. The second plot (**B**) shows results for the PanC4 samples obtained from logistic regression analyses using four separate instrumental variables with four Mendelian randomization methods. Each of the logistic regression models adjusted for age, sex, the top five principal components of genetic ancestry, personal history of diabetes, and smoking history. Abbreviations: cALT, chronically elevated serum alanine aminotransferase; NAFLD, nonalcoholic fatty liver disease; PanC4, Pancreatic Cancer Case-Control Consortium; PanScan, Pancreatic Cancer Cohort Consortium; PC, pancreatic cancer; MR, Mendelian randomization; SNP, single nucleotide polymorphism.

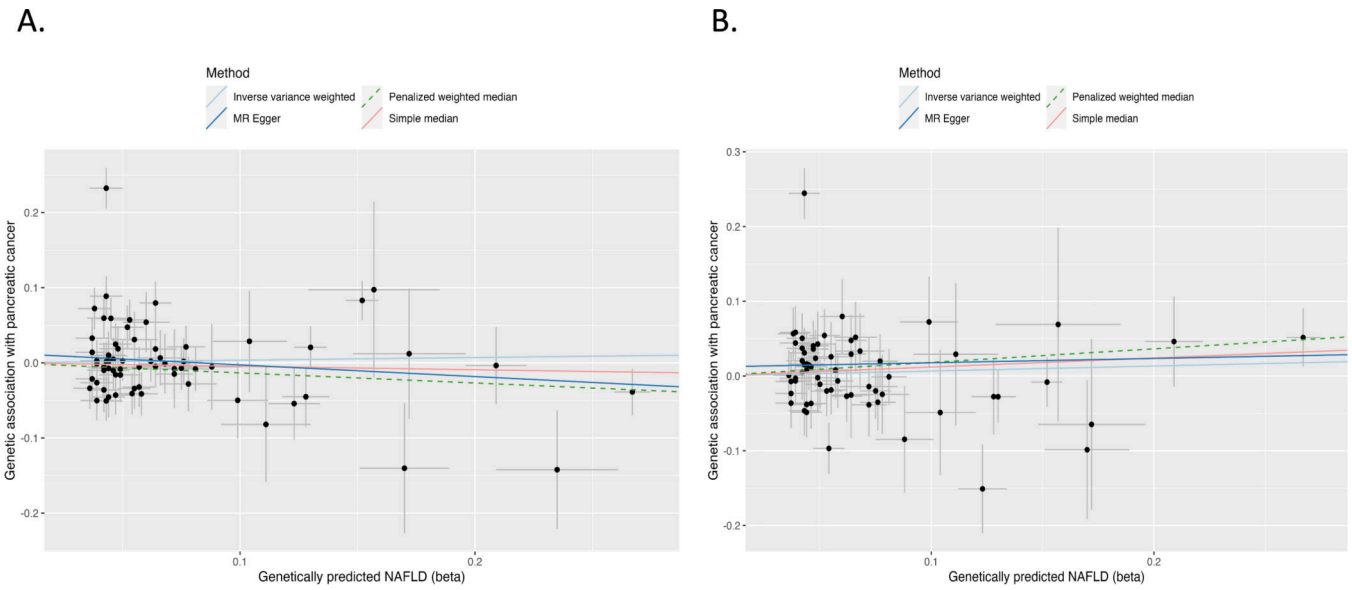

Figure 2: Plot of genetically predicted NAFLD and risk for PC.

The first plot (**A**) shows results from the PanScan data (68 SNPs), and the second plot (**B**) shows results from the PanC4 data (67 SNPs). The following MR methods were used: inverse variance weighting (light blue line), MR Egger (deep blue line), penalized weighted median (dashed green line), and simple median (pink line). Abbreviations: NAFLD, nonalcoholic fatty liver disease; PanC4, Pancreatic Cancer Case-Control Consortium; PanScan, Pancreatic Cancer Cohort Consortium; MR, Mendelian randomization; SNP, single nucleotide polymorphism.