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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Assessing the protective role of allergic disease in gastrointestinal tract cancers using Mendelian randomization analysis

To the Editor,

Immune hypersensitivity featured among allergic individuals has been proposed to enhance immune surveillance, thereby inhibiting abnormal cell growth and thus reduce cancer risk.[1,2] Similarly, the prophylaxis theory suggests that allergy symptoms may prevent cancer development by removing potential carcinogens.[2] This hypothesis

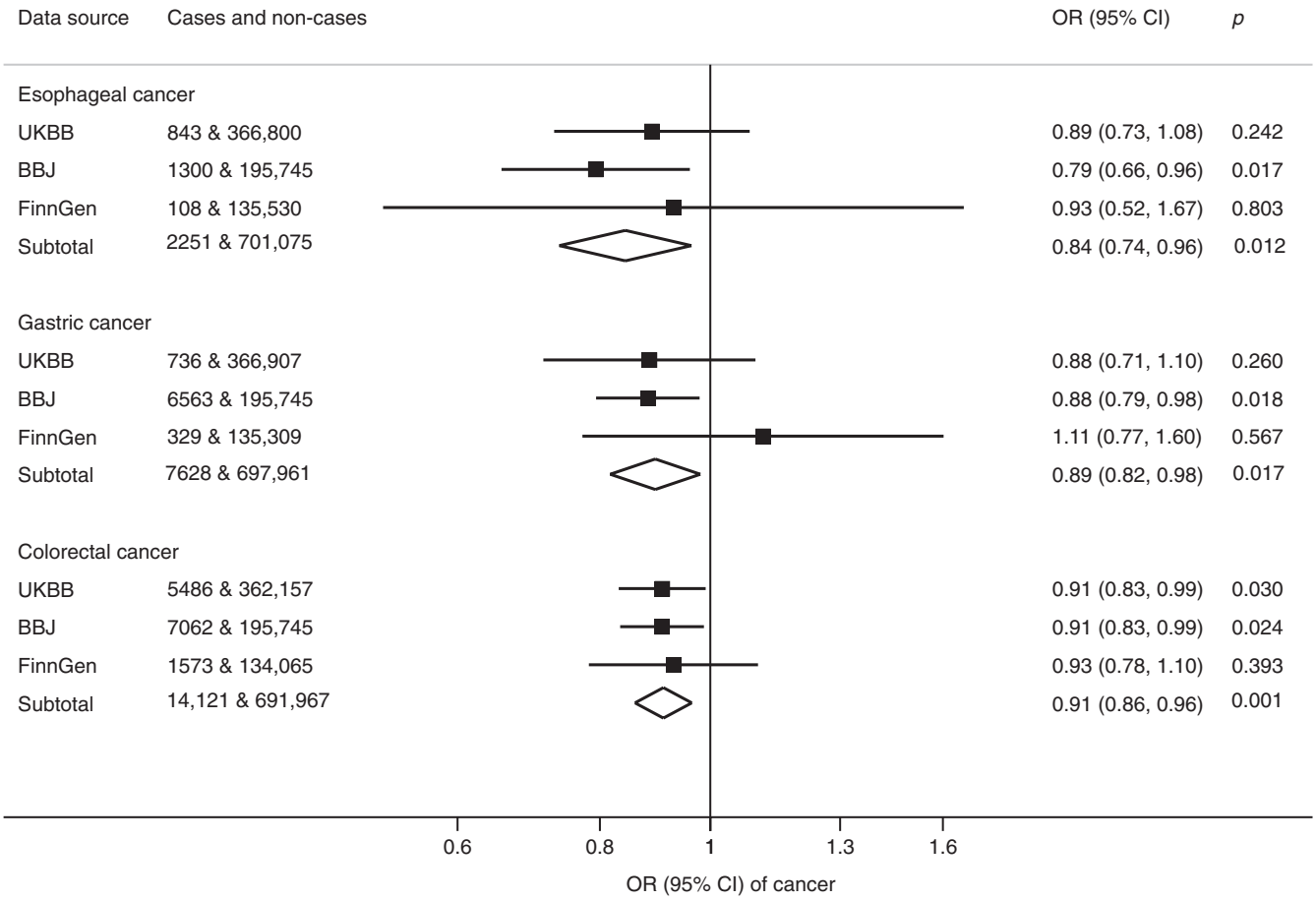

FIGURE 1 Associations of genetic predisposition to allergic disease with esophageal, gastric, and colorectal cancer. BBJ, indicates BioBank Japan; CI, confidence interval; OR, odds ratio; UKBB, UK Biobank

TABLE 1 Associations of genetic predisposition to allergic disease with esophageal, gastric, and colorectal cancer in sensitivity analyses

	Esophageal cancer			Gastric cancer			Colorectal cancer		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
UK Biobank									
IVW-fixed effects method	0.89	0.73, 1.08	.242	0.88	0.72, 1.09	.253	0.91	0.84, 0.98	.015
Weighted median method	0.92	0.69, 1.23	.571	0.84	0.61, 1.15	.270	0.96	0.84, 1.08	.489
MR-Egger regression	1.01	0.6, 1.68	.976	1.23	0.71, 2.13	.468	0.91	0.73, 1.15	.442
MR-PRESSO method[a]	n/a	n/a	n/a	n/a	n/a	n/a	0.90	0.83, 0.98	.012
Heterogeneity[b]	I^2 = 0%; Cochrane's Q = 114; P_{het} = .877			I^2 = 0%; Cochrane's Q = 137; P_{het} = .393			I^2 = 21%; Cochrane's Q = 168; P_{het} = .021		
Pleiotropy[c]	Intercept = −0.007; $P_{pleiotropy}$ = .601			Intercept = −0.018; $P_{pleiotropy}$ = .208			Intercept = 0.000; $P_{pleiotropy}$ = .944		
BioBank Japan									
IVW-fixed effects method	0.79	0.66, 0.96	.017	0.88	0.81, 0.96	.004	0.91	0.83, 0.99	.022
Weighted median method	0.65	0.49, 0.86	.003	0.94	0.82, 1.07	.332	0.87	0.76, 0.99	.034
MR-Egger regression	0.65	0.37, 1.14	.130	0.83	0.61, 1.13	.237	0.84	0.66, 1.08	.181
MR-PRESSO method[a]	n/a	n/a	n/a	0.93	0.84, 1.02	.138	n/a	n/a	n/a
Heterogeneity[b]	I^2 = 0%; Cochrane's Q = 92; P_{het} = .833			I^2 = 31%; Cochrane's Q = 154; P_{het} = .002			I^2 = 3%; Cochrane's Q = 109; P_{het} = .407		
Pleiotropy[c]	Intercept 0.011; $P_{pleiotropy}$ = .453			Intercept = 0.003; $P_{pleiotropy}$ = .682			Intercept = 0.004; $P_{pleiotropy}$ = .541		
FinnGen consortium									
IVW-fixed effects method	0.93	0.52, 1.67	.803	1.11	0.79, 1.56	.537	0.93	0.79, 1.09	.352
Weighted median method	0.79	0.34, 1.85	.586	1.21	0.72, 2.02	.477	1.11	0.88, 1.4	.38
MR-Egger regression	0.30	0.06, 1.43	.129	1.00	0.37, 2.67	.999	0.88	0.55, 1.39	.578
MR-PRESSO method[a]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Heterogeneity[b]	I^2 = 0%; Cochrane's Q = 81; P_{het} = .998			I^2 14%; Cochrane's Q 140; P_{het} = .103			I^2 16%; Cochrane's Q 143; P_{het} = .078		
Pleiotropy[c]	Intercept = 0.061; $P_{pleiotropy}$ = .127			Intercept 0.006; $P_{pleiotropy}$ = .818			Intercept 0.003; $P_{pleiotropy}$ = .797		

[a]There was no corrected estimate (n/a) if no outlier was identified. One outlier was identified and removed in the analysis of colorectal cancer based on UK Biobank (*P* value for the distortion test was.815) and two outliers were identified and removed in the analysis of gastric cancer based on Biobank Japan (*P* value for the distortion test was.137).

[b]We observed significant heterogeneity among used SNPs in the analysis of colorectal cancer based on UK Biobank and gastric cancer based on Biobank Japan (P_{het} < .05).

[c]Pleiotropy was measured by the intercept from MR-Egger regression. Pleiotropy was not detected in any analysis (all P > .05).

envisages a preventive role specifically for cancers of tissues that interface with the external environment, such as gastrointestinal tract cancers.[2] A reduced risk of gastrointestinal tract cancer among individuals with self-reported allergic conditions has been observed in several but not all observational studies.[3,4] However, whether the associations are causal remains unclear as observational studies are prone to residual confounding. Therefore, we conducted a Mendelian randomization study[5] to determine the causal role of genetic liability to allergic disease in esophageal, gastric, and colorectal cancers.

One hundred and thirty-six single-nucleotide polymorphisms (SNPs) associated with at least one allergic disease (asthma, allergic rhinitis, or eczema) at $P < 3\times10^{-8}$ in 180 129 cases and 180 709 non-cases of European ancestry were considered as instrumental variables.[6] The 136 SNPs were independent and not in linkage disequilibrium defined by distance >1 Mb and r^2 < 0.02. The SNPs explained around 2.6% of phenotypic variance. Summary-level data for the associations of those SNPs with esophageal, gastric, and colorectal cancers were obtained from the UK Biobank, BioBank Japan, and FinnGen consortium. The main analysis was based on the multiplicative random-effects inverse-variance weighted method, and estimates from the different studies were combined using fixed effects meta-analysis. The inverse-variance weighted method under a fixed effects model and the weighted median, MR-Egger regression, and MR-PRESSO methods were employed as sensitivity analyses. The I^2 (%) statistic and Cochrane's Q value were calculated to assess heterogeneity among estimates of individual SNPs. We considered

associations with *P* values below .017 (where *P* = .05/3) to represent strong evidence of causal associations and associations with *P* values below .05 but above .017 as suggestive evidence of associations.

Genetic liability to allergic disease was associated with lower risk of the gastrointestinal tract cancers in the meta-analysis of UK Biobank, BioBank Japan, and FinnGen, though the association with gastric cancer was not statistically significant after correcting for multiple testing (Figure 1). The combined odds ratio was 0.85 (95% confidence interval, 0.75, 0.97; *P* = .016) for esophageal cancer, 0.90 (95% confidence interval, 0.82, 0.98; *P* = .020) for gastric cancer, and 0.91 (95% confidence interval, 0.86, 0.96; *P* = .001) for colorectal cancer for one unit increase in log-transformed odds of allergic disease. The associations were consistent across data sources with the exception of the estimate for gastric cancer in FinnGen which was above one but with a broad confidence interval that overlapped the estimates in UK Biobank and BioBank Japan. Results were consisent in sensitivity analyses for all three cancer outcomes (Table 1).

A potential limitation arises from the fact that we used an instrument for liability to allergic disease that was developed using genetic data from individuals of European ancestry and applied to a Japanese population. However, a consistent effect of risk alleles of SNPs for allergic disease on asthma in BioBank Japan indicates a high validity of used instrumental variables and a negligible population bias. In addition, a robust pattern of established associations in both Asian and European populations suggested that the associations were portable across populations of distinct ancestries. A further limitation of this work is that we cannot make specific inferences about the impact of food allergies on cancer risk.

In summary, this MR study supports a protective effect of allergic disease against esophageal and colorectal cancer and possibly gastric cancer. This finding may be useful for further laboratory studies to understand the immunological pathways involved in gastrointestinal tract carcinogenesis.

ACKNOWLEDGMENTS

Genetic instruments for allergic disease were obtained from a published meta-analysis of genome-wide association studies.[6] Genetic association estimates for esophageal, gastric, and colorectal cancers were obtained from the UK Biobank study, BioBank Japan, and FinnGen consortium. The authors thank all investigators for sharing these data. Analyses of UK Biobank data were performed under application 29202.

CONFLICT OF INTEREST

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ETHICAL APPROVAL

All studies included in cited genome-wide association studies had approved by a relevant review board. The present MR analyses were approved by the Swedish Ethical Review Authority (2019-02793).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Chronic exposure to benzo(a)pyrene-coupled nanoparticles worsens inflammation in a mite-induced asthma mouse model

To the Editor,

Asthma is a highly prevalent chronic inflammatory disease of the airways characterized by airway hyperresponsiveness (AHR) and mucus hyperproduction. In the last decades, asthma has been affecting approximately 20% of the population worldwide and genetic changes alone cannot explain this rapid increase. During the same period, increased vehicular traffic and other combustion processes have resulted in a significant increase in ambient particle matter (PM) that can bind polycyclic aromatic hydrocarbons (PAHs) on their surface. PAHs from diesel exhaust and other sources were shown to play a role in the exacerbation of allergic immune responses in humans.[1] In acute asthma models, co-exposure to the PAH, benzo(a)pyrene (B(a)P), and ovalbumin enhances the production of allergen-specific IgE, systemic Th2 response, and airway inflammation in mice.[2]

Nanoparticles (≤0.1 μm), that represent only 2.3% of total PM mass, contribute to 23-30% of the PAHs alveolar deposition coming from roadside sources. Moreover, their small size allows evading clearance from the lung, leading to long-term retention.[3] This suggests that nanoparticles are significant contributors of PAHs deposition in the lung and thus, may contribute to acute and chronic inflammation. However, few studies have evaluated the impact of chronic exposure to this pollutant on allergic asthma. Therefore, we established a murine allergic asthma model using the house dust mite (HDM) allergen, to explore the impact of chronic exposure to nanoparticles coupled to PAHs on airway inflammation (Figure S1A for exposure model). In this study, we used carbon black nanoparticles from printers uncoated as reference (NP-Ø) and B(a)P-coated (NP-B(a)P) as a model of nano-particulate pollutant.

We analyzed the effects of chronic exposure to NP-B(a)P on different asthma parameters. As expected, exposure to HDM-induced allergic asthma including increased AHR (Figure S1B), HDM-specific IgE, and IgG1 in sera (Figure S1C) and pulmonary inflammation, characterized by elevated total cell numbers in the broncho-alveolar lavage (BAL) composed of eosinophils, neutrophils, lymphocytes, and macrophages compared to PBS control mice (Figure 1A). Moreover in this model, we did not observe airway remodeling (data not shown). Neither NP-Ø nor NP-B(a)P nanoparticles alone induced airway inflammation. However, NP-B(a)P but not NP-Ø increased AHR in non-sensitized mice, suggesting that B(a)P has a specific effect on AHR independently of HDM. In HDM-sensitized mice, HDM-induced AHR was abolished by NP-Ø and decreased by NP-B(a)P although this one remained increased compared to the PBS control group (Figure S1B). Surprisingly, both nanoparticles co-exposed with HDM did not modify inflammatory cell recruitment in the BAL (Figure 1A) and did not induce bronchial remodeling (data not shown). However, this result was not supported by cellular infiltration of lung tissue as shown by hematoxylin and eosin histological stain (Figure S1D) and total lung single cell suspension (Figure 1B). Indeed, increased total cell numbers were enhanced in the lungs of HDM + NP-B(a)P mice compared to HDM-sensitized mice (Figure 1B). This cellular infiltration was mainly due to a significant increase of eosinophils, $Ly6C^-$ monocytes/macrophages, and $CD4^+$ T cells in HDM-sensitized mice compared to the PBS group (Figure 1B). Interestingly, NP-B(a)P significantly modifies the HDM-induced cell recruitment. Indeed, $Ly6C^+$ as well as $Ly6C^-$ monocytes/macrophages were significantly elevated in HDM + NP-B(a)P compared to HDM-sensitized mice. Moreover, neutrophils, NKT-like cells and $CD8^+$ T cells, not recruited in HDM-sensitized mice, were significantly increased in lungs from HDM + NP-B(a)P mice (Figure 1B). NKT-like cells differ from classical NKT by recognizing antigen presented through major histocompatibility complex and not through CD1d,