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Correlation between allergy and cancer: a systematic review and meta-analysis

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The relationship between allergies and cancer has been a topic of debate for decades. This study conducted a systematic review and meta-analysis of 53 studies to evaluate the association between allergies and cancers. Case–control and cohort studies were analyzed, focusing on cancer incidence. The results showed significant negative correlations between allergies and cancers such as colorectal cancer, lymphoma, pancreatic cancer, leukemia, and brain cancers. For colorectal cancer, the pooled odds ratio (OR) for any allergy was 0.77 (95% CI 0.67–0.87). Asthma was associated with a reduced risk of lymphoma (OR 0.81, 95% CI 0.70–0.94) and gynecological cancers (OR 0.72, 95% CI 0.53–0.97). For Pancreatic cancer, any allergy was associated with an OR of 0.68 (95% CI 0.59–0.77). Hay fever showed a strong inverse association with brain cancer risk (OR 0.66, 95% CI 0.58–0.76). However, atopic allergy was positively linked to an increased risk of lymphoma (OR 2.02, 95%CI 1.10–3.70). The study highlighted significant variations in the effects of different allergy types on cancer risks. These findings suggest that allergies may act as protective factors against certain cancers, while atopic allergy may increase the risk of certain cancers. However, the certainty of evidence, assessed using the GRADE framework, was low to very low, and results should be interpreted with caution. In particular, associations for lung cancer, leukemia, and gastrointestinal cancers were supported by very low-certainty evidence, primarily due to reliance on observational designs, heterogeneity among studies. These findings underscore the complex and heterogeneous relationship between allergies and cancer, and highlight the need for further high-quality research to elucidate the underlying mechanisms and assess clinical implications.

Keywords Allergy, Cancer, AllergoOncology, Meta-analysis

Allergies and cancer are increasingly prevalent health challenges in both developing and developed countries[1]. Allergies are caused by the hypersensitivity reaction of the immune system to normally harmless substances in the environment, including hay fever, food allergies, atopic dermatitis, allergic asthma, and anaphylactic shock[2]. Cancer is one of the leading causes of death worldwide, and according to the latest estimates by the International Agency for Research on Cancer (IARC), there will be 20 million new cases and 9.7 million deaths worldwide in 2022. This disease with high morbidity and mortality has placed a heavy burden on all countries[3].

Although allergies and cancers appear to be distinctly different diseases, both are profoundly influenced by the regulatory status of the immune system. As research advances, it has become clear that the immune system plays a pivotal role in the onset and progression of numerous diseases[4]. Beyond its role as a defense against foreign pathogens, the balance (or imbalance) of the immune system has a profound impact on all aspects of human health[5]. During an allergic reaction, the immune system mistakenly identifies a harmless allergen as a threat, activating its defense mechanisms. This triggers mast cells and basophils to release large amounts of inflammatory mediators, such as histamines and leukotrienes. These mediators cause a range of allergic symptoms, including skin itching and airway constriction, and in severe cases, can even lead to anaphylactic shock[6,7]. In summary, allergies stem from immune imbalance, which puts the body into a state of "hyper-defense", leading to excessive inflammation and self-damage. In contrast, a hallmark of tumor development is the immune system's inability to recognize and eliminate abnormal cells[8]. Under normal conditions, immune surveillance can detect and clear

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early tumor cells, inhibiting their growth and spread[9]. However, certain tumor cells possess immune evasion mechanisms, allowing them to escape immune detection by expressing immunosuppressive factors (such as PD-L1 and TGF-β) or altering the tumor microenvironment to suppress T-cell activity[10,11]. These immune evasion strategies are central to current cancer immunotherapy research, which aims to restore immune suppression in tumors by enhancing anti-tumor immune responses[12].

Despite growing interest in the immunological interactions between allergic diseases and cancer, existing meta-analyses remain limited in scope, often concentrating on specific allergic phenotypes or single cancer types, and lacking a unified analytical framework. To address these limitations, the present study systematically evaluates the associations between various allergic conditions and multiple cancer outcomes, with the aim of determining whether a history of allergic disease is associated with an increased or decreased risk of specific cancers. This provides a comprehensive and up-to-date assessment to enhance our existing understanding of the relationship between allergies and cancer.

Methods

This Systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline[13]. The study protocol was registered with PROSPERO (CRD42024602718).

Literature search strategy

The research included searches in databases such as PubMed, Google Scholar, and ScienceDirect. The search covered studies published before November 2024. The search strategy was described in detail in Supplementary Table 1. With a primary focus on the Last 20 years. Older studies were included only if they were deemed particularly relevant. The following restrictions applied:

1) Language: Only studies published in English were considered.
2) Publication Date: The focus was on studies published in the Last 20 years.
3) Study Types: Only peer-reviewed studies and clinical trials were included. Unpublished studies or non-peer-reviewed sources, such as conference abstracts, were not be considered unless particularly significant.

Inclusion and exclusion criteria

This systematic review aimed to evaluate the available research evidence on the relationship between cancer and allergy to reveal the common mechanisms of the two in immune regulation, to evaluate the impact of allergies on cancer comprehensively, and then provide new insight for future treatment directions of cancer. The inclusion and exclusion criteria were outlined as follows.

Inclusion criteria

1) Diagnosis of Cancer: Participants had a confirmed diagnosis of cancer, regardless of cancer type or stage, classified according to standard clinical criteria (e.g., ICD codes).
2) History of Allergic Conditions: Participants had a documented history of at least one allergic condition, which may include allergic rhinitis, asthma, eczema, atopic dermatitis, food allergies, or other allergies.
3) Study Design: The systematic review focused on observational studies, specifically cohort studies and case–control studies, to examine the relationship between allergies and cancer outcomes.
4) Geographic Location: Participants from any geographic location were eligible, provided they met the other inclusion criteria.

Exclusion criteria

1) Acute Allergic Reactions Related to Oncology Treatment: Patients who experienced acute allergic reactions due to cancer treatment were excluded.
2) Severe Comorbidities Affecting Immune Response: Individuals with severe comorbidities, especially those that affect immune response (e.g., autoimmune diseases or immunodeficiency disorders), were excluded, as these may interfere with cancer- or allergy-related outcomes.
3) Non-Allergic Immune Disorders: Studies focused on immune disorders unrelated to allergies, such as autoimmune diseases, were excluded.
4) Case reports, letter to editors, unpublished reports, duplication, in vitro and in vivo studies were not considered as eligible.
5) Studies Without Relevant Comparisons: Studies that did not compare cancer outcomes between patients with and without a history of allergies were excluded.

Data extraction

The data extraction process was carried out in a systematic manner. Initially, two independent reviewers, X. Fan and S. Guo, screened the titles and abstracts of all identified studies based on the pre-specified eligibility criteria. Studies that met the inclusion criteria advanced to full-text review, and any disagreements during the screening process were resolved through discussion or by consulting a third reviewer W. Li. Subsequently, the full-text articles of studies that passed the initial screening were independently reviewed by the same two reviewers to confirm adherence to all inclusion and exclusion criteria. Studies that did not meet these criteria were excluded, and the reasons for exclusion were documented. Data to be extracted included study characteristics such as first author, year, country, study type, study period, cancer identification, exposure assessment, number of cases, number of controls, allergy type, cancer type. Main outcomes focused on data related to cancer incidence, with

effect measures presented as odds ratios (OR), hazard ratio (HR), or relative risk (RR), along with 95% confidence intervals (CIs) for each primary outcome. Furthermore, information on confounding factors, adjustments made during analysis, and study Limitations was also collected. All extracted data were recorded in a structured electronic database to ensure completeness and organization. The final dataset encompassed all relevant information necessary for meta-analysis or qualitative synthesis and was stored securely for reference throughout the review process. In the data extraction process, we also paid particular attention to the classification of allergy types. Across the 53 included studies, we identified 26 distinct terms describing allergic conditions (e.g., "any allergy," "asthma," "hay fever," "drug allergy," "eczema," "rhinitis," "food allergy," etc.). To ensure consistency and analytical power, only allergy subtypes that were reported in more than 10 studies were included in the subgroup meta-analyses. These subtypes were: any allergy (n = 34), asthma (n = 24), hay fever (n = 16), food allergy (n = 15), drug allergy (n = 14), eczema (n = 11), and allergic rhinitis (n = 10). Beyond categorizing allergy subtypes, we also organized the data according to cancer types. The top ten cancer types with the highest number of studies were included in our meta-analysis, and we conducted individual meta-analyses for each cancer type to examine the relationship with allergies. This approach allowed us to systematically assess the association between allergies and cancer risk, progression, or mortality for each specific cancer type. The results of these analyses provide a comprehensive overview of the potential protective or risk-enhancing role allergies may play in various cancers, considering the heterogeneity across cancer types.

Quality assessment

The studies included in this meta-analysis were observation study including cohort study and case–control study. The quality of each included study was assessed using Newcastle–Ottawa scale (NOS) by two independent authors. The scoring criteria for the Newcastle–Ottawa Scale (NOS) are as follows: a total score of 0 to 3 indicates low quality, a score of 4 to 6 indicates moderate quality, and a score of 7 to 9 indicates high quality[14].

The GRADE (Grading of Recommendations, Assessment, Development and Evaluations) assessment was used to assess the quality of evidence of the main outcomes. All assessments were performed using the GRADEpro online platform to ensure methodological transparency and reproducibility.

Statistical analysis

For each study reporting the association between allergy type and cancer risk, we calculated the pooled OR, RR, or HR and its 95% CI and combined them to present all results as OR and 95% CI. Data were combined according to the random-effect model in the presence of heterogeneity, otherwise, the fixed-effect model was performed. Statistical heterogeneity was assessed using the chi-squared based Q-test or the I^2 method[15]. To assess the stability of the results, sensitivity analysis was performed using subgroup analysis and leave-one-out analysis (sequentially omitting individual studies). A Baujat plot was further applied to identify studies contributing most to heterogeneity and to evaluate their influence on the pooled estimates. We also performed random-effects meta-regression to examine the influence of potential moderators, including geographic region, allergy assessment method, age, smoking status, alcohol consumption, and gender when substantial heterogeneity ($I^2 > 70\%$) was detected. Additionally, To assess the robustness of the findings, a sensitivity analysis excluding studies with a NOS score < 3 was conducted. Funnel plots and Egger's test were performed to detect potential publication bias[16]. The trim-and-fill method was employed to assess and, if necessary, correct for potential publication bias. All p-values were two-sided, and values < 0.05 were considered statistically significant. Extracted data were combined into a meta-analysis using STATA 16.0 analysis software (Stata Corporation, College Station, TX).

Results

Literature search results

A Literature search was conducted until November 2024 using the PubMed, ScienceDirect, and Google Scholar databases with the search terms:"hypersensitivity"or"allergy"AND"cancer"or"tumor"or"neoplasms"or"malignancy"(Supplementary Table 1). A total of 109 articles from 3 scientific databases were identified: PubMed (66), ScienceDirect (17), and Google Scholar (26). After excluding irrelevant and duplicate studies (duplicate n = 25, irrelevant n = 16, other reasons n = 2), we obtained 66 studies. By evaluating these 66 studies in detail, we found that 13 studies did not meet our inclusion criteria (see Table 1 for specific reasons). Therefore, 53 studies were finally included in the systematic review and meta-analysis (Fig. 1).

Exclusion reasons	No. of Studies
1) Exposure did not meet the predefined inclusion criteria	2
2) Effect estimates were not reported or extractable	3
3) Outcome or exposure definitions not comparable	2
4) Study design did not meet inclusion criteria	4
5) No control group	2
Total	13

Table 1. Excluded studies and reasons for exclusion.

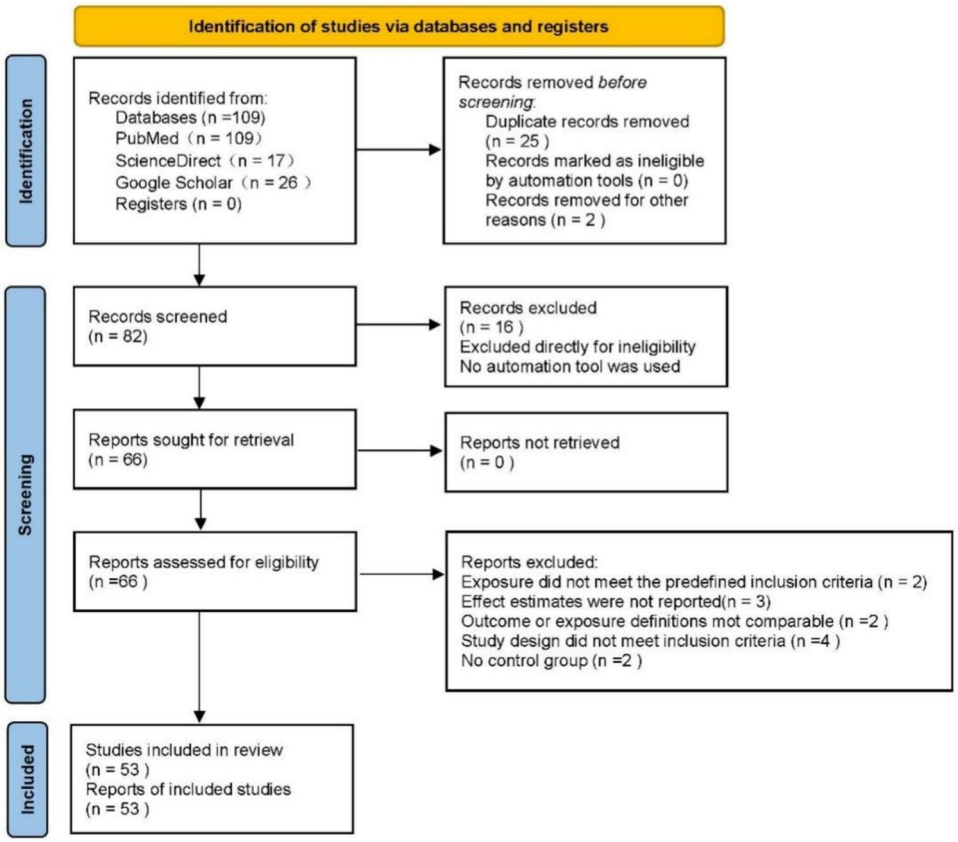

Fig. 1. PRlSMA flow diagram of article selection for systematic review and meta-analysis of the association between allergy and cancer.

Quality assessment

All 53 studies included in this meta-analysis were observational studies, including cohort and case–control designs. Two reviewers independently assessed the methodological quality of each study using the Newcastle–Ottawa Scale (NOS). Among the included studies, 18 were rated as high quality, 29 were rated as moderate quality, and 6 were rated as low quality. (Supplementary Table 2).

Study characteristics

Two authors independently extracted data from full-text articles. Details of the studies were recorded on a standardized form, including the following data elements: first author, year, country, study type, study period, cancer identification, exposure assessment, number of cases, number of controls, allergy type, cancer type.

A total of 53 studies were included in this meta-analysis, including 36 case–control studies and 17 cohort studies. The articles were classified by cancer site and specifically analyzed the top ten most common cancer types included in the studies, including colorectal cancer, breast cancer, lymphoma, pancreatic cancer, lung cancer, prostate cancer, leukemia, brain cancer, gastrointestinal cancers, and gynecological cancers. The exposure types analyzed mainly included: any allergy, atopic allergy, asthma, eczema, food allergy, drug allergy, and hay fever. (Table 2).

Meta-analysis

As outlined in the methods section, after data extraction, we categorized all studies based on cancer types. We included the top ten cancer types with the highest number of studies in our meta-analysis: colorectal cancer (n = 17), breast cancer (n = 13), lymphoma (n = 13), pancreatic cancer (n = 12), lung cancer (n = 10), prostate cancer (n = 9), leukemia (n = 8), brain cancers (n = 8), gastrointestinal cancers (n = 7), and gynecological cancers (n = 7). Individual meta-analyses were then conducted to assess the relationship between each cancer type and allergies.

Colorectal cancer

17 studies investigated the relationship between allergies and colorectal cancer. The combined odds ratio for the 17 studies investigating the association with colorectal cancer was 0.82 (95% CI 0.76–0.89; $I^2 = 51.5\%$), indicating a negative correlation between allergies and colorectal cancer. Of the 17 studies, 12 were cohort studies, and 5 were case–control studies (Fig. 2a). In this study, we assessed the potential for publication bias using Egger's test and a funnel plot. The result of Egger's test (p-value > 0.05) indicated no significant publication

Study ID	Year	Country	Study Type	Study period	Cancer identification	Exposure assessment	No.of cases	No.of controls	Allergy type	Cancer type
Fekrazad et al.[46]	2024	Italy	Case–control	April 2016—April 2019	Histologically	self-report(Interview)	300	379	Any Allergy, Asthma,Allergic rhinitis,Eczema/Atopic dermatitis,Food allergy,Drug allergy	All HNSCC,Lip and oral cavity,Pharynx,Larynx,Other HNC
Aryaie et al.[47]	2024	Italy	Case–control	November 2017-July 2018	Histologically	self-report(Interview)	556	556	Activity cough,Matter itching or urticaria,Pet allergy,Allergy since age 10,Seasonal cruise,Night cough,Food itching or urticaria,Matter itching or urticaria,Childhood common cold,Pet allergy,Allergy since age 10,Night cough,Matter itching or urticaria	Colorectal Cancer,Breast Cancer,Lung Cancer
Choi et al.[48]	2023	Korean	Cohort-studies	2009–2017	Histologically	Exposure frequency	5,125,888	4,766,745	Allergic Diseases(allergic rhinitis;asthma;allergic dermatitis)	Gastrointestinal Cancers,Esophagus,Stomach, CRC,Liver, GB/BT, Pancreas
Kim et al.[49]	2022	Korean	Cohort-studies	January 2005-December 2013	Histologically	Exposure frequency	67,279	338,239	Allergic,Atopic dermatitis,Asthma,Allergic rhinitis,Atopic dermatitis,Two or more allergies,	Liver cancer,Hepatocellular carcinoma,Intrahepatic cholangiocarcinoma
Zhou et al.[50]	2021	China	Case–control	January 2017 to December 2020	Histologically	/	Allergy:139 No allergy:4592	Allergy:2213 No allergy:22,193	Allergy	Gastrointestinal cancer(GICA)
Carneiro et al.[51]	2021	Brazil	Case–control	/	Histologically	medical diagnosis	60	20	Allergy	Cancer
Shirkhoda et al.[52]	2018	Iran	Case–control	2014–2015	Histologically	self-report(Interview)	59	53	Allery rhinitis,Total allergy	Papillary Thyroid Cancer
Huang et al.[53]	2018	United States	Cohort-studies	1993–2012	cancer registries	self-report(Interview)	49,696	137,530	atopic allergic conditions (AACs),use of antihistamines,AACs with medication use	Pancreatic cancer
Liao et al.[54]	2016	China (Taiwan)	Case–control	September 2010–30 March 30 2015	Histologically	self-report(Interview);IgE	576	740	Any allergy symptom,Nasal allergy,Skin allergy,Food allergy,Drug allergy,Asthma	All head and neck cancer,Oral cavity,Oropharynx,Hypopharynx,Larynx
Kozłowska et al.[55]	2016	Poland	Case–control	2014	Histologically	Skin prick tests	1525	1544	Any Allergy,allergic rhinitis, conjunctivitis, atopic dermatitis, and bronchial asthma	Cancer, Lung cancer, Colon cancer, Breast cancer, Skin cancer
Helby et al.[56]	2015	European	Cohort-studies	30 years	Histologically	IgE	37,747		Hazard ratio (95% CI) for a tenfold higher IgE	All cancer (except skin)Chronic lymphocytic leukemia,Multiple myeloma,Other non-Hodgkin lymphoma,Oral cavity and pharynx,Lung,Esophagus,Colon,Stomach,Ovarian (women),Liver and biliary tract,Sarcoma,Cervix uteri (women),Prostate (men),Brain and nervous tissue,Larynx,Endometrial (women),Kidney,Hodgkin lymphoma,Other leukemia,Urinary tract,Melanoma,Pancreas,Testis (men),Thyroid,Breast (women),Metastasis, primary
Taghizadeh et al.[57]	2015	European	Cohort-studies	1965–1990	Histologically	Skin prick tests,IgE	8465		Eosinophils (ln),Skin test positivity,Total IgE	Any cancer,colorectal cancer,Lung Cancer,Prostate cancer,Breast cancer
Continued										
Hofmann et al.[58]	2015	United States	Cohort-studies	1993–1997	cancer registries	self-report(Interview)	710	81,660	Allergy history and rhinitis symptoms,Rhinitis,Symptoms only,History of atopy	NHL neoplasms,DLBCL,FL,CLL/SLL,MM
Filippidis et al.[59]	2015	Germany	Case–control	1998–2000	Histologically	self-report(Interview)	229	769	Any allergy,Type I allergy,Type IV allergy	Laryngeal cancer
Tambe et al.[60]	2015	United States	Cohort-studies	1993–2010	cancer registries	self-report(Interview)	51,973	147,139	AAC: Atopic allergic conditions	CRC : Colorectal cancer,Rectum,Right Colon
Hollander et al.[61]	2015	Denmark,Sweden	Case–control	October 1999-August 2002	Histologically	self-report(Interview)	585	3187	Allergic rhinitis,Childhood eczema,Asthma	All HL,Nodular Sclerosis HL,Mixed-Cellularity HL,EBV-Positive HL,EBV-Negative HL
Shu et al.[62]	2014	European	Case–control	2004–2008	Histologically	self-report(Interview)	352	646	Any atopic condition,Asthma,Wheezing,Eczema,Allergic rhinitis,Any atopic condition	All brain tumors,Glioma (ependymoma, astrocytoma, other gliomas),Other brain tumors

Study ID	Year	Country	Study Type	Study period	Cancer identification	Exposure assessment	No.of cases	No.of controls	Allergy type	Cancer type
Cotterchio et al.[63]	2014	Canada	Case–control	February 2011-August 2012	Histologically	self-report(Interview)	345	1285	Any allergy,Asthma,Allergic asthma,Nonallergic asthma,Atopy,Hay fever,Dust or mold allergy,Animal/ pet allergy,Insect bite/sting allergy,Food allergy,Medication allergy,Chemical or metal allergy,Eczema/atopic dermatitis,Skin prick test positive	Pancreas cancer
Weiss et al.[64]	2014	Canada	Case–control	2005–2009	Histologically	self-report(Interview)	1936	1995	Allergy, asthma,hay fever,Allergy and hay fever	Prostate cancer
Turner et al.[25]	2013	Australia, Canada, France, Israel, and New Zealand	Case–control	2000–2004	Histologically	self-report(Interview)	Glioma 793 Meningioma 832 Acoustic neuroma 394	2374 2252 1436	Any allergy,Asthma,Hay Fever,Eczema	Glioma,Meningioma, Acoustic neuroma
Lowcock et al.[65]	2013	Canada	Case–control	2002–2003	Histologically	self-report(Interview)	3101	3471	allergies/hay fever Lasting more than 1 year,asthma,Premenopausal allergies/hay fever Lasting more than 1 year,Premenopausal diagnosed with asthma,Postmenopausal allergies/hay fever Lasting more than 1 year,Postmenopausal diagnosed with asthma	Breast cancer
Continued										
Dikalioti et al.[66]	2012	Greece	Case–control	1996–2008	Histologically	self-report(Interview)	330 NHL 239 HL	1478 959	Allergy-associated symptoms/ conditions,Asthma	Non-Hodgkin's lymphoma Hodgkin's lymphoma
Chae et al.[67]	2012	United States	Cohort-studies	1988–1994	Histologically	self-report(Interview)	RC:2188 WZ:743	1669	allergic rhinitis wheezing	All cancer,Breast,Uterine,Cervix,Colorectal
Grimmer et al.[68]	2012	United States	case–control	1991–2009	Histologically	medical diagnosis	2063	22,289	Allergy,Eczema, Asthma	Hemangioma
Stott-Miller et al.[69]	2012	United States	case–control	1985–1989 and 1990–1995	Histologically	self-report(Interview)	400	613	Any allergy,Airborne, allergies,Pollens,Dust,Mold,Antibiotic allergies,Penicillin,Sulfa drugs,Food allergies,Animal allergiesd,Cats,Dogs,Bee stings	Oral squamous cell carcinoma
Engkilde et al.[70]	2011	European	Cohort-studies	November 1984-December 2008	Histologically	Skin prick tests	16,922		contact allergy	Pancreas,Brain/CNS,Cervix uteri,Leukaemia,Lip, oral cavity and pharynx,Corpus uteri,Rectum and anus,Melanoma of skin,Prostate,Colon,Bladder, Lung,Colorectal,Breast,Skin, non-melanoma,All sites but non-melanoma skin cancer

Study ID	Year	Country	Study Type	Study period	Cancer identification	Exposure assessment	No.of cases	No.of controls	Allergy type	Cancer type
Maisonneuve et al.[71]	2010	Australia, Canada, the Netherlands, and Poland	case–control	January 1983-July 1988	Histologically	self-report(Interview)	823	1679	Any Allergy,Asthma,Eczema,Hay fever,Other allergy	Pancreatic cancer
ElMasri et al.[72]	2010	United States	case–control	2001	Histologically	medical diagnosis	1582	4744/21,830	Asthma	Ovarian Cancer
Becker et al.[73]	2007	European	Case–control	1998–2004	Histologically	self-report(Interview)	2362	2465	Hay fever,Mite/dust allergy,Asthma,Food allergy,Respir. allergy,Med. allergy/Durg allergy	Lymphoma,Hodgkin lymphoma: HL,NHL:Non-Hodgkin's lymphoma,B-non-Hodgkin lymphoma,diffuse large B-cell lymphoma (DLBL),follicular lymphoma (FL),multiple myeloma (MM),B-CLL: chronic lymphocytic leukaemia of B-cell type,Others B-NHL:B-non-Hodgkin lymphoma (B-NHL),T-non-Hodgkin lymphoma
Olson et al.[74]	2007	United States	Case–control	April 2003-February 2007	Histologically	self-report(Interview)	405	212	Allergies,Hay fever, pollen, grass, seasonal,Any medications,Antibiotics,Pain relievers,Other medications,Any animals,Cats,Dogs,Other animals,Any foods,Dust,Mold	Pancreatic cancer
Continued										
Cozen et al.[75]	2007	United States	case–control	July 1998-June 2000	Histologically	self-report(Interview)	1321	1057	Any allergy,Asthma,Eczema,Any allergy (Excluding allergy to medications),Hay fever,Food allergies,Animal allergies,Insect allergies,Dust allergies,Allergies to Medications	All NHL cases,DLBCL Cases :diffuse large B-cell lymphoma, Follicular: follicular lymphoma
Wigertz et al.[76]	2007	Nordic-UK	Case–control	2000–2004	Histologically	self-report(Interview)	Glioma 1527 Meningioma 1210	3309	Any allergy,Asthma,Eczema,Hay fever,Food allergy,	Glioma,Meningioma
Prizment et al.[77]	2007	United States	Cohort-studies	1986–2004	Histologically	self-report(Interview)	6765	14,527	Allergy,Allergy except asthma,Asthma,Hay fever,Skin allergies,Other allergies	Colorectal cancer,Colon cancer,Proximal colon cancer,Distal colon cance,Rectal cancer
Wang et al.[78]	2006	Germany	Case–control	June 2000-December 2002	Histologically	self-report(Interview);IgE	Prostate cancer 318 Breast cancer 381 Lung cancer 196 Colorectal cancer 477	1904 2367 4271 4271	Atopy,Asthma,Hay fever,Atopic dermatitis,Any atopy-related diseases	Prostate cancer,Breast cancer,Lung cancer,Colorectal cancer
Becker et al.[79]	2005	Germany	Case–control	1999–2002	Histologically	self-report(Interview)	710	710	Any allergy,Allergy to pollen (hay fever),Mite-dust allergy,Food allergy,Allergic asthma,Allergic contact eczema,by chromium or nickel (only),by chemical products (only),Allergy to any medication,to antibiotics (only),to analgesics (only)	All lymphomas,Follicular lymphoma, Diffuse large B-cell lymphoma,CLL,Multiple myeloma,MALT, B-NHL total, T-NHL,HL

Study ID	Year	Country	Study Type	Study period	Cancer identification	Exposure assessment	No.of cases	No.of controls	Allergy type	Cancer type
Eriksson et al.[80]	2005	European Sweden	Cohort-studies	1976–1999	Histologically	Skin prick tests	13,811		Atopy	All cancer types, Pharynx,Stomach, Colon,Rectum, Pancreas,Larynx,Lung and trachea,Breast,Corpus uteri,Uterus Unspecified,Ovaric,Prostate,Kidney,Bladder,Melanoma of skin,Other skin,Brain and other nervous system,Thyroid gland, Other endocrine,Connective tissue,Non-Hodgkin's lymphoma,Hodgkin's disease,Multiple myeloma,Acute lymphatic leukem,Acute myeloid leukemia,Chronic myeloid leukemia
Turner et al.[81]	2005	United States	Cohort-studies	1982–2000	Histologically	self-report(Interview)	1,102,247		asthma and hay fever	All cancer,Lung cancer,Pancreatic cancer,Non-Hodgkin's lymphoma,Leukemia,Multiple myeloma,Brain cancer,Colorectal cancer,Stomach cancer,Prostate cancer,Breast cancer (women),Ovarian cancer,Cancer of the corpus and uterus, not otherwise specified
Lindelöf et al.[82]	2005	European	Cohort-studies	1988–2000	Histologically	IgE	70,136		IgE Highly elevated	Total cancers
Continued										
Bosetti et al.[83]	2004	Italy	Case–control	1991–2000	Histologically	self-report(Interview)	Oral cavity and pharynx 579 Oesophagus 282 Colon 1145 Rectum 694 Larynx 446	4566	History of allergy	Oral cavity and pharynx,Oesophagus,Colon,Rectum,Larynx
Talbot-Smith[84]	2003	Australia, Canada	Cohort-studies	1981–1999	Histologically	Skin prick tests	3308		Asthma,Hay fever,Any atopy,House dust mites,Rye grass pollen,Barley pollen,Orchard grass pollen,Wild oat pollen	Prostate cancer, breast cancer,colorectal cancer,Leukemia,Lymphoma, lung cancer,melanoma
Holly et al.[85]	2003	United States	Case–control	1994–2001	Histologically	self-report(Interview)	532	1701	Any allergy,House dust,Plants, Mold,Any animals,Dogs,Cats,Other animals,Insect bites or stings,Any foods,Eggs,Dairy products,Seafood or shellfish,Wheat,Peanuts,Citrus fruit,Other foods,Eczema,Allergies and eczema,Allergies only,Eczema only	Pancreatic cancer
Hedderson et al.[86]	2003	United States	Case–control	January 1983-April 1990	cancer registries	self-report(Interview)	723	958	Any atopic history,Allergy to grass, hay, trees, pollen,Allergy to dust,chalk, mold,Allergy to animals,Food allergy,Medication allergy,Insect bite/sting allergy,Other allergy	Breast cancer

Study ID	Year	Country	Study Type	Study period	Cancer identification	Exposure assessment	No.of cases	No.of controls	Allergy type	Cancer type
Briggs et al.[87]	2002	United States	Case–control	1984–1988	Histologically	self-report(Interview)	952	1691	Allergy history,Plants ,Dust,Food,Animals,Medication,Insect bite or sting,Specific chemical,Class of compound,Tobacco smoke,Fabrics	NHL
Negri et al.[88]	1999	Italy	Case–control	1992–1996	Histologically	self-report(Interview)	Colon 1225 Rectum 728	4154	Allergy	Colorectum,Colon,Rectum
Petroianu et al.[89]	1995	Brazil	Case–control	1971–1984	Histologically	self-report(Interview)	400 with allergy:109 without allergy:291	400 with allergy:161 without allergy:239	Allergies	Cancer
Eriksson et al.[90]	1995	European	Cohort-studies	1976- 1989	Histologically	Skin prick tests	6593		Atopy	All sites,Stomach,Colon, Rectum,Pancreas,Larynx,Lung and trachea,Breast,Corpus uteri,Uterus Unspecified,Ovaric,Prostate, Kidney,Urinary Bladder,Malignant melanoma,Skin,Brain,Thyroid gland,Unspetified,Malignant lymphomas,Non-Hodgkin's lymphoma,Hodgkin's disease,Multiple myeloma, Acute lymphatic leukem,Acute myeloid leukemia,Chronic myeloid leukemia
Dai et al.[91]	1995	China	Case–control	1992 –1993	Histologically	self-report(Interview)	108	275	Any allergy,Drug allergy,Food allergy,Contact dermatitis,Urticaria,Asthma,Allergic rhinitis	Pancreatic cancer
Mills et al.[92]	1992	United States	Cohort-studies	1976–1982	cancer registries	self-report(Interview)	34,198		History of any allergy	Colon,Rectum,Prostate,Lung,Bladder,Malignant melanoma,Stomach,Kidney,Breast,endometrium,Cervix,Ovary,Lymphoma, Leukemia,Myeloma,Sarcoma
Vecchia et al.[93]	1991	Italy	Case–control	1985–1990	Histologically	self-report(Interview)	Colon 673 Rectum 405	1501	Drug allergy	Colon,Rectum
McDuffie et al.[94]	1991	Canada	Case–control	1991	Histologically	Skin prick tests	176	209	Skin prick test positive	Lung
Vecchia et al.[95]	1990	Italy	Case–control	1983–1988	Histologically	self-report(Interview)	247	1089	Drug allergy	Pancreatic cancer
Continued										
Severson et al.[96]	1989	United States	Case–control	1981–1984	Histologically	self-report(Interview)	98	133	Allergy,Drugs allergy (Penicillin), Sulfa drugs,Other antibiotics,Other drugs, Dust, Eggs/feathers, Foods,Pollen,Bee/insect stings, Dogs/cats, Other allergies	AML
McWhorter et al.[97]	1988	United States	Cohort-studies	1971–1975	Histologically	self-report(Interview)	1840	4268	Any allergy,Hives,Asthma,Hay fever,Food allergy,Other allergy	Any cancer

Table 2. Characteristics of the studies included in the meta-analysis.

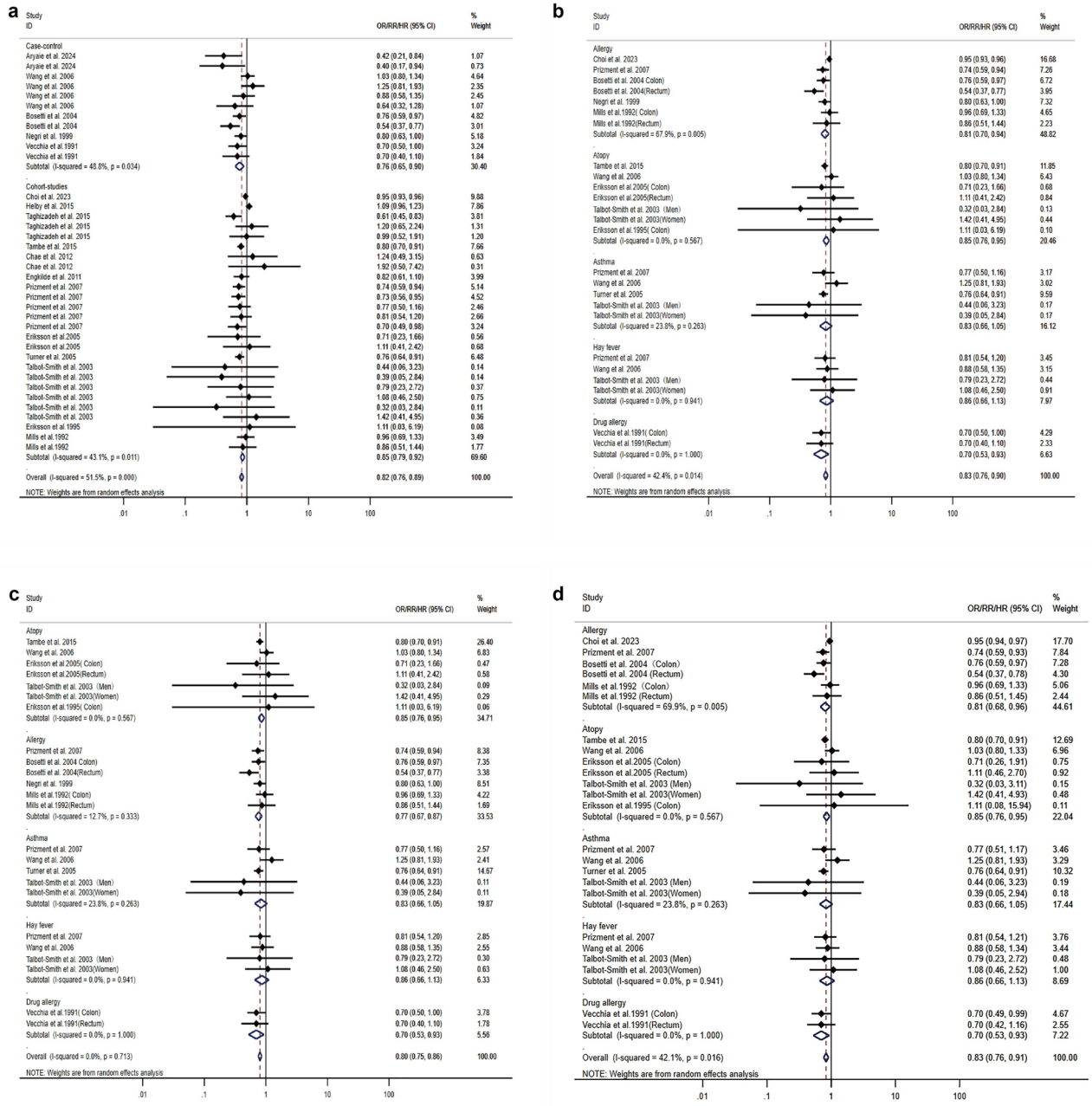

Fig. 2. Random-effects meta-analysis of association of colorectal cancer incidence and allergy. (**a**). Forest plot is stratified by study design. (**b**). Forest plot is stratified by different allergy type. (**c**). Forest plot is stratified by different allergy type, results were adjusted based on sensitivity analysis. (**d**). Forest plot of the association after excluding low-quality studies (NOS < 3) to assess robustness of the pooled estimate. If HR, RR, or OR are provided, they were used for the calculations. If these measures were not provided, the OR value was calculated based on the raw data from the original articles. OR, odds ratio; RR: relative risk; HR: hazard ratio; CI, confidence interval.

bias. Furthermore, the funnel plot did not show any obvious asymmetry, further supporting the reliability of the results (Supplementary Fig. 1a). Sensitivity analysis using a leave-one-out approach demonstrated that the pooled estimates remained robust, with no single study significantly influencing the overall results (Supplementary Fig. 2a). The Baujat plot was used to illustrate the impact of individual studies on overall heterogeneity and the pooled effect (Supplementary Fig. 3a). The results of subgroup analysis for different allergy types are shown in Fig. 2b and Table 3a. In the subgroup heterogeneity analysis, the study by Choi contributed the most to the observed heterogeneity in the association between allergy and colorectal cancer. After excluding the Choi study, (The Choi study defined allergies based on Korean insurance claims data, which may have led to misclassification of allergic diseases. Additionally, environmental and lifestyle factors specific to the Korean population may have differed from those in other regions.) heterogeneity decreased substantially ($I^2 = 12.7\%$), while the overall

(a) Meta-analysis results for the association between allergies and colorectal cancer, including subgroup and sensitivity analyses						
	OR	95%CI	I^2(%)	P Value for meta-analysis	No. of study	GRADE
Total	0.82	0.76 to 0.89	51.5	< 0.0001	17	Low
Allergy type						
Allergy	0.81	0.70 to 0.94	67.9	0.005	5	
Atopy	0.85	0.76 to 0.95	0	0.567	5	
Asthma	0.83	0.66 to 1.05	23.8	0.263	4	
Hay fever	0.86	0.66 to 1.13	0	0.941	3	
Drug allergy	0.70	0.53 to 0.93	0	1.000	1	
Sensitivity analysis (excluding NOS < 3)	0.83	0.76 to 0.91	42.1	0.016	11	
Q-test for subgroup differences: Q = 4.10, df = 4, p = 0.3927.						
(b) Meta-analysis results for the association between allergies and breast cancer, including subgroup and sensitivity analyses						
	OR	95%CI	I^2(%)	P Value for meta-analysis	No. of study	GRADE
Total	0.97	0.89 to 1.05	58.2	< 0.0001	13	Low
Allergy type						
Allergy	1.06	0.83 to 1.35	86.5	< 0.0001	3	
Atopy	1.14	0.90 to 1.45	35.7	0.183	5	
Asthma	0.96	0.83 to 1.11	44.5	0.109	4	
Hay fever	1.09	0.76 to 1.56	0	0.556	2	
Drug allergy	0.98	0.76 to 1.27	0	0	1	
Food allergy	0.83	0.60 to 1.15	0	0	1	
Q-test for subgroup differences: Q = 2.48, df = 5, p = 0.779.						
(c) Meta-analysis results for the association between allergies and lymphoma cancer, including subgroup and sensitivity analyses						
	OR	95%CI	I^2(%)	P Value for meta-analysis	No. of study	GRADE
Total	0.85	0.79 to 0.92	49.6	< 0.0001	13	Low
Allergy type						
Allergy	0.85	0.68 to 1.07	72.2	0.003	6	
Atopy	1.36	0.63 to 2.96	62.3	0.021	4	
Asthma	0.81	0.70 to 0.94	18.8	0.287	7	
Hay fever	0.74	0.62 to 0.88	0	0.438	4	
Drug allergy	1.15	0.91 to 1.45	45.1	0.162	3	
Food allergy	0.76	0.60 to 0.96	39.2	0.177	4	
Eczema	0.93	0.62 to 1.41	42.1	0.178	3	
Sensitivity analysis (excluding NOS < 3)	0.88	0.79 to 0.98	50.6	0.001	12	
Q-test for subgroup differences: Q = 11.56, df = 6, p = 0.0724.						
(d) Meta-analysis results for the association between allergies and pancreatic cancer, including subgroup and sensitivity analyses						
	OR	95%CI	I^2(%)	P Value for meta-analysis	No. of study	GRADE
Total	0.75	0.69 to 0.82	68.8	< 0.0001	12	Very low
Allergy type						
Allergy	0.72	0.56 to 0.91	85.6	< 0.0001	6	
Atopy	0.82	0.57 to 1.19	77.1	0.013	3	
Asthma	0.89	0.65 to 1.23	55.2	0.082	4	
Hay fever	0.53	0.37 to 0.75	39.3	0.193	3	
Drug allergy	0.94	0.69 to 1.27	0	0.510	4	
Food allergy	0.79	0.58 to 1.07	0	0.614	3	
Eczema	0.71	0.56 to 0.91	27.1	0.253	3	
Q-test for subgroup differences: Q = 8.46, df = 6, p = 0.2066.						
(e) Meta-analysis results for the association between allergies and lung cancer, including subgroup and sensitivity analyses						
	OR	95%CI	I^2(%)	P Value for meta-analysis	No. of study	GRADE
Total	0.99	0.82 to 1.19	71.5	< 0.0001	10	Very low
Allergy type						
Allergy	2.86	0.35 to 23.38	93.1	< 0.0001	2	
Continued						

(e) Meta-analysis results for the association between allergies and lung cancer, including subgroup and sensitivity analyses						
	OR	95%CI	I^2(%)	P Value for meta-analysis	No. of study	GRADE
Atopy	0.76	0.48 to 1.20	0	0.776	3	
Asthma	0.84	0.60 to 1.17	17.9	0.301	3	
Hay fever	0.66	0.26 to 1.70	25.9	0.259	2	
Q-test for subgroup differences: Q = 2.37, df = 3, p = 0.4987.						
(f) Meta-analysis results for the association between allergies and prostate cancer, including subgroup and sensitivity analyses						
	OR	95%CI	I^2(%)	P Value for meta-analysis	No. of study	GRADE
Total	1.07	0.98 to 1.17	18.2	0.215	9	Low
Allergy type						
Allergy	1.08	0.88 to 1.32	41.7	0.190	2	
Atopy	1.41	1.05 to 1.88	4.7	0.350	3	
Asthma	1.10	0.89 to 1.37	37.9	0.185	3	
Hay fever	1.06	0.80 to 1.40	0	0.747	2	
Q-test for subgroup differences: Q = 0.07, df = 3, p = 0.9945.						
(g) Meta-analysis results for the association between allergies and leukemia cancer, including subgroup and sensitivity analyses						
	OR	95%CI	I^2(%)	P Value for meta-analysis	No. of study	GRADE
Total	0.49	0.35 to 0.68	81.3	< 0.0001	8	Very low
Allergy type						
Allergy	0.68	0.18 to 2.57	90.7	0.001	2	
Atopy	1.21	0.18 to 8.35	0	0.934	2	
Asthma	0.83	0.63 to 1.09	0	0.384	2	
Hay fever	2.54	0.73 to 8.79	0	0.424	1	
Drug allergy	0.73	0.34 to 1.58	67.1	0.081	2	
Food allergy	0.31	0.08 to 1.28	90.3	0.001	2	
Q-test for subgroup differences: Q = 11.48, df = 5, p = 0.0427.						
(h) Meta-analysis results for the association between allergies and brain cancer, including subgroup and sensitivity analyses						
	OR	95%CI	I^2(%)	P Value for meta-analysis	No. of study	GRADE
Total	0.77	0.73 to 0.82	39.6	0.012	8	low
Allergy type						
Allergy	0.71	0.64 to 0.79	0	0.726	2	
Atopy	1.02	0.75 to 1.38	0	0.988	3	
Asthma	0.78	0.64 to 0.95	40.2	0.171	4	
Hay fever	0.66	0.58 to 0.76	0	0.920	2	
Food allergy	0.66	0.50 to 0.87	-	-	1	
Eczema	0.73	0.57 to 0.93	52.5	0.122	3	
Q-test for subgroup differences: Q = 8.31, df = 5, p = 0.14.						
(i) Meta-analysis results for the association between allergies and gastrointestinal cancers, including subgroup and sensitivity analyses						
	OR	95%CI	I^2(%)	P Value for meta-analysis	No. of study	GRADE
Total	0.84	0.52 to 1.37	96.4	< 0.0001	7	Very low
Allergy type						
Allergy	0.62	0.29 to 1.35	98.1	< 0.0001	4	
Atopy	1.36	0.90 to 2.07	16.1	0.275	2	
Asthma	0.96	0.71 to 1.30	-	-	1	
Sensitivity analysis (excluding NOS < 3)	0.98	0.86 to 1.12	22	0.268	6	
Q-test for subgroup differences: Q = 4.88, df = 2, p = 0.0874.						
(j) Meta-analysis results for the association between allergies and gynecological cancers, including subgroup and sensitivity analyse						
	OR	95%CI	I^2(%)	P Value for meta-analysis	No. of study	GRADE
Total	0.87	0.69 to 1.10	38.3	0.124	7	Low
Allergy type						
Allergy	0.75	0.36 to 1.55	-	-	1	
Atopy	1.16	0.90 to 1.51	0	0.549	2	
Continued						

(j) Meta-analysis results for the association between allergies and gynecological cancers, including subgroup and sensitivity analyse						
	OR	95%CI	I^2(%)	P Value for meta-analysis	No. of study	GRADE
Asthma	0.72	0.53 to 0.97	37.1	0.208	2	
Sensitivity analysis (excluding NOS < 3)	1.00	0.80 to 1.24	7.7	0.355	4	
Q-test for subgroup differences: Q = 5.98, df = 2, p = 0.0502.						

Table 3. Meta-analysis results for the association.

association remained consistent (Fig. 2c). In addition, we performed a sensitivity analysis excluding studies with a Newcastle–Ottawa Scale (NOS) score lower than 3 to assess the robustness of the pooled estimates. The results were consistent with the original analysis, indicating that our findings were robust and were not significantly affected by the inclusion of low-quality studies (Fig. 2d).

Breast cancer

13 studies investigated the association between allergies and breast cancer. Among them, nine were cohort studies, and four were case–control studies. The pooled odds ratio of the 13 studies was 0.97 (95% CI 0.89–1.05; $I^2 = 58.2\%$), indicating little to no association (Fig. 3a). The results from Egger's test ($p > 0.05$) and the symmetrical distribution of the funnel plot did not suggest the presence of publication bias (Supplementary Fig. 1b). Sensitivity analysis using a leave-one-out approach demonstrated that the pooled estimates remained robust, with no single study significantly influencing the overall results (Supplementary Fig. 2b). The Baujat plot indicated that Aryaie et al. contributed notably to heterogeneity and the pooled effect, but excluding this study did not reduce the overall heterogeneity (Supplementary Fig. 2b-3b). Subgroup analysis results for different allergy types are presented in Fig. 3b, and no significant associations were observed across the various allergy subtypes (Table 3b). However, sensitivity analysis within the allergy subgroup showed that, after excluding the study by Aryaie et al., the pooled odds ratio for the remaining two studies was 0.90 (95% CI 0.80–1.01; $I^2 = 52.5\%$) (Fig. 3c). Based on the Newcastle–Ottawa Scale assessment, all included studies were of moderate to high quality, with no studies rated as low quality. Therefore, no subgroup analysis based on study quality was conducted.

Lymphoma

13 studies investigated the association between allergies and lymphoma. The pooled odds ratio of the 13 studies was 0.85 (95% CI 0.79–0.92; $I^2 = 49.6\%$), indicating a negative association between allergies and lymphoma. Among the studies, seven were cohort studies, and six were case–control studies (Fig. 4a). Egger's test ($p < 0.05$) and the asymmetry of the funnel plot suggest the potential for publication bias (Supplementary Fig. 1c). Sensitivity analysis using a leave-one-out approach demonstrated that the pooled estimates remained robust, with no single study significantly influencing the overall results (Supplementary Fig. 2c). The Baujat plot was used to illustrate the impact of individual studies on overall heterogeneity and the pooled effect (Supplementary Fig. 3c). Subgroup analysis results for different allergy types are presented in Fig. 4b and Table 3c. The analysis revealed that heterogeneity primarily arose from differences in study design between cohort and case–control studies (Fig. 4c). (The cohort studies by Hofmann and Mills contributed significantly to the overall heterogeneity. After excluding these studies, the I^2 value significantly decreased, indicating that design differences were the key factor driving the increased heterogeneity. After exclusion, the I^2 value dropped to 37.7%, and the pooled odds ratio of the remaining four studies was 0.88 (95% CI 0.74–1.05).For the analysis of atopy (four studies) and lymphoma, the pooled odds ratio was 1.36 (95% CI 0.63–2.96; $I^2 = 62.3\%$). After excluding the Hofmann study based on study type, the I^2 value decreased to 0%, and the pooled odds ratio for the remaining three studies was 2.02 (95% CI 1.10–3.70).) In addition, we performed a sensitivity analysis excluding studies with a Newcastle–Ottawa Scale (NOS) score lower than 3 to assess the robustness of the pooled estimates. The results were consistent with the original analysis, indicating that our findings were robust and were not significantly affected by the inclusion of low-quality studies.(Fig. 4d).

Pancreatic cancer

12 studies investigated the association between allergies and Pancreatic cancer. The pooled odds ratio of the 12 studies was 0.75 (95% CI 0.69–0.82; $I^2 = 68.8\%$), indicating a negative association between allergies and pancreatic cancer. Among the studies, six were cohort studies, and six were case–control studies (Fig. 5a). Egger's test and the funnel plot suggest the potential for publication bias ($p < 0.05$) (Supplementary Fig. 1d). Sensitivity analysis using a leave-one-out approach demonstrated that the pooled estimates remained robust, with no single study significantly influencing the overall results (Supplementary Fig. 2d). Based on the Baujat results, studies by Turner, Olson, Engkilde, Cotterchio, and Holly were identified as major contributors to heterogeneity. However, sequential exclusion of these studies did not materially reduce the overall heterogeneity. (Supplementary Fig. 2d-3d). In addition, due to the high level of heterogeneity observed among studies investigating the association between allergy and pancreatic cancer, we conducted both meta-regression and subgroup analyses to identify potential sources of heterogeneity. The meta-regression results suggest that whether adjust alcohol consumption may partially account for the between-study heterogeneity(Supplementary Fig. 4). Subgroup analysis results for different allergy types are presented in Fig. 5b and Table 3d. In the subgroup analysis of atopy and pancreatic cancer (3 studies), heterogeneity was high, with $I^2 = 77.1\%$. Sensitivity analysis showed that Huang's study

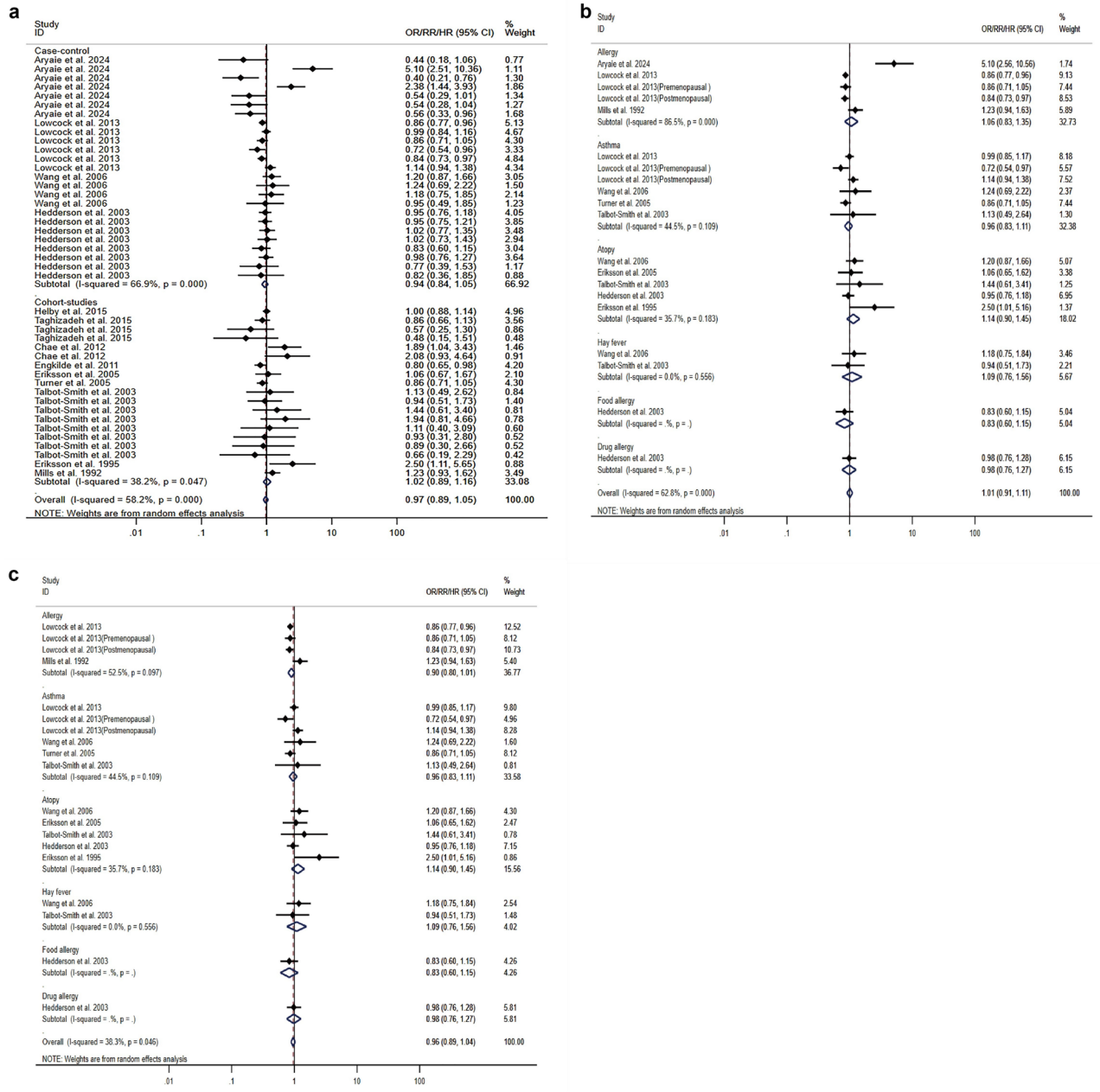

Fig. 3. Random-effects meta-analysis of association of breast cancer incidence and allergy. (**a**). Forest plot is stratified by study design. (**b**). Forest plot is stratified by different allergy type. (**c**). Forest plot is stratified by different allergy type, results were adjusted based on sensitivity analysis. If HR, RR, or OR are provided, they were used for the calculations. If these measures were not provided, the OR value was calculated based on the raw data from the original articles. OR, odds ratio; RR: relative risk; HR: hazard ratio; CI, confidence interval.

(This study scored lower (only four stars) on the NOS scale compared to the other two, suggesting that it may have introduced higher heterogeneity due to data quality issues.) was the main source of heterogeneity. After excluding this study, I^2 dropped to 0%, and the trend of results remained the same. Similarly, for allergy and pancreatic cancer, Choi's study contributed the most to heterogeneity. After excluding this study, I^2 dropped to 0%, and the trend of results remained the same (Fig. 5c).

Lung Cancer

Ten studies investigated the relationship between allergy and lung cancer, with a pooled odds ratio of 0.99 (95% CI 0.82–1.19; $I^2 = 71.5\%$), suggesting no significant association (Fig. 6a). Egger's test and funnel plot analysis showed no significant asymmetry, suggesting that publication bias did not affect the results (Supplementary Fig. 1e). Sensitivity analysis using a leave-one-out approach demonstrated that the pooled estimates remained robust, with no single study significantly influencing the overall results (Supplementary Fig. 2e). The Baujat

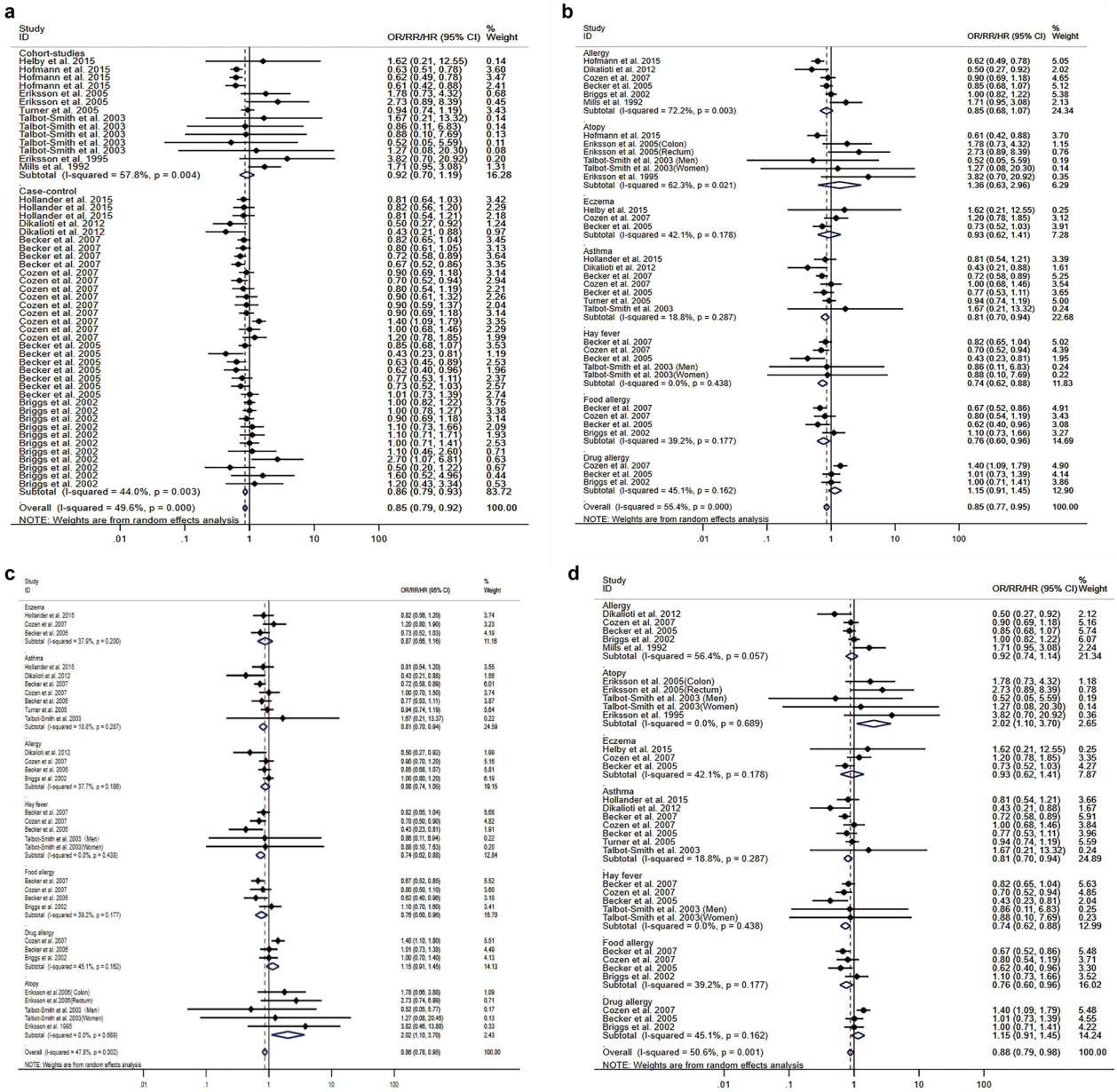

Fig. 4. Random-effects meta-analysis of association of lymphoma cancer incidence and allergy. (**a**). Forest plot is stratified by study design. (**b**). Forest plot is stratified by different allergy type. (**c**). Forest plot is stratified by different allergy type, results were adjusted based on sensitivity analysis. (**d**). Forest plot of the association after excluding low-quality studies (NOS < 3) to assess robustness of the pooled estimate. If HR, RR, or OR are provided, they were used for the calculations. If these measures were not provided, the OR value was calculated based on the raw data from the original articles. OR, odds ratio; RR: relative risk; HR: hazard ratio; CI, confidence interval.

plot indicated that the study by Aryaie et al. contributed substantially to heterogeneity, but its inclusion or exclusion did not alter the direction or significance of the overall pooled effect (Supplementary Fig. 2e-3e). To further explore potential sources of heterogeneity, meta-regression and subgroup analyses were performed for lung cancer, but none of the examined covariates showed a significant effect (Supplementary Fig. 5). Subgroup analysis showed no significant associations between any specific type of allergy and lung cancer (Fig. 6b, Table 3e).Based on the Newcastle–Ottawa Scale assessment, all included studies were of moderate to high quality, with no studies rated as low quality. Therefore, no subgroup analysis based on study quality was conducted.

Prostate cancer

Nine studies investigated the relationship between allergy and prostate cancer, with a pooled odds ratio of 1.07 (95% CI 0.98–1.17; $I^2 = 18.2\%$), suggesting no significant evidence of an association. Among these, seven

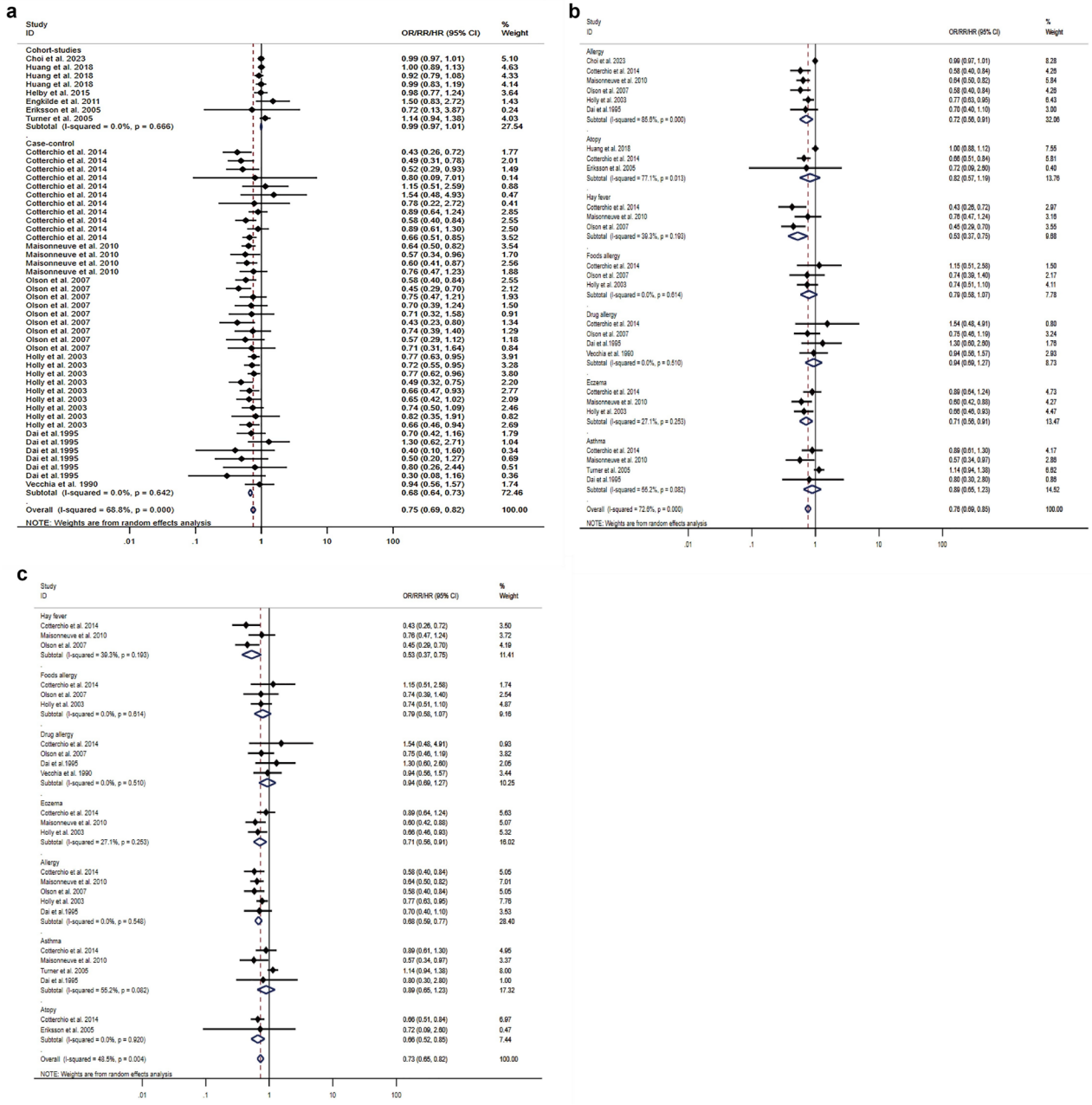

Fig. 5. Random-effects meta-analysis of association of pancreatic cancer incidence and allergy. (**a**). Forest plot is stratified by study design. (**b**). Forest plot is stratified by different allergy type. (**c**). Forest plot is stratified by different allergy type, results were adjusted based on sensitivity analysis. If HR, RR, or OR are provided, they were used for the calculations. If these measures were not provided, the OR value was calculated based on the raw data from the original articles. OR, odds ratio; RR: relative risk; HR: hazard ratio; CI, confidence interval.

were cohort studies, and two were case–control studies (Fig. 7a). Egger's test (p = 0.135) and the symmetrical distribution of the funnel plot indicated no publication bias (Supplementary Fig. 1f.). Sensitivity analysis using a leave-one-out approach demonstrated that the pooled estimates remained robust, with no single study significantly influencing the overall results (Supplementary Fig. 2f.). The Baujat plot was used to illustrate the impact of individual studies on overall heterogeneity and the pooled effect (Supplementary Fig. 3f.). Subgroup analysis indicated a significant positive association between atopy and prostate cancer risk (OR 1.41, 95% CI 1.05–1.88), while no significant associations were found for other allergy types (Fig. 7b, Table 3f). Based on the Newcastle–Ottawa Scale assessment, all included studies were of moderate to high quality, with no studies rated as low quality. Therefore, no subgroup analysis based on study quality was conducted.

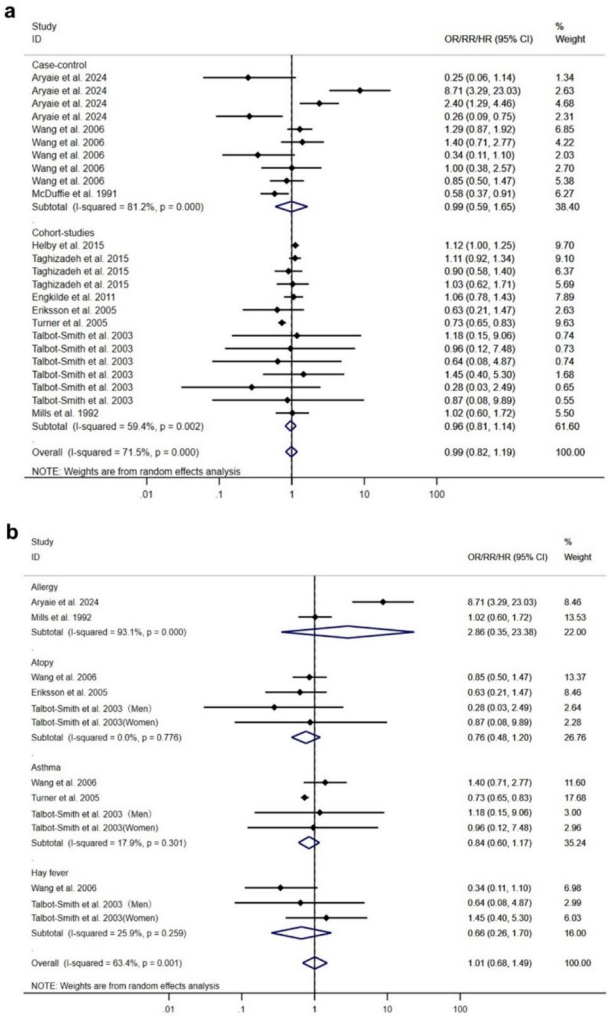

Fig. 6. Random-effects meta-analysis of association of lung cancer incidence and allergy. (**a**). Forest plot is stratified by study design. (**b**). Forest plot is stratified by different allergy type. If HR, RR, or OR are provided, they were used for the calculations. If these measures were not provided, the OR value was calculated based on the raw data from the original articles. OR, odds ratio; RR: relative risk; HR: hazard ratio; CI, confidence interval.

Leukemia

Eight studies investigated the relationship between allergy and leukemia, with a pooled odds ratio of 0.49 (95% CI 0.35–0.68; $I^2 = 81.3\%$), indicating a negative association between allergy and leukemia. Among these, six were cohort studies, and two were case–control studies (Fig. 8a). Egger's test ($p < 0.05$) and funnel plot analysis suggested potential publication bias (Supplementary Fig. 1 g). Sensitivity analysis using a leave-one-out approach demonstrated that the pooled estimates remained robust, with no single study significantly influencing the overall results (Supplementary Fig. 2 g). Based on the Baujat plot, the study by Talbot-Smith et al. and Severson et al. were considered the main contributor to heterogeneity. However, excluding either study did not substantially reduce the overall heterogeneity (Supplementary Fig. 2 g-3 g). In addition, given the substantial heterogeneity ($I^2 = 81.3\%$) observed among studies examining the association between allergy and leukemia, we performed both meta-regression and subgroup analyses to explore potential sources of heterogeneity. The meta-regression results indicated that geographic region, allergy assessment method, age, gender, alcohol consumption, and smoking status may each partially contribute to the between-study variability (Supplementary Fig. 6). The Q-test for subgroup differences reached statistical significance ($Q = 11.48$, $df = 5$, $p = 0.0427$), suggesting potential variation among allergy types. However, subgroup analysis revealed no significant associations between any specific allergy type and leukemia risk (Fig. 8b, Table 3g). None of the included studies met the criteria for low methodological quality according to the NOS score.

Brain cancer

Eight studies investigated the relationship between allergy and brain cancer, with a pooled odds ratio of 0.77 (95% CI 0.73–0.82; $I^2 = 39.6\%$), indicating a negative association between allergy and brain cancer. Among these, five were cohort studies, and three were case–control studies (Fig. 9a). Egger's test ($p < 0.05$) and funnel

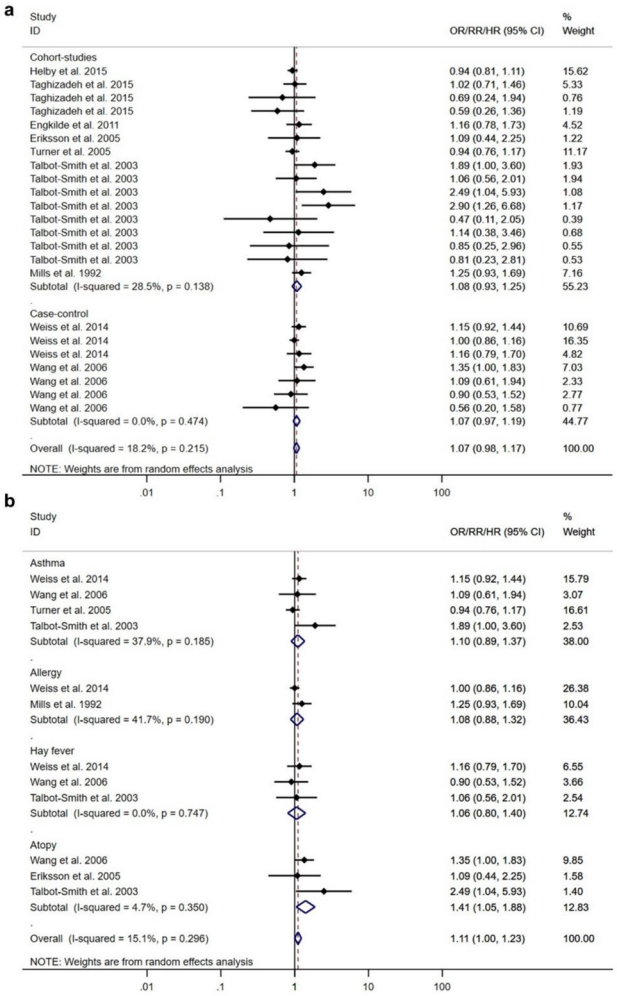

Fig. 7. Random-effects meta-analysis of association of prostate cancer incidence and allergy. (**a**). Forest plot is stratified by study design. (**b**). Forest plot is stratified by different allergy type. If HR, RR, or OR are provided, they were used for the calculations. If these measures were not provided, the OR value was calculated based on the raw data from the original articles. OR, odds ratio; RR: relative risk; HR: hazard ratio; CI, confidence interval.

plot analysis suggested evidence of publication bias (Supplementary Fig. 1 h). Sensitivity analysis using a leave-one-out approach demonstrated that the pooled estimates remained robust, with no single study significantly influencing the overall results (Supplementary Fig. 2 h). The Baujat plot was used to illustrate the impact of individual studies on overall heterogeneity and the pooled effect (Supplementary Fig. 3 h). Subgroup analysis showed that most allergy types were significantly associated with a reduced risk of brain cancer (Fig. 9b, Table 3h). Based on the Newcastle–Ottawa Scale assessment, all included studies were of moderate to high quality, with no studies rated as low quality. Therefore, no subgroup analysis based on study quality was conducted.

Gastrointestinal cancers

Seven studies investigated the relationship between allergy and gastrointestinal cancers, with a pooled odds ratio of 0.84 (95% CI 0.52–1.37; $I^2 = 96.4\%$), suggesting little to no evidence of an association. Among these, five were cohort studies, and two were case–control studies (Fig. 10a). Egger's test and funnel plot analysis did not show significant asymmetry (Supplementary Fig. 1i). The leave-one-out sensitivity analysis indicated that the pooled association between allergy and gastrointestinal cancers risk was notably affected by the exclusion of the study by Zhou et al. (Supplementary Fig. 2i). Consistently, the Baujat plot identified Zhou et al. as a major contributor to both heterogeneity and the overall effect, with I^2 decreasing from 96.4% to 33% upon its removal (Supplementary Fig. 2i-3i). In addition, due to the high level of heterogeneity observed among studies investigating the association between allergy and gastrointestinal cancers, we conducted both meta-regression and subgroup analyses to identify potential sources of heterogeneity. The meta-regression results suggest that geographic region may partially account for the between-study heterogeneity (Supplementary Fig. 7). Subgroup analysis revealed no significant associations between specific allergy types and the risk of gastrointestinal cancers (Fig. 10b, Table 3i). However, sensitivity analysis within the allergy subgroup showed that, after excluding the study by Zhou et al., (The quality assessment of this study was only three stars, and the article did not report

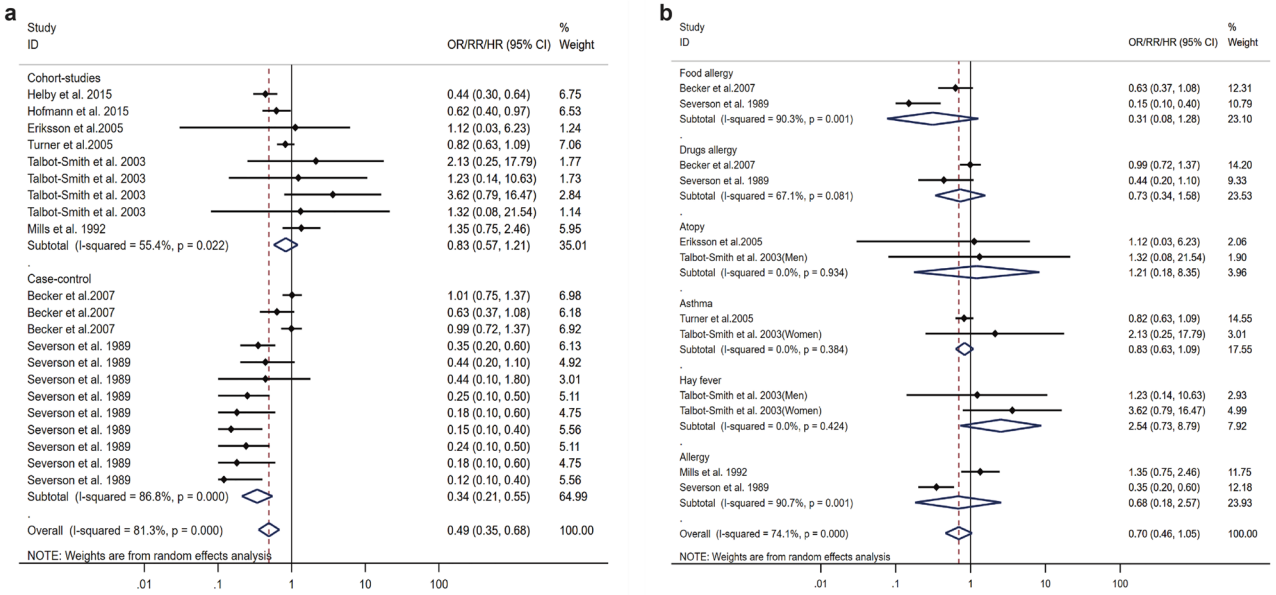

Fig. 8. Random-effects meta-analysis of association of leukemia cancer incidence and allergy. (**a**). Forest plot is stratified by study design. (**b**). Forest plot is stratified by different allergy type. If HR, RR, or OR are provided, they were used for the calculations. If these measures were not provided, the OR value was calculated based on the raw data from the original articles. OR, odds ratio; RR: relative risk; HR: hazard ratio; CI, confidence interval.

direct odds ratios, instead calculating them. Additionally, the Zhou study, based on a Chinese population, may have been influenced by regional differences, data collection methods, and varying reporting standards, leading to inconsistent results and high heterogeneity.) the pooled odds ratio was 0.94 (95% CI 0.93–0.95; $I^2 = 0\%$), suggesting a potential inverse association between allergy and gastrointestinal cancers (Fig. 10c). In addition, we performed a sensitivity analysis by excluding studies with a Newcastle–Ottawa Scale (NOS) score below 3 to assess the robustness of the pooled estimates. The effect sizes remained largely consistent with the original analysis, while the heterogeneity was substantially reduced (Fig. 10d). This suggests that our findings are robust and that some of the observed heterogeneity may be attributed to lower-quality studies.

Gynecological cancers

Seven studies investigated the relationship between allergy and gynecological cancers (including uterine cancer, cervical cancer, endometrial cancer, and uterine body cancer), with a pooled odds ratio of 0.87 (95% CI 0.69–1.10; $I^2 = 38.3\%$), indicating little to no evidence of an association. Among these, six were cohort studies, and one was a case–control study (Fig. 11a). Egger's test ($p = 0.866$) and the symmetrical distribution of the funnel plot indicated no publication bias, further confirming the stability of the results (Supplementary Fig. 1j). Sensitivity analysis using a leave-one-out approach demonstrated that the pooled estimates remained robust, with no single study significantly influencing the overall results (Supplementary Fig. 2j). The Baujat plot was used to illustrate the impact of individual studies on overall heterogeneity and the pooled effect (Supplementary Fig. 3j). Subgroup analysis indicated that asthma was significantly associated with a reduced risk of gynecological cancers (OR 0.72, 95% CI 0.53–0.97) (Fig. 11b, Table 3j). In addition, we performed a sensitivity analysis by excluding studies with a Newcastle–Ottawa Scale (NOS) score below 3 to assess the robustness of the pooled estimates. The effect sizes remained largely consistent with the original analysis, while the heterogeneity was substantially reduced (Fig. 11c). This suggests that our findings are robust and that some of the observed heterogeneity may be attributed to lower-quality studies.

GRADE assessment

GRADE assessments were conducted for above meta-analyses. The certainty of evidence was rated as low for colorectal cancer, breast cancer, lymphoma, prostate cancer, brain cancer, and gynecological cancers, and as very low for pancreatic cancer, lung cancer, leukemia, and gastrointestinal cancers. (Table 4).

Discussion

This study utilized a systematic review and meta-analysis approach to comprehensively explore the relationship between allergies and cancer, aiming to elucidate the potential patterns within this complex interaction. Through stringent data selection criteria, we identified the cancer types most frequently studied in association with allergies, with a particular focus on the top ten cancer types: colorectal cancer (n = 17), breast cancer (n = 13), lymphoma (n = 13), pancreatic cancer (n = 12), lung cancer (n = 10), prostate cancer (n = 9), leukemia (n = 8), brain cancers (n = 8), gastrointestinal cancers (n = 7), and gynecological cancers (n = 7). Here, n represents the

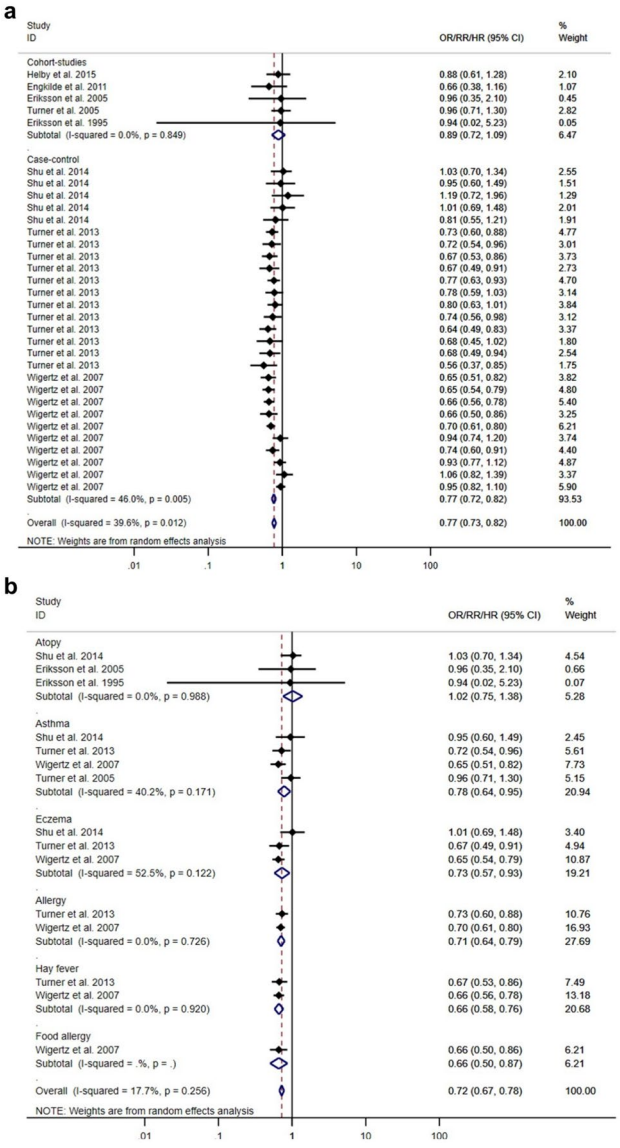

Fig. 9. Random-effects meta-analysis of association of brain cancer incidence and allergy. (**a**). Forest plot is stratified by study design. (**b**). Forest plot is stratified by different allergy type. If HR, RR, or OR are provided, they were used for the calculations. If these measures were not provided, the OR value was calculated based on the raw data from the original articles. OR, odds ratio; RR: relative risk; HR: hazard ratio; CI, confidence interval.

number of studies included in the analysis for each cancer type. In the preliminary meta-analysis, we observed potential inverse associations between general allergy and several cancer types, including colorectal cancer, lymphoma, pancreatic cancer, leukemia, and brain cancers. Although the pooled analysis suggested a negative association between allergy and leukemia, the substantial heterogeneity ($I^2 = 81.3\%$) could not be effectively reduced through sensitivity analyses, subgroup analyses, or meta-regression, indicating that the observed association should be interpreted with caution. Moreover, we did a subgroup analysis based on the subtype of the allergy. And we found for colorectal cancer, any allergy, atopy, and drug allergy, were showed a negative correlation. For brain cancer, most allergy types, particularly any allergy, asthma, hay fever, food allergy, and eczema, were significantly associated with a reduced risk of brain cancer. And for pancreatic cancer, subgroup analysis indicated that any allergy, hay fever, eczema was significantly associated with a reduced risk of pancreatic cancer, while no significant associations were observed for food allergies, drug allergies, or any allergy overall. For lymphoma, subgroup analysis showed that asthma, hay fever, and food allergies were significantly associated with a reduced risk of lymphoma, while no significant associations were observed for eczema, drug allergies, or any allergy overall. These findings suggest no consistent evidence supporting an inverse association between certain allergy subtypes and cancer risk.

Based on the findings of this study, the relationship between cancer and allergies is both multifaceted and complex. In addition, several other studies have explored the association between specific cancers and allergies

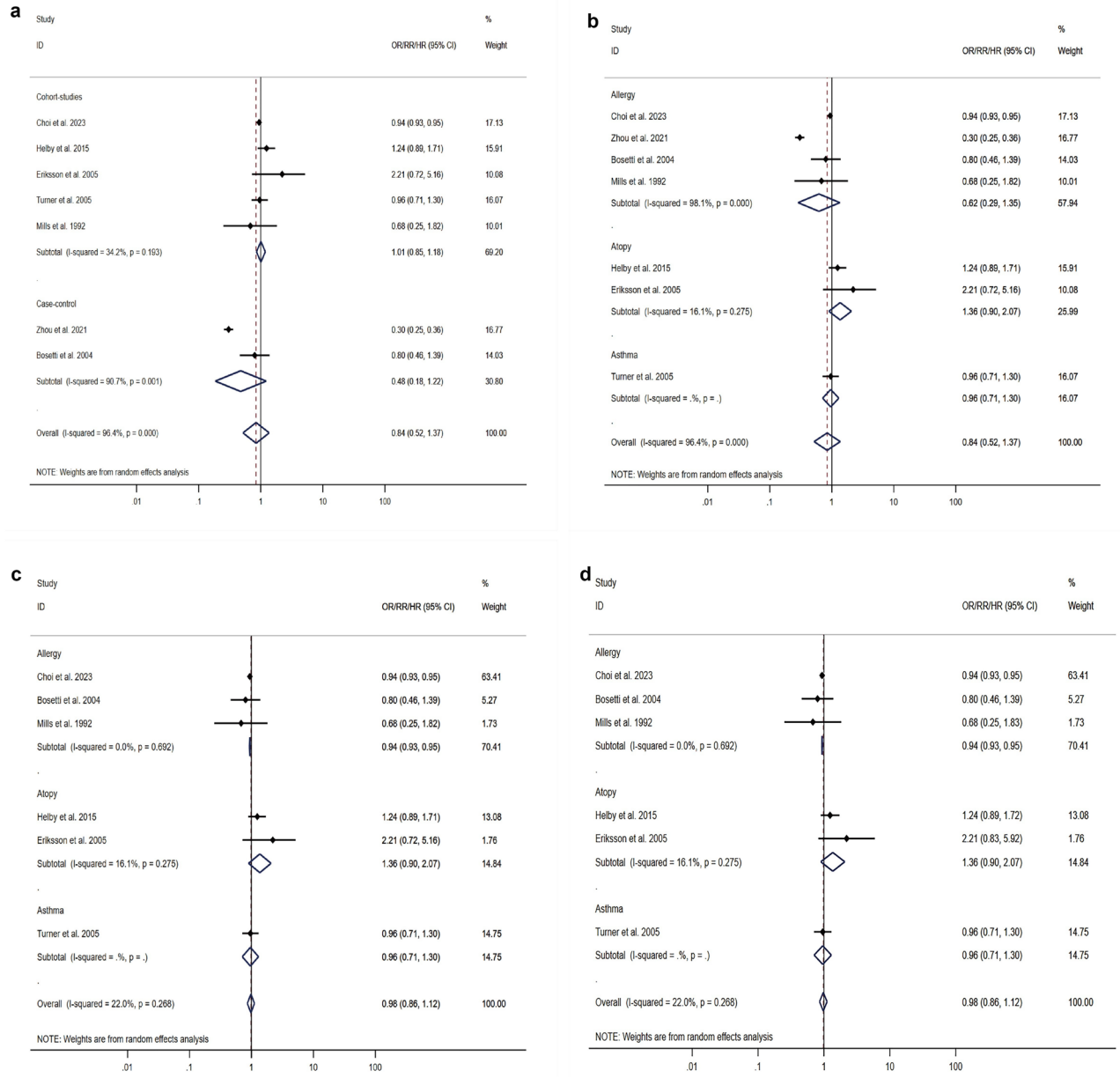

Fig. 10. Random-effects meta-analysis of association of gastrointestinal cancers incidence and allergy. (**a**). Forest plot is stratified by study design. (**b**). Forest plot is stratified by different allergy type. (**c**). Forest plot is stratified by different allergy type, results were adjusted based on sensitivity analysis. (**d**). Forest plot of the association after excluding low-quality studies (NOS < 3) to assess robustness of the pooled estimate. If HR, RR, or OR are provided, they were used for the calculations. If these measures were not provided, the OR value was calculated based on the raw data from the original articles. OR, odds ratio; RR: relative risk; HR: hazard ratio; CI, confidence interval.

using meta-analysis. Below we also summarize the main results of these studies. Atopic diseases, asthma, hay fever, and allergies to animals, have been linked to a reduced risk of pancreatic cancer, suggesting a potential protective effect[17–20]. However, allergies related to food or drugs do not show any significant association with pancreatic cancer[19]. In terms of prostate cancer, hay fever and asthma exhibit significant inverse associations with cancer-specific mortality, indicating that these allergic conditions may be associated with improved survival rates in patients with prostate cancer[21,22]. On the other hand, atopy or any allergy does not appear to be directly linked to a reduced risk of developing prostate cancer itself[21]. Asthma has been identified as both a risk factor for lung cancer in some studies, while others report a significant inverse association between asthma and lung cancer-specific mortality, indicating a complex relationship between asthma and lung cancer[23,24]. Regarding glioma, a history of any allergy or allergies of any type appears to offer a protective effect against the development of this type of brain cancer[25]. Furthermore, asthma has shown significant inverse associations with breast cancer-specific mortality, suggesting that individuals with asthma may have a better prognosis in breast cancer[21]. Finally,

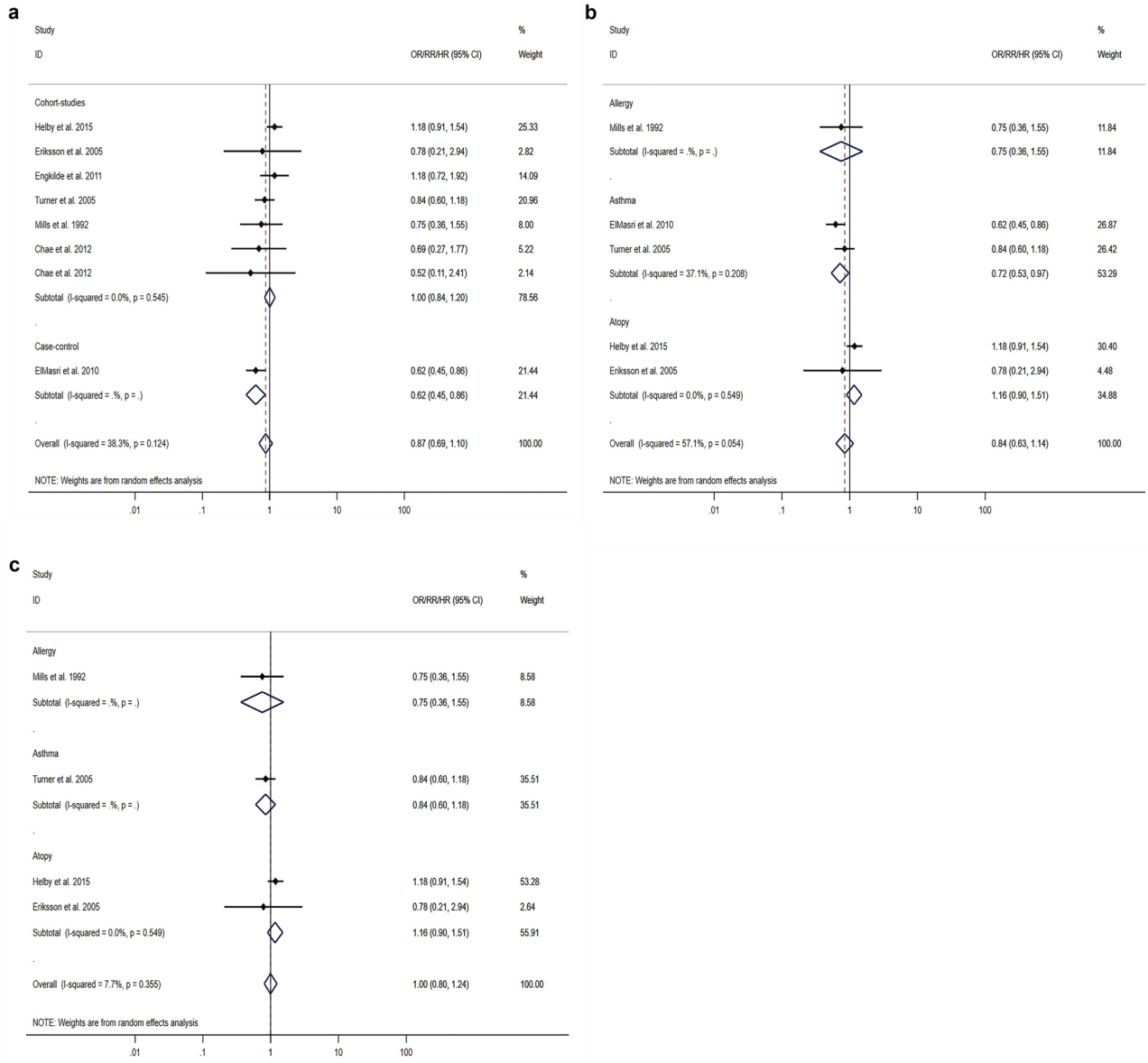

Fig. 11. Random-effects meta-analysis of association of gynecological cancers incidence and allergy. (**a**). Forest plot is stratified by study design. (**b**). Forest plot is stratified by different allergy type. (**c**). Forest plot of the association after excluding low-quality studies (NOS < 3) to assess robustness of the pooled estimate. If HR, RR, or OR are provided, they were used for the calculations. If these measures were not provided, the OR value was calculated based on the raw data from the original articles. OR, odds ratio; RR: relative risk; HR: hazard ratio; CI, confidence interval.

atopic diseases are inversely associated with colorectal cancer (CRC), indicating that allergic conditions may reduce the risk of CRC[21]. However, a history of allergy does not show a significant association with CRC risk[26]. These mixed results highlight the need for further research to understand the nuanced relationship between allergic diseases and the risk of different types of malignant cancers.

Traditionally, allergic conditions have been considered a form of chronic inflammation that increases the risk of malignancy. Persistent inflammatory microenvironments may contribute to carcinogenesis through multiple mechanisms, including accelerated cell turnover, increased production of reactive oxygen species (ROS), impaired DNA repair, and remodeling of the extracellular matrix[27]. For instance, ulcerative colitis has been linked to colorectal cancer, chronic pancreatitis to pancreatic cancer, and gastroesophageal reflux disease to esophageal adenocarcinoma[28]. However, emerging evidence suggests that allergic inflammation may, in some contexts, be inversely associated with cancer risk. One potential explanation is that allergic responses may enhance immune surveillance by activating specific immune pathways, thereby offering protective effects against tumor development[29]. Support for this hypothesis has also emerged from preclinical studies. For example, in the observed inverse correlation between asthma and brain cancers, asthma is a type 2 immune-mediated disease characterized by elevated levels of IL-4, IL-5, and IL-13, accompanied by prominent eosinophilic inflammation,

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparison	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Colorectum cancer												
17	non-randomised studies	not serious	not serious	not serious	not serious	none	5,193,460 cases 4,945,128 controls		**OR 0.82** (0.76 to 0.89)		⨁⨁◯◯Low	IMPORTANT
							-	48.0%		**49 fewer per 1,000** (from 68 to 29 fewer)		
Breast cancer												
13	non-randomised studies	not serious	not serious	not serious	not serious	none	7692 cases 9021 controls		**OR 0.97** (0.89 to 1.05)	-	⨁⨁◯◯ Low	IMPORTANT
							-	54.0%		**8 fewer per 1,000** (from 29 fewer to 12 more)		
Lymphoma												
13	non-randomised studies	not serious	not serious	not serious	not serious	none	6970 cases 92,248 controls		**OR 0.85** (0.79 to 0.92)	-	⨁⨁◯◯ Low	IMPORTANT
							-	93.0%		**11 fewer per 1,000** (from 17 to 6 fewer)		
Pancreatic cancer												
12	non-randomised studies	not serious	serious[a]	not serious	not serious	none	5,178,044 cases 4,910,516 controls		**OR 0.75** (0.69 to 0.82)	-	⨁◯◯◯ Very low[a]	IMPORTANT
							-	48.0%		**71 fewer per 1,000** (from 91 to 49 fewer)		
Lung cancer												
10	non-randomised studies	not serious	serious[a]	not serious	not serious	none	928 cases 3132 controls		**OR 0.99** (0.82 to 1.19)	-	⨁◯◯◯ Very low[a]	NOT IMPORTANT
							-	77.0%		**2 fewer per 1,000** (from 37 fewer to 29 more)		
Prostate cancer												
9	non-randomised studies	not serious	not serious	not serious	not serious	none	2254 cases 3899 controls		**OR 1.07** (0.98 to 1.17)	-	⨁⨁◯◯ Low	IMPORTANT
							-	63.0%		**16 more per 1,000** (from 5 fewer to 36 more)		
Leukemia												
8	non-randomised studies	not serious	serious[a]	not serious	not serious	none	3170 cases 84,258 controls		**OR 0.48** (0.34 to 0.66)	-	⨁◯◯◯ Very low[a]	IMPORTANT
							-	96.0%		**40 fewer per 1,000** (from 69 to 19 fewer)		
Brain Cancer												
8	non-randomised studies	not serious	not serious	not serious	not serious	none	5108 cases 10,017 controls		**OR 0.77** (0.73 to 0.82)	-	⨁⨁◯◯ Low	IMPORTANT
							-	66.0%		**61 fewer per 1,000** (from 74 to 46 fewer)		
Gastrointestinal cancers												
7	non-randomised studies	not serious	serious[a]	not serious	not serious	none	5,129,173 cases 4,773,524 controls		**OR 0.84** (0.52 to 1.37)	-	⨁◯◯◯ Very low[a]	NOT IMPORTANT
							-	48.0%		**43 fewer per 1,000** (from 156 fewer to 78 more)		
Gynecological cancers												
7	non-randomised studies	not serious	not serious	not serious	not serious	none	4513 cases 6413 controls		**OR 0.87** (0.69 to 1.10)	-	⨁⨁◯◯ Low	IMPORTANT
							-	59.0%		**34 fewer per 1,000** (from 92 fewer to 23 more)		

Table 4. Grade assessment using GRADEpro. CI: **confidence interval;** OR: **odds ratio.** a. There is significant heterogeneity in the results of different studies.

IgE production, and activation of mast cells and basophils. These cytokines and effector cells can influence the tumor microenvironment[30]. A murine model demonstrated that allergic airway inflammation (AAI) delayed glioblastoma progression by reprogramming microglia toward a pro-inflammatory phenotype. This shift was associated with enhanced infiltration of $CD4^+$ T cells into the tumor microenvironment and an increase in circulating effector memory T cells[31]. In line with this, Chatterjee et al. reported that asthma may suppress glioma formation through decorin-mediated inhibition of microglial activity via T cell signaling[32]. These findings suggest that asthma-associated immune activation may contribute to antitumor immune responses in the central nervous system. In addition, studies have shown that elevated IgE levels in allergic individuals may contribute to antitumor immunity by binding tumor-associated antigens and facilitating antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis (ADCP)[29]. Notably, epidemiological evidence suggests that individuals with allergic diseases or elevated serum IgE levels may have a reduced risk of developing a variety of specific site malignancies, including colorectal cancer, pancreatic cancer, and especially gliomas. Glioma has the most consistent negative correlation with these tumors, and some studies have further suggested that higher IgE levels may confer a survival benefit[29,33,34]. This is also consistent with the findings of this meta-analysis. Conversely, certain allergic mediators may have pro-tumorigenic effects in specific contexts. For instance, histamine has been shown to impair the efficacy of cancer immunotherapy by activating histamine H1 receptors on macrophages, which may dampen antitumor immune responses. A clinical study found that melanoma and lung cancer patients receiving H1 antihistamines during anti-PD-1/PD-L1 therapy experienced significantly improved overall survival compared to those who did not. A similar trend of reduced mortality was observed in breast and colon cancer patients under the same treatment conditions[35]. These findings, however, appear to contradict our meta-analysis results, which showed a negative association between allergy and such cancer, suggesting that the relationship between allergy and cancer may be context-dependent and influenced by cancer type, immune milieu, and specific allergic pathways.

Collectively, these findings reflect the multifaceted and context-dependent immunological consequences of allergic inflammation. Activated immune cells such as M1 macrophages[36], dendritic cells (DCs)[37], NK cells[38], Th1 cells[39], follicular T helper cells (TFH)[40], CD8 + T cells, B lymphocytes[41], and eosinophils[37] typically have an inhibitory effect on tumorigenesis, while tolerogenic cells like M2 macrophages[36], tolerogenic DCs, and T and B regulatory lymphocytes[39] tend to support carcinogenesis. Moreover, Mast cells exhibit dual roles, balancing immune tolerance with tumor inhibition[42]. Additionally, immune molecules such as IgE and CCL5 chemokines are associated with anti-cancer effects, whereas IgG4, IL-10, TGF-β, lipocalin-2, and CCL1 chemokines tend to promote cancer progression[43]. Notably, these immune cells and molecules are also integral to allergic reactions, further complicating the understanding of how allergic responses influence tumorigenesis and progression. For instance, macrophages, DCs, B cells, TFH13 cells, mast cells, and eosinophils are all critical players in allergy pathophysiology, with their roles extending into immune activation, antigen presentation, and cytokine secretion[43–45]. Taken together, the association between allergy and cancer risk, progression, or mortality is not consistent across all cancer types. These seemingly contradictory theories emphasize the relevance of the allergy-cancer relationship and highlight the urgent need for mechanistic studies to elucidate its underlying causal relationships and biological pathways.

In summary, this study synthesizes existing evidence to reveal potential inverse associations between allergies and certain cancer types. While our findings provide preliminary insights into the possible protective effects of allergies against specific cancers, the overall certainty of evidence, evaluated using the GRADE framework, was rated as low to very low. Specifically, the associations observed for lung cancer, leukemia, and gastrointestinal cancers were supported by very low-certainty evidence. This was primarily due to the observational design of all included studies, which limits causal inference. Additionally, substantial heterogeneity across studies, the potential for publication bias, and the presence of residual confounding further reduce the robustness of the findings. Therefore, these associations should be interpreted with caution and warrant confirmation through large-scale prospective cohort studies, randomized controlled trials, and mechanistic in vivo experiments. Despite the above-mentioned limitations, we believe that this study not only provides important insights into the relationship between allergies and cancer, but also lays the foundation for exploring the underlying immunological mechanisms. Future research should focus on addressing these limitations and deepening our understanding of how allergies may influence cancer development, progression, and mortality.

Data availability

The data used in this study are available upon reasonable request by contacting the corresponding author.

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Author contributions

S.G and X.F performed the literature search, study inclusion, and data extraction for the included studies. S.G

and X.F, W.L. participated in the concept, design, statistical analysis, and manuscript writing. J.B. and E.M. supervised the study process and reviewed the data. H.J. provided critical guidance on the methodology and interpretation of the results. All authors read and approved the final manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

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