

Agent Orange and Head and Neck Cancer: a Systematic Review and Meta-Analysis

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BACKGROUND

- The Vietnam War spanned two decades and resulted in millions of Americans being stationed in southeast Asia. According to the United States department of Veterans Affairs (VA), over 6,000,000 of those veterans are still living and reside in the US. Herbicides were widely used in Vietnam to eliminate underbrush and destroy crops used by the Vietnamese forces.¹
- Agent Orange, the most frequently used herbicide in the Vietnam War,^{2,3} has been a hot topic of medical investigation for more than 45 years.⁴⁻⁷
- Agent Orange contains a mixture of chemicals, but in Vietnam, it was highly contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), the most dangerous dioxin to humans.²
- While the mechanism is not well understood, Agent Orange has been linked to several cancers.^{5,8,9} A recent database study in 2020 found it to be associated with oropharyngeal, nasopharyngeal, and laryngeal cancers.¹⁰ Head and neck cancer (HNC) has long been associated with exposures (e.g., tobacco and alcohol use, human papillomavirus),¹¹⁻¹³ but the link to Agent Orange is a relatively recent development; this is not unexpected given the latency period for exposure-related cancers.
- HNC, encompassing neoplasms of the head and neck region excluding skin, brain, skull-base, and endocrine cancers, comprises up to 4% of all cancers within the US.^{14,15} Mortality rates vary widely based on subsite and stage, but 5-year survival rates range from just over 30% to almost 90% depending on subsite, risk factors, stage, etc.¹¹
- Importantly, HNC carries considerable morbidity, often secondary to oncologic resection, radiation, chemotherapy, or a combination of the three.
- We performed this review to further investigate the association between Agent Orange exposure and HNC.

METHODS

- This study was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Individual search strategies are detailed in supplemental data.
- Studies reporting rates of HNC in patients based on exposure to agent orange were included. Abstracts were screened separately by two reviewers (NPM and KAD) to identify relevant articles.
- HNC outcomes and demographic data were extracted independently by two reviewers (NPM and KAD). Outcomes were extracted by HNC subsite when available.
- Meta-Analysis of continuous measures was performed using Comprehensive Meta-Analysis version 4 (Biostat Inc, Englewood, NJ, USA). Meta-analysis of proportions and comparison of proportions were performed using MedCalc (MedCalc Software, Ostend, Belgium)

RESULTS

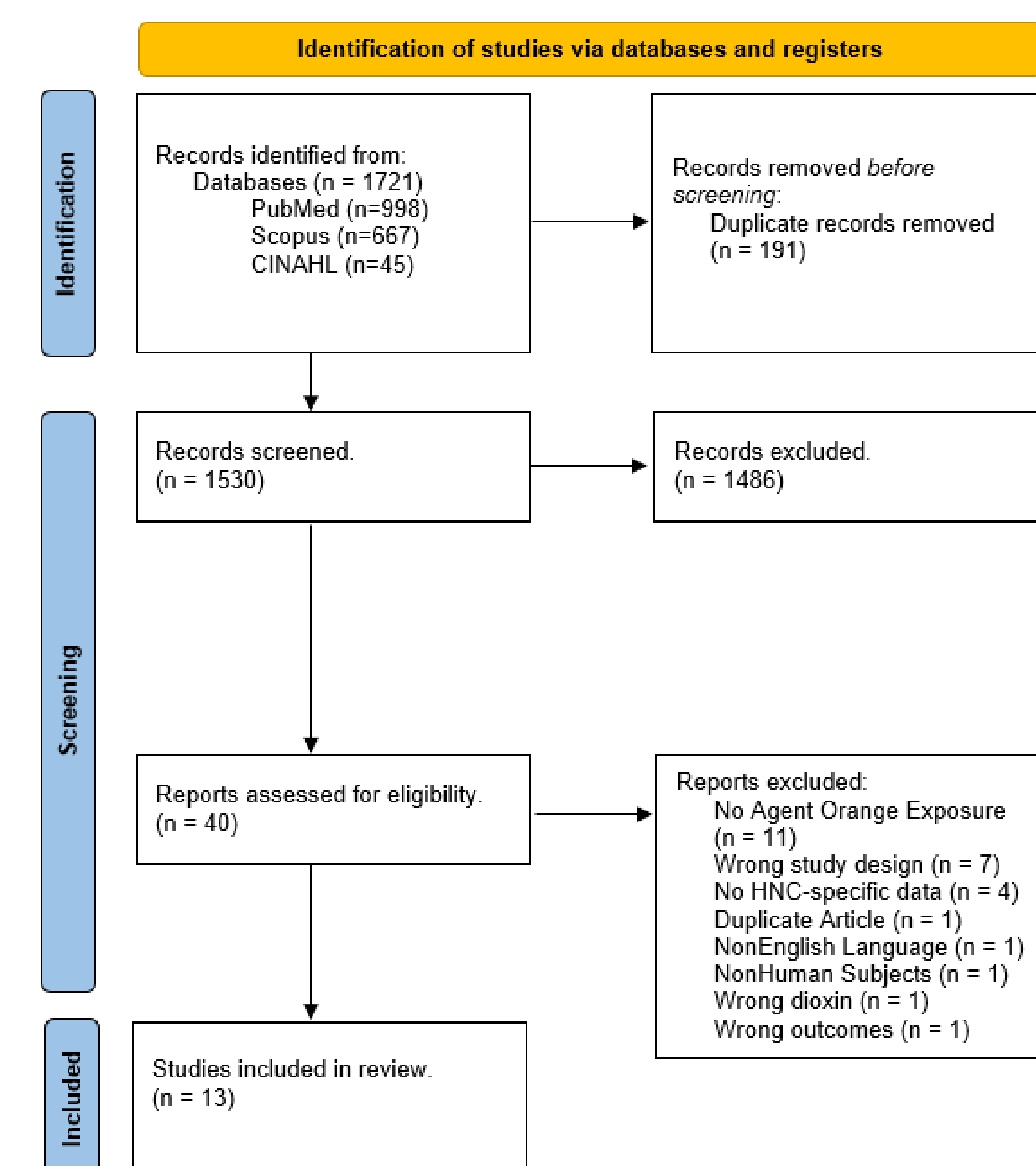


Figure 1: PRISMA diagram outlining the systematic review process

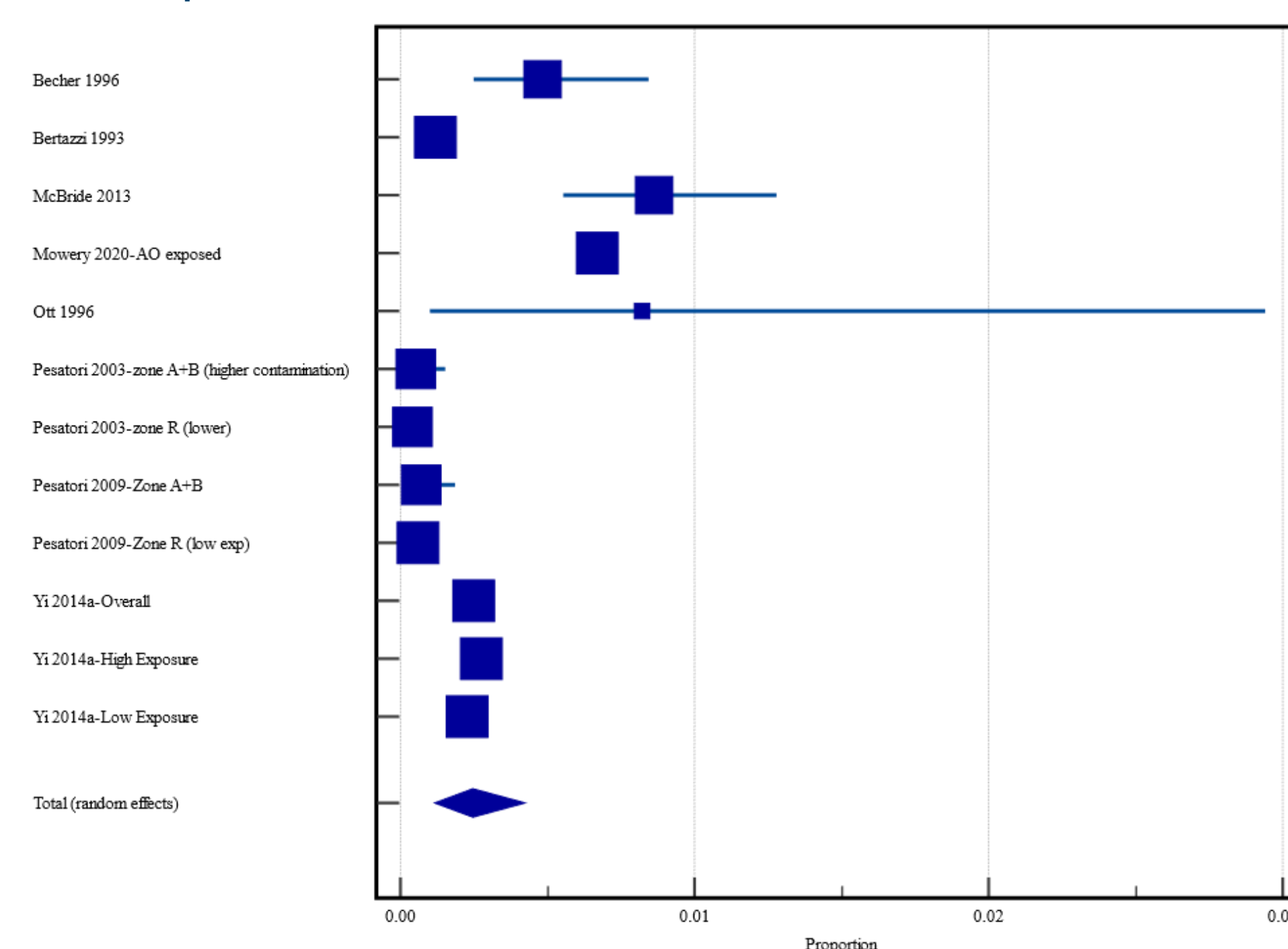


Figure 2: Forest Plot of Meta-Proportions of HNC of all subsites incidence with exposure to Agent Orange.

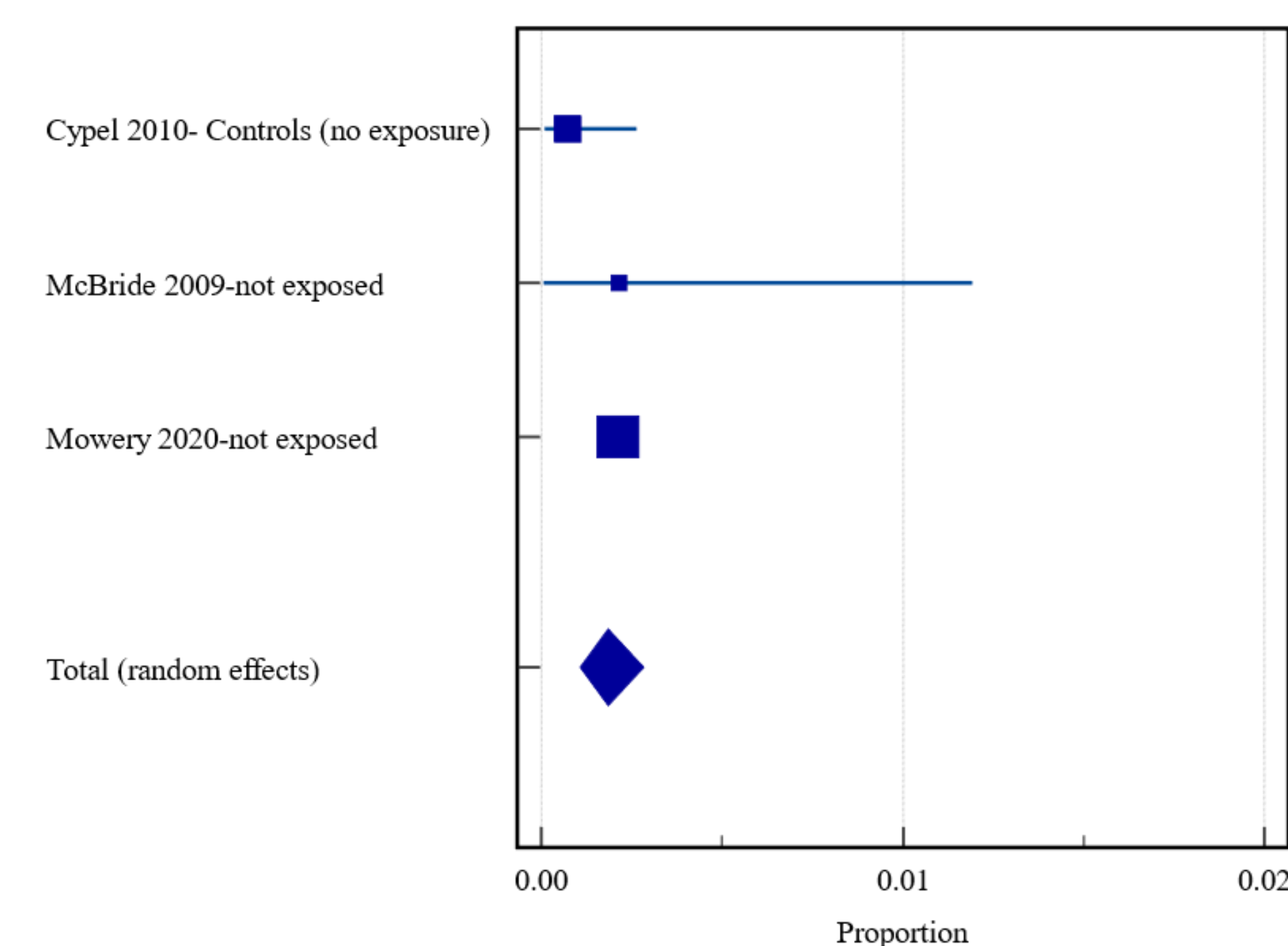


Figure 3: Forest Plot of Meta-Proportions of HNC of all subsites in controls.

RESULTS

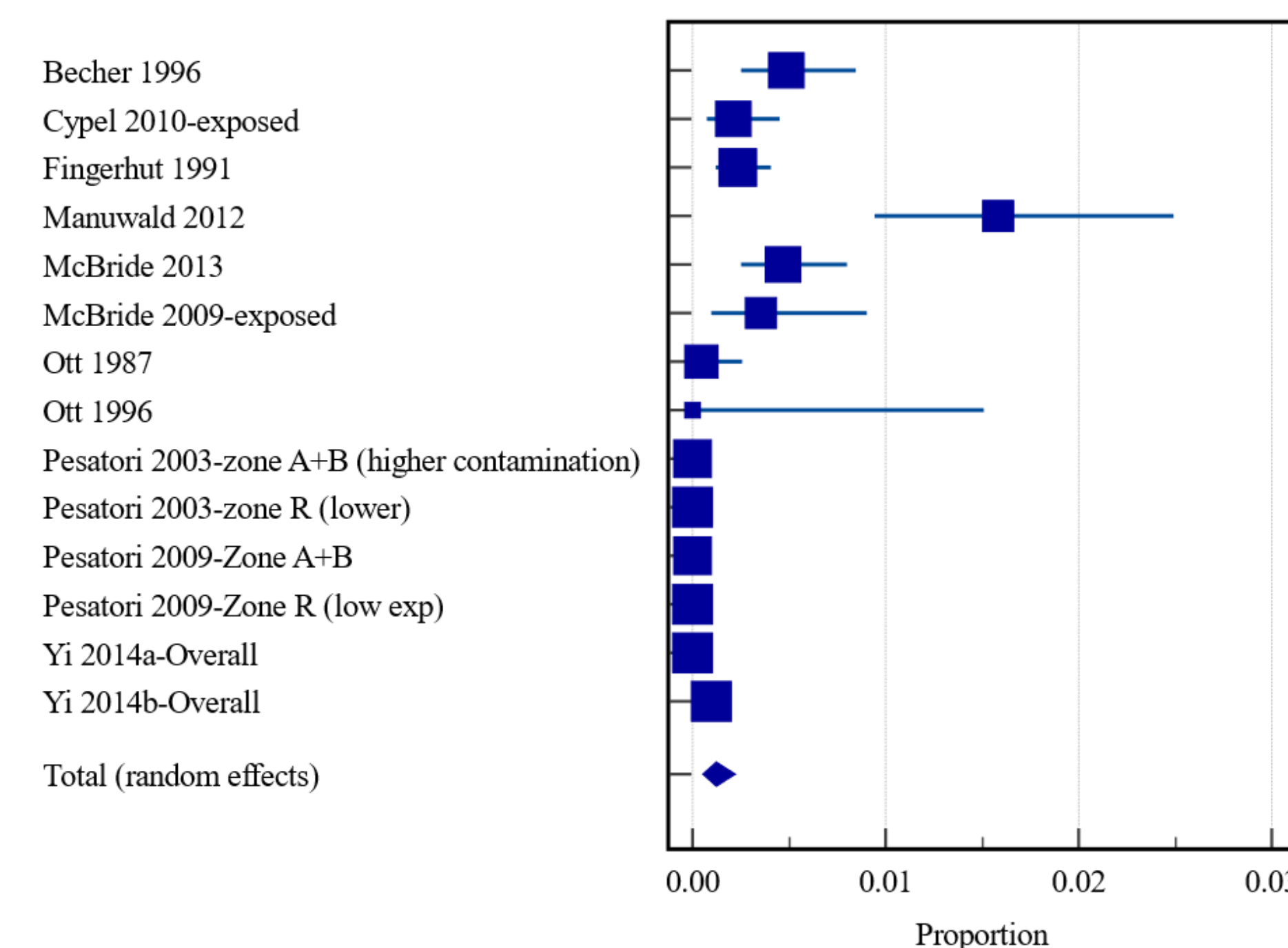


Figure 4: Forest Plot of Meta-Proportions of HNC of all subsites mortality with exposure to Agent Orange.

Table 1: Meta-Proportions of HNC incidence following exposure to Agent Orange

Site	Number of Subjects (n)	Incidence (%)	95% Confidence Interval (%)
HNC of All Sites	2,441,409	0.25	0.12 – 0.42
Oral Cavity	2,365,689	0.10	0.04 – 0.18
Oropharynx	2,328,791	0.05	0.00 – 0.14
Hypopharynx	2,326,312	0.02	0.02 – 0.02
Larynx	2,331,574	0.12	0.07 – 0.18
Nasopharynx	2,362,967	0.03	0.02 – 0.04
Salivary	2,326,312	0.01	0.00 – 0.04

Table 2: Meta-Proportions of HNC incidence in controls without documented exposure to Agent Orange

Site	Number of Subjects (n)	Incidence (%)	95% Confidence Interval (%)
HNC of All Sites	6,915,363	0.21	0.21 – 0.21
Oropharynx	6,914,898	0.13	0.13 – 0.13
Larynx	6,912,626	0.16	0.16 – 0.16

Table 3: Comparison of proportions of incidence between exposed individuals and controls

Site	Difference (%)	95% Confidence Interval (%)	p Value
HNC of All Sites	0.06	0.04 – 0.08	<0.0001
Oropharynx	0.08	0.79 – 0.87	<0.0001
Larynx	0.04	0.04 – 0.05	<0.0001

INCLUDED STUDIES AND DEMOGRAPHICS

A total of 13 studies were included in our meta-analysis. A PRISMA diagram outlining our search is shown in Figure 1. These studies were published from 1987 to 2020 and were conducted in 5 different countries. Descriptions of the individual studies and selected patient characteristics are displayed in supplemental data. A funnel plot (Supplemental Data) with Egger's test (2.7, 95%CI: -2.3 to 7.7, p = 0.2631) demonstrated all studies lie within the funnel with little asymmetry, suggesting little publication bias. There were a total of 8,890,769 patients included in our meta-analysis. Of 160,449 with reported race, 83% were white, 9.1% were Black. The most common risk of bias was that of selecting study participants for inclusion in the study or analysis (Figure 5).

Table 4: Meta-Proportions of HNC mortality with exposure to Agent Orange

Site	Number of Subjects (n)	Mortality (%)	95% Confidence Interval (%)
HNC of All Sites	451,833	0.12	0.05 – 0.22
Oral Cavity	190,720	0.07	0.02 – 0.15
Oropharynx	12,793	0.25	0.08 – 0.52
Larynx	373,982	0.07	0.05 – 0.10

Table 5: Standardized Mortality Ratios

Site	Point Estimate	Standard Error	I ² (%)*	p Value
HNC of All Sites	32.35	15.96	100	0.04
Oral Cavity and Oropharynx*	1.60	0.66	98.9	0.02
Oropharynx*	44.76	43.25	100	0.30
Larynx	54.75	50.07	100	0.27

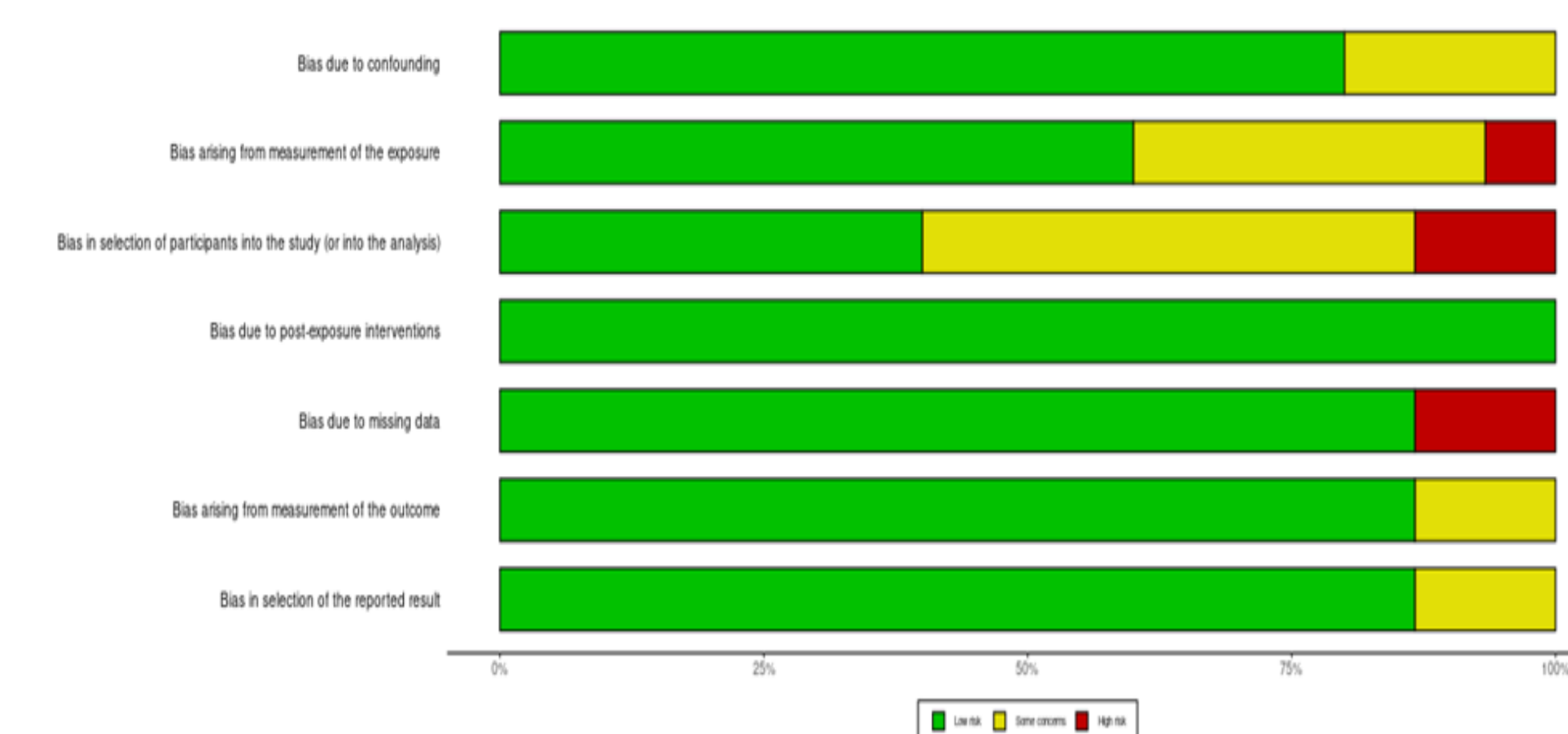


Figure 5: Summary of ROBINS-E risk of bias assessment

CONCLUSIONS

In a powerful study including almost 9 million included patients, our findings suggest that HNC is more common in those exposed to Agent Orange than those who are not, with the most common subsites including oral cavity and larynx. Additionally, we found that individuals exposed to Agent Orange were more likely to die from HNC. Further investigation is warranted to evaluate subsite-specific incidence and outcomes given the limitations of our study design.

REFERENCES and SUPPLEMENTAL DATA

PLEASE SCAN QR CODE FOR REFERENCES AND SUPPLEMENTAL DATA

