Wood Smoke: Protocol for Evaluating Human Cancer Studies

Report on Carcinogens Monographs

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National Institute of Environmental Health Sciences
Your Environment. Your Health.

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1. Evaluating Human Cancer Studies of Exposure to Wood Smoke

Background and Objectives

Background

Wood smoke is a complex mixture consisting of particulate matter, gasses, and hundreds of different chemicals, including U.S. EPA hazardous pollutants and carcinogens (e.g., PAHs, benzene). In the United States, wood smoke is emitted primarily from wood stoves, fireplaces, and boilers used for heating; however, some restaurants use wood for cooking. Over 2 million U.S. households use wood as their primary heating fuel. Biomass and coal together comprise solid fuel. Biomass fuels are considered fuels such as wood, charcoal, animal dung, and agricultural residues. Recently, concerns about woodstove use in the United States have attracted media attention (Kruzman 2022). Wildfires are increasing in severity and numbers due to climate change.

IARC (2006, published in the 2010 monograph) has characterized indoor emissions from household combustion of biomass fuel (primary wood) as *probably carcinogenic to humans* (2A). The IARC working group concluded there was limited evidence for a causal association with lung cancer.

Because exposure to wood smoke poses a potential carcinogenic hazard for people living in the United States, NIEHS is conducting a cancer hazard evaluation of wood smoke for potential listing in the Report on Carcinogens, a congressionally mandated, science-based public health document. Our review focuses on wood smoke because wood, but not other biomass fuels, is used widely in the United States. The overall cancer hazard evaluation will (1) assess and integrate the evidence from human and animal cancer studies and mechanistic studies, and (2) apply the RoC listing criteria to the assessment to reach a listing recommendation. A separate evaluation will be conducted for exposure to wildfires if the database is adequate. This document is the protocol for the cancer hazard evaluation of the human epidemiology studies.

Overall Objective and Aims

Overall Objective

To reach conclusions about the level of evidence of the carcinogenicity to wood smoke provided by human epidemiology studies based on the RoC listing criteria (see Section 1.6)

Specific aims and key questions

1. To conduct a systematic review of several cancer outcomes and exposure to wood smoke. Since the 2006 IARC evaluation, there have been over 20 human cancer studies published, including a larger database of cancers other than lung.
    - What are the study characteristics and key issues to consider in the evaluation?

    - Which cancer outcomes have an adequate database for review?
    - How is wood smoke exposure characterized (e.g., proxies such as wood use or wood smoke components), measured (e.g., assessment methods), or quantified (e.g., metrics) in the studies?
    - What are the key scientific issues?
  - How informative (e.g., risk of bias, study sensitivity) are the studies for the evaluation?
    - What are the potential confounders and effect modifiers for cancer risk for the tumor sites of interest in these studies?
    - What are the potential biases, the impact of the biases, and study sensitivity of the study's findings?
  - What is the level of evidence for carcinogenicity for each cancer outcome?
    - Is there a credible association between wood smoke and cancer across studies?
    - If so, can the relationship between each cancer outcome and wood smoke be explained by chance, bias, or confounding?
2. To conduct a meta-analysis of studies of lung cancer, which has the largest database of studies. The meta-analysis can inform the hazard conclusion, provide input on potential sources of heterogeneity, and potentially be used to calculate a population attributable risk.
  - What is the overall quantitative risk (magnitude and precision) for lung cancer from exposure to wood smoke?
  - What are potential sources of heterogeneity or issues to evaluate in subgroup analysis?

Protocol contents and evaluation process

This document describes the (1) completed scoping and problem formulation steps used to develop the framework (Section 1.1) and (2) proposed methods that will be used to conduct the cancer hazard evaluation, including the study evaluation (Section 1.2) and evidence integration (Section 1.3). Section 1.4 describes data extraction methods and reporting elements. The methods are based on applying the specific issues relevant to wood smoke to the procedures outlined in the RoC handbook. The roles of the researchers and the literature search terms are described in Appendix A.

Figure 1.1 provides a schematic of how the protocol (Step 2) fits into the cancer hazard evaluation process. The protocol is informed by the scoping and problem formulation (i.e., developing the framework) done in Step 1, and the methods in the protocol are then used to conduct the cancer hazard evaluation and write the RoC monograph (Step 3). Note that Steps 1 and 2 are iterative.

Figure 1.1. Cancer hazard evaluation process

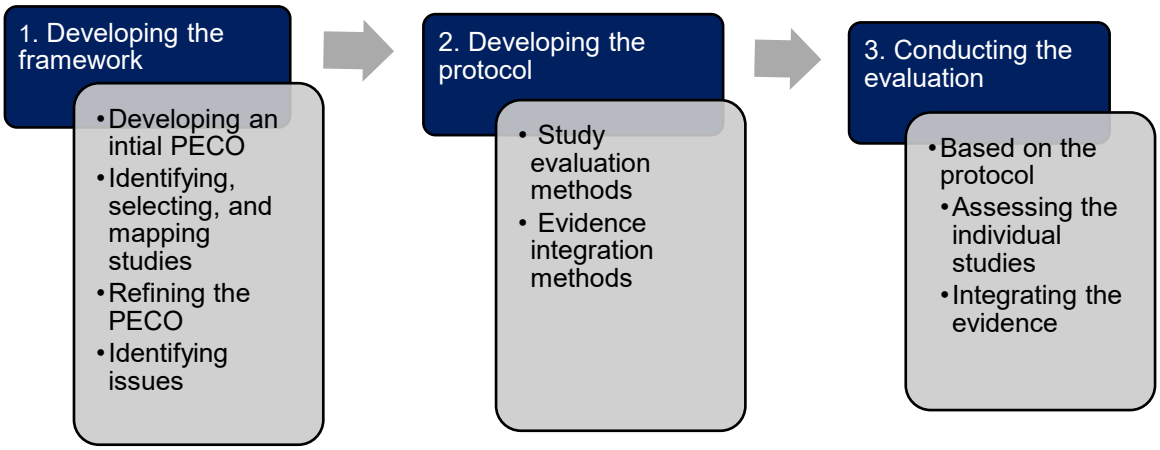


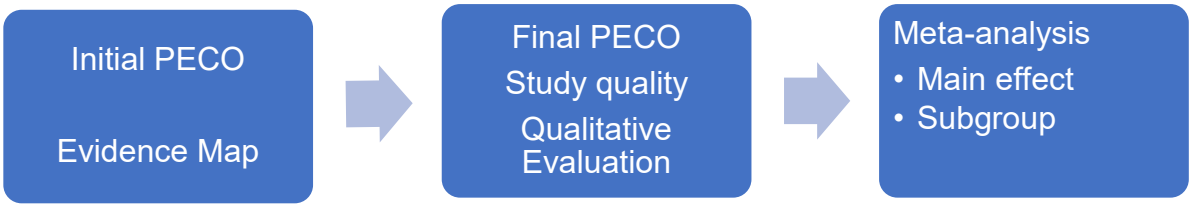
Figure 1.1 depicts the cancer hazard evaluation process. Scoping, problem formulation, and evidence mapping lead to the development of the framework (Step 1), which includes the overall objective and aims, PECO statements (i.e., body of evidence) to address the study objective(s), and identification of hazard specific issues to be explored in the evaluation. This step has been completed and the findings are reported in Section 1.1. This step also informed the methods, i.e., the protocol (Step 2) for conducting the cancer hazard evaluation (Step 3), the results of which will be captured in the RoC monograph. The methods focus on study evaluation (risk of bias and study sensitivity, Section 1.2) and evidence integration (Section 1.3). **PECO** = **P**opulation, **E**xposure, **C**omparison group, and **O**utcome.

1.1. Developing the Framework

Preliminary scoping and problem formulation activities informed the evaluation framework for the entire cancer hazard evaluation for wood smoke, which includes the evaluation of human cancer epidemiology studies using the methods described in this protocol, as well as evaluation of animal cancer studies and mechanistic studies in humans, animals, and cells (methods described in separate protocols).

These activities informed the research questions for human epidemiology studies (e.g., Specific Aim 1: overall objective) and the body of evidence to answer the research questions. For human studies, the body of evidence is defined by the PECO (**P**opulation, **E**xposure, **C**omparison Group, **O**utcome) Statements. The initial PECO was used to search and select the literature for the wood smoke database (see Figure 1.2). Based on evidence mapping and a review of the literature database, we further refined the initial PECO to develop a final PECO for studies to be included in the qualitative cancer hazard evaluation. In addition, we refined the final PECO for studies to be combined for a meta-analysis (Specific Aim 2). Details are discussed in Sections 1.1.1 and 1.1.2.

Figure 1.2 PECO statements



Population	All (no restrictions)
Exposure	Exposure to wood smoke or wildfires
Comparison	No or lower exposure to wood smoke or wildfires
Outcome	Cancer (any type)

Population	All (no restrictions)
Exposure	Use wood (or combination of wood and biomass[a] but not coal) for cooking/ heating
Comparison	No or lower exposure to wood for cooking/ heating and not using biomass or coal for cooking/ heating
Outcome	Lung, nasopharyngeal, esophageal cancer

Population	All (no restrictions)
Exposure	Use wood (not in combination with other fuels) for cooking/heating**
Comparison	No or low exposure to wood and not using biomass or coal for heating/ cooking
Outcome	Lung cancer

[a]Includes charcoal
** studies with wood in combination with other biomass fuels will be evaluated in sensitivity analysis.

Figure 1.2 provides the criteria for the initial, final, and meta-analysis PECO statements and associated products (e.g., evidence map, qualitative evaluation). PECO = Population, Exposure, Comparison group and Outcome.

1.1.1. Identifying and Selecting the Literature

Citation databases, including PubMed, Scopus, and Web of Science, were searched for human cancer studies and exposure to wood smoke or wildfire by combining search terms for exposure to wood smoke or wildfire (see Appendix A), cancer (see RoC Handbook), and epidemiology studies (see RoC Handbook) using the procedures outlined in the RoC Handbook. We also searched cited references, the Interagency for Cancer Research (IARC) Monograph on Household Use of Solid Fuels and High Temperature Frying (2010), and conducted a full text search of a PDF library of occupational case-control studies. We did not search for studies of firefighters in general because exposure to firefighters is not specific for wood smoke. However, studies specific for wetland or wildland firefighters would be identified by the terms (wetland* and (fire*) OR (wildland* and fire*) or wildfire*. We may miss studies of firefighters that report specific analysis for wildfire studies and do not mention that in the keywords, title, and abstract and that are not part of our database of occupational case-control studies.

Search results were processed in Endnote and imported into a content management system [e.g., Health Assessment Workplace Collaborative (HAWC)] software to select relevant literature (Shapiro et al. 2018). All search results relevant to a particular topic or

exposure were combined in HAWC; numbers of cited references for epidemiological studies are not tracked separately.

Studies were initially included in the evaluation if they met any of the following inclusion criteria when conducting a Level 1 (title and abstract) and a subsequent Level 2 (full text) screening reviews:

- Primary studies (analytical epidemiologic studies or pooled analyses of multiple studies) meeting the initial PECO statement (see Figure 1.2). Other criteria or details are listed below
    - Study clearly indicates exposure to wildfire, or combustion of wood (including in combination with other biomass fuels such as charcoal, animal dung, grass and straw). Charcoal is made primarily from wood, especially in low- and middle-income countries (LMICs) where most of the studies were conducted. Studies of coal or of biomass not mentioning wood were excluded. We recognize that non-wood biomass may be somewhat similar to wood however some mechanistic studies have shown differences in smoke composition and biological effects (Marchetti et al. 2019; Sussan et al. 2014; Verma et al. 2021).
    - Study reports a risk estimate (or information to calculate a risk estimate) for cancer.
- Studies providing supporting information for topics relevant to the evaluation of the human epidemiologic evidence. These include, but are not limited to, qualitative reviews or letters to the editor, and information on co-exposures or potential confounders.
- Meta-analyses, and systematic and narrative reviews.

1.1.2. Mapping the Evidence

Citations in HAWC were tagged by cancer type and type of study (primary epidemiology studies versus supporting studies). We identified three studies of Australian firefighters (male paid and volunteer firefighters, and female firefighters) that reported risk estimates for landscape fire incidents for all cancers (Glass et al. 2019) or specific cancers (Glass et al. 2017; Glass et al. 2016). However, it seems likely that the same firefighters responded to non-landscape related incidents (i.e., the risk estimate is not specific for wet land firefighters). No additional cancer epidemiological studies of exposure specific to wildfires were identified. If new studies specific for wildfires are identified, we will conduct a cancer hazard evaluation if the database is adequate.

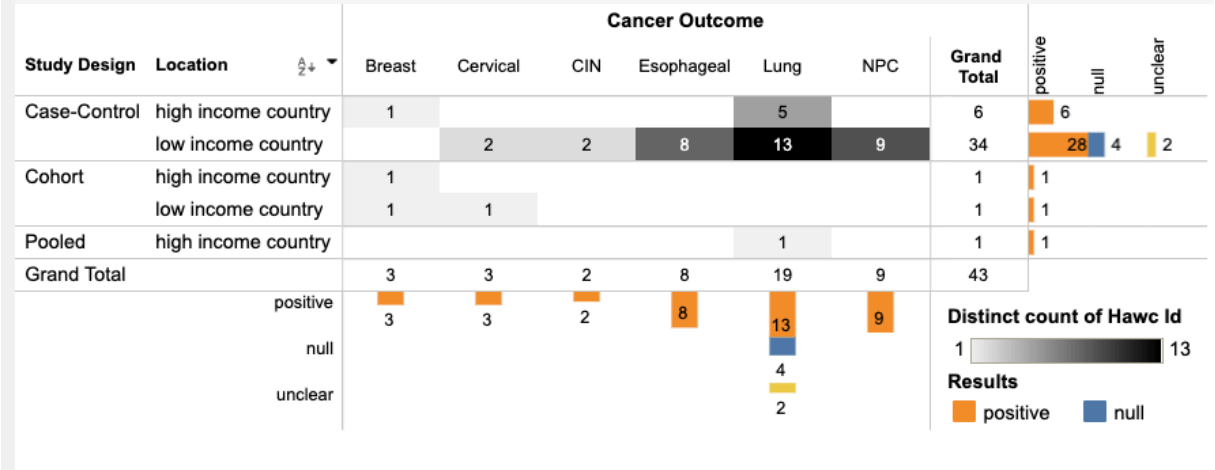
Citations and related information for cancer types and wood smoke with at least five studies [lung, esophageal, and nasopharyngeal cancer (NPC)] in addition to citations for breast cancer, cervical cancer, and cervical intraepithelial neoplasia (CIN), were downloaded from HAWC to MS Excel (N=44). Data were extracted from each of the 44 studies related to specific issues for each cancer outcome and wood smoke. The pooled analysis by Hosgood et al. (2010) includes an IARC multi-center case control study conducted in Central and Eastern Europe (Lissowska et al. 2005), therefore it is not counted as an independent study population, reducing the number of studies meeting the

initial PECO to 43. Separate publications reporting results from the same study population on the same outcome were considered a single study. Of note, there were three pairs of studies with potentially overlapping study populations (García-Sancho et al. 2012a; García-Sancho et al. 2012b; Ko et al. 1997; Lee et al. 2001; Phukan et al. 2014; Saikia et al. 2014). While no authors mentioned overlap with another study, the possibility was inferred from overlapping, but not identical enrollment dates, and cases/controls being drawn from similar but not identical geographic areas or hospitals. The overlap is not expected to be substantial, so at this stage, the studies will be considered individual studies while recognizing the potential overlap. We were unable to get author clarifications on overlap for any of these studies; however, we will adjust our approach if we receive additional information.

Initial PECO

The findings for the 43 studies, one of which had risk estimates for two different cancer types, are visualized in a visual analytic platform (Tableau, see Human Cancer Tab and Figure 1.3a). In addition to the tumor sites visualized in Tableau, we also identified five studies that evaluated various types of head and neck cancers, and four studies on other types of cancers (not shown). Cancers that are grouped together, such as the individual sites in head and neck cancers, are often heterogeneous and may have different etiologies. Thus, we will not combine studies evaluating different head and neck cancers. No specific head and neck cancers had at least four studies.

Figure 1.3a. Evidence map: Initial PECO



One cohort study reported on breast and cervical cancer; null is defined as OR ≤ 1.

Figure 1.3a shows the evidence map of the 43 studies of the three cancer types meeting the final PECO [esophageal, lung, and nasopharyngeal cancer (NPC)], plus breast cancer, cervical cancer, and cervical intraepithelial neoplasia (CIN).

Final PECO

All studies assessed exposure to wood smoke using questionnaires/interviews on wood use for cooking, heating, or both. Based on the evidence mapping, the database was considered adequate to evaluate cancers of the esophagus, lung, and nasopharynx.

Although most studies were conducted in low- and middle-income countries (LMICs), we concluded that the database was relevant for assessing hazard for high-income populations, including the United States, because (1) some studies were conducted in high-income countries (HICs), and (2) approximately 500,000 to 600,000 low-income U.S. residents are likely exposed to levels exceeding World Health organization guidelines of 24hr average 25 µg/m^3 for PM2.5 of hazardous air pollutants from burning solid fuel (wood, coke, coal) in within their homes (Rogalsky et al. 2014), although this estimate of the U.S. at-risk population may be conservative (Noonan et al. 2015).

Review of the evidence database showed that several studies had coal use as the referent category. Because coal smoke is a carcinogen, we excluded studies with coal use as the referent in the final PECO.

Figure 1.3b. Evidence map: Final PECO

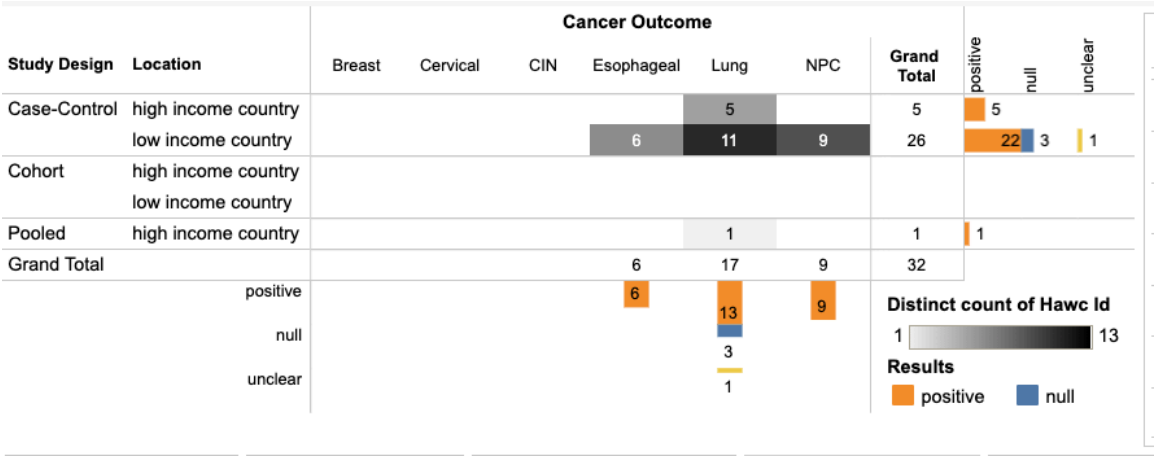


Figure 1.3b shows the evidence map filtered for the 33 studies of the three cancer types meeting the final PECO

Of the 32 studies included in the final PECO, 32 were case-control studies and one was a pooled analysis of 4 case-control studies, including a multi-center study in six countries in Central and Eastern Europe by Lissowska et al. (2005). The pooled analysis included only high-income countries (Canada, U.S., Eastern/Central Europe) in its wood smoke (wood use) analysis. In addition to evaluating ever or predominant use of wood, 16 studies provided more detailed exposure information (e.g., duration, timing of wood use). Some studies also calculated gender-specific risk estimates or were restricted to women only, while some stratified by smoking status or were restricted to non- or never-smokers. These and other factors will be systematically evaluated in the evidence integration step (see Section 1.3, Table 1.7).

Figure 1.3c. Evidence map: Exposure metrics

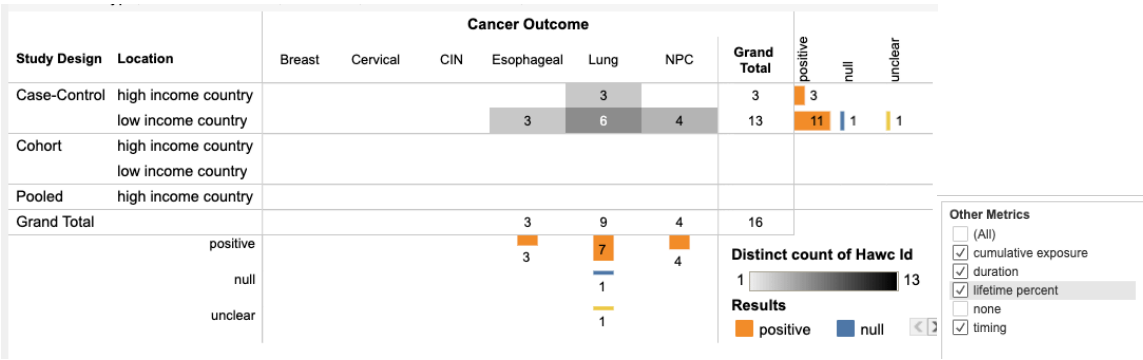


Figure 1.3c shows the evidence map filtered for 16 studies meeting the final PECO and reporting additional exposure metrics

Meta-analysis: Lung Cancer

Meta-analysis can help inform the cancer hazard conclusions and potentially be used to calculate a population attributable risk. Because the number of lung cancer studies with similar and comparable exposure assessments (i.e., questionnaire/interview assessment of wood use) was adequate, we considered it appropriate to combine them for meta-analysis (Specific Aim 2). We restricted the meta-analysis to the 11 studies specific for wood use (i.e., wood alone, not in combination with charcoal or other non-coal biomass) as this will reduce any bias in the quantitative risk estimate due to the potential carcinogenicity of other biomass. We also excluded studies where the reference group may have substantial exposure to wood albeit lower than the exposed group (e.g., the reference group was exposed to shorter duration of wood smoke, but the duration was for 20 years years).

Figure 1.3d. Evidence map: Lung Cancer Meta-analysis

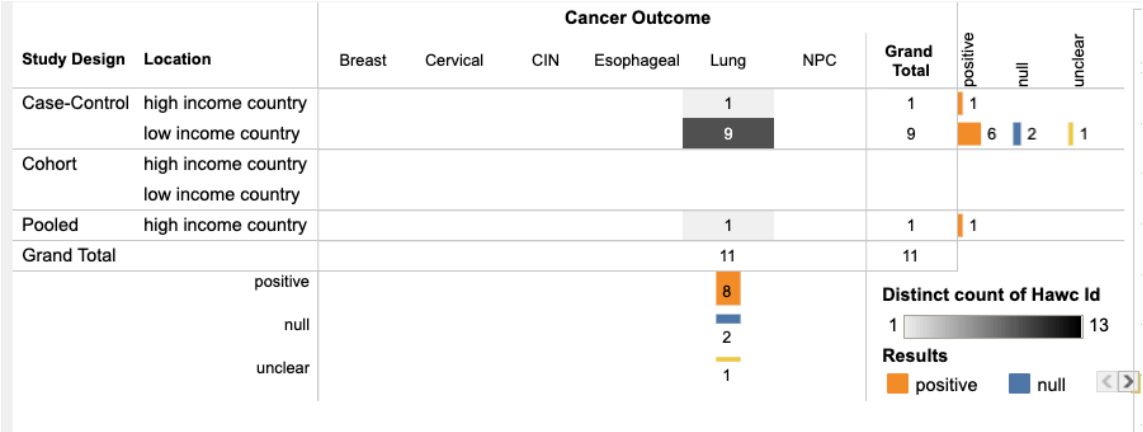


Figure 1.3d shows the evidence map filtered for the 13 studies meeting inclusion criteria for the lung cancer meta-analysis (risk of wood smoke).

1.2. Study evaluation of individual epidemiologic studies

Each primary study is systematically evaluated for its ability to inform the cancer hazard evaluation using five domains related to risk of bias – selection and attrition bias,

exposure assessment, outcome assessment, potential confounding, and analysis – and one domain related to study sensitivity [or the ability of the study to detect a true effect (Cooper et al. 2016)]. The methods are adapted from the RoC Handbook (update in progress). Reporting quality may also be noted (e.g., missing information).

The evaluation of the potential for bias (i.e., risk of bias) in each domain is captured by core questions for each domain. For each core question, a series of signaling and follow-up questions are used to address specific issues related to the core question. These questions are used to provide guidance and transparency for the domain-level judgment (options for domain-level judgements are described below). Responses to signaling and follow-up questions are then captured in the rationale for the response to the core question. These questions are meant to provide guidance, not to be a checklist. When adequate study information is available a domain-level judgment is made for the direction and distortion of each bias.

- ***No/minimal concern:*** The study characteristics being evaluated for the domain closely resemble ideal study characteristics. The potential for bias is considered minimal, recognizing the general limitations of observational studies.
- ***Some concern:*** The study design or methodologies are less than ideal for this domain. However, although there may be possible bias, these studies are generally considered informative for the cancer hazard evaluation.
- ***Moderate/major concern:*** The study design or methodologies suggests that the potential for a specific type of bias is high. However, depending on the direction and distortion of the potential bias, the study may still be informative for cancer hazard evaluation but should be viewed with caution.
- ***Critical concern:*** Distortion of bias would make the study findings unreliable for cancer hazard identification. This category is rare.
- ***No information:*** The information in the study is inadequate to evaluate the level of concern for the domain.
- ***Direction of bias:*** ↑ Away from the null or overestimate of effect; ↓ towards the null or underestimate of effect; not known (direction cannot be inferred).
- ***Magnitude of bias:*** Probably minimal, moderate, major, or unknown. In most cases this is subjective but, if available, will likely be informed by sensitivity analysis.

Our approach will be to evaluate the components of study quality separately for studies reporting on each cancer type using the questions, domain level ratings, and guidelines given below.

1.2.1. Selection and Attrition Bias

At the writing of this protocol, all the studies included in the evaluation of esophageal, lung, and nasopharyngeal cancer are case-control studies, or part of a pooled analysis of case-control studies. Cohort study guidance is included to address possible future publications.

No unique issues related to wood smoke were identified for this type of bias.

Questions and guidance

Core question: Is there a concern that selection into the study or out of the study was related to both exposure (e.g., wood smoke) and to cancer?

Table 1.1 Selection bias questions, guidance, and response options

Signaling question	Guidance	Response Options
Selection into the study: All study designs		**No/minimal concern**
Are there concerns that the selection methods, such as eligibility criteria (inclusion/exclusion) or recruitment strategies, for cases and controls or exposed and non-exposed are not adequately conducted or differ by case or exposure status?	Ideally, the wood smoke-exposed and unexposed groups or cases and controls should be similar in all respects except for exposure status (in cohort studies) or disease status (in case-control studies), and from the same underlying population. In addition, participation should not be related to both outcome and exposure status. Controls should not be diagnosed with outcomes that are potentially linked to exposure to wood smoke (e.g., respiratory illness, cardiovascular diseases, certain cancers).	Cases and controls, or exposed and non-exposed groups, were selected from the same population by similar methods and criteria. There is no evidence that selection of the participants was related to both wood smoke exposure and cancer. For case-control studies, the cases and controls are selected from the same underlying population. For cohort studies, the cohort is clearly defined (e.g., includes groups of those exposed to wood smoke and unexposed to smoke from wood, other carcinogenic biomass fuels, or coal, for a specific time period/location with no evidence that follow-up differs between the exposed and non-exposed.

Signaling question	Guidance	Response Options
Is there concern that cases and controls in a case-control study or exposed or non-exposed in a cohort are not representative of the same underlying population during a similar time period? • In case-control and cross-sectional studies, is there a concern that participation differs according to outcome status and is related to exposure status? • In cohort studies, is there concern that the health of a participant may have affected their selection into the study (e.g., the healthy worker hire effect or the healthy volunteer effect) or that the cohort was selected based on a cancer cluster, leading to underlying differences between exposed and unexposed individuals?		**Some concern** Cases and controls, or exposed and non-exposed groups, were selected by similar methods and criteria, however, there is some evidence that study selection and/or cohort attrition may be related to both exposure and outcome. **Moderate/major concern** Cases and controls, or exposed and non-exposed groups, were selected in such a manner that they are unlikely to represent the exposure distribution in the underlying population. **Critical concern** There is substantial evidence that selection or attrition of participants was clearly related to wood smoke exposure and outcome.
Selection out of the study: Cohort study Is there concern about attrition bias or incomplete follow-up? • If there is a concern, is selection out of the study related to both exposure and outcome status? Is there concern that an analysis that is conditioned on censoring is related to both exposure and outcome?	Ideally, rigorous methods should be used to ascertain case status and should not differ by wood smoke exposure status.	

Signaling question	Guidance	Response Options
All Study designs: Selection/attrition issues		
Are there analyses to control for any selection (in or out) bias or sensitivity analyses to address the extent of any bias?	Ideally, studies should conduct sensitivity analysis to estimate the extent of selection bias or control for it if methods are available (such as with the healthy worker survivor effect).	
Is there concern that selection (in or out of a study) of study participants is related to exposure and outcome status?		
If there is concern about the potential for selection or attrition bias, what is the predicted direction or distortion of the effect estimate (if there is enough information)?		

1.2.2. Exposure Measurement Error and Exposure Misclassification

One of the most important aspects of an epidemiologic study is its ability to correctly classify study participants at the individual level with respect to their exposure status. This involves several dimensions: carefully defining the exposure used in the study, knowing information about the exposure setting, selecting appropriate data collection tools and methods for using or modeling the exposure data, evaluating the quality of the exposure assessment methods, determining whether individuals can be adequately separated in terms of their level of exposure, and assessing whether knowledge of the outcome may have affected the reporting of exposure.

Questions and guidance

Core question: Is there concern that the exposure assessment did not distinguish between exposed and non-exposed people or among exposure categories at a relevant time window of exposure?

Table 1.2 Exposure measurement/misclassification bias questions, guidance, and response options

Signaling question	Guidance	Response Options
Exposure surrogate Is there a concern that the exposure proxy did not adequately represent the exposure of interest and the appropriate time window of exposure for the outcome of interest? • If yes, was this true for all exposure metrics, or a particular metric?	Ideally, studies would have measurement of wood smoke or its components over the relevant time period. All available studies assessed wood smoke exposure (exposure of interest) by a proxy, use of wood for cooking or heating. This is a reasonable surrogate; however, it does not adequately capture wood smoke level or intensity, which may be more relevant for evaluating causality. Evaluation of wood use as an adequate proxy for wood smoke exposure is population dependent. In general, wood use may be a better surrogate for LMIC than HIC as in the later, wood use includes both individuals using wood in fireplaces primarily for ambience and those who use wood for heating, possibly with older or less efficient furnaces/stoves (usually participants of lower SES).	**No/minimal concern** The exposure assessment proxy (measurement of wood smoke components) used in the study closely approximates the exposure of interest. Alternatively, the study used a proxy (such as wood use) that has been validated with exposure measurements and/or has extensive exposure questionnaire information. Exposure groups are adequately separated. Any measurement error is non-differential and small in relation to between-individual variation compared to differences between groups.
	Information on ventilation may be informative for how well wood use approximates wood smoke exposure. Exposure misclassification of wood smoke because of using wood use is likely to be non-differential and bias towards the null.	**Some concern** Study may use a proxy such as self-reported wood use and collects extensive exposure information allowing for good discrimination between exposed and non-exposed, and potentially between exposure categories, and the study characterizes multiple metrics of wood use, as well as providing categories for exposure to other sources of fuel commonly used in the study population (e.g., coal). Any measurement error is non-differential.

Signaling question	Guidance	Response Options
Exposure measurement Is there concern about measurement error of the proxy or exposure of interest? Is there concern about the use of the collected data to classify exposure groups?	As of this report, no validated instruments are in use for assessing exposure to wood smoke. All studies use categorical exposure data and thus the studies may still be able to distinguish between exposed (e.g., ever, predominant) and unexposed groups with some non-differential classification. Given the wide exposure range possible for 'ever wood use', studies that categorize wood use as 'predominant use' are likely to be more informative than those that use 'ever'.	**Moderate/major concern** The exposure proxy (wood use) does not capture the exposure (wood smoke exposure) well or the exposure assessment is not extensive enough to be confident that exposed and non-exposed, and/or exposure categories, do not overlap somewhat. Minimal additional exposure metrics are available. Nonetheless, it is evident that the exposed are, on average, more highly exposed to wood smoke than the 'unexposed'. There is a possibility of differential recall bias, but it is unlikely to be substantial.
If yes to either, is there concern that measurement error resulted in inadequate separation of groups with respect to exposure? • Did any misclassification vary by exposure category (such as non-exposed, high and low exposure) Is there concern that the exposure classification did not capture the variability of exposure?	Ideally, participants would provide extensive enough information so that additional exposure metrics could be examined [e.g., duration of wood use, exposure timing (measured via age at exposure), etc.] from all sources of wood smoke exposure (e.g., cooking and heating or the source most relevant for the population). These studies may be better able to differentiate between the most highly exposed from those with inconsequential exposure. They should receive higher assessment ratings. Across studies, definitions of wood use for cooking and/or heating should be similar; thus, exposure categories of wood use that include non-wood biomass such as straw, dung, or charcoal (either implicitly or explicitly) would increase non-differential misclassification of exposure, unless the proportion is known to be very small.	**Critical concern** Exposure assessment is not at the individual level and/or the exposure assessment proxy does not approximate the exposure of interest and there is strong evidence that it is unable to differentiate exposed and unexposed participants. No additional exposure metrics. Differential recall bias is clearly present.

Signaling question	Guidance	Response Options
	In LMICs there is a clear trend over time for fuel use to change from solid biomass fuels to more modern non-solid fuels as availability and resources allow. Consequently, for current/recent wood use, the non-exposed group may have had past exposure to wood smoke, which would bias the results toward the null.	
Observation and differential recall bias Is there concern that knowledge of the outcome (e.g., observation or recall bias) may be differential and potentially bias the exposure assessment (away from the null)?	There may be differential recall bias if cases remember wood smoke differently than controls due to prior respiratory conditions linked to wood smoke exposure or intervention studies. However, this may not be likely in LMICs where awareness of the potential carcinogenicity of wood smoke may be low. There is less concern for differential recall bias in (1) studies using records such as residential history, or (2) studies finding the risk estimate differs by cancer type or an effect modifier. Blinding interviewers / assessors to disease status reduces the potential for observer bias, which can be differential; however, that is often difficult to do in case-control studies.	
Is there concern that presence of the outcome (e.g., reverse causality) may potentially bias the exposure assessment?	"Reverse causality" is not a concern in wood smoke studies.	
Is any misclassification differential or nondifferential, and what is the predicted direction or distortion of the effect estimate (if there is adequate information)?	Non-differential exposure misclassification most likely biases towards the null and is most likely present in all studies. Differential recall bias is not expected to play a role in hospital-based case control studies and is expected to be minor in population-based studies in LMIC.	

1.2.3. Outcome misclassification

Assessment of the potential for bias (i.e., risk of bias) due to measurement error or other outcome misclassification types considers (1) how well the study outcome actually represents the outcome of interest, (2) the accuracy of the outcome measurement methods, and (3) the potential for observation bias. The evaluation of follow-up length is usually considered in the assessment of study sensitivity.

Relevant cancer statistics

Incidence and mortality rates and 5-year survival for the major cancer sites of interest for wood smoke – lung, esophagus, and nasopharynx – are presented below.

Lung cancer

Globally, the highest age-adjusted lung cancer incidence rates are among males in Micronesia/Polynesia, Eastern Europe, and Eastern Asia, with similarly high incidence in the United States. The highest rates among women are in North America, Northern and Western Europe, and Eastern Asia at about two-thirds to one-half the highest rates in men. Because of short 5-year survival rates even in high-income countries, lung cancer mortality rates are generally similar to incidence rates (Bray et al. 2018), suggesting that either incidence or mortality data would be informative.

Considering the study populations within our wood smoke and lung cancer database, we examined lung cancer incidence rates per 100,000 (age-standardized to the world population, Globocan 2020 projections) in relevant high- and low- and middle-income countries (HICs and LMICs) and found that HICs had generally higher lung cancer incidence rates than LMICs with the notable exception of China (which has high smoking rates). For example, incidence rates for several HICs included in the wood smoke database were Japan (32.1), Canada (28.9), and Poland (36.2). Relevant LMICs include China (34.8), India (5.4), and Mexico (5.3). It should be noted that cancer registries in many LMICs have poor population coverage, and/or inaccurate reporting, which may contribute to differences in incidence (Bray et al. 2014; Torre et al. 2016).

In the United States 2014-2018 SEER data, the age-adjusted annual incidence of lung cancer was 53.1 per 100,000 per year (men: 60.1, women: 47.9), age-adjusted annual mortality rate (2015-2019 data) was 36.7 per 100,000 per year, and 5-year relative survival was 21.7% (2011-2017 data).

Esophageal cancer

Internationally, the highest esophageal cancer incidence rates (age-adjusted, per 100,000) in both males and females are in Eastern Asia (men: 17.9, women: 6.8); Southern Africa (men: 11.1, women: 5.0), and Eastern Africa (men: 9.7, women: 7.1). Esophageal cancer is usually two to three times more common in males than in females, although more extreme differences are observed in some regions (Bray et al. 2018).

The highest mortality rates among countries with available data are in Kazakhstan (12.8/100,000 and 6.3/100,000 males and females, respectively) and South Africa (15.3/100,000 and 6.2/100,000 males and females, respectively).

In the U.S., the 5-year survival for esophageal cancer is 19.9%. As with lung cancer, this low survival rate in a high-income country suggests that mortality data may serve as a reasonable proxy for esophageal cancer incidence.

Nasopharyngeal cancer

Nasopharyngeal cancer is relatively common in Southeast Asia with Brunei, Maldives, Singapore, Indonesia and Malaysia having the top 5 highest rates. Incidence rates in these countries range from 6.3 to 9.9 per 100,000 persons (9.5 to 12.7 per 100,000 in men and 2.8 to 6.9 per 100,000 in women). Nasopharyngeal cancer has a moderate 5-year survival rate (60.1%,), suggesting that using incidence data for cancer hazard assessment is preferable, as some cases with longer survival and later death would be missed if mortality data were used.

Questions and guidance

Core question: Is there a concern that the outcome measure does not reliably distinguish between the presence or absence of the cancer under study?

Table 1.3 Outcome misclassification questions, guidance, and response options

Signaling question	Guidance	Response Options
Is there concern that the method of measuring outcome did not represent the outcome of interest? If mortality data are used, do they adequately reflect incidence?	Because survival is low for lung and esophageal cancer, mortality and incidence data are adequate for evaluating them; however, mortality is not useful for nasopharyngeal cancer.	**No/minimal concern** Outcome methods clearly distinguish between participants diagnosed with a specific cancer type and participants not diagnosed with that cancer. Follow-up and diagnoses are conducted independent of exposure status. Cancers are histologically/cytologically verified (documented in hospital/personal medical records or cancer registry).
Is there concern that the disease was not accurately diagnosed? For example:	Ideally, cases of cancer should be histologically confirmed and/or undergo independent pathology review (e.g., on a subset of the cases) by the study investigator.	**Some concern** Cancer diagnoses, or a substantial proportion of cancer diagnoses, are histologically/cytologically verified. Some diagnoses may be verified only clinically but criteria are well documented.
• Does misclassification of outcome vary across exposure groups or levels of exposure? • If so, were there methods to adjust for any potential bias?	Incidence data from population-based cancer registry sources or hospital pathology data are generally more detailed and accurate than death certificates, as their sources are medical records and cancer registry data.	**Moderate/major concern** Cancer diagnosis and type are self-reported, and neither are verified by cancer registry or medical/hospital records.
• Is there concern that the control group may have cancer?	Cancer incidence registries, especially population-based registries, are generally preferred; however, these registries are not consistently available or reliable in LMICs and will miss cases. Hospital and medical records should be used for studies conducted in such countries	**Critical concern** There is strong evidence that follow-up and cancer diagnoses are likely related to exposure status or that the methods do not discriminate between diseased and non-diseased participants (unlikely in most cancer studies).

Signaling question	Guidance	Response Options
	Self-reports (or a large percentage of them) should be medically confirmed. Most studies used hospital records, registry, or death records. Proportion of cases ascertained by method(s) other than histological confirmation, and the potential for this to be related to exposure, should be noted.	
Is there concern about observer bias?	Ideally, the outcome assessors do not have knowledge of the participant's exposure status, nor are they influenced by exposure status, which could result in differential bias. This is not likely to be a concern in the wood smoke studies.	
Is any misclassification differential or nondifferential, and what is the predicted direction or distortion of the effect estimate (if there is adequate information)?	Nondifferential outcome misclassification is possible, but very unlikely, and will bias results toward the null	

1.2.4. Confounding bias

The evaluation of confounding is a multi-step process that involves consideration of both study methods and study findings. This section discusses (1) the potential confounders which would ideally be considered in studies of the four cancers and wood smoke exposure in both high-income and LMIC countries, and (2) methods for evaluating how the authors assessed confounding in the study and/or provided information to inform the evaluation of confounding. Methods for assessing the impact of potential confounders on study findings is discussed in Section 1.3. Note that controlling for variables that would lead to imprecision but not bias the effect estimate (i.e., not true confounders) is discussed in the analysis domain.

Potential confounders

For the three cancers under consideration (i.e., lung, esophageal, and nasopharyngeal), candidates for evaluation as potential confounders are shown in Table 2-2. Factors which have been established as known risk factors (e.g., identified from authoritative sources such as IARC, RoC, World Cancer Research Fund) for the cancer of interest are shown in Column 2; the factors likely to be related to wood smoke are considered critical potential confounders and shown in Column 3. Major potential confounders are defined as those factors which are likely to be associated with exposure and strongly associated with disease, are not in the causal pathway, and are not correlated with other risk factors. Because the relationship between a cancer risk factor (such as smoking or alcohol consumption) and exposure (wood smoke) may vary by population, it may not be possible to identify a common set of confounders that should be considered in all studies; confounding will need to be evaluated in a study-specific manner. Also, there are likely to be population-specific risk factors (e.g., diet, household ventilation) associated with socioeconomic status (SES); controlling for SES may only partially control for these features. Finally, because data on the relationship between wood smoke and most potential confounders is lacking, we considered several exposures as potential confounders if it seemed reasonable that they could be associated with wood smoke exposure.

Confounders or effect modifiers across cancer types

Age, gender, race/ethnicity: Ideally, age, gender, and race/ethnicity should be evaluated as potential effect modifiers by stratified analyses in addition to being controlled for in overall analyses. Although many studies use the term sex in classifying subjects, they are most likely classifying study participants based on gender (i.e., social construct) rather than biological sex.

Socioeconomic status. In LMICs, populations using various types of stoves or fuels are often inherently different with regard to poverty-related characteristics (and other factors) than those using other types of fuels/stoves. There are close links between socioeconomic status, fuel and energy use patterns, and health outcomes that often make the confounding nearly intractable (Peel et al. 2015). For example, in LMICs, users of higher-priced fuels tend to be of higher socioeconomic status and often more urbanized than users of traditional biomass and coal fuels. Within high-income countries, data indicate while

households in higher income brackets are more likely to have a fireplace that could burn wood, those at lower income levels who burn wood consume more on average (U.S. Energy Information Association 2014). Ideally socioeconomic factors should be evaluated as potential effect modifiers in stratified analyses in addition to being controlled for in overall analyses. Consideration of SES may also adjust, in part and in some populations, for personal behaviors such as smoking.

Tobacco smoking: Tobacco smoking is a strong risk factor for the three types of cancer we are evaluating. However, it is unclear whether exposure to smoking correlates with exposure to wood smoke; this may vary depending on the income level or cultural aspects of smoking in the country or countries included a study. For example, there is some evidence to suggest that tobacco smoking is not strongly correlated with the presence (White and Sandler 2017) or use (White et al. 2014) of indoor fireplaces or wood-burning stoves in higher income countries, but this may not be true in LMIC countries. In addition, wood smoke and tobacco smoke are both complex mixtures and share similar components. Ideally, studies would evaluate personal smoking exposure as an effect modifier in addition to evaluating it as a potential confounder. Adjusting by pack years is preferred over smoking status; however, as the relationship between wood smoke and tobacco smoking is unclear, adjusting by smoking status will be considered adequate in the studies.

Chemical co-exposures

Several substances are risk factors for lung cancer including arsenic, radon, indoor coal use, diesel exhaust, and air pollution. Whether these substances vary with wood smoke use likely depends on the particular population under study. Global maps showing significant arsenic in groundwater (Groundwater Assessment Platform Maps) could be used to locate study sites to assess whether arsenic levels should be included in models to avoid confounding the association of wood smoke with lung cancer. The World Health Organization drinking water guideline for arsenic is 10 µg/L (WHO 2018).

Non-neoplastic diseases particularly respiratory diseases were not considered to be confounders as they are potentially in the casual pathway.

Table 1.4. Potential confounders for cancers of the lung, nasopharynx, and esophagus for wood smoke used in cooking and heating.

Cancer site	Cancer risk factors	Potential confounders
Lung	*Increase risk*: High dose beta-carotene supplements, opium use, frying (emissions from high temperature), tobacco smoking, passive smoking, arsenic, radon, ionizing radiation, soot, indoor coal use, diesel exhaust, outdoor air pollution, dioxins, diazinon, numerous occupational chemicals and industries, family history of cancer/lung cancer *Decrease risk:* Vegetable and fruit consumption	*Age, gender, SES*[a] *Major:* tobacco smoking (e.g., status and intensity), indoor coal use *Minor:* passive smoking, emissions from high temperature cooking, arsenic in drinking water, radon (high income countries), diesel exhaust, air pollution, family history of cancer/lung cancer, vegetable and fruit consumption *Population dependent:* Race/ethnicity[a] occupational exposures
Esophagus	*Demographic factors:* male gender Acetaldehyde associated with alcoholic beverages, alcohol consumption, tobacco smoking and smokeless tobacco, obesity [high body mass index (BMI)], drinking hot beverages, chewing betel leaves with and without tobacco, pickled vegetables, opium use, ionizing radiation, rubber production industry, family history of esophageal cancer	*Age, gender, SES*[a] *Major*: alcohol consumption, tobacco smoking or use of smokeless tobacco *Minor*: obesity, family history, pickled vegetables *Population dependent:* Race/ethnicity [a], drinking hot beverages, chewing betel leaves with and without tobacco
Nasopharynx	Family history, Epstein-Barr virus (EBV), salt preserved fish (Cantonese style) tobacco smoking, formaldehyde, wood dust, pickled vegetables	*Age, gender, family history, SES*[a] *Major*: tobacco smoking, EBV P*opulation dependent:* Race/ethnicity[a] salt-preserved fish and pickled vegetables.

Sources: IARC 2022; WCRF 2018
[a]Ideally, age, gender, SES, race/ethnicity should be considered in the analysis as effect modifiers.

Questions and guidance

Core question: Is there a concern that either the methods are inadequate or there is inadequate information to evaluate potential confounding?

Table 1.5 Confounding questions, guidance, and response options

Signaling question	Guidance	Response Options
Is there concern about the measurement of co-exposures or lifestyle risk factors measured in the study? If no data are provided about confounders, are surrogate data on potential confounders available?	Ideally, quantitative information on lifestyle factors should be assessed by in-person interview by interviewers blinded to the status of the respondent, rather than via proxy respondents. However, blinding is rarely feasible for case-control studies of incident cancer when especially when cases are interviewed in the hospital.	**No/minimal concern** The study measured all major potential confounders (see above) and/or used appropriate statistical analyses or designs (e.g., analysis on never smokers) to address them. Final statistical models should, however, only include "actual" confounders and not variables that have minimal effect on the risk estimate.
	Residual confounding is more likely when only limited qualitative information on a given risk factor (dichotomous yes/no) is available. Studies should provide, at minimum, data on the distribution of potential confounders among the exposed and unexposed in cohort studies, or among the cases and controls in case-control studies. Coal use may be a potential confounder in studies where the extent (if any) of coal use among participants who use wood is not clearly documented (Studies with documented coal use in the reference or wood-exposed groups are excluded from the evaluation).	**Some concern** Statistical models or designs did not address all major confounders; however, external other information was available to evaluate them, or the analysis controlled for surrogates of the potential confounder. **Moderate/major concern** Statistical models or designs did not address major confounders, particularly smoking, or where coal use is uncertain in the wood-exposed and unexposed groups.

Signaling question	Guidance	Response Options
	In some cases, data may be available on potential confounders in sub-samples, which can help provide interpretation of the prevalence of the potential confounder in the exposed and unexposed or cases and controls. In addition, data on diseases associated with wood smoke (e.g., respiratory diseases such as COPD) may provide indirect information about risk factors for specific cancer endpoints of concern.	**Critical concern** There is strong evidence that the effects of the exposure cannot be distinguished from the effects of potential confounders.
Is there concern that the design or analysis may not adequately address important confounding through matching, stratification, multivariable analysis, or other approaches?	Negative confounding could also occur when the unexposed (referent) group is users of charcoal or other biomass potentially linked to cancer. Positive confounding would occur if the exposed groups were also exposed to coal.	
• Is there additional information available to evaluate potential confounding or conduct sensitivity analyses (indirect adjustment)? • Is there concern that controlling for particular variable would result in bias (e.g., variable is in the causal pathway or other reasons)? • Is there concern that not adjusting for one or more confounders is expected to differentially favor outcomes in those with higher or lower levels of exposure?	External information can be used to account for potential confounding. Care should be taken to assess whether models are over-controlled and controlling for a particular factor would introduce a bias. For example, studies in LMICs may consider multiple factors potentially associated with wood smoke exposure (e.g., ventilation, cooking in enclosed spaces). These are likely to be correlated with the exposure intensity and would partly control for the correlated risk factor.	
What is the direction and magnitude of confounding?	Positive confounding biases the estimated risk estimate away from the null and negative confounding towards the null.	

1.2.5. Analysis bias

Currently all studies included in the evaluation are case-control studies, including a pooled analysis of case-control studies. Some studies included matched controls (individually or frequency matched).

Note that controlling for unnecessary variables (i.e., control that reduces precision but does not bias the risk estimate) is addressed in this domain as an analytic issue, while analysis related to actual confounding is addressed in the confounding domain. Since no studies analyzed continuous wood use data, those questions related to data assumptions (RoC Handbook) are not relevant for wood smoke and are not covered below.

Questions and guidance

Core question: Is there a concern that the data assumptions and analysis were not adequate or that the study did not conduct relevant analyses of available data?

Table 1.6 Analysis bias questions, guidance, and response options

Signaling question	Guidance	Response options
Statistical model and methods		**No/minimal concern**
Is there concern about the appropriateness of the statistical model for the study design and adequacy of the methods? If the study data were adequate, did the study appropriately evaluate exposure-response, conduct subgroup analyses, and incorporate exposure lag-time?	Ideally, a study should use the appropriate models (logistic regression reporting odds ratios) for the study design (pooled analysis, case-control study), including if and how the study cases and controls were matched. Studies that match on an individual level should be well described (matching factors, case: control ratio) and use conditional logistic regression. If exposure-response and exposure lag were evaluated, models and modeling techniques would be statistically appropriate.	Appropriate models were chosen and adequately conducted, e.g., matching factors were handled by conditional logistic regression (individual-level matching) or by being incorporated into the model (frequency-matching). If conducted, models evaluating exposure-response (e.g., trend test) were appropriate. No evidence that missing data was a concern. **Some concern** Analytic techniques for handling matching factors were not well described but there was no evidence they were handled incorrectly. Minor levels of missing data.
Is there concern about "over-controlling", i.e., controlling for variables that are not necessary?	Controlling for variables that are not related to exposure or disease will most likely cause a loss in precision of the risk estimate.	**Moderate/major concern** High proportion of missing data for key variables (exposure, strong confounders) and no attempt made to ameliorate any bias arising from differentially missing data.

Signaling question	Guidance	Response options
Is there concern that missing data may have biased the findings? • Is there concern that missing data for exposure, outcome, or any potential confounders is substantial? • Is there concern that missing data varied by exposed vs unexposed groups or cases vs controls? Is there concern missing data was not handled by an analytically appropriate method (e.g., sensitivity analysis, imputation of missing data)?	Ideally, there should be little to no concern that 'missingness' of data is related to both exposure and disease.	**Critical concern** Strong evidence that the study's analytical methods (as above) were so limited that the findings were uninterpretable or distorted.
What is the direction, magnitude, and impact of this bias on the effect estimate?	It may be difficult to ascertain for most analyses whether any bias is differential or non-differential.	

1.2.6. Study sensitivity

Study sensitivity is the ability of a study to detect a true effect or hazard (Cooper et al. 2016) and is analogous to the term "informativeness" used in the preamble to the IARC Monographs (IARC 2019; Samet et al. 2020). Studies with low risk of bias but insensitive may not be informative for reaching public health decisions about a potential causal relationship between exposure and outcome. Consideration of both sensitivity and the potential for bias are needed to identify the most informative studies and to identify those study elements that may help to explain heterogeneity across the body of literature. Failure to consider sensitivity may result in overweighting the results from insensitive studies, or erroneously interpreting evidence as being conflicting (Cooper et al. 2016). Study sensitivity should be evaluated with the same rigor as risk of bias.

Our assessment of study sensitivity includes consideration of (1) study size or the numbers of exposed and non-exposed participants or cases and controls, (2) exposure contrast and window, and (3) latency. The overall sensitivity evaluation requires an integration of these factors.

Questions and guidance

Core question: Does the study have adequate sensitivity to detect an effect from exposure (if present)?

Table 1.6 Study sensitivity questions, guidance, and response options

Signaling question	Guidance	Response
Statistical power:		**Minor concern**
Is there concern that the numbers of exposed cases are not adequate for detection of an effect in the exposed population and/or subgroups of the exposed population?	When both exposure and disease are rare, statistical power is largely determined by the number of exposed cases, and larger studies are considered to be more informative.	The study has an adequate number of exposed participants, with substantial exposure (propensity, duration, or range) and with adequate duration of follow-up for latency status.

Signaling question	Guidance	Response
Exposure contrast and window: Is there concern that the levels, duration, or range of exposure of the population at risk in cohort and case-control studies are not sufficient or adequate for detection of an effect of exposure?	Dilution of risk estimates comparing exposed and referent groups can occur when there is large variation in exposure level and/or duration within the group(s) defined as exposed. Studies using clean fuel as the referent group are likely to have better exposure contrast. In LMIC countries, women are expected to have higher exposure to wood smoke as they are the primary cooks. Studies with large proportion of men may be less sensitive.	**Some concern** Study has fewer exposed participants than ideal and/or a narrower range of exposure or duration than desirable however, duration of follow-up is adequate for latency. **Moderate/major** The exposure group is wood combined with non-coal biomass (e.g., charcoal, feces, straw) Other factors are few exposed cases, short duration, and inadequate follow-up. Exposure periods may not be etiologically relevant.
• Does the exposed group include individuals with a low or unknown probability of exposure?	In high income countries, irregular and infrequent use of woodstoves among the exposed may make it difficult to detect an effect. Further, the ability to evaluate exposure-response relationships depends on an adequate range of exposure (in intensity or duration) among the study participants, and adequate numbers of participants in each exposure category.	**Critical/major concern** A modest or small study with few exposed participants and/or there is very minimal exposure contrast.
Latency: Is there sufficient elapsed time between when the exposure occurred and when outcome occurred to allow for a cancer induction period?	Cancer latency information specific for wood smoke is not available. Minimal estimates for latency for specific cancer based using Weibull Model (Nadler and Zurbenko 2014). Lung: 13.6 years; Esophageal 25.2 However, it is possible that latency may be shorter in sensitive subpopulations who may have underlying health conditions or diseases. Latency can be inferred by duration of exposure.	

1.2.7. Judgment for study informativeness for health hazard evaluation

How well a study can inform the cancer hazard assessment is based on consideration of both the potential (or risk) for biases (i.e., study quality) and consideration of study sensitivity for each database. Serious concerns about risk of biases would result in lower utility ranking; however, a well-designed study with low study sensitivity (such as few exposed/expected cases for a specific endpoint) could be given a lower ranking. When adequate information is available, a judgment is made for the direction and distortion from the overall biases for a study or whether it has low sensitivity to detect an effect. Studies with critical concern for bias in a domain are considered to be uninformative and are usually not brought forward to the cancer evaluation. The impact of the bias on the risk estimate is considered in the cancer hazard evaluation.

- High (low/minimal concerns for most biases and high sensitivity rating)
- Moderate (low/minimal or some concerns for most biases and high or moderate sensitivity rating)
- Low (major concerns for several biases, sensitivity rating varies)
- Inadequate (critical concerns for bias, sensitivity rating varies, rarely based on critical concerns for sensitivity without critical concerns for bias)

1.3. Evidence Interpretation

Level of evidence conclusions are reached by (1) interpreting the confidence in the evidence from each study, (2) integrating the evidence across studies, and (3) applying the RoC listing criteria (below) to the assessment. The most informative studies (i.e., lowest risk of bias and greatest sensitivity to detect an effect) are given the most weight in the evaluation. The identification of the potential for specific types of uncontrolled bias or confounding, the assessment of study sensitivity, and the presence of effect modification are also used to interpret the findings from studies and to help explain heterogeneity across studies. For lung cancer, a quantitative risk estimate (meta-analysis) will be conducted as part of the evidence integration step.

Report on Carcinogens Listing Criteria

Sufficient evidence of carcinogenicity from studies in humans

- Causal relationship between exposure to the agent, substance, or mixture, and human cancer

Limited evidence of carcinogenicity from studies in humans

- Causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded.

1.3.1. Evaluation of the evidence from individual studies

The presence of potential bias (such as selection bias or information bias from misclassification of exposure or outcome or confounding) in a study does not necessarily mean that the study will be excluded from the assessment. Conclusions about the evidence from each study will consider the strengths and weaknesses of the study, the direction and distortion of the biases, and the strength of the association between exposure to the substance and the cancer end point.

The level of confidence in the evidence from the individual studies (rated as "moderate to strong evidence", "some evidence", "null", or "inconclusive") will be reached by considering the strength of the association, the potential for specific biases or confounding, the expected directions of distortions, and the impact of these potential biases or unaddressed confounding on the effect estimate, and the sensitivity of the study to detect an effect. In addition to considering the potential of biases in context with strength of the findings (magnitude and exposure response relationships), confidence in a study also considers other factors such as internal consistency.

Guidelines for evaluating the overall confidence in the evidence from each study are as follows:

Moderate to strong evidence: Elevated risk estimates for wood use are found for different exposure metrics of wood use for cooking or heating, or in different subgroup analyses; at least one estimate has confidence intervals that do not include one. The evidence is usually reported in studies with lower potential for bias. However, the evidence may come from studies with a higher potential for bias if the potential bias is towards the null or the impact of the bias is not expected to explain all the excess risk. Evidence of an association can also come from a positive study that has low sensitivity to detect a true effect.

Some evidence: Elevated effect estimates with moderate precision are found for at least one metric of wood use. Studies with higher potential for bias can provide evidence of an association if the potential for bias is towards the null, the impact of the bias is not expected to explain all the excess risk, or the study is positive despite having low sensitivity.

Null: Studies which are considered "null" show effect estimates ≤ 1.0.

Inconclusive: Findings vary; the overall direction of potential biases is unknown; potential confounding may explain the findings. Alternatively, studies have very low precision, and the findings may be due to chance.

1.3.2. Evidence Integration: Qualitative Assessment

Application of the RoC listing criteria (see Section 1.6) to the body of studies meeting final PECO criteria on a specific substance involves evaluating (1) whether there is credible evidence for an association between exposure to the substance and cancer, and (2) whether such an observed association can be explained by chance, bias, or confounding. Level of evidence conclusions are based on an in-depth and cohesive integration of the body of the evidence that systematically evaluates consistency and the

key issues – impact of biases, sensitivity, exposure metrics, and effect modification across the studies (Arroyave et al. 2021). We plan to use triangulation methods that integrate findings from different approaches with potentially different sources of biases to evaluate the evidence. For example, consistent results from studies with different sources of biases can help strengthen the confidence of the conclusions (Lawlor et al. 2016). Finally, additional overall considerations — strength of the association, consistency across studies, evidence of an exposure-response gradient, and temporality of exposure (Hill 1965) — are used to help guide the evaluation of these questions. However, it should be noted that that these are not criteria; except for temporality, no single element is required to demonstrate causality (Rothman and Greenland 2005).

As mentioned in Section 1.1, three types of cancers had an adequate database for conducting a systematic review – lung, esophageal, and nasopharyngeal. Lung cancer had the largest number of studies, and we consider the database adequate to conduct both a qualitative and quantitative assessment. The approach to reaching level of evidence conclusions for each cancer type is as follows:

- Integrate the overall confidence of evidence judgements for the individual studies (see Section 1.3.1) to evaluate the strength of the findings and consistency for that cancer. The meta-analysis may also help inform consistency.
- Systematically evaluate key issues identified to date (e.g., using forest plots and/or text) – overall study informativeness, specific biases and key confounders, exposure metrics, effect modification, confounders, and the country's income level (see Table 1.7 for number of studies reporting on specific factors) – using triangulation methods (when appropriate) across studies
- Consider other causality considerations (e.g., Hill guidelines) such as temporality and strength of the association (e.g., magnitude and exposure/duration response)
- Integrate the findings from the quantitative analysis for wood smoke and lung cancer
- Apply the RoC listing criteria.

Finally, for each cancer, the confidence of carcinogenic hazard may be contextualized further based on the evidence. As mentioned in Section 1.2, there are three sets of lung cancer studies with some potential overlap (García-Sancho et al. 2012a; García-Sancho et al. 2012b; Ko et al. 1997; Lee et al. 2001; Phukan et al. 2014; Saikia et al. 2014) that will be counted as individual studies for the qualitative evaluation, as the overlap is expected to be small.

Table 1.7 lists key issues or exposure metrics that could be explored across studies for three specific cancer types (lung, esophageal, and nasopharyngeal) using forest plots and/or in narrative text. Studies that examine age at exposure (a proxy for exposure timing) may help address whether and/or what the windows of susceptibility for wood smoke exposure and specific cancers might be. The most common exposure metric was exposure duration; however, in addition to the metrics in the table, one lung cancer study evaluated exposure-response relationship using a measure of cumulative exposure (duration*hours/day) (Báez-Saldaña et al. 2021). For lung cancer, it may be possible to evaluate combinations of factors such as never-smokers among women, timing, or age of

exposure and never smokers, or smoking and gender; these may be addressed better by calculating a quantitative risk estimate in the meta-analysis. The databases for esophageal and nasopharyngeal cancers are largely inadequate for evaluating effect modifiers and different exposure metrics across studies.

Table 1.7 Metrics and issues in wood smoke cancer epidemiology studies

Metric/Issue	Lung (n=17[a])	Esophageal (n=6)	Nasopharyngeal (n=9)
Predominant vs. ever use	10 vs. 6	1 vs 6	2 vs 7
Exposure duration	4	1	1
Exposure timing	4	2	3
Country income: High vs low	6 vs 11	0 vs 6	0 vs 9
Gender: Women only vs men only [b]	12 vs 2	0	1 vs. 1
Smoking status: Never-smokers vs. smokers[c]	11 vs. 4	0	2 vs. 2
Cancer subtype	3	0	0
Combined fuels[d]	5	3	1
Informativeness	TBD	TBD	TBD

TBD = To be determined after study evaluation.
[a] One study was a pooled analysis of four studies. Three pairs of studies have potentially partial overlapping populations; overlap is not thought to be substantial.
[b]Study included only women or had a risk estimate specific for women or men.
[c]Study included only never-smokers or had a risk estimate specific to never-smokers or smokers.
[d] Esophageal studies: 3 wood/charcoal; Lung studies: 2 wood/charcoal, 2 wood/straw, 1 wood/feces; Nasopharyngeal studies: 1 wood/charcoal.

In addition to evaluating the impact of biases on individual studies, we will also evaluate impact of bias across studies. Smoking is the most important confounder for lung, esophageal, and nasopharyngeal cancers thus studies of never-smokers will be informative for ruling out confounding by smoking.

The findings from the meta-analysis discussed below will be integrated in with the qualitative evaluation to reach conclusions regarding the level of evidence for the carcinogenicity of wood smoke.

1.3.3. Evidence Integration: Quantitative Assessment (meta-analysis) for Lung Cancer

As depicted in Figure 1.2, more stringent criteria were developed from the final PECO for a possible meta-analysis of lung cancer and wood smoke exposure. These criteria include restricting main effects and currently planned sub-analyses to wood use categories [i.e., excluding exposure to wood in combination with other biomass such as charcoal or straw (Ko et al. 1997; Koo et al. 1983; Lee et al. 2001; Sobue et al. 1990; Vermeulen et al. 2019)]. In many LMIC study populations, study participants classified as wood users likely also used other biomass e.g., agricultural waste, dung) as cooking or

heating fuels. However, studies that explicitly categorize exposure as wood combined with other biomass may be less specific for wood smoke exposure than studies categorizing individuals as just wood users because (1) they may include participants with mainly non-wood biomass use or (2) the proportion of non-wood biomass use may be higher in the studies. We will include these studies in sensitivity analysis in the meta-analysis; these studies are also retained in the qualitative evaluation. Because there are an adequate number of studies (11) with a similar exposure metric (wood use), we believe the data are adequate for conducting a meta-analysis of wood smoke exposure and lung cancer risk. The findings of the meta-analysis (Specific Aim 2) will provide information on the direction and strength of the association, which will inform the level of evidence conclusions. It will also provide a means to explore heterogeneity (and possible sources of any heterogeneity) and risk estimates for specific subpopulations. Lastly, it could inform attributable risk or cancer burden calculations.

Data Synthesis: Steps

Methods for the first four steps are the same as those for the qualitative analysis. Steps 1 to 3 have been completed.

1. Development of research question (Section 1.1.1)
2. Literature search strategy and study selection based on inclusion and exclusion criteria (Section 1.1.2 and Appendix A)
3. Evidence mapping and meta-analysis PECO (Section 1.1.3)
4. Data extraction Section 1.4.1)
5. Study evaluation including risk of bias and study sensitivity (Section 1.2)
6. Qualitative evaluation of key issues and heterogeneity (Section 1.3)
7. Meta-analysis strategy and methods (discussed below)

Meta-analysis: Statistical considerations and strategy

We discuss the statistical considerations and strategy for conducting the meta-analyses on 11 cancer publications that meet the meta-analysis PECO below and in Tables 1.8 and 1.9. Newly published studies will be added to the meta-analysis based on the meta-analysis PECO. Our strategy is to calculate pooled estimates (main effects, subgroup) using random-effects models, and conduct sensitivity analyses and other analyses to evaluate the extent of any heterogeneity and publication bias. In meta-analysis, heterogeneity across studies is expected as the studies are conducted in populations that differ in geographical location, socioeconomic conditions, and exposure patterns (Higgins et al. 2009). Interpretation of heterogeneity and publication bias and their associated assessments are challenging. Heterogeneity may affect interpretation of funnel plot asymmetry (visual inspection and related analysis), which is typically used to assess publication bias. We also plan to conduct sensitivity analyses to explore our inclusion criteria for the “main-effect” estimate (e.g., potentially overlapping studies, and studies restricted to never smokers).

Table 1.8 Lung Cancer Meta-analysis: Statistical considerations

Factor	Specifics	Comment	References
Pooled effect estimate	Meta-OR and 95% CI	All studies identified to date are case-control studies or a pooled analysis of independent case-control studies. Newly published studies will be included if they meet the meta-analysis PECO. The least biased estimate will be used (see text on Main effects).	
Model	Random effects	Estimates across studies.	Borenstein et al. 2010
	Fixed effects	Collapsing categories for an estimate from a single study (e.g., never- and ever-smokers in studies not reporting overall risk estimates).	
Heterogeneity	I^2 statistic, H statistic	Heterogeneity is to be expected and its interpretation can be challenging. The *p* value associated with the Cochran *Q* test (equivalent to the *p* value for I^2) has poor power to detect heterogeneity in meta-analyses with few studies. It will be reported, but not relied on to assess heterogeneity. I^2 is the percentage of variation across studies due to heterogeneity rather than chance. However, it is not a measure of absolute heterogeneity (i.e., does not provide the predicted range of effect sizes due to heterogeneity). Although there have been some guidelines for I^2 percentages, interpretation also depends on the methodologic diversity of the studies and the magnitude and direction of the study effects. For I^2, cut points of 25%, 50%, and 75% are generally used to represent low, moderate, or substantial levels of heterogeneity. H^2 is the relative excess of Q over the degrees of freedom; H=1 denotes homogeneity.	Borenstein et al. 2017; Higgins and Greenland 2008; Higgins and Thompson 2002; Higgins et al. 2003
	Sensitivity analysis: Leave one out	Used to determine if the potential association between wood smoke and lung cancer is highly influenced by any single study.	
	Subgroup analyses	See Table 1.9 for details	
Publication bias	Funnel plot asymmetry: contour-enhanced plots. Additional tests dependent on the extent of heterogeneity	Interpretation of publication bias assessments are also challenging. Funnel plot asymmetry and associated tests for analyses (e.g., Eggers, trim and fill) testing can be due to many factors in addition to small study effects, e.g., methodologic quality, heterogeneity, and statistical significance. We plan to use contour-enhanced funnel plots considering study quality and heterogeneity. Depending on the degree of heterogeneity (e.g., based on I^2 and the funnel plot), we may also conduct regression test and trim and fill methods.	Peters et al. 2006; 2008
Visualization	Forest plots, Galbraith plots, funnel plots		

Factor	Specifics	Comment	References
Software	STATA	STATA version 17 using the *metan*, *metareg*, *metafunnel*, *metabias*, *metatrim. metaforestplot, and metaforestplot* packages	Palmer and Sterne 2016
	R	Forest plots	

Main effect

We will use the random-effects model to pool ORs from 11 studies, using the risk estimates that are (in priority order) 1) the least biased and 2) the most relevant to cancer risk (i.e., most specific to wood and longest duration). Examples of least biased ORs are ones from fully adjusted models or using least biased controls. For studies that report subgroup estimates only (e.g., men and women; smokers and nonsmokers; cancer subtypes), we will combine the ORs from the subgroups using fixed effect models and use the combined OR in the main effects meta-analysis, recognizing that the combined OR will not be adjusted for the stratified variable (e.g., smoking, sex).

Table 1.9 Lung Cancer Meta-analysis: Strategy

Factor	Specifics	Comment
Main effect[a,b]	Most relevant and least biased for wood use (n=11)	Combined OR for studies reporting on highest exposure, predominant, or ever wood use. When a study has multiple risk estimates, the preference will be to use, in priority order, the highest exposure (e.g., longest duration, lifetime), predominant wood use, and ever wood use, while always giving preference to the least biased (usually the most fully adjusted) estimate.
Sub-analysis: gender	Women (n=7)	Combined OR for studies reporting estimates for women only combining smokers and non-smokers Inadequate number of men-only estimates for a combined estimate.
Sub-analysis: gender and smoking	Never-smoker women (n=4)	Combined OR for studies reporting on never-smoker women; inadequate numbers of studies reporting on smoking women or never-smoker men for a combined estimate.
Subgroup analysis: referent group	Modern fuel as referent (n=6)	Combined OR for studies reporting modern fuel as referent.
Stratified analysis: Smoking status	Never smokers (n=7); smokers (n=4)	Combined ORs for studies reporting on never smokers and ever smokers
Stratified analysis: Study quality	TBD Low study quality Moderate/high study quality	Not known. If appropriate, note impact of bias. If there are common biases across studies, stratified by those biases.

Factor	Specifics	Comment
Sensitivity analysis: potentially overlapping study populations	Pairs of studies conducted in Mexico and northeast India (n=4; 2 pairs)[b]	For each pair of studies with potential overlap: Inclusion of both studies, and each one separately.
Sensitivity analysis: all studies	All studies; N=16	Includes five studies of wood combined with another biomass fuel (Ko et al. 1997; Koo et al. 1983; Lee et al. 2001; Sobue et al. 1990; Vermeulen et al. 2019). Ko et.al. 1997 and Lee et.al. 2001 will be assessed for overlap.

TBD = To be determine after study evaluation
[a]Excludes 2 studies restricted to never-smokers.
[b]Two pairs of studies have potential overlap in study populations

Subgroup analyses

Subgroup analyses (see Table 1.8) will be conducted to explore heterogeneity, inform the hazard conclusions (e.g., smoking satus, study informativeness), and provide population-specific quantitative risk estimates (e.g., women only) for public health reasons. Ideally, these analyses will supplement and not duplicate the qualitative hazard evaluation (e.g., forest plots). Additional subgroup analyses (such as exposure metrics, population- vs. hospital-based controls in case-control studies) may be conducted based on heterogeneity analyses (see Table 1.9) or the addition of new studies. Women in LMIC may have higher exposure to wood smoke because they do most of the cooking, and thus women may serve as a proxy for exposure level. The numbers of studies for the proposed subgroup analyses are available in the Tableau dashboard. For example, Figure 1.4 provides a map of studies meeting the meta-analysis criteria and that have risk estimates for never smokers.

Figure 1.4. Studies of wood use and lung cancer among never smokers

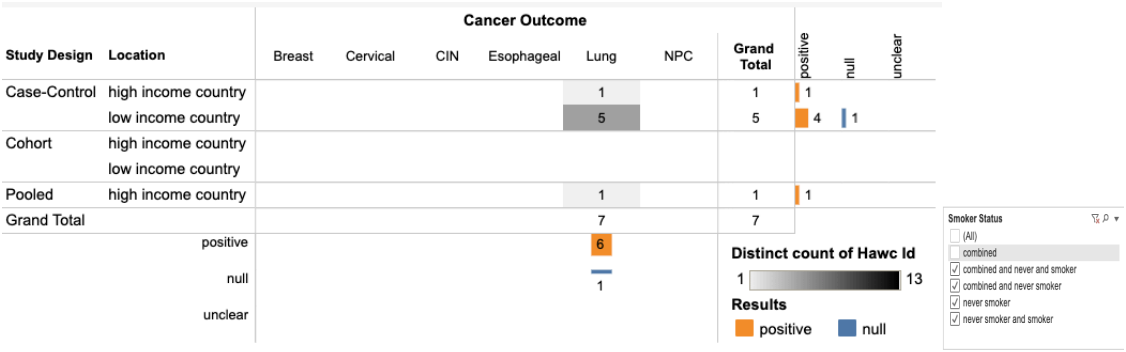


Fig 1.4 Evidence map of lung cancer studies eligible for the meta-analysis that either provide a risk estimate specific for never smokers or are restricted to never smokers.

Sensitivity analysis

We plan to conduct sensitivity analyses to address any heterogeneity due to one study (or groups of studies, see Table 1.9) and the impact of potentially overlapping populations (discussed below). We will also conduct sensitivity analysis excluding the two studies

with only never smokers (García-Sancho et al. 2012a; Hernández-Garduño et al. 2004). Lung cancer risk may differ between smokers and never smokers (García-Sancho et al. 2012a; Hernández-Garduño et al. 2004) because wood smoke and cigarette smoke share similar components, and smoking is a strong risk factor for lung cancer. Lastly, we will conduct sensitivity analysis that includes five studies from the qualitative evaluation that have estimates for wood combined with other biomass (Ko et al. 1997; Koo et al. 1983; Lee et al. 2001; Sobue et al. 1990; Vermeulen et al. 2019).

Strategy for studies of potentially overlapping populations

The 13 lung cancer publications identified that meet the meta-analysis criteria report on 11 completely independent study populations. As mentioned in Section 1.2, two studies report on potentially overlapping populations in Mexico City (García-Sancho et al. 2012a; García-Sancho et al. 2012b), and two on potentially overlapping study populations in northeast India (Phukan et al. 2014; Saikia et al. 2014). The third set of overlapping studies from Taiwan do not the meet the inclusion criteria (PECO) for the meta-analysis (see Figure 1.2). For each of these sets, the authors do not directly state there is overlap with another study population; the potential for overlap is inferred from descriptions of cases/controls being drawn from similar but not exactly the same geographic region (Phukan et al. 2014; Saikia et al. 2014) or hospital (García-Sancho et al. 2012a; García-Sancho et al. 2012b), and overlapping, but not identical, enrollment dates. Based on enrollment dates and inclusion criteria, potential overlap may be small and thus both reports are included in the meta-analysis with relevant sensitivity analysis. However, this approach may change if we receive additional information on the extent of overlap.

García-Sancho et.al. (2012b) reported on combined smokers and non-smokers while García-Sancho et al. (2012a) reported only on never smokers. The former will be included in the main effect analysis, and the latter in the sub-analysis of never smokers Note that because different enrollment years were used, the never smokers in the García-Sancho et al. (2012b) study overlap somewhat but are not the same as the non-smokers in the García-Sancho et al. (2012a) study.

Phukan et al. (2014) reported on women only, whereas Saikia et al. (2014) reported on men and women (overall and stratified by gender). Because the enrollment years are different and an adjoining geographic region was included in the Saikia et al. study, the women in the latter study may overlap but are not all the same as the women in the Phukan et al. study. Both studies in this northeast Indian population will be included in the main analysis (with planned sensitivity analysis excluding each one). Both Saikia et al. (2014) and Phukan et al. (2014) provide estimates for women only, so both will be included in the women-only sub-analysis with sensitivity analysis as above.

1.4. Reporting

1.4.1. Systematic extraction of data from the epidemiologic studies

The latest published follow-up or update for each of the cohort, nested case-control, and case-control studies is extracted for each cancer type included in the study. Additional relevant information (such as exposure data or re-analyses) from earlier and/or related

publications on the same or overlapping study population(s) is also included if these publications provide unique or additional data to inform either the primary cancer study evaluation or the cancer hazard evaluation.

Detailed information regarding study data and methods abstraction from individual studies is described in the RoC Handbook, Part D, Section 3 (update in progress). Briefly, data are selected and entered into web-based content management system (NTP Table Builder, a database specifically created for entering information from scientific publications in a systematic manner using standardized instructions, questions, and language [Shapiro et al. 2018]). The database contains fields that are specific for the different types of extracted information (e.g., study population characteristics, exposure and disease assessment, analytical methods, confounders, and results). Questions and guidelines are available to describe the specific type of information that should be summarized or entered in each field; selected fields are used to populate monograph tables. In addition to the data extracted into Table Builder and in the evidence map, data is extracted for the key scientific issues that will be evaluated in the evidence integration (both the qualitative and quantitative assessments) (see Tableau evidence maps and Section 1.3). These include participant and population characteristics (e.g., gender, race/ethnicity, smoking status, country income); exposure metrics (e.g., ever use, duration, timing) and information (type of biomass, type of use); cancer subtype; and other potential effect modifiers (genotype).

1.4.2. Reporting

We plan to include the following elements in our monograph:

- An overview of study characteristics (e.g., population characteristics, exposure assessment methods, outcomes) included in the review, even if not included in the evidence integration for bias, quality, or other reasons.
- A discussion of biases and limitations for each bias domain across studies, in addition to the rationale for the risk-of-bias at the study level.
- A scientific narrative of the interpretation of study findings including a discussion of the confidence in the evidence of each study, heterogeneity across studies (not limited to potential for biases) and the rationale for the conclusion (e.g., consideration of dose-response relationships, consistency, ruling out chance, bias and confounding).
- Findings from studies – reported in summary tables and graphed in forest plots.
- Preliminary level of evidence conclusions for cancers of the lung, esophagus, and nasopharynx.

Appendix A

Wood Smoke Human Epidemiology Studies Search Terms

Database	Search String
Pubmed	("wood carboniz*"[Title/Abstract] OR "carbonized wood"[Title/Abstract] OR "collier*"[Title/Abstract] OR ("fires"[MeSH Terms] OR ("wood smoke*"[Title/Abstract] OR "woodsmoke"[Title/Abstract] OR "wood fired"[Title/Abstract] OR "wood burning*"[Title/Abstract] OR "burning wood"[Title/Abstract] OR "wood stove*"[Title/Abstract] OR "woodstove*"[Title/Abstract]))) OR ("biomass fired"[Title/Abstract] OR "biomass stove*"[Title/Abstract] OR "burn biomass"[Title/Abstract] OR "burning biomass"[Title/Abstract] OR "biomass fuel*"[Title/Abstract] OR "biomass cook*"[Title/Abstract])) OR ("cookstove*"[Title/Abstract] OR "cooking/instrumentation"[MeSH Terms] OR "cooking stove*"[Title/Abstract] OR "cook stove*"[Title/Abstract]) OR ("cooking"[MeSH Terms] OR "cook*"[Title/Abstract] OR ("heating"[MeSH Terms] OR "heat*"[Title/Abstract])) AND ("air pollut*"[Title/Abstract] OR "air pollutants/adverse effects"[MeSH Terms] OR ("smoke"[Title/Abstract] OR "smoky"[Title/Abstract] OR "smoke"[MeSH Terms]) OR ("wood"[Title/Abstract] OR "biomass"[Title/Abstract] OR "fuel*"[Title/Abstract])) OR (("charcoal"[All Fields] OR "charcoal"[All Fields] OR "charcoals"[All Fields]) NOT ("coal"[All Fields] OR "coal"[All Fields])) OR(((wetland*) and (fire*)) OR ((wildland*) and (fire*)) OR (wildfire*)) AND RoC Epidemiology Terms AND RoC Cancer terms
Scopus	TITLE-ABS-KEY(wood-smoke* OR woodsmoke OR wood-fired OR wood-burning* OR burn-wood OR burning-wood OR wood-stove* OR woodstove* OR Wood-carbonis* OR carbonising-wood OR carbonised-wood OR Wood-carboniz* OR carbonizing-wood OR carbonized-wood OR collier* OR biomass-fired OR biomass-stove* OR burn-biomass OR burning-biomass OR biomass-fuel* OR biomass-cook* OR cook-biomass OR cooking-biomass OR cookstove* OR cooking-stove* OR cook-stove*) OR (TITLE-ABS-KEY(cook* OR heat*) AND TITLE-ABS-KEY(air-pollut* OR smoke OR smoky OR wood OR biomass OR fuel*)) OR TITLE-ABS-KEY(charcoal* NOT Coal*) OR TITLE-ABS-KEY (fire* AND wetland*) OR TITLE-ABS-KEY (fire* AND wildland*) OR TITLE-ABS-KEY(wildfire*) AND RoC Epidemiology Terms AND RoC Cancer terms
Web of Science	TS=(wood-smoke* OR woodsmoke OR wood-fired OR wood-burning* OR burn- wood OR burning-wood OR wood-stove* OR woodstove* OR Wood-carbonis* OR carbonising-wood OR carbonised-wood OR Wood-carboniz* OR carbonizing-wood OR carbonized-wood OR collier* OR biomass-fired OR biomass-stove* OR burn-biomass OR burning-biomass OR biomass-fuel* OR biomass-cook* OR cook-biomass OR cooking-biomass OR cookstove* OR cooking-stove* OR cook-stove*) OR ((TS=(cook* OR heat*)) AND (TS=(air-pollut* OR smoke OR smoky OR wood OR biomass OR fuel*))) OR TS=(charcoal* NOT coal*) OR TS=(Fire* AND wetland*) OR TS=(Fire* AND wildland*) OR TS=(Wildfire*) AND RoC Epidemiology Terms AND RoC Cancer terms

Evaluation team:

Evaluation teams are composed of federal staff and contractor staff. Procedures are in place to avoid actual or perceived conflicts of interest. Members of the evaluation team have experience or training in conducting literature searches and/or evaluating occupational and environmental epidemiology studies.

Project Leader

Develops research concept, rationale, and framework; serves as a researcher

- Ruth M. Lunn, DrPH, NIEHS

Information specialists

Develop search terms, conduct literature searches, and manage literature (e.g., endnote libraries, HAWC uploads)

- Jessica Geter, ILS (no longer part of the team)
- Rachel Kalsch, ILS - an Inotiv Company

Epidemiologists

Primary researchers

Screen and map literature, develop the protocol, conduct study evaluation (risk of bias, study sensitivity), conduct qualitative and quantitative evidence (i.e., meta-analysis) integration, prepare tables and figures, and write original draft cancer hazard evaluation

- M. Elizabeth Hodgson, PhD, ILS – an Inotiv Company
- Ruth M. Lunn DrPH, NIEHS

Supporting researchers

Provide input on protocol development, assist with, or resolve, conflicts in study evaluations, provide technical input and assistance for meta-analysis and forest plots, critically review, and provide input on draft cancer hazard evaluation

- Whitney Arroyave, PhD, ILS – an Inotiv Company
- Suril S. Mehta, DrPH, NIEHS

Screened and mapped literature, and contributed to protocol development

- Pamela Schwingl, PhD, ILS (retired)

Data visualization

Create data visualization in Tableau

- Courtney Lemeris, ICF

Protocol Peer Reviewers

- Kyla Taylor, NIEHS
- Alexandra White, NIEHS

- Amir Sapkota, University of Maryland

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