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The effect of occupational exposure to welding fumes on trachea, bronchus and lung cancer: A systematic review and meta-analysis from the WHO/ILO Joint Estimates of the Work-related Burden of Disease and Injury

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ABSTRACT

Background: The World Health Organization (WHO) and the International Labour Organization (ILO) are the producers of the WHO/ILO Joint Estimates of the Work-related Burden of Disease and Injury (WHO/ILO Joint Estimates). Welding fumes have been classified as carcinogenic to humans (Group 1) by the WHO International Agency for Research on Cancer (IARC) in IARC Monograph 118; this assessment found sufficient evidence from studies in humans that welding fumes are a cause of lung cancer. In this article, we present a systematic review and meta-analysis of parameters for estimating the number of deaths and disability-adjusted life years from trachea, bronchus, and lung cancer attributable to occupational exposure to welding fumes, to inform the development of WHO/ILO Joint Estimates on this burden of disease (if considered feasible).

Objectives: We aimed to systematically review and meta-analyse estimates of the effect of any (or high) occupational exposure to welding fumes, compared with no (or low) occupational exposure to welding fumes, on trachea, bronchus, and lung cancer (three outcomes: prevalence, incidence, and mortality).

Data sources: We developed and published a protocol, applying the Navigation Guide as an organizing systematic review framework where feasible. We searched electronic databases for potentially relevant records from published and unpublished studies, including Medline, EMBASE, Web of Science, CENTRAL and CISDOC. We also

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searched grey literature databases, Internet search engines, and organizational websites; hand-searched reference lists of previous systematic reviews; and consulted additional experts.
Study eligibility and criteria: We included working-age (≥15 years) workers in the formal and informal economy in any Member State of WHO and/or ILO but excluded children (<15 years) and unpaid domestic workers. We included randomized controlled trials, cohort studies, case-control studies, and other non-randomized intervention studies with an estimate of the effect of any (or high) occupational exposure to welding fumes, compared with occupational exposure to no (or low) welding fumes, on trachea, bronchus, and lung cancer (prevalence, incidence, and mortality).
Study appraisal and synthesis methods: At least two review authors independently screened titles and abstracts against the eligibility criteria at a first review stage and full texts of potentially eligible records at a second stage, followed by extraction of data from qualifying studies. If studies reported odds ratios, these were converted to risk ratios (RRs). We combined all RRs using random-effects meta-analysis. Two or more review authors assessed the risk of bias, quality of evidence, and strength of evidence, using the Navigation Guide tools and approaches adapted to this project. Subgroup (e.g., by WHO region and sex) and sensitivity analyses (e.g., studies judged to be of "high"/"probably high" risk of bias compared with "low"/"probably low" risk of bias) were conducted.
Results: Forty-one records from 40 studies (29 case control studies and 11 cohort studies) met the inclusion criteria, comprising over 1,265,512 participants (≥22,761 females) in 21 countries in three WHO regions (Region of the Americas, European Region, and Western Pacific Region). The exposure and outcome were generally assessed by job title or self-report, and medical or administrative records, respectively. Across included studies, risk of bias was overall generally probably low/low, with risk judged high or probably high for several studies in the domains for misclassification bias and confounding.
Our search identified no evidence on the outcome of having trachea, bronchus, and lung cancer (prevalence). Compared with no (or low) occupational exposure to welding fumes, any (or high) occupational exposure to welding fumes increased the risk of acquiring trachea, bronchus, and lung cancer (incidence) by an estimated 48 % (RR 1.48, 95 % confidence interval [CI] 1.29–1.70, 23 studies, 57,931 participants, I^2 24 %; moderate quality of evidence). Compared with no (or low) occupational exposure to welding fumes, any (or high) occupational exposure to welding fumes increased the risk dying from trachea, bronchus, and lung cancer (mortality) by an estimated 27 % (RR 1.27, 95 % CI 1.04–1.56, 3 studies, 8,686 participants, I^2 0 %; low quality of evidence). Our subgroup analyses found no evidence for difference by WHO region and sex. Sensitivity analyses supported the main analyses.
Conclusions: Overall, for incidence and mortality of trachea, bronchus, and lung cancer, we judged the existing body of evidence for human data as "sufficient evidence of harmfulness" and "limited evidence of harmfulness", respectively. Occupational exposure to welding fumes increased the risk of acquiring and dying from trachea, bronchus, and lung cancer. Producing estimates for the burden of trachea, bronchus, and lung cancer attributable to any (or high) occupational exposure to welding fumes appears evidence-based, and the pooled effect estimates presented in this systematic review could be used as input data for the WHO/ILO Joint Estimates.
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1. Introduction

1.1. Background

The World Health Organization (WHO) and the International Labour Organization (ILO) produce the WHO/ILO Joint Estimates of the Work-related Burden of Disease and Injury (WHO/ILO Joint Estimates) (Pega et al., 2021a,b; World Health Organization and International Labour Organization 2021a,b). The organizations estimate the numbers of deaths and disability-adjusted life years (DALYs) that are attributable to selected occupational risk factors. The WHO/ILO Joint Estimates are based on already existing WHO and ILO methodologies for estimating the burden of disease for selected occupational risk factors (International Labour Organization 2014; World Health Organization 2016). They expand these existing methodologies with estimation of the burden of several prioritized additional pairs of occupational risk factors and health outcomes. For this purpose, population attributable fractions, the proportional reduction in burden from the health outcome achieved by a reduction of exposure to the theoretical minimum risk exposure level (Murray et al. 2004), are calculated for each additional risk factor-outcome pair. These fractions are applied to the total burden of disease envelopes for the health outcome from the WHO Global Health Estimates (World Health Organization 2017).

The WHO/ILO Joint Estimates may include a methodology for estimating, and estimates of, the burden of trachea, bronchus, and lung cancer from occupational exposure to welding fumes if feasible, as one of the additional prioritized risk factor-outcome pairs. To select parameters with the best and least biased evidence for their estimation models, WHO and ILO, supported by a large number of individual experts, have conducted a systematic review and meta-analysis of studies on the relationship between occupational exposure to welding fumes and trachea, bronchus, and lung cancer according to protocol (Pega et al. 2020a); we present these analyses in this study record article. The organizations are also conducting or have completed several other systematic reviews and meta-analyses on other additional risk factor-outcome pairs (Descatha et al. 2018; Godderis et al. 2018; Li et al. 2018; Mandrioli et al. 2018; Hulshof et al. 2019; Paulo et al. 2019; Rugulies et al. 2019; Teixeira et al. 2019; Tenkate et al. 2019; Descatha et al. 2020; Li et al. 2020; Hulshof et al. 2021a,b; Pachito et al. 2021; Rugulies et al. 2021; Teixeira et al. 2021a,b; World Health Organization 2021; Schlünssen Under review). One of these was focused on pairs with cancer outcomes: occupational exposure to solar ultraviolet radiation and the risk of malignant skin melanoma and non-melanoma skin cancer, respectively (World Health Organization 2021). To our knowledge, these are the first systematic reviews and meta-analyses, with a pre-published protocol, conducted specifically for an occupational burden of disease study. An editorial provides an overview of this series of systematic reviews and meta-analyses from the WHO/ILO Joint Estimates and outlines its scientific, methodological, policy, editorial, and other innovations (Pega et al. 2021c). Several new systematic review methods were also developed specifically for the WHO/ILO Joint Estimates (Pega et al. 2020b; Momen et al. 2022; Pega et al. 2022a,b). The WHO/ILO joint estimation methodology and the WHO/ILO Joint Estimates are separate from these systematic reviews, and they are described in more detail and reported elsewhere (Pega et al., 2021a,b; World Health Organization and International Labour Organization 2021a,b). For example, WHO/ILO Joint Estimates have been published of the global, regional, and national burdens of ischemic heart disease

and stroke attributable to exposure to long working hours for 194 countries (Pega et al. 2021a).

1.2. Rationale

To consider the feasibility of estimating the burden of trachea, bronchus, and lung cancer from occupational exposure to welding fumes, and to ensure that potential estimates of burden of disease are reported in adherence with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) (Stevens et al. 2016), WHO and ILO require a systematic review and meta-analysis of studies with estimates of the relative effect of any (or high) occupational exposure to welding fumes on the prevalence of, incidence of or mortality from trachea, bronchus, and lung cancer, compared with the theoretical minimum risk exposure level of no (or low) occupational exposure to welding fumes. The theoretical minimum risk exposure level is the exposure level that would result in the lowest possible population risk, even if it is not feasible to attain this exposure level in practice (Murray et al. 2004).

In 2017, a WHO International Agency for Research on Cancer (IARC) Monograph 118 working group reported their findings on welding fumes (Guha et al. 2017; International Agency for Research on Cancer 2018). Welding fumes comprise a mix of fine solid particles, including metal oxides, silicates, and fluorides. They are released during welding, which joins metals, usually by electricity (arc welding) or by a fuel gas (gas welding). The IARC Monograph 118 details that welding fumes were classified as "carcinogenic to humans" (Guha et al. 2017; International Agency for Research on Cancer 2018). IARC based this assessment on "sufficient evidence" from the >50 epidemiologic studies on the effect of exposure to welding fumes (generally assessed indirectly through welding process or material, branch of industry, occupation, job title, job task, expert assessment or self-report) on lung cancer (International Agency for Research on Cancer 2018).

We are aware of four published meta-analyses reporting on the effect of welding fume exposure on development of lung cancer (Sjogren et al. 1994; Moulin 1997; Ambroise et al. 2006; Honaryar et al. 2019). While these meta-analyses vary in eligibility criteria of included studies, all suggested an increased risk in the development of lung cancer. The earliest meta-analysis, which only included studies that accounted for tobacco smoking and exposure to asbestos, examined stainless steel welders (assessed indirectly by the worker through self-report or by a workplace manager or the worker's spouse) and the occurrence of lung cancer (Sjogren et al. 1994). The pooled risk ratio (RR) from three case-referent (case-control) and two cohort studies included in the meta-analysis was 1.94 (95 % CI 1.28–2.93). However, the authors neither tested for nor measured heterogeneity in the meta-analysis, nor assessed the quality of the body of evidence.

A 2006 meta-analysis, an update of Moulin (1997), included population surveys, case-control studies, and industry-based cohort studies to assess the relationship between lung cancer and welding (Ambroise et al. 2006). The pooled RR for the cohort studies was 1.29 (95 % CI 1.19–1.40; χ^2 20.6, p 0.99), and that for the case-control studies was 1.27 (95 % CI 1.11–1.46; χ^2 13.0, p 0.60) when only studies without reporting bias were included in the analysis. No further assessment of the quality of the evidence was reported. The authors attempted to control for confounding by tobacco smoking, and – when crude and adjusted RRs were available – it appeared that no or only slight confounding by tobacco smoking was detected.

The most recently published meta-analysis (Honaryar et al. 2019) analysed the studies included in the IARC assessment conducted in 2017 (Guha et al. 2017; International Agency for Research on Cancer 2018). Pooled effect estimates, stratified by study design, suggested increased RRs in development of lung cancer of 1.29 (95 % CI 1.20–1.39; I^2 26.4 %) across 22 cohort studies; 1.87 (1.53–2.29; I^2 44.1 %) across 15 case-control studies; and 1.17 (1.04–1.38; I^2 41.2 %) across eight case-control studies that accounted for confounding by tobacco smoking and exposure to asbestos.

However, to our knowledge, no systematic review has been conducted of studies with estimates of the effect of *occupational* exposure to welding fumes on trachea, bronchus, and lung cancer. We did not identify any systematic review protocol on the topic up to the year 2020 (PROSPERO – accessed May 14, 2020). Subsequently, we published the protocol for this systematic review in the same year (Pega et al. 2020a).

Different contexts may result in different exposures and effects of these exposures on the health outcome. Work in the informal economy, for example, may lead to different exposures and exposure effects than does work in the formal economy. The informal economy is defined as "all economic activities by workers and economic units that are – in law or in practice – not covered or insufficiently covered by formal arrangements", but excluding "illicit activities, in particular the provision of services or the production, sale, possession or use of goods forbidden by law, including the illicit production and trafficking of drugs, the illicit manufacturing of and trafficking in firearms, trafficking in persons and money laundering, as defined in the relevant international treaties" (p4) (104th International Labour Conference 2015). Therefore, we considered the formality of the economy studied as a key contextual factor in studies included in our systematic review.

Our systematic review and meta-analysis differ from previous efforts in that it:

- Is tailored to the needs of estimation of burden of disease of disease.
- Is based on a pre-published, peer-reviewed protocol (Pega et al. 2020a).
- Includes studies of working-age (≥15 years) workers in the formal and informal economy.
- Includes a broader set of non-randomized intervention studies, such as quasi-experimental, controlled before-after studies and interrupted time series studies.
- Followed all stages of a systematic review as defined in the Navigation Guide framework (Woodruff and Sutton 2014), including assessments of the risk of bias, quality of evidence, and strength of evidence, with the Navigation Guide's tools and approaches (Lam et al. 2016a).
- Includes only occupational exposure to welding fumes (not all exposures including environmental ones).
- Updates prior review and meta-analytic evidence on lung cancer, but also includes trachea and bronchus cancer in the outcome definition.
- Includes studies published up to 30 April 2020, plus studies awaiting classification identified up to 30 April 2022.

1.3. Description of the risk factor

The definition of the risk factor, the risk factor levels, and its theoretical minimum risk exposure level are presented in Table 1. The risk factor is defined as having two levels: Any (or high) occupational exposure to welding fumes and no (or low) occupational exposure to welding fumes. The assumed theoretical minimum risk exposure level is no (or low) occupational exposure to welding fumes. If studies reported

Table 1
Definitions of the risk factor, risk factor levels, and the minimum risk exposure level.

Concept	Definition
Risk factor	Occupational exposure to welding fumes from welding any material by any welding process
Risk factor levels	1. Any (or high) occupational exposure to welding fumes 2. No (or low) occupational exposure to welding fumes
Theoretical minimum risk exposure level	No (or low) occupational exposure to welding fumes

Footnote: Adapted from the protocol (Pega et al. 2020a).

exposure levels differing from the standard levels we define here, then, if possible, we converted the reported levels to the standard levels and, if not possible, we reported analyses on these alternate exposure levels as supplementary information in the systematic review.

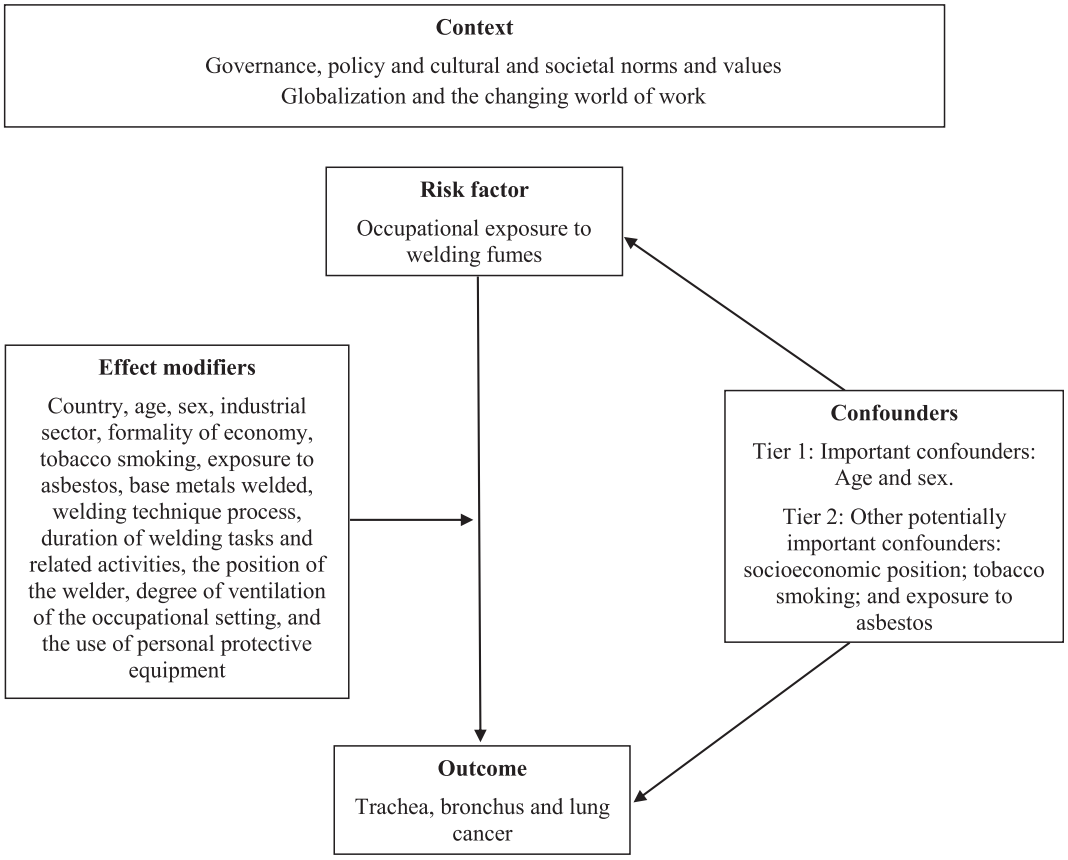
1.4. Description of the outcome

The WHO Global Health Estimates group outcomes into standard burden of disease categories (World Health Organization 2017), based on standard codes from the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) (World Health Organization 2015). The relevant WHO Global Health Estimates category for our systematic review is: "II.A7. Trachea, bronchus, and lung cancer" (World Health Organization 2017), and this category covers ICD-10 codes "C33 Malignant neoplasm of trachea" and "C34 Malignant neoplasm of bronchus and lung". Our systematic review covers the entire burden of disease of the relevant WHO Global Health Estimates category.

1.5. How the risk factor may impact the outcome

Official health estimates of the burden of disease attributable to an occupational risk factor require a sufficient level of scientific consensus that the risk factor causes the disease or other specified health outcome (Stevens et al. 2016). The above mentioned conclusion of the working group of individual experts convened by IARC in 2017 is the most recent scientific consensus that exposure to welding fumes is a sufficient cause of lung cancer in humans (Guha et al. 2017; International Agency for Research on Cancer 2018). or The working group for the IARC Monograph Volume 118 reported that, for the mechanistic data, there was strong evidence to suggest that welding fumes are carcinogenic through chronic inflammation and immune suppression, and moderate evidence to suggest genotoxicity, induction of oxidative stress, and altered cell proliferation or death (International Agency for Research on Cancer (2018), p262–263). The working group reported "limited evidence in experimental animals for the carcinogenicity of gas metal arc stainless steel welding fumes" (International Agency for Research on Cancer (2018), p265). It judged there to be "sufficient evidence in humans for the carcinogenicity of welding fumes" and that "welding fumes cause cancer of the lung" (International Agency for Research on Cancer (2018), p265). Its overall evaluation, based on a synthesis of evidence streams of mechanistic, animal, and human studies, was that "Welding fumes are carcinogenic to humans and cause cancer of the lung (Group 1)" (International Agency for Research on Cancer (2018), p265). Therefore, welding fumes are an established risk factor for human health. The IARC hazard identification did not focus specifically on the effect of occupational exposure to welding fumes (as opposed to any exposure, including environmental ones), but this is the focus of the current systematic review and meta-analysis.

Causal diagrams are useful tools in epidemiologic research and evidence synthesis, because they provide transparent, graphical solutions for organizing the current state of knowledge about research topics (Rehfuess et al. 2013). Causal diagrams, such as directed acyclic graphs (Greenland et al. 1999) and logic models (Anderson et al. 2011), visually present complex relationships between variables and provide the framework for identifying study inclusion/exclusion criteria, guiding the literature search strategy, informing the variables for data extraction, and examining the factors that may contribute to differences between studies. The exposure and outcome of interest, as well as potential effect modifiers (variables that may modify the effect of the exposure on



Footnote: Adapted from the protocol (Pega et al. 2020a).

Fig. 1. Logic model of the possible causal relationship between occupational exposure to welding fumes and trachea, bronchus, and lung cancer.

the outcome) and confounders (variables that are associated with and precede both the exposure and outcome), are presented on a single diagram, with arrowheads showing the directionality in the relationships.

Fig. 1 presents the logic model for our systematic review and meta-analysis of the causal relationship between occupational exposure to welding fumes (risk factor) and trachea, bronchus, and lung cancer (outcome). This is an a priori, process-orientated logic model (Rehfuess et al. 2018) that seeks to capture the complexity of the risk factor-outcome causal relationship (Anderson et al. 2011). The Tier 1: "Important confounders" are age and sex. The Tier 2: "Other potentially important confounders" are socioeconomic position, tobacco smoking and exposure to asbestos, which was commonly used as an insulating material in ships, the material covering rod electrodes, the cylinders holding acetylene gas, and the heat-protective equipment of welders and blankets to slow cooling of the weld (Fig. 1). Potential effect modifiers are: country, age, sex, industrial sector, formality of economy, tobacco smoking, exposure to asbestos, base metals welded, welding technique/process, duration of welding tasks, and related activities (preparation, clean-up, breaks, etc.), the position of the welder, degree of ventilation of the occupational setting, and the use of personal protective equipment. Furthermore, the welders' level of experience may also influence the particles generated from welding fumes (Chang et al. 2013); increased exposure may occur for apprentice welders or welders with minimal training (Graczyk et al. 2016).

2. Objectives

To systematically review and meta-analyse randomized control studies, cohort studies, case-control studies, and other non-randomized intervention studies with estimates of the relative effect of any (or high) occupational exposure to welding fumes on the prevalence of, incidence of or mortality from trachea, bronchus, and lung cancer in any year among the working-age population, compared with the minimum risk exposure level of no (or low) exposure to welding fumes.

3. Methods

3.1. Developed protocol

The Navigation Guide (Woodruff and Sutton 2014) for systematic reviews in environmental and occupational health was used as our guiding methodological framework and applied wherever feasible. The Navigation Guide applies established systematic review methods from clinical medicine, including standard Cochrane methods for systematic reviews of interventions, to the field of environmental and occupational health to ensure systematic and rigorous evidence synthesis that reduces bias and maximizes transparency (Woodruff and Sutton 2014). The need for further methodological development and refinement of the relatively novel Navigation Guide has been acknowledged (Woodruff and Sutton 2014). Our systematic review used most of the Navigation Guide framework; steps 1–6 for the stream on human data were conducted; we left out steps for the stream on non-human data, opting instead for a brief narrative synthesis of that evidence (see Section 1.4).

We developed and published our protocol (Pega et al. 2020a). This protocol adheres with the preferred reporting items for systematic review and meta-analysis protocols statement (PRISMA-P) (Moher et al. 2015; Shamseer et al. 2015), with the abstract adhering with the reporting items for systematic reviews in journal and conference abstracts (PRISMA-A). Any modification of the methods stated in the protocol is reported in Section 8 in this article. Our review has been presented in concordance with the preferred reporting items for systematic review and meta-analysis statement (PRISMA) (Page et al. 2021b). The reporting of the parameters for estimating the burden of trachea, bronchus, and lung cancer that is attributable to occupational exposure to welding fumes in the systematic review adheres to the requirements of the GATHER guidelines (Stevens et al. 2016) because the WHO/ILO Joint Estimates that may be produced consecutive to this systematic review must also adhere to these reporting guidelines.

All methods and reporting guidelines were standardised across all systematic reviews conducted for the WHO/ILO Joint Estimates (Pega et al. 2021c).

3.2. Searched literature

3.2.1. Electronic academic databases

We searched the seven following electronic academic databases to the specified date:

1. International Clinical Trials Register Platform (inception to 15 April 2020).
2. CENTRAL (1 January 1996 to 15 April 2020).
3. Ovid Medline (1 January 1946 to 30 April 2020).
4. PubMed (1 January 1946 to 15 April 2020).
5. EMBASE (1 January 1947 to 15 April 2020).
6. Web of Science (1 January 1945 to 15 April 2020).
7. CISDOC (1 January 1901 to 31 December 2012).

The Ovid MEDLINE search strategy was presented in the protocol (Pega et al. 2020a). The full search strategies for all databases were revised by an information scientist and are presented in Appendix 1 in the Supplementary data. We performed searches in electronic databases operated in the English language using a search strategy in the English language between March and May 2020. When we neared completion of the review, we conducted a search of the Ovid MEDLINE and PubMed databases on 14 March 2022 to capture the most recent publications (e.g., publications ahead of print). Deviations from the planned search strategy are documented in Section 8.

3.2.2. Electronic grey literature databases

We searched the following two electronic academic databases up to 21 April 2020:

1. OpenGrey (https://www.opengrey.eu/).
2. Grey Literature Report (https://www.nyam.org/library/collections-and-resources/grey-literature-report//).

3.2.3. Internet search engines

We also searched Google (https://www.google.com) and Google Scholar (https://www.google.com/scholar) and screened the first 100 hits for potentially relevant records, as has previously been done in Cochrane Reviews (Pega et al. 2022c).

3.2.4. Organizational websites

The websites of the seven following international organizations and national government departments were searched in May 2020:

1. International Labour Organization (https://www.ilo.org).
2. World Health Organization (https://www.who.int).
3. International Agency for Research on Cancer (https://www.iarc.fr).
4. European Agency for Safety and Health at Work (https://www.osha.europa.eu).
5. Eurostat (https://www.ec.europa.eu/eurostat/web/main/home).
6. China National Knowledge Infrastructure (https://www.cnki.net).
7. Finnish Institute of Occupational Health (https://www.ttl.fi/en).
8. United States National Institute of Occupational Safety and Health (NIOSH) of the United States of America, using the NIOSH data and statistics gateway (https://www.cdc.gov/niosh/data).

3.2.5. Hand-searching and expert consultation

We hand-searched for potentially eligible studies in:

- Reference lists of previous systematic reviews.

- Reference lists of all included study records.
- Study records published over the past 24 months in the three peer-reviewed academic journals with the largest number of included studies.
- Study records that have cited the included studies (identified in the Web of Science citation database).
- Collections of the review authors.

Additional experts were contacted with a list of included studies, with the request to identify potentially eligible additional studies.

3.3. Selected studies

Study selection was carried out in Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). All study records identified in the search were downloaded, and duplicates were identified and deleted. Afterwards, at least two review authors, working in pairs, independently screened titles and abstracts (step 1), and then full texts (step 2) of potentially relevant study records. A third review author resolved any disagreements between the first two review authors. Study records were not assigned to reviewers who had been authors of that study. The study selection was documented in a flow chart in the systematic review, as per PRISMA guidelines.

3.4. Eligibility criteria

The population, exposure, comparator, and outcome (PECO) criteria (Morgan et al. 2018) are described below.

3.4.1. Types of populations

We included studies of working-age (≥15 years) workers in the formal and informal economy. Studies of children (aged < 15 years) and unpaid domestic workers were excluded. Participants residing in any Member State of WHO and/or ILO and working in any industrial sector or occupation were included. Occupational exposure to welding fumes may potentially have further population reach (e.g., as an environmental exposure, through the release of welding fumes from the workplace into the community); the scope of our systematic reviews did not capture these populations and impacts on them. Appendix A in the Supplementary data for Pega et al. (2020a) provides a briefer overview of the PECO criteria.

3.4.2. Types of exposures

We included studies of occupational exposure to welding fumes in accordance with our standard definition (Table 1). Occupational exposure to welding fumes may be measured in several ways:

- Directly with quantitative measurement (e.g., by means of technology, such as air monitoring).
- Directly by observation of the work process.
- Indirectly by proxy of occupation (or job title), such as relevant codes and/or titles of the International Standard Classification of Occupations (ISCO) (International Labour Organization 1966; 1987; 2012) (Table 2).
- Indirectly by job task of welding.
- Indirectly by classification in a job-exposure matrix (JEM) based on expert judgment or data external to the study.
- Indirectly by judgment of scientists with subject matter expertise.
- Indirectly by self-report by a worker or their workplace manager or spouse.

Studies using any of the preceding methods to identify occupational exposure to welding fumes were eligible for inclusion. However, studies of workers whose jobs may include occasional or infrequent welding, such as plumbers, pipefitters or vehicle repairers, were excluded from this exposure definition, but could be considered in subsequent updates. Studies using industrial sector as a proxy, which may be measured using the codes of the International Standard Industrial Classification of All Economic Activities (United Nations 2008), were also excluded, because we judged measurements of industrial sector unable to identify workers occupationally exposed to welding fumes. Similarly, studies that combined occupation as a welder into broad groups with other occupations or industrial sectors were also ineligible, as these groupings lack specificity for occupational exposure to welding fumes (International Agency for Research on Cancer 2018).

If a study presented both direct and indirect measurements, and/or objective and subjective measurements, then we prioritized direct and objective measurements. We included studies with measures from any data source, including registry data.

3.4.3. Types of comparators

The included comparator was participants exposed to the theoretical minimum risk exposure level of no (or low) occupational exposure to welding fumes (Table 1). As the aim of the systematic review and meta-analysis is risk quantification (rather than hazard identification), and we are therefore pursuing the most accurate risk estimates, we excluded all other comparators, including comparators that may have included welders, such as the general population (see also text on standardized rate ratios and odds ratios [ORs] in below Section 3.4.6).

3.4.4. Types of outcomes

We included studies that defined trachea, bronchus, and lung cancer in accordance with our standard definition of this outcome (see Section 1.3). We included studies that classified these cancers using the relevant diagnostic codes in ICD-10 (see above), ICD-9 (i.e., "162 Malignant neoplasm of trachea, bronchus, and lung") or other versions of the ICD. Studies were also included if they measured the outcome with methods that we judged to approximate the ICD-10 criteria (e.g., where an ICD code was not reported, it was inferred from the information on the cancer site reported in the study record).

The following measurements of trachea, bronchus, and lung cancer were regarded as eligible:

(i) Diagnosis by a physician with imaging.

Table 2
International Standard Classification of Occupation (ISCO) codes and titles of occupations classified as occupationally exposed to welding fumes.

ISCO revision	Code	Title
ISCO-68 (International Labour Organization 1966)	87200	Welders
	87210	Gas & electric welders (general)
	87215	Gas welders
	87220	Electric arc welders (hand)
	87225	Electric arc welders (machine)
	87230	Thermite arc welders
	87235	Resistance welders
ISCO-88 (International Labour Organization 1987)	7212	Welders and flame cutters
ISCO-08 (International Labour Organization 2012)	7212	Welders and flame cutters

Footnotes: ISCO-68 codes adopted from Kendzia et al. (2013).

(ii) Hospital discharge records.
(iii) Other relevant administrative data (e.g., records of sickness absence or disability).
(iv) Registry data for diagnosis of and/or treatment for an eligible trachea, bronchus, and lung cancer.
(v) Medically certified cause of death.
(vi) Self-reported diagnosis.

All other measures were excluded from this systematic review.

Objective and subjective measures of the outcome were eligible. If a study presented both objective and subjective measurements, then the objective ones were selected.

3.4.5. Types of studies

We included studies that investigated the effect of occupational exposure to welding fumes on trachea, bronchus, and lung cancer, for any study year(s), and over any period. Eligible study designs were randomized controlled trials (including parallel-group, cluster, cross-over and factorial trials), cohort studies (both prospective and retrospective), case-control studies, and other non-randomized intervention studies (including quasi-randomized controlled trials, controlled before-after studies, and interrupted time series studies). We included a broader set of observational study designs than is commonly included, because an augmented Cochrane Review of complex interventions identified valuable additional studies using such a broader set of study designs (Arditi et al. 2016). As we have an interest in quantifying risk and not in qualitative assessment of hazard (Barroga and Kojima 2013), we excluded all other study designs (e.g., uncontrolled before-and-after, cross-sectional, qualitative, modelling, case, and non-original studies).

Study records published in any year and any language were included. The search was conducted using English language terms, so that records published in any language that presented essential information (i.e., title and abstract) in English were included. If a record was written in a language other than those spoken by the authors of this review, then the record was translated into English. Published and unpublished studies were included. Studies conducted using unethical practices were excluded (e.g., randomized controlled trials that deliberately exposed humans to a known risk factor to human health).

3.4.6. Types of effect measures

We included measures of the effect of any (or high) occupational exposure to welding fumes on the risk of having, acquiring or dying from cancer of the trachea, bronchus or lung, compared with the theoretical minimum risk exposure level (i.e., no or low, such occupational exposure). Included were relative effect measures, namely RRs and ORs for prevalence measures, and hazard ratios for incidence measures (e.g., acquired or died from a trachea, bronchus, and lung cancer). Measures of absolute effects (e.g., mean differences in risks or odds) were converted into relative effect measures, but if conversion was impossible, they were excluded. To ensure comparability of effect estimates and facilitate meta-analysis, if a study presented an OR, then we converted it into a RR, if possible, using the guidance provided in Cochrane's handbook for systematic reviews of interventions (Deeks et al. 2019; Higgins et al. 2021; Schünemann et al. 2021). As described by Hogue et al. (1983), this can be done by using the baseline risk. As there is some debate over the point at which to convert ORs into RRs, (Xiao et al. 2020; Doi et al. 2022a; Doi et al. 2022b; Xiao et al. 2022) for the main meta-analysis per outcome, we also meta-analysed the ORs first, and then converted the resultant pooled OR into a RR. To be comprehensive, we report these alternative analyses in an appendix.

If a study reported an eligible effect estimate without measure of uncertainty (e.g., 95 % CI or standard deviation), but did report another statistic that could be used to back-calculate (or estimate) an eligible measure of uncertainty (e.g., a p value from a regression analysis), then we calculated the measure of uncertainty. That is, for the effect estimate reported in the study by Steenland et al. (1986), we calculated its 95 % CI from the p value reported, using the method outlined by Altman and Bland (2011). If we entered a study with such a back-calculated measure of uncertainty in a meta-analysis, we conducted a sensitivity analysis of the meta-analysis with the effect estimate removed and used this analysis to assess if the study made a substantive difference to the meta-analysis. We report the methods and input data for such calculations in an appendix.

To ensure an unexposed comparison group, studies that included a general population comparator group were excluded from this systematic review, as the general population may include persons potentially occupationally exposed to welding fumes. Therefore, standardized RRs, for example or standardized ORs, where the rates or odds of prevalence, incidence or mortality among the exposed population were compared with the rates or odds amongst the general population, were excluded from the systematic review (see also Section 3.4.3).

If a study presented estimates for the effect from two or more alternative models that had been adjusted for different variables, then we systematically prioritized the estimate from the model that we considered best adjusted, applying the lists of potential effect modifiers and confounders identified in our logic model (Fig. 1). We generally prioritized estimates from models adjusted for more potential confounders over those from models adjusted for fewer. For example, if a study presented estimates from a crude, unadjusted model (Model A), a model adjusted for one potential confounder (Model B), and a model adjusted for two potential confounders (Model C), then we prioritized the estimate from Model C. However, we also considered the potential for over-adjustment in models that included non-confounders as covariates. We prioritized estimates from models unadjusted for mediators over those from models that adjusted for mediators, because adjustment for mediators can introduce bias. For example, if Model A had been adjusted for two confounders and Model B had been adjusted for the same two confounders and a potential mediator (e.g., biomarkers of exposure to welding fumes), then we chose the estimate from Model A. We prioritized estimates from models that could adjust for time-varying confounders that were at the same time also mediators, such as marginal structural models (Pega et al. 2016), over estimates from models that could only adjust for time-varying confounders, such as fixed-effects models (Gunasekara et al. 2014), over estimates from models that could not adjust for time-varying confounding. If a study presented effect estimates from two or more potentially eligible models, we provide an explanation as to why we prioritized the model we selected.

If adjustment for one or both Tier 1 confounders was somewhat unclear (due to unclear reporting), but we reasonably assumed it to have occurred, we did include this study in the meta-analysis, but conducted a sensitivity analysis without this study to check the impact of the study on the meta-analysis (see Section 3.9).

For case-control studies matched by Tier 1 confounding variables (i.e., age and sex), we applied the following eligibility criteria, as applied in a previous systematic review for the WHO/ILO Joint Estimates (World Health Organization 2021). As Pearce (2016) has pointed out, "Matching in a case-control study does not control for confounding by the matching factors" (p.1), so it may be necessary to control for the matching factors in the analysis. Matching, without controlling for the matching factors may create an association with the matching factor, even if no such association existed before matching (Pearce 2016). Therefore, if a case-control study matched by one or both Tier 1 confounders, but did not adjust for these matching variables (e.g., in a regression analysis), we included this study in the systematic review, but excluded it from the meta-analysis (as done previously (World Health Organization 2021)). As stated by Pearce (2016), a matched (conditional) analysis is not always required, and standard (unconditional) analysis may be valid and appropriate; therefore, we included effect estimates regardless of conditionality of analysis.

For the Kendzia et al. (2013) individual participant data analysis, we referred to the original study record(s) of an included study to systematically identify the best effect estimate(s) for this included study (i.e.,

the one(s) reported in the original study record(s) or the recalculated one(s) reported in the study record of the Kendzia analysis).

3.5. Data extraction and data items

We used the standard data extraction sheet that WHO and ILO have developed for their series of systematic reviews for the WHO/ILO Joint Estimates. The data extraction sheet was trialled until data extractors reached convergence and agreement. At least two review authors independently extracted data on study characteristics (including study authors, study year, study country, participants, exposure, and outcome), study design (including study type, comparator, epidemiological model(s) used, and effect estimate measure), and risk of bias (including source population representation, blinding, exposure assessment, outcome assessment, confounding, incomplete outcome data, selective outcome reporting, conflict of interest including statements of declarations of interest and funding sources, and other sources of bias). A third review author resolved conflicts in data extraction. Data were entered into and managed with Excel (Microsoft, Redmond, United States of America (USA)).

3.6. Requested missing data

We did not request missing data (see Section 8).

3.7. Assessed risk of bias

Standard risk of bias tools do not exist for systematic reviews for hazard identification or those for risk assessment in occupational and environmental health (Rooney et al. 2016). The five such tools developed specifically for occupational and environmental health are for either or both hazard identification and risk assessment, and they differ substantially in the types of studies (randomized, observational, and/or simulation studies) and data (e.g., human, animal and/or in vitro) they seek to assess (Rooney et al. 2016). However, all five tools, including the Navigation Guide, assess risk of bias in human studies similarly (Rooney et al. 2016).

Consistent with using the Navigation Guide as our organizing framework, we used its risk of bias tool, which builds on the standard risk of bias assessment methods of Cochrane (Higgins et al. 2021) and the US Agency for Healthcare Research and Quality (Viswanathan et al. 2008), and has been successfully applied in several systematic reviews (Koustas et al. 2014; Lam et al. 2014; Vesterinen et al. 2015; Johnson et al. 2016; Lam et al. 2016a,b; Lam et al. 2017; Lam et al. 2021). To adhere with the latest methods in the Navigation Guide, we used updates from a version published in the protocol for a recent systematic review (Lam et al. 2016b; Lam et al. 2021).

We assessed risk of bias on the individual study level and across the body of evidence for each outcome. To judge the risk of bias in each domain, we applied a priori instructions (Li et al. 2018), adapted from the Navigation Guide systematic review (Lam et al. 2016b; Lam et al. 2021), and further described in our protocol (Pega et al. 2020a). The assessment was conducted along the Navigation Guide risk of bias domains, including consideration of source population representation, blinding, exposure assessment, outcome assessment, confounding, incomplete outcome data, selective outcome reporting, conflict of interest, and other sources of bias.

All risk of bias assessors jointly trialled the application of the risk of bias criteria until they had synchronized their understanding and application of these criteria. Two or more study authors independently assessed the risk of bias for each study by outcome. Where individual assessments differed, a third author resolved the conflict. For each included study, we reported the risk of bias assessment by domains in a standard "Risk of bias" table (Higgins et al. 2021). For the entire body of evidence, we presented the study-level risk of bias ratings for each individual study by domains in a "Risk of bias summary" figure (Higgins et al. 2021).

During the systematic review, we identified the need to further develop our criteria for assessments of risk of bias due to exposure misclassification. We agreed that for studies that based exposure assignment on an occupation or a job title of "welder" (or similar) alone, we would rate risk of bias in this domain to be relatively higher than for studies that assigned exposure based on a job task of "welding" or employed a welding-specific questionnaire or more complex job exposure matrix. We present the fully updated risk of bias assessment criteria in Appendix 2. This supersedes the criteria presented in the protocol (see Appendix C in Pega et al. (2020a)).

3.8. Synthesised evidence (including conducted meta-analysis)

We conducted meta-analyses separately for estimates of the effect on prevalence, incidence, and mortality. If we found two or more studies with an eligible effect estimate, two or more review authors independently investigated the clinical heterogeneity (Deeks et al. 2011) of the studies in terms of participants (including country, sex, age, and industrial sector or occupation), level of risk factor exposure, comparator, and outcomes, following our protocol (Pega et al. 2020a). Differences by country could include or be expanded to include differences by country group (e.g., WHO region or World Bank income group). If the effect estimates differed considerably by WHO region, sex, and/or age or a combination of these, then we synthesised evidence for the relevant populations defined by these variables or combination thereof. If we found effect estimates to be clinically homogeneous across WHO regions, sex, and/or age groups, then we combined studies from all these populations into one pooled effect estimate that would be applied across all combinations of WHO regions, sexes, and age groups in the WHO/ILO Joint Estimate.

If we judged two or more studies for the relevant combination of WHO region, sex, and age group or combination thereof, to be sufficiently clinically homogeneous to potentially be combined using quantitative meta-analysis, then we tested the statistical heterogeneity of the studies using the I^2 statistic (Figueroa 2014). If two or more clinically homogeneous studies were found to be sufficiently homogeneous statistically to be combined in a meta-analysis, we pooled the effect estimates of these studies in a quantitative meta-analysis, using the inverse variance method with a random effects model to account for cross-study heterogeneity (Figueroa 2014). We prepared the data for entry using Excel and conducted the meta-analysis in RevMan version 5.4.1 (Nordic Cochrane Centre, Copenhagen, Denmark). We input RRs (log–-transformed) and their standard errors into RevMan with a precision of two decimal places. Standard errors were calculated from the lower confidence limits, which sometimes results in small discrepancies between the upper confidence limit reported in the original study record and that displayed in the forest plot of the relevant meta-analysis.

If a study reported two or more estimates of the effect of different levels of exposure, as compared with no (or low) exposure (reference group), the estimates associated with these comparisons were not independent, as the study participants in the reference group were shared across the comparisons. Therefore, these estimates could not be included in the same meta-analysis as if they came from separate studies. In such cases, we computed a composite (average) study-level effect estimate for the comparison of each exposure level versus the reference group, by taking within-study correlation into consideration as suggested in the Cochrane handbook for systematic reviews of interventions (McKenzie and Brennan 2021). We followed the principles outlined by (Borenstein et al. 2009). We then entered this pooled effect estimate for this study in the meta-analysis and reported more detailed methodological information and data inputs in an appendix.

We neither quantitatively combined data from studies with different designs (e.g., did not combine cohort studies with case-controls studies), nor unadjusted effect estimates with adjusted ones. We only combined studies that we judged to have a minimum acceptable level of

adjustment for confounders (i.e., a study must have adjusted for at least one of the two Tier 1 confounders of age or sex). In instances where two or more studies of the same data source (e.g., the same study cohort) were eligible for inclusion in the meta-analysis, we prioritized in this order: i) the study with the most informative assessment of exposure to welding fumes; ii) the study with the longest follow-up period; and iii) the study with the most complete control of relevant potential confounders. If our pre-specified rules for selecting a study's result did not allow us to uniquely identify-one for inclusion, we randomly selected one study. If quantitative synthesis was not feasible, we synthesised the study findings narratively and identified the estimates that we judged to be the highest quality evidence available.

3.9. Conducted subgroup and sensitivity analyses

We conducted the following subgroup analyses for the main meta-analysis:

- WHO region (six categories: African Region, Region of the Americas, Eastern Mediterranean Region, European Region, South-East Asian Region, and Western Pacific Region).
- Sex (three categories: female, male, and other).
- Occupation (ISCO codes).
- Cancer site (four categories: trachea, bronchus, lung cancer, and two or more of these sites).
- Publication year of the study (four categories: 1980 s, 1990 s, 2000 s, and 2010 s).

We found insufficient data to conduct our planned subgroup analyses by:

- Age group (13 categories: 15–19, 20–24, 25–29, …, 90–94, and $\geq$ 95 years).
- Socio-economic status (e.g., education or income level).
- Industrial sector (ISIC codes).
- Formality of the economy (two categories: informal economy, and formal economy).

We conducted the following sensitivity analyses:

- Studies judged to be of "high"/"probably high" risk of bias in any domain, compared with "low"/"probably low" risk of bias in all domains.
- Studies judged to be of "high"/"probably high" risk of bias from exposure misclassification, compared with "low"/"probably low" risk of bias in this domain.
- Studies judged to be of "high"/"probably high" risk of bias from conflict of interest, compared with "low"/"probably low" risk of bias in this domain.
- Studies judged to be of "high"/"probably high" risk of confounding, compared with "low"/"probably low" risk of confounding.
- Studies with documented or approximated ICD-10 diagnostic codes (e.g., as recorded in administrative health records), compared with studies without ICD-10 codes (e.g., self-reports).
- Studies with adjustment for tobacco smoking and/or exposure to asbestos, compared with studies with adjustment for neither tobacco smoking, nor exposure to asbestos.
- Meta-analysis with the inverse variance heterogeneity (IVhet) model (Doi et al. 2017), compared with the standard inverse variance meta-analysis with random effects.
- For meta-analyses with two or more individual effect estimates from the same study, conducted a meta-analysis with the individual effect estimates included individually, compared with a meta-analysis with the individual effect estimates first pooled in a fixed effect meta-analysis and then the pooled effect estimate included in the meta-analysis per study.
- For meta-analyses with one or more included effect estimates for which adjustment for one or both Tier 1 confounders was assumed but somewhat unclear (see Section 3.4.6), conducted a meta-analysis with these effect estimates included or compared with a meta-analysis with these effect estimates excluded.
- For case-control studies, meta-analyses with ORs converted to RRs before conducting the quantitative meta-analysis, compared with meta-analyses with ORs pooled in the quantitative meta-analysis and then the pooled OR being converted to a RR.
- For cohort studies, those that reported RRs as the effect estimate, compared with those that reported hazard ratios.
- Studies for which we calculated average effect estimates from two or more effect estimates of different exposure levels using the method developed by Borenstein et al. (2009), compared with studies for which we did not have to do such calculations.
- Studies for which we back-calculated the standard error from a p value, compared with studies for which we back-calculated the standard error from a 95 % CI.
- Following peer-review, we conducted meta-analyses with RR among non-smokers or never-smokers, compared with meta-analyses with RR among smokers.

We also conducted leave-one-out analyses to explore changes in heterogeneity and pooled effect estimates.

3.10. Assessed quality of evidence

We assessed quality of evidence using a modified version of the Navigation Guide quality of evidence assessment approach (Lam et al. 2016b). The approach is based on the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach (Schünemann et al. 2011) adapted specifically to systematic reviews in occupational and environmental health (Morgan et al. 2016).

A group of review authors comprising members of the working group of individual experts assessed quality of evidence for the entire body of evidence by outcome, through a consensus process. All review authors were subsequently given the opportunity to review and propose revisions to the assessments. The ratings and justifications presented here are the final consensus ratings and justifications of the working group of individual experts. We adapted the latest Navigation Guide instructions (Lam et al. 2016a) for assessing the quality of evidence and presented the adapted instructions in our protocol (Pega et al. 2020a). We graded the quality of the entire body of evidence by outcome, using the three Navigation Guide standard quality of evidence ratings: "high", "moderate", and "low" (Lam et al. 2016b). We downgraded the quality of evidence for the following five reasons: (i) risk of bias; (ii) inconsistency; (iii) indirectness; (iv) imprecision; and (v) publication bias (Balshem et al. 2011).

If our main meta-analysis included ten or more studies, we generated an Egger's funnel plot to judge our level of concern regarding publication bias (Egger et al. 1997). Additionally, we also produced a Doi plot and Luis Furuya-Kanamori (LFK) index. Briefly, the Doi plot is a variant of the normal quintile versus effect plot using a rank-based measure of precision (z-score), instead of the standard error, which is plotted against the effect size (Furuya-Kanamori et al. 2018). The most precise studies define the midpoint around which results scatter, whereas smaller, less precise studies produce an effect size that scatters increasingly widely, and the absolute z-score gradually increases for both smaller and larger effect sizes on either side of the precise studies. Doi plot asymmetry was quantified with the LFK index (Furuya-Kanamori et al. 2018; Furuya-Kanamori et al. 2020). The LFK index quantifies the difference between the two areas under the Doi plot, created by the perpendicular line to the X-axis from the effect size with the lowest absolute Z score on the Doi plot (Furuya-Kanamori et al. 2018). A symmetrical, mountain-like Doi plot and LFK index $<|1|$ indicate no asymmetry; an LFK index between $|1|$ and $|2|$ indicates minor

asymmetry; and an LFK index >|2| indicates major asymmetry (Furuya-Kanamori et al. 2018). In empirical simulation studies, these methods have demonstrated greater power to detect publication bias with as few as five estimates than p value driven methods (Furuya-Kanamori et al. 2020). If our main meta-analysis included four or fewer studies only, we judged the risk of publication bias qualitatively.

Within each of the relevant domains, we rated the concern for the quality of evidence, using the ratings "no or only minor concerns", "serious concerns", and "very serious concerns". As per Navigation Guide, randomized studies start at "high" quality of evidence and observational studies at "moderate" quality of evidence". Quality of evidence was downgraded for a rating of "serious concerns" by one level and for one of "very serious concerns" by two levels. We upgraded the quality of evidence for a large effect size, evidence of a dose–response relationship, and residual confounding and bias not plausibly explaining the effect. There had to be compelling reasons to upgrade or downgrade. If we had serious concerns for risk of bias in a body of evidence consisting of observational studies, but had no other concerns, and had no reasons for upgrading, then we downgraded the quality of evidence by one level from "moderate" to "low".

Regarding large effect size, our protocol did not pre-specify criteria for judging what constitutes large and very large effect sizes in this systematic review (Pega et al. 2020a). Moreover, we judged the definitions of large and very large effect sizes provided in the GRADE handbook (2013) to not represent typical findings in environmental and occupational epidemiology even when materially important risks are observed (Huangfu and Atkinson 2020). Initially, we considered the cut-off of change in RR by $\geq$ 25 % (i.e., an RR of $\leq$ 0.75 or $\geq$ 1.25) as indicative of a large effect size, informed by a previous WHO/ILO systematic review on the effect of occupational exposure to noise on cardiovascular disease outcomes (Teixeira et al. 2021b), which had been informed by a WHO evidence review on the health effects of environmental exposure to noise (van Kempen et al. 2018). However, this criterion was adopted from a different risk factor-health outcome pair and may be seen as arbitrary. During the peer-review process it was suggested that we could adopt the strategy used in a recent WHO evidence review on the effect of long-term air pollution on mortality (Huangfu and Atkinson 2020), which calculated the so-called E-values and considered a reference confounder to assess the likelihood of residual confounding (Verbeek et al. 2021). Briefly, this approach attempts to judge the magnitude of an observed effect (pooled RR) of risk factor relative to a critical threshold (i.e., the E-value), which the effect of a plausible unmeasured confounder would have to exceed to attenuate the effect of said risk factor to 1.00. That is, if an unmeasured confounder (e.g., tobacco smoking or exposure to asbestos) has an effect on both the risk factor (i.e., occupational exposure to welding fumes welding) and the outcome (i.e., trachea, bronchus, and lung cancer prevalence, incidence or mortality) equal to or larger than the E-value, then it can be assumed that there is no evidence of a large effect, as the pooled RR of the risk factor could be reduced to null. Conversely, if this threshold is not exceeded by the effect of the confounder, one can assume a large effect of the risk factor. Since neither of the two approaches is beyond reproach, we applied them both judiciously and in tandem. We therefore relied on two approaches to determine whether the quality of evidence should be upgraded for a large effect size.

3.11. Assessed strength of evidence

Our systematic review included observational epidemiologic studies of human data only, and no other streams of evidence (e.g., no studies of non-human data). The standard Navigation Guide methodology (Lam et al. 2016b) allows for rating human and non-human animal studies separately, and then combining the strength of evidence for each stream for an overall strength of evidence rating. However, the Navigation Guide also allows for rating one stream of evidence based on the factors described above (i.e., risk of bias, indirectness, inconsistency, imprecision, publication bias, large effect, dose–response, and residual confounding and bias) to arrive at an overall rating of the quality of evidence as "high", "moderate" or "low" (see above and the protocol). The approach of evaluating only the human evidence stream is consistent with the GRADE methodology that has adopted the Bradford Hill considerations (Schünemann et al. 2011) So, using the method above based on the Navigation Guide incorporates the considerations of Bradford Hill (see Appendix 3 in the Supplementary data).

An additional step described in the protocol integrates the quality of the evidence (as described above) with other elements including direction of effect, confidence in the effect, and other compelling attributes of the data that may influence our certainty to allow for an overall rating that consists of "'sufficient evidence of harmfulness", "limited evidence of harmfulness", "inadequate evidence of harmfulness", and "evidence of lack of harmfulness" based on human evidence. This approach to evaluate only the human evidence has been applied in previous systematic reviews (Lam et al. 2016b; Lam et al. 2017) and verified by the US National Academy of Sciences (National Academies of Sciences Engineering and Medicine). It also provides two steps that integrate Bradford Hill criteria (evaluating the quality of the evidence and then evaluating the overall strength of evidence). Finally, the GRADE quality of evidence ratings (which are the same as for Navigation Guide and the IARC Monographs) are analogous to the final ratings from Bradford Hill for causality (Schünemann et al. 2011) (Table 3).

4. Results

4.1. Study selection

A flow diagram of the study selection is presented in Fig. 2. Forty-one records from 40 studies fulfilled the eligibility criteria and were included in the systematic review. For the 30 excluded studies that most closely resembled inclusion criteria the reasons for exclusion are listed in Appendix 4 in the Supplementary data. Of the 40 included studies, 35 were included in one or more quantitative meta-analyses.

4.2. Characteristics of included studies

The characteristics of the included studies (ordered alphabetically) are summarized in Table 4.

4.2.1. Study type

Two-thirds of included studies (29) were case-control studies, and the other third were cohort studies (11). The type of effect estimate most commonly reported was ORs (29 studies), followed by risk or rate ratios (seven studies) and hazard ratios (four studies).

Thirty-eight studies adjusted for any of our pre-specified Tiers 1 and 2 confounders (including by restriction), but two studies did not adjust for any of these potential confounders. The confounders most commonly adjusted for were the two Tier 1 confounder of sex (37 studies, including 33 studies that restricted their study populations to males) and age (35 studies). Fewer studies adjusted for socioeconomic status (eight studies).

4.2.2. Population studied

The effective (or analysis) sample sizes of the included studies captured >1,265,512 workers in total, with at least 22,761 females and 1,231,171 males studied.

Thirty-five and four studies examined male workers and workers of both sexes, respectively. No studies examined females only. For one study it was unclear whether females were included in the analyses.

For many studies, the age group being studied was unclear. Several studies did not indicate an upper or lower age range, instead reporting age ranges such as between < 40 years and > 70 years.

Over half of the included studies examined populations in the WHO European Region (23 studies from 17 countries, including two multinational studies). Almost all of the remaining studies investigated

Table 3
Interpretation of the GRADE ratings of the overall quality of evidence, and the Navigation Guide and IARC Monographs ratings for strength of evidence evaluation.

GRADE rating for quality of evidence	Interpretation of GRADE rating	Navigation Guide rating for strength of evidence for human evidence	Interpretation of Navigation Guide rating	IARC Monographs rating (descriptor) for strength of evidence descriptor for carcinogenicity in humans	Interpretation of IARC Monographs rating
High	There is high confidence that the true effect lies close to that of the estimate of the effect.	**Sufficient evidence of harmfulness**	A positive relationship is observed between exposure and outcome where chance, bias, and confounding can be ruled out with reasonable confidence. The available evidence includes results from one or well-designed, well conducted studies, and the conclusion is unlikely to be strongly affected by the results of future studies.	**Sufficient strength of evidence**	A causal association has been established: A positive association has been observed in the body of evidence on exposure to the agent and cancer in studies in which chance, bias, and confounding were ruled out with reasonable confidence.
		Evidence of lack of harmfulness	The available evidence includes consistent results from well designed, well conducted studies, and the conclusion is unlikely to be strongly affected by the results of future studies; for human evidence, more than one study showed no effect on the outcome of interest at the full range of exposure levels that humans are known to encounter, and bias and confounding can be ruled out with reasonable confidence; the conclusion is limited to the age at exposure and/or other conditions and levels of exposure studied.		
Moderate	There is moderate confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	**Limited evidence of harmfulness**	A positive relationship is observed between exposure and outcome where chance, bias, and confounding cannot be ruled out with reasonable confidence. Confidence in the relationship is constrained by such factors as: the number, size or quality of individual studies or inconsistency of findings across individual studies. As more information becomes available, the observed effect could change, and this change may be large enough to alter the conclusion.	**Limited strength of evidence**	A causal interpretation of the positive association observed in the body of evidence on exposure to the agent and cancer is credible, but chance, bias, or confounding could not be ruled out with reasonable confidence.
Low	The panel's confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.	**Inadequate evidence of harmfulness**	The available evidence is insufficient to assess effects of the exposure. Evidence is insufficient because of: the limited number or size of studies, low quality of individual studies or inconsistency of findings across individual studies. More information may allow an assessment of effects.	**Inadequate strength of evidence**	A causal interpretation of the positive association observed in the body of evidence on exposure to the agent and cancer is credible, but chance, bias, or confounding could not be ruled out with reasonable confidence.
Very low	There is little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.				

Footnotes: Adapted from World Health Organization (2021), based on Schünemann et al. (2011), Lam et al. (2016a), and Samet et al. (2020).

populations in the Region of the Americas (16 studies from three countries, with Canada included in studies by itself and in one of the multinational studies). Only two studies from two countries were from the Western Pacific Region. The most commonly studied countries were the United States (10 studies), followed by Italy (six studies), Canada (five studies), and Germany (three studies).

Several studies included multiple or all industrial sectors, and/or several occupations.

4.2.3. Exposure studied

Out of the total of 40 studies, 22 measured occupational exposure to welding fumes using face-to-face surveys (although two used a combination of face-to-face and telephone surveys).

No studies measured exposure directly, and all studies measured exposure indirectly. Most studies measured exposure using self-reported data, e.g., occupation, job title, job tasks or self-reported exposures. For some studies, industrial hygienists assessed exposure based on these self-reports. Two studies relied on reports from people other than the

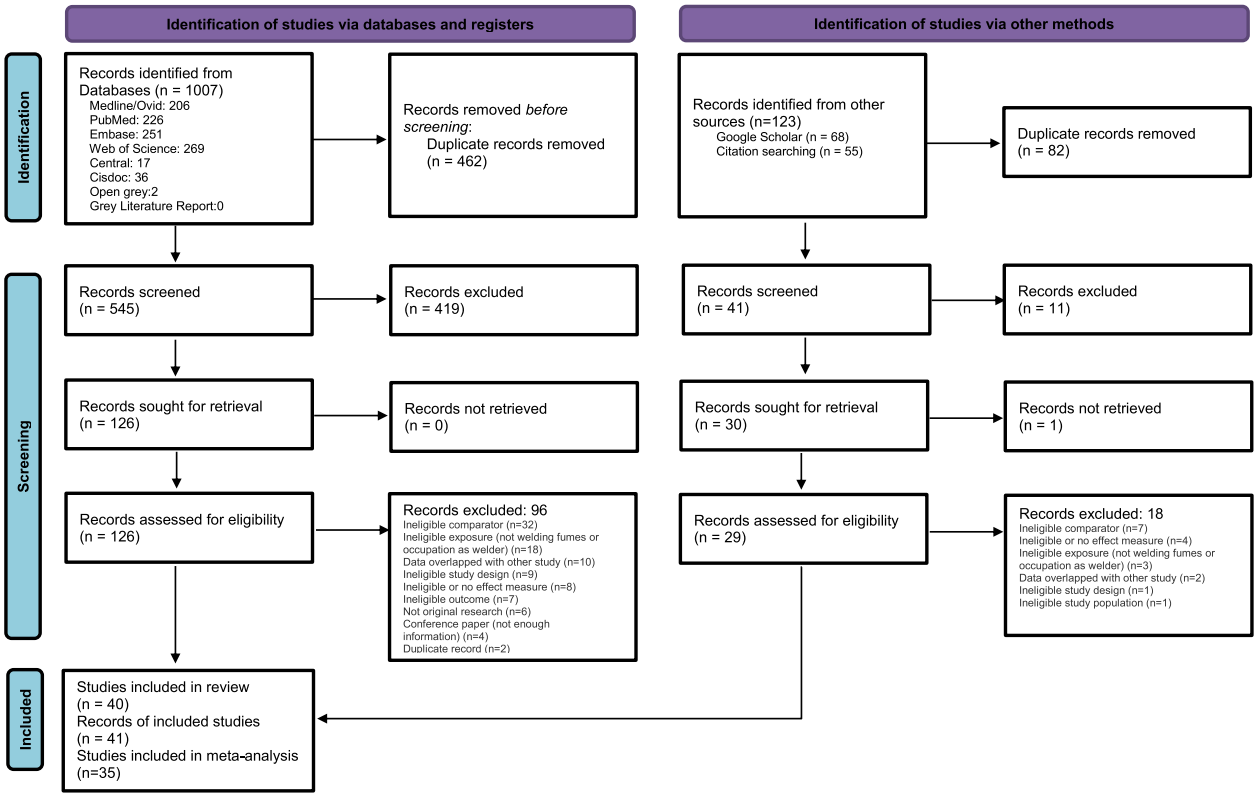


Fig. 2. PRISMA 2020 flow diagram of study selection. Footnote: PRISMA 2020 flow chart template sourced from Page et al. (2021a).

workers themselves, namely their workplace supervisors, spouses or colleagues. Three studies used information on occupation as recorded in administrative records (i.e., death certificates or cancer registry records).

Some studies measured exposure to occupational exposure to welding fumes, whereas other studies assigned those who had the occupation or job title of "welder" as exposed. For some studies, exposure was required for a minimum period (e.g., six months or one year) for a participant to be assigned to be exposed.

4.2.4. Comparator studied

The comparator in studies was workers with no (or low) occupational exposure to welding fumes, which was often assigned by proxy of occupation as workers who did not have the occupation (or job title or equivalent) of "welder".

4.2.5. Outcomes studied

The 40 studies in our systematic review and meta-analysis reported on two different health outcomes: trachea, bronchus, and lung cancer incidence (32 studies) and mortality (eight studies). No study reported on the prevalence of these cancer sites.

The outcome was most commonly assessed through medical records, often linked into population-based cancer registries. However, some studies used other sources for outcome assessment, such as death certificates.

4.3. Characteristics of studies awaiting classification

We identified two recently published studies (published since our original search was conducted, as identified in our updated search) that may potentially be eligible for inclusion in our systematic review but are still awaiting classification (Table 5).

4.4. Risk of bias within studies

The detailed justification for the risk of bias rating for each domain at the level of the included individual study by outcome (as shown in Figs. 3 and 4) is presented in Appendix 5 in the Supplementary data.

4.4.1. Acquired trachea, bronchus, and lung cancer (incidence)

The ratings for the 32 included studies for this outcome are presented in Fig. 3.

4.4.1.1. Bias in selection of participants into the study. Are the study groups at risk of not representing their source populations in a manner that might introduce selection bias?

We judged the risk of bias in selection of participants into the study to be "low" for 17 studies, "probably low" for 13 studies, "probably high" for two studies, and "high" for no studies. The "probably high" ratings were due to insufficient descriptions of the participation rates between cases and controls, but indirect evidence suggested selection was inconsistent across groups.

4.4.1.2. Bias due to a lack of blinding of study personnel. Was knowledge of the group assignments inadequately prevented (i.e., blinded or masked) during the study, potentially leading to subjective measurement of either exposure or outcome?

We rated the risk of bias due to a lack of blinding of study personnel as "low" for 21 studies, "probably low" for seven studies, "probably high" for four studies, and "high" for no studies. Our "probably high" ratings were given to studies for which we judged it unclear whether blinding occurred, and for which we deemed that a lack of blinding could have biased the exposure assessment.

4.4.1.3. Bias due to exposure misclassification – Were exposure assessment methods lacking accuracy?. We rated risk of bias in this domain as "low" for two studies, "probably low" for 15 studies, "probably high" for 13

Table 4
Characteristics of included studies: the effect of occupational exposure to welding fumes on trachea, bronchus, and lung cancer.

Study ID	Study population									Study type		
	Total number of study participants	Number of female study participants	Number of male study participants	Country of study population	Geographic location	Industrial sector	Occupation [a]	Age	Formality of economy	Study design	Study period (month of first collection of any data and month of last collection of any data)	Follow-up period (period in months between exposure and outcome)
(Becker 1999)	2901	Unclear	Unclear	Germany	National	24 Manufacture of basic metals; 25 Manufacture of fabricated metal products, except machinery and equipment	7212	Unclear	Formal	Cohort study	1989–1995	Minimum 19 years (1970–89) –maximum 45 years (1950–95)
(Brenner 2010)	1393	798 (Cases 236, Controls 562)	595 (Cases 209, Controls 386)	Canada	Region (Toronto)	Unclear	Unclear	<35–>75 years	Formal	Case-control study	1997–2002	Unclear
(Breslow 1954)	986	0	986	United States	Region (California)	Unclear	7212, 7213	<40–>70 years	Both	Case-control study	1949–1952	At least 5 years up to entire working life
(Bruske-Hohlfeld 2000)	4517	0	4517	Germany	Region (area surrounding Bremen and the Frankfurt area; West and East Germany, Nordrhein-Westfalen, Rheinland-Pfalz, Bayern, the Saarland, Thüringen, and Sachsen)	See footnote [b]	87200, 87210, 87215, 87220, 87225, 87230, 87235 (ISCO 1968)	Unclear for sample in Kendzia et al. (2013). In original study record the average age of controls 60.4 (8.6) and of cases 60.4 (8.5)	Unclear	Case-control study	1988–1996	Unclear
(Buiatti 1985)	1157	0	1157	Italy	Region (Toscana and Florence)	Unclear	7212	<45–>74 years	Unclear	Case-control study	1981–1983	Unclear
(Consonni 2010)	2840	0	2840	Italy	Region (Lombardy)	See footnote [b]	87200, 87210, 87215, 87220, 87225, 87230, 87235 (ISCO 1968)	Unclear for sample in Kendzia et al. (2013). In original study record, participants were 35–79 years of age at diagnosis (cases) or at sampling/ enrolment (controls), and the average age of controls 66.8 (SD 7.9) and cases 65.8 (SD 8.1)	Both	Case-control study	2002–2005	Unclear

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Table 4 (*continued*)

Study ID	Study population									Study type		
	Total number of study participants	Number of female study participants	Number of male study participants	Country of study population	Geographic location	Industrial sector	Occupation [a]	Age	Formality of economy	Study design	Study period (month of first collection of any data and month of last collection of any data)	Follow-up period (period in months between exposure and outcome)
(Corbin 2011)	536	0	536	New Zealand	National	See footnote [b]	87200, 87210, 87215, 87220, 87225, 87230, 87235 (ISCO 1968)	Unclear for sample in Kendzia et al. (2013). In original study record the age breakdown at interview was: controls 10.2 % 20–50 years, 23.2 % 51–60 years, 53.5 % 61–70 years, 13.0 % ≥71 years; cases 9.4¤ 20–50 years, 25.8 % 51–60 years, 62.1 % 61–70 years, 2.6 % ≥71 years	Unclear	Case-control study	2007–2008	Unclear
(Danielsen 1993)	4,571	0	4,571	Norway	Local (shipyard workers)	30 Manufacture of other transport equipment	7212	Unclear for entire cohort. Range 16–74 years	Formal economy	Cohort study (retrospective)	Observations from 1953 to 1990	Workers employed between 1940 and 1979 followed until 1990
(Danielsen 2000)	Unclear	0	Unclear	Norway	Local (shipyard workers)	30 Manufacture of other transport equipment	7212	Unclear for entire cohort. Range 16–24 years	Formal economy	Cohort study (retrospective)	1945–1991	1945–1991
(Elci 2003)	2,873	0	2,873	Turkey	Region (Marmara)	Unclear	7212	Unclear	Formal economy	Case-control study	1979–1984	Unclear
(Finkelstein 1995)	3,788	0	3,788	Canada	Local (two cities in Ontario)	Unclear	8335 (SOC 1980)	45–75 years	Both	Case-control study	1979–1988	Working life
(Fortes 2003)	512	0	512	Italy	Region (Lazio)	See footnote [b]	87200, 87210, 87215, 87220, 87225, 87230, 87235 (ISCO 1968)	35–90 years	Unclear	Case-control study	1993–1996	Unclear
(Gottlieb 1980)	5,606	0	5,606	United States	Region (Louisiana)	19 Manufacture of coke and refined petroleum products	7212	0–>35 years. For all industries combined the median age at death was 62.8 for cases and 61.4 for controls	Both	Case-control study	1960–1975	Unclear

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Table 4 (*continued*)

Study ID	Study population									Study type		
	Total number of study participants	Number of female study participants	Number of male study participants	Country of study population	Geographic location	Industrial sector	Occupation [a]	Age	Formality of economy	Study design	Study period (month of first collection of any data and month of last collection of any data)	Follow-up period (period in months between exposure and outcome)
(Guida 2011; Matrat 2016)	5056	0	5056	France	National	Unclear	8–72 ISCO	<50–≥70 years. Mean age for cases at recruitment 60 (SD 9.0), for controls 58 years (SD 9.9)	Both	Case-control study	2001–2007	Median 38 years between exposure and interview
(Gustavsson 2000)	3294	0	3294	Sweden	Region (Stockholm County)	See footnote [b]	87200, 87210, 87215, 87220, 87225, 87230, 87235 (ISCO 1968)	40–75 years	Both	Case-control study	1985–1990	1950–1990
(Jöckel 1998)	1678	0	1678	Germany	Region (Bremen and Frankfurt)	See footnote [b]	87200, 87210, 87215, 87220, 87225, 87230, 87235 (ISCO 1968)	Range 33–80 years. Mean age of cases 61.1 years (SD 8.9), controls 61.4 years (SD 9.0)	Both	Case-control study	1988–93	1926–1993
(Kazma 2012)	343	0	343	Canada, Czech Republic, Hungary, Poland, Romania, Russian Federation, Slovakia, and United Kingdom	Region	See footnote [b]	87200, 87210, 87215, 87220, 87225, 87230, 87235 (ISCO 1968)	Mean age of cases 61.4 (SD 9.6) and 55.7 for controls (SD 14.1)	Unclear	Case-control study	Unclear	Working life
(Keller 1993)	13,449	0	13,449	United States	Region (Illinois)	060 (1980 United States Census Industrial Classification System)	783 (1980 United States Census Occupational Classification System)	Mean age of lung cancer cases 63.8 years among construction workers and 64.4 years among other subjects	Unclear	Case-control study	Unclear-cancer cases diagnosed 1986–1989	Unclear
(Kromhout 1992)	603	0	603	The Netherlands	Local	Unclear	Unclear	61–82 years at time of questionnaire on medical status	Both	Cohort	1960–1986	Exposure assessed 1977–1978 and health status last assessed in 1985
(Lauritsen 1996)	533	0	533	Denmark	National	Unclear	Unclear	Unclear	Formal	Case-control study (Nested case-control study)	1968–1985	1–21 + years

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Table 4 (*continued*)

Study ID	Study population									Study type		
	Total number of study participants	Number of female study participants	Number of male study participants	Country of study population	Geographic location	Industrial sector	Occupation [a]	Age	Formality of economy	Study design	Study period (month of first collection of any data and month of last collection of any data)	Follow-up period (period in months between exposure and outcome)
(Lerchen 1987)	832	0	832	United States	Region (New Mexico)	Unclear	7212	25–84 years	Both	Case-control study	1980–1982	From 12 years of age until diagnosis
(Lopez-Cima 2007)	1343	0	1343	Spain	Region (Northern Spain)	See footnote [b]	87200, 87210, 87215, 87220, 87225, 87230, 87235 (ISCO 1968)	30–85 years	Unclear	Case-control study	2000–2005	Unclear
(MacLeod 2017)	1,108,410	0	1,108,410	Canada	National	Unclear	J195 (SOC-91)	25–74 years	Unclear (maybe both)	Cohort (retrospective)	1991–2010	0–19 years
(Morabia 1992)	5021	0	5021	United States	Region	Unclear	7212	Unclear	Unclear (maybe both)	Case-control study	1980–1989	Working life
(Pezzotto 1999)	356	0	356	Argentina	Local (Rosario City)	See footnote [b]	87200, 87210, 87215, 87220, 87225, 87230, 87235 (ISCO 1968)	Unclear	Both	Case-control study	1992–1998	Working life
(Richiardi 2004)	2003	0	2003	Italy	Region	See footnote [b]	87200, 87210, 87215, 87220, 87225, 87230, 87235 (ISCO 1968)	Unclear from Kendzia et al. (2013), but in the original study cases had a mean age of 62.4 years (SD 7.4) and controls 63.3 years (SD 7.8)	Formal	Case-control study	1990–1992	Working life
(Ronco 1988)	510	0	510	Italy	Local	Unclear	7212	30–89 years for controls	Formal	Case-control study	Unclear	Working life
(Sankila 1990)	Unclear (6,878 cases)	0	Unclear (6,878 cases)	Finland	National	Unclear	655 (Nordic Classification of Occupations)	26–64 years	Unclear	Cohort study (retrospective)	1971–1980	Working life
(Schoenberg 1987)	1663	0	1663	United States	Region (New Jersey)	Unclear	Unclear	Unclear	Formal	Case-control study	1980–1981	Working life
(Siew 2008)	Unclear – original sample includes 1.2 million but the selected effect estimate relates only to the unexposed and high exposure groups	0	Unclear – original sample includes 1.2 million but the selected effect estimate relates only to the unexposed and high exposure groups	Finland	National	Unclear	Unclear	20–65 years	Both	Cohort study (retrospective)	1971–1995	25 years

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Table 4 (*continued*)

Study ID	Study population									Study type		
	Total number of study participants	Number of female study participants	Number of male study participants	Country of study population	Geographic location	Industrial sector	Occupation [a]	Age	Formality of economy	Study design	Study period (month of first collection of any data and month of last collection of any data)	Follow-up period (period in months between exposure and outcome)
(Soskolne 2007)	358	0	358	Italy	Region (Campania)	Unclear	Unclear	35–74 years	Unclear	Case-control study	1988–1990	Working life
(Steenland 1986)	8679	Unclear	Unclear	United States	Local (Western Washington)	Unclear	7212	Unclear	Formal	Cohort study (retrospective)	1950–1976	1–27 years
(Steenland 2002)	8745	0	8745	United States	Region (mid-western United States)	Unclear	7212	Unclear	Formal	Cohort study (prospective)	1974–1998	Up to 37 years
(Stücker 2002)	522	0	522	France	Region (Paris and Besançon)	See footnote [b]	87200, 87210, 87215, 87220, 87225, 87230, 87235 (ISCO 1968)	Unclear for sample in Kendzia et al. (2013). In original study record the average age of controls 59.3 (SD 9.6) and cases 59.6 (SD 9.9)	Unclear	Case-control study	1988–1992	1926–1992
('t Mannetje, 2012)	4492	0	4492	Czech Republic, Hungary, Poland, Romania, Russian Federation, Slovakia, and United Kingdom	National	Unclear	Unclear	<45–≥65 years	Unclear	Case-control study	1998–2001	Working life
(Tse 2012)	2277	0	2277	People's Republic of China	Region (Hong Kong)	Unclear	Unclear	35–79 years	Both	Case-control study	2004–2006	Working life
(Vallieres 2012)	1416	0	1416	Canada	Local (Montreal)	See footnote [b]	87200, 87210, 87215, 87220, 87225, 87230, 87235 (ISCO 1968)	35–75 years	Both	Case-control study	1976–1986 and 1996–2001	Working life
(van Loon 1997)	Unclear as unknown number of participants excluded due to lacking information on covariates (but participant on welding fume exposure held for 1828)	0	Unclear as unknown number of participant excluded due to lacking information on covariates (but information on welding fume exposure held for 1828)	The Netherlands	National	Unclear	Unclear	55–69 years. Mean age of 61.4 years among unexposed and 60.3 years among exposed	Both	Cohort study (prospective)	1986–1990	Working life

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Table 4 (*continued*)

Study ID	Study population									Study type		
	Total number of study participants	Number of female study participants	Number of male study participants	Country of study population	Geographic location	Industrial sector	Occupation [a]	Age	Formality of economy	Study design	Study period (month of first collection of any data and month of last collection of any data)	Follow-up period (period in months between exposure and outcome)
(Wong 2017)	50,983	21,678	29,305	United States	National	Unclear	7212	57–64 years	Both formal and informal economy	Cohort (prospective)	2002–2009	Working life
(Yiin 2007)	4388	285	4103	United States	Local (Portsmouth and New Hampshire)	30 Manufacture of other transport equipment	Unclear	Average age at vital status assessment for controls 83 and for cases 82 years	Formal	Case-control study (nested case-control study)	1952–1996	4–44 years

Study ID	Exposure assessment										Co-exposure with other occupational risk factors
	Exposure definition (i.e., how was the exposure defined?)	Unit for which exposure was assessed	Mode of exposure data collection	Exposure assessment methods	Type of exposure measurement or estimate	Dates covered by exposure assessment (years)	Shortest and longest exposure period	Levels/intensity of exposure (unit)	Number of study participants in exposed group	Number of study participants in unexposed group	Potential co-exposure with other occupational risk factors (co-exposure and level of exposure)
(Becker 1999)	Arc welders exposed to fumes containing nickel and chromium	Individual level	Face-to-face survey	Indirectly reported by workplace supervisor	Unclear	1950–1970	≥6 months	Unclear	1213	1688	Unclear
(Brenner 2010)	Ever worked with or been exposed to welding fumes	Individual level	Face-to-face and telephone surveys	Self-reported	Lifetime prevalence	Participants' lifetime of exposure	Unclear	Unclear	76	1317	Asbestos[c], solvents, paints or thinners, pesticides, grain elevator dust, wood dust, smoke-soot or exhaust[c], and environmental tobacco smoke[c] (NB: factors considered separately, not in an adjusted model)

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Table 4 (*continued*)

Study ID	Exposure assessment										Co-exposure with other occupational risk factors
	Exposure definition (i.e., how was the exposure defined?)	Unit for which exposure was assessed	Mode of exposure data collection	Exposure assessment methods	Type of exposure measurement or estimate	Dates covered by exposure assessment (years)	Shortest and longest exposure period	Levels/intensity of exposure (unit)	Number of study participants in exposed group	Number of study participants in unexposed group	Potential co-exposure with other occupational risk factors (co-exposure and level of exposure)
(Breslow 1954)	Welder or sheet metal workers doing welding	Individual level	Face-to-face survey	Interviews coded by an industrial hygienist	Lifetime prevalence	Working life	Unclear	Welder or sheet metal workers doing welding for ≥5 years	16	970	Polycyclic aromatic hydrocarbons, mineral fibers and dusts[c], and others according to various occupational codes (but not considered in adjusted models)
(Bruske-Hohlfeld 2000)	Ever worked as a welder (Kendzia et al. 2013)	Individual level	Face-to-face survey	Job title history	Lifetime prevalence	Working life	≥1 year (as in Kendzia et al. (2013); in original study record was ≥6 months)	Job title was "welder" for ≥1 year	150	4367	Adjustment for ever working in an occupation involving lung cancer risk, excluding welding-related occupations
(Buiatti 1985)	"Ever worked" in welding	Individual level	Face-to-face survey	Job title and self-reported chemical exposures	Lifetime prevalence	Working life	≥1 year	Worked in the occupation of welding for ≥1 year	12	1145	16 known carcinogens (although these exposures not detailed among welders)
(Consonni 2010)	Ever worked as a welder (Kendzia et al. 2013)	Individual level	Computer-administered face-to-face survey	Hygienists' assessment	Lifetime prevalence	Working life	≥1 year (as in Kendzia et al. (2013); in original study record was ≥6 months)	Job title was "welder" for ≥1 year	79	2761	Adjustment for ever working in an occupation involving lung cancer risk, excluding welding-related occupations
(Corbin 2011)	Ever worked as a welder Kendzia et al. (2013)	Individual level	Face-to-face and telephone surveys	Job title and task description	Lifetime prevalence	Working life	≥1 year	Job title was "welder" for ≥1 year	30	506	Adjustment for ever working in an occupation involving lung cancer risk, excluding welding-related occupations
(Danielsen 1993)	Occupational inhalation exposure to fumes from	Individual level	Administrative records	The exposure was assessed according to worker's job title	Unclear	1940–1979	Unclear; ≤6 months to ≥10 years of employment-	In 1973, The welding fume samples showed concentrations of	623	3948	Asbestos[c]

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Table 4 (*continued*)

Study ID	Exposure assessment										Co-exposure with other occupational risk factors
	Exposure definition (i.e., how was the exposure defined?)	Unit for which exposure was assessed	Mode of exposure data collection	Exposure assessment methods	Type of exposure measurement or estimate	Dates covered by exposure assessment (years)	Shortest and longest exposure period	Levels/intensity of exposure (unit)	Number of study participants in exposed group	Number of study participants in unexposed group	Potential co-exposure with other occupational risk factors (co-exposure and level of exposure)
	welding defined by work category of welder			and the environmental monitoring were also conducted			analysis split in to ≤5 years employment and >5 years employment	total dust from 0 to 8 to 9–5 mg/m^3 (median 2–5 mg/m^3).In 1985, Concentrations of total dust ranged from 0 to 6 to 22mg/m^3 (median 2–6 mg/m^3). All chromium concentrations were below 0–05 mg/m3. For nickel, the results in the welding shop ranged from the lowest detectable concentration			
(Danielsen 2000)	Occupational inhalation exposure to fumes from welding defined by work category of welder	Individual level	Administrative records	The exposure was assessed according to worker's job title and the environmental monitoring were also conducted	Unclear	1945–1991	Unclear	In 1973, the mean concentration of welding fumes in the work air was 14.5 mg/m^3 ranging from 4.2 to 54.4 mg/m.3. In 1977, The highest welding fume concentration was 2.1 mg/m^3 In 1989, Among mild steel welders the mean concentration of welding fumes was 1.87 mg/m^3, with concentrations inside air-stream helmets below 0.70 mg/m^3 Stainless steel welders working in confined spaces were exposed to high levels of total fume, ranging from 7.0 to 38.0mg/m^3,	Unclear	3619	Asbestos[c]

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Table 4 (*continued*)

Study ID	Exposure assessment										Co-exposure with other occupational risk factors
	Exposure definition (i.e., how was the exposure defined?)	Unit for which exposure was assessed	Mode of exposure data collection	Exposure assessment methods	Type of exposure measurement or estimate	Dates covered by exposure assessment (years)	Shortest and longest exposure period	Levels/intensity of exposure (unit)	Number of study participants in exposed group	Number of study participants in unexposed group	Potential co-exposure with other occupational risk factors (co-exposure and level of exposure)
								with iron, chromium, manganese, and nickel as the principal elements. The stainless steel welders in the machine shop were exposed to total fume concentrations ranging from 0.28 to 1.03 mg/m^3 inside air-stream helmets.			
(Elci 2003)	Occupation of "welder"	Individual level	Face-to-face survey	Occupational history	Prevalence – unclear type	Occupational history was taken but unclear if this or current occupationwas used	Unclear	Unclear	Unclear	Unclear	Unclear
(Finkelstein 1995)	Job and industry described in death certificate	Individual level	Administrative records	Death certificate	Lifetime prevalence	Working life	Unclear	Unclear	Unclear	Unclear	Unclear
(Fortes 2003)	Ever worked as a welder (Kendzia et al. 2013)	Individual level	Face-to-face survey	Self-reported occupational exposure to carcinogens	Lifetime prevalence (unclear in original record, but from information in Kendzia et al. 2013)	Working life (from Kendzia et al. 2013)	Unclear	Unclear	5	507	Unclear
(Gottlieb 1980)	Occupation of "welder"	Individual level	Administrative records	Death certificate	Prevalence – type unclear	Unclear	Unclear	Unclear	10	5596	Unclear
(Guida 2011; Matrat 2016)	At least one job period as welder in the strict sense of the word (i.e., coded 8–72 in ISCO code)	Individual level	Face-to-face survey	Occupational history and task description	Lifetime prevalence	Working life	Classified as ≤10 years or >10 years	Exposure classified in ≤35 and >35 years since first exposure and then into other two sub-classes ≤10 and >10 ys of exposure. For regular welders also available frequency of welding, classified in ≤5% and >5%	167	3666	Asbestos[c]

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Table 4 (*continued*)

Study ID	Exposure assessment										Co-exposure with other occupational risk factors
	Exposure definition (i.e., how was the exposure defined?)	Unit for which exposure was assessed	Mode of exposure data collection	Exposure assessment methods	Type of exposure measurement or estimate	Dates covered by exposure assessment (years)	Shortest and longest exposure period	Levels/intensity of exposure (unit)	Number of study participants in exposed group	Number of study participants in unexposed group	Potential co-exposure with other occupational risk factors (co-exposure and level of exposure)
(Gustavsson 2000)	Ever worked as a welder (Kendzia et al. 2013)	Individual level	Face-to-face survey	Hygienist assessment (based on self-reports)	Lifetime prevalence	Working life	≥1 year (as in Kendzia et al. (2013))	Job title was "welder" for ≥1 year (as in Kendzia et al. (2013))	267	3081	Unclear
(Jöckel 1998)	Ever worked as a welder (Kendzia et al. 2013)	Individual level	Face-to-face survey	Self-reported	Lifetime prevalence	Working life	≥1 year (as in Kendzia et al. (2013))	Job title was "welder" for ≥1 year (as in Kendzia et al. (2013))	60	1334	Unclear
(Kazma 2012)	Ever worked as a welder (Kendzia et al. 2013)	Individual level	Face-to-face survey	Unclear	Lifetime prevalence	Working life	≥1 year	Job title was "welder" for ≥1 year	4	339	Adjustment for ever working in an occupation involving lung cancer risk, excluding welding-related occupations
(Keller 1993)	Current occupation code or longest lifetime occupation code equal to 783 in the 1980 US Census Occupation Classification System	Individual level	Administrative records	Occupation coded in cancer registry	Lifetime prevalence	Working life	Unclear	Current occupation code or longest lifetime occupation code	Unclear	Unclear	Unclear
(Kromhout 1992)	Self-reported occupational exposure to welding materials, welding fumes	Individual level	Questionnaire	Self-reported job title; job-exposure matrix	Lifetime prevalence	Working life prior to questionnaire	25 years	Exposure to welding materials, welding fumes during their job history	Unclear	Unclear	Twenty-six other chemicals or groups of chemical agents (including passive smoking[c], dust (asbestos, cement, wood, chalk, quartz)[c])
(Lauritsen 1996)	Welding ever, yes/no	Individual level	Questionnaire	Telephone or personal interview of spouses and/or colleagues	Lifetime prevalence	Lifetime exposure	Classified in groups from 1 to 5 years to ≥21 years	Welding ever, yes/no; time from first to last exposure	Unclear	Unclear	Welding, grinding, asbestos[c]and cutting oil exposures
(Lerchen 1987)	Occupation of welder for ≥6 months	Individual level	Questionnaire	Self-reported	Lifetime prevalence	Working life	≥6 months	Occupation as a welder for ≥6 months	29	803	Occupational exposure to 18 agents: asbestos[c], radiation[c], coal soot, tar or coke[c],

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Table 4 (*continued*)

Study ID	Exposure assessment										Co-exposure with other occupational risk factors
	Exposure definition (i.e., how was the exposure defined?)	Unit for which exposure was assessed	Mode of exposure data collection	Exposure assessment methods	Type of exposure measurement or estimate	Dates covered by exposure assessment (years)	Shortest and longest exposure period	Levels/intensity of exposure (unit)	Number of study participants in exposed group	Number of study participants in unexposed group	Potential co-exposure with other occupational risk factors (co-exposure and level of exposure)
											nickel[c], chromium[c], arsenic[c], chloromethyl ether, polyurethane, formaldehyde, insecticides and pesticides, vegetable and animal dust, wood dust, leather dust, petroleum and petroleum products, and solvents
(Lopez-Cima 2007)	Ever worked as a welder (Kendzia et al. 2013)	Individual level	Computer-administered face-to-face survey	Hygienists' assessment	Lifetime prevalence (unclear in original record, but from information in Kendzia et al. 2013)	Working life (from Kendzia et al. 2013)	≥1 year	Job title was "welder" for ≥1 year	89	1254	Adjustment for ever working in an occupation involving lung cancer risk, excluding welding-related occupations
(MacLeod 2017)	Standard Occupational Classification 1991 (SOC-91) code J195 for welders and soldering machine operators	Individual level	Administrative records	Self-reported	Point prevalence	1991	0–19 years	Occupation as a welder or solder machine operator	12,845	1,095,565	Iron, manganese, aluminium, cadmium[c], silica[c], lead, ultraviolet radiation, and asbestos[c]
(Morabia 1992)	Occupation as a welder or flame cutter	Individual level	Face-to-face survey	Occupational history (job title and self-reported chemical exposures)	Lifetime prevalence	Working life	Unclear	"Usual occupation" as a welder or flame cutter	Unclear	Unclear	Interviewed about exposure to 44 different agents, but information not used in analysis on welding
(Pezzotto 1999)	Employed for more than one year as a welder	Individual level	Pen-and-paper survey	Questionnaire (job title, tasks, and self-reported chemical exposures)	Lifetime prevalence	Working life	≥1 year	Employed for more than one year as a welder	33	323	Unclear

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Table 4 (*continued*)

Study ID	Exposure assessment										Co-exposure with other occupational risk factors
	Exposure definition (i.e., how was the exposure defined?)	Unit for which exposure was assessed	Mode of exposure data collection	Exposure assessment methods	Type of exposure measurement or estimate	Dates covered by exposure assessment (years)	Shortest and longest exposure period	Levels/intensity of exposure (unit)	Number of study participants in exposed group	Number of study participants in unexposed group	Potential co-exposure with other occupational risk factors (co-exposure and level of exposure)
(Richiardi 2004)	Ever worked as a welder (Kendzia et al. 2013)	Individual level	Face-to-face survey	Occupational history (job title)	Lifetime prevalence	Working life	At least 1 year (as in Kendzia et al. (2013); in original study record was ≥6 months)	Job title was "welder" for ≥1 year	24	1358	Adjustment for ever working in an occupation involving lung cancer risk, excluding welding-related occupations
(Ronco 1988)	Occupation of welder for ≥6 months	Individual level	Face-to-face survey	Reported by next of kin	Lifetime prevalence	Working life	≥6 months	Employed for ≥6 months as a welder	13	497	Foundries and metal production
(Sankila 1990)	Welder (code 655)	Individual level	Administrative records	Unclear	Unclear	Unclear	Unclear	Working as a welder	57	Unclear	Unclear
(Schoenberg 1987)	"Combined welders" group as many of the same subjects were employed as welders or burners, sheetmetal workers, and boilermakers	Individual level	Face-to-face survey	Occupational history (job title, tasks, and self-reported chemical exposures)	Lifetime prevalence	Working life	≥3 months	Was in the "combined welders" group	28	Unclear	Unclear
(Siew 2008)	Occupational inhalation exposure to fumes from welding	Individual level	Industrial hygienists' assessment	Job-exposure matrix	Lifetime prevalence	Up to 1970	≤20 years	Cumulative exposure: No exposure; low: 0.1–99.9 mg/m^3-years; medium: 100–199.9 mg/m^3-years; and high: ≥200 mg/m^3-years	Unclear	Unclear	Asbestos[c] and silica[c]
(Soskolne 2007)	Exposed to welding fumes	Individual level	Face-to-face survey	Industrial hygienist assessment based on self-reported occupational history	Lifetime prevalence	Working life	Unclear	Exposed versus unexposed to welding fumes	Unclear (in the entire study 13 of 415 were exposed, but this was not the effective sample)	Unclear	No
(Steenland 1986)	Worked as a welder for ≥3 years (and a member of union 1950–1976)	Individual level	Administrative records	Unclear	Period prevalence	1950–76	≥3 years	Welder versus non-welder	3247	5432	Unclear

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Table 4 (*continued*)

Study ID	Exposure assessment										Co-exposure with other occupational risk factors
	Exposure definition (i.e., how was the exposure defined?)	Unit for which exposure was assessed	Mode of exposure data collection	Exposure assessment methods	Type of exposure measurement or estimate	Dates covered by exposure assessment (years)	Shortest and longest exposure period	Levels/intensity of exposure (unit)	Number of study participants in exposed group	Number of study participants in unexposed group	Potential co-exposure with other occupational risk factors (co-exposure and level of exposure)
(Steenland 2002)	Worked as a welder for ≥2 years	Individual level	Administrative records	Job title history	Period prevalence	1950–1987	Classified in groups of ≥2 years up to >20 years	Worked as a welder for ≥2 years versus non-welder	4459	4286	No
(Stücker 2002)	Ever worked as a welder (Kendzia et al. 2013)	Individual level	Face-to-face survey	Self-reported	Lifetime prevalence	WorkingWorking life	≥1 year	Job title was "welder" for ≥1 year	14	308	Adjustment for ever working in an occupation involving lung cancer risk, excluding welding-related occupations
('t Mannetje 2012)	Ever exposed to welding fumes (each job on welding or gas cutting and if any welding or gas cutting was done near the subject)	Individual level	Face-to-face survey	Questionnaire including questions on each job in welding or gas cutting or if these tasks were carried out near the subject	Lifetime prevalence	Working life	1 year–>35 years	Exposed to welding fumes versus not exposed	1104	3388	Asbestos[c], silica[c], and metal in jobs not exposed to welding fumes
(Tse 2012)	Regular occupational exposure to welding fumes at least once a week for ≥6 months	Individual level	Face-to-face survey	Hygienist assessment (based on self-reports)	Lifetime prevalence	Working life	≥6 months	Regular occupational exposure to welding fumes at least once a week for ≥6 months versus not exposed	160	2117	No
(Vallieres 2012)	Ever worked as a welder (Kendzia et al. 2013)	Individual level	Face-to-face survey	Hygienist assessment (based on self-reports)	Lifetime prevalence	Working life (unclear if Kendzia et al. (2013) maintained categorisation of those participants exposed only in the 5-year period prior to recruitment as unexposed)	≥1 year	Job title was "welder" for ≥1 year	45	1371	Adjustment for ever working in an occupation involving lung cancer risk, excluding welding-related occupations
(van Loon 1997)	Exposure to welding fumes by job title	Individual level	Pen-and-paper survey	Hygienist assessment (based on self-reports)	Lifetime prevalence	Working life	Unclear	Ever versus never; no exposure to welding fumes, possible exposure (probability <30%), probable exposure (probability 30%-90%), and nearly certain exposure (probability >90%)	Unclear (but 202 exposed among those for whom welding fume exposure was held)	Unclear (but 1626 unexposed among those for whom welding fume exposure was held)	Other occupational exposures adjusted for (asbestos[c], paint dust, polycyclic aromatic hydrocarbons)

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Table 4 (*continued*)

Study ID	Exposure assessment										Co-exposure with other occupational risk factors
	Exposure definition (i.e., how was the exposure defined?)	Unit for which exposure was assessed	Mode of exposure data collection	Exposure assessment methods	Type of exposure measurement or estimate	Dates covered by exposure assessment (years)	Shortest and longest exposure period	Levels/intensity of exposure (unit)	Number of study participants in exposed group	Number of study participants in unexposed group	Potential co-exposure with other occupational risk factors (co-exposure and level of exposure)
(Wong 2017)	Worked as a welder (but not a foundry worker) for ≥1 year	Individual level	Pen-and-paper survey	Self-reported	Lifetime prevalence	Working life	≥1 year–≥25 years	Worked as a welder for ≥1 year versus did not work as a welder	2311	48,672	Unclear
(Yiin 2007)	Exposure to welding fumes	Individual level	Administrative records	Shop and job-title combinations used with cumulative industrial hygiene monitoring records assessed by hygienist	Period prevalence	1952–1992	Unclear	Welding fume TLV level category <0.5, 0,5–1, 1–2, 2–4, 4+	978	3410	Asbestos[c], ionizing radiation[c]

Study Study ID	Outcome assessment Definition of outcome	Which International Classification of Diseases (ICD) code was reported for the outcome (if any)?	Method of outcome assessment	Diagnostic assessment method	Specification of outcome	Number of cases with outcome of interest in exposed group	Number of non-cases (i.e., without outcome of interest) in exposed group	Number of cases with outcome of interest in unexposed group	Number of non-cases (i.e., without outcome of interest) in unexposed group	Comparator Definition of comparator (define comparator group, including specific level of exposure)
(Becker 1999)	Trachea, bronchus, and lung cancer	ICD-9 Code 162	Death certificate	Administrative record	Trachea, bronchus, and lung cancer mortality	28	1185	38	1650	Turners
(Brenner 2010)	Trachea, bronchus, and lung cancer	ICD O 3 (but specific code not reported)	Pathology	Medical records, cases were histologically confirmed	Trachea, bronchus, and lung cancer diagnosis	33	43	412	905	Never worked with or been exposed to welding fumes
(Breslow 1954)	Lung cancer	Unclear	Pathology	Physician diagnostic record	Lung cancer diagnosis	14	2	479	491	Had not worked as a welder or sheet metal worker doing welding
(Bruske-Hohlfeld 2000)	Lung cancer	Unclear	Pathology	Physician diagnostic record (histologically or cytologically confirmed)	Lung cancer diagnosis	101	49	2099	2268	Not worked in welding-related occupations for ≥1 year
(Buiatti 1985)	Trachea, bronchus, and lung cancer	ICD-8 code 162 (the study mentions lung cancer only and does not explicitly mention this code for the outcome, but controls excluded those with cancers with ICD-8 162)	Pathology	Physician diagnostic record	Trachea, bronchus, and lung cancer diagnosis	7	5	333	812	Not worked for ≥1 year in welding

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Table 4 (*continued*)

Study Study ID	Outcome assessment Definition of outcome	Which International Classification of Diseases (ICD) code was reported for the outcome (if any)?	Method of outcome assessment	Diagnostic assessment method	Specification of outcome	Number of cases with outcome of interest in exposed group	Number of non-cases (i.e., without outcome of interest) in exposed group	Number of cases with outcome of interest in unexposed group	Number of non-cases (i.e., without outcome of interest) in unexposed group	Comparator Definition of comparator (define comparator group, including specific level of exposure)
(Consonni 2010)	Kendzia et al. (2013) only mentions lung cancer, but original study specifies trachea, bronchus, and lung cancer. As effect estimate taken from Kendzia et al. (2013), included as lung in subgroup analyses	ICD-O 3 (but specific code not reported)	Pathology	Physician diagnostic record	Lung cancer diagnosis	40	39	1312	1449	Not worked in welding-related occupations for ≥1 year
(Corbin 2011)	Lung cancer	Unclear	Pathology	Administrative record	Lung cancer diagnosis	15	15	162	344	Not worked in welding-related occupations for ≥1 year
(Danielsen 1993)	Trachea, bronchus, and lung cancer	ICD-7 162	Pathology	Administrative record	Trachea, bronchus, and lung cancer diagnosis	9	614	56	3892	Other shipyard production workers
(Danielsen 2000)	Trachea, bronchus, and lung cancer	ICD-7 162	Pathology	Administrative record	Trachea, bronchus, and lung cancer diagnosis	4	Unclear	36	3583	Other shipyard production workers
(Elci 2003)	Trachea, bronchus, and lung cancer	ICD-O codes 162.0, 162.2, 162.3, 162.4, 162.5, 162.9	Pathology	Administrative record	Trachea, bronchus, and lung cancer diagnosis	18	Unclear	1336	Unclear	Did not report working as a welder
(Finkelstein 1995)	Lung cancer	Unclear	Death certificate	Administrative record	Lung cancer mortality	18	45	949	2776	Occupation of welder not reported on death certificate
(Fortes 2003)	Lung cancer	Unclear	Pathology	Physician diagnostic record	Lung cancer diagnosis	4	1	265	242	Not worked in welding-related occupations for ≥1 year
(Gottlieb 1980)	Lung cancer	Unclear	Death certificate	Administrative record	Lung cancer mortality	8	2	2795	2801	Occupation of welder not reported on death certificate
(Guida 2011; Matrat 2016)	Trachea, bronchus, and lung cancer	ICD-O code C33 and C34	Pathology	Administrative record	Trachea, bronchus, and lung cancer diagnosis	100	69	1629	2037	No welding
(Gustavsson 2000)	Original study states bronchus and lung cancer	ICD-7 code 162.1	Pathology	Physician diagnostic record	Bronchus and lung cancer diagnosis	99	168	923	2158	Not considered exposed to welding fumes
(Jöckel 1998)	Newly diagnosed cases with histologically or cytologically confirmed lung cancer	Unclear	Pathology	Physician diagnostic record	Lung cancer diagnosis	42	18	637	697	Not worked in welding-related occupations for ≥1 year
(Kazma 2012)	Lung cancer	Unclear	Unclear	Administrative record/Unclear	Lung cancer diagnosis	2	2	138	201	Not worked in welding-related occupations for ≥1 year

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Study Study ID	Outcome assessment Definition of outcome	Which International Classification of Diseases (ICD) code was reported for the outcome (if any)?	Method of outcome assessment	Diagnostic assessment method	Specification of outcome	Number of cases with outcome of interest in exposed group	Number of non-cases (i.e., without outcome of interest) in exposed group	Number of cases with outcome of interest in unexposed group	Number of non-cases (i.e., without outcome of interest) in unexposed group	Comparator Definition of comparator (define comparator group, including specific level of exposure)
(Keller 1993)	Lung cancer	Unclear	Pathology	Administrative record	Lung cancer diagnosis	Unclear	Unclear	Unclear	Unclear	Current occupation code or longest lifetime occupation code not welder
(Kromhout 1992)	Trachea, bronchus, and lung cancer	ICD-8 code 162	Unclear – medical examination and self-reported morbidity (verified by contacting participant's general practitioner)	Physician diagnostic record	Trachea, bronchus, and lung cancer diagnosis	Unclear	Unclear	Unclear	Unclear	No exposure to welding materials, welding fumes during their job history
(Lauritsen 1996)	Trachea, bronchus, and lung cancer	ICD-8 code 162.0–162.1	Pathology	Administrative record	Trachea, bronchus, and lung cancer mortality	46	Unclear	38	Unclear	No welding
(Lerchen 1987)	Primary lung cancer, other than bronchiolovalveolar carcinoma	Unclear	Pathology	Administrative record	Lung cancer diagnosis	19	10	314	489	Did not work as a welder for ≥6 months
(Lopez-Cima 2007)	Lung cancer	Unclear	Pathology	Hospital discharge record	Lung cancer diagnosis	51	38	651	603	Not worked in welding-related occupations for ≥1 year
(MacLeod 2017)	Lung cancer	Unclear	Histology	Administrative record	Lung cancer diagnosis	265	12,580	Unclear	Unclear	Non-welders
(Morabia 1992)	Trachea, bronchus, and lung cancer	ICD-9 codes 162.0–162.9	Pathology	Physician diagnostic record	Trachea, bronchus, and lung cancer diagnosis	18	22	1775	3206	Usual occupation not welder/flame cutter
(Pezzotto 1999)	Lung cancer	ICD-O (M) but codes used unclear	Pathology	Physician diagnostic record	Lung cancer diagnosis	11	22	98	225	Administrative staff
(Richiardi 2004)	Lung cancer	Unclear	Pathology	Hospital records	Lung cancer diagnosis	43	34	822	1104	Not worked in welding-related occupations for ≥1 year
(Ronco 1988)	Lung cancer	Unclear	Death certificate	Administrative record	Lung cancer mortality	6	7	Unclear	Unclear	Not employed as a welder for ≥6 months
(Sankila 1990)	Lung cancer	Unclear	Cancer registry	Administrative record	Lung cancer diagnosis	Unclear	Unclear	Unclear	Unclear	All other economically active Finnish men (i.e., not employed as a welder)

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Table 4 (*continued*)

Study Study ID	Outcome assessment Definition of outcome	Which International Classification of Diseases (ICD) code was reported for the outcome (if any)?	Method of outcome assessment	Diagnostic assessment method	Specification of outcome	Number of cases with outcome of interest in exposed group	Number of non-cases (i.e., without outcome of interest) in exposed group	Number of cases with outcome of interest in unexposed group	Number of non-cases (i.e., without outcome of interest) in unexposed group	Comparator Definition of comparator (define comparator group, including specific level of exposure)
(Schoenberg 1987)	Trachea, bronchus, and lung cancer	ICD code 162	Pathology and death certificates	Physician diagnostic record and administrative records	Trachea, bronchus, and lung cancer diagnosis	17	11	Unclear	Unclear	Did not work in the "combined welders" group
(Siew 2008)	Lung cancer	Unclear	Cancer registry	Administrative record	Lung cancer diagnosis	287 in medium exposure group, 67 in high exposure group	Unclear	27,192	Unclear	Not exposed to welding fumes (cumulative exposure <0.1 mg/m^3-years)
(Soskolne 2007)	Lung cancer	Unclear	Pathology	Physician diagnostic record	Lung cancer diagnosis	Unclear	Unclear	Unclear	Unclear	Not exposed to welding fumes
(Steenland 1986)	Lung cancer	Unclear	Death certificate	Administrative record	Lung cancer mortality	50	3197	87	5345	Non-welders (in the same union)
(Steenland 2002)	Trachea, bronchus, and lung cancer	ICD-9 code 162	Death certificate	Administrative record	Trachea, bronchus, and lung cancer mortality	108	4351	128	4158	Non-welders who had worked for ≥2 years
(Stücker 2002)	Lung cancer	Unclear	Pathology	Physician diagnostic record	Lung cancer diagnosis	7	7	258	250	Not worked in welding-related occupations for ≥1 year
('t Mannetje 2012)	Lung cancer	Unclear	Pathology	Physician diagnostic record	Lung cancer diagnosis	582	522	1615	1773	Never exposed to welding fumes
(Tse 2012)	Lung cancer	Unclear	Pathology	Hospital discharge record	Lung cancer diagnosis	112	48	1096	1021	Did not report regular occupational exposure to welding fumes
(Vallieres 2012)	Lung cancer	Unclear	Pathology	Hospital discharge record	Lung cancer diagnosis	29	16	595	776	Not worked in welding-related occupations for ≥1 year
(van Loon 1997)	Lung cancer	Unclear	Pathology	Hospital discharge record	Lung cancer diagnosis	Unclear (but 63 exposed cases among those for whom welding fume exposure information was held)	Unclear (but 139 exposed controls among those for whom welding fume exposure information was held)	Unclear (but 457 exposed controls among those for whom welding fume exposure information was held)	Unclear (but 1169 unexposed controls among those for whom welding fume exposure information was held)	No exposure to welding fumes
(Wong 2017)	Lung cancer	Unclear	Pathology	Physician diagnostic record	Lung cancer diagnosis	101	2210	1824	46,848	Never welder or foundry worker
(Yiin 2007)	Trachea, bronchus, and lung cancer	ICD-9 code 162; ICD-8 code 162; ICD-6 and ICD-7 codes 162 or 163	Death certificate	Administrative record	Trachea, bronchus, and lung cancer mortality	290	688	807	2603	Unexposed workers (TLV-1<0.5)

Study Study ID	Prioritized model Are two or more alternative models reported?	Which of the alternative models was prioritized/ selected for use in the review and/or meta-analysis?	Reason for prioritization/ selection	Adjustments of effect estimates in model prioritized by reviewers Adjusted for confounding by age	Adjusted for confounding by sex	Other potential confounders adjusted for (please specify)	Interactions adjusted for[g]	Adjustment for clustering (if any)
(Becker 1999)	No	N/A	N/A	Yes[d]	Unclear - a previous study record by the authors suggests this study could be restricted to males	No (socioeconomic status not directly adjusted for although, internal analyses indirectly adjust for several potential confounders including socioeconomic status)	No	No
(Brenner 2010)	Yes – in original study and in Kendzia et al. (2013)	Model from the original study record including the total population	The full population is included, and the model is adjusted for tobacco smoking, which is preferable to restricting to non-smokers. Kendzia et al. (2013) does not include females	Yes[d]	Yes[d]	Pack-years of tobacco smoking among ever and current smokers, education, and ethnicity[f]	No	No
(Breslow 1954)	No	N/A	N/A	No – controls were matched within 5 years of age	Yes – restricted to males[e]	Patients were also matched by race	No	No
(Bruske-Hohlfeld 2000)	Yes – in original study and in Kendzia et al. (2013)	Ever versus never welder, reported in Kendzia et al. (2013)	The original study does not report analyses on welding fumes/ welders	Yes[d]	Yes – restricted to males[e]	Tobacco smoking as pack-years as a continuous variable, time since quitting tobacco smoking, ever working in an occupation involving lung cancer risk excluding welding-related occupations, study location[f]	No	No
(Buiatti 1985)	No	N/A	N/A	Yes[d]	Yes – restricted to males[e]	Place of birth	No	No
(Consonni 2010)	Yes – in original study and in Kendzia et al. (2013)	Ever versus never welder, reported in Kendzia et al. (2013)	Additional ever welders included in Kendzia et al. (2013) analysis	Yes[d]	Yes – restricted to males[e]	Tobacco smoking as pack-years as a continuous variable, time since quitting tobacco smoking, ever working in an occupation involving lung cancer risk excluding welding-related occupations, study location[f]	No	No
(Corbin 2011)	Yes – in original study and in Kendzia et al. (2013)	Ever versus never welder, reported in Kendzia et al. (2013)	Additional ever welders included in Kendzia et al. (2013) analysis	Yes[d]	Yes – restricted to males[e]	Tobacco smoking as pack-years as a continuous variable, time since quitting tobacco smoking, ever working in an occupation involving lung cancer risk excluding welding-related occupations, study location[f]	No	No
(Danielsen 1993)	Yes	Model with lag time (10 years). Two effect estimates were extracted: employment ≤5 years and employment > 5 years	It is likely that a lag time exists between exposure to welding fumes and lung cancer initiation	No	Yes – restricted to males[e]	No	No	No
(Danielsen 2000)	Yes	Worked ≥15 years as a welder (Table 6) due to latency period for trachea, bronchus, and lung cancer	95% confidence intervals provided (not provided for both point estimates in stratified analysis). Highest exposure level.	No	Yes – restricted to males[e]	No	No	No
(Elci 2003)	No	N/A	N/A	Yes[d]	Yes – restricted to males[e]	Tobacco smoking (ever/never)[f]	No	No
(Finkelstein 1995)	No	N/A	N/A	Yes[d]	Yes – restricted to males[e]	Year of death, city of residence	No	No
(Fortes 2003)	No	N/A	N/A	Yes[d]	Yes – restricted to males[e]	Tobacco smoking as pack-years as a continuous variable, time since quitting tobacco smoking, ever working in an occupation involving	No	No

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Study Study ID	Prioritized model Are two or more alternative models reported?	Which of the alternative models was prioritized/ selected for use in the review and/or meta-analysis?	Reason for prioritization/ selection	Adjustments of effect estimates in model prioritized by reviewers Adjusted for confounding by age	Adjusted for confounding by sex	Other potential confounders adjusted for (please specify)	Interactions adjusted for[g]	Adjustment for clustering (if any)
						lung cancer risk excluding welding-related occupations, study location[f]		
(Gottlieb 1980)	No	N/A	N/A	No – stratified by age at death	Yes – restricted to males[e]	Controls matched to the lung cancer cases by sex, race, year of death, parish of residence at death, and age of death[f]	No	No
(Guida 2011; Matrat 2016)	Yes	Regular welders versus no welding	Compares regular welders	Yes[d]	Yes – restricted to males[e]	Department, number of jobs, cumulative tobacco smoking index, and asbestos[f]	No	No
(Gustavsson 2000)	Yes – in original study and in Kendzia et al. (2013)	Ever versus never welder, reported in Kendzia et al. (2013)	Although the original study provides a larger number and analyses on exposure to welding fumes (rather than job title), Kendzia et al. (2013) provides a dichotomous analysis, without risk of overadjustment	Yes[d]	Yes – restricted to males[e]	Tobacco smoking as pack-years as a continuous variable, time since quitting tobacco smoking, ever working in an occupation involving lung cancer risk excluding welding-related occupations, study location[f]	No	No
(Jöckel 1998)	Yes – in original study and in Kendzia et al. (2013)	Ever versus never welder, reported in Kendzia et al. (2013)	It is not clear that age was adjusted for in Jockel 1998 (only matched), however it adjusted for in Kendzia et al. (2013)	Yes[d]	Yes – restricted to males[e]	Tobacco smoking as pack-years as a continuous variable, time since quitting tobacco smoking, ever working in an occupation involving lung cancer risk excluding welding-related occupations, study location[f]	No	No
(Kazma 2012)	Yes – in original study and in Kendzia et al. (2013)	Ever versus never welder, reported in Kendzia et al. (2013)	Kazma 2012 does not report analysis on welders	Yes[d]	Yes – restricted to males[e]	Tobacco smoking as pack-years as a continuous variable, time since quitting tobacco smoking, ever working in an occupation involving lung cancer risk excluding welding-related occupations, study location[f]	No	No
(Keller 1993)	No	N/A	N/A	Yes[d]	Yes – restricted to males[e]	Known history of tobacco use[f]	No	No
(Kromhout 1992)	Yes	Model with 25 years of follow-up, with occupational exposure classified in a strict way	Long lag period likely for the outcome	Yes[d]	Yes – restricted to males[e]	Tobacco smoking habits (pack-years up to 1960)[f]	No	No
(Lauritsen 1996)	Yes	Adjusted ever/never welding exposure	Dichotomous exposed used in preference in main meta-analysis over years exposed	No – matched on 5 year age groups	Yes – restricted to males[e]	Tobacco smoking (unclear, but at least never/rarely, daily smoker)[f]	No	No
(Lerchen 1987)	Yes	Welders in all industries versus non-welders, logistic model adjusted for age, ethnicity and tobacco smoking	More adjusted and uncontaminated reference group	Yes[d]	Yes – restricted to males[e]	Tobacco smoking (never, ex-smoker, current), ethnicity[f]	No	No
(Lopez-Cima 2007)	No (taken from Kendzia et al. (2013) as López-Cima 2007 does not report welding analysis)	N/A	N/A	Yes[d]	Yes – restricted to males[e]	Tobacco smoking as pack-years as a continuous variable, time since quitting tobacco smoking, ever working in an occupation involving lung cancer risk excluding welding-related occupations, study location[f]	No	No
	Yes			Yes[d]		Region, education level[f]	No	No

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Study Study ID	Prioritized model Are two or more alternative models reported?	Which of the alternative models was prioritized/ selected for use in the review and/or meta-analysis?	Reason for prioritization/ selection	Adjustments of effect estimates in model prioritized by reviewers Adjusted for confounding by age	Adjusted for confounding by sex	Other potential confounders adjusted for (please specify)	Interactions adjusted for[g]	Adjustment for clustering (if any)
(MacLeod 2017)		Cox proportional hazards analysis of welders, adjusted for age, region, and education level, with non-welders as the reference group	More adjusted and wider reference group		Yes – restricted to males[e]			
(Morabia 1992)	No	N/A	N/A	Yes[d]	Yes – restricted to males[e]	Race, age, hospital, cigarette tobacco smoking history (never smoker, ex-smoker, current smoker of 1–19 cigarettes per day, current smoker of 20+ cigarettes per day)[f]	No	No
(Pezzotto 1999)	No	N/A	N/A	Yes[d]	Yes – restricted to males[e]	Tobacco smoking habit (non-smoker, ex-smoker, smoker), and lifelong cigarette consumption[f]	No	No
(Richiardi 2004)	Yes – in original study and in Kendzia et al. (2013)	Ever versus never welder, reported in Kendzia et al. (2013)	Additional ever welders included in Kendzia et al. (2013) analysis	Yes[d]	Yes – restricted to males[e]	Tobacco smoking as pack-years as a continuous variable, time since quitting tobacco smoking, ever working in an occupation involving lung cancer risk excluding welding-related occupations, study location[f]	No	No
(Ronco 1988)	Yes	Logistic regression	Adjusted for age and tobacco smoking	Yes[d]	Yes – restricted to males[e]	Tobacco smoking (cumulative life-long cigarette consumption was considered (non-smokers; up to 120,000 cigarettes smoked, corresponding to a consumption of about 15 cigarette a day for 20 years; 120,000–-240,000; 240,000–-360,000; >360,000)[f]	No	No
(Sankila 1990)	No	N/A	N/A	Yes[d]	Yes – restricted to males[e]	No	No	No
(Schoenberg 1987)	Yes	Model for "combined welders", restricting to those not exposed to asbestos	Presumably including more workers due to wider exposure definition. Controls for asbestos	Yes[d]	Yes – restricted to males[e]	Tobacco smoking (never, smokers of pipes/cigars/<10 cigarettes a day, smokers of 10–-29 cigarettes a day, smokers of 30+ cigarettes a day)[f]	No	Area
(Siew 2008)	Yes	Model for all lung cancers, high cumulative exposure versus no cumulative exposure	Covers most diagnoses. It was not possible to combine exposure groups due to reporting of only number of cases. High exposure was chosen as provides the greatest contrast in exposure.	Yes[d]	Yes – restricted to males[e]	Tobacco smoking (proportion of those in the occupation who smoked daily, according to data from annual surveys on the health behavior of the Finnish adult population in 1978–1991), period of follow-up, socioeconomic status[f]	No	No
(Soskolne 2007)	No	N/A	N/A	Yes[d]	Yes – restricted to males[e]	Tobacco smoking (no/very low-level smoking i.e., <5 cigarette pack-years, low-level smoking i.e., 5–< to <30 cigarette pack-years; moderate-level smoking i.e., 30–< to < 60 cigarette	No	No

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Table 4 (*continued*)

Study Study ID	Prioritized model Are two or more alternative models reported?	Which of the alternative models was prioritized/ selected for use in the review and/or meta-analysis?	Reason for prioritization/ selection	Adjustments of effect estimates in model prioritized by reviewers Adjusted for confounding by age	Adjusted for confounding by sex	Other potential confounders adjusted for (please specify)	Interactions adjusted for[g]	Adjustment for clustering (if any)
						pack-years); high-level smoking (60+ cigarette pack-years)[f]		
(Steenland 1986)	Yes	Cox regression with age as the time variable age and dichotomous classification of welding	Able to calculate 95% confidence interval using method from Altman and Bland (see study record for details)	Yes[d]	Yes[d]	No	Unclear – backwards stepwise procedure tested for interaction	No
(Steenland 2002)	Yes	Model for dichotomised exposure	Provides estimate for entire cohort	Yes[d]	Yes – restricted to males[e]	Race, calendar time[f]	No	No
(Stücker 2002)	Yes – in original study and in Kendzia et al. (2013)	Ever versus never welder, reported in Kendzia et al. (2013)	The original study does not report analyses on welding fumes/ welders	Yes[d]	Yes – restricted to males[e]	Tobacco smoking as pack-years as a continuous variable, time since quitting tobacco smoking, ever working in an occupation involving lung cancer risk excluding welding-related occupations, study location[f]	No	No
('t Mannetje 2012)	Yes	Model from study reporting OR of ever exposure to welding fumes, adjusted for age, center, education, tobacco, and asbestos, silica and metals in the work environment	Considers exposure to welding fumes	Yes[d]	Yes – restricted to males[e]	Tobacco consumption (continuous variable for cumulativelifetime tobacco use) , asbestos, silica, and metals in the work environment, education[f]	No	Centre
(Tse 2012)	Yes	All lung cancer cases, with reference group of those never exposed to welding fumes	Considers exposure to welding fumes (as opposed to Kendzia et al. (2013), which considers occupation as welder). Does not restrict referents based on other exposures or sex.	Yes[d]	Yes – restricted to males[e]	Tobacco smoking status (never, ex-smoker, current smoker), tobacco smoking pack-years, alcohol drinking, residential radon exposure, history of lung diseases, and cancer in first-degree relatives, meat intake, education level, place of birth[f]	No	No
(Vallieres 2012)	Yes – in original study and in Kendzia et al. (2013)	Ever versus never welder, reported in Kendzia et al. (2013)	Estimates for arc and gas welders are reported separately in Vallieres et al. (2012), but the groups are not mutually exclusive so cannot be combined	Yes[d]	Yes – restricted to males[e]	Tobacco smoking as pack-years as a continuous variable, time since quitting tobacco smoking, ever working in an occupation involving lung cancer risk excluding welding-related occupations, study location[f]	No	No
(van Loon 1997)	Yes	Unexposed versus exposed	Dichotomous	Yes[d]	Yes – restricted to males[e]	Other occupational exposures, tobacco smoking (never/ex/current and pack-years), intake of vitamin C, β-carotene, and retinol[f]	No	No
(Wong 2017)	Yes	Ever welder, never foundry worker versus never welder, never foundry worker	Dichotomous	Yes[d]	Yes[d]	Race/ethnicity, education, centred pack-years of tobacco smoking at randomisation, tobacco smoking status at randomisation (current or former), centred body mass index at baseline, first degree relative with lung cancer, history of diagnosed chronic bronchitis and emphysema, education level[f]	No	Trial arm
(Yiin 2007)	Yes – different effect estimates			Yes – conditional logistic regression	Yes – conditional logistic regression	Ionizing radiation monitoring status, tobacco smoking habit surrogates	No	No

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Table 4 (*continued*)

Study Study ID	Prioritized model Are two or more alternative models reported?	Which of the alternative models was prioritized/ selected for use in the review and/or meta-analysis?	Reason for prioritization/ selection	Adjustments of effect estimates in model prioritized by reviewers Adjusted for confounding by age	Adjusted for confounding by sex	Other potential confounders adjusted for (please specify)	Interactions adjusted for[g]	Adjustment for clustering (if any)
	depending on level of exposure	Levels combined using Borenstein et al. (2009) method	The Borenstein et al. (2009) produced an effect estimate with a dichotomous exposure	with matching for birth cohort[d]	with matching for sex[d]	(socioeconomic status and birth cohort), asbestos[f]		

Study Study ID	Estimate of effect of exposure on outcome Model prioritized by reviewers (if more than one potentially eligible model reported)	Effect estimate measure type	Point estimate [h]	Standard deviation	Lower confidence limit [h]	Upper confidence limit [h]	Included in a meta-analysis?	Exposure-response (or dose–response) analysis conducted
(Becker 1999)	N/A – the model presents risk ratios of the welders in relative to the internal comparison group of turners	Risk ratio	1.3	Not reported	0.8	2.12	Yes – supporting evidence (cohort studies), mortality	Table 5 presents standardized mortality rates for duration of exposure
(Brenner 2010)	Total population adjusted for pack-years of tobacco smoking, age, sex, education, and ethnicity	Odds ratio	1.7	Not reported	1.0	3.0	Yes – main meta-analysis, incidence	No
(Breslow 1954)	Not reported, but possible to calculate odds ratios from Table 10	Odds ratio	1.77	Not reported	1.46	2.16	No – not included as insufficient adjustment for age	No
(Bruske-Hohlfeld 2000)	Ever versus never welder, reported in Kendzia et al. (2013)	Odds ratio	1.75	Not reported	1.14	2.61	Yes – main meta-analysis, incidence	No
(Buiatti 1985)	N/A	Odds ratio	2.8	Not reported	0.9	8.5	Yes – main meta-analysis, incidence	No
(Consonni 2010)	Ever versus never welder, reported in Kendzia et al. (2013)	Odds ratio	0.94	Not reported	0.56	1.59	Yes – main meta-analysis, incidence	No
(Corbin 2011)	Ever versus never welder, reported in Kendzia et al. (2013)	Odds ratio	1.43	Not reported	0.57	3.58	Yes – main meta-analysis, incidence	No
(Danielsen 1993)	Model with lag time (10 years). Two effect estimates were extracted: employment ≤5 years and employment >5 years	Risk ratio	Employment ≤5 years 1.8; employment >5 years 3.2	Not reported	Employment ≤5 years 0.5; employment >5 years 1.3	Employment ≤5 years 5.7; employment >5 years 8.1	No – not included as insufficient adjustment for age	Employment of ≤5 years or >5 years- but different analyses
(Danielsen 2000)	Worked ≥15 years as a welder (Table 6) due to latency period for trachea, bronchus, and lung cancer	Risk ratio	1.9	Not reported	0.67	5.38	No – not included as insufficient adjustment age	Yes – duration of employment as welder at the yard
(Elci 2003)	N/A	Odds ratio	0.9	Not reported	0.5	1.7	Yes – main meta-analysis, incidence	No
(Finkelstein 1995)	N/A	Odds ratio	1.07	Not reported	0.57	1.91	Yes – main meta-analysis, mortality	No
(Fortes 2003)	N/A	Odds ratio	7.65	Not reported	0.59	99.8	Yes – main meta-analysis, incidence	No
(Gottlieb 1980)	N/A	Odds ratio	Age at death <60: 1.89; age at death ≥60 years: 0.93	Not reported	Age at death <60: 0.48; age at death ≥60 years: 0.25	Age at death <60: 7.37; age at death ≥60 years:: 3.46	No – not included as no adjustment for age	No
(Guida 2011; Matrat 2016)	Risk of lung cancer associated with welding among regular welders	Odds ratio	1.66	Not reported	1.11	2.49	Yes – main meta-analysis, incidence	Yes
(Gustavsson 2000)	Ever versus never welder, reported in Kendzia et al. (2013)	Odds ratio	1.52	Not reported	0.86	2.67	Yes – main meta-analysis, incidence	Yes – in original study record
(Jöckel 1998)	Exposure to welding fumes analysis presented in Jöckel 1998	Odds ratio	1.87	Not reported	1.03	3.42	Yes – main meta-analysis, incidence	Yes – in original study record
(Kazma 2012)	Ever versus never welder, reported in Kendzia et al. (2013)	Odds ratio	0.37	Not reported	0.02	9.03	Yes – main meta-analysis, incidence	No
(Keller 1993)	N/A	Odds ratio	1.68	Not reported	1.03	2.76	Yes – main meta-analysis, incidence	No

(*continued on next page*)

Table 4 (*continued*)

Study Study ID	Estimate of effect of exposure on outcome Model prioritized by reviewers (if more than one potentially eligible model reported)	Effect estimate measure type	Point estimate [h]	Standard deviation	Lower confidence limit [h]	Upper confidence limit [h]	Included in a meta-analysis?	Exposure-response (or dose–response) analysis conducted
(Kromhout 1992)	Model with 25 years of follow-up, with occupational exposure classified in a strict way	Hazard ratio	1.54	Not reported	0.37	6.30	Yes – supporting evidence (cohort studies), incidence	No
(Lauritsen 1996)	Adjusted ever/never welding exposure	Odds ratio	1.5	Not reported	1.0	2.4	No – not included as no adjustment for age	Yes
(Lerchen 1987)	Welders in all industries versus non-welders, logistic model adjusted for age, ethnicity, and tobacco smoking	Odds ratio	3.2	Not reported	1.4	7.4	Yes – main meta-analysis, incidence	No
(Lopez-Cima 2007)	Ever versus never welder, reported in Kendzia et al. (2013)	Odds ratio	1.09	Not reported	0.66	1.80	Yes – main meta-analysis, incidence	No
(MacLeod 2017)	Cox proportional hazards analysis of welders, adjusted for age, region, and education level, with non-welders as the reference group	Hazard ratio	1.16	Not reported	1.03	1.31	Yes – supporting evidence (cohort studies), incidence	No
(Morabia 1992)	N/A	Odds ratio	1.5	Not reported	0.8	2.7	Yes – main meta-analysis, incidence	no
(Pezzotto 1999)	N/A	Odds ratio	1.1	Not reported	0.4	3.1	Yes – main meta-analysis, incidence	No
(Richiardi 2004)	Ever versus never welder, reported in Kendzia et al. (2013)	Odds ratio	1.77	Not reported	1.05	2.98	Yes – main meta-analysis, incidence	No
(Ronco 1988)	Logistic regression	Odds ratio	2.93	Not reported	0.87	9.82	Yes – main meta-analysis, mortality	No
(Sankila 1990)	N/A	Risk ratio	1.51	Not reported	1.16	1.95	Yes – supporting evidence (cohort studies), incidence	No
(Schoenberg 1987)	Model for "combined welders", restricting to those not exposed to asbestos	Odds ratio	2.5	Not reported	1.1	5.5	Yes – main meta-analysis, incidence	No
(Siew 2008)	Model for all lung cancers, high cumulative exposure versus no cumulative exposure	Risk ratio	1.15	Not reported	0.90	1.46	Yes – supporting evidence (cohort studies), incidence	Yes
(Soskolne 2007)	N/A	Odds ratio	3.91	Not reported	1.03	14.95	Yes – main meta-analysis, incidence	No
(Steenland 1986)	Cox regression with age as the time variable and dichotomous classification of welding (with 95% confidence interval calculated from p value)	Hazard ratio	1.29	Not reported	0.89	1.87	Yes – supporting evidence (cohort studies), mortality	No
(Steenland 2002)	Model for dichotomised exposure	Risk ratio	1.22	Not reported	0.93	1.59	Yes – supporting evidence (cohort studies), mortality	Yes
(Stücker 2002)	Ever versus never welder, reported in Kendzia et al. (2013)	Odds ratio	0.56	Not reported	0.18	1.70	Yes – main meta-analysis, incidence	No
('t Mannetje 2012)	Model from study reporting OR of ever exposure to welding fumes, adjusted for age, center, education, tobacco, and asbestos, silica, and metals in the work environment	Odds ratio	1.18	Not reported	1.01	1.38	Yes – main meta-analysis, incidence	Yes
(Tse 2012)	All lung cancer cases, with reference group of those never exposed to welding fumes	Odds ratio	1.69	Not reported	1.11	2.58	Yes – main meta-analysis, incidence	No
(Vallieres 2012)	Ever versus never welder, reported in Kendzia et al. (2013)	Odds ratio	2.21	Not reported	1.10	4.41	Yes – main meta-analysis, incidence	No
(van Loon 1997)	Unexposed versus exposed	Risk ratio	0.86	Not reported	0.46	1.58		Yes

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Table 4 (*continued*)

Study Study ID	Estimate of effect of exposure on outcome Model prioritized by reviewers (if more than one potentially eligible model reported)	Effect estimate measure type	Point estimate [h]	Standard deviation	Lower confidence limit [h]	Upper confidence limit [h]	Included in a meta-analysis?	Exposure-response (or dose–response) analysis conducted
							Yes – supporting evidence (cohort studies), incidence	
(**Wong 2017**)	Ever welder, never foundry worker versus never welder, never foundry worker	Hazard ratio	1.12	Not reported	0.91	1.37	Yes – supporting evidence (cohort studies), incidence	Yes
(**Yiin 2007**)	Levels combined using Borenstein et al. (2009) method	Odds ratio	1.28	Not reported	1.03	1.59	Yes – main meta-analysis; mortality	Yes

Footnotes:

[a] ISCO-08 code specified unless the study used a different classification system (in which case this is stated); for subgroup analyses, relevant crosswalks were used where identified (Statistics Canada https://www.statcan.gc.ca/en/subjects/standard/concordances/soc1980-soc1991#n1, U.S. Bureau of Labor Statistics https://www.bls.gov/soc/soccrosswalks.htm, Kendzia et al. (2013), Hardy et al. (2018) to ascertain whether codes were equivalent to ISCO-08 7212. Where a crosswalk was not identified, the job title was used and studies specifying occupation as welder were assumed to be ISCO-08 code 7212.

[b] Classification of welders in industries in Kendzia et al. (2013) was as follows (ISIC revision 2): Construction, plumbers, and other building services: 5000, 9100, 4101, 9310, 4102, 4103, 6320, 8324, 8310; Manufacture of machines, equipment, appliances: 3819, 3813, 3829, 3811, 3824, 3800, 3821, 3822, 3833, 3831, 3812, 3823, 3851, 3830, 3832, 3839, 3810, 3820, 3825; Manufacture of motor vehicles, motor bikes, bikes: 3843, 3844; Shipbuilding and repairing: 3841; Repair of transport equipment: 3842, 3845, 6100, 7111, 9513, 7112, 7110, 3849, 7100, 7131; Others: 3710, 3699, 1110, 3511, 3530, 2100, 3320, 3513, 3529, 3909, 2901, 3720, 3833, 3831, 3812, 3823, 3851, 3830, 3832, 3839, 3810, 3820, 3825, 3843, 3844, 3841, 3842, 3845, 6100, 7111, 9513, 7112, 7110, 3849, 7100, 7131, 3710, 3699, 1110, 3511, 3530, 2100, 3320, 3513, 3529, 3909, 2901.

[c] Group 1 carcinogen for the IARC category of Lung cancer, as classified in the IARC Monographs 1–132 (International Agency for Research on Cancer 2022).

[d] Adjusted for Tier 1 confounder (see Fig. 1).

[e] Restricted on Tier 1 confounder (see Fig. 1).

[f] Adjusted for one or more Tier 2 confounders (see Fig. 2).

[g] Interaction occurs when two or more exposures are greater than they would be if purely additive.

[h] Presented to the decimal place reported in the study record or capped at two decimal places.

studies, and "high" for two studies. We assigned "high" and "probably high" ratings where we considered assignment of exposure by proxy of occupation or job title as "welder" could lead to misclassification of occupational exposure to welding fumes through other tasks or participants were asked to recall past exposure to particular carcinogens, with risk of recall bias.

4.4.1.4. Bias due to outcome misclassification – Were outcome assessment methods lacking accuracy?. Risk of this bias was rated as "low" for three-quarters of the included studies (29 studies), "probably low" for two studies, "probably high" for one study, and "high" for no studies. The "probably high" rating was assigned when we judged the described methods were not robust, as described by our pre-specified criteria.

4.4.1.5. Confounding – Was potential confounding inadequately incorporated?. We judged risk of confounding was "low" in 11 studies, "probably low" in 16 studies, "probably high" in four studies, and "high" for one study. Risk of confounding was judged to be "high" or "probably high" when there was a lack of adjustment for Tier 1 or Tier 2 confounders.

4.4.1.6. Bias due to incomplete outcome data – Were incomplete outcome data inadequately addressed?. Risk of this bias was rated as "low" for three-quarters of the included (29 studies)) and "probably low" for three studies. We judged no study to have a "high" risk of bias in this domain.

4.4.1.7. Bias due to selective reporting – Does the study report appear to have selective outcome reporting?. Three-quarters of the included studies were judged as at "low" risk of bias due to selective reporting. Four studies were judged as "probably low". We judged no studies to be at "probably high" or "high" risk of this bias. Most studies were case-control studies, which we generally considered at low risk of bias due to selective reporting. We note, however, that we did not find any study protocols.

4.4.1.8. Bias due to conflict of interest. Did the study receive any support from a company, study author, or other entity having a financial interest in any of the exposures studied?

The risk of this bias was rated as "low" for one quarter of included studies (nine studies), "probably low" for half of the studies (21 studies), "probably high" for two study, and "high" for no studies. For most studies, either the authors declared no conflicts of interest or there we had no reasons to believe that conflicts of interest would have affected the study results (i.e., author affiliations were from government or academic/non-industry settings).

4.4.1.9. Other bias – Did the study appear to have other problems that could put it at a risk of bias?. We judged almost all of the included studies to be at "low" risk of other bias, with the exception of one study, which was judged to be "probably high" because cancer patients served as control subjects, which hinders generalization of findings to the general working population (Morabia et al. 1992).

4.4.2. Died from trachea, bronchus, and lung cancer (mortality)

The ratings for the eight included studies for this outcome are presented in Fig. 4.

4.4.2.1. Bias in selection of participants into the study. Are the study groups at risk of not representing their source populations in a manner that might introduce selection bias?

We rated risk of bias in selection of participants into the study as "low" for over half (five) of the included studies, "probably low" for one study, "probably high" for two studies, and "high" for no studies. For one study rated as "probably high" risk in this domain, the study sample was built from previous cohort studies. For the other, the effective sample was only a proportion of the total cohort. In neither case were the methods reported in sufficiently detail.

4.4.2.2. Bias due to a lack of blinding of study personnel. Was knowledge of the group assignments inadequately prevented (i.e., blinded or masked) during the study, potentially leading to subjective measurement of either exposure or outcome?

Risk in this bias domain was rated as "low" in over half of the studies (five studies), "probably low" in two studies, "probably high" for one study, and "high" for no studies. For most studies, we judged blinding was effective or that lack of blinding was unlikely to influence the exposure and/or outcome assessments.

4.4.2.3. Bias due to exposure misclassification – Were exposure assessment methods lacking accuracy?. Risk of bias due to exposure misclassification was rated as "low" for no studies. Over half of the included studies had a "probably low" risk of this bias. Two studies and one study had a "probably high" and "high" risk in this bias domain. We rated studies as "high" and "probably high" risk if they assigned exposure via proxy of occupation at time of death (from the death certificate) or job title as recalled by next of kin. Exposure misclassification could have occurred because occupation at time of death could not reflecting usual job history and because of recall bias, respectively.

4.4.2.4. Bias due to outcome misclassification – Were outcome assessment methods lacking accuracy?. We judged six studies to be at "low" risk of bias due to outcome misclassification. The other two studies were rated as "probably low" risk of this bias. No studies were at "probably high" or "high" risk. Deaths were ascertained either with a death certificate or extracted from administrative registers.

4.4.2.5. Confounding – Was potential confounding inadequately incorporated?. Risk of confounding was judged to be "low" for one study, "probably low" for three studies, "probably high" for three studies and "high" for one study.

4.4.2.6. Bias due to incomplete outcome data – Were incomplete outcome data inadequately addressed?. Almost all (seven) studies were rated as at "low" risk of bias due to incomplete outcome data. The eighth study was judged as at "probably low" risk of this bias. No studies were at "probably high" or "high" risk. The studies were either case-control studies, in which outcome was known at the start of the study or we judged follow-up was long enough to assess mortality well.

4.4.2.7. Bias due to selective reporting – Does the study report appear to have selective outcome reporting?. Seven studies were judged at "low" risk of bias due to selective reporting. The eighth study was "probably low" in reporting bias risk. No studies had "probably high" or "high" risk. We did not find any study protocols to compare reporting against. We nevertheless judged all studies to be free of selective reporting.

4.4.2.8. Bias due to conflict of interest. Did the study receive any support from a company, study author, or other entity having a financial interest in any of the exposures studied?

We judged none of the included studies to be at "low" risk of bias due to conflict of interest. Almost all studies were rated as "probably low" risk of this bias. We judged one study had a "probably high" risk of bias due to conflict of interest, but none as at "high" risk for this bias.

4.4.2.9. Other bias – Did the study appear to have other problems that could put it at a risk of bias?. Risk of other bias was rated as "low" for all studies and "probably low", "probably high" and "high" for no studies. We did not identify other sources of substantive bias in included studies.

Table 5
Characteristics of studies awaiting classification.

Study ID	Study population			Study type	Exposure assessment		Comparator	Outcome assessment	
	Total number of study participants	Country of study population	Industrial sector/ Occupation		Exposure definition	Exposure measurement		Outcome definition	Outcome measurement
DeBono 2021 (DeBono et al. 2021)	2,188,300	Canada	Multiple	Cohort study	Welding and flame cutting occupations	Occupation coded by Workplace Safety and Insurance Board as part of the claim review process	All other occupations	Malignant neoplasms of the pleura (ICD-10 code C38.4) or mesothelioma (ICD-10 code: C45) including peritoneal disease (ICD-10 code: C45.1)	Compensation claims with Canadian province of Ontario Cancer Registry
Chung 2021 (Chung et al. 2021)	6326	Republic of Korea	Shipyard workers	Cohort study	Workers exposed to nickel, chromium, and welding fumes (CO^2 welding, stainless steel welding)	Occupational environment assessment of the shipyard showed the geometric mean exposure to welding fumes was 0.63 mg/m^3 (maximum value: 41.53 mg/m^3), to nickel was 0.88 μg/m^3 (maximum value: 73.00 μg/m^3), and to chromium was 1.38 μg/m^3 (maximum value: 63.60 μg/m^3)	Unexposed workers (based on assessment of their work environment)	Lung cancer (Lung-RADS category ≥ 3)	Lung imaging reporting and data system (Lung-RADS) (imaging classification system using a larger minimum nodule size than the NLST criteria)

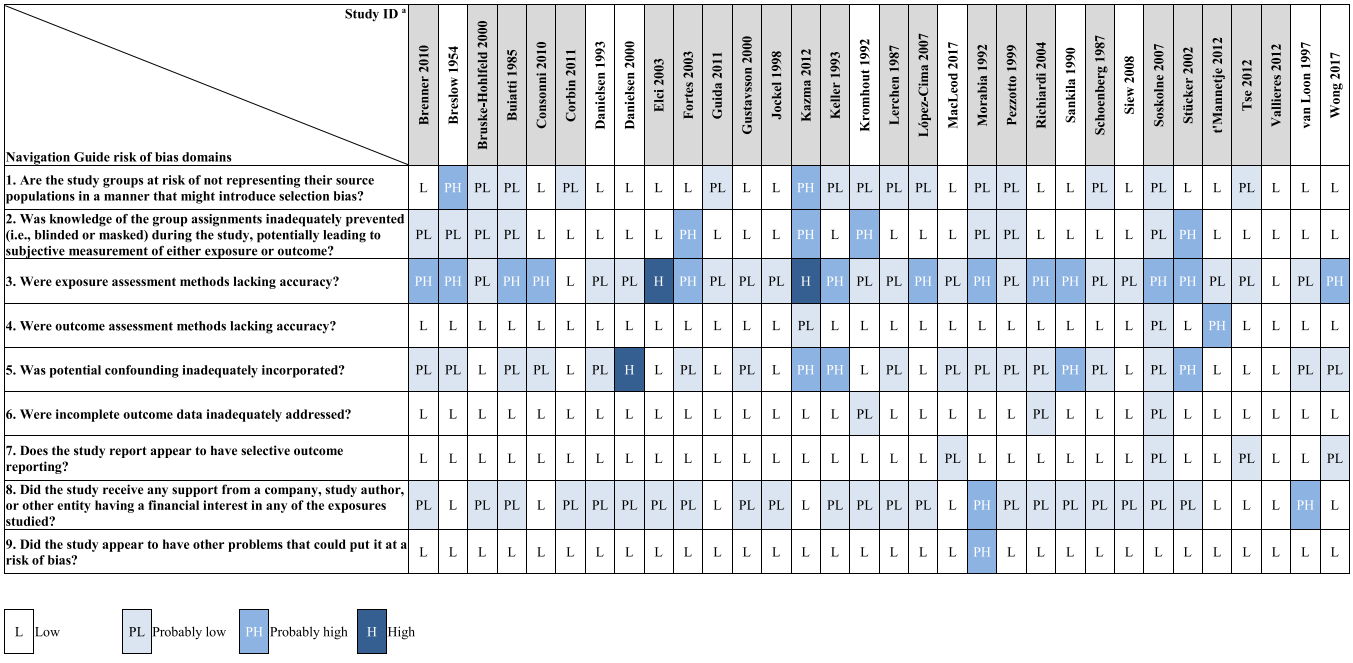

Fig. 3. Summary of risk of bias in included studies on trachea, bronchus, and lung cancer incidence. Footnote: [a] Study IDs marked in grey were included in the main meta-analysis.

4.5. Evidence synthesis

Our search did not identify any evidence on prevalence of trachea, bronchus, and lung cancer but we did find evidence for incidence and mortality of trachea, bronchus, and lung cancer.

4.5.1. Acquired trachea, bronchus, and lung cancer (incidence)

A total of 32 studies (24 case-control studies and eight cohort studies) with over 1,227,096 participants reported estimates on the effect of any (or high) occupational exposure to welding fumes on the outcome of trachea, bronchus, and lung cancer incidence, compared with no (or low) occupational exposure to welding fumes. The total

Navigation Guide risk of bias domain \ Study ID [a]	Becker 1999	Finkelstein 1995	Gottlieb 1980	Lauritsen 1996	Ronco 1988	Steenland 1986	Steenland 2002	Yiin 2007
1. Are the study groups at risk of not representing their source populations in a manner that might introduce selection bias?	L	L	PL	L	L	PH	L	PH
2. Was knowledge of the group assignments inadequately prevented (i.e., blinded or masked) during the study, potentially leading to subjective measurement of either exposure or outcome?	L	L	PL	PL	L	PH	L	L
3. Were exposure assessment methods lacking accuracy?	PL	H	PH	PL	PH	PL	PL	PL
4. Were outcome assessment methods lacking accuracy?	L	PL	PL	L	L	L	L	L
5. Was potential confounding inadequately incorporated?	PH	PH	H	PL	PL	L	PL	PH
6. Were incomplete outcome data inadequately addressed?	L	L	L	L	L	PL	L	L
7. Does the study report appear to have selective outcome reporting?	L	L	L	L	L	PL	L	L
8. Did the study receive any support from a company, study author, or other entity having a financial interest in any of the exposures studied?	PH	PL	PL	PL	PL	PL	PL	PL
9. Did the study appear to have other problems that could put it at a risk of bias?	L	L	L	L	L	L	L	L

L Low PL Probably low PH Probably high H High

Fig. 4. Summary of risk of bias in included studies on trachea, bronchus, and lung cancer mortality. Footnote: [a] Study IDs marked in grey were included in the main meta-analysis.

sample size comprised 22,476 (1.8 %) females and 1,204,620 (98.2 %) males, counting effective sample sizes (Table 4). Occupational exposure to welding fumes was generally assessed via survey, and most studies included in their exposure group workers who had been employed or reported their occupation as job title as a welder (i.e., exposure assignment via proxy; Table 4). We meta-analysed evidence from different study designs separately (as per our pre-published protocol). In our risk of bias assessment (Section 4.4.1), we judged that case-control studies generally have a lower risk of confounding from tobacco smoking. Additionally, more of the case-control studies consider exposure to asbestos for this outcome. Moreover, the pooled effect estimate from the meta-analysis of the case-control studies for the outcome is based on a much larger cumulative sample size and has better temporal coverage, as we have many more case-control studies in our dataset, including recently published ones. Our main meta-analysis for this outcome is consequently that of the relevant case-control studies as the prioritized evidence. We consider the evidence from the cohort study as supporting evidence.

4.5.1.1. Case-control studies (prioritised evidence). Twenty-four studies comprising 57,931 participants (798 [1.4 %] females and 58,119 [98.6 %] males) from three WHO regions (Region of the Americas, European Region, and Western Pacific Region) reported estimates of the effect of occupational exposure to welding fumes on acquiring (incident) trachea, bronchus, and lung cancer, compared with no (or low) occupational exposure to welding fumes. Of these, all but one could be included in a quantitative meta-analysis. We converted ORs to RRs using the median baseline risk in the unexposed population (i.e., 24.9 cases per 100,000 persons) reported for this outcome in the cohort studies included in this systematic review (Danielsen et al. 1993; van Loon et al. 1997; Danielsen et al. 2000; Siew et al. 2008; Wong et al. 2017), and present the conversions in Table 6. For 't Mannetje, 2012, we added the effect estimate from the original study record, as opposed to the individual effect estimates reported for different countries in the Kendzia et al. (2013) individual participant data analysis. Additionally, instead of the effect estimate in Kendzia et al. (2013), we included the effect estimate from the original study records for Brenner et al. (2010) due to the inclusion of females, and for Tse et al. (2012) due to the consideration of exposure to welding fumes (rather than via proxy of ever/never welder). These studies that we pooled in our meta-analysis were somewhat heterogeneous in their exposure definitions (in that some studies assigned exposure based on occupation or job title of "welder", whereas others measured occupational exposure to welding fumes more directly), the comparator (in that some studies included participants who had been exposed for less than a specified period of time as unexposed), and the outcome (in that some studies considered only lung cancer, but others considered two or more of trachea, bronchus, and lung cancer). However, we considered the studies similar enough to warrant inclusion in the meta-analysis. Compared with no (or low) occupational exposure to welding fumes, any (or high) occupational exposure to welding fumes increased the risk of acquiring trachea, bronchus, and lung cancer (RR 1.48, 95 % confidence interval [CI] 1.29–1.70, 23 studies, 57,931 participants, I^2 24 %, Fig. 5). We also used an alternative method to run the meta-analysis, in which we included ORs in the meta-analysis and then converted the pooled OR to a RR (Appendix 6 in the Supplementary data). This resulted in a pooled OR of 1.50 (95 % CI 1.29–1.73, I^2 29 %). Converting this gave a summary RR of 1.48 (95 % CI 1.28–1.72). We judged this to be comparable to the pooled RR from the main meta-analysis.

One case-control study that was included in the systematic review was excluded from the meta-analysis (Breslow et al. 1954). The reason for this exclusion from the meta-analysis was that this study did not

provide an effect estimate adjusted for all Tier 1 confounders (i.e., not adjusted for age), nor the data to calculate such an adjusted estimate. Because this study did not report an unadjusted effect estimate either, we calculated the unadjusted RR from raw counts reported in the study record (see Appendix 7 in the supplementary data for details). The unadjusted RR was 1.77 (95 % CI 1.46–2.16) (Appendix 7 for forest plot).

We explored how each study impacted the pooled RR and I^2 heterogeneity indicator in a leave-one-out analysis (Table 7). Changes were generally small, however excluding **'t Mannetje (2012)** registered the largest increase in the pooled RR and the largest reduction in statistical heterogeneity (1.55, 95 % CI 1.35–1.77, I^2 5 %). Leaving Lerchen et al. (1987) out resulted in the largest reduction in the pooled RR (1.44, 95 % CI 1.26–1.64, I^2 18 %). The largest increase in statistical heterogeneity was observed when removing Corbin et al. (2011) (RR 1.48, 95 % CI 1.29–1.71, I^2 28 %).

4.5.1.2. Cohort studies (supporting evidence). Eight studies with over 1,171,445 participants (21,678 [1.9 %] females and at least 1,149,767 [98.1 %] males) from two WHO regions (Region of the Americas and European Region) reported estimates of the effect of any (or high) occupational exposure to welding fumes on acquiring trachea, bronchus, and lung cancer (incidence), compared with no (or low) occupational exposure to welding fumes. Six of these studies could be included in a quantitative meta-analysis. These studies were somewhat heterogeneous in terms of the definition of exposure (some studies considered occupation or job title of "welder" and some considered occupational exposure to welding fumes; see Table 4) and the comparator (some studies included people who had been exposed for less than a specified period of time as unexposed). All these studies examined lung cancer diagnosis only, except the Kromhout et al. (1992) study, which examined trachea, bronchus, and lung cancer diagnosis.. However, we considered the studies sufficiently similar to warrant inclusion in the same meta-analysis. Compared with no (or low) occupational exposure to welding fumes, any (or high) occupational exposure to welding fumes increased the risk of acquiring trachea, bronchus, and lung cancer (RR 1.18, 95 % CI 1.08–1.29, 6 studies, ≥1,166,874 participants, I^2 0 %; Fig. 6).

The findings from two cohort studies not included in this meta-analysis are presented in Table 8. Danielsen et al. (1993) and Danielsen et al. (2000) both reported an increased risk for participants with the work category of "welder", but this was only statistically significant in those employed as a welder for > 5 years in Danielsen et al. (1993).

4.5.1.3. Synthesis across designs. The prioritized body of evidence of case-control studies showed that, compared with no (or low) occupational exposure to welding fumes, any (or high) occupational exposure to welding fumes led to an estimated increase in trachea, bronchus, and lung cancer, providing an RR of 1.48 (95 % CI: 1.29–1.70). The evidence from the one case-control study and eight cohort studies excluded from the main meta-analysis are generally supportive of the findings from the main meta-analysis.

4.5.2. Died from trachea, bronchus, and lung cancer (mortality)

A total of eight studies (five case-control studies, three cohort studies) comprising 35,150 participants (at least 285 females [0.8 %] and 23,285 males [66.2 %]) reported estimates on the effect of any (or high) occupational exposure to welding fumes on the outcome of trachea, bronchus and/or lung cancer mortality, compared with no (or low) occupational exposure to welding fumes. Occupational exposure to welding fumes was generally assessed via administrative records or surveys (Table 4). We meta-analysed evidence from different study designs separately (as per our pre-published protocol; Pega et al. (2020a)). In our risk of bias assessment (see Section 4.4.2), we judged that case-control studies generally have a lower risk of confounding from tobacco smoking. Additionally, more of the case-control studies consider exposure to asbestos for this outcome. Our main meta-analysis for this outcome is consequently that of the relevant case-control studies. We again also consider the evidence from the cohort studies as supporting evidence.

4.5.2.1. Case-control studies (prioritised evidence). Five studies comprising 14,825 participants (285 [1.9 %] females and 14,540 [98.1 %] males) from two WHO regions (Region of the Americas and European Region) reported estimates of the effect of any (or high) occupational exposure to welding fumes on dying of trachea, bronchus, and lung cancer (mortality), compared with no (or low) occupational exposure to welding fumes. Of these, three studies could be pooled in the same quantitative meta-analysis. The effect estimate from Yiin et al. (2007) was calculated using the Borenstein et al. (2009) method (see Appendix 8 in the Supplementary data for details of the calculation). We converted ORs to RRs using the baseline risk in the unexposed population (i.e., 29.9 per 100,000 persons) reported for this outcome in the cohort studies included in this systematic review. As this was reported in two studies (Steenland et al. 1986; Steenland 2002), we selected the baseline risk from the more recent estimate and from the study with longer follow-up: Steenland (2002). The conversions are presented in Table 9. Compared with no (low) exposure to welding fumes, any (or high) occupational exposure welding fumes increased the risk of dying of trachea, bronchus, and lung cancer (RR 1.27, 95 % CI 1.04–1.56, 3 studies, 8,686 participants, I^2 0 %; Fig. 7). We also used an alternative method to run the meta-analysis, in which we included ORs in the meta-analysis and then converted the pooled OR to a RR (Appendix 6 in the Supplementary data). This resulted in a pooled OR of 1.29 (95 % CI 1.03–1.61, I^2 3 %) and a summary RR of 1.28 (95 % CI 1.02–1.60). We judged this to be comparable to pooled RR from the main meta-analysis.

The findings from the two cohort studies excluded from the meta-analysis are presented in Table 10. All three studies reported an increased OR following occupational exposure to welding fumes, but for Gottlieb (1980) this increase was limited to those who died at < 60 years of age. For those aged ≥ 60 years at death, Gottlieb (1980) reported lower odds of death in the exposed. The 95 % CI for both effect estimates

Table 6
Effect estimates (odds ratios converted to risk ratios) of the effect of occupational exposure to welding fumes on trachea, bronchus, and lung cancer incidence reported in 23 case-control studies included in the main meta-analysis (median baseline risk: 0.025).

Study ID	Odds ratio (95 % CI) [a]	Converted risk ratio (95 % CI)
Brenner, 2010	1.7 (1.0–3.0)	1.67 (0.96–2.89)
Brüske-Hohlfeld 2000	1.75 (1.14–2.61)	1.72 (1.14–2.60)
Buiatti 1985	2.8 (0.9–8.5)	2.68 (0.87–8.23)
Consonni 2010	0.94 (0.56–1.59)	0.94 (0.56–1.59)
Corbin 2011	1.43 (0.57–3.58)	1.41 (0.56–3.55)
Elci 2003	0.9 (0.5–1.7)	0.90 (0.49–1.66)
Fortes 2003	7.65 (0.59–99.8)	6.56 (0.5–85.31)
Guida 2011	1.66 (1.11–2.49)	1.63 (1.09–2.45)
Gustavsson 2000	1.52 (0.86–2.67)	1.50 (0.85–2.64)
Jockel 1998	1.87 (1.03–3.42)	1.83 (1.00–3.33)
Kazma 2012	0.37 (0.02–9.03)	0.38 (0.02–7.99)
Keller 1993	1.68 (1.03–2.76)	1.65 (1.01–2.70)
Lerchen 1987	3.2 (1.4–7.4)	3.03 (1.32–6.97)
López-Cima 2007	1.09 (0.66–1.80)	1.09 (0.66–1.80)
Morabia 1992	1.5 (0.8–2.7)	1.48 (0.81–2.72)
Pezzotto 1999	1.1 (0.4–3.1)	1.10 (0.39–3.05)
Richiardi 2004	1.77 (1.05–2.98)	1.74 (1.03–2.93)
Schoenberg 1987	2.5 (1.1–5.5)	2.41 (1.08–5.39)
Soskolne 2007	3.91 (1.03–14.95)	3.64 (0.96–13.89)
Stucker 2002	0.56 (0.18–1.7)	0.57 (0.18–1.74)
't Mannetje 2012	1.18 (1.01–1.38)	1.17 (1.00–1.37)
Tse 2012	1.69 (1.11–2.58)	1.66 (1.09–2.53)
Vallières 2012	2.21 (1.10–4.41)	2.15 (1.07–4.30)

Footnote: [a] Presented to the decimal place reported in the study record or capped at two decimal places.

from Gottlieb (1980) were however wide. Overall, these studies provide some support for the findings from the meta-analysis.

We explored how each study impacted the pooled RR and heterogeneity indicator (I^2) in a leave-one-out analysis (Table 11). Removing either Finkelstein (1995) or Yiin et al. (2007) resulted in a pooled RR of 1.48, whereas removing Ronco et al. (1988) resulted in a pooled RR of 1.25. Removing Ronco et al. (1988) lead to the same statistical heterogeneity (I^2 0 %), whereas removing Yiin et al. (2007) and Finkelstein (1995) increased the statistical heterogeneity to I^2 47 % and 35 %, respectively.

4.5.2.2. Cohort studies (supporting evidence). Three studies with 20,325 participants from two WHO regions (Region of the Americas and European Region) reported estimates of the effect of occupational exposure to welding fumes on dying of trachea, bronchus, and lung cancer, compared with no (or low) occupational exposure to welding fumes. In terms of study participants' sex, the studies comprised ≥ 8,745 [45.0 %] males; one study had no female participants, and in the other two studies the numbers of female and male participants were unclear. Steenland et al. (1986) reported an effect estimate with a p value, but no 95 % CI. Details of the back-calculation of the uncertainty measure can be found in Appendix 9 in the Supplementary data. All three studies could be included in the same quantitative meta-analysis. These studies that we pooled in our meta-analysis were somewhat heterogeneous in the exposure, with different minimum durations of working as a welder being included in the exposed group. Additionally, the Steenland et al. (1986) study reported that it examined lung cancer only, but did not report ICD codes to confirm this. ICD codes reported in the other two studies showed they examined trachea, bronchus, and lung cancer. Despite these differences between studies, we considered these studies similar enough to warrant inclusion in the same meta-analysis. Compared with no (or low) occupational exposure to welding fumes, any (or high) such occupational exposure increased the risk of dying of trachea, bronchus, and lung cancer (RR 1.25, 95 % CI 1.02–1.53, three studies, 20,325 participants, I^2 0 %; Fig. 8).

4.5.2.3. Synthesis across designs. Our synthesis of the prioritized body of evidence of case-control studies found that, compared with no (or low) occupational exposure to welding fumes, any (or high) occupational exposure to welding fumes led to an estimated increase in trachea, bronchus, and lung cancer mortality. The main meta-analysis produced an RR of 1.27 (95 % CI 1.04–1.56). We judged the evidence from the one case-control study and three cohort studies that we excluded from the main meta-analysis is generally supportive of the findings from the main meta-analysis.

Table 7
Pooled effect estimates of the effect of occupational exposure to welding fumes on trachea, bronchus, and lung cancer incidence in case-control studies, when each study is omitted from the main meta-analysis one at a time.

Study excluded from meta-analysis	Pooled effect estimate (95 % confidence interval)	I^2 (%)
None excluded (all studies)	1.48 (1.29–1.70)	24
Brenner, 2010	1.47 (1.27–1.70)	26
Brüske-Hohlfeld 2000	1.46 (1.26–1.69)	25
Buiatti 1985	1.46 (1.27–1.68)	24
Consonni 2010	1.51 (1.31–1.74)	22
Corbin 2011	1.48 (1.29–1.71)	28
Elci 2003	1.51 (1.31–1.73)	23
Fortes 2003	1.47 (1.28–1.69)	24
Guida 2011	1.47 (1.27–1.70)	26
Gustavsson 2000	1.48 (1.28–1.72)	27
Jöckel 1998	1.47 (1.27–1.69)	25
Kazma 2012	1.48 (1.29–1.71)	26
Keller 1993	1.47 (1.27–1.70)	26
Lerchen 1987	1.44 (1.26–1.64)	18
López-Cima 2007	1.51 (1.31–1.74)	25
Morabia 1992	1.48 (1.28–1.72)	27
Pezzotto 1999	1.49 (1.29–1.72)	27
Richiardi 2004	1.47 (1.27–1.70)	26
Schoenberg 1987	1.46 (1.27–1.67)	23
Soskolne 2007	1.46 (1.27–1.67)	22
Stücker 2002	1.49 (1.30–1.70)	21
't Mannetje 2012	1.55 (1.35–1.77)	5
Tse 2012	1.47 (1.27–1.70)	26
Vallières 2012	1.46 (1.27–1.68)	23

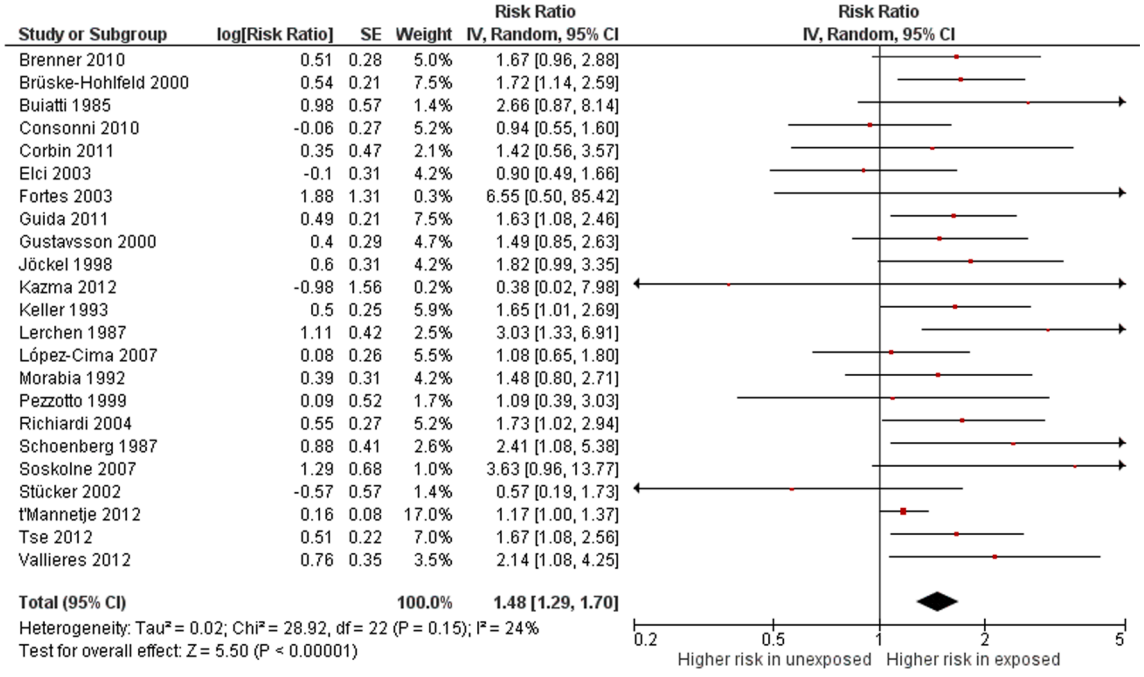

Fig. 5. Forest plot with the main meta-analysis of the prioritized evidence (case-control studies), Outcome: Acquired trachea, bronchus, and lung cancer, Comparison: Any (or high) occupational exposure to welding fumes, compared with no (or low) occupational exposure to welding fumes.

4.6. Additional analyses

4.6.1. Subgroup analyses

Subgroup analyses were performed on data from the main meta-analysis. The forest plots and results of additional subgroup analyses are presented in Appendix 10 in the Supplementary data.

4.6.1.1. Acquired trachea, bronchus, and lung cancer (incidence). These analyses include subgrouping by WHO region, sex, occupation, and cancer site (Table 12). No evidence was found for meaningful subgroup differences by WHO region, cancer site or publication year. Regarding cancer site in the Gustavsson et al. (2000) study, the original study record specified that bronchus and lung cancers were studied, but the Kendzia et al. (2013) analysis, from which the effect estimate for this study was extracted, did not specify the exact cancer sites studied. Zero studies included only females, and the pooled estimate for studies including males only was similar to that of the main-meta-analysis. Limiting the meta-analysis to studies that only included participants with occupations coded as 7212 – welder in ISCO-08 (or equivalent) provided a pooled RR similar to that found in the main meta-analysis.

4.6.1.2. Died from trachea, bronchus, and lung cancer (mortality). We were able to conduct subgroup analyses by WHO region, sex, occupation, cancer site, and publication year (Table 13). These subgroup analyses found no evidence for meaningful subgroup differences by WHO region, cancer site or publication year. No study included only female participants; the pooled effect estimate for studies with only male participants was similar to that from the main meta-analysis. The pooled effect estimate for studies that included participants in occupations with the ISCO-08 code 7212 (or equivalent) only provided a pooled RR similar to that from the main meta-analysis.

4.6.2. Sensitivity analyses

Sensitivity analyses were also performed for data from the main meta-analysis. Their forest plots are presented in Appendix 11 in the Supplementary data.

4.6.2.1. Acquired trachea, bronchus, and lung cancer (incidence). The sensitivity analyses for incident trachea, bronchus, and lung cancer found no evidence for meaningful subgroup differences by risk of bias for conflict of interest, risk of confounding, use of documented or approximated ICD codes, adjustment for confounding by tobacco smoking and/or exposure to asbestos or assumed but unclear adjustment for Tier 1 confounders (Table 14). However, the pooled effect estimate was higher (RR 1.74, 95 % CI 1.45–2.09) for studies with "low"/"probably low" risk of bias in all domains, compared with the pooled effect estimate for studies with "high"/"probably" high risk of bias in any domain (RR 1.29, 95 % CI 1.08–1.55; p value for subgroup differences 0.02). Additionally, there was no evidence for differences (p 0.61) between cohort studies reporting RR as the effect estimate (RR 1.24, 95 % CI 0.85–1.61) and cohort studies reporting hazard ratios (RR 1.15, 95 % CI 1.04–1.28). The meta-analysis using the inverse variance heterogeneity (IVhet) model (Doi et al. 2017) produced a similar but slightly lower pooled estimate than in the main meta-analysis (RR 1.38, 95 % CI 1.17–1.63).

Table 8
Results from studies excluded from the meta-analysis of the supporting evidence and reasons for their exclusion from this meta-analysis.

Study ID	Effect estimate	Reason for exclusion from meta-analysis
Danielsen 1993	RR for employment ≤ 5 years 1.8 (95 % CI 0.5–5.7) RR for employment > 5 years 3.2 (95 % CI 1.3–8.1)	Only crude effect estimate reported and no data to calculate an adjusted effect estimate
Danielsen 2000	RR 1.90 (95 % CI 0.67–5.38)	Only crude effect estimate reported and no data to calculate an adjusted effect estimate

We found information about the risk among never smokers in one of the prioritized studies (Brenner et al. 2010): an OR of 3.4 (95 % CI 1.1–10.4) for never smokers. This was larger than the prioritized effect estimate for the total population (i.e., ever and never smokers) used for the main meta-analysis for this study of 1.7 (95 % CI 1.0–3.0). It was not possible to draw any conclusions from this, as we were unable to back-calculate an OR for ever smokers, due to the addition of pack-years of smoking as a confounder in the analysis for the total population, and because this evidence comes from one study, in one location. Analyses by smoking status were provided in the pooled analysis by Kendzia et al. (2013), from which some effect estimates were taken. They reported that the OR for lung cancer among welders who were never-smokers was 2.34 (95 % CI 1.31–4.17); whereas the OR for lung cancer among welders who were ever-smokers was 1.33 (95 % CI 1.14–1.54) (29,947 participants, 15 studies). Additionally, interaction between welding and smoking was tested for. A p value of 0.22 and a relative excess risk due to interaction of 3.72 (95 % CI 1.19–6.25) were reported (29,947 participants, 15 studies), with the authors concluding no significant interaction. However, the individual effect estimates per study for welders and non-welders were not reported, so we were unable to reproduce this analysis or use these in our systematic review.

4.6.2.2. Died from trachea, bronchus, and lung cancer (mortality). Our sensitivity analyses for this outcome found no evidence for meaningful

Table 9
Effect estimates (odds ratios converted to risk ratios) of the effect of occupational exposure to welding fumes on trachea, bronchus, and lung cancer mortality reported in three case-control studies included in the main meta-analysis (median baseline risk: 0.03).

Study ID	Odds ratio (95 % CI)	Converted risk ratio (95 % CI)
Finkelstein 1995	1.07 (0.57–1.91)	1.07 (0.58–1.95)
Ronco 1988	2.93 (0.87–9.82)	2.77 (0.82–9.31)
Yiin 2007	1.28 (1.03–1.59)	1.27 (1.02–1.58)

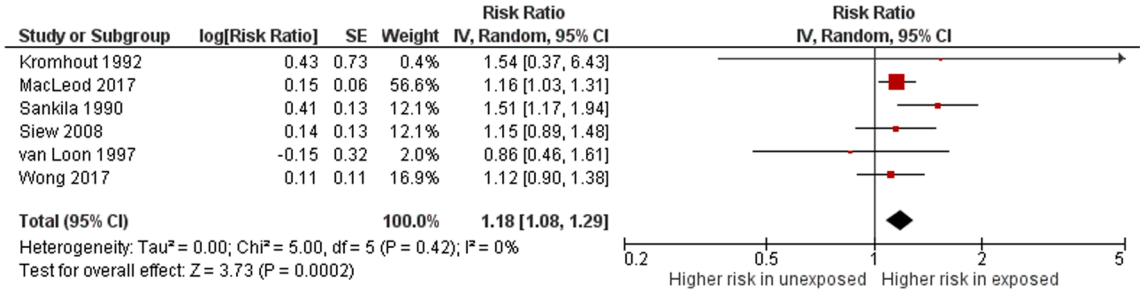

Fig. 6. Forest plot with the meta-analysis of the supporting evidence (cohort studies), Outcome: Acquired trachea, bronchus, and lung cancer, Comparison: Any (or high) occupational exposure to welding fumes, compared with no (or low) occupational exposure to welding fumes.

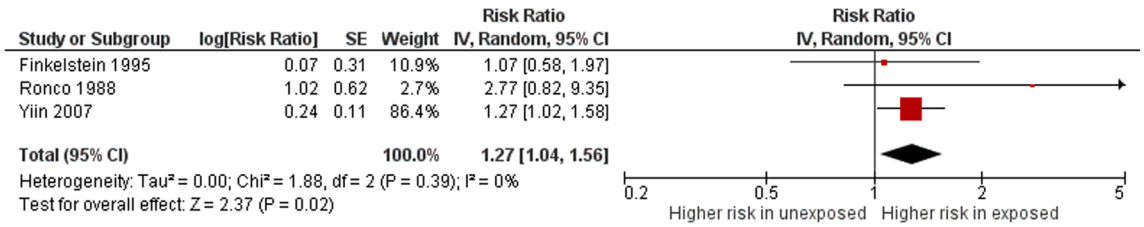

Fig. 7. Forest plot with the main meta-analysis of the prioritized evidence (case-control studies), Outcome: Died from trachea, bronchus, and lung cancer, Comparison: Any (or high) occupational exposure to welding fumes, compared with no (or low) occupational exposure to welding fumes.

Table 10
Results from studies excluded from the meta-analysis of the prioritized evidence and reasons for their exclusion from this meta-analysis.

Study ID	Effect estimate	Reason for exclusion from meta-analysis
Gottlieb 1980	OR for age < 60 years at death 1.89 (95 % CI 0.48–7.37) OR for age ≥ 60 years at death 0.93 (95 % CI 0.25–3.46)	Adjustment was not made for the Tier 1 confounder of age. Instead, ORs were provided stratified on age, which combined would not have sufficiently controlled for age.
Lauritsen 1996	OR 3.20 (95 % CI 1.00–2.40)	Age was matched on but was not adjusted for.

Table 11
Change in pooled effect estimate of the effect of occupational exposure to welding fumes on trachea, bronchus, and lung cancer incidence in case-control studies, when each study is omitted from the main meta-analysis one at a time.

Study excluded from meta-analysis	Point pooled estimate (95 % CI)	I^2 (%)
None excluded (all studies)	1.27 (1.04–1.56)	0
Finkelstein 1995	1.48 (0.81–2.71)	35
Ronco 1998	1.25 (1.02–1.53)	0
Yiin 2007	1.48 (0.61–3.59)	47

subgroup differences by risk of bias in any domain, risk of bias for conflict of interest, risk of confounding, use of documented or approximated ICD codes or adjustment for confounding by tobacco smoking and/or exposure to asbestos (Table 15). We also carried out a sensitivity analysis to remove Yiin et al. (2007), as the effect estimate was calculated using the Borenstein et al. (2009) method. This resulted in a pooled effect estimate of 1.48 (0.61–3.58; see Table 11). We judged this to be potentially different to the pooled RR from the main meta-analysis (i.e., 1.27, 95 % CI 1.04–1.56).

Additionally, we carried out two sensitivity analyses relating to cohort studies. There were no differences between cohort studies reporting RRs as the effect estimate (RR 1.24, 95 % CI 0.98–1.57) and cohort studies reporting hazard ratios (RR 1.28, 95 % CI 0.88–1.86; p 0.87). Furthermore, as the 95 % CI was back-calculated for Steenland et al. (1986), we carried out a sensitivity analysis, removing this cohort study from the meta-analysis of cohort studies reporting on trachea, bronchus, and lung cancer mortality. This resulted in a pooled effect estimate of 1.24 (95 % CI 0.98–1.57), compared with the effect estimates of 1.25 (95 % CI 1.02–1.53) when Steenland et al. (1986) was included, which we judged to be very similar.

4.7. Quality of evidence

4.7.1. Acquired trachea, bronchus, and lung cancer (incidence)

4.7.1.1. Downgrade domain – Risk of bias. We judged there to be some concern over the risk of bias in the domain called "risk of bias due to exposure assessment". On the one hand, the sensitivity analysis that we conducted on this domain showed no subgroup difference between studies judged to be at "high"/"probably high" and those judged to be at "low"/"probably low" risk of bias in this domain (see Table A11.1.2 in Appendix 11), and studies that were larger in size (and contribution to the main meta-analysis) and those that were prioritized evidence that contributed to the main meta-analysis were judged to be generally at lower risk of bias in this domain. On the other hand, we judged this risk of bias to have potentially attenuated the effect estimate towards the null, which would be equally concerning as an overestimation of the effect size, since the aim of the meta-analysis is risk quantification (to produce a RR that is as accurate as possible that will be used to produce estimates of the burden of disease, if any), rather than establishing harmfulness (carcinogenicity)/direction of the effect. We had no or only minor concerns for risk of bias in all other domains. With that in mind, we had serious, but not very serious, concerns for risk of bias and downgraded the quality of evidence by only one level in this downgrade domain.

4.7.1.2. Downgrade domain – Indirectness. The included studies covered populations in 21 countries in three WHO regions. Most included studies primarily or only covered males, but we judged this to not be concerning because it is likely representative of the population of workers exposed to welding fumes who we judged to also be primarily males. Additionally, we were unaware of any evidence suggesting that there is a biological difference in the effect of occupational exposure to welding fumes on the outcome between males and females (i.e., no effect modification by sex). The included studies also covered populations across several decades of time. The exposures and populations in the included studies reasonably well capture the exposure and global population of interest to this systematic review. We, therefore, had no or

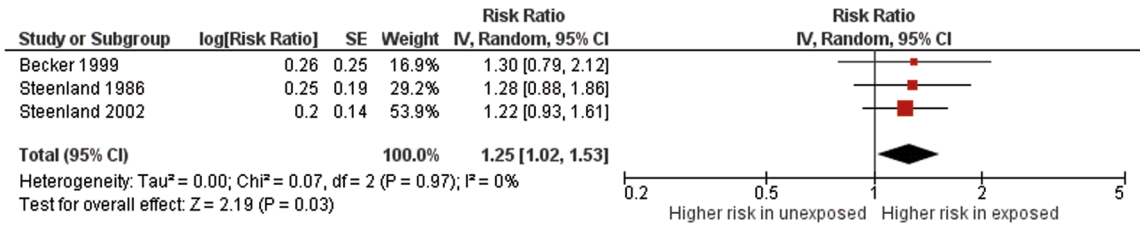

Fig. 8. Forest plot with the meta-analysis of the supporting evidence (cohort studies), Outcome: Died from trachea, bronchus, and lung cancer, Comparison: Any (or high) occupational exposure to welding fumes, compared with no (or low) occupational exposure to welding fumes.

Table 12
Summary of results from subgroup analyses for outcome of Acquired trachea, bronchus, and lung cancer.

Subgroup	Pooled effect estimate for subgroup	Test for subgroup differences
WHO region		p = 0.18
Americas (7 studies)	1.79 (1.40–2.30)	
Europe (16 studies)	1.36 (1.13–1.62)	
Western Pacific (2 studies)	1.62 (1.09–2.39)	
Sex		p = N/A
Males only (22 studies)	1.47 (1.27–1.70)	
Occupation		p = N/A
ISCO-08 7212 or equivalent (16 studies)	1.51 (1.29–1.78)	
Cancer site		p = 0.92
Lung (16 studies)	1.46 (1.22–1.75)	
Bronchus and lung (1 study)	1.49 (0.85–2.63)	
Trachea, bronchus, and lung (6 studies)	1.56 (1.21–2.00)	
Publication year		p = 0.09
Published in 1980s (3 studies)	2.69 (1.61–4.49)	
Published in 1990s (4 studies)	1.58 (1.16–2.16)	
Published in 2000s (8 studies)	1.39 (1.04–1.85)	
Published in 2010s (3 studies)	1.36 (1.13–1.64)	

Footnote: p values in the table relate to tests for subgroup differences.

only minor concerns for indirectness and did not downgrade the quality of evidence.

4.7.1.3. Downgrade domain – Inconsistency. We judged statistical heterogeneity to be low, since the I^2 of 24 % for the main meta-analysis of the prioritized evidence is relatively low. The leave-one-out analysis also did not result in large changes in the already low I^2, with the exception being that leaving out the 't Mannetje 2012 study ('t Mannetje, 2012) resulted in a reduction of the I^2 to 5 %. We therefore had no or only minor concerns for inconsistency and did not downgrade the quality of evidence.

4.7.1.4. Downgrade domain – Imprecision. We judged that the main meta-analysis was able to estimate the effect with good precision given that the 95 % CI around the pooled effect estimate was relatively narrow. The 95 % CI ranged from an increase by 29 % to an increase to 70 %. We also judged the 95 % CI of the effect estimate in absolute terms to suggest good precision, with between 32.1 and 42.3 incident cases per 100,000 among exposed workers, compared with 24.9 incident cases per 100,000 among unexposed workers. This indicates a range between a large increase (7.2 additional incident cases/100,000 persons) and a very large increase in risk (17.4 additional incident cases/100,000 persons), suggesting a precise estimate, in absolute terms. We therefore had no or only minor concerns for imprecision and did not downgrade the quality of evidence.

Table 13
Summary of results from subgroup analyses for outcome of Died from trachea, bronchus, and lung cancer.

Subgroup	Pooled effect estimate for subgroup	Test for subgroup differences
WHO region		p = 0.20
Americas (2 studies)	1.25 (1.02–1.53)	
Europe (1 study)	2.77 (1.13–1.62)	
Sex		p = N/A
Males only (2 studies)	1.48 (0.61–3.58)	
Occupation		p = N/A
ISCO-08 7212 or equivalent (2 studies)	1.48 (0.61–3.58)	
Cancer site		p = 0.74
Lung (2 studies)	1.48 (0.61–3.58)	
Trachea, bronchus, and lung (1 study)	1.27 (1.02–1.58)	
Publication year		p = 0.39
Published in 1980s (1 study)	2.77 (0.82–9.35)	
Published in 1990s (1 study)	1.07 (0.58–1.97)	
Published in 2000s (1 study)	1.27 (1.02–1.58)	

Footnote: p values in the table relate to tests for subgroup differences.

4.7.1.5. Downgrade domain – Publication bias. We judged both the funnel plot (Fig. 9) and the Doi plot (Fig. 10) to show no signs of major asymmetry. Moreover, the LFK index statistic from the Doi plot was 1.41, which can be interpreted as indicative of only "minor asymmetry". We therefore had no or only minor concerns for publication bias and did not downgrade the quality of evidence.

4.7.1.6. Upgrade domain – Large effect size. Based on the criteria we adopted for a large effect size, the effect estimate of an RR of 1.48 from the main meta-analysis for this outcome exceeded the fixed 1.25 cut-off. The E-value was 2.32 for the pooled RR (Appendix 12). The major risk factors that could confound the effect of occupational exposure to welding fumes on trachea, bronchus, and lung cancer are tobacco smoking and occupational exposure to asbestos. We could not find evidence that reported the prevalence of occupational exposure to asbestos among welders and non-welders, so used tobacco smoking as the

Table 14
Summary of results from sensitivity analyses on effect estimates for trachea, bronchus, and lung cancer incidence.

Subgroup for sensitivity analysis	Pooled effect estimate for subgroup	Test for subgroup differences
"High"/"probably high" risk of bias in any domain		p = 0.02
Any "High"/"probably high" (12 studies)	1.29 (1.08–1.55)	
All "Low"/"probably low" (11 studies)	1.74 (1.45–2.09)	
Risk of bias for misclassification of the exposure		p = 0.32
"High"/"probably high" (12 studies)	1.35 (1.07–1.71)	
"Low"/"probably low" (11 studies)	1.57 (1.31–1.89)	
Risk of bias for conflict of interest		p = 0.99
"High"/"probably high" (1 studies)	1.48 (0.80–2.71)	
"Low"/"probably low" (22 studies)	1.48 (1.28–1.72)	
Risk of confounding		p = 0.42
"High"/"probably high" (3 studies)	1.03 (0.43–2.49)	
"Low"/"probably low" (20 studies)	1.49 (1.29–1.72)	
With documented or approximated ICD codes		p = 0.84
Yes (5 studies)	1.45 (1.13–1.88)	
No (18 studies)	1.50 (1.27–1.78)	
Adjustment for tobacco smoking and/or exposure to asbestos		p = 0.79
Tobacco smoking only (20 studies)	1.47 (1.23–1.76)	
Both (3 studies)	1.53 (1.20–1.96)	
Studies where Tier 1 adjustment was assumed but unclear		p = 0.22
Assumed but unclear (1 study)	2.41 (1.08–5.83)	
Specified (22 studies)	1.45 (1.27–1.67)	

Footnote: p values in the table relate to tests for subgroup differences.

reference confounder. Applying a bias factor, calculated based on the associations between tobacco smoking, and both the exposure and the outcome resulted in an "unconfounded RR" of 1.19, meaning that that the reference confounder could reduce the observed RR to a value of 1.19 (i.e., not null). Unmeasured residual confounding could have a similar effect as tobacco smoking. Therefore, we judged the pooled effect estimate for this outcome to be large in size and consequently upgraded the quality of evidence by one level.

4.7.1.7. Upgrade domain – Dose response effect. We did not consider the existing evidence from included studies that reported effect estimates for different levels (or doses or intensities) of cumulative exposure to consistently indicate a dose–response relationship. The only included such study that reported a formal statistical test for a dose–response relationship found evidence for a positive trend where a higher level of cumulative exposure also had a higher RR (p for test of trend 0.02; Guida et al. (2011); Table 16). The other studies that reported relevant analyses did not report statistical tests for such trends and also used a range of different proxies for level of cumulative exposure, so we were unable to draw meaningful conclusions from these regarding the presence or not of a dose–response relationship (Table 16). We therefore judged there to be no suggestion of a dose–response and did not upgrade the quality of evidence for this outcome in this upgrade domain.

4.7.1.8. Upgrade domain – Residual confounding and bias not plausibly explaining the effect. We did not consider residual confounding or bias to be plausible and therefore did not upgrade the quality of evidence in this upgrade domain.

4.7.1.9. Final rating. We started the assessment at a rating of "moderate quality of evidence" for human observational studies as per the Navigation Guide methodology (see Section 3.10). We downgraded the quality of evidence by one level for serious concerns for risk of bias in the domain of risk of bias due to exposure assessment and upgraded the quality of evidence by one level for a large effect size. In summary, we started at moderate quality of evidence, and downgraded by one level and upgraded by one level. In conclusion, the final rating of quality of evidence is "moderate quality of evidence"; further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Table 15
Summary of results from the sensitivity analyses on the effect estimates for trachea, bronchus, and lung cancer mortality.

Subgroup for sensitivity analysis	Pooled effect estimate for subgroup	Test for subgroup differences
"High"/"probably high" risk of bias in any domain		p = N/A
Any"High"/"probably high" (3 studies)	1.48 (0.61–3.58)	
All "Low"/"probably low" (0 studies)	N/A	
Risk of bias for misclassification of the exposure		p = N/A
"High"/"probably high" (3 studies)	1.48 (0.61–3.58)	
"Low"/"probably low" (0 studies)	N/A	
Risk of bias for conflict of interest		p = N/A
"High"/"probably high" (0 studies)	N/A	
"Low"/"probably low" (3 studies)	1.48 (0.61–3.58)	
Risk of confounding		p = 0.17
"High"/"probably high" (2 studies)	1.07 (0.58–1.97)	
"Low"/"probably low" (1 study)	2.77 (0.82–9.35)	
With documented or approximated ICD codes		p = N/A
Yes (0 studies)	N/A	
No (3 studies)	1.48 (0.61–3.58)	
Adjustment for tobacco smoking and/or exposure to asbestos		p = 0.17
Neither (2 studies)	1.07 (0.58–1.97)	
Both (1 study)	2.77 (0.82–9.35)	

4.7.2. Died from trachea, bronchus, and lung cancer (mortality)

4.7.2.1. Downgrade domain – Risk of bias. We judged there to be concerns over the risk of bias in the domains called "risk of bias due to exposure assessment" and "risk of confounding". For exposure assessment bias, we, however, judged the risk of this bias to have attenuated the effect estimate towards the null, leading to an underestimation of the effect size; this increased our confidence in the effect detected. Our sensitivity analysis on this risk of bias domain found no evidence for a difference between studies judged to be at "high"/"probably high" and the one study judged to be at "probably low" risk of bias in this domain (see Table A11.2.2 in Appendix 11 in the Supplementary data). The study Yiin et al. (2007) that was largest in sample size and contributed the greatest weight to the main meta-analysis was judged to be at relatively lower risk of bias in this domain, however it was judged to be at "probably high" risk of bias due to selection of participants into the study. For confounding, our sensitivity analysis found no evidence for a difference between studies judged to be at "high"/"probably high" and the one study judged to be at "probably low" risk of confounding (see Table A11.2.4 in Appendix 11 in the Supplementary data). However, we judged the largest study with the greatest weight in the main meta-analysis to be of "probably high" risk of confounding as it used birth cohort as a proxy for tobacco smoking. We had no or only minor concerns for risk of bias in all other domains. In conclusion, we therefore had serious concerns for risk of bias and downgraded the quality of evidence by one level in this downgrade domain.

4.7.2.2. Downgrade domain – Indirectness. The included studies covered populations in two WHO regions and five countries, all of which are high-income countries. Most included studies primarily or only covered males, but we judged this to not be concerning, because it is likely representative of the population of workers exposed to welding fumes who we judged to also be primarily males. Additionally, we were unaware of any evidence suggesting that there is a biological difference in the effect of occupational exposure to welding fumes on the outcome between males and females (i.e., no effect modification by sex). However, the studies covered only industrial sectors within manufacturing (or the sector covered was unclear), and although several decades were covered by the studies, none of these were recent decades. We, therefore, had serious, but not very serious, concerns for indirectness. We downgraded the quality of evidence by one level.

4.7.2.3. Downgrade domain – Inconsistency. Regarding inconsistency, we judged the statistical heterogeneity to be low, since the I^2 for the main meta-analysis of the prioritized evidence is 0 %. The leave-one-out analysis resulted in large increases in the I^2 and the effect estimate. The 95 % CI includes the null for two of the included studies. While we judged that there was no evidence of serious inconsistency, we note that few studies are included in the main meta-analysis and that one of the studies is largely driving the meta risk estimate. The supporting evidence indicated increased risks among the exposed as well. We, therefore, had no or only minor concerns for inconsistency. We did not downgrade the quality of evidence for inconsistency.

4.7.2.4. Downgrade domain – Imprecision. Overall, we judged that precision is relatively low in this body of evidence. Precision was not achieved in the relative effect estimate, with the 95 % CI of the RR ranging

from a very small or small increase by 4 % (considering that we assume a 25 % change to indicate a large effect (van Kempen et al. 2018)) to a very large increase by 56 %. We also judged the 95 % CI of the effect estimate in absolute terms to suggest poor precision, with between 31.1 and 46.6 deaths per 100,000 among exposed workers, compared with 29.9 deaths per 100,000 among unexposed workers. This indicates a range between no meaningful difference (1.2 additional deaths/100,000 persons) and a large increase in risk (16.7 additional deaths/100,000 persons), suggesting an imprecise estimate, in absolute terms. We had serious concerns for imprecision, and therefore downgraded the quality of evidence in this downgrade domain.

4.7.2.5. Downgrade domain – Publication bias. We judged there to be no evidence of publication bias, even though we did not identify protocols for any included studies. We, therefore, had no or only minor concerns for publication bias and did not downgrade the quality of evidence.

4.7.2.6. Upgrade domain – Large effect size. The pooled effect estimate of 1.27 for this outcome was similar to the 1.25 cut-off value. The E-value was 1.84 for this pooled RR (Appendix 12). Applying a bias factor, calculated based on the associations between tobacco smoking and both the exposure and the outcome, resulted in an "unconfounded RR" of 1.02. The, meaning that that the reference confounder could reduce the observed RR to a value of 1.02 (i.e., close to null). Unmeasured residual confounding could have a similar effect as confounding by tobacco smoking. Therefore, we did not judge there to be evidence to upgrade the quality of evidence for a large effect size.

4.7.2.7. Upgrade domain – Dose-response effect. We judged that there was also no evidence for a dose–response effect. The one study (Lauritsen and Hansen 1996) reporting level of exposure was excluded from the prioritized evidence and did not report a test of trend, making it difficult to assess the evidence of a dose–response effect from this study. We therefore did not upgrade the quality of evidence for this outcome in this upgrade domain.

4.7.2.8. Upgrade domain – Residual confounding and bias not plausibly explaining the effect. We did not consider residual confounding or bias to be plausible. We did not upgrade the quality of evidence in this upgrade domain.

4.7.2.9. Final rating. We started the assessment at a rating of "moderate quality of evidence" for human observational studies, applying the Navigation Guide methodology (see Section 3.10). We downgraded the quality of evidence by one level each for serious concerns for risk of bias, indirectness, and imprecision, respectively, and did not upgrade it. In summary, we started at "moderate quality of evidence", and downgraded by three levels.. In conclusion, we judged this body of evidence to be of "low quality of evidence"; further research is very likely to have an important impact on our confidence in the effect estimate and is likely to change the estimate.

4.8. Strength of evidence

4.8.1. Acquired trachea, bronchus, and lung cancer (incidence)

4.8.1.1. Quality of evidence. We judged this body of evidence on this outcome to be of "moderate quality of evidence". To that end, we have downgraded the quality of evidence by one level for serious concerns for risk of bias (in the domain of risk of bias due to exposure assessment) and upgraded it by one level for a large effect size.

4.8.1.2. Direction of effect estimate. We judged the pooled effect estimate from the main meta-analysis of the prioritized evidence to indicate a clear increase in risk. The pooled effect estimate from the main meta-analysis was large in size and estimated with good precision. The individual studies included in this main meta-analysis also consistently reported an increase in risk. Supporting evidence from non-prioritized included studies also reported effect estimates in the same direction. Not one single included study reported a point estimate that indicated a reduced risk. We therefore judged the body of evidence on this outcome to indicate an increased risk consistently and clearly. In conclusion, chance, bias, and confounding could be ruled out in concluding that occupational exposure to welding fumes leads to an increase in incident trachea, bronchus, and lung cancer.

4.8.1.3. Confidence in the effect estimate. We are also confident in the effect estimate, which is supported by evidence on causal pathways and biological plausibility. We judged the effect to be of a large size, estimated precisely, and indicating a meaningfully increased risk. Our leave-one-out analysis for this outcome (incidence) showed that the

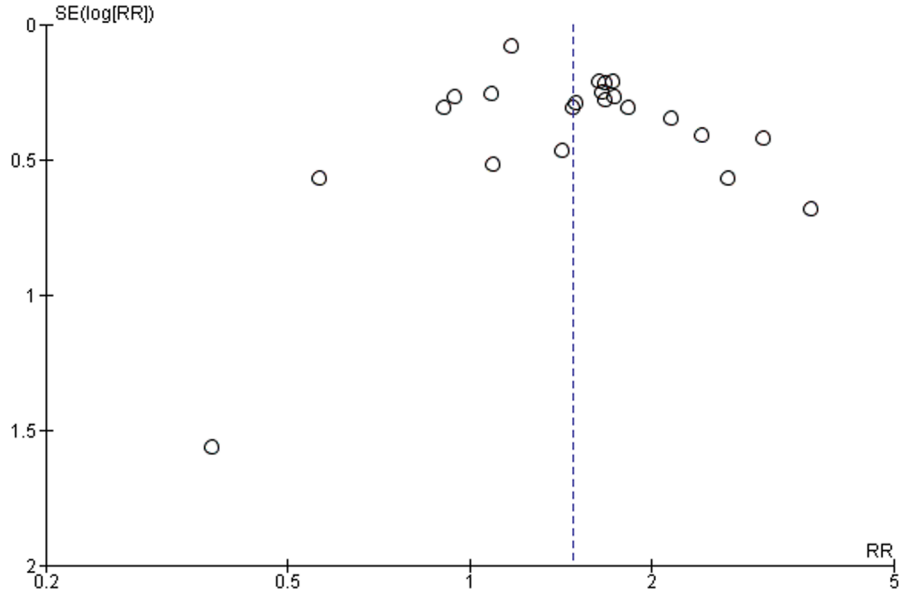

Fig. 9. Funnel plot for the studies included in the main meta-analysis of the prioritized evidence (case-control studies), Outcome: Acquired trachea, bronchus, and lung cancer, Comparison: Any (or high) occupational exposure to welding fumes, compared with no (or low) occupational exposure to welding fumes.

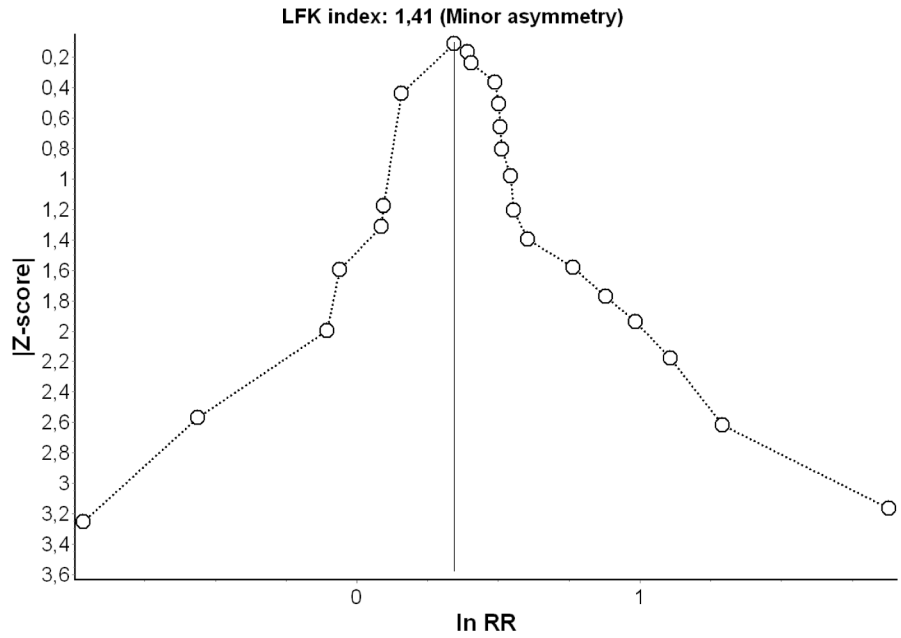

Fig. 10. Doi plot with LFK index for the studies included in the main meta-analysis of the prioritized evidence (case-control studies), Outcome: Acquired trachea, bronchus, and lung cancer, Comparison: Any (or high) occupational exposure to welding fumes, compared with no (or low) occupational exposure to welding fumes.

Table 16
Effect estimates from studies reporting on the association between occupational exposure to welding fumes, in terms of cumulative exposure, and trachea, bronchus, and lung cancer incidence.

Study ID	Included in main meta-analysis	Exposure definition	Level of exposure	Adjusted odds ratio (95 % confidence interval)	*P* value for trend (as reported)
Danielsen 1993	No – unadjusted	Length of employment as a welder (years) compared with other shipyard production workers (with 10-year lag time)	Unexposed ≤ 5 > 5	1.0 (-) 1.8 (0.5–5.7) 3.2 (1.3–8.1)	Not reported
Danielsen 2000	No – unadjusted	Length of employment as a welder (years) compared with other shipyard production workers	Unexposed < 2 2–4 5–14 ≥ 15	1.0 (-) 2.42 (0.73–8.01) 0.66 (0.09–4.85) 0.56 (0.08–4.17) 1.90 (0.67–5.38)	Not reported
Guida 2011	Yes	Duration of regular welding (years)	No welding ≤ 10 > 10	1.0 (-) 1.53 (0.91–2.55) 1.96 (0.98–3.92)	0.02
Gustavsson 2000	Yes – but these cumulative exposure estimates are from a different analytical model than that used in the main meta-analysis)	Duration of exposure to welding fumes (years)	0 > 0–9 10–29 ≥ 30	1.0 (-) 1.70 (0.97–2.96) 1.45 (0.96–2.20) 1.25 (0.82–1.90)	Not reported
Jöckel 1998	Yes – but these cumulative exposure estimates are from a different analytical model than that used in the main meta-analysis)	Lifetime exposure to welding (cumulated hours)	Never 0–1,000 1,000–6,000 >6,000	1.0 (-) 1.38 (0.91–2.09) 1.14 (0.73–1.79) 1.10 (0.73–1.66)	Not reported
Siew 2008	No – cohort study	Cumulative exposure to welding fumes (mg/m^3 – years)	None Low (0.1–10) Medium (10.1–49.9) High (≥50)	1.0 (-) 1.09 (1.05–1.14)	Not reported

Footnotes: One study that was included in the main meta-analysis reported an analysis on duration of exposure: Guida 2011 (Guida et al. 2011; Matrat et al. 2016). This analysis considered duration of work in an occupation of regular welder and provides support for a dose–response relationship, with the OR for those who were welders for > 10 years higher than the OR for those who were welders for ≤ 10 years (p for the trend 0.02). Although the effect estimates used in the main meta-analysis for Jöckel et al. (1998) and Gustavsson et al. (2000) were taken from Kendzia et al. (2013), the original Jöckel et al. (1998), and Gustavsson et al. (2000) study records also presented an analysis by cumulated hours exposed to welding fumes. Additionally, the association in terms of cumulative exposure was presented in Danielsen et al. (1993), Danielsen et al. (2000), and Siew et al. (2008). None of these studies reported a test for trend.

effect estimate remained consistently high no matter which individual included study was removed from the main meta-analysis. Moreover, our many sensitivity analyses also did not find any evidence of bias or other problems. Supporting evidence also reported effects in the same direction.

4.8.1.4. Other compelling attributes. The IARC classification of welding fumes as a Group 1 carcinogen is a compelling attribute (International Agency for Research on Cancer 2018). This assessment comprehensively integrated mechanistic, animal, and human evidence streams into the final assessment. Additionally, this assessment concluded that there was also limited evidence for the carcinogenicity of welding fumes on cancer

of the kidney (International Agency for Research on Cancer, 2018).

4.8.1.5. Final rating. We judged the strength of evidence for this outcome as "sufficient evidence of harmfulness"; for human evidence a positive relationship is observed between exposure and outcome where chance, bias, and confounding, can be ruled out with reasonable confidence. See Table 3 for the full definitions of the strength of evidence ratings.

4.8.2. Died from trachea, bronchus, and lung cancer (mortality)

4.8.2.1. Quality of evidence. We judged the body of evidence to be of "low quality of evidence" for this outcome. We downgraded the quality of evidence by three levels, namely-one level each for serious concerns for risk of bias (in the domains of risk of bias due to exposure assessment and risk of confounding), indirectness and imprecision, respectively.

4.8.2.2. Direction of effect estimate. We judged the pooled effect estimate from the main meta-analysis of the prioritized evidence (i.e., an RR of 1.27) to indicate a clear increase in risk (as for the incidence outcome; see Section 4.8.1.2). The pooled point estimate from the main meta-analysis indicated a large effect and was estimated with reasonable precision. All three individual studies included in this main meta-analysis also reported point estimates indicating increased risk. Supporting evidence from non-prioritized included studies also reported increased risks. The only exception was that Gottlieb (1980) reported a point estimate that indicated a small decrease in risk (OR 0.93), at least for the cohort of people aged $\geq$ 60 years at death. We therefore judged the body of evidence on this outcome to, overall, indicate an increased risk. We have some certainty of this direction of the effect.

4.8.2.3. Confidence in the effect estimate. The pooled effect estimate was driven primarily by one study (Yiin et al. 2007), as the leave-one-out analyses also found. The body of prioritized evidence only comprised three studies. The lower 95 % CI limit is 1.04, which – while meaningful at the population level – is a small increase in risk only. We cannot rule out chance due to the small number of studies (three) included in the main meta-analysis. Additionally, the risks of bias in selection of participants into the study and bias due to exposure misclassification cannot be ruled out. Risk of confounding could also not be ruled out in these studies. Our confidence in the effect estimate is low.

4.8.2.4. Other compelling attributes. The IARC classification of welding fumes as a Group 1 carcinogen is again also a compelling attribute for this outcome (International Agency for Research on Cancer 2018). The IARC assessment comprehensively considered and integrated mechanistic, animal, and human evidence streams, and also reported limited evidence for the carcinogenicity of welding fumes on cancer of the kidney (International Agency for Research on Cancer 2018).

4.8.2.5. Final rating. We judged the strength of evidence for this outcome as "limited evidence of harmfulness"; for human evidence; a positive relationship is observed between exposure and outcome where chance, bias, and confounding cannot be ruled out with reasonable confidence (Table 3 for the rating's full definition).

5. Discussion

5.1. Summary of evidence

As shown in the table of summary of findings (Table 17), our systematic review and meta-analysis found "moderate quality of evidence" for the effect of occupational exposure to welding fumes on trachea, bronchus, and lung cancer incidence. There was consistent evidence of an increased risk. The body of evidence was rated as of "moderate quality of evidence" due to the potential for risk of bias due to exposure misclassification. Most studies reported a crude exposure classification of ever versus never based on occupation or job title of "welder". This exposure assignment likely underestimates the prevalence of occupational exposure to welding fumes as this method does not account for persons in other occupations or job titles that may be performing welding tasks and/or occupationally exposed to welding fumes. This strengthens our confidence in the effect estimate. We concluded that there was "sufficient evidence of harmfulness" of occupational exposure to welding fumes for acquiring trachea, bronchus, and lung cancer, from the human evidence stream. Additionally, we judged the evidence we found to be of "low quality of evidence" for the effect of occupational exposure to welding fumes on trachea, bronchus, and lung cancer mortality. We concluded that there was "limited evidence of harmfulness" from human evidence for dying from trachea, bronchus, and lung cancer, because chance, bias, and confounding could not be ruled out with reasonable confidence.

Subgroup and sensitivity analyses did not suggest any differences between subgroups for either outcome. The only exception was that the sensitivity analysis for the outcome of trachea, bronchus, and lung cancer incidence of the effect estimate for studies with a "high"/"probably high" risk of bias rating in any domain (RR 1.29, 95 % CI 1.08–1.55) was lower than that for studies with a "low"/"probably low" risk of bias in all domains (RR 1.74, 95 % CI 1.45–2.09; p value for subgroup differences 0.02). Some methodologists, however, caution against stratification by risk of bias (Stone et al. 2019).

5.2. Comparison to previous systematic reviews

In IARC Monograph Volume 118, a working group of individual experts convened by WHO's IARC has concluded based on a synthesis of evidence streams of mechanistic, animal, and human studies that "Welding fumes are carcinogenic to humans and cause cancer of the lung (Group 1)" (International Agency for Research on Cancer 2018). Exposure to welding fumes is therefore already an established risk factor for human health (International Agency for Research on Cancer 2018).

The four relevant previous reviews and/or meta-analyses (Sjogren et al. 1994; Moulin 1997; Ambroise et al. 2006; International Agency for Research on Cancer 2018; Honaryar et al. 2019) have all reported that exposure to welding fumes is associated with an increased risk of lung cancer incidence and/or mortality. They reported increases in risk ranging from 1.17 to 1.94 (depending on the type of study considered, and combining effect estimates across incidence and mortality). The lower 95 % CI limits also always indicated an increased risk in all reviews and/or meta-analyses (ranging from 1.04 to 1.53). Our systematic review and meta-analysis on the effect of occupational exposure to welding fumes on trachea, bronchus, and lung cancer supports theses previous findings.

However, the relevant previous reviews and/or meta-analyses combined different study types (e.g., combined case-control with cohort studies) and/or different outcomes (i.e., combined incidence with mortality outcome measures) in their pooled analyses. Furthermore, the aim of our review was to provide a pooled estimate of the effect of occupational exposure to welding fumes on trachea, bronchus, and lung cancer (Pega et al. 2020a), whereas relevant previous reviews and/or meta-analyses captured any exposure to welding fumes (even if in practice most commonly these were occupational ones) and only lung cancer (even if this may sometimes have included bronchus as a site, at least in older studies), respectively. Therefore, our systematic review and meta-analysis is not – strictly speaking – comparable with those from previous reviews and/or meta-analyses. Nevertheless, the pooled effect estimates we produced for the outcomes of trachea, bronchus, and lung cancer incidence (RR 1.48, 95 % CI 1.29–1.70) and mortality (RR 1.27, 95 % CI 1.04–1.56) are in the same direction (increase in risk) and of similar size (a moderate to large increase) as those reported in the previous reviews and/or meta-analyses. The findings from this

systematic review and meta-analysis are thus still aligned with and support the conclusions reached in the previous relevant reviews and/or meta-analyses.

5.3. Limitations and strengths of this systematic review

5.3.1. Limitations

Our systematic review and meta-analysis has several limitations. First, even though the search strategy included many academic and grey literature databases, potentially eligible studies may have been missed (e.g., those published in languages other than those we collectively covered, or those only indexed in additional databases like CINAHL, which could be included in future updates of the systematic review). However, this is unlikely given that consultation with subject matter experts did not lead to the identification of any additional eligible studies. Given the large number of included studies and consequently large number of included study participants, the overall findings would not have been affected by eligible studies that our literature search (which would likely be relatively smaller in sample size).

Second, in several studies, exposure was assigned using occupation or job title as proxies or measured by asking participants to self-report their occupational exposures. Objective assessments of occupational exposure to welding fumes using personal monitoring devices may have provided more accurate, valid, and reliable estimates from which to assess the effect of occupational exposure to welding fumes on trachea, bronchus, and lung cancer, but these were not available in any included study. However, direct, objective exposure measurements are realistically only feasible in prospective cohort and intervention studies; indirect, subjective measurements (e.g., use of occupation, job title or job tasks as a proxy for exposure) or direct but subjective (self-reported) exposure to welding fumes are the most common and still acceptable assessment methods in case-control study designs assessing retrospective lifetime occupational exposure history. Further, the use of occupation or job title of "welder" as a proxy to occupational exposure to welding fumes may misclassify those occupationally exposed to welding fumes (e.g., themselves involved in welding tasks or exposed at the workplace from another workers' welding) but who were not "welders". Nevertheless, the risk of bias assessment recognized this limitation and was considered in the final evaluations of the quality and strength of the bodies of evidence.

Third, no eligible study was found on the effect of occupational exposure to welding fumes on trachea, bronchus, and lung cancer prevalence. Relatively few studies were identified for the outcome of mortality from trachea, bronchus, and lung cancer, with only three eligible for inclusion in the main meta-analysis for this outcome. Additionally, no study estimated the exposure's effect on both incidence and mortality, so it was not possible to look at these two outcomes within the same population. This limits the comprehensiveness of the available body of evidence.

Fourth, the health outcome of interest in this review is trachea, bronchus, and lung cancer, in line with the relevant WHO Global Health Estimates category (World Health Organization 2018), but most included studies stated that they investigated "lung cancer" only. Some studies reported on "lung cancer" as their outcome of interest, but the ICD codes that they then specified in the study records for this outcome were those for two or more of trachea, bronchus, and lung cancer. Since ICD-10 (World Health Organization 2015) classifies lung and bronchus cancer as part of the same cancer site, if a study reports on "lung cancer" and that it used the relevant ICD code for "bronchus and lung cancer", it is unclear if the study covered the site of lung only or both sites of lung and bronchus, presenting possible discrepancies in reporting of outcomes in such studies.

5.3.2. Strengths

Our systematic review and meta-analysis also has a number of strengths. First, some relevant previous reviews and/or meta-analyses have not reported clearly whether all the steps of a systematic review have been performed, but our systematic review and meta-analysis have done so, including use of a pre-published protocol (Pega et al. 2020a), which represents a substantial improvement in systematic review methods on the subject. Some relevant previous reviews and/or meta-analyses have also not comprehensively reported the analytic steps of the review and/or meta-analysis for comparisons of any (or high) occupational exposure to welding fumes with no (or low) occupational exposure to welding fumes. That our systematic review and meta-analysis has done this provides another improvement in accuracy of systematic review and meta-analytic evidence on this topic.

Second, previous reviews and/or meta-analyses on this topic have not sought to differentiate trachea, bronchus, and lung cancer prevalence from incidence from mortality as separate outcomes, but our systematic review and meta-analysis improves accuracy by differentiating these different outcomes.

Third, our systematic review and meta-analysis differed from previous work in that studies that may have included welders in the comparator (e.g., general population) were excluded per WHO/ILO methodology. This exclusion of a potentially contaminated reference group avoided potential bias of the pooled effect estimates towards the null.

Fourth, whereas some previous review and meta-analytic evidence has not comprehensively assessed risk of bias and quality of evidence using established systematic review frameworks with dedicated tools and approaches, we have rigorously applied the Navigation Guide framework in this systematic review and meta-analysis, which should have ensured comprehensiveness, rigor, and transparency.

Fifth, in previous reviews and/or meta-analyses, the strength of evidence was not commonly assessed. The IARC Monograph Volume 118 (International Agency for Research on Cancer 2018) did assess strength of evidence as part of its hazard identification (as reported above). In our systematic review and meta-analysis, we have applied pre-specified, pre-published criteria (Pega et al. 2020a) to rate the strength of evidence for each included outcome.

Sixth, in our systematic review and meta-analysis, we conducted many sensitivity analyses to investigate the robustness of our results. For example, we conducted an additional sensitivity analysis using the alternative IVhet estimator for the main meta-analysis for acquired trachea, bronchus, and lung cancer.

Finally, to our knowledge, this is the first systematic review and meta-analysis on this topic conducted specifically for an occupational burden of disease study, here for the WHO/ILO Joint Estimates. It can provide a model for future systematic reviews and meta-analyses that will help ensure that such global health estimates adhere fully with the GATHER Guidelines for Accurate and Transparent Health Estimates Reporting (Stevens et al. 2016).

6. Use of evidence for burden of disease estimation

This systematic review and meta-analysis was conducted by WHO and ILO, supported by a large number of individual experts, for the WHO/ILO Joint Estimates (Pega et al. 2021a,b; World Health Organization and International Labour Organization 2021a,b). More specifically, it provides the crucial evidence base for the organizations to consider producing estimates of the burden of deaths and DALYs from trachea, bronchus, and lung cancer that is attributable to occupational exposure to welding fumes. The systematic review found a large body of evidence from several case-control studies for comparison of persons with any (or low) occupational exposure to welding fumes with those with no (or low) occupational exposure to these fumes for the incidence of trachea, bronchus, and lung cancer. We judged this body of evidence to be of "moderate quality of evidence" and to provide "sufficient evidence of harmfulness". The systematic review found a smaller body of evidence from case-control studies for comparison of persons occupationally exposed to welding fumes with those occupationally unexposed

Table 17
Table of summary of findings.

Trachea, bronchus, and lung cancer among workers with any (or high) occupational exposure to welding fumes compared with among workers with no (or low) occupational exposure to welding fumes

Population: workers
Settings: all countries and work settings
Exposure: any (or high) occupational exposure to welding fumes
Comparison: no (or low) occupational exposure to welding fumes

Outcome	Illustrative comparative risks (95 % CI)		Relative effect (95 % CI)	No. of participants (studies)	Navigation Guide (Woodruff and Sutton 2014) quality of the evidence rating	Navigation Guide strength of evidence rating	Comments
	Assumed risk Unexposed workers	Corresponding risk Exposed worker					
Has trachea, bronchus, and lung cancer (prevalence)	–	–	–	–	–	–	No eligible study found.
Acquired trachea, bronchus, and lung cancer (incidence) (assessed using medical records) [a]	**24.9 per 100,000**	**36.9 per 100,000** (32.1–42.3)	**RR 1.48** (1.29–1.70)	57,931 participants (23 studies)	Moderate quality of evidence[c,d]	Sufficient evidence of harmfulness	The pooled effect estimate from the eight case-control studies (main meta-analysis) indicated that occupational exposure to welding fumes lead to a clinically meaningful increase in risk of trachea, bronchus, and lung cancer incidence. Evidence was supported by eight cohort studies that were included in a meta-analysis, along with one case-control study and two cohort studies that were not included in a meta-analysis.
Died from trachea, bronchus, and lung cancer (mortality) (assessed using administrative records, such as death certificates) [b]	**29.9 per 100,000**	**37.9 per 100,000** (31.1–46.6)	**RR 1.27** (1.04–1.56)	8,686 participants (3 studies)	Low quality of evidence [e]	Limited evidence of harmfulness	The pooled effect estimate from three case-control studies (main meta-analysis) indicated that occupational exposure to welding fumes lead to a clinically meaningful increase in risk of trachea, bronchus, and lung cancer mortality. Some support was provided by three cohort studies that were included in a meta-analysis, along with two case-control studies that were not included in a meta-analysis.

CI: confidence interval; **RR**: risk ratio

Navigation Guide quality of evidence ratings
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Navigation Guide strength of evidence ratings
Sufficient evidence of harmfulness: The available evidence usually includes consistent results from well-designed, well-conducted studies, and the conclusion is unlikely to be strongly affected by the results of future studies. For human evidence a positive relationship is observed between exposure and outcome where chance, bias, and confounding, can be ruled out with reasonable confidence.
Limited evidence of harmfulness: The available evidence is sufficient to determine the effects of the exposure, but confidence in the estimate is constrained by such factors as: the number, size or quality of individual studies, the confidence in the effect or inconsistency of findings across individual studies. As more information becomes available, the observed effect could change, and this change may be large enough to alter the conclusion. For human evidence a positive relationship is observed between exposure and outcome where chance, bias, and confounding cannot be ruled out with reasonable confidence.
Inadequate evidence of harmfulness: Studies permit no conclusion about a toxic effect. The available evidence is insufficient to assess effects of the exposure. Evidence is insufficient because of: the limited number or size of studies, low quality of individual studies or inconsistency of findings across individual studies. More information may allow an estimation of effects.
Evidence of lack of harmfulness: The available evidence includes consistent results from well-designed, well-conducted studies, and the conclusion is unlikely to be strongly affected by the results of future studies. For human evidence more than one study showed no effect on the outcome of interest at the full range of exposure levels that humans are known to encounter, where bias and confounding can be ruled out with reasonable confidence. The conclusion is limited to the age at exposure and/or other conditions and levels of exposure studied.

Footnotes:
[a] For the outcome of trachea, bronchus, and lung cancer incidence, we took the median baseline risk in the unexposed population reported for this outcome in the cohort studies included in this systematic review (Danielsen et al. 1993; Danielsen et al. 2000; Siew et al. 2008; Wong et al. 2017).
[b] For the outcome of trachea, bronchus, and lung cancer mortality, the baseline risk was taken from Steenland (2002).
[c] Downgraded by one level, because we had serious concerns for risk of bias.
[d] Upgraded by one level as we judged the effect estimate to be large in size.
[e] Downgraded by three levels, because we had serious concerns for each of: risk of bias, indirectness, and imprecision.

to this risk factor for mortality from trachea, bronchus, and lung cancer. This body of evidence was judged to be of "low quality of evidence" and to provide "limited evidence of harmfulness".

Producing estimates of the burden of trachea, bronchus, and lung cancer attributable to occupational exposure to welding fumes appears evidence-based and warranted. Applying the standards outlined previously (Pega et al. 2021a; World Health Organization and International Labour Organization 2021a), the parameters reviewed (including the pooled RR from the main meta-analysis) from the body of evidence regarding trachea, bronchus, and lung cancer incidence appear suitable as input data for WHO/ILO modelling of work-related burden of disease.

7. Conclusions

We judged the existing bodies of evidence as "sufficient evidence of harmfulness" for occupational exposure to welding fumes and trachea, bronchus, and lung cancer incidence, and as "limited evidence of harmfulness" for occupational exposure to welding fumes and trachea, bronchus, and lung cancer mortality. The RR for the comparisons between those occupationally exposed and unexposed to welding fumes is suitable as input data for the WHO/ILO Joint Estimates.

The quality of evidence could be improved in future research studies to improve the available bodies of evidence on the effect of occupational exposure to welding fumes on trachea, bronchus, and lung cancer prevalence, incidence, and mortality in three ways. First, the main concerns for risk of bias were related to the domain called "risk of bias due to exposure misclassification". All studies measured occupational exposure indirectly, either through self-reported data on occupation, job title, job tasks or exposures; reports from supervisors, spouses, colleagues or other third parties; or administrative records. Ideally, future studies would assess occupational exposure to welding fumes directly. The risk of trachea, bronchus, and lung cancer from occupational exposure to welding fumes would be affected by numerous factors (e.g., ventilation and use of protective equipment). Any two welders may not be occupationally exposed to welding fumes at the same level, despite both being considered "exposed" if, for example, occupation or job title is used to assign exposure status. Direct measures of exposure would enable more specific and sensitive exposure assignment, with potential for improved RRs becoming available for use in burden of disease estimation through future updates of this systematic review and meta-analysis. Second, future research should investigate all three outcomes (i.e., prevalence, incidence, and mortality) in the same study, so it is possible to estimate the exposure effect on these three outcomes within the same population over time. Third, it should be noted that the current bodies of evidence cover only three WHO Regions: the Region of the Americas, the European Region, and the Western Pacific Region. There may be some differences in protections for workers and levels of occupational exposure to welding fumes between countries in these regions compared with other WHO regions. While the current bodies of evidence have been judged to provide sufficient evidence for the production of WHO/ILO Joint Estimates, more studies covering more WHO regions and more countries would be beneficial for burden of disease estimation in the future.

8. Differences between protocol and systematic review

- We further developed the conceptual framework presented in the protocol (Pega et al. 2020a) in two ways. First, we added as effect modifiers: tobacco smoking, exposure to asbestos, base metals welded, welding technique process, duration of welding tasks and related activities, the position of the welder, degree of ventilation of the occupational setting, and the use of personal protective equipment. Second, we removed as mediators: base metals welded, welding technique process, duration of welding tasks and related activities, the position of the welder, degree of ventilation of the occupational setting, and the use of personal protective equipment. This brings the conceptual framework in better alignment with the statistical and epidemiological definitions of effect modifiers and mediators, respectively.
- In the section "Types of exposures", we changed our definition of the risk factor levels from"Any occupational exposure to welding fumes" in the protocol to "Any (or high) occupational exposure to welding fumes" in the systematic review and from "No occupational exposure to welding fumes" to "No (or low) occupational exposure to welding fumes", respectively. The reason was that this revised definition was more realistic and better aligned with prior definitions of risk factor levels used in burden of disease studies (Concha-Barrientos et al. 2004; World Health Organization 2021).
- In the section "Types of exposures", we changed the definition of the theoretical minimum risk exposure level from "No occupational exposure to welding fumes" in the protocol to "No (or low) occupational exposure to welding fumes" in the systematic review. This reflected the changes made to the definition of the relevant risk factor level (see above bullet point).
- We added in sections "Types of comparators" and "Types of effect measures" that standardized RRs or standardized ORs, where the rate or odds of mortality or incidence among the exposed population were compared with the rates or odds amongst the general population, were excluded from the systematic review.
- Added was also in section "Types of effect measures" that: For case-control studies matched by Tier 1 confounding variables (i.e., age and sex), we applied the following eligibility criteria. As Pearce has pointed out, "Matching in a case-control study does not control for confounding by the matching factors" and "A matched design may require controlling for the matching factors in the analysis" (p1) (Pearce 2016). Pearce argues that matching does not remove confounding, and it is still necessary to control for confounding by the matching factors, and in fact " the matching process in a case-control study changes the association between the matching factor and the outcome, and can create an association even if there were none before the matching was conducted" (p2) (Pearce 2016). Therefore, if a case-control study matched by Tier 1 confounders but did not adjust for these matching variables (e.g., in a regression analysis), we included this study in the systematic review, but excluded it from the meta-analysis. Additionally, Pearce states that "A "standard" (unconditional) analysis may be most valid and appropriate, and a "matched" (conditional) analysis may not be required or appropriate". (p1) (Pearce 2016). Therefore, we included effect estimates regardless of conditionality of analysis.
- We added in section "Types of effect measures" that, for the Kendzia et al. (2013) individual participant data analysis, we referred to the original study records of included studies to systematically identify the best effect estimate for the included studies.
- For studies that were included in IARC Monograph 118 (International Agency for Research on Cancer 2018) or a subsequent meta-analysis (Honaryar et al. 2019), we planned in our protocol to use existing data extractions for some selected data such as RRs and study characteristics, but in the systematic review we conducted separate data extractions for all included studies to ensure optimal fit with our specific systematic review objectives.
- In the protocol, we intended to request missing data from the principal study author by email or phone, using the contact details provided in the principal study record, but in the end did not do so, because we preferred to use peer-reviewed, published data only.
- For risk of bias assessment, we planned to use a modification of a previous method to identify and assess undisclosed financial interests of authors (Forsyth et al. 2014). Where no financial disclosure or conflict of interest statements were available, we planned to search the name of all authors in other study records gathered for this study and published in the prior 36 months and in other publicly available declarations of interests. However, this step was not carried out due to lack of working group capacity.

- For risk of bias assessment, we further developed our pre-specified criteria for assessment of risk of bias due to exposure misclassification. For studies that assigned exposure based on an occupation or a job title of "welder" alone, risk of bias in this domain was considered to be relatively higher than for studies that assigned exposure based on a job task of "welding" or that employed a welding-specific questionnaire or more complex exposure matrix.
- We added specification of methods for back-calculating measures of variance for effect estimates for which the point estimate was reported without a measure of variance, but with a statistic from which the variance could be derived.
- We also added specification that we used the Borenstein et al. (2009) methods for calculating a summary effect estimate from two or more individual effect estimates extracted from comparisons of different levels of exposure with the same comparator.
- Our protocol did not plan to conduct a subgroup analysis by cancer site, but in the systematic review we did conduct and report such an analysis, because reported cancer sites differed across studies included in the main meta-analysis, and we wanted to investigate if this had introduced heterogeneity in this meta-analysis.
- Additionally, our protocol did not plan to conduct a subgroup analysis by publication year, but this was added it following a suggestion made during the peer-review process.
- We also added a sensitivity analysis for meta-analyses with studies for which the measure of variance was derived, rather than reported. In such sensitivity analyses, the study with a derived variance was excluded to see if adding this study had made any difference.
- Added was also a sensitivity analysis of studies judged to be of "high"/"probably high" risk of bias from exposure misclassification, compared with studies at "low"/"probably low" risk of bias in this domain.
- Added was further also a sensitivity analysis for cohort studies, comparing those that reported RRs as the effect estimate with those that reported hazard ratios, because we saw the need to explore if the type of effect estimate impacted the results of such meta-analyses.
- Added was also a sensitivity analysis for case-control studies with ORs converted to RRs before conducting the quantitative meta-analysis, compared with case-control studies with ORs pooled in the quantitative meta-analysis and then the pooled OR being converted to a RR. This enabled us to assess if the point at which OR-to-RR conversions were made impacted the final, pooled RR estimate.
- We also added sensitivity analyses in which we removed studies whose effect estimates were calculated using the method developed by Borenstein et al. (2009) or whose measures of variance for effect estimates were back-calculated.
- We added a further sensitivity analysis with studies for which we back-calculated the standard error from a p value, compared with studies for which we back-calculated the standard error from a 95 % CI.
- We had planned to potentially conduct a sensitivity dose–response meta-analysis of studies that reported categorical risk estimates. This would have enabled us to investigate potential threshold effects. We did not conduct such analyses, however, as the working group did not have the capacity for them.
- Additionally, following peer-review, we added sensitivity analyses in which we conducted meta-analyses with RR to look at relative risks among non-smokers or /never-smokers, compared to meta-analyses with RR among smokers. However, there was insufficient information available in studies to carry out this sensitivity analysis.
- In addition to producing Egger's funnel plots to access publication bias as per protocol, we also produced Doi plots and LFK indices, enabling us to base our assessment on a more comprehensive set of metrics for detecting publication bias.
- For quality of evidence assessment, we did not quantify what effect size we would judge as indicative of a "large effect size" and "very large effect size" for upgrading the quality of evidence in our protocol. Initially, in the systematic review we applied a change in RR by ≥ 25 % (i.e., an RR of ≤ 0.75 or ≥ 1.25) as indicative of a large effect size, based on a prior systematic review from the WHO/ILO Joint Estimates (Teixeira et al. 2021b) that had adopted this limit value from WHO guidelines on exposure to environmental noise (van Kempen et al. 2018). However, during the peer-review process it was suggested that we could adopt the strategy used in a recent WHO evidence review on the effect of long-term air pollution on mortality (Huangfu and Atkinson 2020), which calculated the so- called E-values and considered a reference confounder to assess the likelihood of residual confounding (Verbeek et al. 2021). Since, neither of the two approaches is beyond reproach, we applied them both judiciously and in tandem. We therefore relied on two approaches to determine whether the quality of evidence should be upgraded for a large effect size.

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Author contributions

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Were the lead reviewers of this systematic review: DL, AMD.

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Contributed substantially to the design of the systematic review: DL, NCM, NC, NG, RLM, MMS.

Conducted the search: MMS.

Selected studies: DL, AMD, NC, AD, NG, S-KK, AM, RLM, MMS, AS, SZ.

Extracted data: DL, AMD, NC, AD, NG, S-KK, AM, RLM, MMS, AS, SZ.

Assessed risk of bias: DL, AMD, NC, AD, NG, S-KK, AM, RLM, MMS, AS, SZ.

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Developed the standards and wrote the template for all systematic reviews in the series: FP.

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Revised the manuscript critically for important intellectual content: All authors.

Ensured tailoring of the systematic review for WHO/ILO estimation

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Ensured harmonization across systematic reviews in the series: FP, NCM.

Approved the final version of the systematic review to be published: All authors.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary material

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