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Welding Fumes Exposure and the Risk of Head and Neck and Gastrointestinal Cancer: A Systematic Review and Meta-Analysis

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Abstract

Background: *The association between welding fumes and cancers other than lung cancer remains undefined. We conducted a systematic review and meta-analysis on occupational exposure to welding fumes and the risk of head and neck cancer (HN, comprising oral, pharynx, and larynx) and gastrointestinal cancer (GI, comprising esophagus, stomach, colorectal, liver, and pancreas).* **Methods:** *A systematic search was performed in PubMed, Scopus, and Embase using PRISMA guidelines. Cohort studies on occupational exposure to welding fumes were identified. Study quality was assessed through the CASP score. Data were analyzed in random-effects models to calculate the relative risks (RR) and 95% confidence intervals (CI) of HN and GI cancer overall and stratified by cancer site.* **Results:** *Seven independent studies with data on oral, pharynx, larynx, esophagus, stomach, colorectal, liver, or pancreas cancer were identified. We observed the following associations: HN RR=1.10 (95% CI 1.00-1.22); GI RR= 1.03 (95% CI 0.97-1.10); oral and pharynx RR=1.06 (95% CI 0.93-1.20, eleven risk estimates); larynx RR=1.17 (95% CI 1.01-1.37, nine risk estimates); esophagus RR=0.98 (95% CI 0.83-1.15, three risk estimates); stomach RR= 1.10 (95% CI 1.02-1.19, five risk estimates); colorectal RR=0.99 (95% CI 0.85-1.15, seven risk estimates); liver RR=1.23 (95% CI 0.79-1.90, five risk estimates); and pancreas cancer RR=1.05 (95% CI 0.94-1.16, three risk estimates).* **Conclusions:** *We observed an association between occupational exposure to welding fumes and larynx and stomach cancer. No association was found for other HN or GI cancers. Our study stresses the need to investigate the risk of cancers other than lung following occupational exposure to welding fumes.*

1. Introduction

Welding is a process in which heat (over 4000°C) and/or pressure fuses two materials, typically metals, together [1]. When metals are heated to these high temperatures, welding fumes (WF) are produced, especially when the consumable metal electrode is volatilized. Welders are exposed to chemical compounds and metals such as iron, aluminum, cadmium, copper, molybdenum, zinc, nickel, beryllium, lead, manganese, and hexavalent chromium [1]. The vaporized metals react with air, producing metal oxides that condense and form particles of respirable size [1]. Gases such as ozone, nitrogen dioxide, carbon dioxide, carbon monoxide, and hydrogen fluoride are also produced during welding [1]. Over 80

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different types of welding and allied processes have been identified [2], and depending on the welding type, shielding gases, current, ventilation, and metals involved, the composition and rate of generation of WF can vary, especially in what concerns the particle size distribution, which is an essential factor in determining the likelihood of the particles being inhaled by welders [1].

Since 2017, the International Agency for Research on Cancer (IARC) has classified WF as an established human carcinogen [3, 4], following a previous classification as a possible carcinogen (Group 2B) [5]. This classification has mainly been driven by consistent data on the association between exposure to WF and lung cancer, based on results of over forty case-control and cohort studies [6]. In contrast, the evidence for kidney cancer was limited [7]. Furthermore, ultraviolet emissions from welding are included as a carcinogenic agent with sufficient evidence in humans about eye cancer [7].

However, the association between occupational exposure to WF and other cancers remains an open question. A systematic review and meta-analysis on gastrointestinal (GI) and head and neck (HN) cancers would be especially interesting. First, we hypothesize that the same compounds present in WF that cause lung cancer could also carry a carcinogenic risk for the upper respiratory tract. A 2020 case-control study concluded that the same mechanisms responsible for the WF lung carcinogenicity could play a carcinogenic role for other parts of the respiratory tract [8].

Similarly, we considered that WF and its compounds, once inhaled, could be redistributed from the upper respiratory tract to the upper GI tract and overwhelm the stomach's reductive capacity. Therefore, they could potentially reach the small intestine, colon, and rectum, ultimately increasing the risk of GI cancers. Thus, we aimed to conduct a systematic review and meta-analysis of cohort studies on the association between occupational exposure to WF and HN and GI cancers.

2. Methods

This systematic review and meta-analysis were conducted according to COSMOS-E guidelines [9], and the report was based on the PRISMA guidelines. The protocol for the study was registered in the PROSPERO database (Registration No. CRD42021252458). This work is part of a more extensive systematic review and meta-analysis on occupational exposure to WF and cancers other than the lungs.

The systematic review was based on the PECOS criteria: participants were workers occupationally exposed to WF, WF constituted exposure, the comparison was populations unexposed to WF (depending on the specific study, either the general population or an unexposed cohort), outcome was the incidence or mortality from oral, pharynx, larynx, esophagus, stomach, colorectal, liver or pancreas cancer, and the included study designs were prospective cohort studies, including nested case-control studies. We deliberately included only cohort studies, excluding case-control studies unless they were nested within a cohort. This decision was based on the higher methodological quality and reliability of data typically associated with cohort studies. Cohort studies generally provide more precise exposure information, better representation of occupational categories exposed to WF, and detailed data on the duration and intensity of exposure. These attributes enhance the evaluation of potential cause-effect relationships and reduce the likelihood of biases, such as recall and selection bias, which are more common in case-control studies. Furthermore, cohort studies offer a more robust framework for assessing temporal relationships between exposure and outcomes, making them more suitable for evaluating the research question.

Articles were identified by a scientific literature review conducted in June 2021 in PubMed, Scopus, and Embase and updated to the 11th of September 2024. The following string was used to identify studies: (Welding OR (Welding Fumes) OR Welder) AND (Cancer OR Neoplasm OR Leukemia OR Lymphoma OR Cohort). Two authors (GC, MH) independently searched for articles on welders and the risk of any type of cancer other than lung cancer, utilizing the method described above, and a third (PB) resolved any conflicts. If the same population was the subject of multiple reports, the one including the most significant number of cases or deaths was included. Studies were excluded if they assessed exposures to WF other than the occupational one, did not present any data on cancers other than lung cancer, and presented designs other than cohort or nested case-control.

The following data was extracted by two authors (GC, MH) and checked by a third author (PB) from the texts that met the inclusion criteria: publication year, period of follow-up, country, number of subjects and number of cancer cases, gender distribution of the population, cancer type, industry type, type of outcome (incidence or mortality), factors adjusted for in the analysis, the measure of association (odds ratio, risk ratio, rate ratio, standardized mortality ratio or standardized incidence ratio) and the corresponding CI.

Two authors (GC, MH) conducted a quality assessment of the studies individually using the CASP Cohort Study Checklist, based on 11 items for a total score of 14 points [10]. The median of the individually scored studies was utilized; studies scoring 10 points or less were considered low quality, and studies scoring higher than 10 points were regarded as high quality.

This work investigates occupational exposure to WF and HN and GI cancers.

In particular, we conducted a combined meta-analysis for the following types of HN cancers: larynx, oral cavity, and pharynx. Similarly, we conducted a parallel meta-analysis for the following types of GI cancers: esophagus, stomach, colorectum, liver, and pancreas. Summary relative risks (RRs) were calculated for each type of cancer, and the meta-analyses were conducted using the random-effects model [11]. We performed stratified analyses by studying quality, geographical region, type of outcome, and industry type. The heterogeneity for the summary RRs was assessed using the I2 statistic. Subsequently, we performed a leave-one-out meta-analysis to evaluate whether the results would vary considerably if single studies were included or excluded from the meta-analyses. Publication bias was assessed using funnel plots and Egger's test [12].

All the statistical analyses were performed on STATA, version 16.1 (Stata Corp., College Station, TX, US) [13]. The meta-analysis was reported according to PRISMA guidelines [14].

3. Results

Figure 1 displays the selection process for all articles identified in a flow chart. Three thousand two hundred forty articles were identified through the initial search, and 1,349 duplicates were excluded. Of the remaining 1,891 articles, 1,706 were excluded based on title and abstract, leaving 185 articles to be evaluated against the inclusion criteria, thus resulting in a further 152 articles being excluded. 33 suitable articles were identified, of which 24 were excluded because of overlapping data (most being articles relative to studies from Northern European countries whose data were included in the 2009 pooled analysis by Pukkala et al. [15]). Finally, two of the remaining nine studies were excluded as they presented no data on either HN or GI cancers; the present meta-analysis, therefore, includes seven articles (Table 1). Most of the included studies reported results on occupation as a welder as a proxy for exposure to WF.

The overall meta-analysis for HN cancer (Figure 2) resulted in a RR of 1.10 (95% CI 1.00-1.22). The individual analysis for oral and pharynx cancer resulted in a summary RR of 1.06 (95% CI 0.93-1.20) from eleven risk estimates. The summary RR for larynx cancer was 1.17 (95% CI 1.01-1.37) from nine risk estimates. With an I^2 of 0.0% and a p-value of 0.569, there was evidence of low statistical heterogeneity among the studies included in the overall HN meta-analysis.

The overall meta-analysis for GI cancers (Figure 3) resulted in a RR of 1.03 (95% CI 0.97-1.10). The analysis for esophagus cancer resulted in a summary RR of 0.98 (95% CI 0.83-1.15, three risk estimates). The summary RR for stomach cancer was 1.10 (95% CI 1.02-1.19, five risk estimates), that for colorectal cancer was 0.99 (95% CI 0.85-1.15, seven risk estimates), that for liver cancer was 1.23 (95% CI 0.79-1.90, five risk estimates), and that for pancreas cancer was 1.05 (95% CI 0.94-1.16, three risk estimates). With an I^2 of 28.3% and a p-value of 0.102, there was evidence of low statistical heterogeneity among the studies included in the overall GI meta-analysis.

The test for heterogeneity indicated p=0.566 for oral and pharynx cancer, p=0.478 for larynx cancer, p=0.88 for esophagus cancer, p=0.417 for stomach cancer, p=0.023 for colorectal cancer, p=0.269 for liver cancer and p=0.744 for pancreas cancer.

Visual inspection of the funnel plots for the HN and GI meta-analyses showed slight asymmetry (Figure 4), which was not supported by the results of Egger's test. In particular, Egger's test showed

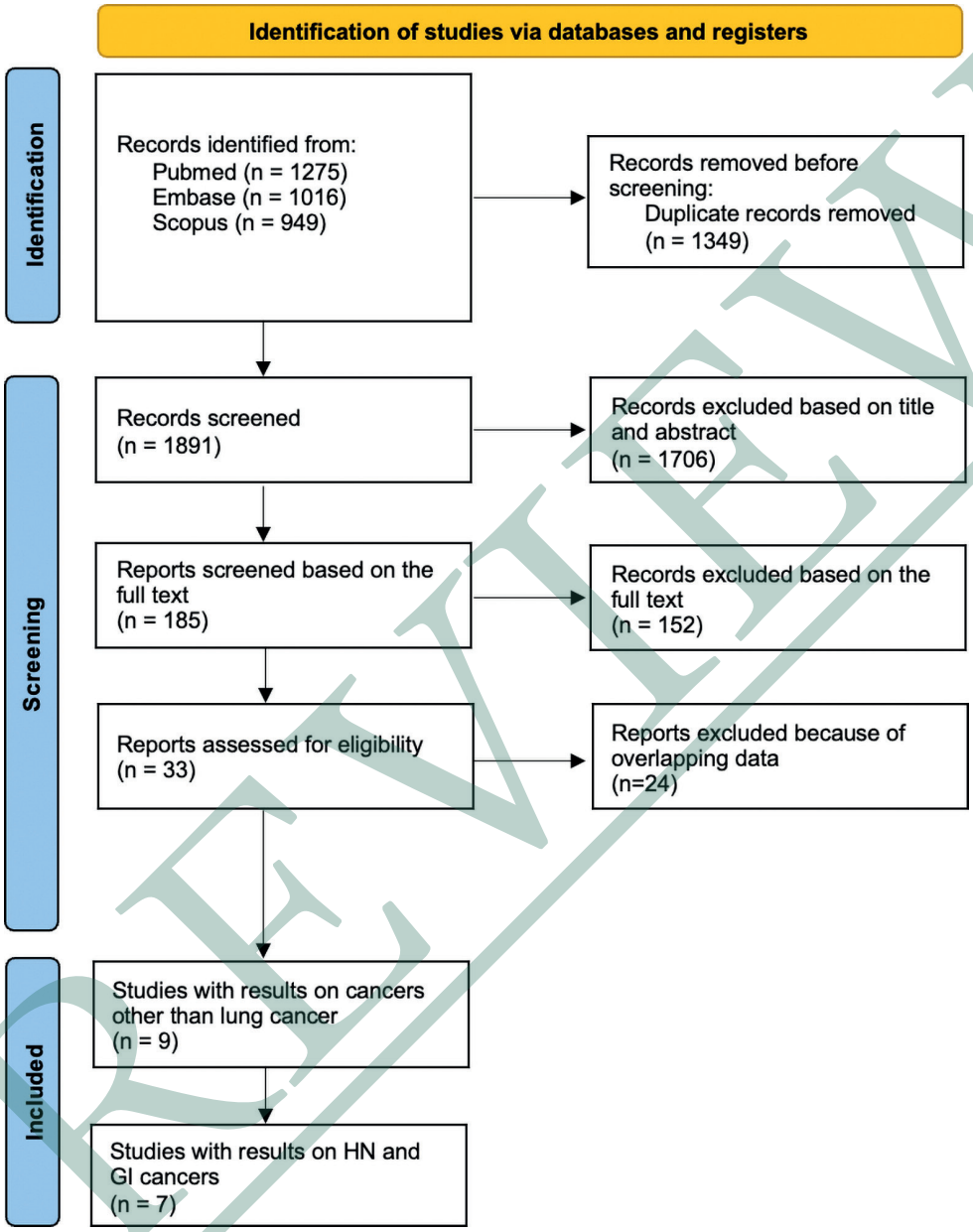

Figure 1. Flow-chart for the selection of studies included in the meta-analysis.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

p-values of 0.967 for the overall HN meta-analysis and 0.349 for the overall GI meta-analysis. In contrast, for the specific cancer sites, the following p-values were found: 0.428 for oral and pharynx cancer, 0.468 for larynx cancer, 0.962 for stomach cancer, 0.784 for colorectal cancer, and 0.028 for liver cancer. Publication bias was not assessed for cancer sites represented by fewer than five studies, such as the esophagus and pancreas, which had only three studies each. The site-specific funnel plots, which can be found in the supplementary section (Figures A1-A5), confirmed an asymmetry towards the right for liver cancer, which, together with the significant p-value of the relative Egger's

Table 1. Characteristics of studies included in the meta-analysis.

Study	Cancer type	Country	Follow Up Period	Cohort size (N=)	Industry	Cases (N=)	Adjustments (Other than age and calendar time)
Puntoni et al., 2001 [16]	Larynx Liver	Italy	1960-1996	3,984	Shipyard	2 3	N/A
Moulin et al., 1993 [17]	Oral and Pharynx Larynx Esophagus Stomach Rectal Liver	France	1975-1988	9,404	Factory and shipyard	6 3 4 6 2 3	Axelson's indirect adjustment †
Becker, 1999 [18]	Oral and Pharynx Larynx Esophagus Stomach Colorectal Pancreas	Germany	1980-1995	1,221	Arc welders	1 1 3 5 2 4	N/A
MacLeod et al., 2017 [19]	Stomach	Canada	1991-2010	2,051,315	Construction and manufacturing	45	Province of residence and educational level
Pukkala et al., 2009 [15]	Oral and Pharynx Larynx Stomach Colorectal Liver Pancreas	Denmark, Finland, Iceland, Norway, Sweden	1961-2005	38,500,000	Welders	213 148 589 1355 123 357	N/A
Krstev et al., 2007 [20]	Oral and Pharynx Larynx	USA	1950-2001	184	Shipyard	5 7	Sex and race
Simonato et al., 1991 [21]	Oral and Pharynx Larynx	Denmark, Finland, Norway, Sweden, England, France, Germany	1950-1991	11,092	Factory and shipyard	21 12	N/A

† Reference: Axelson O. Aspects on confounding in occupational health epidemiology. Scand J Work Environ Health 1978;4:85-9. [22].

test, suggests a possible publication bias in the case of liver cancer due to the absence of smaller studies showing a negative effect.

Stratified analyses by study quality (p for heterogeneity (p-het) for HN cancer = 0,51; p-het for GI cancer = 0,94), geographical region (p-het for HN cancer = 0,44; p-het for GI cancer = 0,19), type of outcome (p-het for HN cancer = 0,82; p-het for GI cancer = 0,73) and industry type (p-het for HN cancer = 0,33; p-het for GI cancer = 0,41) yielded no

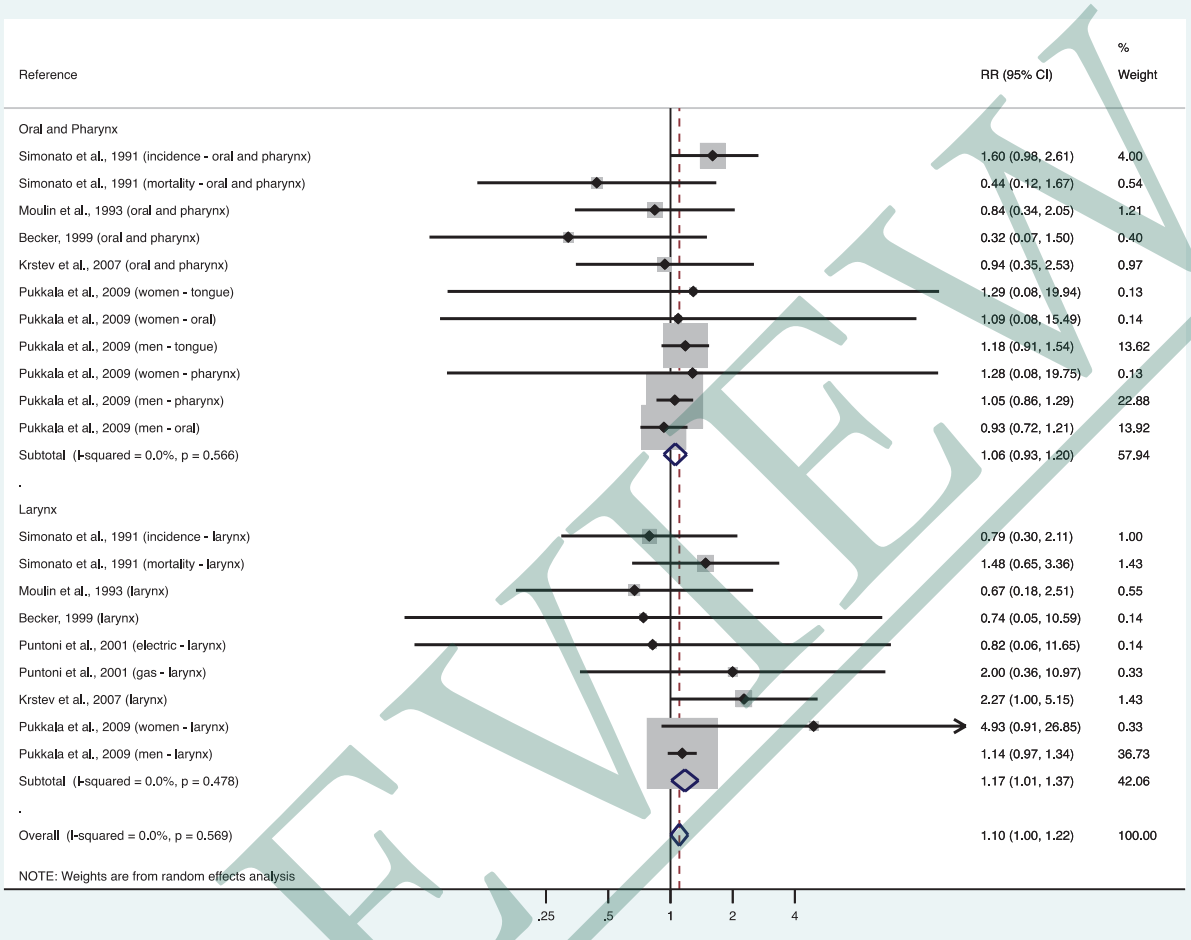

Figure 2. Results of the meta-analyses on HN cancers and occupational exposure to WF, including larynx and oral and pharynx cancer.

evidence of heterogeneity; however, they were impaired by low power of analysis (Figures A6-A13).

Based on the leave-one-out meta-analyses we performed, the association between occupational exposure to WF and larynx cancer seemed to be driven by the sizeable occupational cohort study by Pukkala et al. (2009) [15]. Similarly, the result for stomach cancer was driven by Pukkala et al. (2009) [15] and MacLeod et al. (2017) [19].

4. Discussion

Based on this systematic review and meta-analysis of cohort studies, occupational exposure to WF is associated with a 17% increased risk of larynx cancer and a 10% increased risk of stomach cancer. No association was detected with other HN or GI cancer sites. Our findings align with our initial hypothesis that compounds in WF known to cause lung cancer may also pose a carcinogenic risk to the upper respiratory and GI tracts as they migrate from the upper respiratory to the upper GI tract, affecting areas such as the stomach.

HN and GI cancers remain poorly investigated in welders; to date, results are conflicting. Several case-control studies found no significant association between HN cancers such as oral, hypopharynx, or larynx cancer and occupational exposure to WF [23-34].

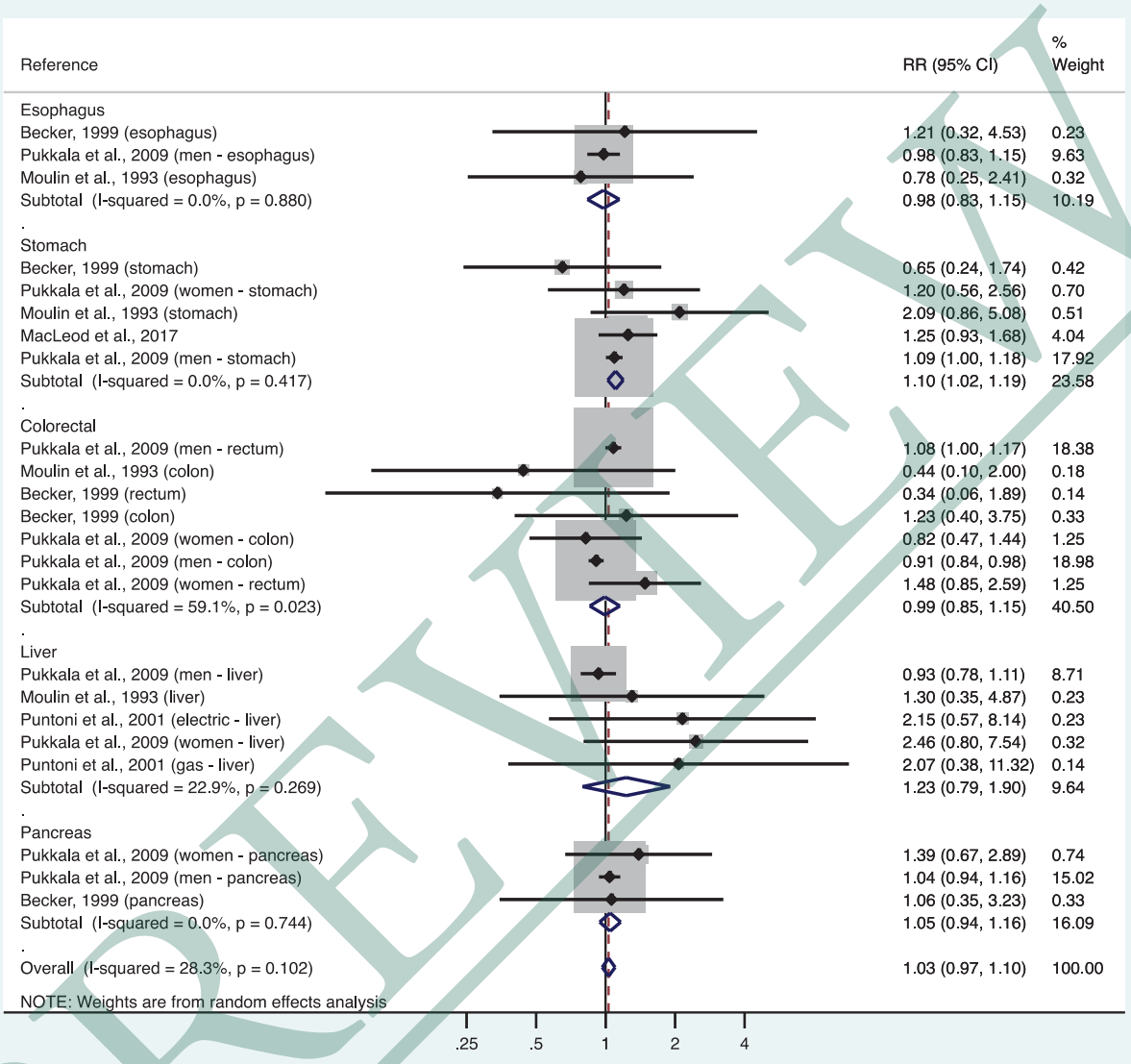

Figure 3. Results of the meta-analyses on GI cancers and occupational exposure to WF, including esophagus, stomach, colorectal, liver, and pancreas cancer.

On the other hand, previous literature has already reported an association between WF and respiratory tract cancers other than lung cancer, which is consistent with our findings. For example, a study by Gustavsson et al. found an association between pharynx [RR 2.3 (95% CI 1.1-4.7)] and larynx [RR 2.0 (95% CI 1.0-3.7)] cancer [35].

Next, Olsen et al. (1984) found that workers exposed to WF had a higher risk of larynx cancer compared to age-matched controls [RR 1.6 (95% CI 1.0-2.4)] [36]. The RR was significantly high [RR 6.3 (95% CI 1.8-21.6)] for subglottic larynx cancer [36]. The authors found this association was limited considerably in cigarette smokers, although this result was considered to be affected by the small fraction of non-smoker cases [36].

Further, in a large 2019 study within the INHANCE consortium, Khetan et al. found HN

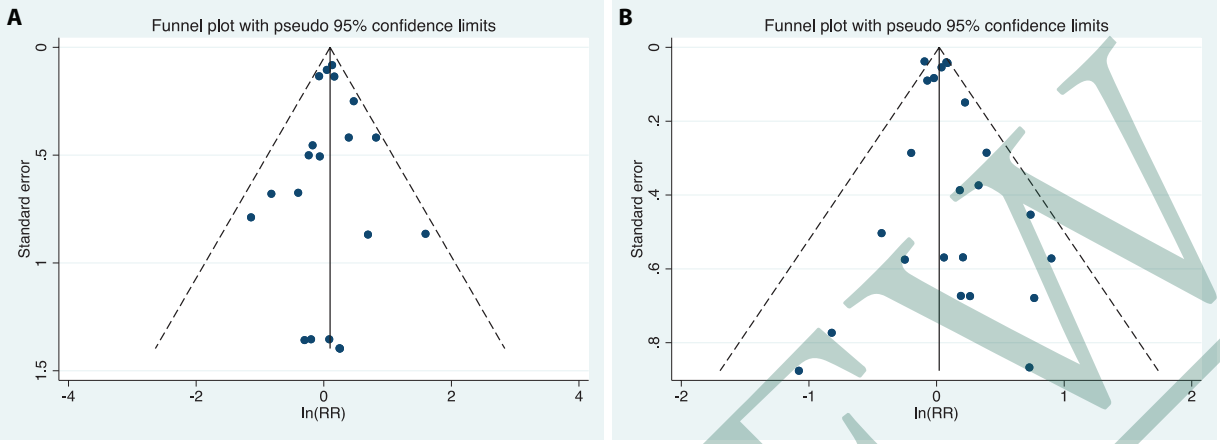

Figure 4. Funnel plots for **(a)** HN and **(b)** GI cancers.

cancers overall to be significantly associated with WF [OR 1.41 (95% CI 1.2-1.64)], particularly in the case of larynx cancer [OR 1.52 (95% CI 1.14-2.02)] [37].

A large case-control study from 2020 by Barul et al. on WF and HN cancer risk similarly found WF to be associated with an increased risk of HN cancer overall [OR 1.31 (95% CI 1.03-1.67)], with the association being strongest for larynx cancer [OR 1.66 (95% CI 1.15-2.38)] [8]. This study possessed the significant advantage of assessing welding as a job task rather than a job title, like census-based studies [8]. Furthermore, the analysis was adjusted for smoking and asbestos exposure, supporting the hypothesis of an independent role of WF on larynx carcinogenesis [8].

The literature does not provide as much evidence about WF and GI cancers. A 1993 case-control study by Keller et al. found stomach cancer to be positively associated with WF [OR 2.11 (95% CI 1.09-4.09)], consistently with our study, while colon cancer and WF presented a negative, albeit borderline significant, association [OR 0.54 (95% CI 0.29-1.00)] [38]. In another case-control study from 1992, heavy exposure to WF was associated with primary liver cancer in men after adjusting for alcohol consumption [OR 13.5 (95% CI 2.02-88.1)] [39].

Our systematic review and meta-analysis synthesized the data provided by cohort studies on the association between HN and GI cancer and occupational exposure to WF. Our findings suggest an association between both larynx and stomach cancer and occupational exposure to WF. However, no association could be found between WF and oral and pharynx, esophagus, colorectal, liver, or pancreas cancer. Data were too sparse to perform any further analyses, as well as to report dose-response results. Similarly, the overall meta-analyses on GI and HN cancers and WF exposure yielded no significant results, with the weak association observed for HN cancers being primarily driven by the association observed for larynx cancer.

The two studies by Pukkala et al. (2009) [15] and MacLeod et al. (2017) [19], which drive the observed association between occupational WF exposure and larynx and stomach cancer, respectively, both assessed WF exposure based on the worker's census-recorded job title, something which might have limited the sensitivity of this data. While approximately 11 million workers worldwide hold the job title of "welder", a further 110 million are estimated to be exposed to welding-related occupational activities [3]. Therefore, a potential limitation of our analysis is that some of the studies, by including those workers holding the job title of welder (and hence using the profession of a welder as a proxy for the exposure to WF), likely include just a fraction of the potential number of the workers exposed to WF in the different industries [3, 6]. This may lead to misclassifying the exposure, with some exposed workers classified as non-exposed, and therefore partially hiding the effect of the investigated risk factor on the outcomes.

A significant limitation of our analysis is the fact that none of the included studies adjusted for tobacco smoking, asbestos exposure, or other potential confounders, including dietary factors, alcohol consumption, body mass index, physical activity, as well as other occupational risk factors and certain site-specific carcinogens such as Helicobacter pylori (important for stomach cancer) and diabetes (important for pancreas cancer) [40-42]. Smoking, a significant risk factor for both GI and HN cancers, including larynx and stomach cancer, was reported in one study to be more common in welders than in the general population [43]. On the other hand, asbestos is a significant occupational carcinogen to which welders working in industries such as shipyards or metallurgy can be directly or indirectly exposed [6]. Next to smoking, the association between exposure to WF and HN or GI cancer could also be subject to the confounding effect of alcohol [44, 45]. A further limitation is the inability to provide dose-response results, as the census-based nature of the exposure assessment in many of the included studies left little room for quantifying the exposure. Finally, our meta-analyses only include data from European and North American countries, limiting the potential to generalize the results globally.

Despite all the aforementioned limitations, our study possesses several elements of strength. First of all, this represents, to our knowledge, the first meta-analysis on occupational exposure to WF HN and GI cancers. This analysis provides novel and valuable insights into the relationship between WF and these specific cancer types, extending the findings of a previously published meta-analysis from our research group that examined genito-urinary cancers [46]. The meta-analyses conducted to support the importance of investigating the association between occupational exposure to WF and cancers other than lung cancer [46]. Moreover, we presented data on several cancer types, two of which were found to be significantly associated with occupational WF exposure.

Additionally, our literature review was based on strict inclusion criteria to focus on relevant types of exposures, and the meta-analysis incorporated several risk estimates. Furthermore, our research was conducted following a protocol based on the state-of-the-art established guidelines, including the quality assessment of the selected studies. We could exclude publication bias through the visual inspection of funnel plots and the Egger's tests performed, except for the liver cancer publications, which showed an asymmetry towards the right, hinting at a possible publication bias. However, it should be noted that while the p values excluded publication bias, the statistical power of Egger's test might have been limited because of the low number of studies.

Although a causal link could not be established, our results support existing evidence of an association between occupational exposure to WF and larynx cancer [8]. While this can reasonably be attributed to the lack of adjustment for smoking status, it is also plausible that fumes inhaled during welding can damage the respiratory tract during their translocation to the lungs [8, 37]. At the same time, our results support an association between WF and stomach cancer, suggesting that the aforementioned WF compounds could indeed pose a carcinogenic risk to the stomach after being inhaled and redistributed to the upper GI tract.

5. CONCLUSION

In conclusion, our systematic review and meta-analysis provide evidence of an association between occupational exposure to WF and larynx and stomach cancers and no association with other HN or GI cancers. However, the causal nature of these associations cannot be established based on available information. Our findings align with our initial hypothesis that compounds in WF known to cause lung cancer may also pose a carcinogenic risk to the upper respiratory and GI tracts, affecting areas such as the stomach.

In light of our systematic review of the existing literature, we stress the importance of further studies to be conducted to clarify the role of WF on HN and GI cancers and confirm our findings. Such studies should account for important confounders, such as smoking, alcohol drinking, and other occupational risk factors, such as asbestos exposure. They should ideally be designed to assess the level of WF exposure quantitatively. Also, it would be essential to gather data from different populations, such as those from Africa, Asia, and Oceania, to obtain

solid, generalizable results. Workers and occupational physicians should be aware of the carcinogenic potential of WF for sites other than the lungs.

Declaration of Interest: The authors declare no conflict of interest.

Author Contribution Statement: PB and G.C. contributed to the design and implementation of the research, A.C.S., G.C., and M.H. contributed to the analysis of the results, and A.C.S. and G.C. contributed to the writing of the manuscript.

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Supplementary Material: Figures A1-A13

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SUPPLEMENTARY MATERIAL A

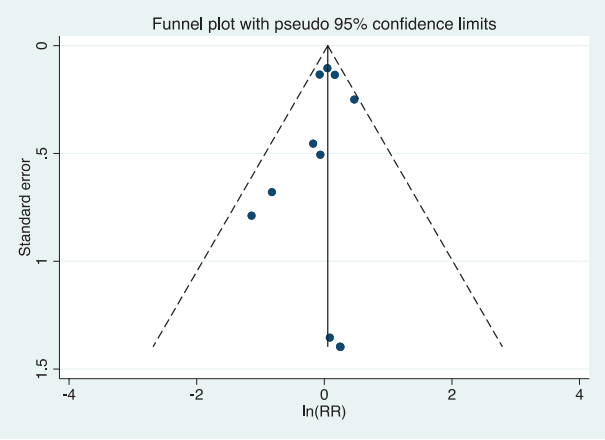

Figure A1. Funnel plot for oral and pharynx cancer.

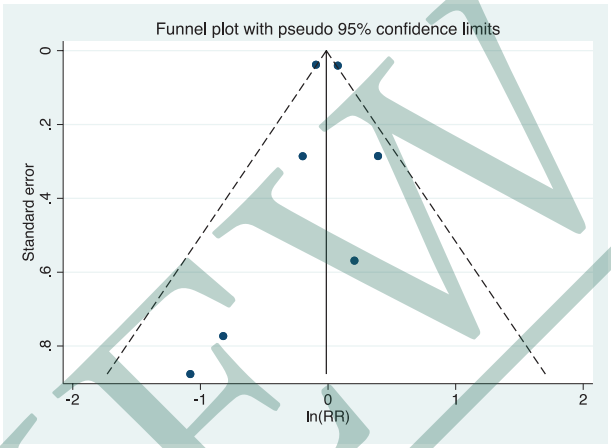

Figure A4. Funnel plot for colorectal cancer.

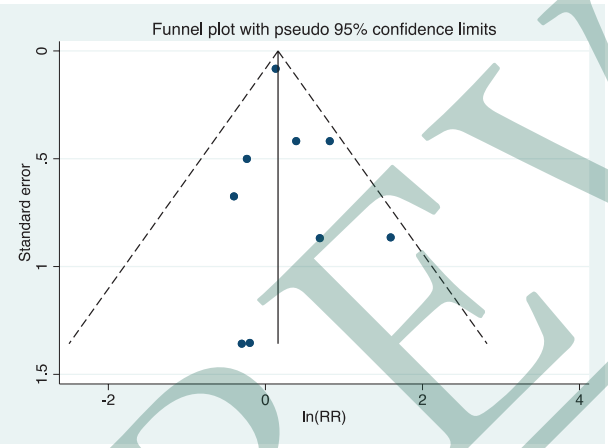

Figure A2. Funnel plot for larynx cancer.

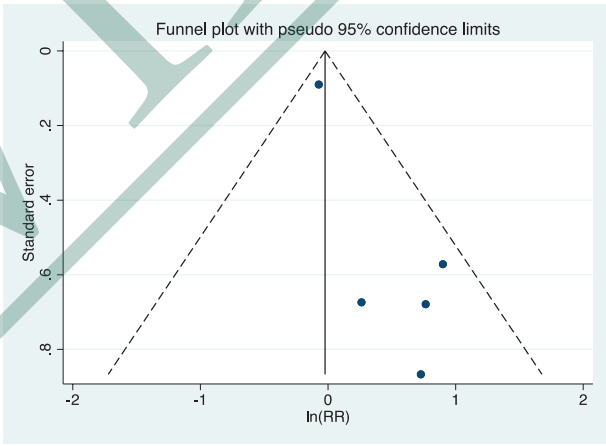

Figure A5. Funnel plot for liver cancer.

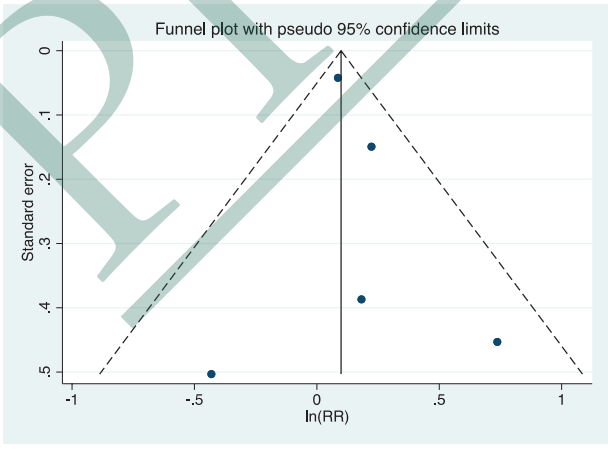

Figure A3. Funnel plot for stomach cancer.

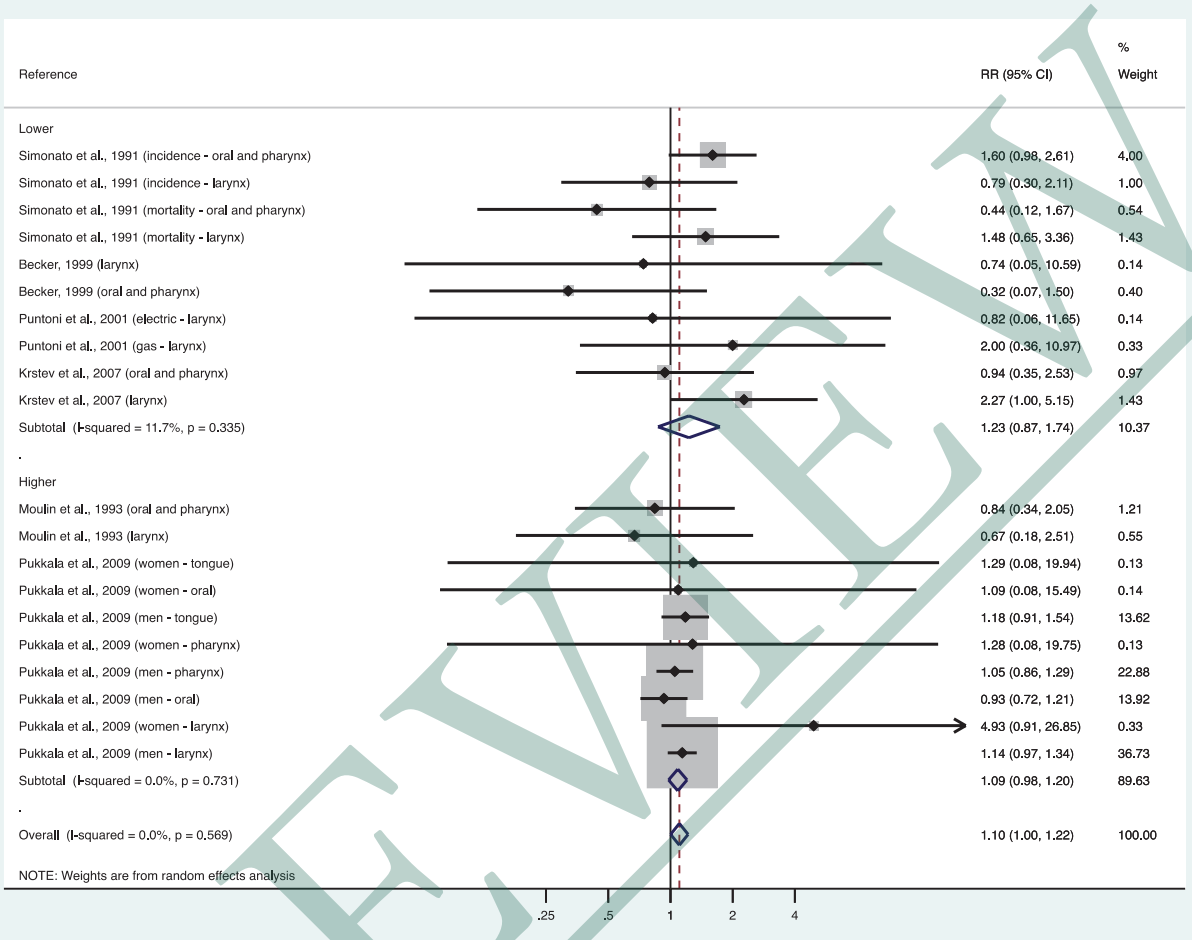

Figure A6. Stratified Analysis of HN Cancers by Study Quality.

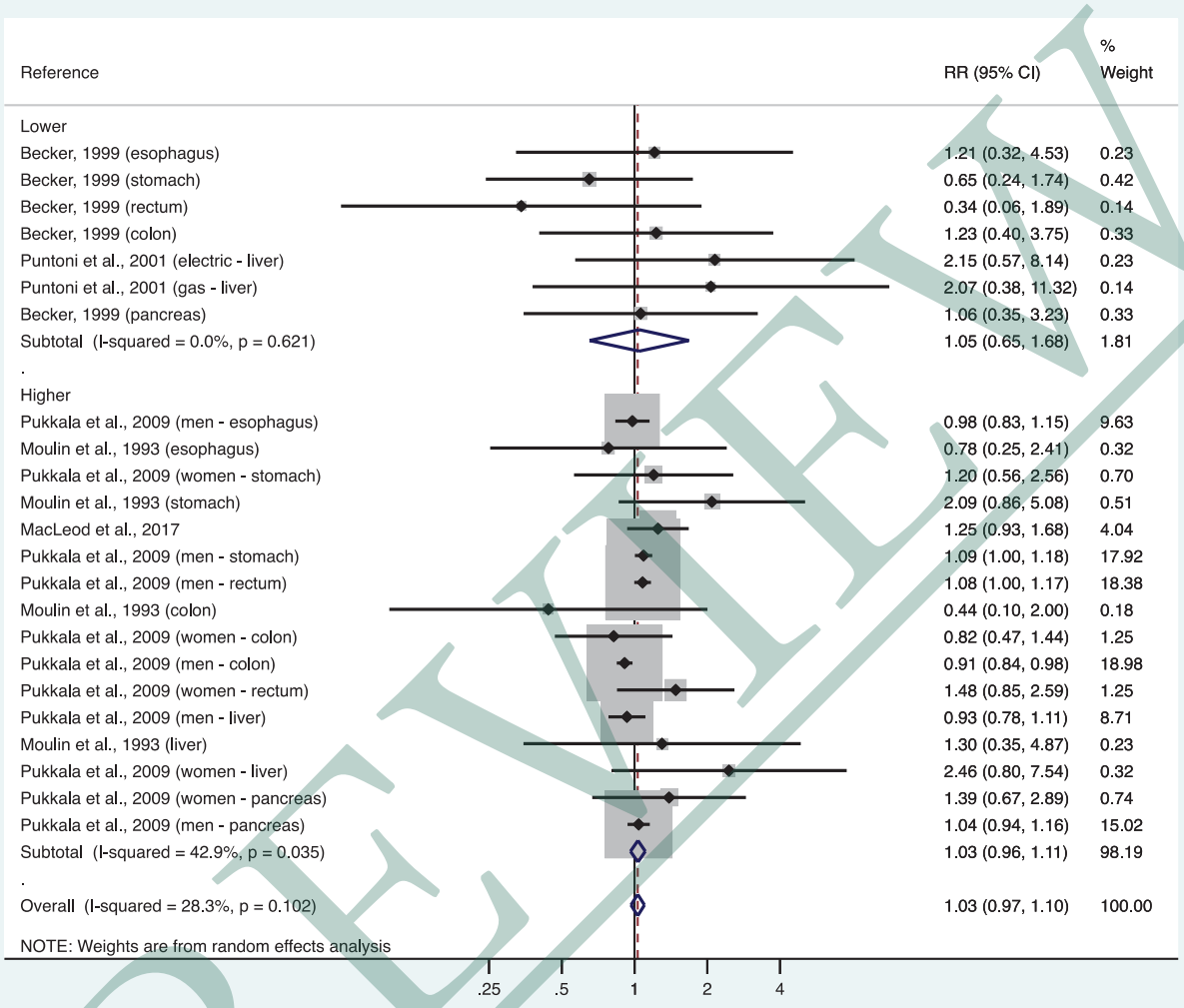

Figure A7. Stratified Analysis of GI Cancers by Study Quality.

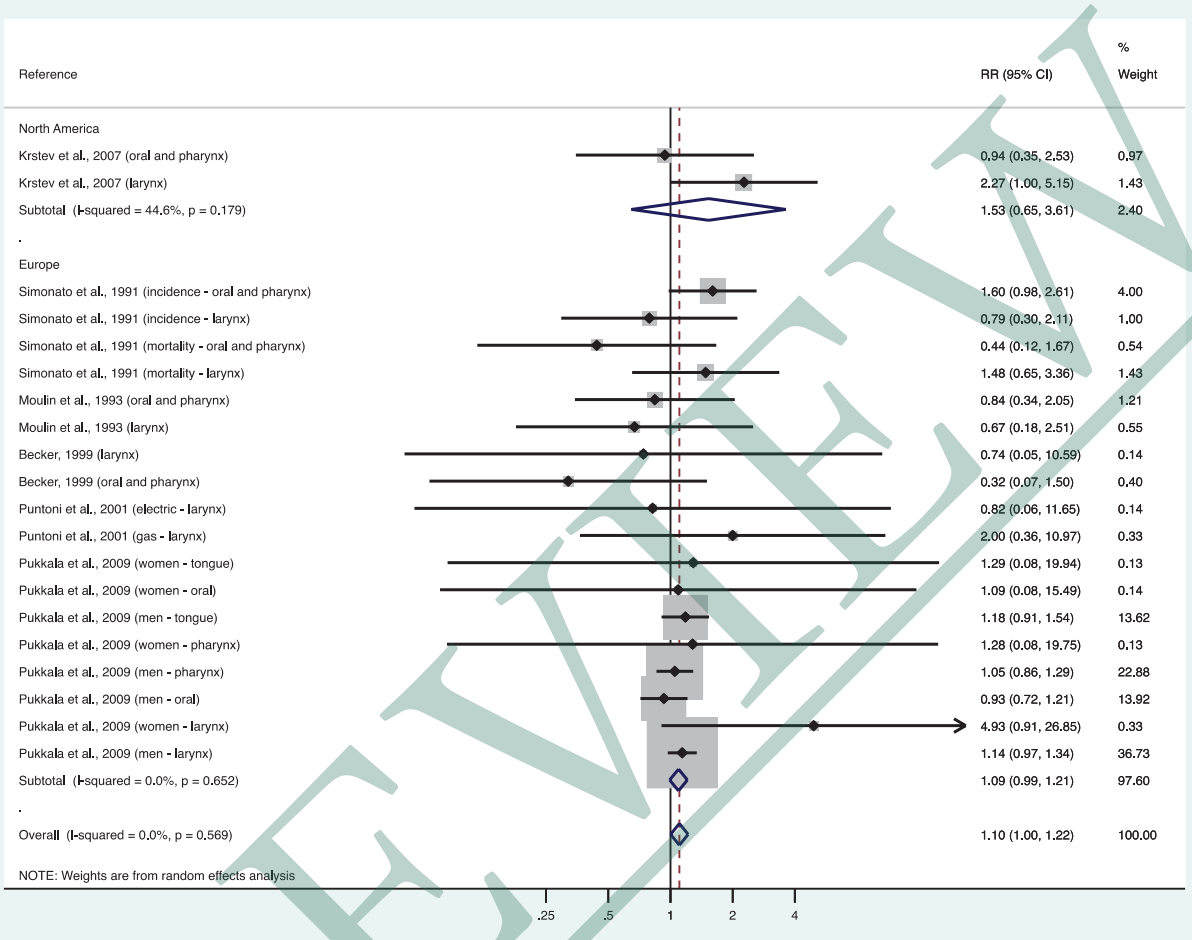

Figure A8. Stratified Analysis of HN Cancers by Geographical Region.

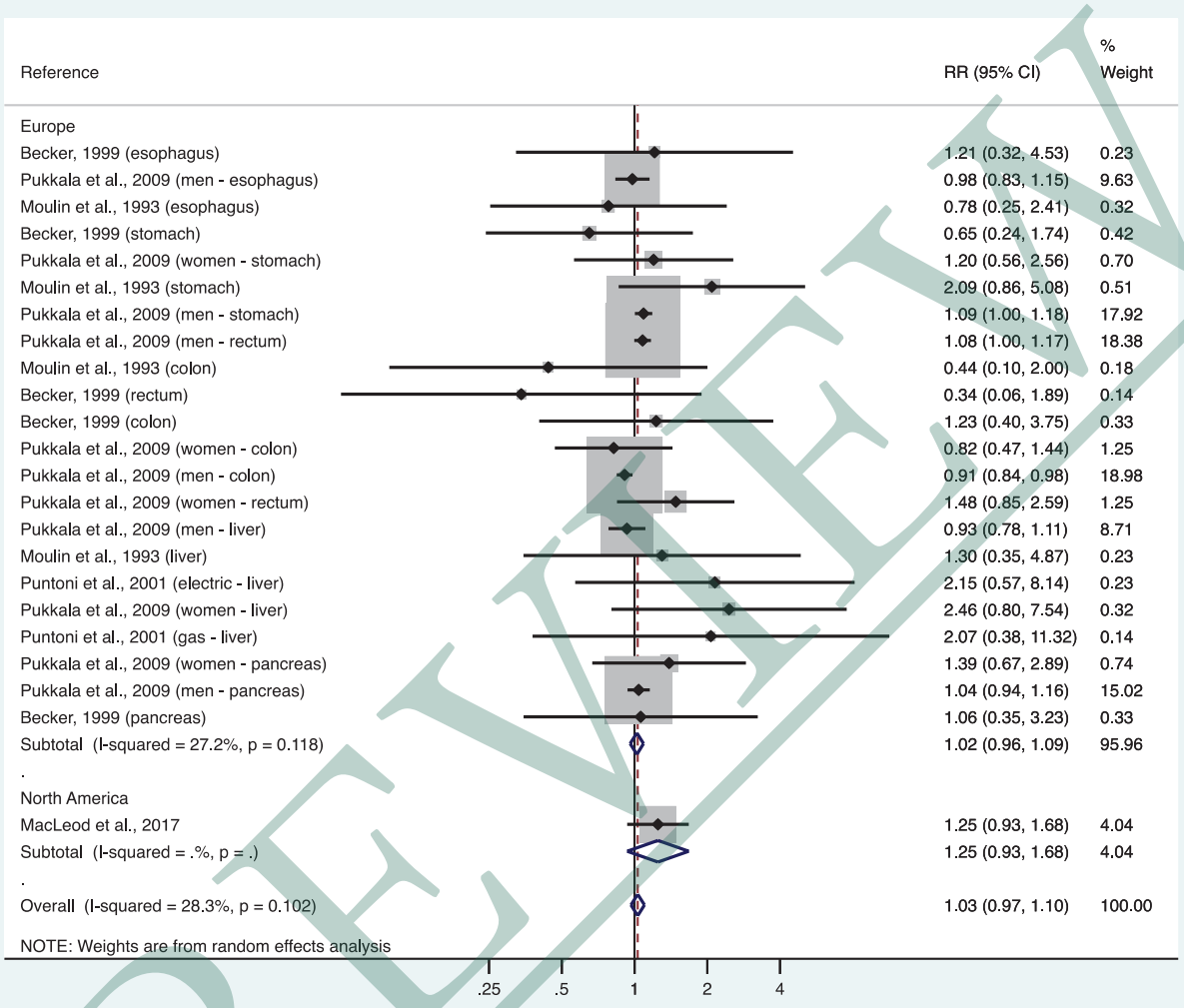

Figure A9. Stratified Analysis of GI Cancers by Geographical Region.

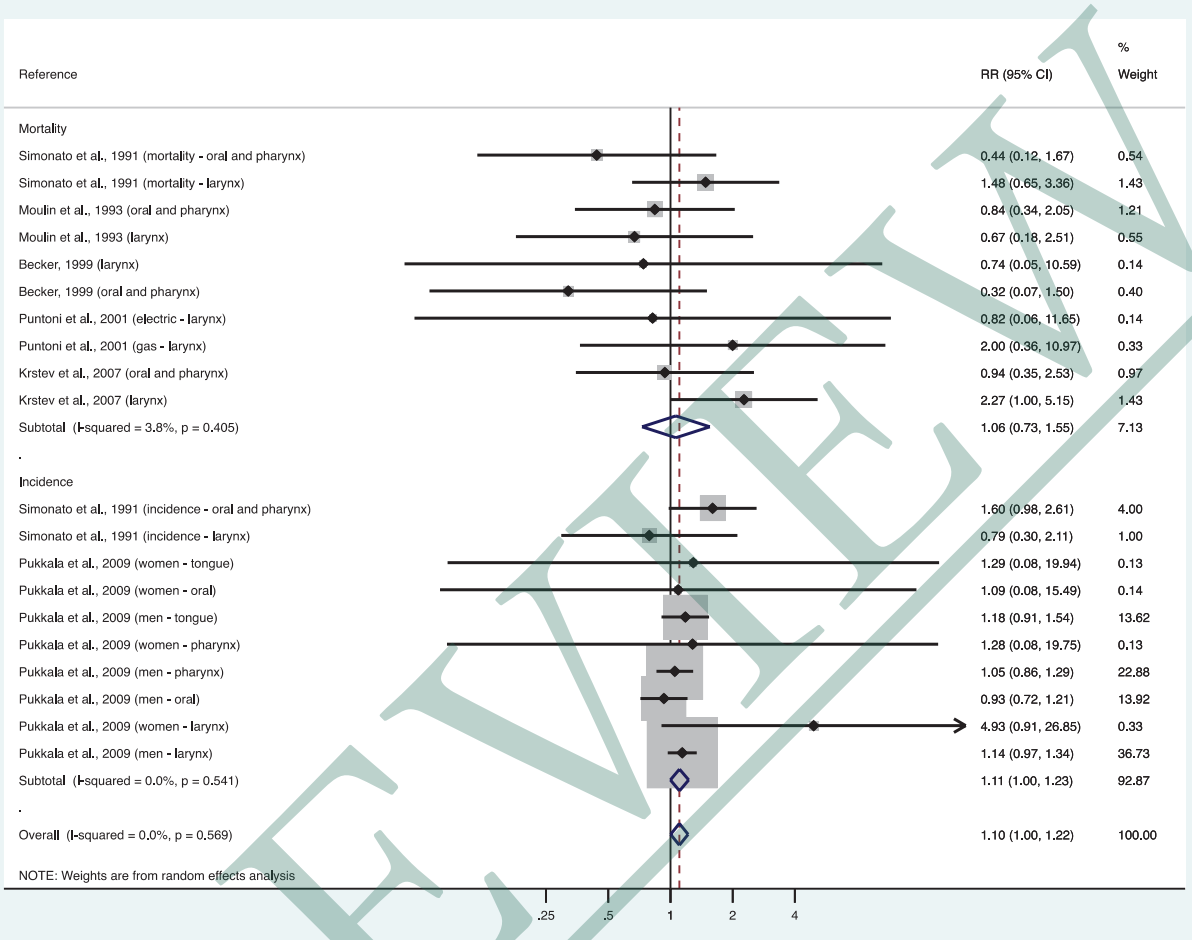

Figure A10. Stratified Analysis of HN Cancers by Type of Outcome.

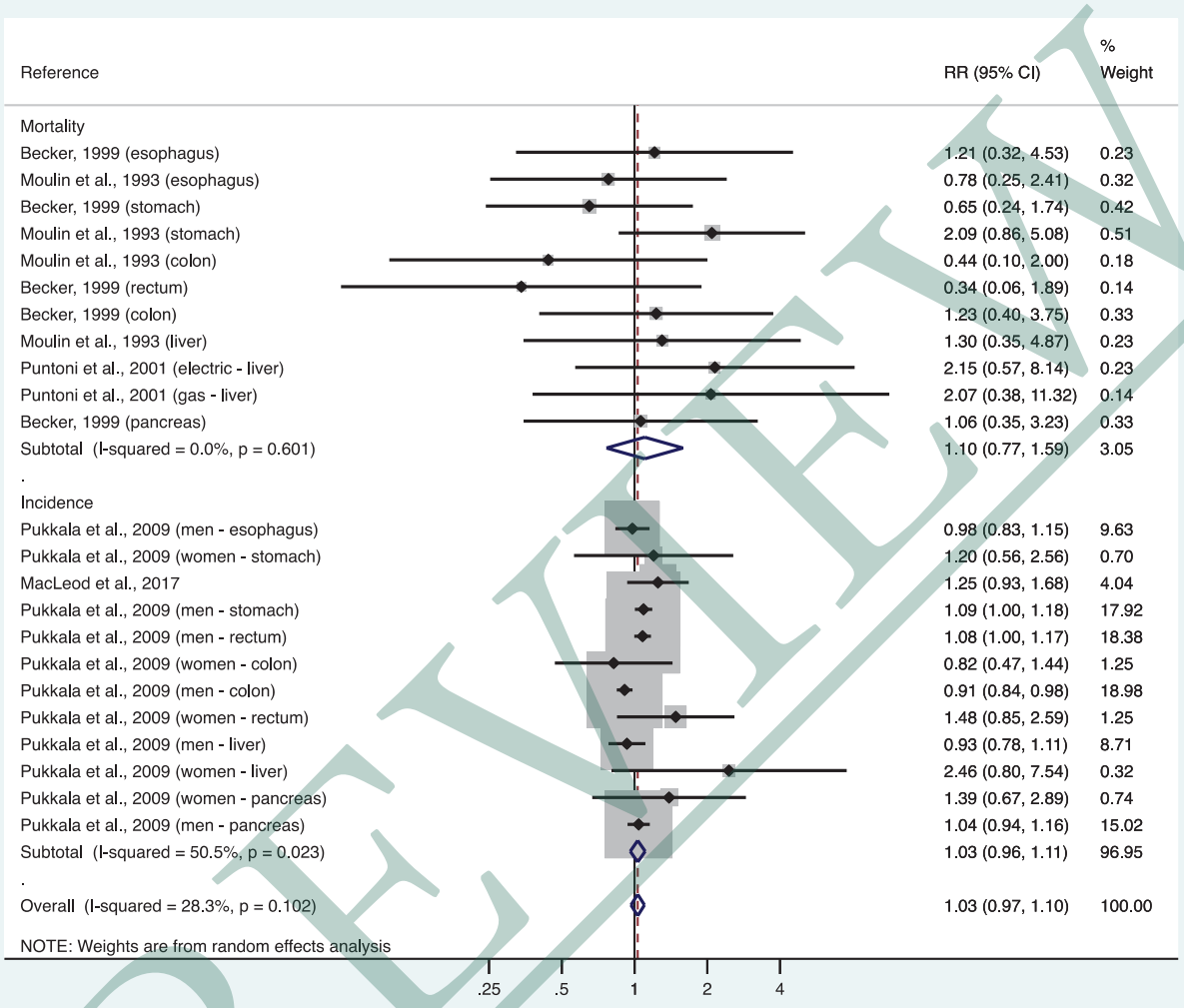

Figure A11. Stratified Analysis of GI Cancers by Type of Outcome.

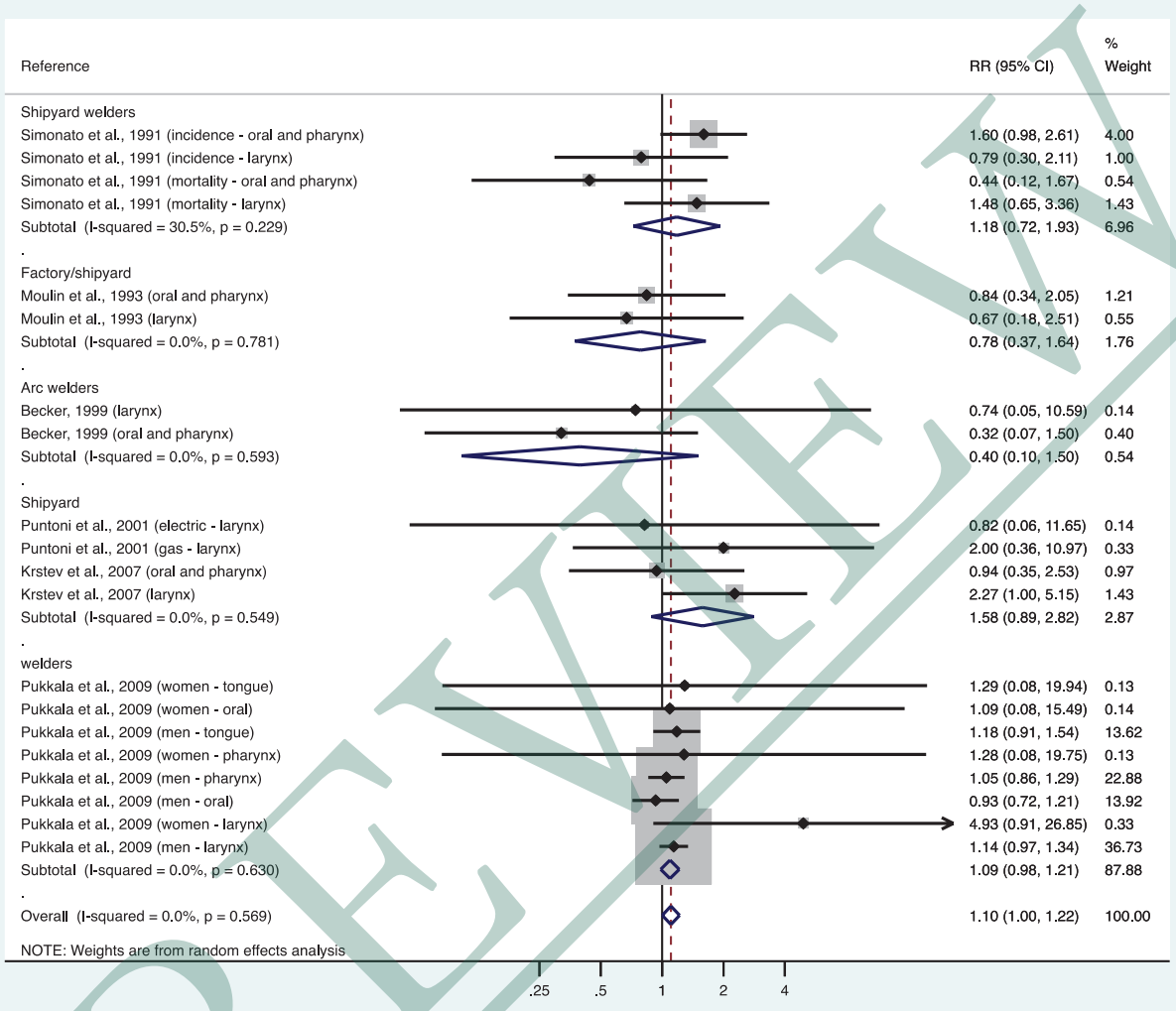

Figure A12. Stratified Analysis of HN Cancers by Industry Type.

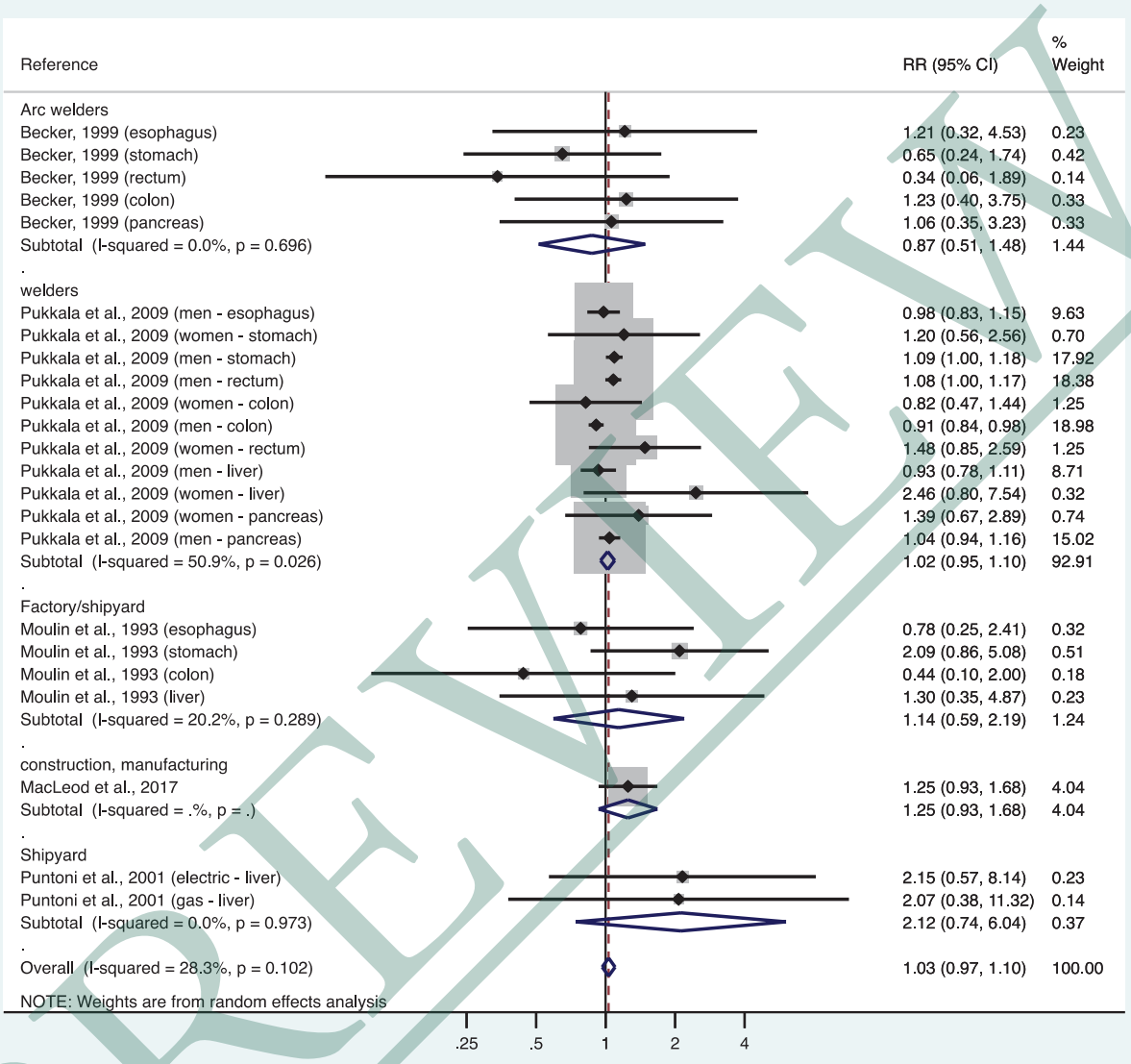

Figure A13. Stratified Analysis of GI Cancers by Industry Type.