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Occupational heat exposure and stomach cancer risk in a pooled analysis of two Spanish case-control studies in the stomach cancer pooling project – StoP consortium

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A R T I C L E I N F O

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A B S T R A C T

Background: Occupational heat stress occurs frequently and is increasing with climate change. Studies of occupational heat exposure and stomach cancer risk are limited. We used data from the international Stomach cancer Pooling (StoP) Project to investigate the relationship between occupational heat exposure and stomach cancer risk in a pooled analysis of two Spanish case-control studies, including 566 stomach cancer cases and 2984 controls.

Methods: The Spanish job-exposure matrix, MatEmEsp, was used to assign heat exposure estimates to participant occupations. We evaluated three exposure indices: ever vs. never exposed, cumulative exposure and duration (years). We calculated odds ratios (ORs) and corresponding 95 % confidence intervals (CIs) using unconditional logistic regression models including terms for potential confounders.

Results: Overall, 60.6 % of cases and 42.7 % of controls were ever occupationally exposed to heat. Occupational heat exposure was associated with a moderately elevated risk of stomach cancer (OR 1.31; 95 % CI 1.05, 1.63) when comparing ever vs. never exposed individuals in both studies combined. Elevated ORs were also observed across categories of cumulative exposure and duration (p-trend = 0.01 and 0.03, respectively). Findings were robust to additional covariate adjustment and in analysis of never smokers. There was no clear evidence for interaction according to exposure status to other suspected occupational stomach carcinogens.

Conclusion: Findings from this study provide some evidence for a positive association between occupational heat exposure and stomach cancer risk. Further research is needed to advance occupational heat assessment tools for epidemiological research as well as studies in more geographically diverse populations.

Abbreviations: BMI, body mass index; CI, confidence interval; FINJEM, Finnish job-exposure matrix; L, level; CNO, National Classification of Occupations; OR, odds ratio; P, prevalence; RR, relative risk; StoP, Stomach cancer Pooling; WBGT, wet bulb globe temperature.

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1. Introduction

Stomach cancer is one of the leading contributors to the global burden of cancer. Despite recent declines in stomach cancer incidence and mortality, it remains the fifth most diagnosed cancer worldwide, representing 4.9 % of new cancer cases, and the fifth leading cause of cancer death (6.8 % of cancer deaths) [1]. In 2022, there were nearly 1 million new cases of stomach cancer diagnosed worldwide, and over 660,000 deaths [2]. There are some well-known risk factors including infection with *Helicobacter pylori (H. pylori),* cigarette smoking, and dietary factors including intake of salted foods [3,4]. There are few established occupational stomach carcinogens including x-radiation, gamma-radiation, and work in rubber manufacturing [5]. For other occupational agents, the evidence in humans is limited.

Heat is a common occupational exposure, with many workers routinely exposed to high air temperatures or radiant heat, which may be exacerbated by physical activity demands, work clothing or personal protective equipment use, and lack of adequate cooling [6]. Globally it is estimated that at least 2.4 billion workers are already exposed to excessive heat representing 71 % of the working population and is increasing due to climate change [7]. Risks of heat stress among outdoor workers in Southern Europe have already been described [8]. Heat stress impacts a range of physiological systems, including the stomach and gastrointestinal tract [9], which may result in reductions in blood flow to the organs, reduced gastric emptying, as well as cramping, nausea, and vomiting. Heat stress has also been shown to act as a genotoxic agent and to also promote inflammation and reactive oxygen species generation [10–14].

Few studies have investigated the potential association between occupational heat exposure and stomach cancer risk. A register-based cohort from Finland followed 413,877 women from 1971 to 1995 and observed 1881 cases of stomach cancer [15]. No association was found for either low or medium/high occupational heat exposure as estimated using the Finnish job-exposure matrix (FINJEM) and there were few exposed cases.

A previous analysis of occupation in the Stomach cancer Pooling (StoP) Project, reported a higher odds of stomach cancer for labour-related occupations (with work in dusty or high-temperature conditions) [16]. In PANESOES, a Spanish multi-case-control study, there were some elevated odds ratios (ORs) of level of occupational heat exposure (based upon the FINJEM) and stomach cancer risk among men, though findings were imprecise and there were small numbers of more highly exposed participants [17].

Studies of other cancer types have had mixed results [18–22]. In the Spanish multi-case control (MCC-Spain) study, there were some positive associations of lifetime occupational heat exposure and colorectal cancer risk observed among women in the highest categories of cumulative exposure and duration [22]. Previous studies used various methodologies, and some had relatively small sample sizes.

This study expands on the limited current knowledge regarding occupational heat exposure and stomach cancer risk using data from the StoP Project. We conducted a detailed analysis of associations between occupational heat exposure and stomach cancer risk in a pooled analysis of data from the Spanish PANESOES and MCC-Spain case-control studies using the Spanish national job-exposure matrix (JEM), MatEmEsp.

2. Materials and methods

2.1. Study data

This study is based on v.3.0 of the StoP Project consortium, including 33 epidemiological studies, 12,753 gastric cancer cases and 30,682 controls (www.stop-project.org). Recruitment of studies and harmonisation of variables is described elsewhere [16,23]. A total of 13 studies contained some occupational information, such as questionnaire-based exposure information, or job titles and durations. The present analysis is based on individual participant data from two Spanish case-control studies with sufficiently detailed information on occupational history and coded job titles, PANESOES and MCC-Spain. Although an additional study, the Nebraska, U.S.A. study was also considered, due to the small number of included cases and lack of a common suitable JEM for exposure assessment across all included studies, this study was excluded here [24]. Participating studies were conducted in accordance with applicable laws, regulations, and guidelines for protection of human subjects, and the StoP Project received ethical approval from the University of Milan Review Board (reference no. 19/15 of 01/04/2015).

PANESOES is a hospital-based multi-case-control study undertaken between 1995 and 1999. Newly diagnosed, histologically confirmed, esophagus, stomach and pancreas cancer cases aged 30–80 years old were recruited from 9 hospitals in the provinces of Alicante and Valencia [17,18]. Controls were selected from the same hospitals as case subjects frequency-matched by age, sex and province. Face-to-face interviews were conducted in hospital for all participants by trained interviewers using a structured questionnaire. Overall, 91.9 % of cases (n = 401) and 99.6 % of controls, for all cancers in the PANESOES study (n = 455), agreed to participate.

MCC-Spain is a multicentre, population-based, case-control study of five cancer types undertaken between 2008 and 2013 (www.mccspain.org) [25]. Histologically confirmed incident stomach cancer cases between 20 and 85 years old were recruited from 18 hospitals across 10 regions. Controls, frequency-matched by age and sex, were identified from primary care centres located in the same area as hospitals from which cases were recruited. A computerised questionnaire was administered by trained personnel in face-to-face interviews. A total of 459 stomach cancer cases and a common set of 3440 controls for all cancer cases were recruited, with response rates of 55 % and 51 %, respectively.

2.2. Occupational heat exposure assessment

Lifetime occupational information was recorded for each participant in MCC-Spain, while in PANESOES, the two longest worked occupations. Jobs were coded into National Classification of Occupations (CNO) 94 codes. Estimates of the proportion of workers exposed (prevalence P) and the proportion of annual working time spent in heat (level L) were assigned using a Spanish JEM, MatEmEsp [26]. MatEmEsp covers the time period 1996–2005 and is an adaptation of the Finnish FINJEM by an expert panel of industrial hygienists. Occupational heat exposure is defined as the average yearly proportion of working time with heat stress, being either of continuous occupational exposure or exposure over long time periods in the year from natural or artificial sources exceeding ISO 7243 wet bulb globe temperature (WBGT) indices.

We defined ever occupational heat exposure as having ever held at least one job with a P ≥ 25 % for a duration of at least one year. We deemed participants that had only held jobs with a P between 5 % (the assessment threshold of the JEM) and 25 % or with occupational heat exposure for less than one year to have uncertain exposure and excluded them from analysis (38 cases; 66 controls). Participants who worked exclusively as a homemaker (117 cases; 315 controls), who had any missing occupational information, including occupational codes or start/finish years (40 cases; 140 controls), and who had missing information on covariates of interest (90 cases; 196 controls) were also excluded. In MCC-Spain, participants that had been recruited as part of a preliminary protocol (176 controls), or who had a personal history of gastrointestinal cancer were also excluded (9 cases; 18 controls). The total number of included stomach cancer cases across the two studies was 566 and controls 2984.

2.3. Statistical analysis

Unconditional logistic regression models were used to estimate the ORs and the corresponding 95 % confidence intervals (CIs) between occupational heat exposure and stomach cancer risk including terms for

5-year age groups, sex, education, cigarette smoking status, body mass index (BMI), family history of stomach cancer in a first degree relative, and study in the pooled dataset. We used three different exposure indices: ever vs. never occupational heat exposure, duration of exposure and cumulative exposure. Overlapping jobs were considered part-time, and duration of these jobs was split. Lifetime cumulative exposure was calculated as the sum of the product of P, L and duration of occupational heat exposure for each job with a P ≥ 25 % and was categorised into tertiles according to the distribution amongst exposed controls. The reference group for all analyses was never occupational heat exposure.

2.4. Sensitivity analyses

We assessed the impact of adjusting models with harmonised variables for cigarettes per day (never, former, current low ≤10, current intermediate 10–20, current high >20), alcohol consumption (ever drinking alcohol at least once a month for at least 1 year), total salt intake (low, medium, high), fruit and vegetable intake (low, intermediate, high), as well as other suspected occupational stomach carcinogens in MatEmEsp [5,27] (below).

Analyses were also conducted according to strata of sex and education, as well as among never smokers. We additionally investigated potential interactions of occupational heat exposure and other suspected occupational stomach carcinogens. Due to the low exposure prevalence of some other occupational exposures, a P of ever exposure for both heat as well as the other occupational agent was defined as having ever held at least one job with a P ≥ 5 % for a duration of at least one year here.

To explore the effect of the a priori ever occupational heat exposure definition, we performed sensitivity analyses using additional P thresholds of ≥ 5 % and ≥ 50 %, and an exposure duration threshold of 5 years. We were unable to implement a lag period in the overall analyses due to a lack of data on start and finish years of occupations in PANESOES. As such, we conducted a sensitivity analysis in MCC-Spain and implemented different lag periods (1, 5, and 10 years). We also performed time window analyses to evaluate the impact of the last heat exposure being < 10 or ≥ 10 years before diagnosis/interview date.

Analyses were conducted using Stata 17 and R version 4.3.1.

3. Results

Table 1 shows characteristics of included cases and controls. The mean (SD) age of cases and controls was similar, 63.9 (12.2) and 62.9 (11.2) years respectively. There was a larger proportion of male than female participants, particularly in PANESOES. Participants in PANESOES tended to have a lower level of educational attainment and were more often current smokers. The mean (SD) BMI was 26.7 (4.3) kg/m^2 among cases and 25.8 (4.4) kg/m^2 among controls.

Overall, 60.6 % of cases and 42.7 % of controls were ever occupationally exposed to heat (Table 2). Participants in PANESOES had an even greater history of occupational heat exposure (67.2 % of cases and 62.8 % of controls). Characteristics of controls ever and never occupationally exposed to heat are presented in Supplemental Table 1. Exposed controls were generally older, male, with a lower level of education, and were more often former smokers. The most common jobs overall and the most common heat exposed jobs are shown in Supplemental Table 2. In terms of common jobs, PANESOES contained a large proportion of skilled agricultural workers, whereas in MCC-Spain office clerks and salespersons. Heat exposed jobs in PANESOES included skilled agricultural workers and bricklayers, and MCC-Spain waiters and bartenders, skilled agricultural workers, and cooks.

Overall, when analysing lifetime occupational exposures for MCC-Spain and the two longest occupations for PANESOES, ever occupational heat exposure was associated with a moderately higher risk of stomach cancer (OR 1.31; 95 % CI 1.05, 1.63) (Table 2). Findings were similar, but less precise, for the MCC-Spain (OR 1.30; 95 % CI 1.00, 1.69) and PANESOES studies individually (OR 1.37; 95 % CI 0.89, 2.14). ORs were elevated across categories of cumulative exposure and duration, with statistically significant positive trends (p-trend = 0.01 and 0.03, respectively), though ORs tended to plateau in the highest exposure categories for both metrics (Fig. 1). Findings were robust to further adjustment for cigarettes per day, alcohol consumption, total salt intake, fruit and vegetable intake, automotive gasoline and lead (not shown). Findings were generally similar in analysis of never smokers, though they were based on fewer participants and were less precise (Supplemental Table 3).

In subgroup analysis, findings were somewhat stronger among males, though there were smaller numbers of exposed females, and there was no clear evidence for an interaction (p-values > 0.05) (Table 3). Although findings among those with a lower level of attained education were also somewhat stronger, there were smaller numbers of more highly educated cases, including of heat exposed cases, and differences were not statistically significant (p-values > 0.05) (Supplemental Table 4). Positive significant trends in ORs across increasing categories of cumulative exposure and duration were observed among those with a lower educational attainment (p-trend = <0.001 and 0.003, respectively).

Table 1
Distribution of characteristics among cases and controls by study.

	Pooled analysis		MCC-Spain		PANESOES		
	N = 3550		N = 3030		N = 520		
	Controls[a]	Cases[a]	Controls[a]	Cases[a]	Controls[a]	Cases[a]	
Total participants	2984	566	2696	334	288	232	**p value**[b]
Age (years) mean (SD)	62.9 (11.2)	63.9 (12.2)	63.0 (11.3)	64.7 (12.6)	62.1 (10.7)	62.7 (11.7)	0.02
Sex							
Male	1834 (61.5 %)	434 (76.7 %)	1592 (59.1 %)	238 (71.3 %)	242 (84.0 %)	196 (84.5 %)	
Female	1150 (38.5 %)	132 (23.3 %)	1104 (40.9 %)	96 (28.7 %)	46 (16.0 %)	36 (15.5 %)	< 0.001
Education							
Primary school or less	1519 (50.9 %)	416 (73.5 %)	1261 (46.8 %)	211 (63.2 %)	258 (89.6 %)	205 (88.4 %)	
More than primary school	1465 (49.1 %)	150 (26.5 %)	1435 (53.2 %)	123 (36.8 %)	30 (10.4 %)	27 (11.6 %)	< 0.001
Smoking							
Never smoker	1261 (42.3 %)	195 (34.5 %)	1152 (42.7 %)	124 (37.1 %)	109 (37.8 %)	71 (30.6 %)	
Former smoker	1103 (37.0 %)	190 (33.6 %)	1009 (37.4 %)	128 (38.3 %)	94 (32.6 %)	62 (26.7 %)	
Current smoker	620 (20.8 %)	181 (32.0 %)	535 (19.8 %)	82 (24.6 %)	85 (29.5 %)	99 (42.7 %)	< 0.001
BMI (kg/m^2) mean (SD)	26.7 (4.3)	25.8 (4.4)	26.7 (4.3)	27.4 (4.1)	26.8 (4.1)	23.5 (3.9)	< 0.001
Family history of stomach cancer							
No/missing	2812 (94.2 %)	503 (88.9 %)	2540 (94.2 %)	290 (86.8 %)	272 (94.4 %)	213 (91.8 %)	
Yes	172 (5.8 %)	63 (11.1 %)	156 (5.8 %)	44 (13.2 %)	16 (5.6 %)	19 (8.2 %)	< 0.001

[a] n (%)
[b] p values for both studies combined; Wilcoxon rank sum test for continuous and Pearson's Chi-squared test for categorical

Table 2
Associations between occupational heat exposure and stomach cancer risk (OR: Odds Ratio; 95 % CI: 95 % Confidence Interval).

	Pooled analysis[a]				MCC-Spain[b]				PANESOES[b]			
	N = 3550				N = 3030				N = 520			
	Controls	Cases	OR	95 % CI	Controls	Cases	OR	95 % CI	Controls	Cases	OR	95 % CI
Never exposure	1709	223	—	—	1602	147	—	—	107	76	—	—
Ever exposure	1275	343	1.31	1.05, 1.63	1094	187	1.30	1.00, 1.69	181	156	1.37	0.89, 2.14
Cumulative exposure[c]												
Low	425	65	1.09	0.79, 1.49	403	50	1.08	0.75, 1.53	22	15	0.87	0.38, 1.96
Medium	429	117	1.42	1.07, 1.89	379	68	1.36	0.96, 1.90	50	49	1.60	0.91, 2.83
High	421	161	1.42	1.07, 1.88	312	69	1.57	1.10, 2.24	109	92	1.42	0.87, 2.33
P-trend				*0.01*				*0.01*				*0.11*
Duration[d]												
Low	440	76	1.23	0.91, 1.66	418	57	1.16	0.82, 1.63	22	19	1.34	0.61, 2.90
Medium	415	123	1.38	1.04, 1.83	351	62	1.36	0.96, 1.92	64	61	1.45	0.85, 2.47
High	420	144	1.32	0.99, 1.76	325	68	1.44	1.00, 2.06	95	76	1.33	0.80, 2.23
P-trend				*0.03*				*0.03*				*0.20*

[a] Odds ratio calculated using unconditional logistic regression adjusted for age, sex, education, BMI, cigarette smoking, family history of stomach cancer and study
[b] Odds ratio calculated using unconditional logistic regression adjusted for age, sex, education, BMI, cigarette smoking and family history of stomach cancer
[c] P*L*duration in years, cut points for all analyses based on the tertiles according to the distribution amongst exposed controls. (Low: >0–174; Medium: >174–630; High >630)
[d] Cut points based on the tertiles according to the distribution amongst exposed controls. (Low: >0–10; Medium: >10–32; High: >32)

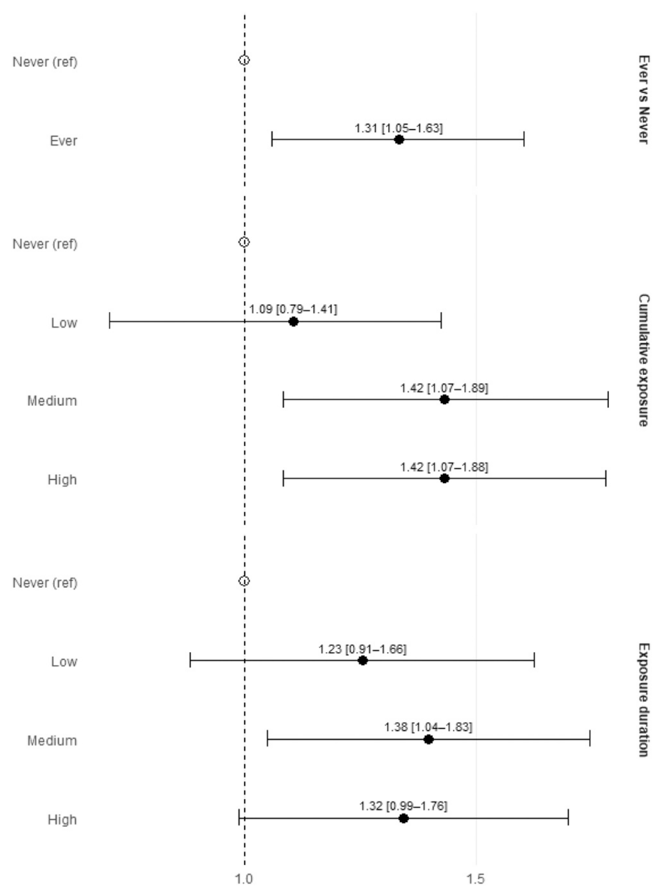

Fig. 1. Associations between occupational heat exposure and stomach cancer risk (OR: Odds Ratio; 95 % CI: 95 % Confidence Interval).

According to other potential occupational carcinogens, 22.8 % of heat exposed participants were ever exposed to automotive gasoline ($P \geq 5$ for both agents). ORs were somewhat stronger among those ever exposed to automotive gasoline though they were imprecise and there was no clear evidence for an interaction (p-values > 0.05) (Supplemental Table 5). There was also no clear evidence for an interaction with occupational lead exposure (p-values > 0.05) with 51.2 % of heat exposed participants ever exposed to lead (Supplemental Table 6). There were 9.7 % of heat exposed participants ever exposed to asbestos with all asbestos exposed participants exposed to heat (not shown).

Findings were similar according to different P and exposure duration thresholds (not shown). In analysis of MCC-Spain only, findings were similar using different lag periods and exposure time windows (not shown).

4. Discussion

In this pooled case-control study, ever being occupationally exposed to heat was associated with a modest increase in stomach cancer risk. We also observed positive trends across categories of cumulative exposure and duration. Findings add to the limited evidence surrounding occupational heat exposure and stomach cancer risk.

Results here contrast with a previous register-based cohort study in Finland, which reported no association for stomach cancer among women, though job assessment was performed only at baseline in that study [15]. In other previous work, we observed some evidence for positive associations for both breast cancer and colorectal cancer risk among women in analysis of MCC-Spain [20,22] but no evidence for an association with prostate cancer in a pooled analysis of three international cancer case-control studies [19].

There were two studies here which strengthened the overall sample size, though statistical power remained limited particularly in subgroup analysis. Multiple testing was performed and some findings may have occurred by chance. We did not observe clear differences in findings when stratifying by sex despite differences in heat exposed occupations between men and women. There are also biological differences in thermoregulation [28]. Indoor and outdoor workers also are likely to have different types and patterns of heat exposure and concomitant occupational exposures.

Findings were somewhat stronger in less educated subjects, leaving open the possibility of residual confounding by social class. In PANESOES, cases and controls were similar in terms of educational attainment and there were high participant response rates in the hospital-based design. In MCC-Spain, response rates for cases and controls were moderate in the population-based study and participating controls had a greater educational attainment than cases. Occupational heat exposures are typically experienced in jobs with lower socioeconomic position, though there is a large amount of variation within and between major occupational groups [26,29]. Stomach cancer also displays an inverse socioeconomic gradient with those of a lower socioeconomic

Table 3
Associations between occupational heat exposure and stomach cancer risk stratified by sex (OR: Odds Ratio; 95 % CI: 95 % Confidence Interval).

	Males[a]				Females[a]				
	N = 2268				N = 1282				
	Controls	Cases	OR	95 % CI	Controls	Cases	OR	95 % CI	p-value interaction
Never exposure	815	134	—	—	894	89	—	—	
Ever exposure	1019	300	1.43	1.11, 1.86	256	43	1.12	0.72, 1.72	0.87
Cumulative exposure[b]									
Low	275	48	1.15	0.78, 1.68	150	17	0.89	0.48, 1.57	
Medium	361	104	1.50	1.09, 2.07	68	13	1.25	0.61, 2.41	
High	383	148	1.58	1.15, 2.16	38	13	1.56	0.72, 3.20	0.20
P-trend				*< 0.01*				*0.30*	
Duration[c]									
Low	281	54	1.30	0.90, 1.87	159	22	1.05	0.60, 1.78	
Medium	335	107	1.46	1.05, 2.01	80	16	1.19	0.61, 2.21	
High	403	139	1.50	1.10, 2.06	17	5	1.32	0.39, 3.80	0.27
P-trend				*0.01*				*0.50*	

[a] Odds ratio calculated using unconditional logistic regression adjusted for age, education, BMI, cigarette smoking, family history of stomach cancer and study
[b] P*L*duration in years, cut points for all analyses based on the tertiles according to the distribution amongst exposed controls. (Low: >0–174; Medium: >174–630; High >630)
[c] Cut points based on the tertiles according to the distribution amongst exposed controls. (Low: >0–10; Medium: >10–32; High: >32)

position at greater risk [30].

A strength of the study includes the availability of harmonised covariate data. However, we were unable to assess the impact of adjustment for *H. pylori* infection. In MCC-Spain, data on *H. pylori* infection was only available for 279 cases, with 93 % positive. Findings also remained in analysis of never smokers, though they were based on fewer participants. Workers regularly contending with high temperatures may compensate for sodium lost in sweating by increasing intake of dietary salt, which may also interact with other stomach cancer risk factors, including *H. pylori* infection [31]. The role of heat shock proteins in gastric tumorigenesis has been described with overexpression in human gastric cancer [32]. Heat shock proteins may also facilitate persistent *H. pylori* infection, including with respect to gastric temperature fluctuations and other chemical or physical stressors [32–34]. There were moderate proportions of heat exposed participants also exposed to other suspected occupational stomach cancer carcinogens and no clear evidence for interaction was observed. Further research regarding potential mechanisms of occupational heat exposure and gastric carcinogenetic is needed.

Estimates in MatEmEsp have been adapted specifically for workers in Spain. However, there are within country differences in exposure that are not captured [29]. Heat exposure estimates covered the period 1996–2005, and more historical or more recent exposures experienced by study participants may have a greater degree of misclassification including in terms of changes in outdoor or indoor thermal environment, work practices, and clothing over time. There are also other personal factors including acclimatisation that are not captured using a job-based approach. Berkson errors would typically arise from assigning group-based JEM exposures estimates. The MatEmEsp JEM is largely expert-based and further work to advance multi-dimensional JEMs to better estimate occupational heat stress in Europe is needed [29]. Nonetheless, the JEM is favourable over self-reported exposures which may be impacted by recall bias.

The proportion of exposed cases and controls was high with 60.6 % of cases and 42.7 % of controls having ever held at least one job with a P ≥ 25 % for at least one year, and was similarly high when using P ≥ 50 % (58.8 % and 39.9 % respectively). Although a large proportion of case and control participants had held heat exposed jobs for more than 10 years (77.8 % and 65.5 % respectively) the mean level, L or proportion of annual working time spent in heat, was typically modest across common jobs, generally reflecting seasonal or intermittent exposures including in outdoor work.

Data were available for the two longest held jobs in PANESOES. However, the overall duration of employment among captured occupations was 33.0 years in PANESOES and 32.6 years in MCC-Spain, thus likely capturing most long-term occupational heat exposures. Further, in PANESOES, data was only available on number of years worked for each occupation and not specific start/finish years. However, when analysing MCC-Spain using various lag periods and exposure time windows, results were not materially changed.

5. Conclusions

This pooled analysis showed some evidence for an association between occupational heat exposure and stomach cancer risk. Future larger-scale studies, including in more geographically diverse populations with refined heat stress exposure metrics, are needed.

Disclaimer

The contributions of the National Institutes of Health (NIH) authors were made as part of their official duties as NIH federal employees, are in compliance with agency policy requirements, and are considered Works of the United States (U.S.) Government. However, the findings and conclusions presented in this paper are those of the authors and do not necessarily reflect the views of the NIH or the U.S. Department of Health and Human Services.

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CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare that they have no competing interests.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.canep.2025.102938.

DATA AVAILABILITY

The data that support the findings of our study are available from the StoP Project but restrictions apply to the availability of these data, which were used under license for this study and so are not publicly available. Data are, however, available from the authors upon reasonable request and permission of the Steering Committee of the StoP Project.

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