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Regional variation in incidence for smoking and alcohol related cancers in Belgium

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ABSTRACT

The prevalence of life habits may vary substantially within a country. Incidence maps of strongly related diseases can illustrate the distribution of these life style habits. In this study we explored the spatial variation in Belgium for different cancers related to alcohol and/or tobacco.

From the Belgian Cancer Registry, municipality specific World Standardised incidence rates for the years 2004–2011 are used to create detailed smoothed cancer maps by subsite or histology for cancers of oral cavity, pharynx, larynx, oesophagus, liver and lung. Cancer incidence is compared both visually (from incidence maps) and with Poisson regression analysis using mortality from chronic liver disease and chronic obstructive pulmonary disease as a proxy for alcohol and tobacco prevalence, respectively.

The incidence rates for oral cavity, pharyngeal and laryngeal cancer were comparable with the alcohol gradient. However, glottic cancer revealed a pattern that was more comparable with lung cancer. These two tumour types resembled more closely to the smoking pattern. Oesophageal cancer showed two patterns: squamous cell carcinoma was highly comparable with the background alcohol consumption, while adenocarcinoma was unrelated to one of our two proxies.

Our approach and results are an encouraging example how data from a young cancer registry can be used in studies describing the regional cancer burden. The results can be useful for primary prevention to increase awareness for the public, authorities and health care professionals in specific subpopulations.

1. Introduction

Cancer registration in Belgium has evolved from a number of regional initiatives in the late nineties towards a national and centralised population based cancer registry. Nationwide data are being collected since the incidence year 2004. In addition to describing cancer patterns and trends in incidence and survival [1–4], the Belgian Cancer Registry (BCR) is involved in (prospective) clinical registration projects, in the evaluation of quality of care in oncology and in the registration for all cyto-histological specimens taken for early diagnosis and screening for breast, colorectal and cervical cancer.

The aim of this study – which is one of the first peer-reviewed articles to come out from the BCR – is to demonstrate possibilities to perform ecological analyses in a young population based cancer registry that has not yet acquired historical time series of cancer data. Our objective was to visualise the spatial variation in Belgium for different cancers with a well-known relation to alcohol and/or tobacco. A further aim is to reveal patterns of specific subsites or histological subtypes of cancers for which there is only limited evidence of an association with alcohol and tobacco consumption.

Smoking and drinking habits may vary substantially within a country. In such a case, there should be a clear spatial variation in incidence of diseases strongly related to the use of alcohol and tobacco. To our knowledge no data are available on drinking or smoking prevalence neither on municipality level nor on an individual level that would allow calculation of prevalence rates for any regional unit in Belgium. Search for data for small regions is further complicated due to strict privacy regulations. The only data on the regional drinking patterns in Belgium are available from the National Health Surveys which is based on small number of participants [5]. Therefore, the only option to get information on spatial distribution is to rely on proxy variables on the drinking and smoking habits in Belgium. For this study, we used mortality rates for chronic liver disease (CLD) and chronic obstructive pulmonary

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disease (COPD) to represent the prevalence of alcohol and tobacco use, respectively.

2. Patients and methods

2.1. Data sources

Belgium, a nation covering an area of 30,528 square kilometres and a population of about 11 million people, is situated in Western Europe in between the Netherlands to the north-northeast, Germany and Luxembourg to the east, France to the south and southwest, and the North Sea to the west.

The BCR is a national population based cancer registry, collecting data on the national level since the incidence year 2004. The specific Cancer Registration Law of December 13th 2006 [6] authorises the BCR to use the national social security identification number (SSIN) as the unique patient identification. This allows the Registry to perform accurate linkage procedures for follow up on vital status and date of death and linkage with the nomenclature of medical acts (diagnostic and therapeutic procedures) and other clinical data [7].

This law also describes the role, objectives and data flow of the BCR. The data flow must rely on clinical information from the oncological care programmes in all hospitals (clinical network) where specifically trained data managers extract cancer registration data from the medical files. They gather data concerning the patient (SSIN, residence, sex, date of birth), tumour characteristics (topography and morphology ICD-O-3 [8], clinical and pathological TNM stage [9]) and treatment. Also the pathology laboratories are required by law to supply the BCR with their data (pathology network). Every (pre-) malignant specimen is encoded by a pathologist, following international classification guidelines (WHO Classification of Tumours [10], SNOMED [11]), and transferred to the BCR accompanied by the report in full text.

An extended set of automated and manual validation procedures based on the IARC guidelines [12] ensure validity and quality of the data. The data source is consulted to provide additional details for cases with an uncertain diagnosis, insufficient or erroneous data or conflicting information.

The completeness was evaluated using the independent dataset method. Record linkage with a dataset for rectal cancer for the incidence years 2005 [1] and 2008 [2] resulted in an overlap of 98.6% and 99.6%, respectively. Linkage with the breast cancer database from the national organised mammography screening programme (incidence 2007–2010) resulted in a 99.5% overlap. Similar results were obtained with one prospective clinical registration project on head and neck cancer (100%) and two non-overlapping projects for prostate cancer (RALP: Robot assisted Laparoscopic Prostatectomy (99.9%) and brachytherapy (98.6%)).

Death certificates have only recently been made available to the registry. A pilot study linking the mesothelioma death statistics (2009–2010) showed that 416 out of 440 deaths (94.5%) mentioned in the death certificates were also known by the BCR. Death statistics do not contain the SSIN; hence the linking process was based on a deterministic approach using a combination of patient identifiers (date of death, birth, sex and residence). Further investigations are ongoing to trace back the remaining 5% and validate the diagnosis of mesothelioma. We estimate the database of the BCR to be more than 95% complete, incompleteness being more likely due to elderly patients with a very poor prognosis at diagnosis and outpatients with a clinical diagnosis only.

2.2. Study population

From the BCR database, incidence data for cancers of the oral cavity (ICD10 [13]: C02.0–C05.0, C06), pharynx (ICD10: C01, C05.1–C05.9, C09–C10, C12–C13), oesophagus (ICD10: C15), liver (ICD10: C22), larynx (ICD10: C32), glottis (ICD10: C32.0), supraglottis (ICD10: C32.1) and lung (ICD10: C34) are extracted for the incidence years 2004–2010. Age standardised incidence rates (using the World Standard Population (WSR)) are calculated for every municipality ($N = 589$), the smallest administrative unit in Belgium. For oesophageal, liver and lung cancer, incidence rates

Table 1
Number of new diagnoses/deaths (*N*), crude rates (CR) and age standardised (using world standard) rates (WSR) for the incidence of the selected cancers in 2004–2010 and for the mortality of chronic obstructive pulmonary disease (COPD) and chronic liver disease (CLD) in 2004–2009.

	Males			Females		
	N	CR	WSR	*N*	CR	WSR
Incidence 2004–2010						
Lung	38,481	105.9	57.7	12,894	34.0	18.8
SCC/SCLC	18,279	50.3	27.1	4,249	11.2	6.1
AC	12,078	33.2	19.1	5,844	15.4	8.8
Oral cavity	2,977	8.2	5.3	1,263	3.3	1.9
Pharynx	4,374	12.0	7.9	1,266	3.3	2.1
Larynx	4,039	11.1	6.7	610	1.6	1.0
Supraglottis	1,041	2.9	1.8	232	0.6	0.4
Glottis	2,289	6.3	3.7	246	0.6	0.4
Oesophagus	4,695	12.9	7.6	1,638	4.3	2.0
SCC	2,214	6.1	3.8	1,042	2.8	1.4
AC	2,266	6.2	3.5	498	1.3	0.5
Liver	2,597	7.1	4.2	1,172	3.1	1.5
HCC	2,015	5.5	3.2	702	1.9	0.9
Cholangio	402	1.1	0.6	330	0.9	0.4
Mortality 2004–2009						
COPD	17,795	57.4	25.2	9,558	29.6	8.8
CLD	5,122	16.5	10.4	3,049	9.4	5.0

SCC: Squamous cell carcinoma.
SCLC: small cell lung cancer.
AC: Adenocarcinoma.
HCC: Hepatocellular carcinoma.

are calculated for different histological subtypes by using the ICD-O-3 morphology codes [14].

Information on mortality for the years 2004–2009 was obtained from the national Directorate-general Statistics and Economic information (ADSEI) [15]. Municipality specific mortality rates (WSR) were calculated for chronic liver disease (CLD; ICD10: K70–K77) and chronic obstructive pulmonary disease (COPD; ICD10: J40–J44).

Table 1 gives an overview of the incidence or mortality rates of the selected diseases.

2.3. Mapping methodology

Incidence and mortality maps for Belgium were created using the methodology developed at the Finnish Cancer Registry [16,17]. The algorithm for this methodology was incorporated into an in house developed software application of the BCR. The geographic representations use municipality specific age standardised rates (WSR). Cities with at least 80,000 inhabitants are directly represented on the map as circles with a diameter relative to the population size and a colour shading indicating the actual calculated WSR in that city. The 19 municipalities of the Brussels Capital Region (more than 1,000,000 inhabitants) were divided in three separate circles. This division was based on socio-economic parameters [2]. The socio-economic status is lowest in the westernmost circle and highest in the easternmost circle.

Rates (WSR) from the remaining municipalities were smoothed. For each grid (0.25 km^2) on the map, a rate was calculated as a weighted average of the WSR in all neighbouring municipalities within 100 km from the centre of the grid. The weights were inversely associated with the distance, the weight being halved at a distance of 12 km. In addition, the weights were directly proportional to the sizes of populations of the municipalities within the radius of 100 km. A relative scale was applied. A change in colour level corresponds to a 1.07 fold change in the WSR.

2.4. Statistical analyses

Poisson regression was applied to model the crude incidence rate for the different cancer types versus the crude mortality rates for CLD and COPD. Mortality for CLD was not included in the model for lung cancer. Observed CLD and COPD crude rates in the same municipality were taken as predictors. The municipality population size was used as an offset in the Poisson models to model the observed crude cancer rates. A negative binomial distribution for the outcome incidence was assumed to allow for overdispersion. Model assumptions were checked using plots of the standardised deviance residuals and both the deviance and Pearson Chi-Square statistics were considered as a measure of goodness-of-fit. The parameter estimates are reported as the expected multiplicative change in mean crude rate (expressed per 100,000) for an increase in the proxy crude rate of 10/100,000. No estimates are reported when the model assumptions were not fulfilled. Statistical modelling was performed with SAS version 9.3 (SAS Institute, Cary, NC, USA.)

3. Results

Mortality rates for CLD and COPD were used as a proxy for the prevalence of the use of alcohol and tobacco in Belgium, respectively. The mortality rates for CLD are two- to threefold higher in the southwest of Belgium than in the northeast (Fig. 1).

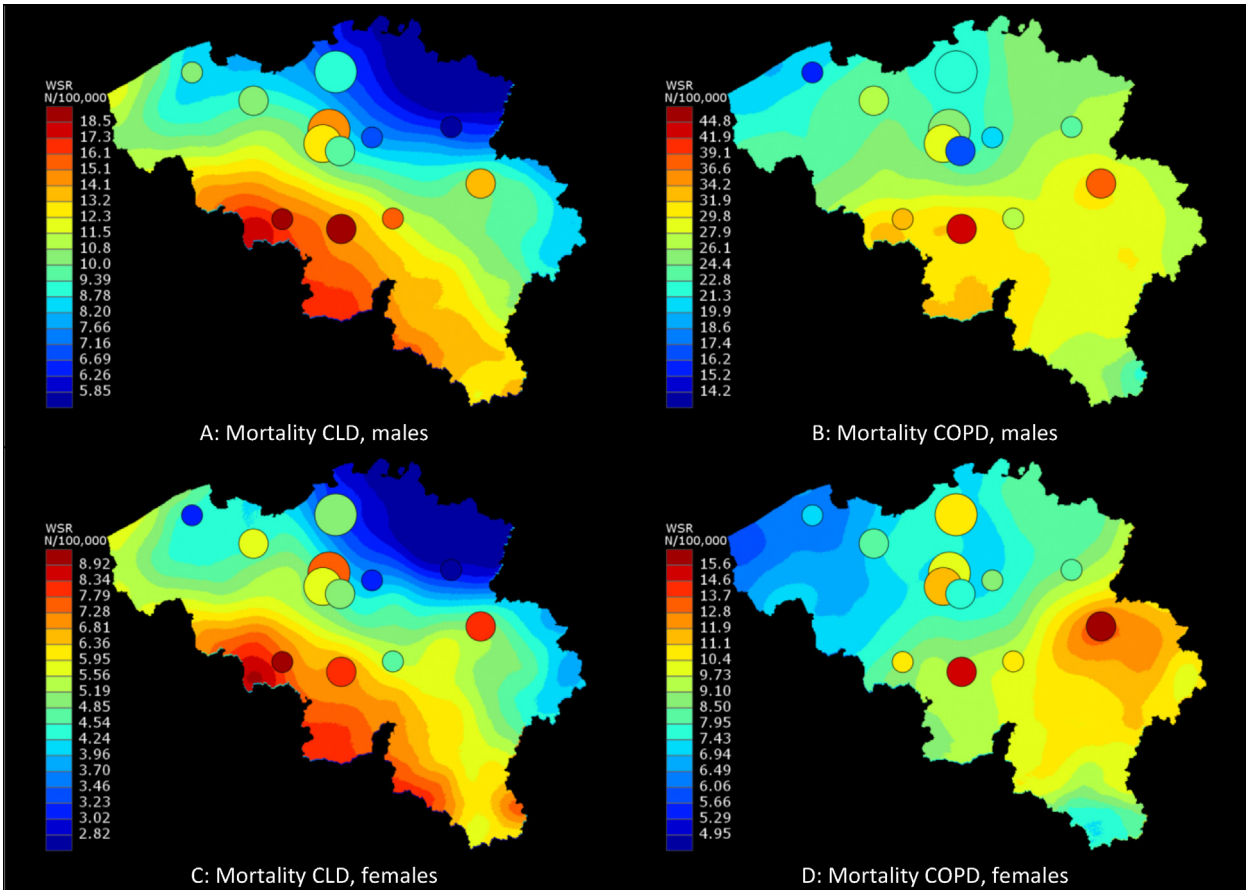

Fig. 1. Age adjusted (WSR) mortality (2004–2009) of chronic liver disease (CLD) and chronic obstructive pulmonary disease (COPD) in Belgium, by sex.

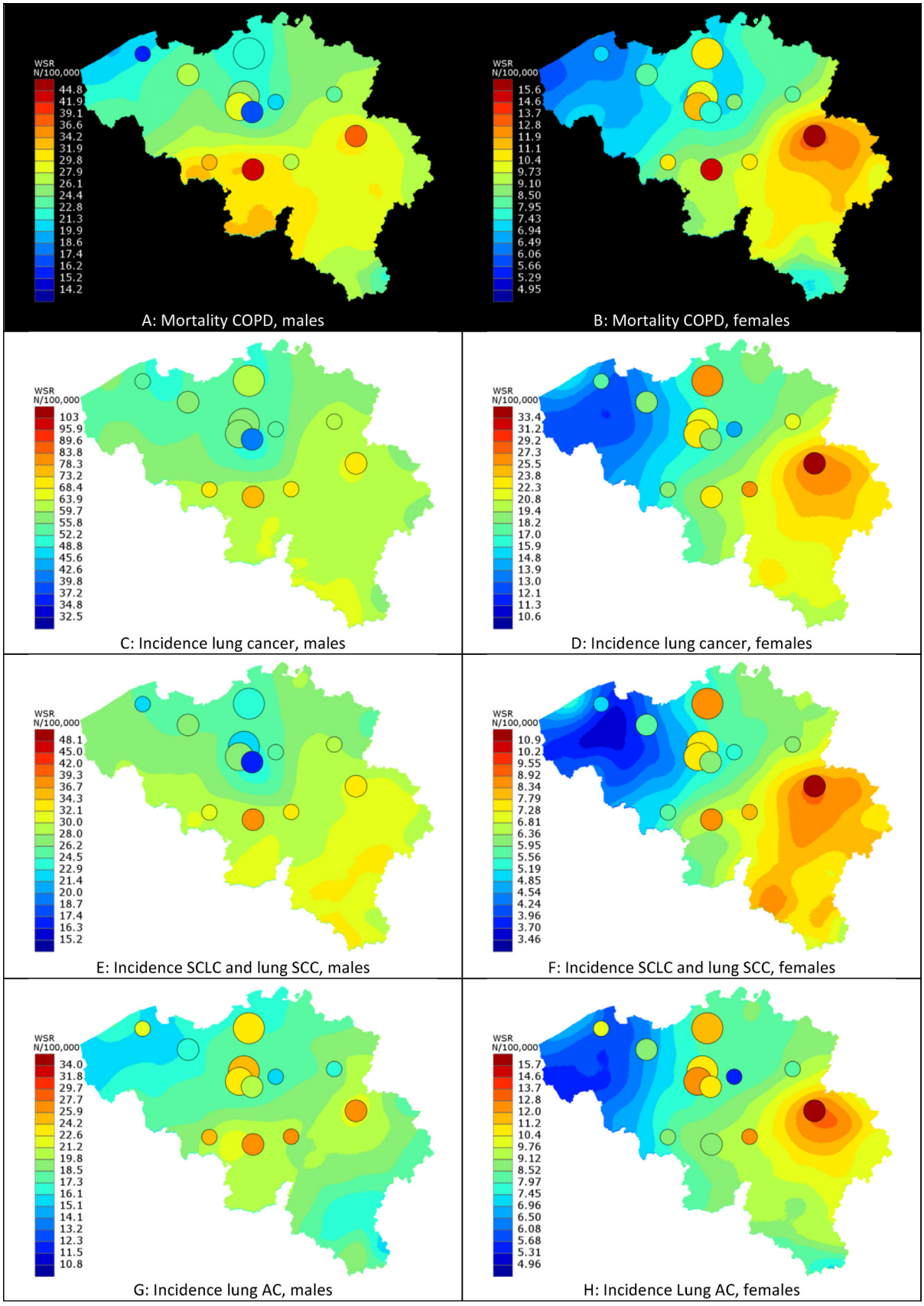

Fig. 2. Age adjusted (WSR) mortality (2004–2009) of chronic obstructive pulmonary disease (COPD); and age adjusted (WSR) incidence (2004–2010) of total lung cancer, small cell lung cancer (SCLC) and squamous cell carcinoma (SCC) and adenocarcinoma (AC) of lung, in Belgium, by sex.

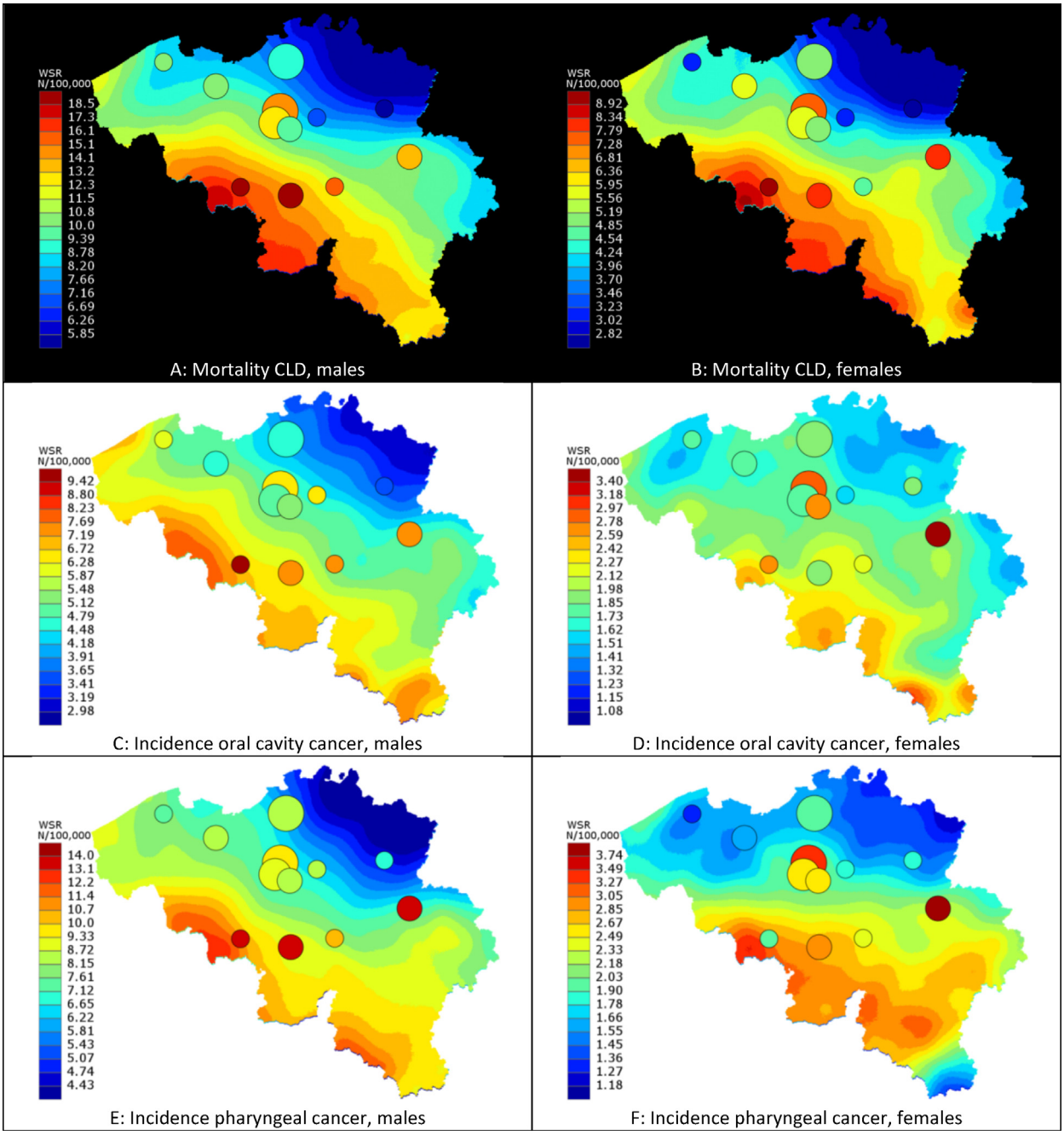

Fig. 3. Age adjusted (WSR) mortality (2004–2009) of chronic liver disease (CLD); and age adjusted (WSR) incidence (2004–2010) of cancers of oral cavity and pharynx in Belgium, by sex.

Mortality rates increase from the northeast parallel to the border with the Netherlands towards the border with France in the southwest of Belgium. Mortality rates for COPD increase twofold from the coastal regions in the west–northwest of Belgium towards the south and southeast of Belgium.

Incidence rates for male lung cancer increase slightly from the west–northwest towards the south–southeast of Belgium (Fig. 2). The gradient for male lung adenocarcinoma is less obvious and higher rates are observed in the urban areas. For female lung cancer there is a strong increasing trend from west to east for both histological sub-types.

Cancers of the oral cavity and pharynx show a two- to threefold increase in incidence from the northeast towards the southwest for both sexes (Fig. 3). A similar pattern is observed for supraglottic cancers of the larynx but not for glottic tumours (Fig. 4).

Incidence rates for male oesophageal squamous cell carcinoma (SCC) increase strongly from the northeast towards the southwest (Fig. 5). The incidence rates for females show a similar pattern but with more dominant urban incidence rates. The rates for adenocarcinoma decrease from the northwest towards the southeast in both sexes.

Hepatocellular carcinoma (HCC) incidence in males increases from the northeast towards the southwest (Fig. 6). The map for female HCC indicates some urban dominance in incidence rates, but no clear spatial trend is observed. The maps for cholangiocarcinoma do not show a distinct trend in incidence rates and the variation seen on the map may well be due to small numbers.

The scatterplot of oral cavity cancer incidence versus chronic liver disease incidence is given in Fig. 7 as an illustration of the data available for the Poisson regression analysis. Poisson regression models for the crude cancer incidence rates versus the crude

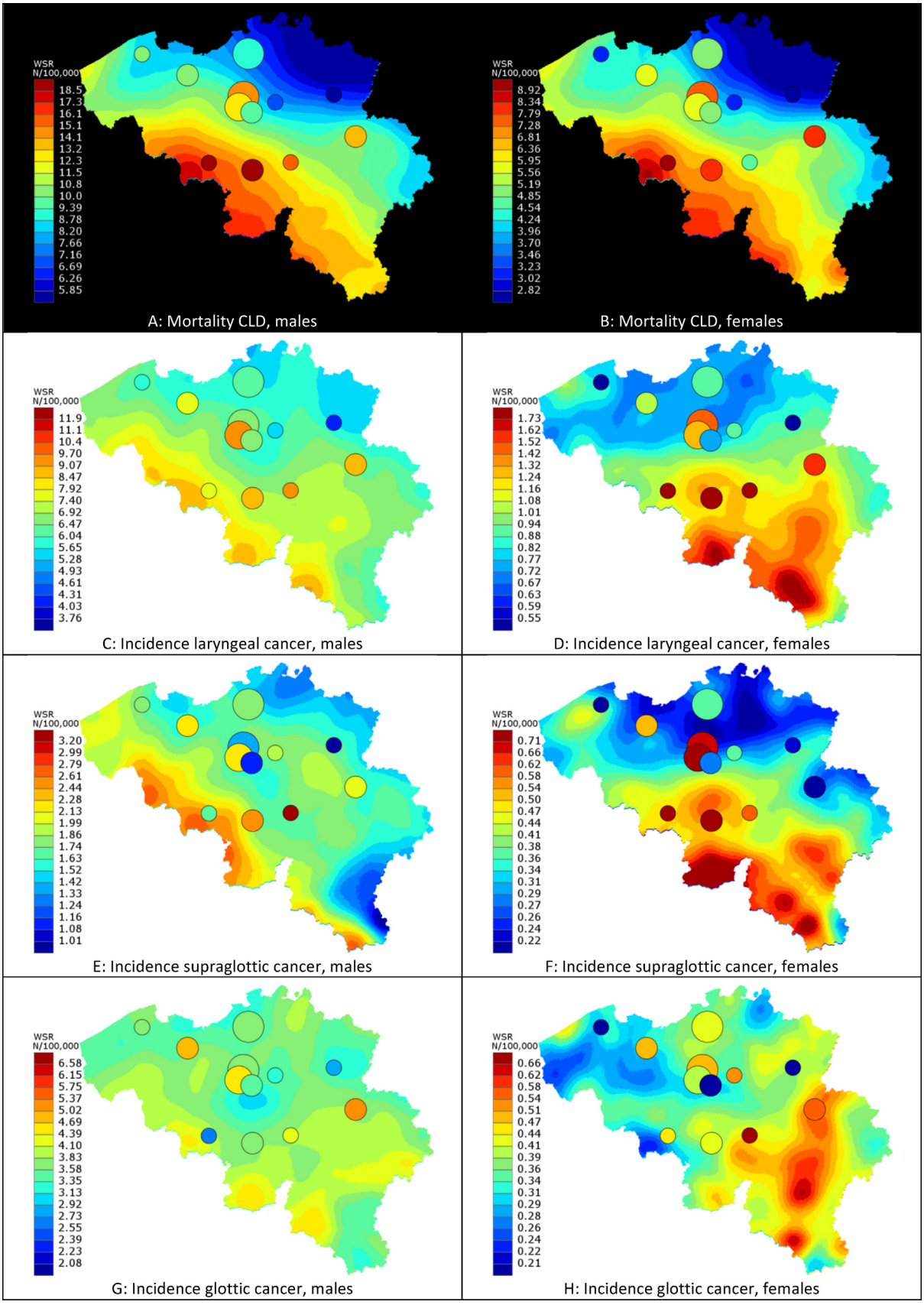

Fig. 4. Age adjusted (WSR) mortality (2004–2009) of chronic liver diseases (CLD); and age adjusted (WSR) incidence (2004–2010) of laryngeal cancer, supraglottic cancer and glottic cancer, by sex.

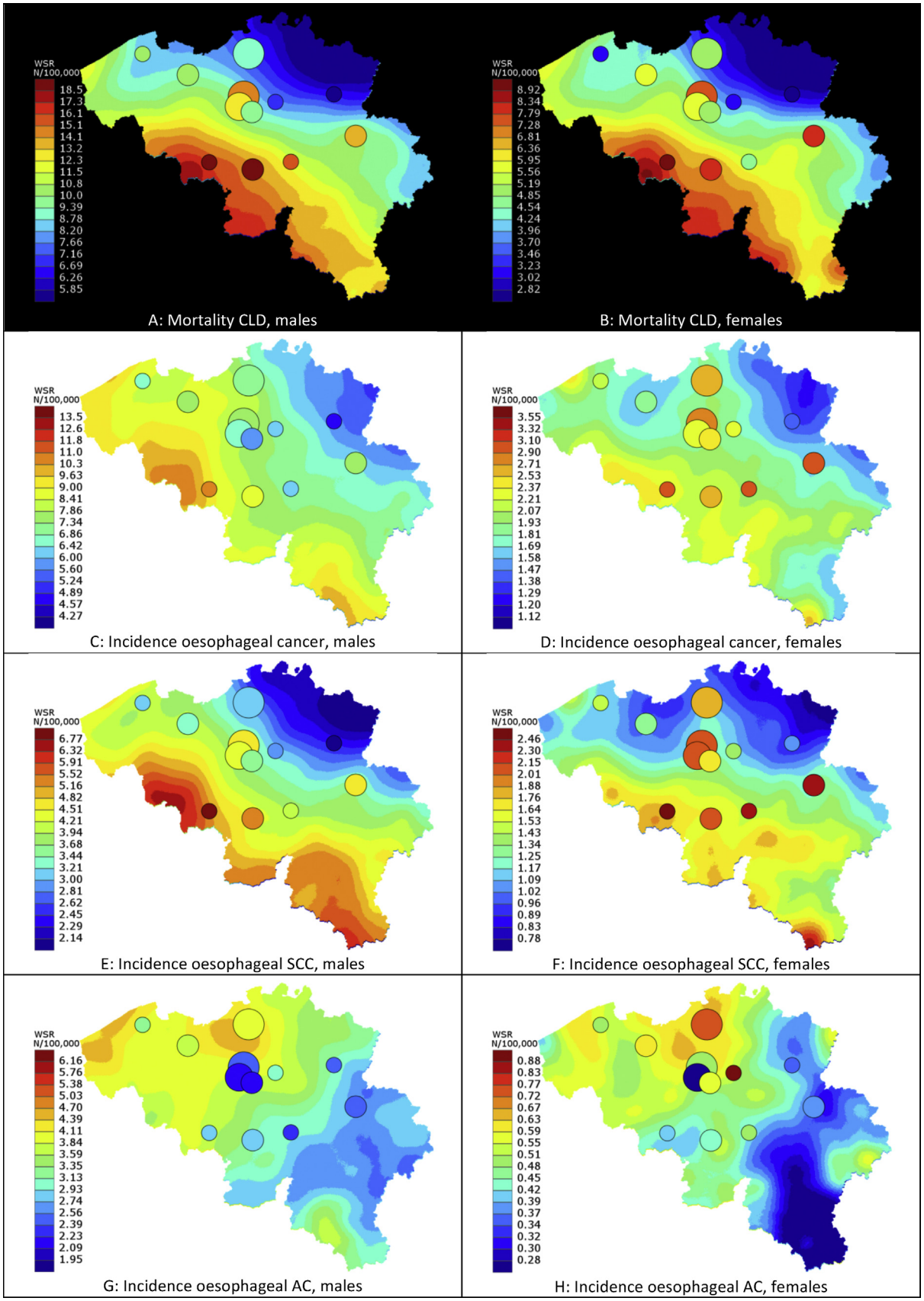

Fig. 5. Age adjusted (WSR) mortality (2004–2009) of chronic liver diseases (CLD); and age adjusted (WSR) incidence (2004–2010) of oesophageal cancer, oesophageal squamous cell carcinoma (SCC) and oesophageal adenocarcinoma (AC), by sex.

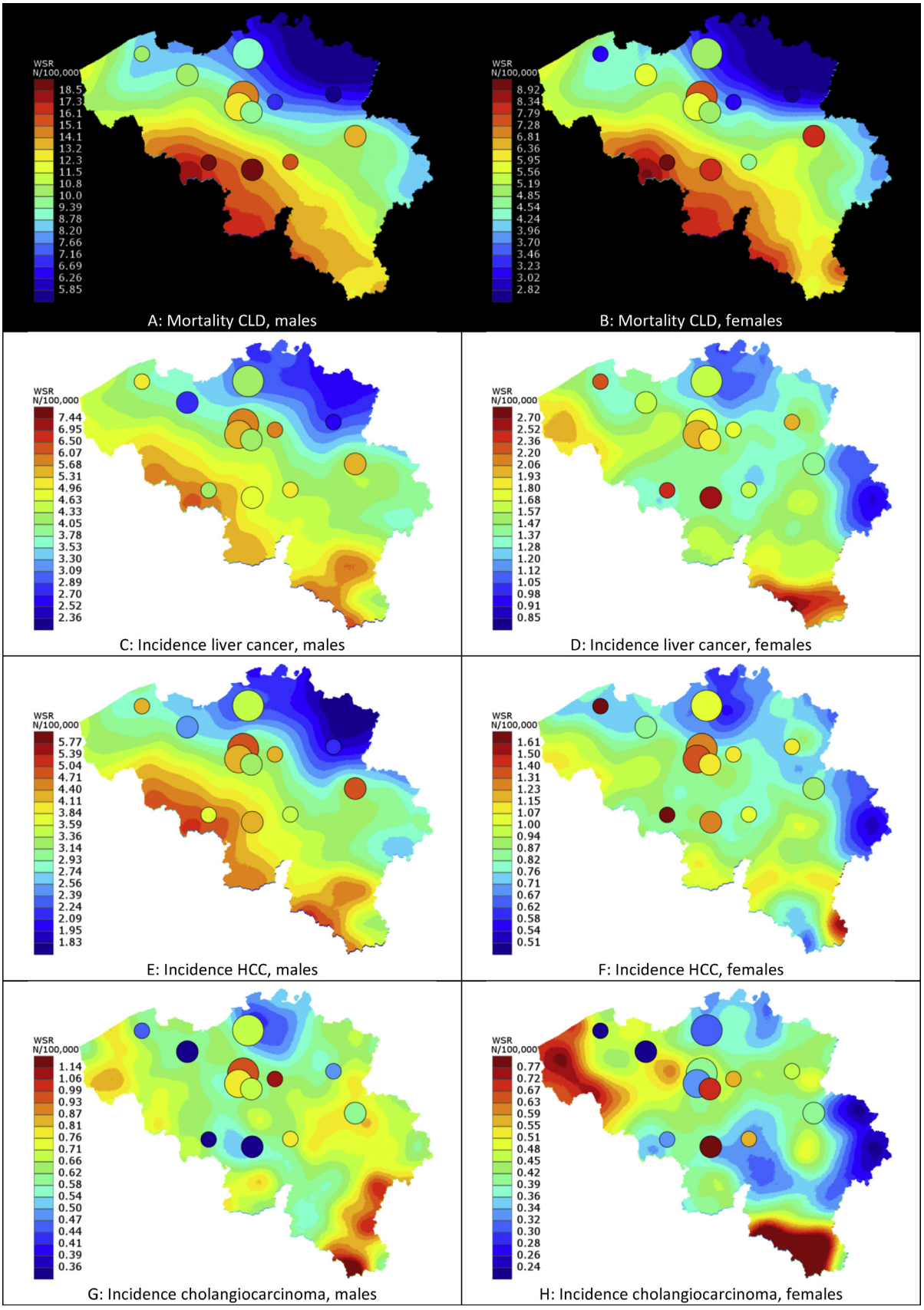

Fig. 6. Age adjusted (WSR) mortality (2004–2009) of chronic liver diseases (CLD); and age adjusted (WSR) incidence (2004–2010) of liver cancer, hepatocellular carcinoma (HCC) and cholangiocarcinoma, by sex.

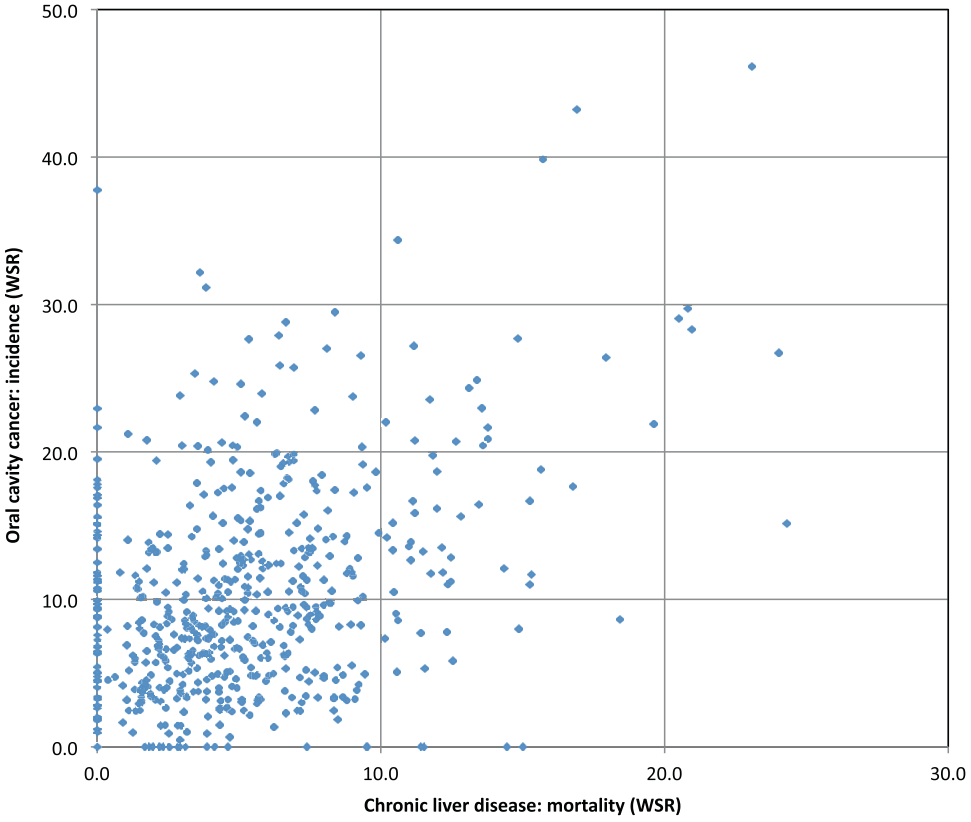

Fig. 7. Scatter plot of WSR incidence for oral cavity cancers versus chronic liver disease WSR mortality, each data point represents one municipality.

mortality of CLD and COPD indicate similar associations that were visually observed from Figs. 2–6. The multiplicative increase in the average cancer incidence rate is more than 30% per increase of 10/100,000 in the municipality specific crude mortality rate of CLD for cancers of the oral cavity and pharynx in both sexes, and for SCC of the oesophagus and HCC in males (Table 2). There was a

Table 2
Parameter estimates for the Poisson regression models for the crude cancer incidence rates versus the crude mortality rates of chronic liver diseases (CLD) and chronic obstructive pulmonary disease (COPD). Estimates on the intercept are not shown. The parameter estimates are expressed as the expected multiplicative change in mean crude rate (per 100,000) for an increase in the proxy crude rate of 10/100,000.

Tumour type	Males				Females			
	CLD		COPD		CLD		COPD	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Lung			1.05****	[1.04,1.06]			1.11****	[1.08, 1.14]
SCC/SCLC			1.05****	[1.03,1.06]			1.14****	[1.09, 1.18]
AC			1.05****	[1.03,1.07]			1.13****	[1.09, 1.17]
Oral cavity	1.33****	[1.26,1.41]	1.02	[0.99, 1.05]	1.33****	[1.19, 1.48]	1.07*	[1.00, 1.13]
Pharynx	1.35****	[1.29, 1.42]	1.05***	[1.02, 1.08]	1.34****	[1.19, 1.50]	1.09*	[1.02, 1.16]
Larynx	1.14****	[1.09, 1.19]	1.04***	[1.02, 1.07]	–[a]		–[a]	
Supraglottis	1.13**	[1.04, 1.24]	1.05*	[1.00, 1.10]	–[a]		–[a]	
Glottis	1.04	[0.98, 1.10]	1.05***	[1.02, 1.09]	–[a]		–[a]	
Oesophagus	1.16****	[1.10, 1.21]	1.02	[0.99, 1.05]	1.25****	[1.13, 1.37]	1.11***	[1.05,1.17]
SCC	1.36****	[1.28, 1.44]	1.03	[0.99, 1.06]	–[a]		–[a]	
AC	0.98	[0.92, 1.05]	1.00	[0.96, 1.04]	–[a]		–[a]	
Liver	1.30****	[1.22, 1.37]	1.01	[0.98, 1.04]	1.15*	[1.02, 1.31]	1.06	[0.99,1.14]
HCC	1.38****	[1.29, 1.47]	1.01	[0.97, 1.04]	–[a]		–[a]	
Cholangio	–[a]		–[a]		–[a]		–[a]	

SCC: squamous cell carcinoma.
SCLC: small cell lung cancer.
AC: adenocarcinoma.
HCC: hepatocellular carcinoma.
[a] Model assumptions were not fulfilled.
**** $p < .0001$
*** $p < .001$
** $p < .01$
* $p < .05$

significant higher incidence rate of all studied cancer types with higher COPD mortality rates except for liver cancer. However, these associations were not always consistent between the sexes.

4. Discussion

In this article, a geographical overview is presented of the incidence rates in Belgium for cancers of the oral cavity, pharynx, larynx, lung, oesophagus and liver; which all have a well-known relation with alcohol and/or tobacco [18–22]. The data available at the BCR enabled the creation of small-area based incidence maps by histology for oesophageal, liver and lung cancer and by sub-localisation for laryngeal cancer.

The National Health Surveys, based on small number of participants [5] suggest that provinces in the southwest of Belgium have a higher percentage of daily drinkers than the provinces in the northeast. The proxy variables we used on the drinking and smoking habits in Belgium demonstrate essentially the same pattern. Because the high correlation between CLD and alcohol is well documented, we believe that the mortality rate for CLD in a population group is a reasonably good proxy for the prevalence of alcohol use.

We used the geographic distribution on COPD as the proxy for tobacco smoking. Lung cancer, where the causal relationship with tobacco was already established during the 1950s [23] and the attributable fraction for smoking is higher than 80%, would be another good proxy for smoking, and indeed the geographical patterns for various histological types of lung cancer and COPD mortality were similar. The Poisson regression models revealed that increases in male and female COPD mortality rates were significantly associated with increasing incidence rates of lung cancer. The visual similarity was least obvious for the incidence of lung adenocarcinoma in men, which is in line with observations that the association with tobacco is weaker for adenocarcinoma than for the other histological types of lung cancer [23].

A strong visual similarity is observed between the maps for cancers of the oral cavity and pharynx and the map for CLD. This result is consistent with the known relation with alcohol for these cancers [19,22]. The observed spatial patterns in Belgium, with high rates close to the French border and much lower rates close to the Dutch border, correspond well with the mortality maps for these tumours published in the Atlas of Cancer Mortality in the European Union [24], showing high mortality rates for cancers of the oral cavity and pharynx in the north of France and markedly lower rates in the Netherlands. The regression models suggest that smoking also has a significant association on ecological level with these cancers but not necessarily as strong as that for the drinking proxy.

The subsites of the larynx, glottis and supraglottis, show different associations with different etiological factors. Due to their anatomic location, the glottis is more highly exposed to inhaled agents while the supraglottis is more exposed to ingested agents [22]. The map for cancer of the supraglottis is more comparable with alcohol prevalence, while the spatial pattern for glottic cancer suggests higher analogy with the pattern of smoking.

Consumption of alcoholic beverages is known to be associated with the risk for SCC of the oesophagus and only to a lesser degree with the risk for oesophageal AC [22]. Our results indicate a rather strong association between alcohol proxy and SCC but no association at all with AC. The association between our proxy for smoking and SCC was weak and for AC not existing. Hence, other risk factors are involved in causation of oesophageal AC. Multiple risk factors are suggested in the development of oesophageal AC, including Barrett's oesophagus, acid peptic disorders and obesity [25–28]. Unfortunately, information on the prevalence of these factors in different regions for Belgium is not available.

The causal relation between the occurrence of malignant tumours of the liver and consumption of alcoholic beverages was some decades ago considered well-known [21] but more recent findings of this issue are more controversial, suggesting more complex associations, e.g., possible interaction with hepatitis B and C. The liver can apparently handle alcohol in modest quantities but not heavy intake [29]. This may be an explanation for our results indicating a strong link between alcohol use and HCC in men but not in women. Although alcohol is considered as a potential risk factor for cholangiocarcinoma [30], no relation was observed with the mortality rates for CLD.

5. Conclusion

Cancer incidence maps are an effective tool to visualise and explore geographical differences and to seek for etiological differences of, e.g., subtypes of a cancer. In oesophageal and laryngeal cancer, two subtypes revealed different spatial patterns and apparently with different causalities. This Belgian study is an encouraging example of an approach how cancer registry data can be used in the exploration of cancer aetiology and factors behind regional cancer burden in circumstances where no long historical time series of cancer data are available.

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The Sources of funding had no role in the study design, in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

Conflict of interest

The authors declare that there is no conflict of interest associated with this manuscript.

Authorship contribution

Study concepts: Henau K., Van Eycken, E., Pukkala, E.; Study design: Henau K., Van Eycken, E., Pukkala, E.; Data acquisition: Henau K.; Quality control of data and algorithms: Henau K.; Data analysis and interpretation: Henau K., Van Eycken, E., Pukkala, E.; Statistical analysis: Silversmit, G.; Manuscript preparation: Henau K., Van Eycken, E., Pukkala, E.; Manuscript editing: Henau K., Van Eycken, E., Pukkala, E.; Manuscript review: Henau K., Van Eycken, E., Silversmit, G., Pukkala, E.

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