Cancer Letters 521 (2021) 238–251

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Worldwide distribution, associated factors, and trends of gallbladder cancer: A global country-level analysis

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ARTICLE INFO

Keywords:
Cholecyst
Malignancy
Incidence
Mortality
Temporal pattern
Risk factors

ABSTRACT

This study aimed to evaluate the global distribution, associated factors, and epidemiologic trends of gallbladder cancer (GBC) by country, sex, and age groups. The *Global Cancer Observatory* was interrogated for the disease burden of GBC using age-standardized rates (ASR). The prevalence of different potential risk factors for each country was extracted from *Global Health Observatory* and their associations with GBC incidence and mortality were examined by linear regression analysis using beta coefficients (β). The *Cancer Incidence in Five Continents I-XI* and the *WHO Mortality database* were searched and Average Annual Percent Change (AAPC) was generated from joinpoint regression analysis. The incidence (ASR = 2.3) and mortality (ASR = 1.7) of GBC varied globally in 2018 and were higher in more developed countries and among females. Countries with higher incidence had higher human development index (β_{male} = 0.37; β_{female} = 0.27), gross domestic products (β_{male} = 0.13) and higher prevalence of current smoking (β_{female} = 0.05), overweight (β_{male} = 0.02), obesity (β_{male} = 0.03), and hypercholesterolaemia (β_{male} = 0.07). Similar patterns of associations were also observed for mortality with an additional association found for diabetes (β_{female} = 0.07). Although there was an overall decreasing trend in mortality, an increasing trend in incidence was observed among some populations, particularly in males (AAPCs, 8.97 to 1.92) and in younger individuals aged <50 years (AAPCs, 12.02 to 5.66). The incidence of GBC varied between countries and was related to differences in the prevalence of potential risk factors. There was an increasing incidence trend among males and younger individuals. More intensive lifestyle modifications and disease surveillance are recommended for these populations.

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https://doi.org/10.1016/j.canlet.2021.09.004
Received 21 July 2021; Received in revised form 31 August 2021; Accepted 5 September 2021
Available online 8 September 2021

Summary.

What is already known about this subject?

- Gallbladder cancer (GBC) has poor prognosis and often incurable when diagnosed.
- Modification of lifestyle habits in the general population and in individuals at high risk has been suggested as a promising approach in preventing GBC-related morbidity and mortality.
- Information is lacking on up-to-date global distribution, associated risk factors, and incidence/mortality trend of GBC.

What are the new findings?

- High variation in the GBC incidence and mortality was noted in 2018, with a higher burden found in more developed countries and among females.
- Countries with higher GBC burden had a higher prevalence of smoking, overweight/obesity, diabetes, and hypercholesterolaemia; furthermore, the associations differed by sex.
- There was an increasing incidence trend in some populations, especially among males and younger individuals, but there was an overall decreasing trend of mortality.

How might it impact clinical practice in the foreseeable future?

- A further increase in the incidence of GBC is expected, especially in males and younger individuals aged <50 years.
- Preventive measures such as control of cigarette smoking, overweight/obesity, diabetes, and hypercholesterolaemia are required, particularly for the at-risk groups identified in this study.
- A more comprehensive surveillance of GBC is needed to monitor its trend of morbidity and mortality in various populations.
- More studies are needed to investigate the reasons underlying these epidemiologic trends to provide further insights into its aetiology and prognosis.

1. Introduction

Gallbladder cancer (GBC) is often incurable at diagnosis and is associated with a huge burden of morbidity and mortality. It accounts for about 1.7% of all cancer mortality and approximately 3.5 million disability-adjusted life years globally [1,2]. GBC is rarely detected at an early stage due to lack of screening and lack of clinical signs from an early stage tumour. Almost 4 in 5 patients with GBC are diagnosed at advanced or metastasized stage [3], making GBC one of the cancers with extremely poor prognosis. For example, the 5-year relative survival rate of patients with GBC is only around 19% [4]. Alongside early detection, a better understanding of the aetiology and risk factors of GBC is essential to reduce its burden.

Gallstones may play an important role in the aetiology of GBC and are associated with a substantially increased risk of GBC incidence and mortality [5,6]. GBC is also related to other diseases of the gallbladder, abnormalities of the bile ducts, and exposure to some toxins and certain chemicals [7]. A number of risk factors for GBC such as age, sex, ethnicity, geography and family history are non-modifiable; however, several potential risk factors including tobacco use, unhealthy diet, obesity, and diabetes are preventable [8].

Nevertheless, evidence on how these factors are associated with GBC-related incidence and mortality remains limited [9]. Owing to a high variation in the disease burden of GBC across different countries [10,11], it is imperative to evaluate its worldwide distribution and associated modifiable factors. This would be useful for providing empirical evidence for the development of risk-adapted public health and clinical guidelines. An examination of the trend of GBC over the past years could provide evidence of how its incidence and mortality have fared by variations in lifestyle and/or improvement in its treatments. Furthermore, assessment of temporal trends of GBC among the younger population is particularly important, as early-onset cancer is well known to be associated with a greater loss of years of life and productivity.

Previous epidemiological studies on GBC were limited to certain regions (i.e. India [12] and Central and South America) [13], or evaluated temporal trends using relatively old data [14,15]. Furthermore, none of these studies examined the role of potential risk factors such as alcohol consumption, current smoking, physical activity, overweight/-obesity, diabetes, hypertension and hypercholesterolaemia at the population level, as well as the global temporal trends among younger populations. This study aimed to evaluate the global distribution, associated factors, and epidemiologic trends of GBC by country, sex, and age groups.

2. Methods

2.1. Source of data

We extracted data from The *Global Cancer Observatory* (*GLOBOCAN*) for the incidence and mortality estimates on GBC in 2018 for 178 countries [16]. The methods used to compile the estimates in *GLOBOCAN* were based on predictions, modelling of incidence-to-mortality ratios, and approximation from neighboring countries at the same period by the International Agency for Research for Research on Cancer (IARC), WHO [17]. The human development index (HDI) in 2018 for each country was retrieved from the United Nations. The HDI is a composite index calculated from: the ability to lead a long and healthy life, measured by life expectancy at birth; the ability to acquire knowledge, measured by mean years of schooling and expected years of schooling; and the ability to achieve a decent standard of living, measured by gross national income per capita. HDI of <0.550, 0.550–0.699, 0.700–0.799, and ≥0.800 were considered as Low, Medium, High, and Very High HDI, respectively [18]. Data on gross domestic products (GDP) per capita in 2018 were extracted from the *World Bank*.

The information on risk factors (2008–2016) for each country was collected from the *Global Health Observatory* (*GHO*) [19]. The *GHO* database estimated from government birth and death registration, health systems, surveys and censuses, and research projects collected by the Member States of WHO [20]. These included the total amount of alcohol consumption (litres) and prevalence (percent) of current smoking, physical inactivity, overweight/obesity, diabetes, hypertension, and hypercholesterolaemia (eTable 1). Alcohol consumption was measured by the total amount of alcohol consumed per capita over a calendar year. Current smoking referred to the current use of smoked tobacco products. Physical inactivity was defined as having ≤150 min of moderate-intensity physical activity per week, or ≤75 min of vigorous-intensity physical activity per week. Overweight and obesity referred to a body mass index (BMI) of ≥25 kg/m^2 and ≥30 kg/m^2, respectively. Diabetes was defined based on fasting blood glucose of ≥7.0 mmol/L or use of any anti-diabetic medications. Hypertension referred to a systolic blood pressure of ≥140 mmHg, diastolic blood pressure of ≥90 mmHg, or use of any anti-hypertensive drugs. Hypercholesterolaemia referred to a total cholesterol of ≥6.2 mmol/L.

For the trend analysis of incidence and mortality, all yearly data available from global or national registries were extracted up to 2017 for 48 countries (eTable 2). To obtain the data on incidence, country/region-specific cancer registries were retrieved from the volumes I-XI of *Cancer Incidence in Five Continents* (*CI5*) [21]. The *WHO mortality* database was searched to retrieve mortality data for each country [22]. To obtain the most updated incidence and mortality data of Northern European countries and the United States, the *Nordic Cancer Registries (NORDCAN)* [23,24] and the *Surveillance, Epidemiology, and End Results*

(SEER) were retrieved [25]. These databases were chosen for they have been externally, extensively, and globally validated in studies investigating the trends of incidence and mortality for cancers. In our analysis, GBC included International Classification of Diseases 10th revision (ICD-10) C23-24. We defined younger population as individuals aged <50 years. To allow meaningful comparison of rates between different populations in various countries from different databases, age-standardization was used to adjust a country's incidence, mortality, and prevalence rate of different risk factors using the same standard population. All estimates were presented as age-standardized rates (ASRs) using the Segi–Doll world population as a reference. [26].

2.2. Statistical analysis

To illustrate the worldwide distribution of GBC, choropleth maps were constructed for the estimation of the overall and gender-specific incidence and mortality of GBC in 2018 for individual countries. Associations between HDI, GDP per capita, and potential risk factors (i.e., prevalence of current smoking, overweight/obesity, diabetes) and GBC incidence and mortality for each country were examined by univariable linear regression analysis for males and females separately. Beta coefficients (β) and the corresponding 95% confidence intervals (CI) were generated from the regression. The β is the degree of change in the outcome variable for every one-unit of change in the predictor variable [27,28]. In the current analysis, the β estimates measure the degree of change in the outcome variable (ASR of incidence or mortality) per unit increase in a predictor variable (risk factor). The most recent 10-year epidemiologic trend in incidence and mortality in different countries were estimated by Average Annual Percent Change (AAPC) and its 95% CIs generated from joinpoint regression analysis [29]. As the joinpoint regression could not be performed when there is a "missing" or "zero" value in any year, countries with such values were excluded for the trend analysis. Additional trend analysis by sex and age groups (≥50 and < 50 years) were conducted for each country. We used 50 years old as the cut-off for analysis as the previous literature defined early-onset cancers using this age point, which reflects relatively recent changes in exposure to carcinogenic factors [30]. Statistical significance was considered if p-value <0.05, and all CIs were presented at 95% level. All statistical analyses and construction of figures were conducted using Stata 14.1 (StataCorp, College Station, Texas).

3. Results

3.1. Incidence of GBC in 2018

Globally, a total of 291,420 new cases of GBC were recorded in 2018 (eTable 3) [16]. The ASR of incidence was 2.3 per 100,000 persons and ranged from 14.0 (Bolivia) to 0.03 (Guinea) for individual countries (Fig. 1). The highest ASR was found in Eastern Asia (3.0), South American (2.8), and Melanesia (2.7), whilst the lowest rates were observed in Middle Africa (0.35), West Africa (0.37), and Eastern Africa (0.74). This represents approximately nine-fold variation across different regions. The overall incidence rates were slightly higher in females (2.4) than in males (2.2). Incidence (ASR) was higher in countries with Very High (2.5), High (2.4), and Medium (2.0) HDI as compared to those with Low (0.55) HDI.

3.2. Mortality of GBC in 2018

Globally, a total of 165,087 GBC-related deaths were reported in 2018 (eTable 3). The ASR of mortality was 1.7 per 100,000 persons and ranged between 10.6 (Bolivia) and 0.01 (Guinea) for individual countries (Fig. 2). The highest mortality rates (ASR) were observed in Eastern Asia (2.4), Melanesia (2.3), and South America (2.0), whilst the lowest rates were found in West Africa (0.28) and Middle Africa (0.29). There was about an eight-fold variation across different regions. Similar to incidence, the overall mortality rates were slightly higher in females (1.8) than in males (1.6). Mortality (ASR) was higher in countries with High (1.9), Very High (1.5), and Medium (1.5) HDI as compared to those with Low (0.45) HDI.

3.3. Associations between HDI, GDP, risk factors, and GBC incidence/mortality by sex

Among males, higher ASR of incidence of GBC was associated with a higher HDI ($\beta = 0.37$, CI 0.22 to 0.53), GDP ($\beta = 0.13$, CI 0.10 to 0.25), and higher prevalence of overweight ($\beta = 0.02$, CI 0.01 to 0.03), obesity ($\beta = 0.03$, CI 0.002 to 0.07), and hypercholesterolaemia ($\beta = 0.07$, CI 0.03 to 0.11; Fig. 3). However, among females, higher incidence was associated with a higher HDI ($\beta = 0.27$, CI 0.09 to 0.45) and prevalence of current smoking only ($\beta = 0.05$, CI 0.01 to 0.08; Fig. 4). Among males, higher ASR of mortality of GBC was associated with a higher HDI ($\beta =$ 0.19, CI 0.06 to 0.31) and prevalence of hypercholesterolaemia ($\beta =$ 0.03, CI 0.001 to 0.07; Fig. 5). By contrast, higher mortality was associated with a higher prevalence of current smoking ($\beta = 0.03$, CI 0.001 to 0.05) and diabetes ($\beta = 0.07$, CI 0.01 to 0.13; Fig. 6) among females.

3.4. Temporal trends of GBC

The incidence and mortality trends of GBC for each country between 1980 and 2017 are shown in eFig. 1, and the trend regression is presented in eFig. 2 and eTable4. The number of counties fulfilling the criteria for joinpoint regression analysis was 45 and 44 for incidence and mortality, respectively.

3.5. Incidence trend

Among males (Fig. 7), five countries – Bahrain (AAPC, 8.97, CI 2.26 to 16.12), Sweden (AAPC, 4.09, CI 1.52 to 6.73), United Kingdom (AAPC, 3.35, CI 1.35 to 5.37), Bulgaria (AAPC, 2.72, CI 0.69 to 4.79), and the Netherlands (AAPC, 1.92, CI 0.27 to 3.59) – had an increase in incidence. By contrast, three countries consisting of Malta (AAPC, −9.12, CI -16.83 to −0.70), Costa Rica (AAPC, −7.66, CI -14.36 to −0.43), and Czech Republic (AAPC, −2.97, CI -4.50 to −1.42) showed a decreasing trend. The patterns of changes in incidence differed by sex. There were 13 countries showing a decreasing trend among females; Colombia (AAPC, −7.97, CI -13.08 to −2.55), Costa Rica (AAPC, −7.16, CI -10.26 to −3.96), Chile (AAPC, −6.17, CI -9.60 to −2.61), Spain (AAPC, −5.30, CI -6.70 to −3.88), and Brazil (AAPC, −4.88, CI -8.57 to −1.03) were found to have the most drastic decrease. However, four countries including India (AAPC, 6.93, CI 1.00 to 13.20), the United Kingdom (AAPC, 4.07, CI 2.91 to 5.25), Thailand (AAPC, 2.83, CI 0.35 to 5.37), and Canada (AAPC, 1.94, CI 0.83 to 3.07) showed an increasing trend.

3.6. Mortality trend

Among males, eight countries had a decrease in mortality (Fig. 8). Countries with the most substantial decrease included Costa Rica (AAPC, −8.40, CI -12.51 to −4.10), the United States (AAPC, −5.26, CI -10.03 to −0.24), France (AAPC, −3.96, CI -4.89 to −3.02), Chile (AAPC, −3.04, CI -4.41 to −1.66) and Australia (AAPC, −2.45, CI -4.67 to −0.18). However, two countries, Ecuador (AAPC, 2.25, CI 0.53 to 3.99) and Germany (AAPC, 1.23, CI 0.07 to 2.40), showed an increasing trend. Among females, 18 countries had a decrease in mortality. Countries with the most substantial decrease included Costa Rica (AAPC, −7.45, CI -12.06 to −2.59), Chile (AAPC, −5.37, CI -6.48 to −4.24), Czech Republic (AAPC, −4.37, CI -5.32 to −3.42), Croatia (AAPC, −4.14, CI -5.71 to −2.53) and France (AAPC, −4.12, CI -5.02 to −3.21). However, the Netherlands (AAPC, 2.87, CI 0.50 to 5.29) and the United Kingdom (AAPC, 2.63, CI 1.78 to 3.49) showed an increasing trend in mortality.

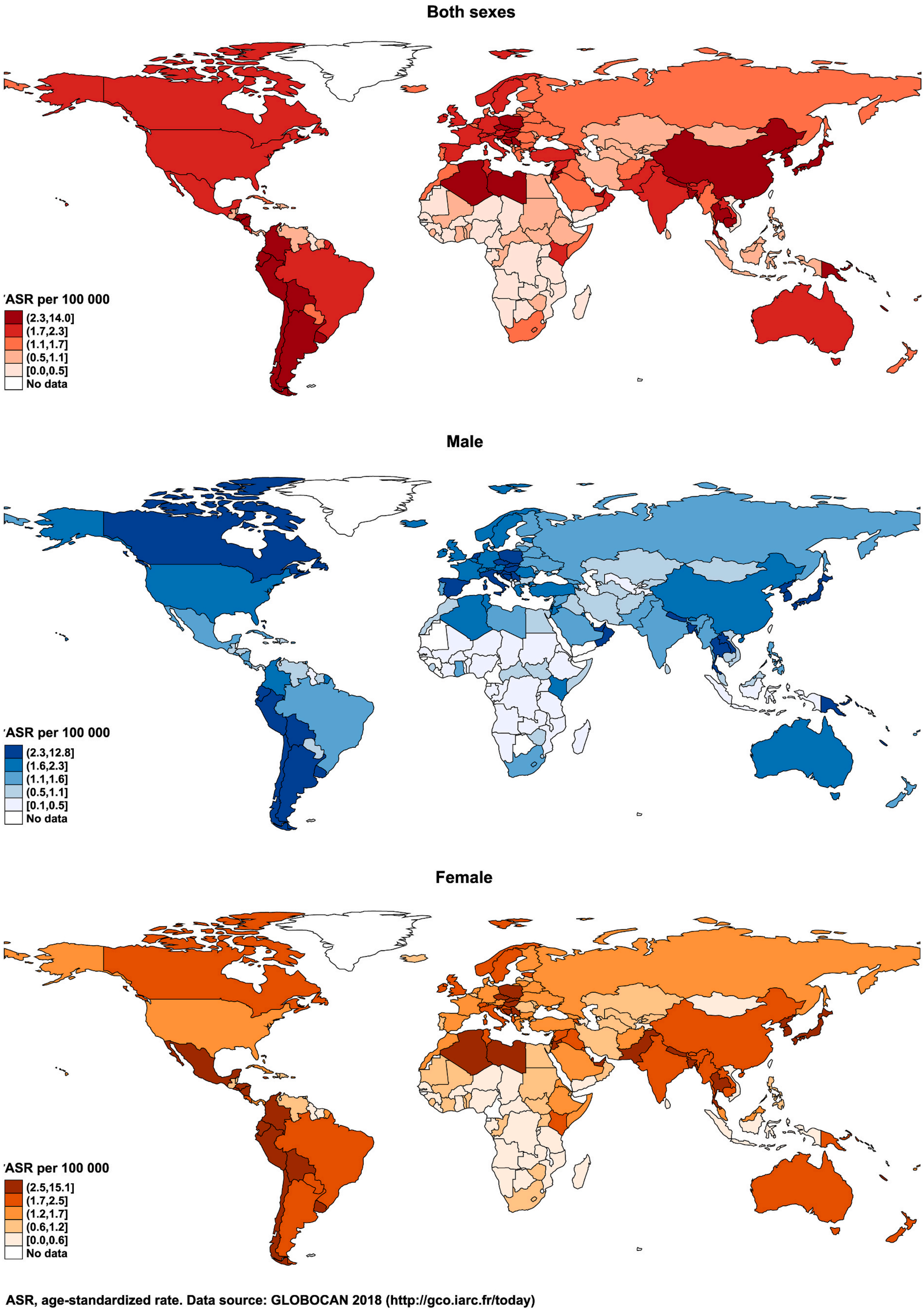

Fig. 1. Global incidence of gallbladder cancer in 2018, both sexes, male, and female.

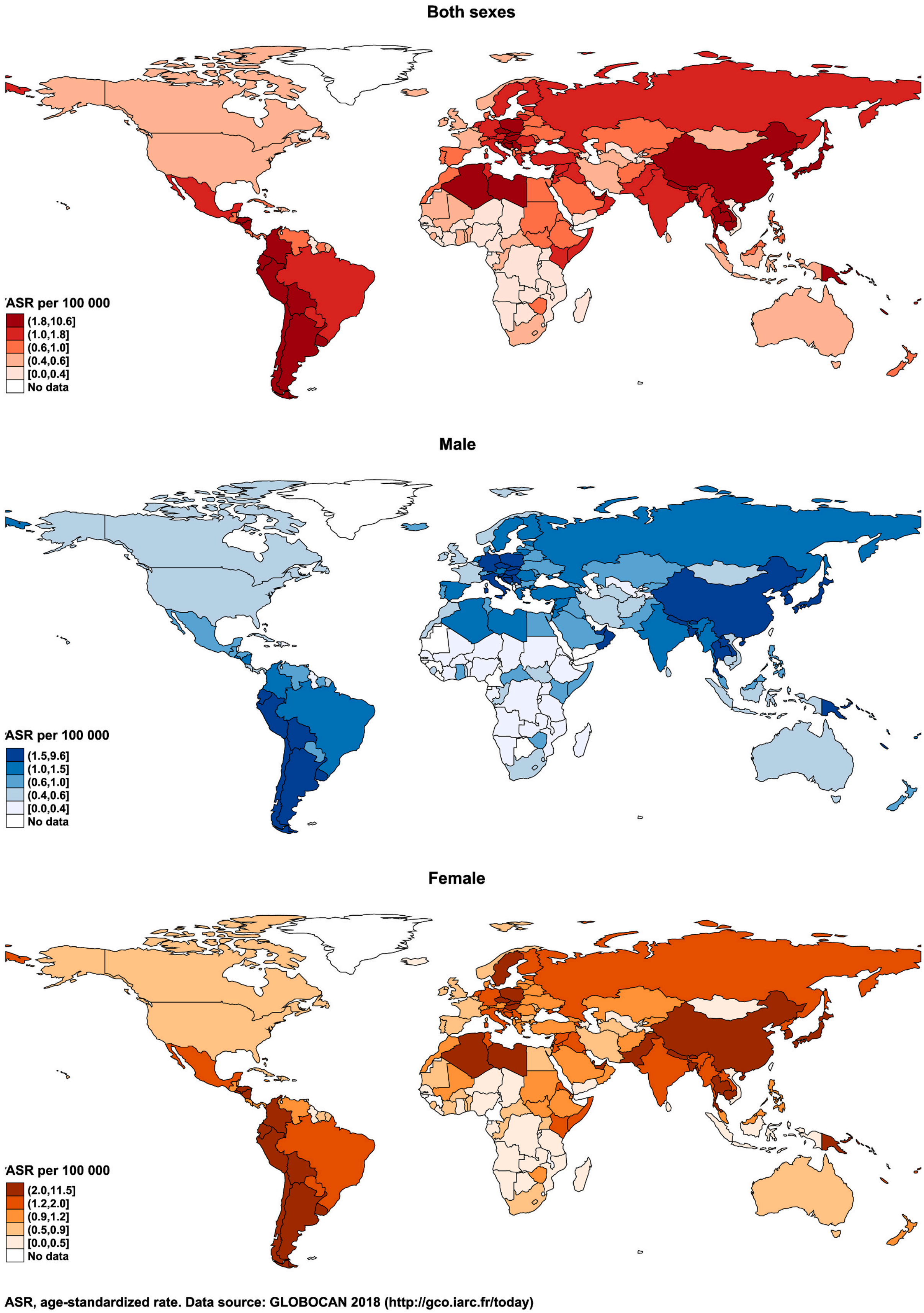

Fig. 2. Global mortality of gallbladder cancer in 2018, both sexes, male, and female.

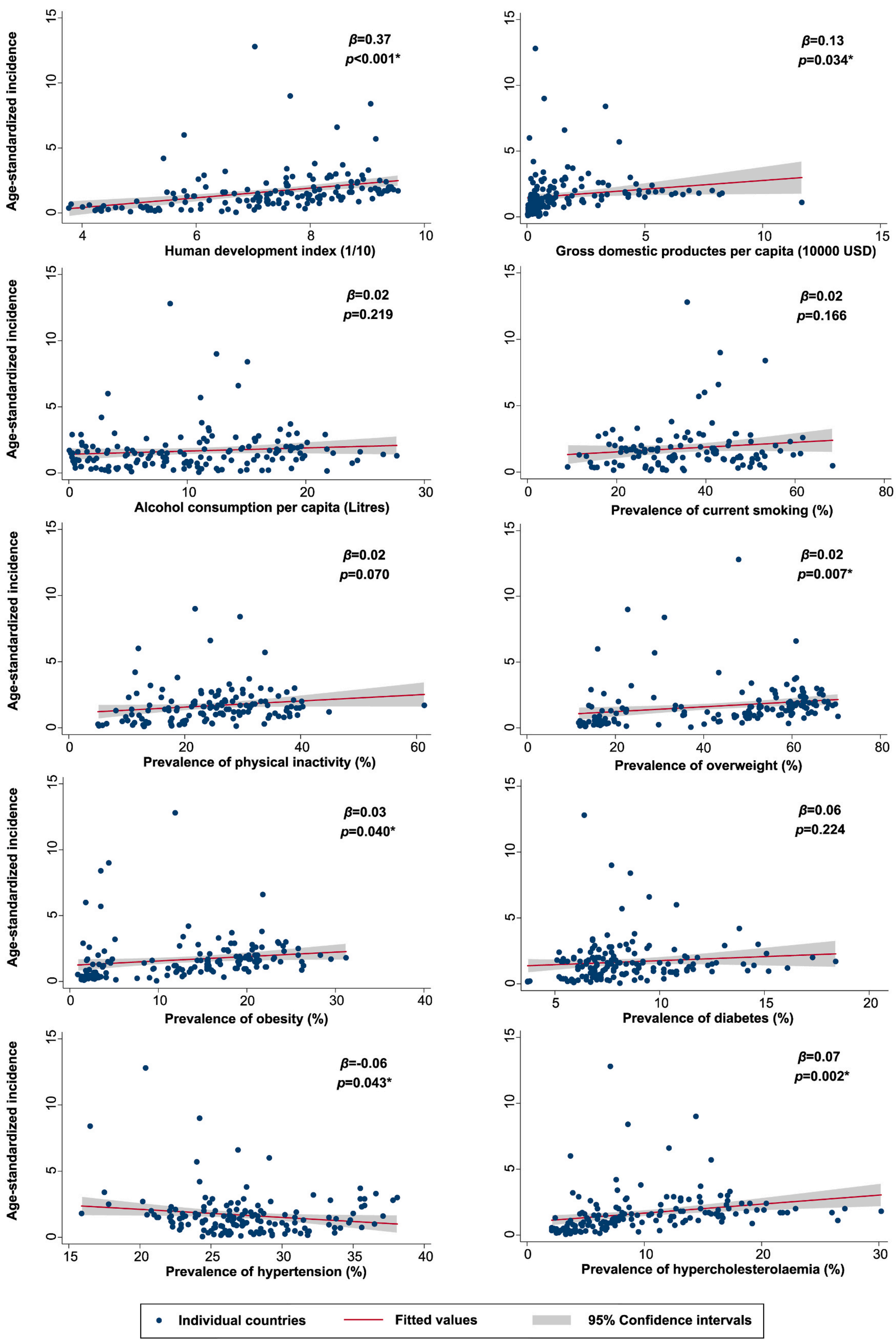

Fig. 3. Associations between risk factors and incidence of gallbladder cancer, male.

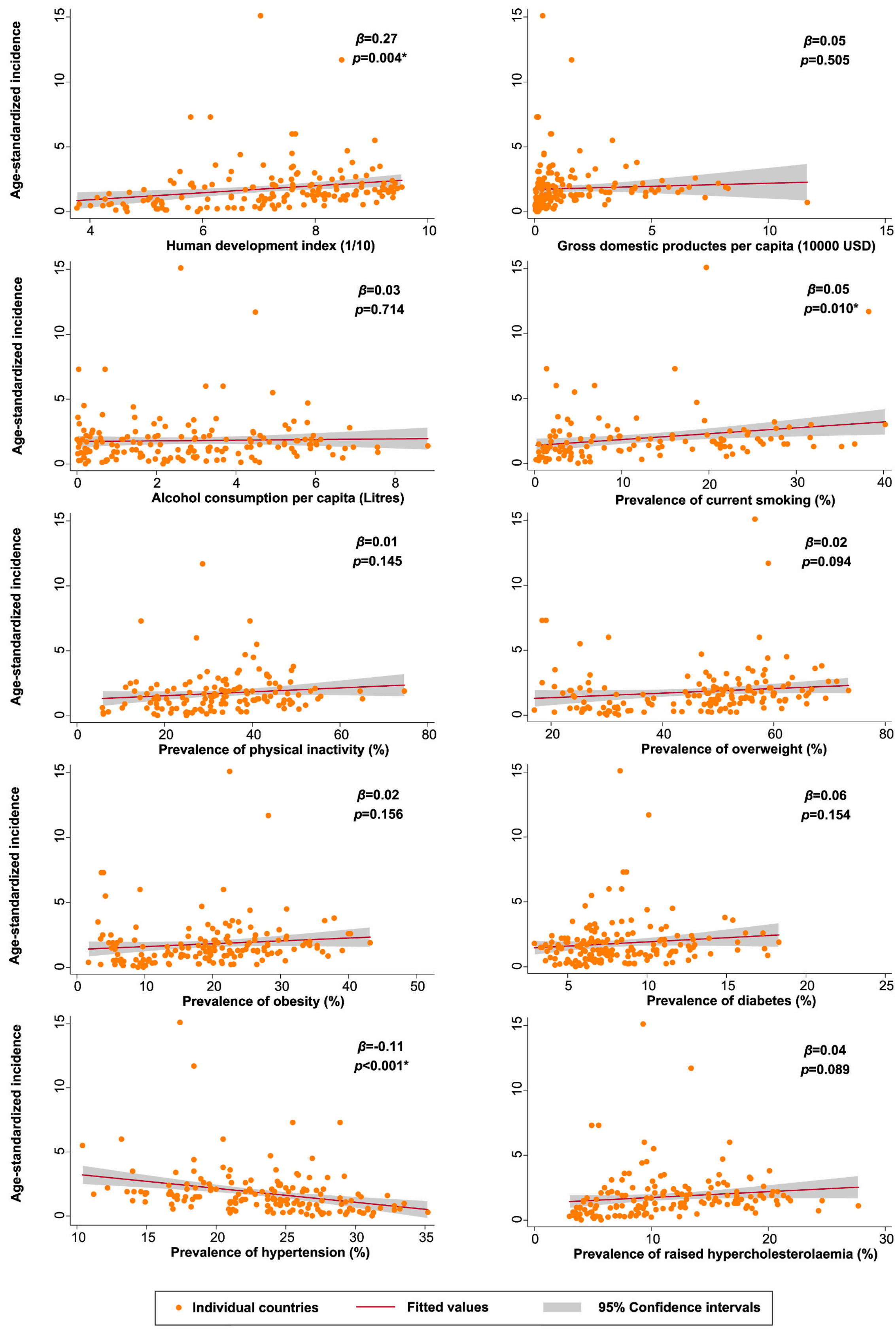

Fig. 4. Associations between risk factors and incidence of gallbladder cancer, female.

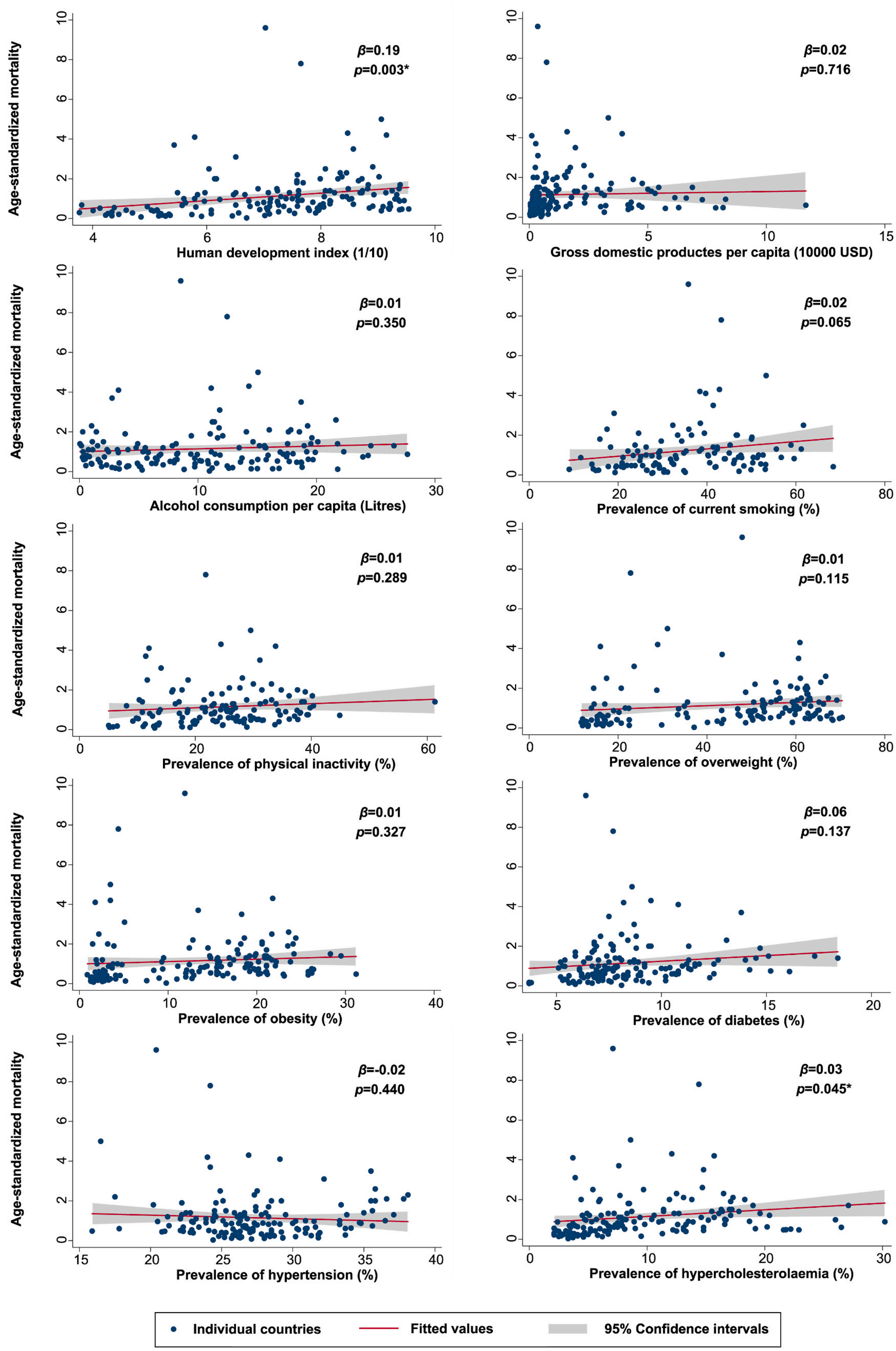

Fig. 5. Associations between risk factors and mortality of gallbladder cancer, male.

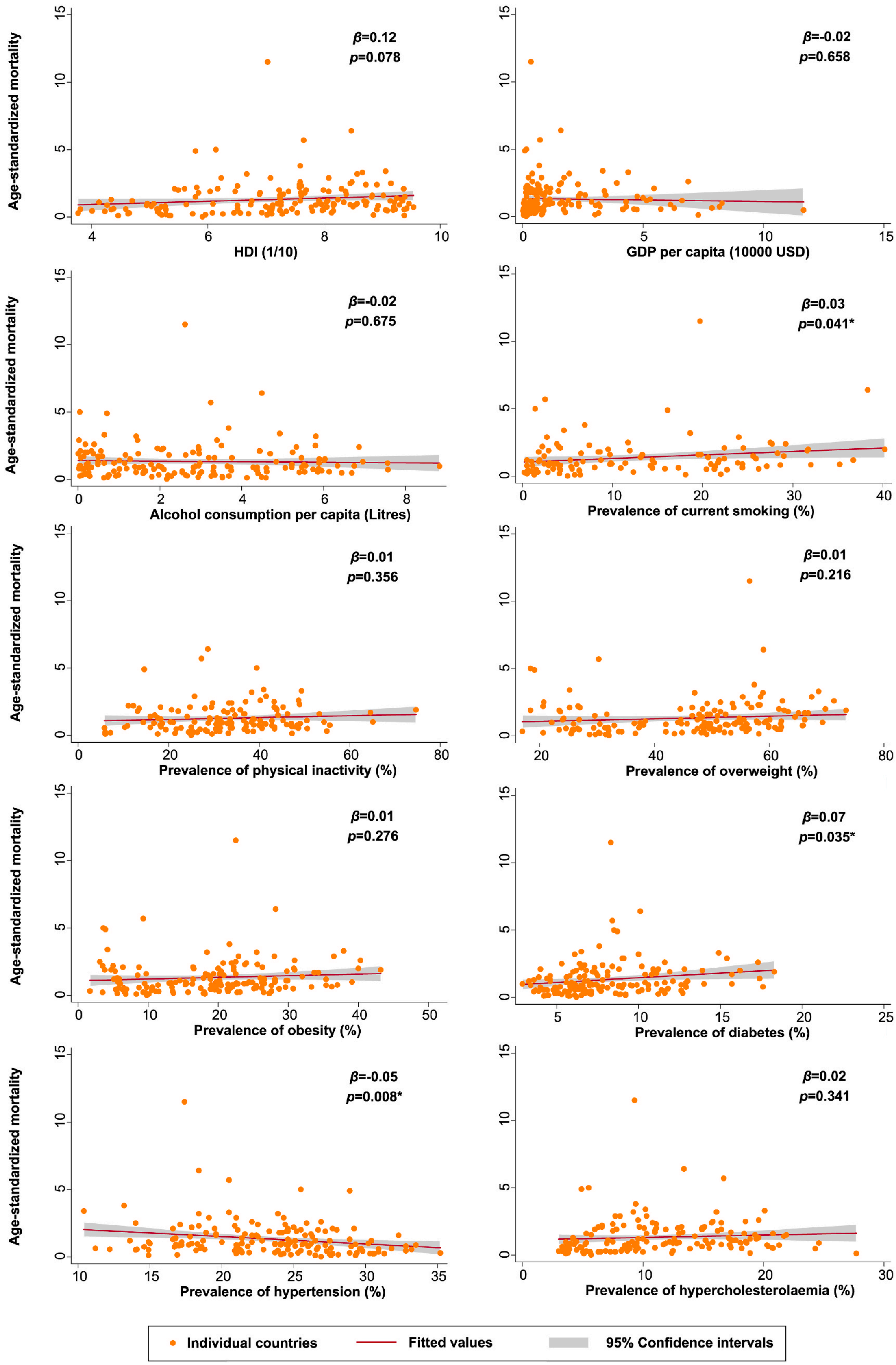

Fig. 6. Associations between risk factors and mortality of gallbladder cancer, female.

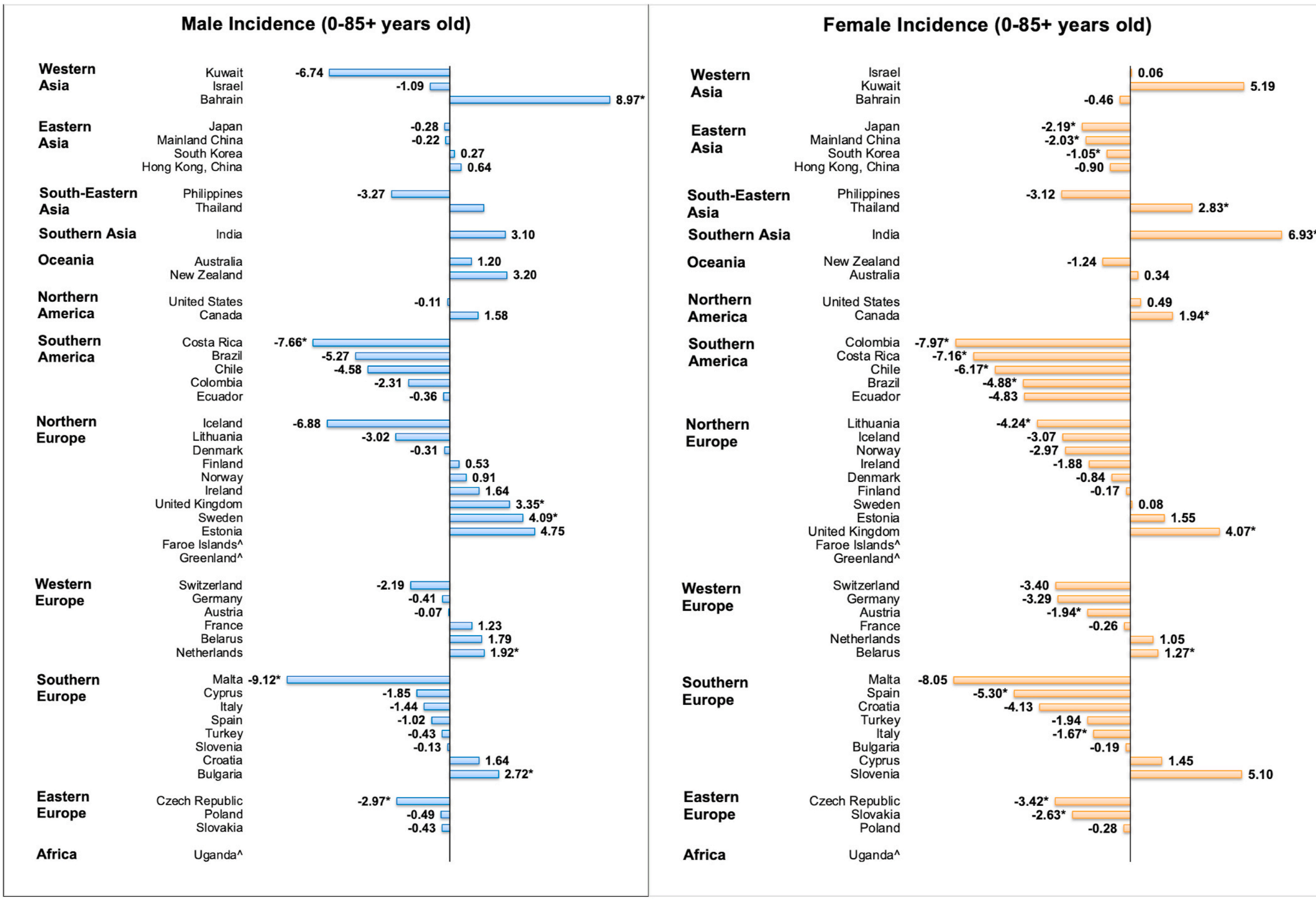

Fig. 7. AAPC of gallbladder cancer incidence in 0–85+ years old, male and female.

Incidence trend among younger (<50 years) vs. older individuals (≥50 years).

Among males aged ≥50 years (Fig. 9), two countries, Malta (AAPC, −8.28, CI -14.92 to −1.11) and Czech Republic (AAPC, −2.78, CI -4.26 to −1.27), had a decrease in incidence. By contrast, Bahrain (AAPC, 10.51, CI 4.32 to 17.07) and the United Kingdom (AAPC, 3.25, CI 1.64 to 4.88) showed an increasing trend. For the analysis among females ≥50 years, 14 countries showed a decreasing trend, with Colombia (AAPC, −8.86, CI -12.67 to −4.88), Costa Rica (AAPC, −7.33, CI (−9.99 to −4.60), Chile (AAPC, −6.61, CI -9.51 to −3.61), Brazil (AAPC, −5.1, CI -10.00 to −1.64), and Spain (AAPC, −5.64, CI -7.03 to −4.23) having the most drastic decrease. However, three countries, including India (AAPC, 8.01, CI 1.16 to 15.33), Slovenia (AAPC, 4.88, CI 1.14 to 8.7), and the United Kingdom (AAPC, 4.12, CI 2.89 to 5.36), showed an increasing trend. Among males aged <50 years, three countries – Norway (AAPC, 12.02, CI 3.36 to 21.40), Bulgaria (AAPC, 11.71, CI 4.22 to 19.74), and Canada (AAPC, 7.90, CI 0.93 to 15.34) – had an increase in incidence, but none of the countries showed a decreasing trend (Fig. 10). For the analysis of females <50 years, two countries reported a decreasing trend – China (AAPC, −8.55, CI 12.84 to −4.05) and Japan (AAPC, −5.41, CI -10.11 to −0.47). However, there was an increasing trend of incidence in Canada (AAPC, 5.66, CI 0.93 to 10.60).

4. Discussion

4.1. Summary of major findings

This analysis provides up-to-date patterns of the worldwide distribution, associated factors, and temporal trends for GBC. Our findings indicate that i) there was a large variation in the incidence and mortality for different regions, with higher burden found in countries with Very High, High, and Medium HDI, and among females; ii) higher disease burden was associated with a higher prevalence of smoking, overweight/obesity, diabetes, and hypercholesterolaemia; and the associations differed by sex; and, iii) there was an increasing trend of incidence in some populations, especially among males and younger individuals, whereas an overall decreasing trend of mortality was observed in almost all the countries.

4.2. Variation in disease burden

We observed a large variation in the burden of GBC across different populations in 2018. The highest incidence and mortality were found in Eastern Asia and South America, which is consistent with previous findings [14,15]. The distribution of potential risk factors for GBC may partially explain its geographical variation. For example, South Americans have a higher susceptibility to gallstone formation [31], which is a well-known risk factor for GBC. The increased risk of GBC in this region may also be due to the higher exposure to aflatoxins because of the high consumption of red chilli peppers [32]. For Eastern Asian, the higher burden of GBC may be related to the higher prevalence of choledochal cysts and anomalous pancreaticobiliary duct junction in this population [33,34].

Our analysis also showed that the incidence and mortality of GBC were higher in regions with higher HDI. There are several possible explanations for this observation. First, this might be related to the higher prevalence of unhealthy lifestyle (i.e., smoking and overweight/obesity), chronic diseases, and ageing population in these countries. Second, the higher incidence of GBC in more affluent countries may also be attributed to better health awareness and high availability and

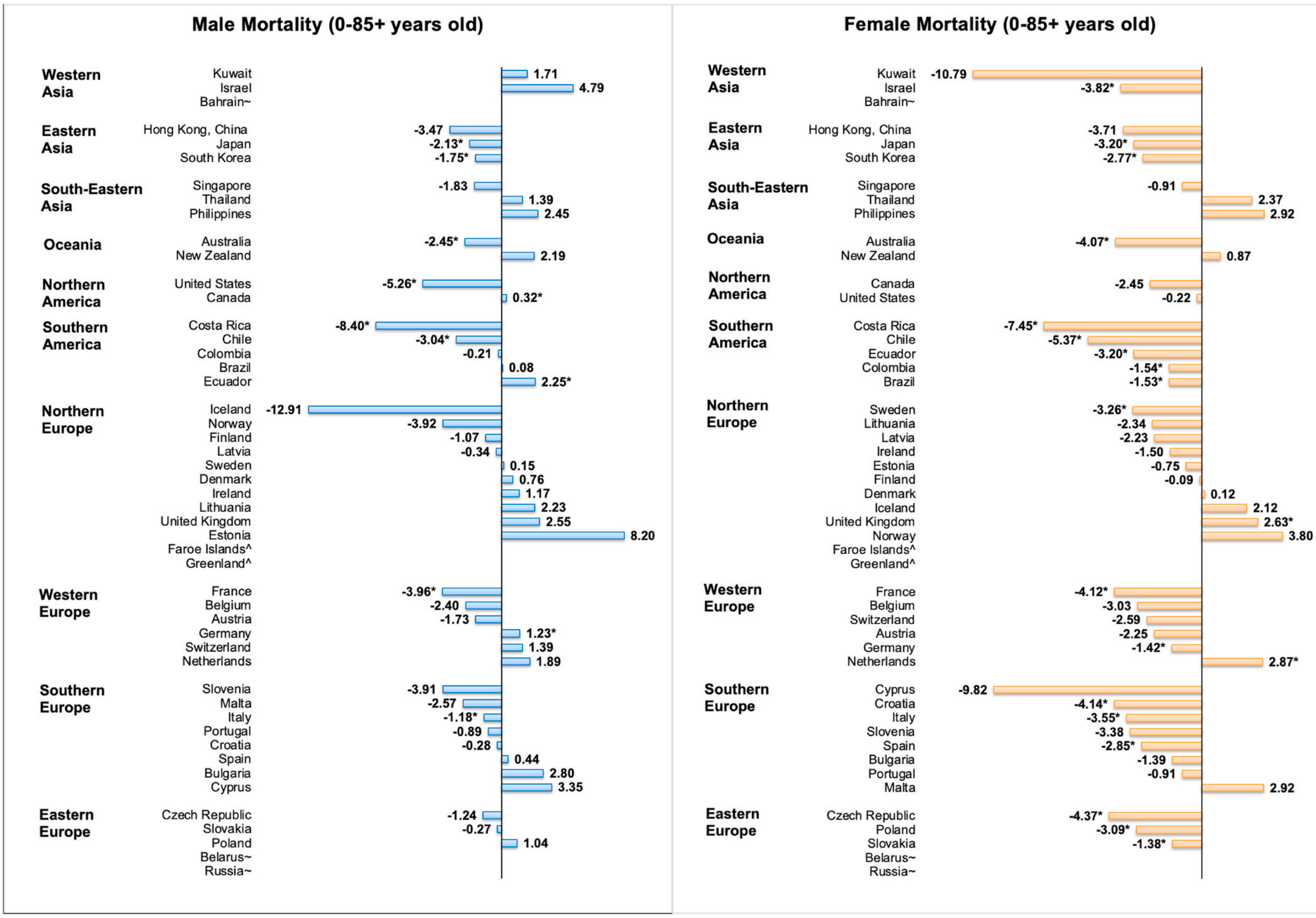

Fig. 8. AAPC of gallbladder cancer mortality in 0–85+ years old, male and female.

utilisation of cholecystectomy [35]. Third, the disproportionately lower burden of GBC in less affluent countries may be due to under-diagnosis and misclassification of GBC-related mortality as mortality from other causes. While males have a higher risk for most types of digestive cancer (e.g. colorectal cancer, liver cancer, gastric cancer, oesophageal cancer, and pancreatic cancer), GBC is more common among females. One possible explanation for this is the association between GBC and hormone-mediated gallstone formation. For example, it has been suggested that oestrogen increases the risk of cholelithiasis, a risk factor for GBC, by elevating the saturation of cholesterol in bile [36]. This pathogenesis is believed to be a major contributor to the higher risk of GBC in women [37].

4.3. Associated lifestyle and metabolic risk factors

This study identified some modifiable risk factors associated with the incidence and mortality of GBC at a country level, including smoking, overweight/obesity, diabetes, and hypercholesterolaemia. In general, the findings are supported by results in previous epidemiological studies investigating the relationship between these risk factors and GBC at an individual level. For instance, a meta-analysis of 11 case-control and cohort studies involving 1178 GBC patients found that smokers had a 45% higher risk of GBC than non-smokers [38]. Overweight and obesity have also been found to be associated with an increased risk of developing GBC, with 15% and 66% elevated risk, respectively [39]. Another meta-analysis of 15 studies with 5902 GBC patients found that the risk of GBC increased by 4% per 1 kg/m^2 increase in BMI [40]. Also, in another meta-analysis of 20 studies, patients with type 2 diabetes mellitus were found to have a 56% higher risk of GBC when compared with those without diabetes [41]. A similar association has also been reported for hypercholesterolemia [42]. The current study also identified variations in the associations between different factors and risk of GBC according to sex. For example, overweight/obesity and hypercholesterolaemia were found to be associated with higher GBC incidence among males, whereas smoking and diabetes were significant factors among females. In addition to the possible influence of genetics and sex hormones, the differential associations observed between females and males may be due to variations in prevalence of potential risk factors. However, we found inverse associations between the prevalence of hypertension and GBC incidence and mortality. This contradicts findings of previous studies wherein no association was detected [43,44]. This might be explained by competing events or confounders that have not been controlled for by the current study design based on population-based, univariable analysis.

4.4. Incidence and mortality trends

The analysis identified an increasing trend of GBC incidence in some populations in the past decade, particularly in males and younger adults. As the incidence of gallstone in females is 2–3 times that of males [45] and the prevalence of tobacco use has been decreasing globally [46], this trend may be driven by other risk factors. These may include a stronger association and more marked increase in the prevalence of obesity and central obesity associated with economic development, urbanisation, and globalisation among males as compared to females. From 1975 to 2016, the prevalence of obesity increased by 3.4 times (3.2%–11.0%) in males compared with 2.3 times (6.4%–15.0%) in females [47]. As for central obesity, a more drastic increase in its prevalence has been found

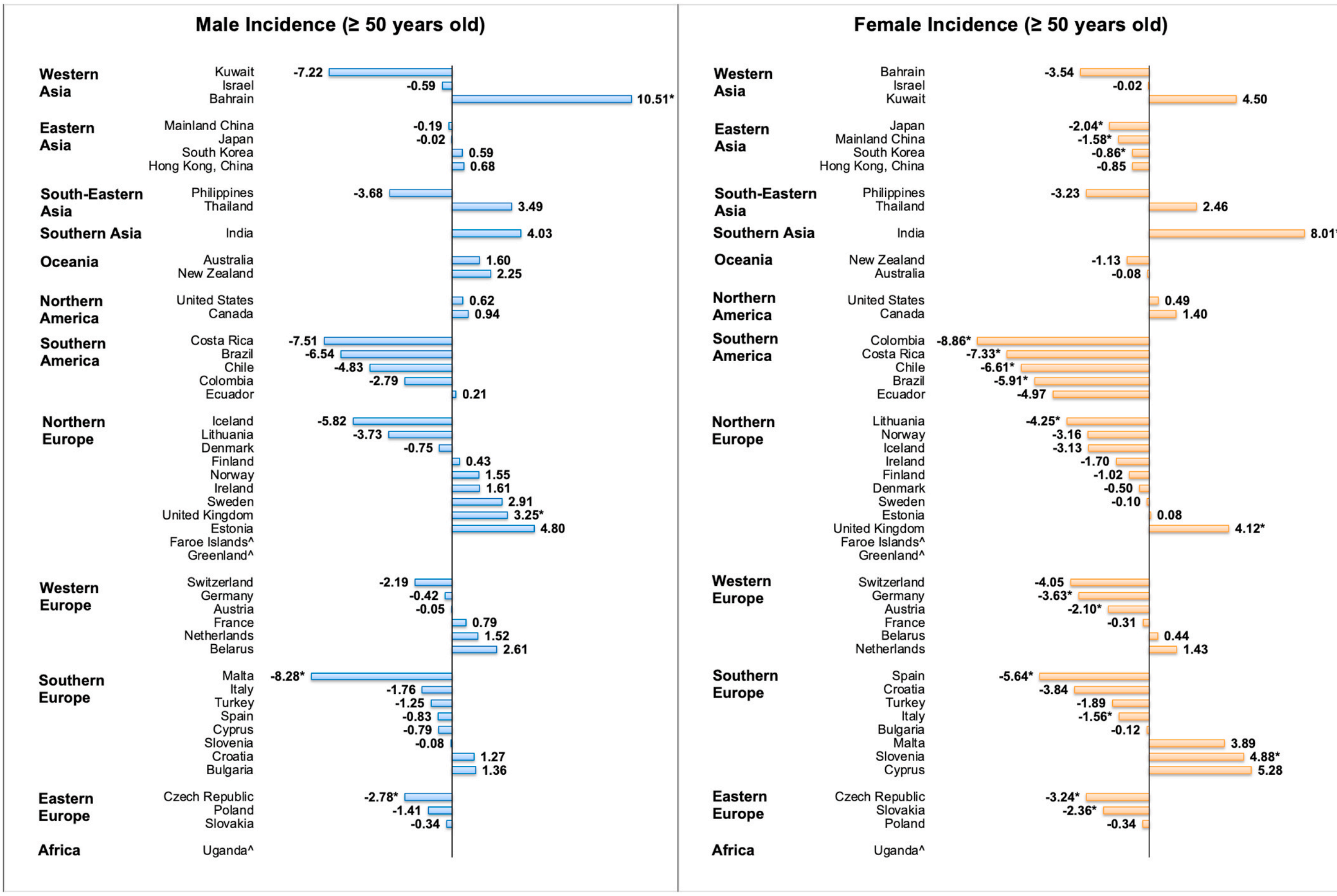

Fig. 9. AAPC of gallbladder cancer incidence in ≥50 years old, male and female.

in males (25.3%–41.6%) compared to females (38.6%–49.7%) from 1985 to 2014 [48]. Similar trends were also found among the younger population. According to the WHO, childhood obesity increased from 4% to 18% (4.5 times) between 1975 and 2016 [49]. For metabolic diseases, a study of 14.6 million participants observed a more drastic increase in the prevalence of metabolic diseases among those aged 15–40 years (7.6%–16.5%) than those aged >40 years or older (33.0%–35.2%) [50]. These trends may also contribute in part to the recent increasing trend of gallstone diseases among the younger population [51,52]. All the above factors might be related to the increasing trend of GBC among males and younger populations. Given the increasing prevalence of these risk factors among various population groups, this trend will likely continue in the next decades.

Even though the mortality of GBC was increasing in some countries, there was an overall decreasing trend in both males and females. The advancements in diagnostic imaging and increasing performance of cholecystectomy for symptomatic gallbladder disease may have contributed to this favourable trend [53]. Cholecystectomy has become increasingly popular in many countries, with the introduction of a lower-risk laparoscopic procedure since the 1980s [54]. This could theoretically decrease GBC mortality by detecting and treating more cancer cases at an earlier age. The decreasing GBC-related mortality might also be associated with an increasing long-term statin use in the developed countries since the 1990s [15]. There exists evidence showing that statin use might decrease the risk of gallstone disease and cancer via suppressing hepatic cholesterol synthesis and biliary cholesterol secretion [55].

However, the recent pandemic of novel coronavirus disease 2019 (COVID-19) could have an impact of incidence and mortality of gallbladder cancer. The alternation in health-seeking behaviour, access to essential cancer diagnostic services, and the availability of treatment due to global pandemic measures will cause a substantial increase in additional cancer mortality in the medium and longer term [56]. Policy interventions are urgently needed to reduce the indirect impact of the COVID-19 pandemic on cancer care. The risk of severe complications from COVID-19 versus the risk of not seeking cancer care should be accurately conveyed.

4.5. Limitations

This analysis provides an important and up-to-date evidence on the worldwide distribution and associated factors of GBC, as well as its epidemiologic trend for individual countries by different sex and age groups. However, there is a possibility of misclassification and under-reporting of cancer cases in under-developed regions, possibly due to low registry coverage and analytical capacity. For countries with higher prevalence of cardiovascular diseases, diabetes and ageing population, competing events may also affect mortality estimates. Furthermore, the populations for the estimate of different risk factors may varied by calendar period in the same country, and their associations with incidence and mortality might also be affected by residual confounders or potential non-linear relationship, as only univariable analysis was conducted because of potential collinearity among the examined variables. Lastly, direct comparison might be difficult for regions where cancer registries change over time in their reporting mechanism and diagnosis confirmation. Nevertheless, estimates from the comparison between different regions, sex groups, and age groups at the same time point may be less affected.

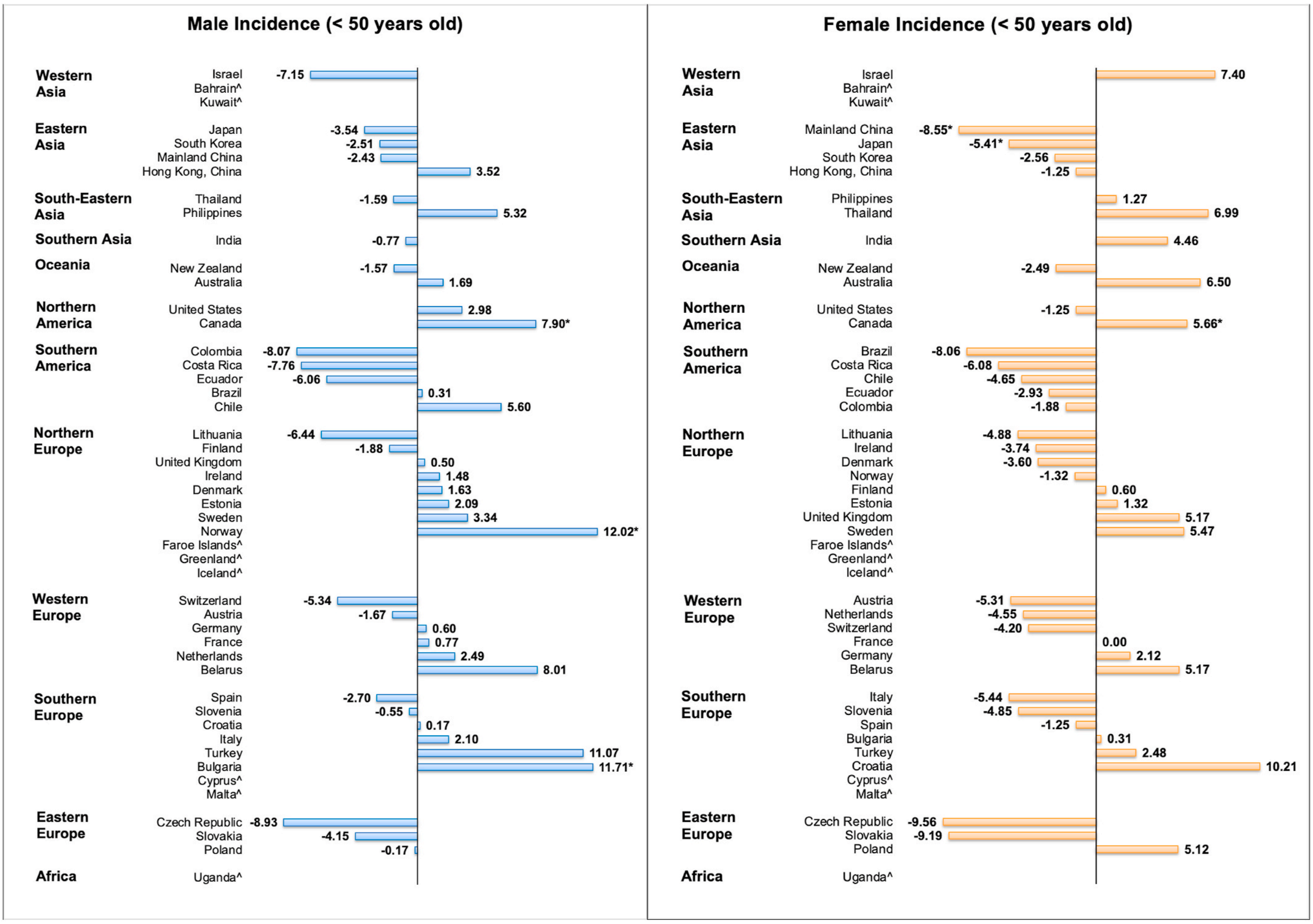

Fig. 10. AAPC of gallbladder cancer incidence in <50 years old, male and female.

4.6. Implications

The incidence of GBC is increasing in some populations, particularly among males and younger individuals. Due to population ageing and urbanization, it is expected that the burden of GBC will continue to increase in the future. For the general population, intensive lifestyle modifications including smoking cessation, weight control, and optimal control of metabolic diseases need to be promoted. Early detection is crucial for reducing the overall burden of GBC. It is also important to improve treatment, surveillance of clinical outcomes, and quality of life for patients with GBC. Lastly, more longitudinal studies are needed to investigate the reasons behind these epidemiologic trends in order to give further insights into the specific aetiology and prognosis of GBC.

Author contributions

MCSW and JH participated in the conception of the research ideas, study design, interpretation of the findings, and writing of the first draft of the manuscript. JH, CHN, CNP, and YB retrieved information from the relevant databases and performed statistical analysis; HKP, DB, VTC, DELP, AK, VL, XL, LZ, JY, WX and ZJZ made critical revisions on the manuscripts and provided expert opinions on implications of the study findings.

Grant support

None.

Patient and public involvement

Our results will be disseminated through media outlets and presentations at scientific conferences and academic events.

Data availability

The data used for the analyses are publicly available from the World Health Organization websites (https://gco.iarc.fr/; https://apps.who.int/gho/data/node.main).

Ethics statement

This study was approved by the Survey and Behavioural Research Ethics Committee, Chinese University of Hong Kong (No. SBRE-20-332).

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.canlet.2021.09.004.

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