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ORIGINAL RESEARCH ARTICLE

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Global Incidence, Mortality, Risk Factors and Trends of Melanoma: A Systematic Analysis of Registries

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Abstract

Background Melanoma of the skin is the most dangerous skin cancer in the world, though the numbers of reported new cases and melanoma-related deaths are low.

Objective This study evaluated the global incidence, mortality, risk factors and temporal trends by age, sex and locations of melanoma skin cancer.

Patients and Methods Cancer Incidence in Five Continents (CI5) volumes I–XI; the Nordic Cancer Registries (NORDCAN); the Surveillance, Epidemiology and End Results (SEER) Program; and the World Health Organization (WHO) International Agency for Research on Cancer (IARC) mortality database were accessed for worldwide incidence and mortality rates. Average Annual Percentage Change (AAPC) was calculated using a Joinpoint regression to examine trends.

Results Age-standardized rates of cancer incidence and mortality were 3.4 and 0.55 per 100,000 worldwide in 2020. Australia and New Zealand reported the highest incidence and mortality rates. Associated risk factors included higher prevalence of smoking, alcohol consumption, unhealthy diet, obesity and metabolic diseases. Increasing incidence trends were observed mostly in European countries, whilst mortality displayed an overall decreasing trend. For both sexes in the age group 50 years and above, a significant increase in incidence trend was observed.

Conclusions Although mortality rates and trends were found to decrease, global incidence has increased, especially in older age groups and males. Whilst incidence increase may be attributed to improved healthcare infrastructure and cancer detection methods, the growing prevalence of lifestyle and metabolic risk factors in developed countries should not be discounted. Future research should explore underlying variables behind epidemiological trends.

Key Points

Increasing incidence trends were observed in mostly European countries, whilst an overall decreasing mortality trend was found.

For both sexes in the age group of 50 years or above, a significantly large increase in incidence trend was observed.

Extended author information available on the last page of the article

1 Introduction

Melanoma of the skin is a type of skin cancer that initiates in the melanocytes, the pigment-producing cells. It is the most dangerous type of skin cancer, although it only accounts for about 1.8% and 0.6% of all newly reported cancer cases and related deaths, respectively, around the globe [1]. The prognosis of melanoma of the skin depends largely on the stage of discovery: localized melanoma of the skin has a 5-year survival rate of 99%, while cases after distant metastases have a 5-year survival rate of merely 25% [2, 3]. Therefore, it is important to develop early detection strategies tailored to each country.

There are some evidence-based potential associated risk factors related to melanoma. These include constitutional factors such as skin colour, tendency to freckle and family history of melanoma [4]. There are also environmental factors such as ultraviolet (UV) exposure, latitudes, ambient temperature and hours of sunlight [5]. However, there may be a confounding effect on these factors, as they are dependent on each other. Nonetheless, further research should be done to evaluate the correlation between prevalent lifestyle and metabolic risk factors, which include smoking habits, the consumption of alcohol, physical activity level and metabolic syndrome and the risk of melanoma.

Previous studies are often limited to the epidemiological trends in certain geographical regions, while some reported only the incidence but did not address to the temporal trends [6–8]. Furthermore, few studies have extensively evaluated associations between preventable risk factors and melanoma at a country level. To fill the current research gap, this study aims to investigate the most updated global melanoma incidence and mortality trend of subgroups of geographical regions, sexes, age cohorts and level of development with the most recent data available. The associations between common lifestyle factors and metabolic factors and melanoma risk were also examined.

2 Methods

2.1 Data Collection

For the collection of the data of melanoma incidence and mortality, different databases were retrieved. The Global Cancer Observatory (GLOBOCAN) database, developed by the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) had the most up-to-date information on the global cancer statistics, which includes both the incidence and mortality data for 183 countries [9, 10]. The gross domestic products (GDPs) and human development index (HDI) for each country were retrieved from the World Bank and United Nations. The HDI is a composite measure of life expectancy, education (years of schooling) and gross national income per capita. Higher scores of HDI indicate greater development [11]. Although HDI and GDP are correlated to some extent, they can have distinctly different implications on risk factors and cancer incidence and mortality [12, 13]. Therefore, a separate analysis is warranted. The Global Health Data Exchange (GHDx) database was retrieved for the prevalence of smoking, alcohol drinking, unhealthy diet, physical inactivity, hypertension, diabetes and lipid disorders.

To analyse the trend of melanoma incidence, the Cancer Incidence in Five Continents Time Trends (CI5plus) [14]; the Nordic Cancer Registries (NORDCAN) [15, 16]; and the Surveillance, Epidemiology and End Results Program (SEER) [17] were utilized to obtain the cancer incidence from 48 countries. The CI5plus database is a comprehensive database that provides cancer incidence rate and the associated demographic characteristics for each cancer site, allowing comparison across countries, sexes and age groups. The NORDCAN database provides comprehensive cancer-related statistics for Scandinavian countries. The SEER program, established by the National Cancer Institute at the US Department of Health and Human Services, provides a detailed record of the cancer statistics in the USA. For the trend analysis on melanoma mortality, the WHO mortality database [18] was accessed for data on cancer-related death in different countries and regions supplemented by more updated data from the NORDCAN and SEER. Data on cancer mortality were collected from the respective national civil cancer registries. Prior to the annual report to the WHO, the registering system logs cancer deaths and causes after having been clinically verified. To make sure the data are comprehensive and accurate, only figures with medium quality or above would be published. To obtain the age-standardized rates (ASR) for different countries, the incidence and mortality figures were standardized by age with the Segi–Doll world reference population [19].

2.2 Statistical Analysis

Choropleth maps were generated on the global melanoma incidence and mortality in 2020. For the analysis on risk factors associations, beta coefficients (β) and the corresponding 95% confidence intervals (CI) were estimated by the univariable linear regression analysis, with β estimates referring to the degree of change in ASR of melanoma incidence or mortality. Additional multivariate regression analysis was conducted to evaluate the relationship between the variables and melanoma incidence or mortality after adjusted for potential confounding factors. To analyse the temporal epidemiological trends of melanoma of skin, the incidence and mortality trends in various countries were evaluated based on the average annual percent change (AAPC) using regression analysis with the software of Joinpoint Regression Program, a statistical software designed for the analysis of trends using joinpoint models. Logarithmic transformation was performed on the data of incidence and mortality, and standard errors were computed. The AAPC was derived as an average of APCs using geometric weighting in the subsets of different age groups ($\geq$ 50 years, < 50 years and < 40 years), sexes and countries from various geographical regions, which include Asia, Oceania, North America, South America, Northern Europe, Western Europe, Southern Europe, Eastern Europe and Africa. Weights equivalent to each segment's length were proportionate to the specified time interval. A trend would be deemed significant only when 0 is not included in the 95% confidence interval (CI), as p-values smaller than 0.05 were considered to be statistically significant.

3 Results

3.1 Global Melanoma Incidence and Mortality in 2020

In 2020, there were 324,635 newly reported cases of melanoma worldwide, and the global ASR was 3.4 per 100,000 (Fig. 1). There was a disparity between the two sexes, as male (ASR = 3.8) has an almost 30% higher incidence rate than female (ASR = 3.0). Incidence varies very significantly among regions, with Australia and New Zealand (ASR = 35.8) having an about 110 times higher incidence than Western Africa (ASR = 0.33). On a whole, European countries (Western Europe ASR = 18.9; Northern Europe ASR = 17.8) had incidence rates higher than the world average, while the Asia (Eastern Asia ASR = 0.39) and Africa (Northern Africa ASR = 0.45) regions had incidence rates significantly lower than the global ASR. In terms of incidence, there was a very significant disparity between populations with different levels of human development index (HDI), as populations

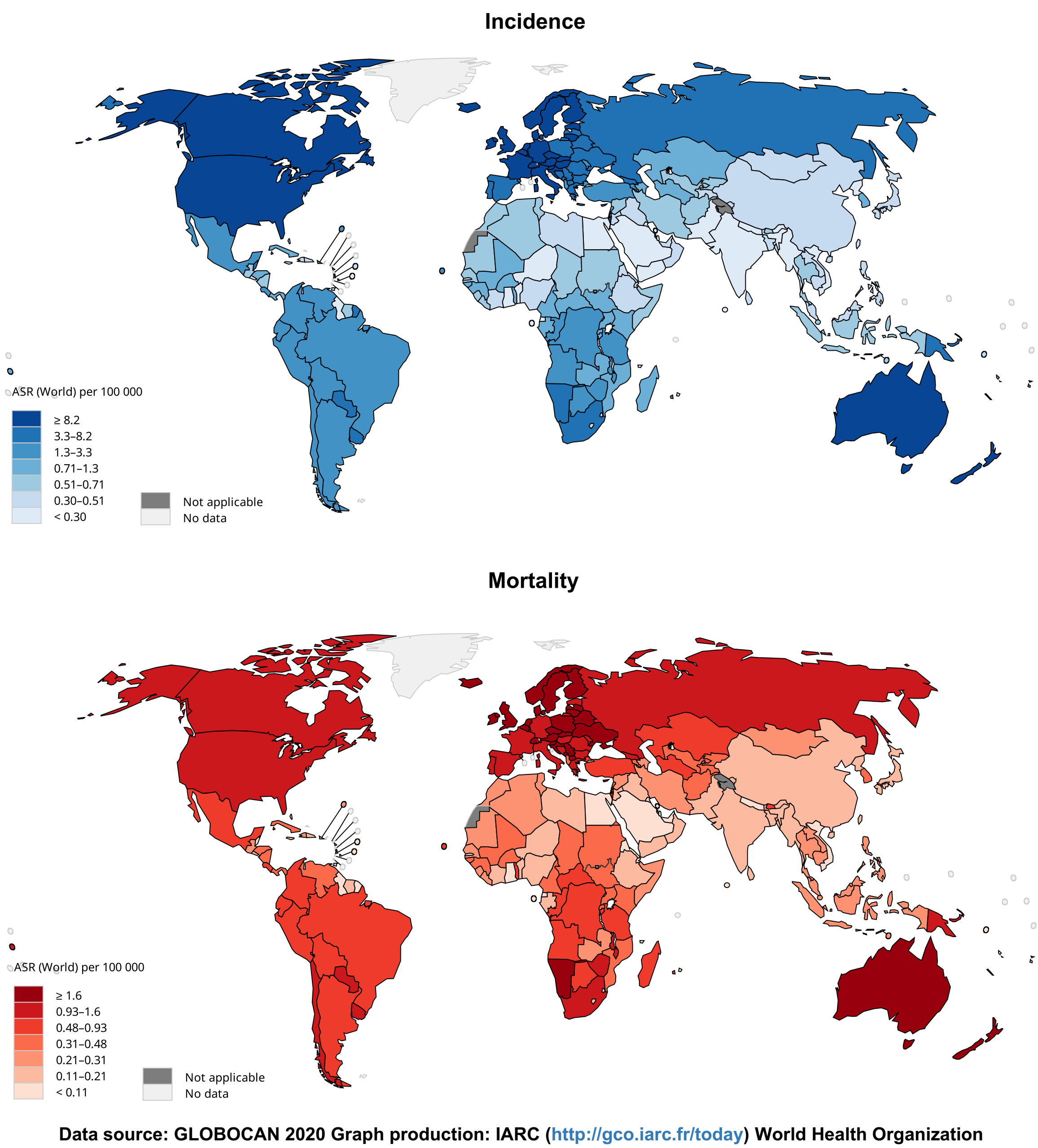


Fig. 1 Global incidence and mortality of melanoma, both sexes, all ages, in 2020. *ASR* age-standardized rates

with very high HDI (ASR 10.2) had an incidence remarkably higher than all the other groups (ASR = 0.34–0.92). As far as mortality is concerned, 57,043 deaths related to melanoma of skin were reported in 2020, with an ASR of 0.56 globally. Similar to incidence, Asian and African regions had relatively lower mortality ASRs ranging from 0.19 to 0.93, and European regions and North America had slightly higher mortality ASRs at around 1.1–1.9, while Australia and New Zealand had a distinctly higher mortality ASR at 2.7. Populations with very high HDIs had the highest mortality (ASR = 1.2), and there was not a remarkable difference among the other groups (ASR = 0.18–0.36).

3.1.1 Associations Between Risk Factors and Melanoma Incidence

Amongst males (Fig. 2), melanoma incidence was associated with HDI (β = 2.102, CI 1.458–2.746, $p < 0.001$), GDP (β = 2.051, CI 1.631–2.472, $p < 0.001$), smoking (β = 0.195, CI 0.058–0.333, $p = 0.006$), alcohol consumption (β = 0.541, CI 0.418–0.663, $p < 0.001$), unhealthy diet (β = 0.078, CI 0.004–0.152, $p = 0.039$), obesity (β = 0.156, CI 0.060–0.253, $p = 0.002$), hypertension (β = 0.287, CI 0.178–0.390, $p < 0.001$), diabetes (β = 0.215, CI 0.021–0.408, $p = 0.030$) and lipid disorders (β = 0.312, CI 0.234–0.389, $p < 0.001$). After adjusting for confounders, melanoma incidence was associated with GDP (β = 1.456, CI 0.870–2.042, $p < 0.001$, Supplementary Table 1), alcohol consumption (β = 0.315, CI 0.135–0.494, $p = 0.001$) and lipid disorders (β = 0.183, CI 0.061–0.304, $p = 0.003$). Amongst females, incidence was associated with HDI (β = 2.089, CI 1.486–2.691, $p < 0.001$), GDP (β = 2.082, CI 1.688–2.475, $p < 0.001$), prevalence of smoking (β = 0.890, CI 0.743–1.037, $p < 0.001$), alcohol consumption (β = 1.306, CI 1.110–1.501, $p < 0.001$), inactivity (β = 0.560, CI 0.258–0.862, $p < 0.001$), obesity (β = 0.102, CI 0.009–0.196, $p = 0.032$), hypertension (β = 0.227, CI 0.113–0.342, $p < 0.001$) and lipid disorders (β = 0.314, CI 0.239–0.389, $p < 0.001$). Meanwhile, multivariate regression showed that it was positively associated with GDP (β = 1.106, CI 0.611–1.601, $p < 0.001$), smoking (β = 0.381, CI 0.166–0.596, $p = 0.001$), alcohol consumption (β = 0.605, CI 0.333–0.878, $p < 0.001$) and lipid disorders (β = 0.096, CI 0.006–0.185, $p = 0.037$), whilst negatively associated with unhealthy diet (β = −0.095, CI 0.182–−0.008, p = 0.032) and diabetes (β = −0.200, CI −0.361–−0.038, $p = 0.016$).

3.1.2 Associations Between Risk Factors and Melanoma Mortality

Amongst males (Fig. 3), melanoma mortality was associated with a higher HDI (β = 0.278, CI 0.178–0.378, $p < 0.001$), GDP (β = 0.213, CI 0.139–0.287, $p < 0.001$), prevalence of smoking (β = 0.045, CI 0.025–0.065, $p < 0.001$), alcohol consumption (β = 0.089, CI 0.071–0.107, $p < 0.001$), unhealthy diet (β = 0.023, CI 0.012–0.034, p < 0.001), obesity (β = 0.037, CI 0.022–0.052, $p < 0.001$), hypertension (β = 0.057, CI 0.041–0.072, $p < 0.001$), diabetes (β = 0.047, CI 0.016–0.077, $p = 0.003$) and lipid disorders (β = 0.049, CI 0.037–0.060, $p < 0.001$). Similarly, melanoma mortality was associated with higher GDP (β = 0.099, CI 0.003–0.194, $p = 0.044$, Supplementary Table 2), alcohol consumption (β = 0.048, CI 0.018_0.078, $p = 0.002$), hypertension (β = 0.020, CI 0.002–0.037, $p = 0.026$) and lipid disorders (β = 0.024, CI 0.004–0.043, $p = 0.019$) after adjusting for potential confounders. Amongst females, mortality was associated with higher HDI (β = 0.146, CI 0.092–0.199, $p < 0.001$), GDP (β = 0.123, CI 0.084–0.163, $p < 0.001$) and prevalence of smoking (β = 0.076, CI 0.063–0.088, $p < 0.001$), alcohol consumption (β = 0.099, CI 0.081–0.117, $p < 0.001$), obesity (β = 0.012, CI 0.003–0.020, $p = 0.007$), hypertension (β = 0.029, CI 0.019–0.038, $p < 0.001$) and lipid disorders (β = 0.024, CI 0.017–0.030, $p < 0.001$). Likewise, melanoma mortality was positively associated with smoking (β = 0.059, CI 0.039–0.079, $p < 0.001$), alcohol consumption (β = 0.031, CI 0.006–0.057, $p = 0.016$) and hypertension (β = 0.013, CI 0.006–0.021, $p = 0.001$), but negatively associated with diabetes (β = −0.032, CI −0.048–−0.015, $p < 0.001$).

3.1.3 Incidence Trends in Subjects Aged 0–85+ Years

For males, 21 countries reported significant increases, of which 20 of them were European countries, as Malta (AAPC = 10.70; 95% CI = 0.99, 21.36; $p = 0.034$), Estonia (AAPC = 7.93; 95% CI = 3.66, 12.37; $p = 0.002$) and Cyprus (AAPC = 7.86; 95% CI = 1.65, 14.46; $p = 0.019$) reported the largest increases (Figure 4). In contrast, significant decreases were observed only in the Philippines (AAPC = −10.29; 95% CI = −17.21, −2.79; $p = 0.014$). For females, 16 countries showed significant increasing trends; likewise, 13 of them were European countries, with Estonia (AAPC = 6.47; 95% CI = 2.87, 10.20; $p = 0.003$), Bulgaria (AAPC = 6.33; 95% CI = 2.70, 10.09; $p = 0.004$) and Japan (AAPC = 6.07; 95% CI = 1.83, 10.48; $p = 0.010$) reporting the most evident increases. Significant decreases were observed in three countries: the Philippines (AAPC = −8.13; 95% CI = −13.29, −2.67; $p = 0.010$), Israel (AAPC = −1.50; 95% CI = −2.96, −0.01; $p = 0.049$) and Australia (AAPC = −0.52; 95% CI = −1.42, −0.39; $p = 0.033$).

3.1.4 Mortality Trends in Subjects Aged 0–85+ Years

For males, four countries showed evident increases, and the most remarkable increases were reported in Thailand (AAPC = 25.11; 95% CI = 3.36, 51.45; $p = 0.022$), Singapore (AAPC = 15.34; 95% CI = 2.81, 29.40; $p = 0.021$) and

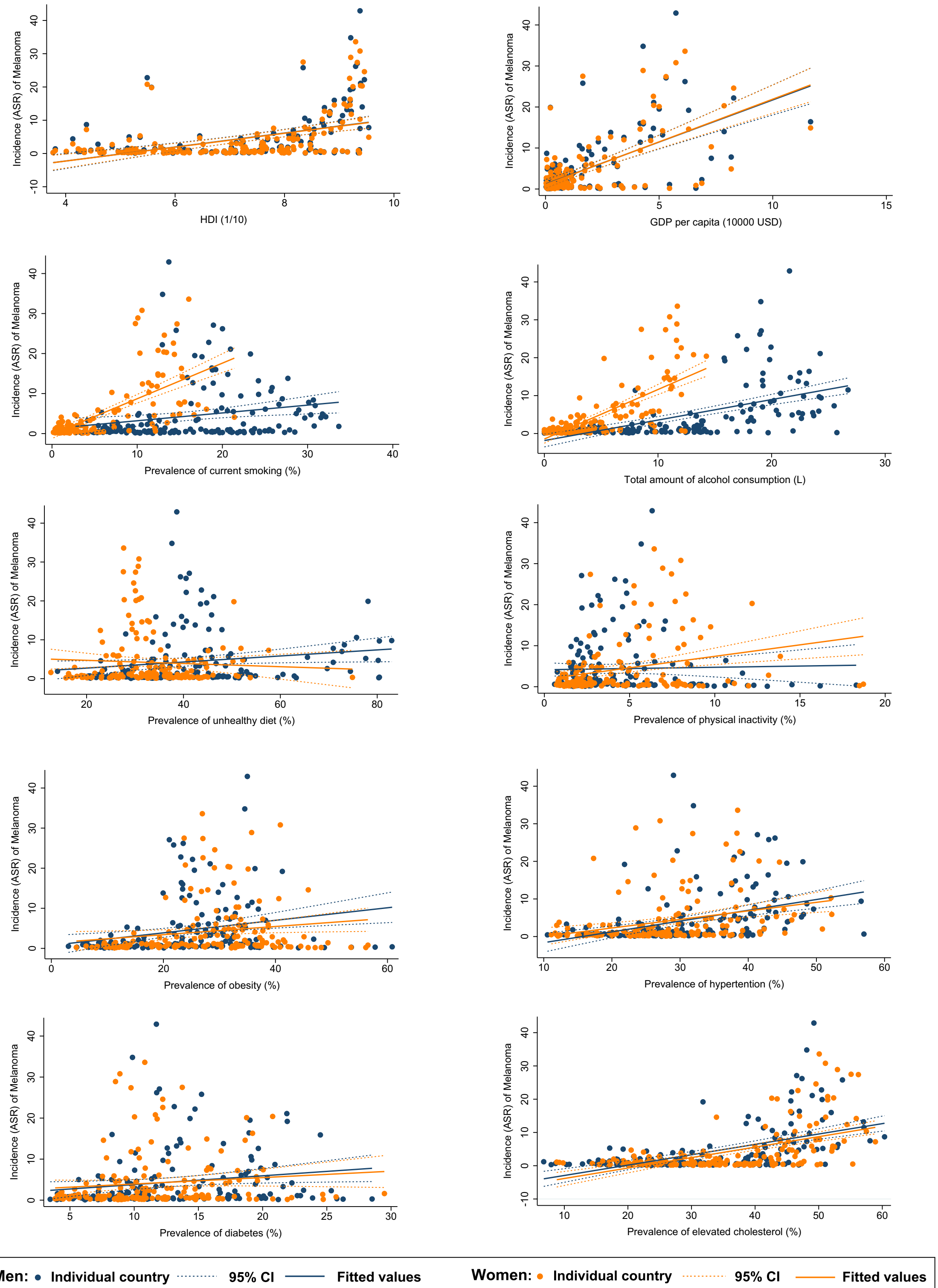


Fig. 2 Associations between risk factors and melanoma incidence. *ASR* age-standardized rates, *GDP* gross domestic product, *HDI* human development index

Colombia (AAPC = 3.40; 95% CI = 1.29, 5.55; $p = 0.006$; Fig. 5). Eight countries showed that incidence decreased, with the largest decreases found in Norway (AAPC = −4.18; 95% CI = −6.22, −2.09; $p = 0.002$), USA white (AAPC = −3.47; 95% CI = −4.89, −2.02; $p < 0.001$) and Australia (AAPC = −3.43; 95% CI = −5.92, −0.87; $p = 0.009$). For

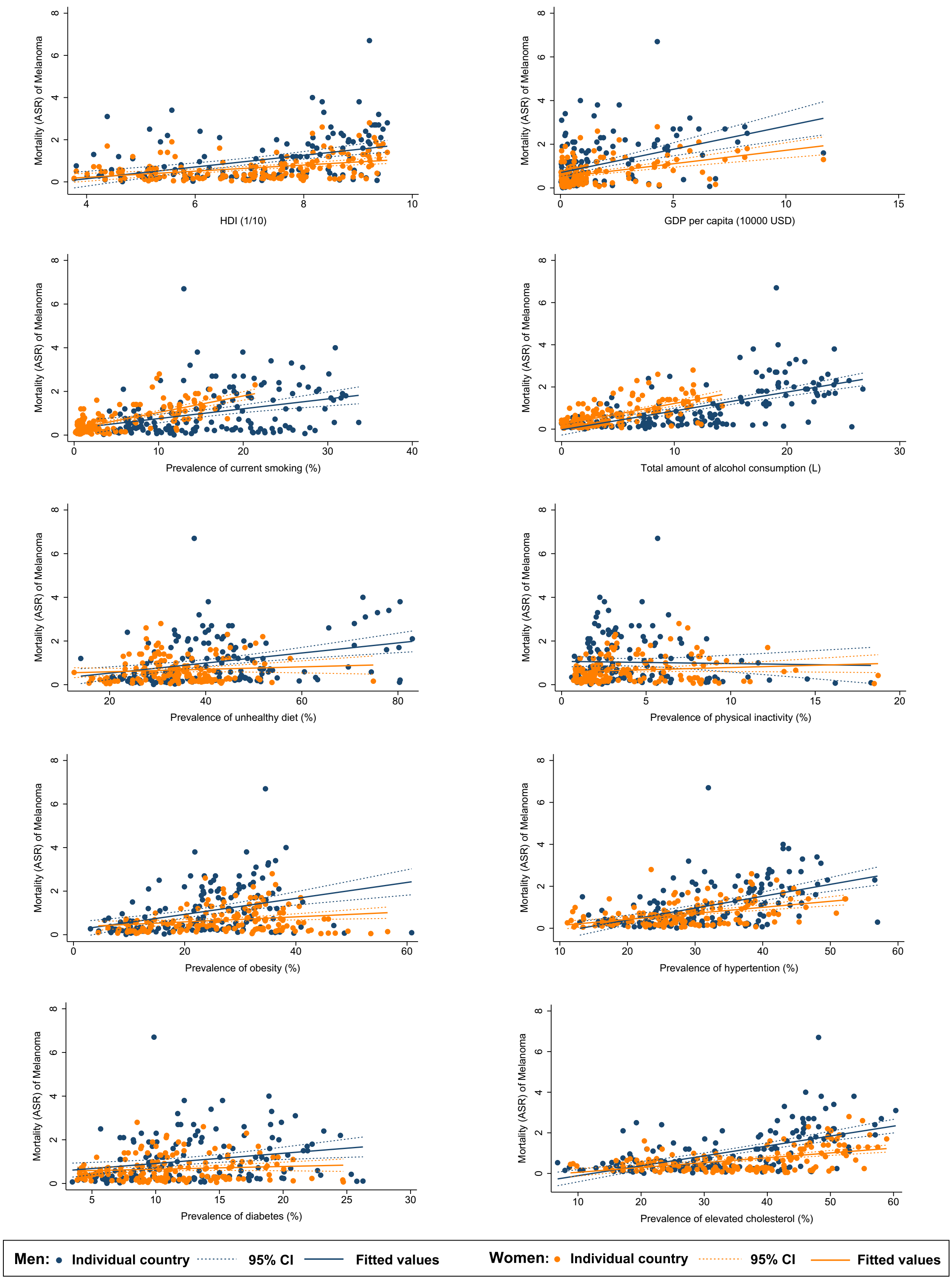
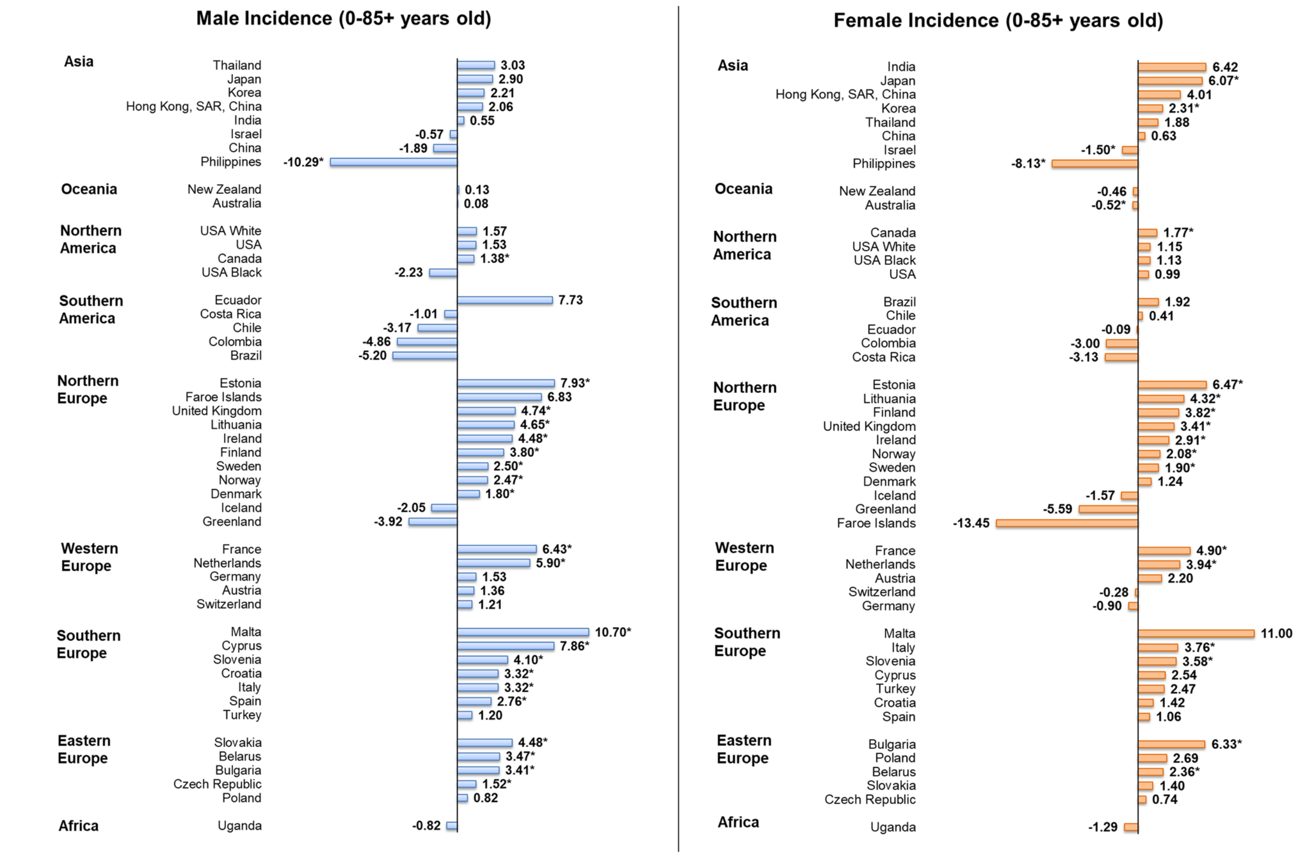


Fig. 3 Associations between risk factors and melanoma mortality. *ASR* age-standardized rates, *GDP* gross domestic product, *HDI* human development index

females, significant increasing trends were observed in three countries: Thailand (AAPC = 23.20; 95% CI = 12.78, 34.58; $p < 0.001$), Korea (AAPC = 2.70; 95% CI = 0.19, 5.27; $p =$ 0.038) and Colombia (AAPC = 2.49; 95% CI = 0.30, 4.74; $p = 0.030$). Eight countries reported significant decreases, with the Philippines (AAPC = −7.18; 95% CI = −10.59,



AAPC, annual percentage change; *p values less than 0.05.

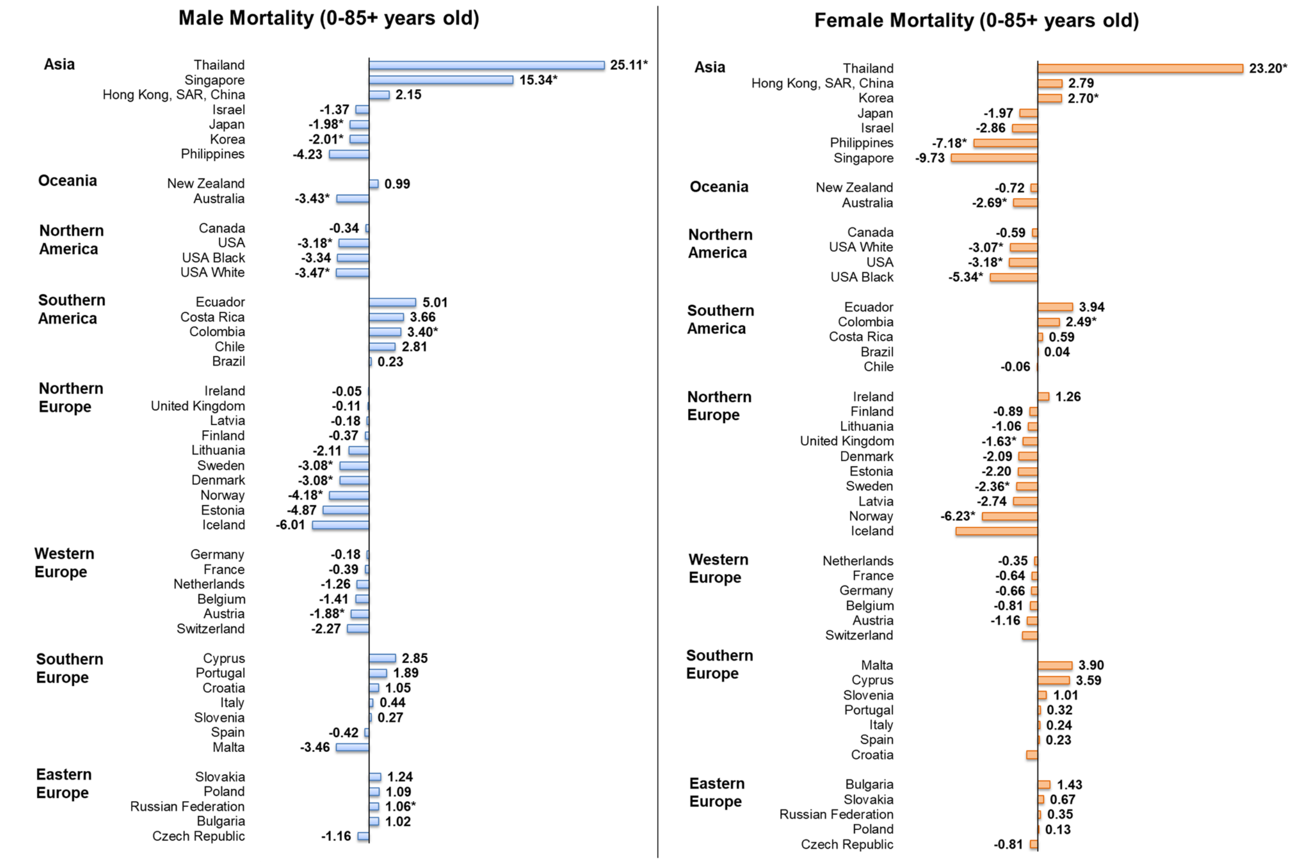
Fig. 4 Average annual percentage change (AAPC) of melanoma incidence, aged 0–85+ years

−3.65; $p = 0.002$), Norway (AAPC = −6.23; 95% CI = −8.64, −3.77; $p < 0.001$) and USA Black (AAPC = −5.34; 95% CI = −8.94, −1.59; $p = 0.012$) reporting the most evident decreases.

4 Discussion

Regions with the highest skin melanoma cancer burden were found in Australia and New Zealand, thus supporting past findings where its incidence was reported as high as 33.6 and 33.3 per 100,000, respectively [20]. By contrast, Asia and Africa reported lower burden of melanoma than the global average, while Europe and North America had slightly higher rates [21, 22]. Higher incidence and mortality rates of melanoma were observed in countries with very high HDI, which could be attributed to early detection for cancer symptoms, advanced diagnostic techniques and improved accessibility to healthcare as suggested by past literature [20, 23]. Skin melanoma incidence and mortality occurred more frequently in males than in females, as it has been previously reported that men having a higher likelihood of developing melanoma might be due to less use of sun protection and increased time spent outside, for work or otherwise, compared with women [20, 22, 24].

The burden of lifestyle-related cancers may be heavier in higher HDI countries due to the increased prevalence of risk factors such as smoking, alcohol consumption, poor diet and chronic health conditions [25]. For skin cancer in particular, 85.6% of all melanoma cases and 67.2% melanoma-related deaths worldwide were observed in very high HDI countries [23]. Although smoking and alcohol intake have been associated strongly with other cancers, mixed findings have demonstrated these factors may be indirectly associated with harm caused by ultraviolet (UV) exposure. Alcohol consumption occurring during outdoor leisure activities may lead to drinkers experiencing more severe sunburns compared with non-drinkers [26], whilst smokers tend to spend more time indoors compared with non-smokers, and inflammatory reactions caused by UV may be reduced, as nicotine from cigarette smoke shields the skin [27]. Thus, substance use may increase susceptibility or potentially protect individuals from melanoma risk due to increased or reduced UV exposure. While UV exposure is a core risk factor for skin melanoma, studies evaluating the effect of lifestyle patterns related to dietary habits and health conditions, such



AAPC, annual percentage change; **p* values less than 0.05.

Fig. 5 Average annual percentage change (AAPC) of melanoma mortality, aged 0–85+ years

as obesity, have provided inconsistent results. A review of dietary factors suggests that diet may influence melanoma development, such as interaction between UV light exposure and psoralens and furocoumarins in citrus fruits stimulating propagation of melanoma cells [28]. Additionally, an inverse relationship was found between caffeine and melanoma suggesting caffeine intake may act as a protective factor, though results varied depending on the anatomical site [29]. Overconsumption of red meat has been indicative of poorer dietary habits and associated with health risks and may also affect melanoma-specific survival, as weekly consumption was associated with worse outcomes [hazard ratio (HR) = 1.84; 95% CI: 1.02–3.30] [30]. Meta-analyses of cohort and case-control studies have suggested that there is a positive correlation between obesity and melanoma risk in men [31–33]. However, this association was absent in women, as females with obesity have even been found to be at lowest risk of melanoma [risk ratio (RR) = 0.9, CI = 0.8–1.0] [34–36]. Similar to previous findings [37], metabolic syndrome including hypertension was found to be associated with melanoma. A possible explanation might be the shared biological mechanisms of hypertension and cancer aetiology related to increased vascular endothelial growth factor (VEGF) receptor production [37]. It was found that tumour hypoxia is associated with increased synthesis of factors, including VEGF receptor [38], and VEGF is involved in the initiation of skin cancers in mice [39].

The findings of the present study strengthen past evaluations of trends wherein melanoma incidence continued to increase up to 4–6% [22]. Difference in mortality rates and incidence trends caused by UV radiation across geographical regions may be explained by Lancaster's "latitude gradient", as countries closer in proximity to the equator tended to report a higher annual incidence of ASRs [40]. This may be less applicable for Asian countries near the equator, as a majority of the population are not fair-skinned and therefore are less at risk of melanoma, and rates have also reportedly been lower [21, 24]. The current study's results mirror findings on older age groups where worldwide melanoma incidence and mortality in males and females aged 50 years and above reported significant increases as individuals above 65 years of age face a higher risk of melanoma [40, 41]. Mortality rates generally peak between ages 45–65 years, with both sexes aged 80 years and above displaying the highest increase in trend in some regions [42–44].

5 Conclusions

In summary, there has been a significant increasing trend in melanoma incidence for both sexes in most countries during the past decade, which may be related to the increasing prevalence of risk factors and improvements in disease detection. By contrast, there was a relatively stable or decreasing trend in mortality, possibly attributable to the improvement in early diagnosis and advanced treatments. Educational programmes regarding risk factors and intensive lifestyle modifications should be promoted, especially among men and younger individuals to ameliorate melanoma morbidity and mortality in different age cohorts. Further research could be conducted to investigate the causes behind these epidemiological trends and the prognosis of melanoma of skin by different subtypes.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40257-023-00795-3.

Declarations

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Competing interests Junjie Huang, Sze Chai Chan, Samantha Ko, Veeleah Lok, Lin Zhang, Xu Lin, Don Eliseo Lucero-Prisno III, Wanghong Xu, Zhi-Jie Zheng, Edmar Elcarte, Mellissa Withers and Martin CS Wong declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

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

Consent to participate Not applicable.

Consent for publication Not applicable.

Data availability statement The data used for the analyses are available upon reasonable request from the corresponding author. The datasets supporting the conclusions of this article are included within the article and its additional files.

Code availability Not applicable.

Transparency statement The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Author contributions JH and MCSW contributed conceptualization and supervision; JH and SCC contributed data curation and formal analysis; SCC and SK contributed manuscript drafting; VL, LZ, XL, DELP, WX, ZJZ, EE, MW and MCSW contributed manuscript review and editing. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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