Original Article

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Association of the national level of human development with the incidence and mortality of congenital birth defects in 2019: A cross-sectional study from 189 countries

Chen Du[1,§], Ziquan Zhang[2,§], Shuzhe Xiao[1,§], Yanwen Li[1], Ruiwen Jiang[1], Weihua Jian[3], Zhuxiao Ren[4], Yiting Lv[1], Zhizhang Pan[1], Jie Yang[1,*]

[1] Department of Neonatology, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China;
[2] School of Artificial Intelligence, Sun Yat-sen University, Zhuhai, Guangdong, China.
[3] Department of Neonatology, Zhongshan City People's Hospital, Zhongshan, Guangdong, China;
[4] Department of Neonatology, Guangdong Women and Children Hospital, Guangzhou, Guangdong, China.

SUMMARY Congenital birth defects (CBD) play a significant role in causing child mortality globally. The incidence and mortality of CBD vary widely across countries, and the underlying causes for this divergence remain incompletely comprehended. We conducted an analysis to investigate the relationship between the incidence and mortality of CBD in 189 countries and their Human Development Index (HDI). In this study, CBD data from 189 countries was used from the Global Burden of Diseases Study (GBD) 2019, and HDI data was collected for the same countries. Later, the relationship between CBD and HDI was analyzed, and the impact of gross national income (GNI) per capita, expected years of schooling, mean years of schooling and life expectancy at birth was quantified using principal component regression. The age-standardized incidence rate (ASIR) varied between 66.57 to 202.24 per 100,000, with a 95% uncertainty interval (UI) of 57.20-77.51 and 165.87-241.48 respectively. The age-standardized mortality rate (ASMR) also showed a rang from 1.38 to 26.53 (14.03-39.90) per 100,000, with the 95%UI of 0.91-2.09 and 14.03-39.90 respectively. Both the incidence and mortality rates of CBD decreased with the increased HDI (incidence: r = -0.38, $p < 0.001$, mortality: r = -0.77, $p < 0.001$). Our investigation revealed significant variations in the incidence and mortality of CBD among countries with different development levels. In conclusion, the global incidence and mortality of CBD vary significantly among countries, possibly due to differences in the accessibility of health services.

Keywords congenital abnormalities, human development index, child death.

1. Introduction

Congenital birth defects (CBD) is one of the leading causes of death among children worldwide (*1*). As embryonic development progresses, CBD appears to be a spectrum of structural, functional, or metabolic abnormalities (*2*). Concurrence of CBD correlates with multi-factors such as genes, environment, economics, education, literacy, and so on (*3,4*). As morality in children below five years is an index of country development, rising incidence of CBD and related mortality have been an issue in developing countries for years. The age-standardized incidence rate (ASIR) and age-standardized mortality rate (ASMR) are statistical measures used for evaluating the different populations' incidence and mortality rates so that the effect of differing age distributions can be eliminated.

The United Nations Development Program (UNDP) established the Human Development Index (HDI) to assess a country's degree of development. The HDI takes into account factors such as education, literacy, gross national income (GNI) per capita, and life expectancy. From 0 to 1, higher values of the index indicate higher levels of development. Gross national income (GNI) measures the total income earned by residents of a country (*5*). Previous studies have shown that socioeconomic, human race, environmental pollution, and hereditary genes affected the incidence of CBD and related mortality, respectively (*6,7*). However, the correlation between HDI and CBD has never been reported.

In this study, we gained ASIR and ASMR of 2019 from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD), which divided the world into 21 regions, GBD, based on the geographic locations of countries around the world. We devided HDI into very high, high, middle, low levels, and investigated the associations of HDI and the incidence of CBD and related mortality.

2. Materials and Methods

2.1. Data sources

ASIR and ASMR of CBD in 2019 are available on the GBD dataset on the website: *https://ghdx.healthdata.org/gbd-results-tool* (accessed 25 Sep 2023) . HDI data were available on the website: *https:// hdr.undp.org/data-center/ human-development-index#/ indicies/HDI* (accessed 20 Oct 2023).

2.2. Case definition

CBD included eleven congenital malformations, deformations, and chromosomal abnormalities (*8*), including congenital heart diseases, congenital musculoskeletal anomalies, gastrointestinal congenital anomalies, neural tube defects, orofacial clefts, Down syndrome, Klinefelter syndrome, Turner syndrome, other chromosomal abnormalities, urogenital congenital anomalies. CBD Case was defined in accordance with the 10th version of the International Classification of Diseases (ICD-10).

The HDI is a comprehensive measure of a country's development level compiled by the UNDP. The UNDP classifies countries into four categories based on their HDI: Very High ($0·80 \leq HDI \leq 1$), High ($0·70 \leq HDI < 0·80$), Medium ($0.55 \leq HDI < 0·70$), and Low ($0 \leq HDI < 0·55$) (*9*).

2.3. Statistical analysis

The ASIR and ASMR were calculated by the GBD global population (*8*). The districts that need higher priority for incidence and mortality reduction were identified based on the 3×4 grouping of districts in tertiles of ASIR and ASMR in 2019 and the four categories of countries classified with HDI (*9*). The Spearman correlation coefficient was assessed between ASR of incidence and mortality with the HDI of the countries in 2019. There is an uncertainty interval (UI) of 95% for the incidence number, deaths, ASIR, and ASMR, which were calculated by using the 25th and 975th sorted values among 1000 draws. ASIR and ASMR were reported per 100,000 populations and later normalized (such that the total rate of each CBD equals 1) and mean-centered before Principal Component Analysis (PCA). The principal component regression was employed to quantify the relative contributions of the four indicators constituting HDI to the ASIR and ASMR of CBD. GraphPad Prism 10 and R version 4.3.1 were used for the statistical analyses. In order to be considered statistically significant, a significance level of $P < 0·05$ was required.

3. Results

3.1. Total CBD

In 2019, data from 189 countries showed variations in the incidence and mortality of CBD at the national level. At the national level, ASIR varied 3.04 times among the 189 countries of the world, ranging from 66.57 (95% UI 57·20-77·51) to 202·24 (165·87-241·48) per 100,000 livebirths (Figure 1A and Supplemental Table S1, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=208*). ASIR was 130 or more per 100,000 livebirths in 25 (75.76%) of the 33 low HDI countries, in 12 (31.58%) of the 38 medium HDI countries, in 11 (21.57%) of the 51 high HDI countries, and in 15 (22.39%) of the 67 very high HDI countries (Figure 1B and Supplemental Table S1, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=208*).

At the national level, ASMR varied 19.22 times among the 189 countries of the world, ranging from 1.38 (0.91-2.09) to 26.52 (14.03-39.90) per 100,000 livebirths (Figure 2A and Supplemental Table S2, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=208*). ASIR was 8 or more per 100,000 livebirths in 31 (93.94%) of the 33 low HDI countries, in 15 (39.47%) of the 38 medium HDI countries, in 13 (25.49%) of the 51 high HDI countries, and in 4 (5.97%) of the 67 very high HDI countries (Figure 2B and Supplemental Table S2, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=208*).

The total incidence and mortality of CBD decreased with increasing HDI (incidence $r = -0.38$, $p < 0.001$ and mortality $r = -0.77$, $p < 0.001$) (Figure 3). Additionally, we discovered that the proportional impact of the four elements comprising HDI on the incidence and mortality of CBD is comparable (Figure 4). Not only should we pay attention to socioeconomic inequalities, but we should also address the disparities prevailing in the education and healthcare systems of different countries.

3.2. Levels and trends of CBD in 21 regions

The incidence and deaths varied significantly among different national levels of human development and regions (Figure 1C-D and Figure 2C-D). While variations in the incidence of CBD were observed across 21 regions, congenital heart diseases ranked highest in affected individuals in nine regions, and

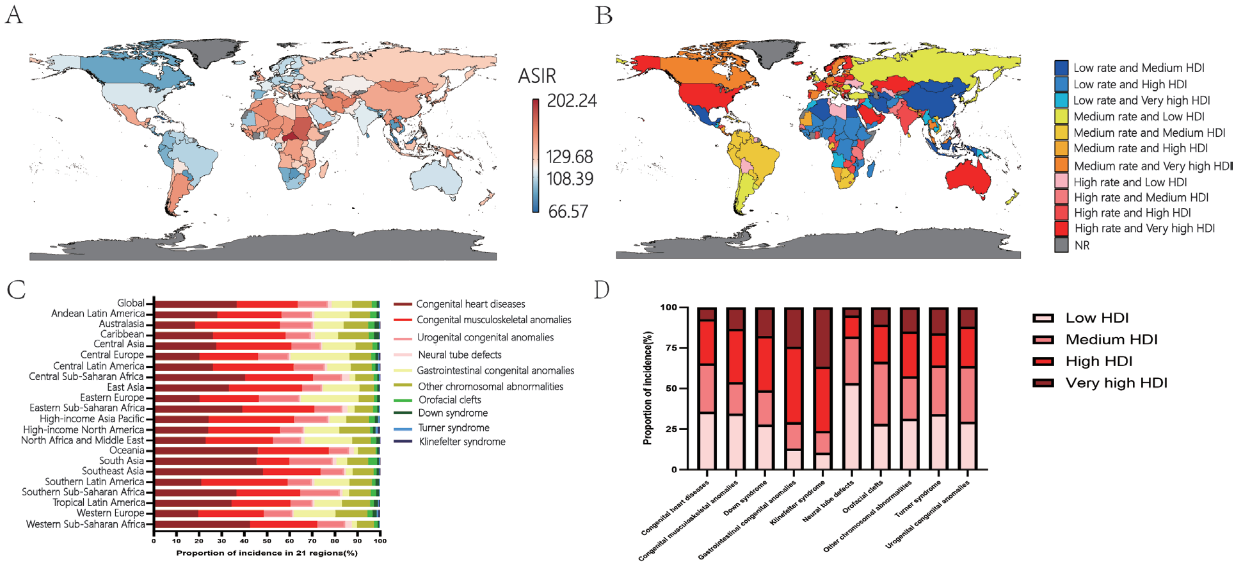

Figure 1. (A) Global distribution map of the total ASIR of CBD in 2019; **(B)** District groupings of the total ASIR of CBD in 2019: High, medium, and low groupings are based on the tertile of the ASIR. The tertile cutoffs for ASIR were 108.39 and 129.68. The HDI was divided into four levels: Very High (HDI ≥ 0.8), High (0.7 ≤ HDI < 0.8), Medium (0.55 ≤ HDI < 0.7), and Low (HDI < 0.55). **(C)** The proportional incidence of various CBD in 21 regions in 2019. **(D)** The proportional incidence of various CBD in 2019 was classified by low, medium, high, and very high HDI globally. ASIR = age-standardized incidence rate, HDI = Human development index.

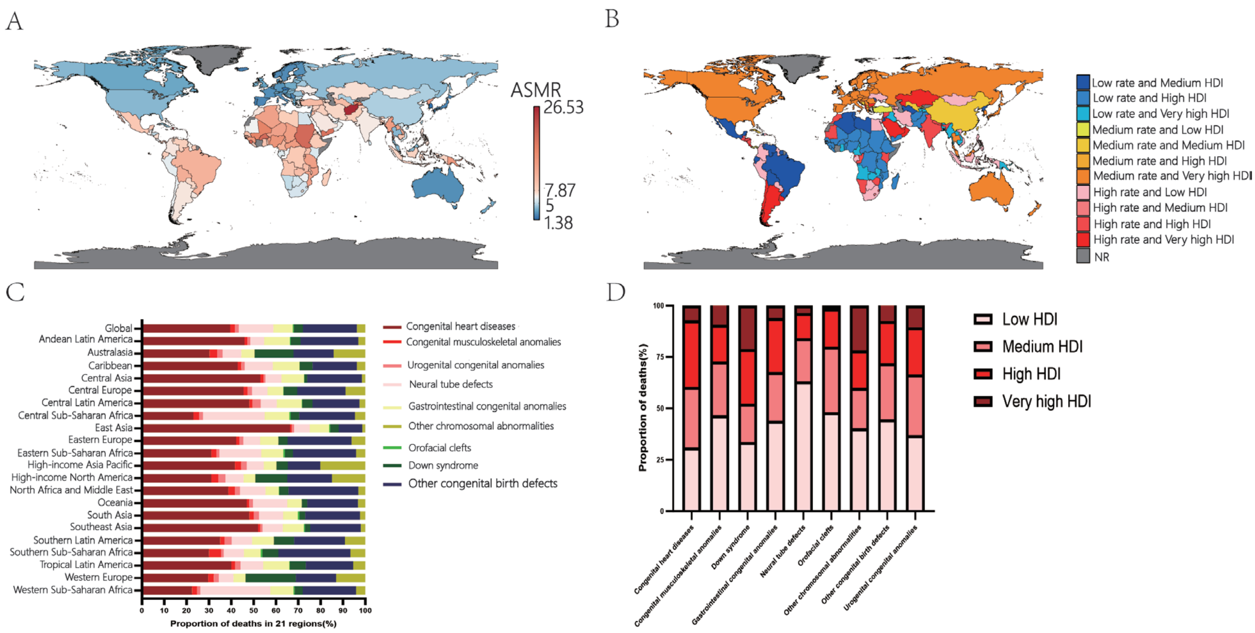

Figure 2. (A) Global distribution map of the total ASMR of CBD in 2019; **(B)** District groupings of the total ASMR of CBD in 2019: High, medium, and low groupings are based on the tertile of ASMR. The tertile cutoffs for age-standardized mortality rate were 5.00 and 7.87. The HDI was divided into four levels: Very High (HDI ≥ 0.8), High (0.7 ≤ HDI < 0.8), Medium (0.55 ≤ HDI < 0.7), and Low (HDI < 0.55). **(C)** The proportional death of various CBD in 21 regions in 2019. **(D)** The proportional death of various CBD in 2019 was classified by low, medium, high, and very high HDI globally. ASMR = age-standardized mortality rate, HDI = Human development index, NR = not report.

congenital musculoskeletal anomalies in twelve regions. Additionally, gastrointestinal congenital anomalies ranked second in ASIR in the Central Europe and Eastern Europe regions (Figure 1C).

Across 21 regions, congenital heart diseases stood out as the primary cause of death in 18 regions. Neural tube defects were a notable cause of death in Central Sub-Saharan Africa and Western Sub-Saharan Africa, while Other CBD played a significant role in Southern Sub-Saharan Africa (Figure 2C). These three regions all belong to Sub-Saharan Africa, which has lots of low HDI countries.

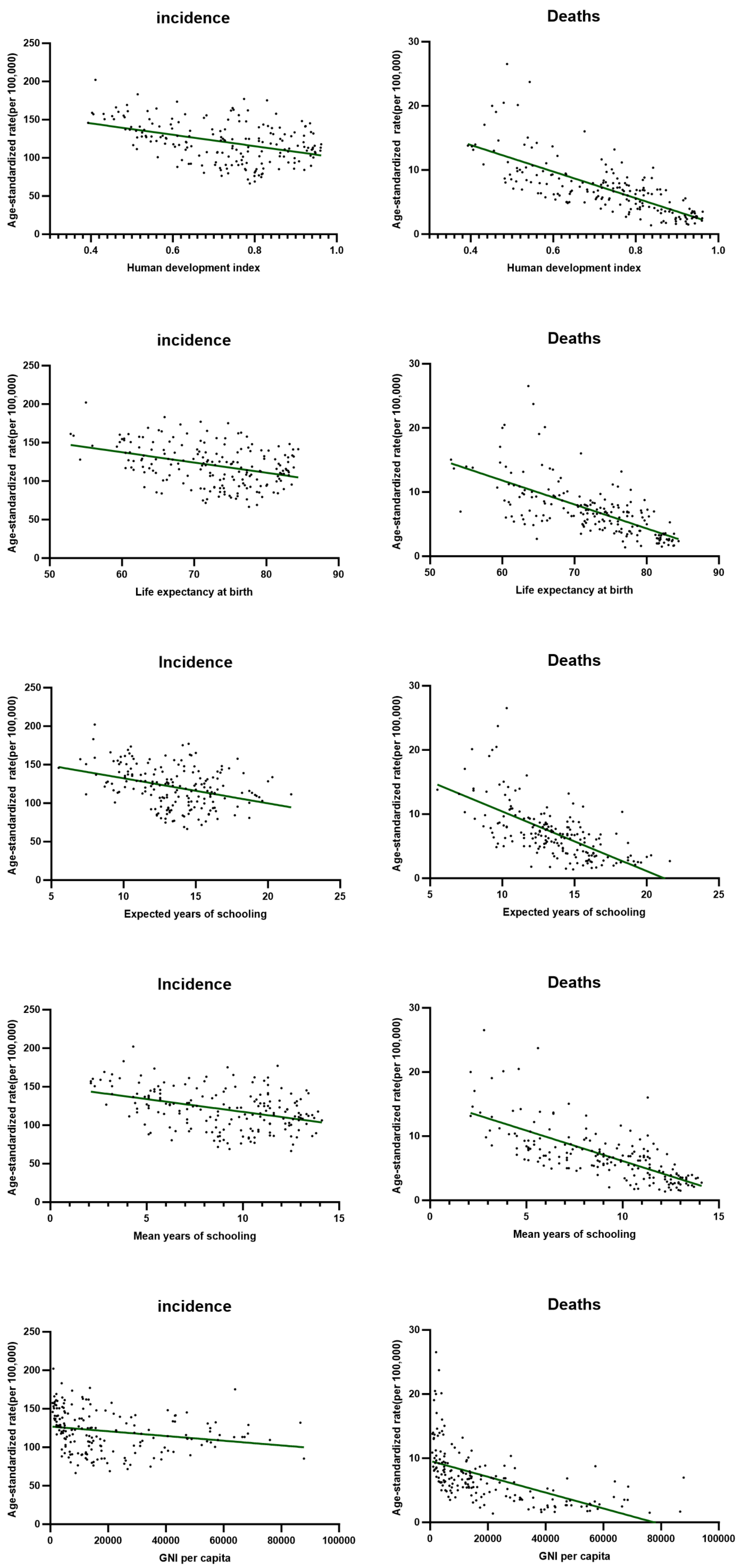

Figure 3. Correlation between the ASIR and ASMR of CBD and HDI, expected years of schooling, mean years of schooling, GNI per capita, and life expectancy at birth.

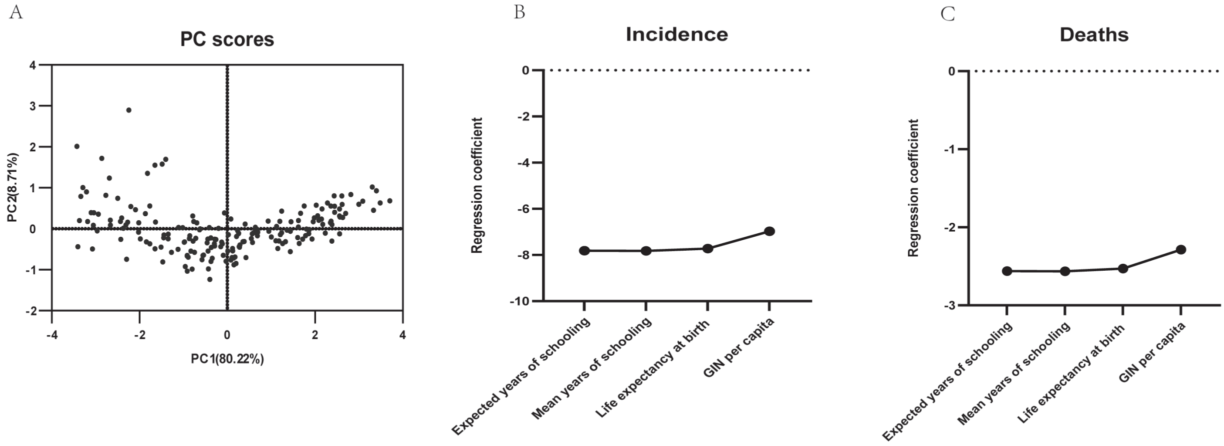

Figure 4. Principal component analysis of the incidence and mortality of CBD. (A) Principal component (PC) score. The first and second principal components are plotted. **(B)** Regression coefficients of ASIR, calculated as a weighted sum, demonstrate the relative contribution to the model of each of the four indicators constituting HDI that were used to generate the model. **(C)** Regression coefficients of ASMR, calculated as a weighted sum, demonstrate the relative contribution to the model of each of the four indicators constituting HDI that were used to generate the model. The four indicators included expected years of schooling, mean years of schooling, GNI per capita, and life expectancy at birth. ASIR = age-standardized incidence rate. HDI = Human Development Index.

Based on the analysis of the incidence and mortality of various CBD in 21 global regions, five specific defects with higher incidence and mortality rates may exert a more significant impact on human development. Consequently, another purpose of our study was to find the correlation between the ASIR and ASMR of five specific birth defects (Figure 5).

3.3. Congenital heart diseases

At the national level, ASIR of congenital heart diseases varied 6.26 times among the 189 countries of the world, ranging from 14.02 (10.13-20.58) to 87.71 (66.73-116.83) per 100,000 livebirths in 189 countries (Supplemental Table S3, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=208*). The ASMR varied 25.92 times among the 189 countries of the world, ranging from 0.38 (10.13-20.58) to 9.85 (4.27-16.17) per 100,000 livebirths in 189 countries (Supplemental Table S3, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=208*). The ASIR of congenital heart diseases decreases with increased HDI (r = -0·77, p < 0.001). Similarly, the ASMR exhibits a reduction with the rise in HDI (r = -0·61, p < 0.001) (Figure 5).

3.4. Congenital musculoskeletal diseases

ASIR of congenital musculoskeletal diseases varied 5.39 times among the 189 countries of the world, ranging from 13.31 (8.08-19.55) to 71.70 (44.44-102.87) per 100,000 livebirths in 189 countries (Supplemental Table S4, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=208*). The ASMR varied 27.33 times among the 189 countries of the world, ranging from 0.03 (0.01-0.05) to 0.82 (0.40-1.31) per 100,000 livebirths in 189 countries (Supplemental Table S4, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=208*). The ASIR of congenital musculoskeletal diseases decreases with increased HDI (r = -0·38, p < 0.001). Similarly, the ASMR exhibits a reduction with the rise in HDI (r = -0·57, p < 0.001) (Figure 5)

3.5. Urogenital congenital anomalies

ASIR of urogenital congenital anomalies varied 4.20 times among the 189 countries of the world, ranging from 6.29 (4.41-8.68) to 26.43 (18.54-37.82) per 100,000 livebirths in 189 countries (Supplemental Table S5, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=208*). The ASMR varied 25.50 times among the 189 countries of the world, ranging from 0.02 (0.01-0.04) to 0.51 (0.25-0.99) per 100,000 livebirths in 189 countries (Supplemental Table S5, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=208*). The ASIR of urogenital congenital anomalies decreases with increased HDI (r = -0·20, p < 0.001). Similarly, the ASMR exhibits a reduction with the rise in HDI (r = -0·49, p < 0.001) (Figure 5).

3.6. Neural tube defects

ASIR of neural tube defects varied 17.56 times among the 189 countries of the world, ranging from 0.43 (0.35-0.53) to 7.55 (5.75-9.62) per 100,000 livebirths in 189 countries (Supplemental Table S6, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=208*). The ASMR varied 292 times among the 189 countries of the world, ranging from 0.02 (0.01-0.03) to 5.84 (2.20-12.40) per 100,000 livebirths in

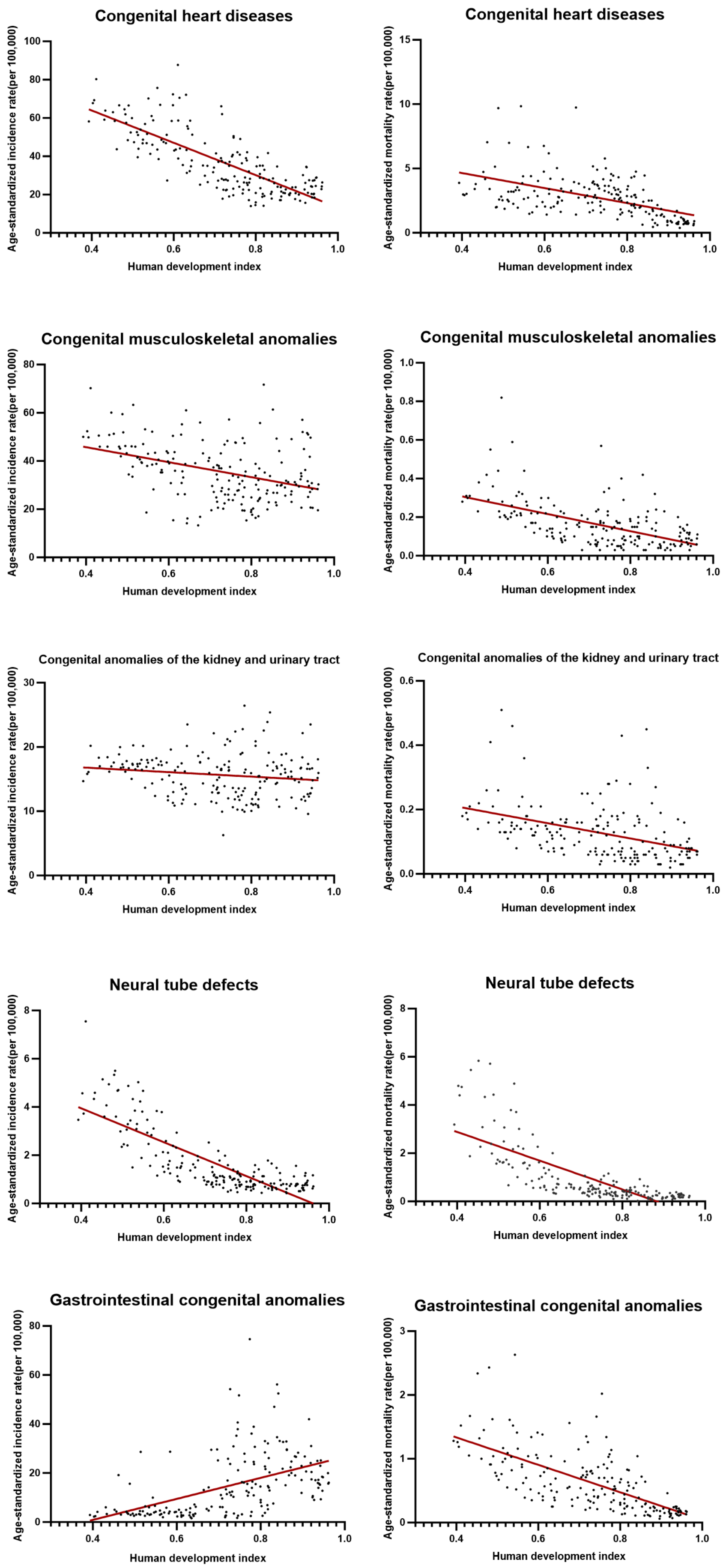

Figure 5. Correlation between the ASIR and ASMR of five types of CBD and HDI.

189 countries (Supplemental Table S6, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=208*). The ASIR of neural tube defects decreases with increased HDI (r = -0·78, p < 0.001). Similarly, the ASMR exhibits a reduction with the rise in HDI (r = -0·84, p < 0.001) (Figure 5).

3.7. Gastrointestinal congenital anomalies

ASIR of gastrointestinal congenital anomalies varied 47.52 times among the 189 countries of the world, ranging from 1.57 (1.21-2.00) to 74.60 (49.75-103.10) per 100,000 livebirths in 189 countries (Supplemental Table S7, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=208*). The ASMR varied 43.83 times among the 189 countries of the world, ranging from 0.06 (0.04-0.12) to 2.63 (0.72-5.13) per 100,000 livebirths in 189 countries (Supplemental Table S7, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=208*). The ASIR of gastrointestinal congenital anomalies decreases with an increased in HDI (r = 0.61, p < 0.001). Similarly, the ASMR exhibits a reduction with the rise in HDI (r = -0·74, p < 0.001) (Figure 5).

4. Discussion

In this study, we revealed a negative correlation of the national levels of human development with the incidence and mortality of CBD. We also quantified the similar contributions of education, life expectancy, and socioeconomic to the incidence and mortality of CBD. Previous studies illustrated the national disparities remained, and there were negative correlations between the annual changes from 1990 to 2019 in ASIR and ASMR with socio-demographic index (SDI) (*4,10*). SDI was based on the assessment of incomes per capita, education level, and fertility rates (*4*). HDI is of greater importance to people's health problems than SDI, as it represents medical accessibility in each country. The difference was that our findings further explain the relationship between national differences in CBD and access to health services by applying the HDI. Our findings suggested the potential targeted countries to decrease the incidence and mortality of CBD.

The similarity in the variability of CBD rates for conditions like congenital heart diseases, congenital musculoskeletal diseases, and urogenital anomalies across 189 countries suggests global consistency in diagnostic standards and genetic prevalence. These conditions are generally recognizable at birth or early infancy, aiding in consistent identification across diverse healthcare systems worldwide (*11-13*), enabling consistent recognition and early treatment worldwide.

Finally, we found that CBD mortality in Haiti and Afghanistan deviates from overall trends. Afghanistan's long-term armed conflict and Haiti's Zika virus outbreak likely contributed to this divergence (*14,15*). Future research should focus on the impact of these factors on CBD in these countries.

On the one hand, the low and medium HDI countries can be the targeted areas to improve their accessibility to health services or their national policy to CBD. In low and medium HDI countries, conflict and social unrest often lead to data based on unverified estimates. Limited diagnostic capabilities, resources, and infrastructure hinder comprehensive CBD surveillance. Severe CBD cases are usually identified, but milder conditions often go undiagnosed and untreated. Enhancing healthcare resources in these nations is a crucial public health priority (*10*). On the other hand, in very high HDI countries, 15 (22.39%) of 67 have high incidence, and 4 (5.97%) have high mortality. Improving management in those with high mortality could enhance outcomes. These countries can learn from better-performing peers, and the data in this article may aid in developing targeted CBD prevention and control policies.

This study also revealed a negative correlation of HDI with the incidence and mortality of congenital heart diseases. Previous research has demonstrated that heterogeneity among geographical regions existed, and the mortality rate declined with increasing SDI (*9,16,17*). They commonly illustrated the importance of access to health care in reducing congenital heart diseases. Prior research has shown that routine ultrasound scans conducted around the 11^{th} to 13^{th} weeks of pregnancy can identify over 50% of congenital heart defects (*18*). There has been a rise in the use of prenatal ultrasound in nations with low and medium HDI (*19*). However, physicians may lack sufficient training in these countries (*20*). Limited access to early pregnancy ultrasounds and underdeveloped healthcare systems may contribute to the higher incidence of congenital heart diseases in these countries. Previous studies have shown that lower income countries face a shortage of cardiac surgeons, with national socioeconomic status positively correlating with access to cardiac surgery (*21*). Therefore, the high mortality from congenital heart diseases in low HDI countries is likely due to limited access to healthcare. Improving healthcare accessibility and quality in these regions is crucial.

Our study revealed a negative correlation of HDI with the incidence and mortality of congenital musculoskeletal diseases. In previous studies, it was demonstrated that the distribution inequity of congenital musculoskeletal diseases was associated with national income, which was consistent with our findings (*22*). Therefore, in low and medium HDI countries, the abilities of these countries' healthcare systems are enhanced, and the experience of the countries that perform better with the same HDI level is learned.

It was illustrated in a past study that the annual change from 1990 to 2019 in the incidence and mortality of urogenital congenital anomalies were negatively associated with HDI (*23*). Our research revealed a negative correlation between the HDI and the mortality rate of urogenital congenital abnormalities across various countries worldwide. Patients with urogenital congenital anomalies, regardless of whether they have abnormal kidney function at birth, require long-term and continuous monitoring of renal function (*24*). Close follow-up by renal specialists and protective measures for renal function, such as avoiding certain antibiotics and optimal timing for surgery, was crucial for the long-term survival of these patients (*24,25*). However, there is still a shortage of renal specialists in low HDI countries (*13,26,27*). To reduce the mortality rate of urogenital congenital anomalies in countries with low HDI, it is crucial to increase the number of renal specialists and improving the accessibility of healthcare services. The relationship between the incidence of urogenital congenital anomalies and HDI was not significant, possibly due to its development being impacted by both hereditary and environmental variables (*13,26,27*).

However, our study focused on the national disparities of ASIR and ASMR of neural tube defects, and we found a negative correlation of HDI with the incidence and mortality of neural tube defects. The leading cause of neural tube defects is pregnant women early in pregnancy if the lack of folic acid (*28,29*). The higher variability in the ASIR of neural tube defects across different countries underscores disparities in folic acid supplementation policies. Low HDI countries often face challenges in awareness and implementation of folic acid programs, leading to higher incidence rates. Nutritional deficiencies in these countries further exacerbate the risk of such birth defects, coupled with a lack of medical resources for early screening and diagnosis. Previous research has indicated that in developing countries, the coverage of folic acid supplementation is low (*28-31*). In contrast, in developed countries, the incidence of neural tube defects has decreased through public initiatives encouraging folic acid supplementation, even implementing fortified foods (*30,32,33*). Therefore, the initial step in low HDI countries is to enhance the crises of nutritional shortages and the healthcare systems. However, in the medium and high HDI countries, policies such as mandatory folic acid consumption and folic acid-enriched food supplements are important.

Our study found a positive correlation between ASIR of gastrointestinal congenital anomalies and HDI. In very high HDI countries, the advanced medical equipment and greater professional training of medical staff likely lead to more diagnosed cases of gastrointestinal anomalies, thus increasing the reported incidence rates. Residents in very high HDI countries may have more frequent exposure to certain environmental factors, such as the use of specific drugs and chemicals, that are linked to gastrointestinal anomalies (*34*). Additionally, the dietary habits inherent in modern lifestyles might also influence fetal development (*35*). We found a negative correlation between ASMR and HDI. Previous studies, consistent with our findings, showed that mortality for gastrointestinal congenital anomalies differs between developing and developed countries (*7*), highlighting the critical role of healthcare accessibility in reducing incidence and mortality.

5. Limitations

Firstly, the study relies on secondary data, which might be subject to reporting biases and inaccuracies, particularly in low and medium HDI countries. In future research, we would testify it in birth cohort so as to mitigate these biases. Secondly, the study identifies significant correlations, it does not establish causation. In our future research, causal relationships should be more explored. The HDI used in our study is highly sensitive to extreme values and cannot comprehensively reflect a national level of human development. Human Development Composite Indices could complement HDI to provide a more comprehensive evaluation of human development in future research (*9*). Thirdly, the estimation data utilized in this study may be subject to the influence of the restricted quality and scope of worldwide GBD data collection, particularly in low and medium HDI countries. Given these limitations, our analysis only demonstrates broad associations rather than causal relationships.

6. Conclusion

In conclusion, this study investigated the latest epidemiologic patterns of and risk factors for CBD at the global, regional, and national levels by HDI (such as education, literacy, GNI per capita, and life expectancy). Compared with other research, our research mainly provided the leading risk factors for the CBD disease burden in different HDI regions, which have important public health significance for the prevention of CBD all over the world.

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[§]These authors contributed equally to this work.
**Address correspondence to:*
Jie Yang, Department of Neonatology, Nanfang Hospital, Southern Medical University, Guangzhou, China
E-mail: jieyang0830@126.com

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