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Time trends in maternal hypertensive disorder incidence in Brazil, Russian Federation, India, China, and South Africa (BRICS): an ageperiod-cohort analysis for the GBD 2021



Xiaochan Wang¹⁺, Fangqun Cheng¹⁺, Qiupeng Fu¹, Peiyu Cheng^{1*}, Jianzhong Zuo^{1*} and Yuhang Wu^{2*}

Abstract

Objectives Maternal hypertensive disorder (MHD) is a leading cause of significant maternal and fetal mortality and morbidity. The BRICS nations are crucial in the global MHD landscape, given their large populations and varied healthcare infrastructures. This investigation evaluates the incidence trends of MHD in BRICS countries from 1992 to 2021.

Study design and methods Data on the number, all-age rate, age-standardized rate (ASR), and the relative change of MHD incidence from this study were sourced from the Global Burden of Disease (GBD) 2021 public dataset to investigate temporal trends in MHD incidence over three decades globally and in BRICS countries. The age-period-cohort (APC) model was used to estimate net drift, local drift, age-specific curves, and period (cohort) relative risks.

Results A 15.87% increase in global MHD cases, alongside a 13.40% decrease in age-standardized incidence rates from 1992 to 2021. MHD incidence rates are declining across various BRICS age groups, except in China and Russian Federation, where most groups exhibit increasing trends. Annual net drift in MHD incidence ranges from – 4.25% in India to 2.38% in China. A shift in the age distribution of MHD cases from younger to older within the childbearing age range is observed in all BRICS nations. Countries exhibit similar age-effect patterns, with decreasing risk with increasing age, and varying period and cohort effects, indicative of differential control measures and temporal incidence trends.

 $^{\dagger}\mathrm{X}iaochan$ Wang and Fangqun Cheng contributed equally to this work.

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Conclusions Global and BRICS-specific reductions in MHD incidence vary in magnitude. Customized preventive strategies, leveraging existing resources, are advisable for BRICS nations to address pregnancy complications. Enhancing primary healthcare and maternal care quality, particularly for older mothers, is imperative.

Keywords Maternal hypertensive disorder, Incidence, Age-period-cohort model, BRICS

Introduction

Maternal hypertensive disorder (MHD), a collective term encompassing various hypertensive conditions that arise during pregnancy, such as gestational hypertension, preeclampsia, eclampsia, and chronic hypertension complicated by superimposed preeclampsia, ranks among the leading causes of maternal and perinatal morbidity and mortality worldwide, affecting an estimated 5-10% of pregnant women [1]. These conditions are characterized by elevated blood pressure, which can precipitate severe complications, including organ damage, premature birth, and, in extreme cases, maternal or fetal mortality [2-4]. The complexity of MHD is further highlighted by its multifactorial etiology, which includes genetic, environmental, and socioeconomic factors [5–7]. Understanding the epidemiology of MHD is essential for developing targeted interventions and enhancing healthcare strategies to mitigate its impact on maternal and child health.

Brazil, Russian Federation, India, China, and South Africa (BRICS) not only account for 43% of the world's population, but also, as World Health Organization (WHO) Director General Margaret Chan declared, "represent a block of countries with a fresh and invigorating approach to global health" [8]. The BRICS countries play a pivotal role in the global context of MHD due to their substantial populations and diverse healthcare systems [9]. These nations confront unique challenges in managing maternal health, including disparities in access to quality care, varying levels of health literacy, and the necessity for culturally sensitive healthcare delivery. The recent update to the Global Burden of Disease (GBD) 2021 database affords a comprehensive and current resource for analyzing the incidence of MHD across these countries [10-13]. This database is invaluable for capturing the latest epidemiological trends and for comparing the burden of MHD both within and among the BRICS nations. Additionally, the Age-Period-Cohort (APC) model represents a sophisticated analytical tool that can be utilized to delineate the effects of age, period, and cohort on MHD incidence [14]. Through the application of the APC model, researchers can identify critical periods for intervention and evaluate how different generations are impacted by MHD, thus providing a more nuanced insight into the disease's epidemiology.

The primary objective of this study is to utilize the GBD 2021 database to investigate the incidence of MHD in the BRICS countries. We will employ the APC model to analyze the interplay between age, period, and cohort effects

on these incidence rates. This approach is designed to elucidate the long-term trends and underlying determinants of MHD incidence within these nations, thereby contributing to a more comprehensive understanding of the disease's epidemiology. The findings of this research are anticipated to inform public health strategies and clinical practices, offering evidence-based guidance for the management of MHD in diverse settings. The significance of this study is underscored by its potential to identify unique challenges and opportunities for intervention in the BRICS countries, which could support efforts to improve maternal and child health outcomes. Ultimately, the insights derived from this research will enrich the global knowledge base on MHD and align with broader objectives to enhance global health.

Method

Data sources

This study utilized data from the GBD 2021 public dataset, which is accessible through the Global Health Data Exchange GBD Results Tool (https://ghdx.healthdata .org/gbd-2021). GBD 2021 provides detailed insights into the disease burden for 371 conditions across 204 countries and territories globally [11–13]. This comprehensive resource encompasses the broadest range of health-related data on disease burden, risks, mortality, and disability, serving as a crucial repository for understanding global health challenges. Notably, GBD 2021 incorporates several enhancements, including the integration of 19,189 additional disability-adjusted life years (DALYs) data sources, the inclusion of 12 new health conditions, and various methodological advancements. Additionally, it accounts for the impact of the COVID-19 pandemic on the global disease burden [11].

In GBD 2021, MHD is defined according to the International Classification of Diseases, 9th edition (ICD-9): 642-642.9 and 10th edition (ICD-10): O10-O16.9 [13]. MHD includes several subcategories: (a) Gestational hypertension is the new onset of hypertension in a pregnant person after 20 weeks' gestation, as defined by having a blood pressure measured>140/90 mmHg on more than one occasion. (b) Preeclampsia is defined by hypertension [>140/90 mmHg] and proteinuria [\geq 0.3 g/l], with or without signs of end-organ damage. (c) Severe preeclampsia is defined by preeclampsia with severe hypertension (>160/100 mmHg) or other signs of end organ damage (liver: low platelets, elevated liver enzymes, coagulation issues; kidney: elevated

creatinine; central nervous system: headaches or visual disturbances), syndrome of hypertension, elevated liver enzymes, low platelets). (d) Eclampsia is defined as hypertension and seizures, with or without proteinuria. This definition excludes chronic hypertension in a pregnant person (hypertension present prior to 20 weeks' gestation) unless superimposed preeclampsia develops. We obtained the incidence numbers, all-age incidence rates, and age-standardized incidence rates for MHD among females on a global scale and within BRICS countries, across various age brackets from 15 to 54 years, covering the period from 1992 to 2021. Notably, the incidence of MHD was estimated by a whole-life population model in the GBD 2021 [11]. Based on the inherent characteristics of the GBD database in terms of model selection, parameter estimation, and the quality and availability of data inputs, the 95% uncertainty intervals (UIs) were obtained by replicating the sample 1000 times, with upper and lower bounds determined by the 2.5th and 97.5th percentiles of the uncertainty distribution [11]. Methodological information and details of the modelling strategy for GBD 2021 have been published elsewhere [11-13]. The relevant data were anonymized and publicly available, and the informed consent waiver was reviewed and approved by the University of Washington Institutional Review Board.

Statistical analysis

Age-period-cohort modelling analysis

In this study, the APC model was employed for data analysis, treating age, period, and cohort as independent variables. The APC model is particularly adept at evaluating the complex interactions between these variables and identifying how they collectively influence the incidence of MHD [15]. Within the APC model, the findings produced several crucial metrics: net drift, local drift, the longitudinal age curve, period relative risk (RR), and cohort relative risk [16]. Net drift represents the log-linear trend across periods and cohorts for the entire population. Local drift indicates the log-linear trend across periods and cohorts within each age group. The longitudinal age curve depicts the anticipated age-specific rates in the reference cohort, adjusted for period effects. The period relative risk quantifies the relative risk of the population across various periods, adjusted for both age and cohort. Similarly, cohort RR quantifies the relative risk across different cohorts, adjusted for age and period [17]. Age, period, and cohort effects were calculated via Poisson regression, expressed as follows:

$$g(Y_j/\mu) = \log(\lambda_j) = u + \alpha \, age_j + \beta \, period_j + \gamma \, cohort_j \quad (1)$$

where λ_j represents the response variable of the net effect on MHD incidence for group j; Y_j and μ represent

the number of incidences and the population at risk, respectively. α , β , and γ represent the coefficients of age, period, and birth cohort of the APC model, respectively. u represents the intercept of the model. Furthermore, we employed the Intrinsic Estimator (IE) method to address the non-identification problem of the APC model, because it is considered to provide the best fit compared to other models [18].

Data arrangement

To ensure consistency with the requirements of the APC model, both age and period data were organized uniformly. Specifically, the incidence of MHD and corresponding population data were categorized according to the following guidelines: age groups were segmented into 5-year intervals (15-19, 20-24, ..., 50-54 years). Notably, age groups below 15 and above 55 were excluded due to the infrequency or nonexistence of MHD cases and related outcomes. Considering transient fluctuations, such as the COVID-19 pandemic, GBD data were harmonized by selecting incidence and population figures from the midpoint of six distinct years (1994, 1999, ..., 2019), rather than employing five-year averages to represent the periods in question. Since birth cohorts are determined by subtracting the age at the time of the event from the corresponding period (i.e., cohort=period - age), the resulting birth cohorts spanned from 1940 to 1944 (median year 1942) to 2000-2004 (median year 2002).

We obtained estimated parameters using APC analyses with the age-period-cohort web tool designed by the National Cancer Institute (https://analysistools.cancer.go v/apc/) and plotted using the ggplot2 package in R statistical program (version 4.2.3). In this web tool, input data consist of age-specific numbers of events, in the form of a rate matrix of paired columns. Output functions include model-based estimators of cross-sectional and longitudinal age-specific rates; period and cohort rate ratios that incorporate the overall annual percentage change (net drift); and estimators of the age-specific annual percentage change (local drifts) [19]. To test the significance of evaluable parameters and functions, the Wald χ 2 test was used, and all statistical tests were two-sided.

Results

Incidence of maternal hypertensive disorder trends from 1992 to 2021

Table 1 presents the population, total incidence, all-age incidence rate, age-standardized incidence rate, and net drift of incidence for the world and BRICS countries. Over the past three decades, the number of MHD cases increased from 15,578 thousand (95% UI 12,916 to 19,075) in 1992 to 18,050 thousand (95% UI 15,336 to 21,519) in 2021, corresponding to a 15.87% increase. The age-standardized incidence rate decreased from 533.44

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18,050 (15,356, 21,519)	403 (321, 522)	359 (309, 428)	249 (185, 338)	291 (224, 372)	2,987 (2,465, 3,696)	2,294 (1,878, 2,835)	1,176 (853, 1,634)	691 (534, 896)	231 (194, 273)	240 (204, 277)
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APC=age-period-cohort

* Parentheses for all GBD health estimate indicate 95% uncertainty intervals due to the inherent characteristics of model selection, parameter estimation, and the quality and availability of data inputs for GBD 2021 # Parentheses for net drift indicate 95% confidence intervals (95% UI 444.86 to 647.87) per 100,000 population in 1992 to 461.94 (95% UI 392.73 to 551.65) per 100,000 population in 2021, indicating a 13.40% decrease. The APC model estimated a net drift of -0.71% (95% confidence interval [CI] -0.98 to -0.43) in the MHD incidence rate from 1992 to 2021 globally (Table 1).

The incidence of MHD cases has significantly decreased in all BRICS countries, except for the Russian Federation and South Africa. Notably, China has demonstrated the most substantial decrease, at 41.24%. In 2021, the all-age incidence rate and age-standardized incidence rate for MHD varied from 99.53 (95% UI 76.92 to 128.96) and 110.12 (95% UI 85.24 to 142.54) per 100,000 population in China to 827.47 (95% UI 705.06 to 956.76) and 754.12 (95% UI 640.35 to 871.73) per 100,000 population in South Africa, respectively. In the Russian Federation, the age-standardized incidence rate of MHD has shown an upward trend from 1992 to 2021, reaching 30.04%. Conversely, the other BRICS countries have exhibited a declining trend. Among these nations, India has experienced the most significant decrease, with a rate of 56.12%, while South Africa has shown the least significant decrease, at 28.22%. According to the APC model estimates, the annual net drift in the MHD incidence rate ranged from -4.25% (95% CI -4.95 to -3.55) for India to 2.38% (95% CI 0.29 to 4.51) for China within the BRICS countries (Table 1).

Time trends in maternal hypertensive disorder incidence across different age groups

Figure 1A depicts the annual percentage change in the incidence rates of MHD for each 5-year age group ranging from 15 to 54 years. Globally, the preponderance of age groups demonstrated local drift values that were predominantly negative, indicative of a decline in the incidence rate of MHD for the majority of age groups. A parallel trend was observed in Brazil, India, and South Africa. Notably, China and the Russian Federation exhibited positive local drift values for most age groups, suggesting an increase in the incidence rates of MHD. Figure 1B illustrates the temporal trends in the number of MHD cases by age group. The majority of global MHD cases were recorded among the female population of childbearing age (20-34 years), and comparable distributions were observed across all BRICS countries. Concurrently, the distribution of MHD cases exhibited a transition pattern from the younger age group (20-24)years) to progressively older age groups (25-29, 30-34, 35-39 years).

Age, period and cohort effects on maternal hypertensive disorder incidence

Figure 2 illustrates the estimates of Age-Period-Cohort (APC) effects derived from the APC model for global

and BRICS countries. Overall, a similar age effect pattern is observed across all nations, with risk decreasing as age increases (Fig. 2A). Globally, period effects have remained relatively consistent over the past three decades, with similar patterns also observed in Brazil. In India and South Africa, period effects exhibit a continuous decline, suggesting effective control of MHD incidence rates over time. However, China and the Russian Federation demonstrate a similar "J" shaped trend, with the risk increasing and remaining above zero (Fig. 2B). Cohort effects have remained relatively stable both globally and across all BRICS countries. Specifically, there is a slight decrease in the successive birth cohort over the past 30 years in global, Brazil, India, and South Africa, whereas China and the Russian Federation exhibit a modest increasing trend followed by a decrease after 1972 (Fig. 2C).

Discussion

To the best of our knowledge, this investigation represents the first use of the APC model for analyzing MHD incidence, thereby enabling comparative insights across both global and BRICS nations. The primary contribution of our research, in contrast to previous GBD 2019 reports [20, 21], is the provision of a more nuanced understanding of disease trajectory, utilizing age, period, and cohort effects to differentiate various incidence risk factors on a global scale and specifically within BRICS countries. A further notable advancement is the quantification of localized changes in the incidence age distributions and age at onset from 1992 to 2021, both globally and within BRICS. This methodology allows for the elucidation of temporal incidence trends within specific age groups and accommodates period- and cohort-specific effects. Our analysis, based on the APC model, supplies crucial information for policymakers and healthcare professionals by delivering a detailed examination of MHD incidence trends and assessing the effectiveness of related health services.

Between 1992 and 2021, the total number of MHD incidences worldwide increased by 15.87%, likely driven by population growth and multiple gestations. A marked heterogeneity exists in the incidence rate and longterm trends of MHD across the BRICS nations. Among the BRICS countries—Brazil, China, India, and South Africa—there are varying degrees of decrease, while the Russian Federation shows an increase. However, after adjusting for variations in age distribution, the pattern of age-standardized incidence of MHD over the past three decades has remained unchanged among the BRICS countries, indicating that, in addition to the impact of demographic shifts, other fundamental factors are driving the observed changes in the incidence of MHD. We have witnessed the vigorous development of the maternal

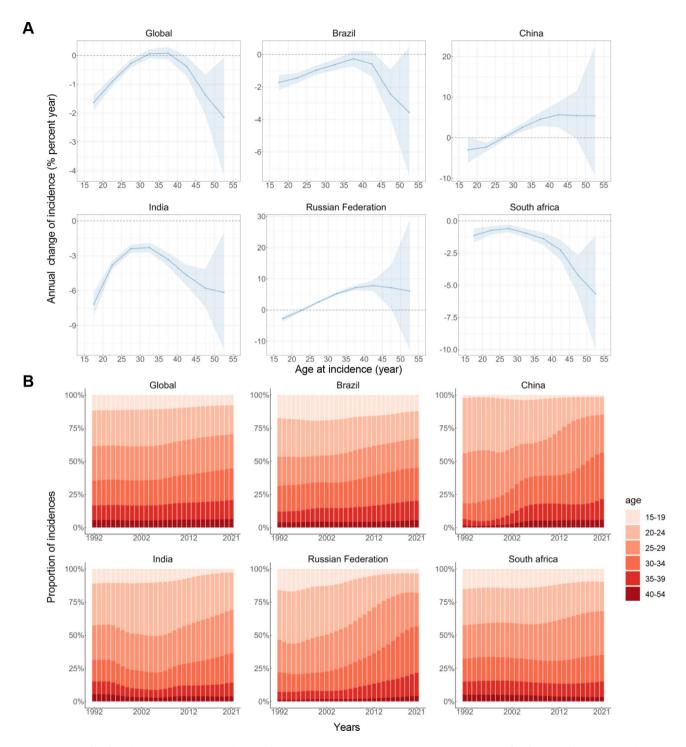


Fig. 1 Local drifts of incidence rate and age distribution of incidences in global and BRICS, 1992–2021. (A) Local drifts of maternal hypertensive disorder incidence rate (estimates from age-period-cohort models) for 8 age groups (15–19 to 50–94 years), 1992–2021. The dots and shaded areas indicate the annual percentage change of incidence rate (% per year) and the corresponding 95% Cls. (B) Temporal change in the relative proportion of maternal hypertensive disorder incidences across age groups, 1992–2021.

and child health construction program and the encouraging progress in the political, economic, and cultural fields over the past three decades [22–25]. However, our results may not substantiate the validity of differentiating priority areas based solely on socioeconomic development, despite the significant role of economic support in gestational healthcare for both pregnant women and their fetuses [26]. The individual-level interaction among diverse determinants across the life course, from conception to death, may indirectly compromise the capacity to

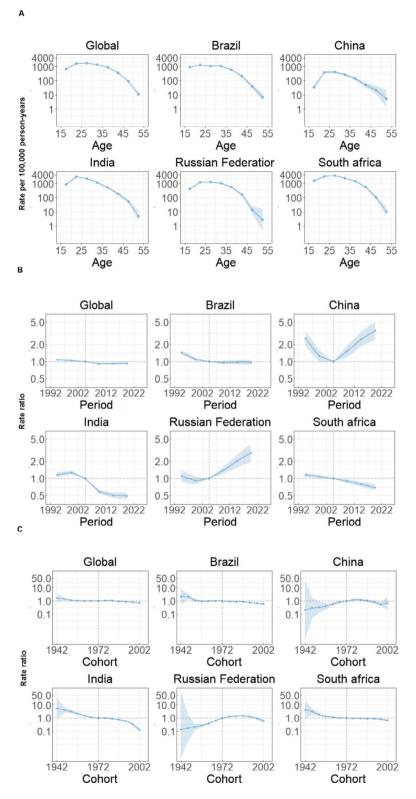


Fig. 2 Age, period and cohort effects on maternal hypertensive disorder incidence in global and BRICS. (A) Age effects are shown by the fitted longitudinal age curves of incidence rate (per 100,000 person-years) adjusted for period deviations. (B) Period effects are shown by the relative risk of incidence rate (incidence rate ratio) and computed as the ratio of age-specific rates from 1992–1996 to 2017–2021, with the referent cohort set at 2002–2006. (C) Cohort effects are shown by the relative risk of incidence rate and computed as the ratio of age-specific rates from the 1940 cohort to the 2004 cohort, with the referent cohort set at 1972. The dots and shaded areas denote incidence rates or rate ratios and their corresponding 95% Cls

manage the disease burden in the context of continuous economic growth and social development. Furthermore, it is noteworthy that an increasing number of cases of MHD have shifted to higher age groups, which may be influenced by the specific national conditions of individual countries [21].

Considerable disparities in the incidence rates of MHD are evident among different countries. National policymakers may assess their country-specific attributes in relation to this issue to inform decision-making, taking into account their country's positioning relative to other nations. However, the potential triggers for MHD are frequently queried, with age, period, and cohort effects requiring further investigation. In light of these considerations, this study has focused on analyzing the incidence patterns of MHD in global and BRICS countries using the APC framework. Our findings consistently indicate an age effect both globally and within the BRICS countries, suggesting that the risk of MHD decreases with increasing age. This finding seems to contradict the consensus established by previous studies, which have posited that "elderly primiparous women should be considered a highrisk population for pregnancy complications, including hypertensive disorders of pregnancy" [27, 28]. However, we acknowledge that in the model employed for the GBD 2021 dataset, the incidence of MHD is computed based on the entire female population across all ages, rather than exclusively on the potentially childbearing population (ages 15-54). The limitation stemming from the raw data may be a significant factor affecting the age effect, which has also been noted in prior research [20]. Consequently, interpretations of findings related to the age effect should be made with caution.

Brazil, India, and South Africa exemplify the impact of relatively favorable period and cohort effects on the incidence rate of MHD. Brazil is among the countries with the highest levels of income inequality worldwide [29]. Over the past few decades, the country has implemented policies aimed at reducing health disparities. Amidst significant political and social transformations, Brazil established the Unified Health System in 1989, granting all Brazilians the right to access free healthcare, funded by taxes and social contributions [30]. Additionally, the Family Health Strategy (FHS) was developed, a community-based approach intended to provide comprehensive primary healthcare [31]. The observed improvements have exerted a favorable influence on the perinatal health of women, incorporating variables such as family income, parental educational level, and access to potable water, among other factors [32]. The Government of India has endeavored to enhance the public health system via various national programs. India's healthcare infrastructure spans primary, secondary, and tertiary levels [33]. Primary health care serves as the first point of care within the Indian public health system [33]. Each primary health care center is staffed with one doctor and three to five nurses [34]. Auxiliary Nurse Midwives (ANMs) are rural healthcare workers who serve as the first point of contact for accessing health services in Indian rural areas. The health services provided by ANMs encompass screening, management, and referral for pregnancy and neonatal complications. Secondary health care in the Indian medical system is administered by the government and includes block hospitals, district hospitals, and mobile medical units. These facilities offer specialized care to patients referred from primary health care centers by specialists. In tertiary health care settings, patients referred from primary and secondary health care centers typically receive specialized curative and preventive care. The Indian government initiated the National Rural Health Mission (NRHM) in 2005, with the aim of expanding health care system coverage to rural areas and improving the existing health care infrastructure [34]. Many risk factors for MHD, such as early pregnancy, multiple gestations, advanced maternal age, anemia, infection in mothers, and socio-economic deprivation, are highly prevalent among South African women, contributing significantly to the regional disease burden of MHD [35]. Despite the adverse environmental and economic conditions, changes in health policies and legislation may have contributed to the limited improvement observed in the poor status of MHD over the past three decades [36].

Despite the multifaceted efforts of the Chinese and Russian governments to alleviate the burden of MHD tailored to their respective national circumstances, these measures appear insufficient to adequately address the challenges posed by socio-environmental factors. Current evidence indicates a complex and fluctuating prevalence of MHD in China. Following the termination of China's distinctive family planning policy, the ephemeral fertility surge and the corresponding increase in maternal age necessitated an expedited response from the region to mitigate the impact of MHD. Moreover, the incidence of MHD in China is clearly influenced by social events, such as increased air pollution, social stress, the prevalence of poor lifestyle habits, and outbreaks of infectious diseases (e.g., the SARS outbreak in 2003 and the COVID-19 pandemic) [37-39]. These challenges need to be addressed as China strives to promote maternal and child health. The vast territory, varying climatic and natural conditions, as well as historical and geopolitical features, have influenced the uneven distribution of the Russian population. High-quality health care in Russia is predominantly provided in a few major centers of the country. This high concentration of resources is not conducive to the equitable provision of maternal health-care services, as less than one-third of the total Russian population resides in

these large urban areas [40]. Behaviors highly associated with blood pressure, such as smoking and alcohol misuse, are prevalent among Russian women of childbearing age and frequently occur concurrently [41]. Additionally, the persistent impact of the Chernobyl nuclear reactor accident in the former Soviet Union on the reproductive health and immunological status of the present-day Russian population may still be an important factor contributing to the high prevalence of pregnancy complications, including MHD, in the region [42].

Admittedly, several limitations warrant acknowledgment. First, the availability and quality of raw data are limiting factors in estimating the incidence of MHD. When high-quality or accessible MHD data from national or local maternal and child health systems were not available, discrepancies were observed in the GBD estimates of MHD. Second, this study is lacking in a more granular analysis to capture subnational variations, given the existence of disparities in health issues and access to healthcare providers and services at the subnational level. Lastly, period and cohort effects were investigated using cross-sectional data from the most recent GBD 2021 estimates, which span from 1992 to 2021. Nevertheless, future cohort studies conducted in various countries are necessary to assess relative risks at specific locations and times, as well as to evaluate the differential risks among susceptible populations.

Conclusion

Significant progress has been made globally, as well as within the BRICS countries, in reducing the incidence of MHD, albeit to varying degrees. Acknowledging the diverse environmental backgrounds among the BRICS nations, we recommend tailoring the implementation of preventive measures for pregnancy complications to specific contexts, leveraging existing policy frameworks, manpower, and financial resources in a gradual manner. Furthermore, it is imperative to establish and refine primary healthcare systems, enhance the accessibility and quality of maternal and perinatal care, with particular attention paid to the older maternal age group.

Abbreviations

APC	Age-Period-Cohort
ANMs	Auxiliary Nurse Midwives
BRICS	Brazil, Russian Federation, India, China, and South Africa
CI	Confidence interval
DALYs	Disability-adjusted life years
FHS	Family Health Strategy
GBD	Global Burden of Disease
ICD	International Classification of Diseases
IE	Intrinsic Estimator
MHD	Maternal hypertensive disorder
NRHM	National Rural Health Mission
RR	Relative risk
Uls	Uncertainty intervals
WHO	World Health Organization

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Author contributions

Xiaochan Wang: conceptualization (lead), writing-original draft (lead), formal analysis (lead), and writing-review and editing (equal). Yuhang Wu: data curation (equal) and software (equal), conceptualization (supporting), formal analysis (supporting), and writing-review and editing (equal). Qiupeng Fu: methodology (lead), formal analysis (supporting), and writing-review and editing (equal). Peiyu Cheng: conceptualization (supporting), data curation (equal), project administration (equal) and writing-review and editing (equal). Fangqun Cheng: resource (equal), conceptualization (supporting), investigation (equal), project administration (equal) and writing-review and editing (equal). Jianzhong Zuo: conceptualization (supporting), supervision (equal), data curation (equal), project administration (equal) and writing-review and editing review and editing (equal). All authors gave their final approval and agree to be accountable for all aspects of the work.

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Data availability

The datasets generated during and/or analyzed during the current study are available in the GBD Data Tool repository (http://ghdx.healthdata.org/gbd-res ults-tool). This public link to the database of GBD study is open, and the use of data does not require additional consent from IHME.

Declarations

Ethics approval and consent to participate

Data were all analyzed anonymously, so ethical approval was not needed. All methods in this paper were performed following the relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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