Comparison of disease burden and major risk factors of early and late-onset neonatal sepsis in China and the USA, 1990-2019

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Research Article

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Abstract

Background: Neonatal sepsis has high morbidity and mortality, and there are differences between developing and developed countries in terms of its risk factors and disease burden. However, no systematic comparative analysis of this disease burden has been reported in recent years.

Methods: Using the Global Burden of Disease Study (GBD) 2019 as a data source, we assessed the prevalence, incidence, and disability-adjusted life years (DALYs) of early and late-onset neonatal sepsis in China and the United States of America (USA). We also analyzed DALYs rates due to short gestation and low birthweight, and summary exposure value (SEV) for these two risk factors. Joinpoint regression models were applied to analyze the temporal trends in associated epidemiological indicators of neonatal sepsis.

Results: From 1990 to 2019, the incidence and prevalence of neonatal sepsis in China showed a significant upwards trend compared with the largely stable trend in the USA. DALYs due to short gestation and low birthweight for neonatal sepsis in both genders showed a decreasing trend in both countries, while years lived with disability (YLDs) in China showed a fluctuating increasing trend.

Conclusions: DALYs attributed to short gestation and low birth-weight for neonatal sepsis in both countries showed a decreasing trend, while the YLDs and SEVs of these two risks are on the rise in China. Therefore, Chinese public health policy needs to be geared towards controlling these risk factors, learning from the advanced health policy planning and perinatal management experiences of developed countries, and improving neonatal follow-up and rehabilitation interventions.

1 Introduction

Neonatal sepsis is a condition characterized by clinical signs of bacteremia and systemic infections [1]. It has significantly higher morbidity and mortality rate in the neonatal period than in any other stage of life [2]. Its prevalence ranges from 1 to 5 cases per 1000 live births in developed countries and 49–170 cases per 1000 live births in developing countries [3]. In a study on the causes of neonatal death in 194 countries, sepsis accounted for 15% of the total mortality [4]. Another survey in developing countries found that sepsis accounted for 40% of neonatal death [5]. With advances in neonatology and the increased survival of low-birth-weight infants, especially very low birthweight infants, neonatal sepsis is not being cured accordingly and the disease burden of sepsis is increasing[6].

The most important risk factors for the development of sepsis in the neonatal period are short gestation and low birthweight [7]. Although the incidence of early neonatal sepsis appears to decrease with the improvement in obstetric care as well as with the use of intrapartum antibiotics [8], it is interesting to note that the incidence of late neonatal sepsis appears to increase with the survival of preterm and very low birthweight infants [9].

The incidence of neonatal sepsis may reflect differences in income levels in different countries, corresponding differences in healthcare resources and healthcare settings, and the level of medical technology [10]. Neonatal sepsis is probably the most treatable and preventable cause of childhood infectious diseases globally [11].

No systematic comparative analysis of neonatal sepsis morbidity, prevalence, and burden of disease between developing and developed countries has been reported in recent years. This study aimed to use data from the

Global Burden of Disease Study (GBD) 2019, taking China and the United States of America (USA) as examples, to estimate the prevalence, incidence, disability-adjusted life years (DALYs), and major risk factors of neonatal sepsis in developing and developed countries. With this, we also aim to highlight measures for improvement in health policy planning and perinatal management, especially in developing countries.

2 Materials and Methods

2.1 Data source and study population

The GBD 2019 is a study that utilizes the Cause of Death Ensemble Model (CODEm) and spatiotemporal Gaussian process regression models to estimate the burden of disease using epidemiological indicators, such as the incidence and prevalence of 369 diseases and injuries in 204 countries and territories, as well as comprehensive indicators such as DALYs including years of life lost (YLLs) and years lived with disability (YLDs) with 87 risk factors attributed to them. Details on the specific methodology used to calculate the burden of disease can be found in the published article[12, 13]. And public information is available online (http://ghdx.healthdata.org/gbd-results-tool). We collected data concerning neonatal sepsis by nation, sex, and day of age from 1990 to 2019 on February 16 to 18, 2022, including the following information of early and late onset neonatal sepsis between males and females in China and the USA: (1) The incidence, prevalence, and mortality; (2) The DALYs, YLLs, and YLDs; (3) All risk factors in GBD 2019 for neonatal sepsis in the above population, and their SEVs values for low birthweight and short gestation [14].

According to GBD 2019, early onset neonatal sepsis occurs in early neonates (0-6 days), while late onset neonatal sepsis occurs in late ones that are 7-27 days old. DALYs are calculated as the sum of years of life lost due to premature death (YLLs) and nonfatal health impairment (YLDs) by cause, age, and sex [15]. Short gestation was defined as a gestational age at birth less than the lowest-risk age (38 weeks), while low birthweight was defined as a birthweight less than the lowest-risk weight (2500 g). Both are leading level 4 risk factors for diseases in children under 5 years of age [16]. The summary exposure value (SEV) represents the exposure dose of a population to a risk factor, which is the result of excess risk-weighted prevalence [17]. SEV values range from 0 to 100, with 0 representing no risk of exposure to the population and 100 representing the highest risk level of exposure [12]. This study was performed in accordance with Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) [18]. Informed consent was not required for this study which was considered non-human study.

2.2 Statistical analysis

To determine the trends of different epidemiological indicators over time, we used the Joinpoint Regression Program (version 4.9.0.0, National Cancer Institute, Rockville, MD, USA) for the analysis. This program finds statistically significant trend segments by establishing the interval segmentation function joinpoints with minimum mean squared errors and its interval function fit after the sequential testing procedure [19]. To ensure the credibility of the results, we selected the maximum number of joinpoints as three and derived the annual percentage change (APC), average annual percentage change (AAPC), and 95% CI for the different stages. AAPC was calculated as the average weighted by the length of the APC interval and was assessed using a Z

test to determine if it was significantly different from 0. Statistical significance was set at $p < 0.05$. All epidemiological indicators were expressed in units of 100,000 live births, except for SEVs, which were expressed as a percentage. Besides, all rates were age-standardized.

3 Results

We have found that the temporal trend changes in mortality of neonatal sepsis derived from the joinpoint regression models are identical to the temporal trend changes in YLLs; therefore, mortality rates were not separately tabulated and plotted.

3.1 The temporal trends in the prevalence and incidence of neonatal sepsis, 1990-2019

The temporal trends in the prevalence and incidence of early and late onset neonatal sepsis by sex in China and the USA are presented in **Figure 1** (A, B) and **Figure 2** (A, B), respectively; their specific APC values are presented in **Supplementary table 1** and **Supplementary table 2**. Details on the values of each epidemiological indicator rate in 1990 and 2019 can be found in **Supplementary table 3**. Regarding the prevalence of early and late onset neonatal sepsis, the temporal trends were essentially the same in the USA and China. Compared to the prevalence of neonatal sepsis in the USA, which has remained roughly constant, the prevalence of neonatal sepsis in China has been trending upwards, showing a significant increase, especially from 2017 to 2019, both in neonates with early (APC 2.6; 95% CI 0.9, 4.2) and late (APC 2.6; 95% CI 1.0, 4.3) onset of neonatal sepsis. Among the early neonates, the incidence of neonatal sepsis showed an overall decreasing trend in the USA and a significant overall increasing trend in China. The incidence of late onset neonatal sepsis increased in both the USA and China, with the increasing trend being higher in Chinese neonates (males: AAPC 0.6; 95% CI 0.3, 0.8; females: AAPC 0.6; 95% CI 0.4, 0.7) than in American neonates (males: AAPC 0.5; 95% CI 0.4, 0.6; females: AAPC 0.2; 95% CI 0.0, 0.3). In addition, when comparing early and late neonates, the incidence of neonatal sepsis in China was higher in the former group than that in the latter in 2019.

3.2 The temporal trends in the DALYs, YLDs, YLLs rates of neonatal sepsis, 1990-2019

The temporal trends in the DALYs, YLDs, and YLL rates of early and late onset neonatal sepsis stratified by sex in China and the USA are presented in **Figure 1** (C, D, E) and **Figure 2** (C, D, E), and the exact values are detailed in the joinpoint regression models in **Table 1** and **Table 2**. The DALYs rates for early onset neonatal sepsis in both countries showed a relatively significant decreasing trend. However, China has shown a consistent and overall decreasing trend in DALYs rates among late onset neonatal sepsis compared with the USA, where it increased, then decreased (starting in 2003 for male neonates and 2006 for female neonates). As of 2019, DALYs rates were higher in both sexes in the USA than in China, higher in male than in female neonates, and higher in neonates with early onset neonatal sepsis than in those with late ones in both countries. For YLDs rates of neonatal sepsis, there was a fluctuating significant increase in male (AAPC 1.4; 95% CI 0.9, 2.0) and female neonates (AAPC 2.6; 95% CI 2.3, 2.8) in China and an overall decreasing trend in male (AAPC -3.1; 95%

CI -3.9, -2.3) and female neonates (AAPC -2.3; 95% CI -2.8, -1.8) in the USA. This change in the curve did not differ significantly between neonates with the early and late onset neonatal sepsis. The trends in YLLs and DALYs rates were essentially the same in both countries.

3.3 The temporal trends in the DALYs rates due to short gestation and low birthweight, 1990-2019

The curves of DALYs rates per year in neonates with neonatal sepsis due to short gestation and low birthweight is shown in **Figure 3** and could be supported by the joinpoint regression models in **Table 1** and **Table 2**. There was a significant downward trend from 1990 to 2019 in the DALYs rates of early onset neonatal sepsis due to short gestation and low birthweight in both the USA and China. Moreover, DALYs rates were lower in both sexes in China than in the USA, and, in terms of decreasing trend, Chinese male early neonates had the maximum rate of change (AAPC -2.0; 95% CI -2.4, -1.6) in DALYs rates due to low birthweight.

DALYs rates for late onset neonatal sepsis due to short gestation and low birthweight in both sexes in the USA increased and then decreased, showing a slight overall upward trend. In contrast, in China, DALYs rates due to these two risk factors showed a stable decreasing trend overall. Although Chinese male late neonates had the highest decreasing trend values among the two age groups stratified by country, they both showed a slightly increasing trend from 2013 to 2019 for DALYs rates due to short gestation (APC -1.7; 95% CI -2.0, -1.4) and low birthweight (APC -2.3; 95% CI -2.7, -2.0). In general, DALYs rates of neonatal sepsis due to these two risk factors were higher in neonates with early onset neonatal sepsis than in those with late ones in both countries.

3.4 The temporal trends in the SEV rates of short gestation and low birthweight, 1990-2019

The curves of SEV rates for short gestation and low birthweight are shown in **Figure 4**. Overall, the SEV rates of both short gestation and low birthweight in early and late onset neonatal sepsis in China were lower than those in the USA, and both rates first decreased, followed by a slightly increase. While in the USA, the SEV rates for these two risk factors first increased and then decreased in early neonates, and steadily decreased in late neonates. The magnitudes of changes in all the above trends were small.

4 Discussion

In this study, the incidence and prevalence of early and late-onset neonatal sepsis in China showed an increasing trend from 1990 to 2019 compared to the USA, which is consistent with the report by Tao Pan et al. [20]. Meanwhile, there has been a decreasing trend in DALYs of neonatal sepsis in both China and the USA and a sustained decline in DALYs due to short gestation and low birthweight in China, which may be related to the better management of risk factors for neonatal sepsis. Moreover, the incidence and DALYs of sepsis in neonates with early-onset presentation were higher than in those with late-onset sepsis. Although YLDs represented only a small percentage of DALYs, they showed a sizable upward trend in China. The first reason could be that with the development of neonatal specialties, the survival rate of short gestation and low

birthweight neonates has increased, but many of them cannot be fully cured and lead to more persistent disabilities instead[21]. Second, a large proportion of neonates in China are discharged early against medical advice and without complete care because of the heavy financial burden on the child's family and lack of comprehensive health insurance coverage [22]. This scenario significantly reduces the survival rate of short-gestation and low-birth-weight neonates and increases the risk of complications, such as cerebral palsy. Therefore, Chinese public health policy should aim at gradually promoting comprehensive health insurance coverage, improving the social welfare system, developing a perinatal regionalization system, and enhancing neonatal follow-up and developmental care [23]. Third, neonatal sepsis may lead to cerebral white matter damage and increase the susceptibility of the brain to subsequent injury through a free radical attack, production of pro-inflammatory cytokines, and hypoxic-ischemic encephalopathy due to hypotension and impaired autoregulation of cerebral blood flow[24]. With the development of measures to assess and document neurocognitive outcomes in recent years, long-term follow-up of high-risk populations has intensified, and the consequences of disability due to neonatal sepsis have been studied [25]. To improve neurological deficits, neonatal brain development can be promoted by enhancing sensory stimulation and other measures [26].

The results of this study suggest that the two top risk factors for the development of neonatal sepsis are short gestation and low birthweight, which are consistent with previous reports [27, 28]. Previous studies have found that the incidence of neonatal sepsis is inversely related to gestational age, with 33% of infants born at less than 28 weeks, and up to 60% of those born at less than 25 weeks, developing neonatal sepsis [27]. Preterms with low birthweight are three to ten times more likely to develop sepsis than full-term infants with normal birthweights [8]. It is well known that low IgG levels in short gestation and low birthweight infants predispose them to infection because of the reduced activation of the complement system, which promotes antibody-dependent cytotoxicity and opsonization [29]. Meanwhile the rapid dominance of Amoeba species in the gut microbiota of such neonates during the first week of life, which remains at high levels until 28 days after birth, also results in low immunity. Additionally, they have a high chance of requiring invasive mechanical ventilation and a long duration of hospital stay. This leads to an increased risk of hospital-acquired infections and a high incidence of necrotizing small-bowel colitis, which can lead to neonatal sepsis [30, 31]. Our study found that in China, SEVs of short-gestation and low-birth-weight neonates decreased and then increased in both early and late-onset neonatal sepsis. The early decline is related to measures such as universal preconception and pregnancy care, early detection of pregnancy complications, and timely intervention in our country [23]. In recent decades, China's rapid economic development has boosted the development of healthcare, especially in 2013 when the Chinese government implemented a risk management strategy to reduce the maternal mortality ratio (MMR). This involved establishing a national referral and treatment network for critically ill mothers and newborns, with 3,369 and 3070 maternal and neonatal intensive care centers respectively [32]. This close relationship between economic development and healthcare is understandable given that GDP is negatively correlated with infant mortality (in the long term) and positively correlated with life expectancy [33]. However, China still has difficulties in perinatal management. First, the two-child policy has led to a significant increase in the proportion of pregnant women of advanced age, menstruating mothers, and irregular prenatal checkups, with a corresponding increase in the proportion of pregnant women at high risk for complications [34]. Second, since 2018, it was regulated that medical expenses for rural women giving birth in hospital will only be paid by the basic medical insurance for urban and rural residents, and the Chinese government will no longer subsidize it [32]. Since providing quality health care to pregnant women is necessary to prevent preterm labor, this move

is likely to have some adverse impact on neonatal care [35]. Third, although the average annual incidence of preterm birth in China fell in the middle to upper range of 204 countries and regions in the world from 1990 to 2019, its incidence in 2019 was still the third highest in the world, merely after India and Pakistan [36]. Finally, improving cure rates still remains a key point for reducing the disease burden of neonatal sepsis in China, during which improvements in treatment practices will help. Therefore, China needs to further learn from the perinatal management practices and experiences of high-income countries, improve its neonatal network and care techniques, optimize obstetrics and drug treatment, and improve health services [22]. Examples of such initiatives include ensuring that all births are attended by skilled staff whenever possible, increasing coverage of prenatal steroid treatment, etc [36]. It is also vital to improve hand hygiene, use less invasive care, increase breastfeeding rates, and provide developmental care for sepsis in preterm infants [37].

This study has some limitations. First, GBD 2019 still faces the challenge of insufficient data availability because the collected data originate from areas with different ways of keeping medical records, and data processing and mathematical modeling are not fully corrected [13]. Second, there is still heterogeneity in diagnostic criteria and detection levels of neonatal sepsis, with inevitably missed diagnoses leading to less comprehensive statistics. Finally, the combined role of risk factors has not been considered; therefore, the estimation of the risk-attributed burden of disease may be flawed.

5 Conclusions

By analyzing data on the burden of neonatal sepsis in China and the USA, this study explores the global differences between developing and developed countries. DALYs for neonatal sepsis and DALYs due to short gestation and low birthweight showed a decreasing trend between 1990 and 2019 in both China and the USA. However, the prevalence, incidence, YLDs, and SEV of short-gestation and low-birth-weight neonates are increasing in China compared to those in the USA. Therefore, Chinese public health policy needs to control the risk factors for both short gestation and low birthweight, further develop neonatal specialties, promote obstetric techniques, enhance perinatal care, and improve neonatal follow-up and rehabilitation interventions.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Public information is available online (http://ghdx.healthdata.org/gbd-results-tool)

The dataset supporting the conclusions of this article is available in the DANS EASY database: Zhang, C.Y. (Zhejiang University School of Medicine) (2023): Epidemiological data on neonatal sepsis in China and the United States. DANS. https://doi.org/10.17026/dans-z4m-bfwe

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Chengyue Zhang and Kaiyu Pan contributed to conception and design of the study. Lianfang Yu extracted the data and organized the database. Xiaoming Pan performed the statistical analysis. Chengyue Zhang wrote the first draft of the manuscript. Yuwei Lu and Kaiyu Pan wrote sections of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 Trends in DALYs, YLDs and YLLs rates of early onset neonatal sepsis by sex in China and the USA, 1990 - 2019, using Joinpoint regression models

	DALYs		YLDs		YLLs		DALYs due to short gestation		DALYs due to low birthweight	
	Time interval	APC (95% CI)	Time interval	APC (95% CI)	Time interval	APC (95% CI)	Time interval	APC (95% CI)	Time interval	APC (95% CI)
China males										
Trend 1	1990-2000	0.3 (-0.1, 0.6)	1990-1995	0.4 (-1.1, 1.9)	1990-2000	0.3 (-0.1, 0.6)	1990-2000	-0.2 (-0.6, 0.1)	1990-2000	-0.6 (-1.0, -0.2) *
Trend 2	2000-2012	-4.8 (-5.1, -4.5)*	1995-1999	7.5 (4.0, 11.1)*	2000-2012	-4.8 (-5.1, -4.5)*	2000-2012	-4.4 (-4.7, -4.1)*	2000-2012	-5.0 (-5.4, -4.7)*
Trend 3	2012-2017	1.8 (0.3, 3.4)*	1999-2011	1.4 (0.9, 1.9)*	2012-2017	1.8 (0.3, 3.4)*	2012-2017	3.2 (1.7, 4.7)*	2012-2017	2.7 (1.1, 4.2)*
Trend 4	2017-2019	-2.7 (-7.2, 2.1)	2011-2019	-0.8 (-1.5, -0.0)*	2017-2019	-2.7 (-7.3, 2.1)	2017-2019	-1.2 (-5.6, 3.4)	2017-2019	-1.8 (-6.4, 3.0)
AAPC	1990-2019	-1.8 (-2.2, -1.4)*	1990-2019	1.4 (0.9, 2.0)*	1990-2019	-1.8 (-2.2, -1.4)*	1990-2019	-1.5 (-1.9, -1.1)*	1990-2019	-2.0 (-2.4, -1.6)*
China females										
Trend 1	1990-2003	-0.1 (-0.5, 0.2)	1990-1995	1.9 (1.3, 2.5)*	1990-2003	-0.1 (-0.5, 0.2)	1990-2003	-0.4 (-0.7, -0.0)*	1990-2003	-0.9 (-1.2, -0.5)*
Trend 2	2003-2007	-7.5 (-10.7, -4.3)*	1995-1999	6.1 (4.8, 7.5)*	2003-2007	-7.6 (-10.8, -4.3)*	2003-2007	-6.9 (-10.0, -3.6)*	2003-2007	-7.6 (-10.6, -4.4)*
Trend 3	2007-2012	-0.8 (-3.0, 1.4)	1999-2010	3.8 (3.6, 4.0)*	2007-2012	-0.8 (-3.0, 1.4)	2007-2012	-0.1 (-2.2, 2.1)	2007-2012	-0.5 (-2.6, 1.6)
Trend 4	2012-2019	1.4 (0.5, 2.3)*	2010-2019	-0.1 (-0.3, 0.2)	2012-2019	1.4 (0.5, 2.4)*	2012-2019	2.4 (1.5, 3.4)*	2012-2019	1.9 (1.0, 2.8)*
AAPC	1990-2019	-0.9 (-1.6, -0.3)*	1990-2019	2.6 (2.3, 2.8)*	1990-2019	-1.0 (-1.6, -0.3)*	1990-2019	-0.6 (-1.2, 0.0)	1990-2019	-1.1 (-1.7, -0.5)*
USA males										
Trend 1	1990-1996	-4.2 (-4.6, -3.8)*	1990-1996	-0.9 (-2.4, 0.6)	1990-1997	-4.2 (-4.6, -3.8)*	1990-1997	-3.4 (-3.6, -3.2)*	1990-1996	-3.8 (-4.1, -3.4)*
Trend	1996-	-0.3	1996-	-14.5	1997-	-0.3	1997-	0.4	1996-	0.2

2	2006	(-0.5, -0.1) *	2000	(-18.3, -10.6)*	2006	(-0.5, -0.1)*	2005	(0.2, 0.7)*	2005	(0.0, 0.5)*
Trend 3	2006-2011	-4.0 (-4.7, -3.3)*	2000-2005	1.1 (-1.7, 4.0)	2006-2011	-4.0 (-4.7, -3.3)*	2005-2012	-3.5 (-3.8, -3.2)*	2005-2012	-3.3 (-3.6, -2.9)*
Trend 4	2011-2019	-0.2 (-0.5, 0.1)	2005-2019	-2.0 (-2.4, -1.6)*	2011-2019	-0.2 (-0.5, 0.1)	2012-2019	-0.0 (-0.3, 0.2)	2012-2019	0.1 (-0.2, 0.4)
AAPC	1990-2019	-1.7 (-1.9, -1.6) *	1990-2019	-3.1 (-3.9, -2.3)*	1990-2019	-1.7 (-1.9, -1.6)*	1990-2019	-1.6 (-1.7, -1.4)*	1990-2019	-1.5 (-1.6, -1.3)*
USA females										
Trend 1	1990-1997	-3.5 (-3.8, -3.2)*	1990-1996	-1.0 (-1.7, -0.2)*	1990-1997	-3.5 (-3.8, -3.2)*	1990-1997	-3.2 (-3.5, -2.9)*	1990-1997	-3.1 (-3.4, -2.8)*
Trend 2	1997-2006	0.3 (0.1, 0.6)*	1996-1999	-9.5 (-13.5, -5.3)*	1997-2006	0.3 (0.1, 0.6)*	1997-2006	0.7 (0.4, 0.9)*	1997-2006	0.7 (0.5, 1.0)*
Trend 3	2006-2011	-3.1 (-3.8, -2.5)*	1999-2017	-2.0 (-2.2, -1.8)*	2006-2011	-3.1 (-3.8, -2.5)*	2006-2011	-3.4 (-4.1, -2.7)*	2006-2011	-3.2 (-3.9, -2.5)*
Trend 4	2011-2019	-0.3 (-0.6, -0.1)*	2017-2019	2.3 (-2.2, 7.1)	2011-2019	-0.3 (-0.6, -0.1)*	2011-2019	-0.4 (-0.6, -0.1)*	2011-2019	-0.2 (-0.5, 0.0)
AAPC	1990-2019	-1.4 (-1.6, -1.2)*	1990-2019	-2.3 (-2.8, -1.8)*	1990-2019	-1.4 (-1.5, -1.2)*	1990-2019	-1.3 (-1.4, -1.1)*	1990-2019	-1.2 (-1.3, -1.0)*

* Significantly different from 0 ($P < 0.05$).

Abbreviation: DALYs disability-adjusted life years; YLDs years lived with disability; YLLs years of life lost; APC annual percent change; AAPC average annual percent change; CI confidential interval

Table 2 Trends in DALYs, YLDs and YLLs rates of late onset neonatal sepsis by sex in China and the USA, 1990 - 2019, using Joinpoint regression models

	DALYs		YLDs		YLLs		DALYs due to short gestation		DALYs due to low birthweight	
	Time interval	APC (95% CI)	Time interval	APC (95% CI)	Time interval	APC (95% CI)	Time interval	APC (95% CI)	Time interval	APC (95% CI)
China males										
Trend 1	1990-1994	0.8 (-0.7, 2.3)	1990-1995	0.6 (-0.9, 2.1)	1990-1994	0.8 (-0.7, 2.3)	1990-1994	0.6 (-0.8, 2.1)	1990-1994	0.4 (-1.0, 1.8)
Trend 2	1994-2001	-2.0 (-2.8, -1.3)*	1995-1999	7.5 (4.0, 11.2)*	1994-2001	-2.1 (-2.9, -1.3)*	1994-2000	-2.2 (-3.2, -1.2)*	1994-2000	-2.6 (-3.6, -1.7)*
Trend 3	2001-2013	-4.4 (-4.7, -4.1)*	1999-2011	1.5 (1.0, 2.0)*	2001-2013	-4.4 (-4.7, -4.1)*	2000-2013	-3.4 (-3.7, -3.2)*	2000-2013	-4.3 (-4.5, -4.0)*
Trend 4	2013-2019	-0.3 (-1.1, 0.5)	2011-2019	-0.9 (-1.7, -0.2)*	2013-2019	-0.3 (-1.1, 0.5)	2013-2019	1.1 (0.3, 1.8)*	2013-2019	0.4 (-0.3, 1.2)
AAPC	1990-2019	-2.3 (-2.6, -2.0)*	1990-2019	1.5 (0.9, 2.0)*	1990-2019	-2.3 (-2.6, -2.0)*	1990-2019	-1.7 (-2.0, -1.4)*	1990-2019	-2.3 (-2.7, -2.0)*
China females										
Trend 1	1990-1997	-0.6 (-1.2, 0.0)	1990-1995	2.1 (1.4, 2.7)*	1990-1997	-0.6 (-1.3, 0.0)	1990-1995	-0.3 (-1.2, 0.7)	1990-1996	-1.0 (-1.8, -0.3)*
Trend 2	1997-2007	-3.7 (-4.1, -3.3)*	1995-1999	6.2 (4.7, 7.7)*	1997-2007	-3.8 (-4.3, -3.4)*	1995-2007	-3.0 (-3.3, -2.8)*	1996-2007	-3.9 (-4.2, -3.6)*
Trend 3	2007-2017	-0.1 (-0.5, 0.4)	1999-2010	3.9 (3.7, 4.1)*	2007-2017	-0.1 (-0.5, 0.4)	2007-2017	1.0 (0.6, 1.4)*	2007-2017	0.3 (-0.1, 0.7)
Trend 4	2017-2019	-3.3 (-7.9, 1.4)	2010-2019	-0.2 (-0.5, 0.0)	2017-2019	-3.4 (-8.0, 1.5)	2017-2019	-2.7 (-6.8, 1.6)	2017-2019	-3.2 (-7.3, 1.1)
AAPC	1990-2019	-1.7 (-2.1, -1.3)*	1990-2019	2.6 (2.4, 2.8)*	1990-2019	-1.8 (-2.1, -1.4)*	1990-2019	-1.2 (-1.5, -0.8)*	1990-2019	-1.8 (-2.2, -1.5)*
USA males										
Trend 1	1990-2003	2.3 (2.1, 2.5)*	1990-1996	-0.9 (-2.4, 0.7)	1990-2003	2.3 (2.1, 2.5)*	1990-1993	1.8 (0.2, 3.5)*	1990-2003	2.8 (2.6, 3.0)*
Trend 2	2003-2007	-1.8 (-3.5,	1996-2000	-14.4 (-18.2,	2003-2007	-1.8 (-3.5,	1993-2004	2.9 (2.6,	2003-2007	-1.5 (3.4,

		0.0)		-10.4)*		0.0)		3.1)*		0.4)
Trend 3	2007-2011	-4.4 (-6.1, -2.7)*	2000-2006	0.7 (-1.4, 2.7)	2007-2011	-4.4 (-6.2, -2.7)*	2004-2012	-3.6 (-4.1, -3.2)*	2007-2011	-4.5 (-6.3, -2.7)*
Trend 4	2011-2019	-1.0 (-1.3, -0.6)*	2006-2019	-2.2 (-2.7, -1.7)*	2011-2019	-1.0 (-1.3, -0.6)*	2012-2019	-0.9 (-1.4, -0.5)*	2011-2019	-0.9 (-1.3, -0.5)*
AAPC	1990-2019	-0.1 (-0.5, 0.2)	1990-2019	-3.1 (-3.9, -2.4)*	1990-2019	-0.1 (-0.5, 0.3)	1990-2019	0.0 (-0.2, 0.2)	1990-2019	0.1 (-0.2, 0.5)
USA females										
Trend 1	1990-2000	2.1 (1.9, 2.4)*	1990-1996	-1.0 (-1.8, -0.2)*	1990-2000	2.1 (1.9, 2.4)*	1990-2001	2.5 (2.3, 2.8)*	1990-2000	2.6 (2.3, 2.8)*
Trend 2	2000-2006	0.5 (-0.2, 1.2)	1996-1999	-9.3 (-13.8, -4.7)*	2000-2006	0.5 (-0.2, 1.2)	2001-2006	0.6 (-0.4, 1.6)	2000-2006	0.9 (0.2, 1.6)*
Trend 3	2006-2011	-3.8 (-4.8, -2.8)*	1999-2017	-2.1 (-2.2, -1.9)*	2006-2011	-3.8 (-4.8, -2.8)*	2006-2012	-3.6 (-4.3, -2.9)*	2006-2011	-3.9 (-4.8, -3.0)*
Trend 4	2011-2019	-0.2 (-0.6, 0.1)	2017-2019	2.2 (-2.8, 7.4)	2011-2019	-0.2 (-0.6, 0.1)	2012-2019	-0.0 (-0.5, 0.4)	2011-2019	-0.2 (-0.5, 0.2)
AAPC	1990-2019	0.1 (-0.1, 0.3)	1990-2019	-2.3 (-2.9, -1.7)*	1990-2019	0.1 (-0.1, 0.3)	1990-2019	0.3 (0.0, 0.5)*	1990-2019	0.3 (0.1, 0.6)*

* Significantly different from 0 ($P < 0.05$).

Abbreviation: DALYs disability-adjusted life years; YLDs years lived with disability; YLLs years of life lost; APC annual percent change; AAPC average annual percent change; CI confidential interval

Figures

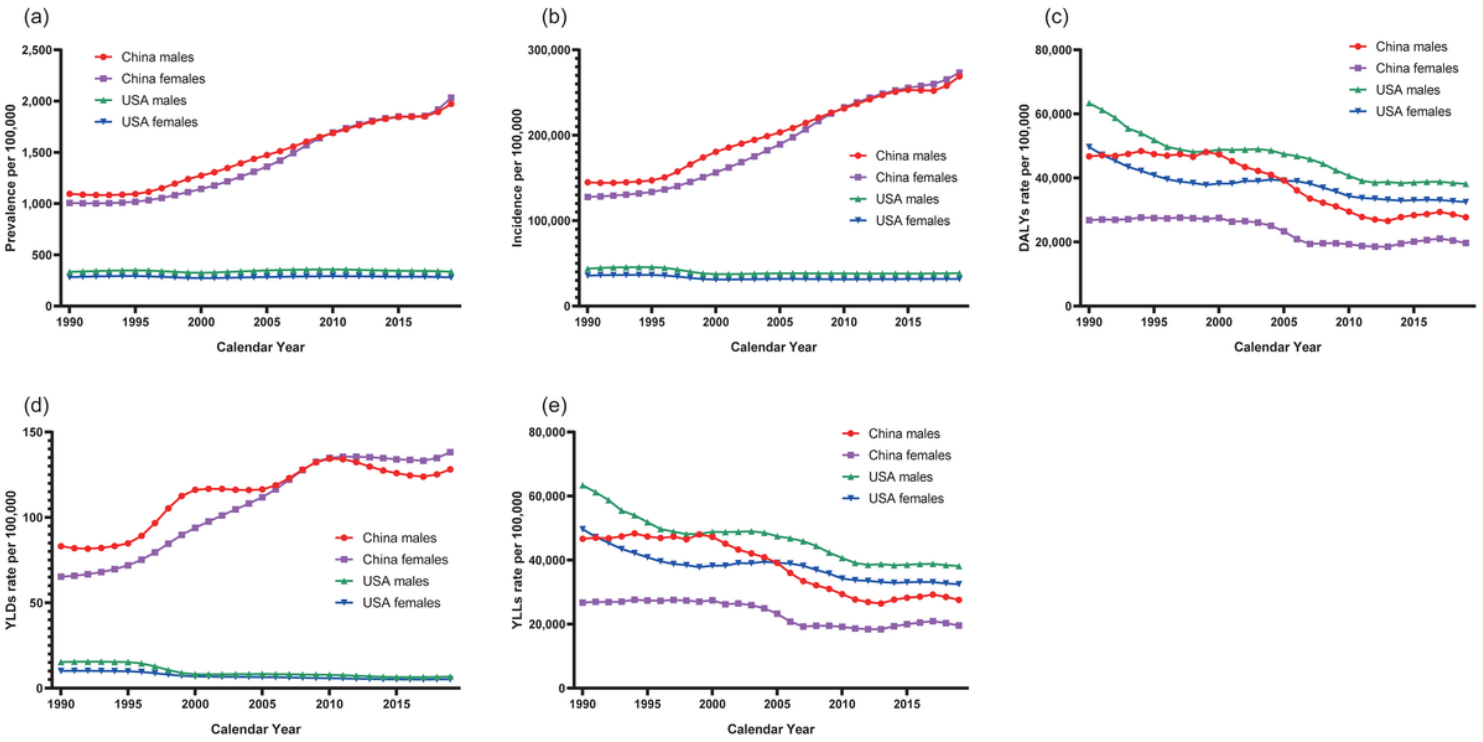

Figure 1

The temporal trends in the age-standardized prevalence, incidence, DALYs, YLDs and YLLs per 100,000 population of neonates with early onset neonatal sepsis by sex in China and the USA, 1990–2019. (a). prevalence. (b). incidence. (c). DALYs. (d). YLDs. (e). YLLs.

Abbreviation: DALYs disability-adjusted life years; YLDs years lived with disability; YLLs years of life lost

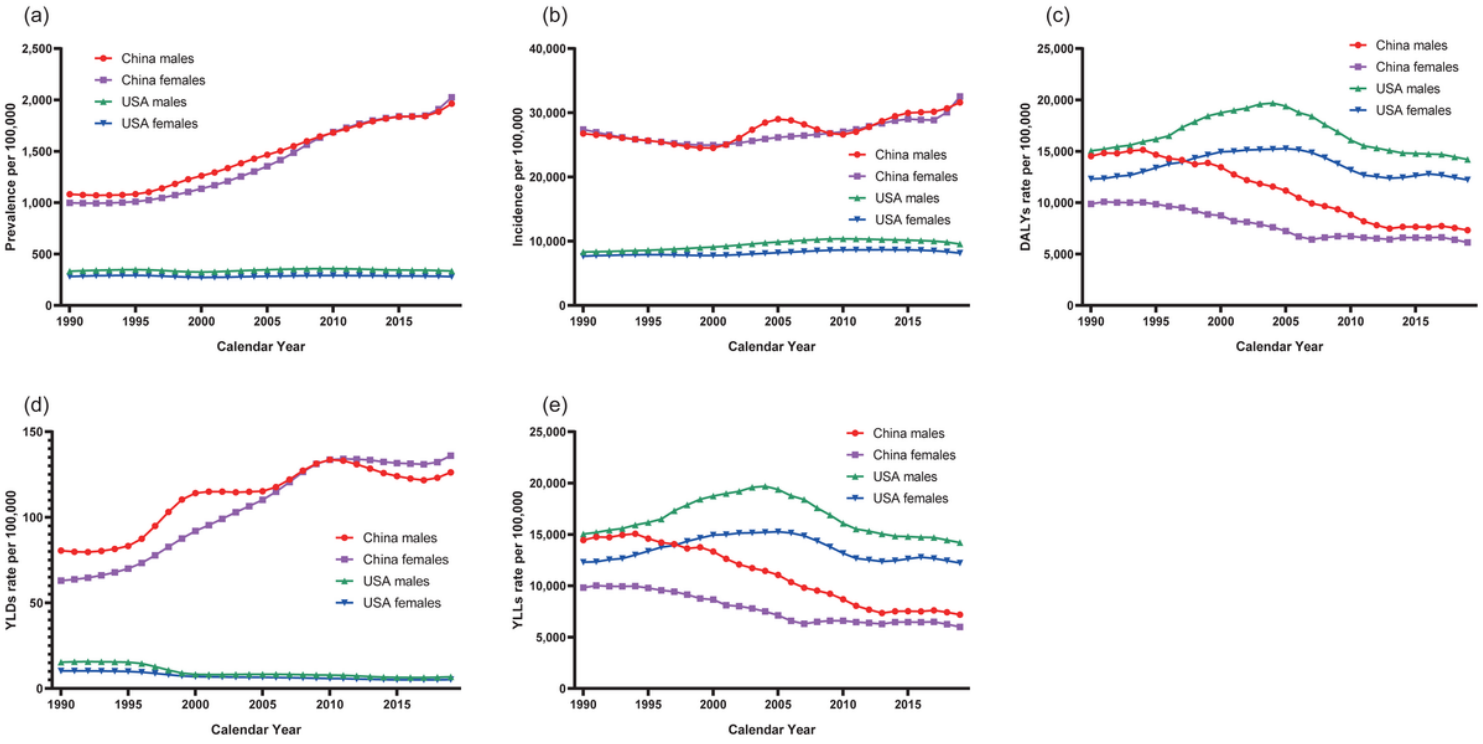

Figure 2

The temporal trends in the age-standardized prevalence, incidence, DALYs, YLDs and YLLs per 100,000 population of neonates with late onset neonatal sepsisby sex in China and the USA, 1990–2019. (a). prevalence. (b). incidence. (c). DALYs. (d). YLDs. (e). YLLs.

Abbreviation: DALYs disability-adjusted life years; YLDs years lived with disability; YLLs years of life lost

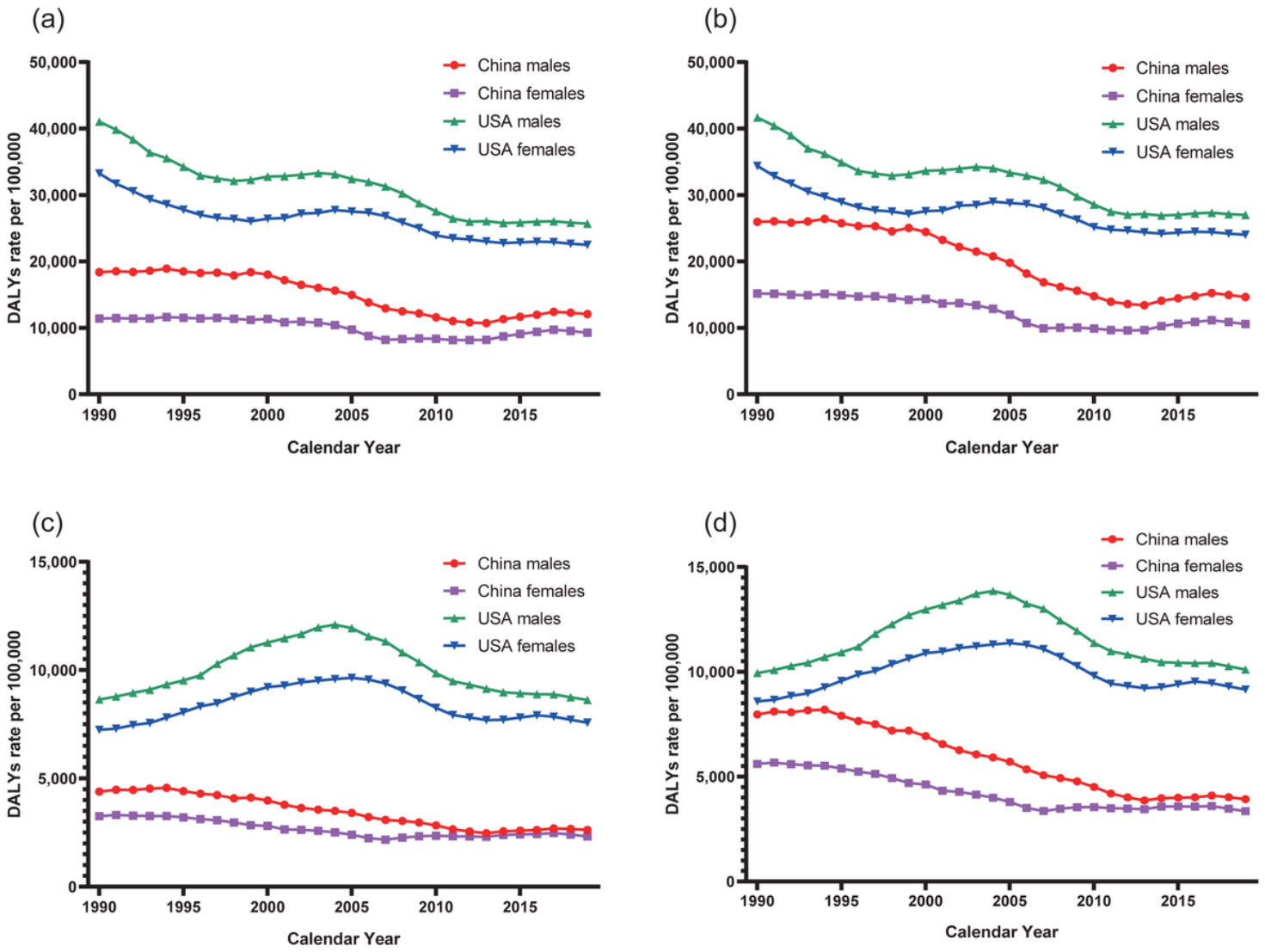

Figure 3

The temporal trends in the age-standardized DALYs per 100,000 population of early and late onset neonatal sepsis due to short gestation and low birth weight by sex in China and the USA, 1990–2019. (a). DALYs due to short gestation in neonates with early onset neonatal sepsis. (b). DALYs due to low birth weight inneonates with early onset neonatal sepsis. (c). DALYs due to short gestation in neonates with late onset neonatal sepsis. (d). DALYs due to low birth weight in neonates with late onset neonatal sepsis.

Abbreviation: DALYs disability-adjusted life years

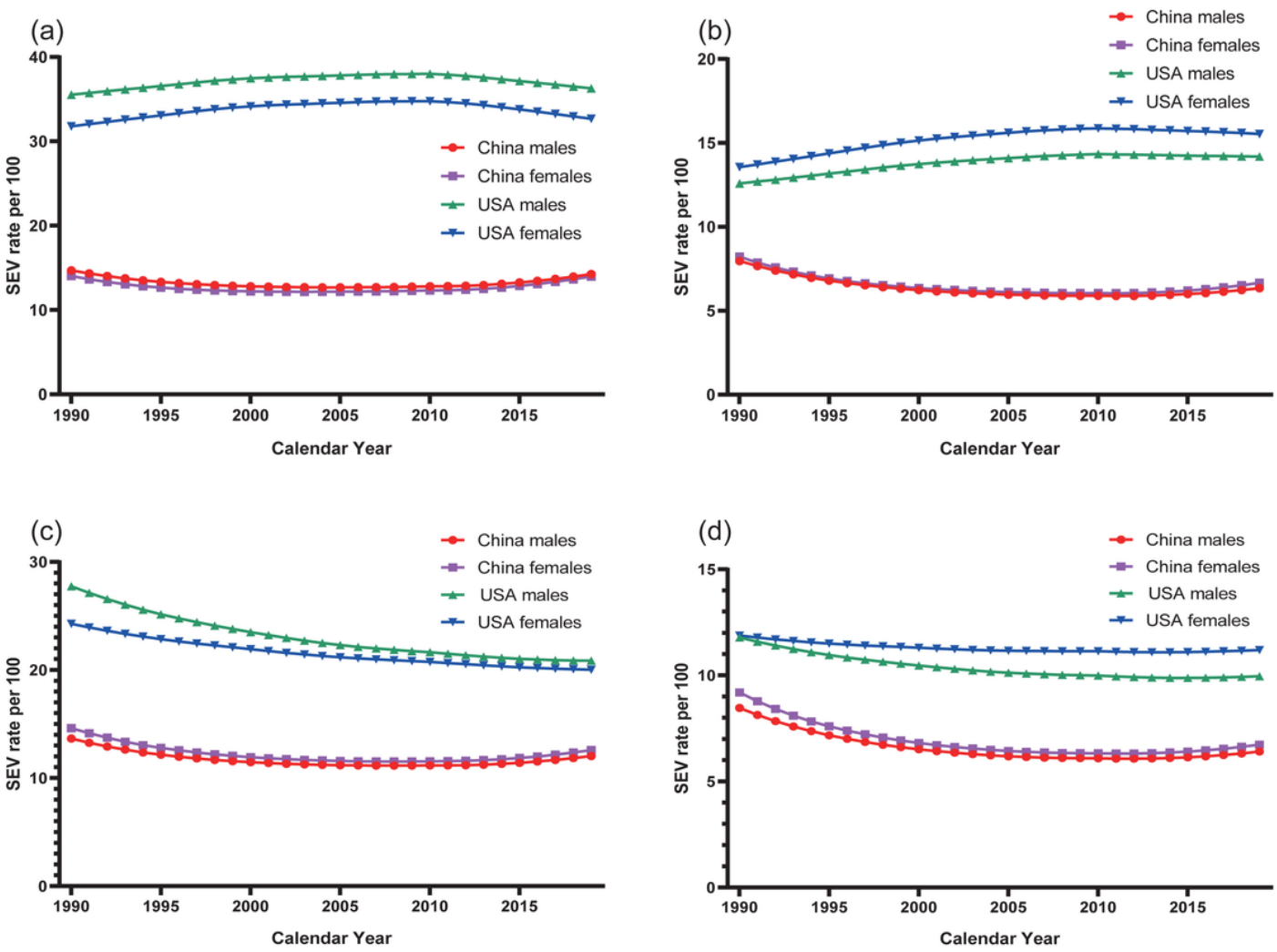

Figure 4

The temporal trends in the age-standardized SEV per 100 population of short gestation and low birth weight in early and late neonates by sex in China and the USA, 1990–2019. (a). SEV of short gestation in early neonates. (b). SEV of low birth weight in early neonates. (c). SEV of short gestation in late neonates. (d). SEV of low birth weight in late neonates.

Abbreviation: SEV summary exposure value

Supplementary Files

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- Supplementarytable1.docx
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- Supplementarytable3.docx