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ARTICLE

Prematurity and race account for much of the interstate variation in infant mortality rates in the United States

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Abstract

Objective To assess the correlation between infant mortality and extreme prematurity by state.

Study design This ecological study included data on 28,526,534 infants from 2007 to 2013 in all 50 US states and DC using CDC WONDER linked birth and infant death records. Regression analyses determined the correlation between infant and neonatal mortality rates and the proportion of extremely preterm, extremely low birth weight, and black births by state.

Results State infant and neonatal mortality rates were directly and highly correlated with the proportion of extremely preterm births (infant, $r^2 = 0.71$, $P < 0.001$; neonatal, $r^2 = 0.77$, $P < 0.001$) and extremely low birth weight births ($r^2 = 0.63$, $P < 0.001$; $r^2 = 0.73$, $P < 0.001$). The proportion of black births also correlated directly with infant and neonatal mortality rates.

Conclusions Interstate variation in infant and neonatal mortality rates are primarily driven by rates of extremely preterm and extremely low birth weight births which is closely related to the proportion of black births.

Introduction

Infant mortality is a benchmark indicator of societal, maternal, and pediatric health [1]. The United States is considered to have one of the highest infant mortality rates among developed nations [2, 3] with large variations between states [4]. Infant mortality rates in the United States ranged from 3.7 infant deaths per 1000 live births in Massachusetts to 8.7 infant deaths per 1000 births in Mississippi in 2017 [5]. Infant mortality is associated with multiple risk factors including preterm births [1, 3], maternal-fetal health, quality of and access to medical care, socioeconomic status, and race [1]. In particular, the proportion of preterm (16.3 per 1000 births among black versus 10.2 per 1000 births among white) and low birth weight births (13.1 per 1000 births among black versus 7.0 per 1000 births among white) varies by race which may contribute to the disparity in infant mortality between black and white infants (11.1 per 1000 among black versus 5.1 per 1000 among white births) [4]. In addition, unsafe sleep practices are a risk factor particularly for postneonatal mortality due to sudden unexplained infant death [6]. Variation in reporting of deaths at the threshold of viability also plays a role in regional differences in infant mortality rates [7, 8].

The rates of preterm and low birth weight infants vary between states. In 2014, the proportion of preterm births in the United States ranged from 7.7 percent of live births in Oregon to 12.9 percent of live births in Mississippi [9]. The proportion of low birth weight births also varied by state from 6.6 percent of live births in Oregon to 11.3 percent of live births in Mississippi [9]. Although the variation in infant mortality rates by state has been associated with

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gestational age and birth weight distribution [3, 10], the extent to which the variation in infant mortality between states is correlated with birth weight and gestational age is unknown. A large proportion of infant deaths occur among extremely preterm and extremely low birth weight infants [4]. Therefore, it is important to determine the magnitude of the effects of gestational age and birth weight on state level infant mortality rates so that public health efforts can be duly allocated. This study was designed to examine the strength of association between interstate variation in infant mortality rates and the proportions of extremely preterm (20–27 6/7 weeks' gestational age), extremely low birth weight (<1000 g birth weight), and black infant births.

Methods

This study used collapsed state level data from the Centers for Disease Control and Prevention WONDER database linked live birth and infant death cohort data files from 2007 to 2013 [5]. Live birth and infant death data from all 50 states and the District of Columbia were included. Infants that were not linked to a birth weight or gestational age were excluded. The study was approved by the Institutional Review Board at the University of Alabama at Birmingham.

The following birth weight subgroups were included: <500 g, 500–999 g, <1000 g (extremely low birth weight), 1000–1499 g, <1500 g (very low birth weight), 1500–1999 g, 2000–2499 g, 1000–2499 g, <2500 g (low birth weight), 2500–2999 g, 3000–3499 g, 3500–3999 g, 4000–4499 g, and 4500–4999 g. Gestational age was calculated using the last menstrual period and obstetrician's estimate was not available during the study years. The following gestational age subgroups were included: 20–23 weeks, 24–27 weeks, 20–27 weeks (extremely preterm), 28–31 weeks, 20–31 weeks (very preterm), 32–35 weeks, 36 weeks, 28–36 weeks, 20–36 weeks (preterm), 37–39 weeks, and ≥40 weeks' gestation. Additional gestational age subgroups included each week of gestation from 20 weeks' gestation to 42 weeks' gestation. The proportion of total live births for each state was calculated using these birth weight and gestational age subgroups.

The primary hypothesis was addressed by correlating each state's infant mortality rate with each corresponding state's extremely low birth weight birth rate and extremely preterm birth rate using linear regression analyses. Similarly, prespecified secondary hypotheses addressed the correlation of infant (<1 year), neonatal (<28 days), and postneonatal (28 days up to 1 year) mortality rates with prespecified birth weight and gestational age subgroups. Analyses of birth weight and gestational age were completed independently using the aforementioned birth weight and gestational age categories rather than exact birth weight and gestational age. The relationship between infant mortality and each corresponding state's proportion of births within birth weight and gestational age subgroups was analyzed using linear regression analyses. Specific birth weight and gestational age subgroups for each state that had <20 deaths during the study period were excluded based on the National Center for Health Statistics standards for reliability and precision. A 7-year period was chosen to allow for an adequate sample size to minimize the exclusion of data based on these standards for reliability and precision.

Independent sample *t*-tests were used to compare black and white infant and neonatal mortality rates. Linear regression analyses were used to compare the proportion of black births to preterm, extremely preterm, low birth weight, and extremely low birth weight rates as well as infant, neonatal, and postneonatal mortality rates by state. Secondary analyses were conducted excluding births <500 g. Multiple regression analyses were used to combine the following: the proportion of black births with extremely low birth weight rates; the proportion of black births with extremely preterm birth rates; the proportion of extremely low birth weight births and extremely preterm births; and the proportion of black births, extremely low birth weight births, and extremely preterm births to determine the combined percent variance in infant, neonatal, and postneonatal mortality rates explained by each combination. A P value of <0.05 was considered significant in all analyses.

Results

Between the years 2007 and 2013, there were 28,532,622 total births and 179,310 total infant deaths. After the exclusion of 6088 births and 855 infant deaths that were not linked to birth weight, a total of 28,526,534 births and 178,455 infant deaths were included in analyses by birth weight. Extremely low birth weight infants made up only 0.72% of total births but 47% of total infant deaths. After the exclusion of 35,850 births and 1581 infant deaths not linked to gestational age, a total of 28,496,772 births and 177,729 infant deaths were included in analyses by gestational age. Extremely preterm infants made up 0.70% of total births and 42% of infant deaths.

As expected, there were marked variations in infant, neonatal, and postneonatal mortality rates between states (4.59–9.65, 2.56–6.74, and 1.20–3.87, per 1000 live births, respectively) and in the percentages of extremely low birth weight infants and extremely preterm infants between states (0.40%–1.26% and 0.45%–1.24%, respectively) (Table S1). There was a direct correlation between infant, neonatal, and postneonatal mortality rates and the rates of extremely low

Table 1 Correlation between state neonatal and infant mortality rates and the proportion of births in each birth weight subgroup.

Birth weight	Neonatal mortality rate			Infant mortality rate		
	Slope	r^2	*P* value	Slope	r^2	*P* value
<500 g	13.28	0.79	<0.001	16.30	0.53	<0.001
500–999 g	4.91	0.70	<0.001	7.12	0.66	<0.001
1000–1499 g	4.60	0.62	<0.001	6.97	0.64	<0.001
1500–1999 g	2.52	0.54	<0.001	3.91	0.59	<0.001
2000–2499 g	0.64	0.39	<0.001	1.10	0.51	<0.001
2500–2999 g	0.17	0.24	0.003	0.29	0.33	<0.001
3000–3499 g	0.07	0.01	0.419	0.13	0.02	0.290
3500–3999 g	0.15	0.27	<0.001	−0.26	0.36	<0.001
4000–4499 g	0.24	0.21	0.001	−0.41	0.27	<0.001
4500–5000 g	1.16	0.18	0.002	−1.82	0.20	0.001
Extremely low birth weight	3.72	0.73	<0.001	5.17	0.63	<0.001
Very low birth weight	2.14	0.71	<0.001	3.08	0.66	<0.001
1000–2499 g	0.49	0.47	<0.001	0.80	0.57	<0.001
Low birth weight	0.45	0.52	<0.001	0.73	0.60	<0.001

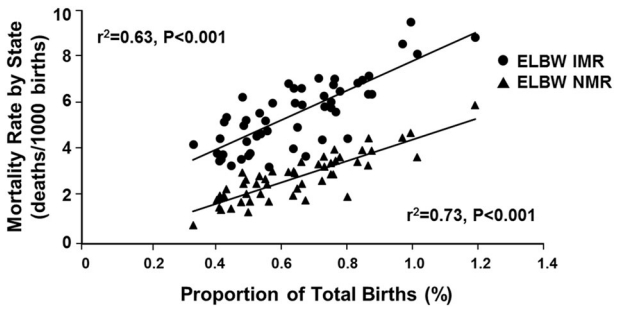

Fig. 1 Correlation of state infant mortality rates (IMR) and neonatal mortality rates (NMR) with the proportion of extremely low birth weight births (<1000 g). Infant and neonatal mortality rates by state are directly and highly correlated with the proportion of extremely low birth weight (ELBW) births by state.

birth weight, very low birth weight, and low birth weight births by state (Tables 1 and S2). States with higher infant and neonatal mortality rates had a higher proportion of infants in each low birth weight subgroup (Table 1), with the strongest correlations seen between neonatal mortality rates and the proportion of births <500 g ($r^2 = 0.79$, $P < 0.001$) and extremely low birth weight births by state ($r^2 = 0.73$, $P < 0.001$) (Fig. 1). After exclusion of infants <500 g, a direct correlation between infant mortality rates and the rates of extremely low birth weight ($r^2 = 0.43$, $P < 0.001$), very low birth weight ($r^2 = 0.44$, $P < 0.001$), and low birth weight infants ($r^2 = 0.51$, $P < 0.001$) remained.

There was also a direct correlation between infant, neonatal, and postneonatal mortality rates and the rates of extremely preterm, very preterm, and preterm infants

Table 2 Correlation between state neonatal and infant mortality rates and the proportion of births in each gestational age subgroup.

Gestational age (weeks)	Neonatal mortality rate			Infant mortality rate		
	Slope	r^2	*P* value	Slope	r^2	*P* value
20–23	11.86	0.79	<0.001	15.74	0.58	<0.001
24–27	5.14	0.65	<0.001	8.16	0.68	<0.001
28–31	2.75	0.60	<0.001	4.41	0.69	<0.001
32–33	0.07	0.01	0.662	0.14	0.01	0.562
34–36	0.06	0.02	0.294	0.16	0.06	0.073
37–39	0.06	0.05	0.125	0.21	0.22	<0.001
≥40	0.06	0.02	0.397	0.13	0.02	0.239
Extremely preterm (<28)	4.07	0.77	<0.001	5.82	0.71	<0.001
Very preterm (<32)	1.72	0.70	<0.001	2.16	0.73	<0.001
28–36	0.32	0.38	<0.001	0.61	0.60	<0.001
Preterm (<37)	0.32	0.44	<0.001	0.58	0.64	<0.001
20	54.55	0.73	<0.001	65.41	0.44	<0.001
21	54.35	0.68	<0.001	67.02	0.47	<0.001
22	43.97	0.78	<0.001	57.61	0.60	<0.001
23	30.69	0.68	<0.001	43.00	0.56	<0.001
24	25.09	0.65	<0.001	38.31	0.63	<0.001
25	20.79	0.64	<0.001	31.48	0.62	<0.001
26	19.08	0.71	<0.001	30.66	0.76	<0.001
27	18.41	0.59	<0.001	28.96	0.65	<0.001
28	13.45	0.59	<0.001	22.95	0.68	<0.001
29	11.57	0.62	<0.001	19.64	0.69	<0.001
30	8.86	0.55	<0.001	14.91	0.61	<0.001
31	7.30	0.47	<0.001	13.42	0.62	<0.001
32	4.99	0.47	<0.001	9.70	0.63	<0.001
33	3.43	0.44	<0.001	6.49	0.58	<0.001
34	2.11	0.35	<0.001	3.90	0.55	<0.001
35	1.19	0.30	<0.001	2.50	0.52	<0.001
36	0.66	0.19	0.001	1.47	0.44	<0.001
37	0.24	0.09	0.031	0.66	0.31	<0.001
38	0.09	0.04	0.144	0.29	0.19	0.001
39	−0.03	0.01	0.635	−0.07	0.01	0.555
40	−0.15	0.17	0.002	−0.35	0.41	<0.001
41	−0.17	0.19	0.001	−0.38	0.37	<0.001
42	−0.37	0.05	0.141	−0.74	0.08	0.083

(Tables 2 and S2) with the strongest correlations seen between neonatal mortality rates and the proportion of births between 20 and 23 weeks ($r^2 = 0.79$, $P < 0.001$) and extremely preterm births by state ($r^2 = 0.77$, $P < 0.001$) (Table 2 and Fig. 2). Higher infant and neonatal mortality rates were also correlated with a higher proportion of infants in each preterm subgroup (Table 2). In analyses by each week of gestational age, higher infant and neonatal mortality rates also correlated with a higher proportion of births

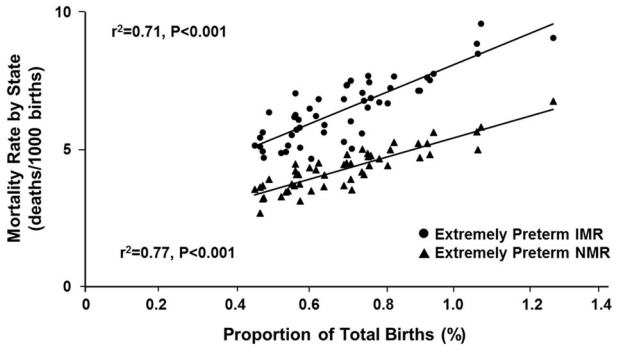

Fig. 2 Correlation of infant mortality rates (IMR) and neonatal mortality rates (NMR) with the proportion of extremely preterm births by state. Infant and neonatal mortality rates by state are directly and highly correlated with the proportion of extremely preterm births by state.

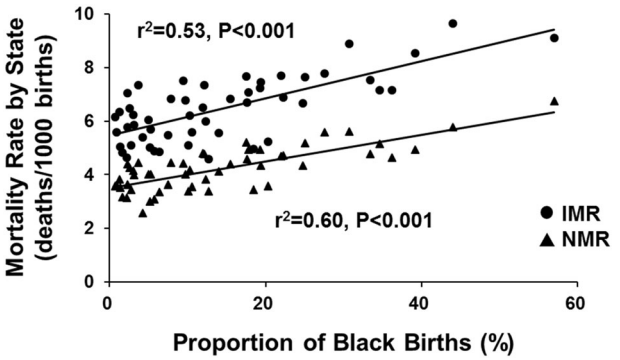

Fig. 3 Correlation of infant and neonatal mortality rates with proportion of black births by state. A higher proportion of black births correlated with higher infant mortality rates (IMR) and neonatal mortality rates by state.

at each gestational age from 20 to 38 weeks and 20 to 37 weeks' gestational age, respectively (Table 2).

There was variation in the proportion of black births across states, ranging from 0.69 to 57% of total births (mean ± SD, 14.3 ± 12.8). Although black births accounted for only 15.9% of total US births, they accounted for 29.5% of all infant deaths. When compared with whites, blacks had a higher rate of low birth weight, extremely low birth weight, preterm, and extremely preterm births, and a higher infant and neonatal mortality rate (Table S3). The proportion of black births by state was directly correlated with the proportions of extremely low birth weight ($r^2 = 0.85$, $P < 0.001$), low birth weight ($r^2 = 0.62$, $P < 0.001$), extremely preterm births ($r^2 = 0.88$, $P < 0.001$), and preterm ($r^2 = 0.52$, $P < 0.001$) births by state. In addition, the proportion of black births by state was directly correlated with higher infant mortality rates ($r^2 = 0.53$, $P < 0.001$) (Fig. 3), neonatal mortality rates ($r^2 = 0.60$; $P < 0.001$) (Fig. 3), and postneonatal mortality rates ($r^2 = 0.19$, $P < 0.001$).

There was a high degree of collinearity between black race, preterm birth, and low birth weight birth. The combination of the proportion of black births and extremely low birth weight births by state was correlated with infant, neonatal, and postneonatal mortality rates ($r^2 = 0.63$, $P < 0.001$; $r^2 = 0.74$, $P < 0.001$; and $r^2 = 0.22$, $P = 0.002$, respectively). The combination of the proportion of black births and extremely preterm births by state was also correlated with infant, neonatal, and postneonatal mortality rates ($r^2 = 0.74$, $P < 0.001$; $r^2 = 0.80$, $P < 0.001$; and $r^2 = 0.31$, $P < 0.001$, respectively). The combination of the proportion of extremely low birth weight births and extremely preterm births by state was correlated with infant, neonatal, and postneonatal mortality rates ($r^2 = 0.72$, $P < 0.001$; $r^2 = 0.78$, $P < 0.001$; and $r^2 = 0.33$, $P < 0.001$, respectively). Finally, the combination of the proportion of black births, extremely low birth weight births, and extremely preterm births by state had the highest correlation with infant, neonatal, and postneonatal mortality ($r^2 = 0.75$, $P < 0.001$; $r^2 = 0.80$, $P < 0.001$; and $r^2 = 0.35$, $P < 0.001$, respectively).

When controlling for the variance in the proportion of black births across states and combining birth weight and gestational age analyses, disparities in state outcomes still existed. After controlling for the proportion of black births by setting the proportion of black births constant across states, the proportion of extremely low birth weight and extremely preterm births explained an additional 21.8% ($P < 0.001$) of the total 74.6% ($P < 0.001$) variance in the infant mortality rates across states, an additional 19.7% ($P < 0.001$) of the total 79.9% variance in neonatal mortality rates, and an additional 15.3% ($P = 0.007$) of the total 34.5% ($P < 0.001$) variance in postneonatal mortality rates.

Discussion

This study demonstrates that interstate variation in infant and neonatal mortality rates are directly and highly correlated with rates of both extremely low birth weight and extremely preterm births. In addition, infant and neonatal mortality rates are directly correlated with the proportion of black births by state. While the associations between extremely low birth weight, extreme prematurity, and race with infant, neonatal, and postneonatal mortality rates may be expected at an individual level, this study provides novel evidence of the magnitude and importance of the correlations between these measures and mortality rates at the state level. These data identify states that may benefit most from targeted interventions to reduce disparities in infant and neonatal mortality rates.

This study using state level data rather than individual patient level data on linked birth and infant death records has several limitations which should be noted. To maintain

reliability and precision, data from some states with low number of births at the lowest gestations and birth weights were excluded per National Center for Health Statistics standards, but these exclusions were compensated by the large available sample size. Data on infants without known gestational age or birth weight were excluded as these data are not available for most states. However, there were higher numbers of deaths among those with missing gestational age and birth weight data suggesting a non-differential issue. The data reflect practice from 2007 to 2013 and it is possible that resuscitation patterns changed over time among infants <500 g and may not reflect more recent years. To attempt to control for unmeasured variation by state or inaccuracies in reporting of live birth and infant or fetal death [7, 8], and changes in resuscitation practices over time, secondary analyses were performed that excluded infants born weighing <500 g. As expected, exclusion of infants <500 g, who have high infant and neonatal mortality rates, attenuated the strength of the association but it was reassuring that the correlations persisted. In addition, it is known that small increases in birth weight [11] and gestational age [4] among periviable infants may be associated with lower mortality, but the CDC WONDER did not include gestational age based on obstetric estimates [12] during the study period and categorizes birth weights by increments rather than by exact infant weight [4, 11]. However, the large sample size included in this population-based study may have improved the accuracy of the estimate of effect sizes and reduced the margin of error. It was not possible to adjust for unmeasured variation in perinatal care practices by state that affect survival in extremely preterm infants [13–15], including rates of active treatment [16, 17] and neonatal resuscitation [18].

The current study highlights the relationship between infant and neonatal mortality rates with the proportion of extremely preterm and extremely low birth weight births by state. Variations in low birth weight, preterm birth, and infant mortality across states have been documented [4, 9], but the link between them has not been clearly delineated. The current study found that much of the variation in the infant and neonatal mortality rates between states in the USA is likely related to birth weight and gestational age distribution rather than gestational age specific mortality rates. The importance of birth weight distribution and gestational age distribution was further illustrated in that extremely low birth weight and extremely preterm births accounted for almost half of all infant deaths although each only accounted for <1% of all infant births. In the current study, infant and neonatal mortality rates were also directly correlated with the rates of low birth weight and preterm births in most birth weight and gestational age subgroups although, and as expected, the association weakened as weight and gestational age increased.

The significant role that periviable births play in infant mortality rates [19] further emphasizes the need for standardized birth and infant death reporting. It is possible that the changes in correlation coefficients after exclusion of infants <500 g in the current study may also be partly explained by the variation in the reporting of infant deaths compared with fetal deaths at the threshold of viability which affects infant mortality rates by state [7, 8]. Prior studies found that if the variation in the registration of fetal compared with neonatal deaths was held constant between geographic regions, estimates for the change in infant mortality rates range from a change of 0.45 deaths per 1000 births [20] to 1.69 deaths per 1000 births [8]. An increase in the proportion of infants born at <500 g and in other low birth weight categories in the early 2000s [9] has also been associated with the relatively smaller decline in the infant mortality rate over time in the USA [19].

The current study highlights and quantifies the strong association between the interstate variation in the proportion of black births with extremely low birth weight births and extremely preterm births. Black infants were three times more likely to deliver extremely preterm or extremely low birth weight compared with white infants. As hypothesized, race was also directly and highly correlated with infant and neonatal mortality rates, which were more than doubled among black infants compared with white infants, due to high degree of collinearity between black race, prematurity, and low birth weight. States with a higher proportion of black births had a higher rate of preterm, extremely preterm, low birth weight, and extremely low birth weight births which was correlated with higher infant, neonatal, postneonatal mortality rates. The addition of black births to models strengthened the correlation between extremely low birth weight births, extremely preterm births, and mortality rates by state indicating that race remains a risk factor for neonatal and infant mortality in the United States. Race has previously been associated with variations in infant mortality rates between states [1] with studies showing a higher overall infant mortality rate and a higher rate of preterm births and low birth weight births among blacks compared with whites due to multiple contributing factors [4, 21–24]. Although black infants may have a gestational age and birth weight specific survival advantage at extremely low gestational ages [11], the current study shows higher infant and neonatal mortality rates in states with higher proportions of black births. While the higher infant and neonatal mortality rates were likely related to the associated increase in extremely low birth weight and extremely preterm births, the rate of black births was still associated with a higher risk of mortality even after controlling for the proportion of extremely preterm infants. Therefore, it is critical to better understand and address racial disparities because many of these factors, such as improving access to comprehensive prenatal care, may be modifiable [23].

In the current study, 75%, 80%, and 35% of the interstate variation in the infant, neonatal, and postneonatal mortality rates, respectively, can be explained by the proportion of extremely preterm, extremely low birth weight, and black births. However, not all the variance in infant mortality rates among states is explained by these variables. Further investigation of other factors associated with infant mortality including access to care, socioeconomic status, congenital abnormalities, and maternal age [4] is warranted to better understand the variation in infant mortality rates among states not explained in this study. The strong correlation between extremely low birth weight, extremely preterm births, and infant mortality further emphasize the need for ongoing public health efforts focused on prevention of extremely low birth weight and extremely preterm births [25]. The results from this study may direct public health efforts to reduce infant mortality rates by targeting evidence-based programs and interventions such as expanded access to prenatal care, preconception care, interconception care, improving pregnancy spacing [26], targeted use of progesterone [27], treatment of cervical incompetence [28], early identification and treatment of pregnancy-related disorders such as preeclampsia, higher use antenatal corticosteroids when indicated [29], smoking cessation programs [30], and other maternal and fetal health programs [31] to states with higher percentages of extremely low birth weight, extremely preterm, and black births.

Conclusions

The current study demonstrates that states with higher rates of extremely low birth weight and extremely preterm infants have higher infant, neonatal, and postneonatal mortality rates. These correlations were most evident among infants at the lowest gestations and birth weights and are mediated in part by the proportion of black births by state. The results of this study emphasize the need to continue efforts to address the issue of extremely low birth weight and extremely preterm births in the United States and the need to better understand and address mechanisms driving extremely low birth weight and extremely preterm births.

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Compliance with ethical standards

Conflict of interest WAC is on the board of MEDNAX, Inc. The other authors declare that they have no conflict of interest.

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