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## Original Investigation

# Changing Ethnic Disparity in Ischemic Stroke Mortality in US Children After the STOP Trial

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**IMPORTANCE** A prior report showed higher stroke mortality in US black children compared with white children (1979-1998), a disparity likely due in part to sickle cell disease, which leads to a high risk of childhood ischemic stroke. We hypothesized that this disparity has diminished since the publication of the Stroke Prevention Trial in Sickle Cell Anemia (STOP trial) in 1998 demonstrating the efficacy of long-term blood transfusions for primary stroke prevention.

**OBJECTIVE** To evaluate the demographics and secular trends in mortality from ischemic and hemorrhagic stroke (as a primary cause of death) in US children (<20 years) and determine if there has been a decrease in the disparity between white and black children since the publication of the STOP trial in 1998.

**DESIGN** We used death certificate data from the National Center for Health Statistics, 1988 through 2007.

**SETTING** United States.

**PARTICIPANTS** Children who died in 1988 through 2007 in the United States.

**INTERVENTION** Publication of the STOP trial.

**MAIN OUTCOME MEASURES** Incidence rate ratios were calculated as the measure of relative risk.

**RESULTS** Among 1.6 billion person-years of US children (1988-2007), there were 4425 deaths attributed to stroke, yielding an average of 221 deaths per year; 20% were ischemic; 67%, hemorrhagic; and 12%, unspecified. The relative risk of ischemic stroke mortality for black vs white children dropped from 1.74 from 1988 through 1997 to 1.27 from 1998 through 2007. The ethnic disparity in hemorrhagic stroke mortality, however, remained relatively stable between these 2 periods: black vs white relative risk, 1.90 (1988-1997) and 1.97 (1998-2007).

**CONCLUSIONS AND RELEVANCE** The excess risk of death from ischemic, but not hemorrhagic, stroke in US black children has decreased over the past decade. This may be related to the implementation of an effective ischemic stroke prevention strategy for children with sickle cell disease.

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Stroke is one of the top 10 leading causes of childhood death in the United States.<sup>1</sup> A decline in pediatric stroke mortality was observed in a recent study in England and Wales that examined birth cohorts from 1921 to 2000. Higher mortality rates in males, compared with females, and infants, compared with older children, were observed; however, the study did not address ethnicity as a risk factor.<sup>2</sup> Older epidemiological studies in the United States have suggested that black children have an increased risk of both incident stroke and stroke mortality. In a study of childhood stroke admissions in California from 1991 to 2000, black children, compared with white children, had a more than 2-fold increased risk of ischemic stroke and 60% increased risk of hemorrhagic stroke.<sup>3</sup> A study of all deaths in the United States from 1979 to 1998 similarly demonstrated that black children, again compared with white children, have a higher mortality from ischemic and hemorrhagic stroke.<sup>4</sup> California newborn screening found that 88% of newborns who tested positive for sickle cell disease were black vs 12% who were nonblack.<sup>5</sup> Sickle cell disease, which predominantly affects black children, likely plays a role in the ethnic disparity in childhood stroke risk. It is a powerful risk factor for childhood ischemic stroke: old natural history studies found that approximately 10% of children with sickle cell disease had an ischemic stroke by the age of 20 years.<sup>6,7</sup>

However, the demographics of childhood stroke may have changed in the past decade with the publication of the Stroke Prevention Trial in Sickle Cell Anemia (STOP Trial) in 1998.<sup>8</sup> The STOP trial demonstrated that, among children identified as high risk for stroke through screening with transcranial Doppler ultrasonography, long-term blood transfusion therapy decreases the risk of stroke by more than 90%. Since 1998, a decline in first-time stroke incidence rates in children with sickle cell disease has been suggested by multiple studies and attributed to increased transcranial Doppler ultrasonography screening and blood transfusion therapy.<sup>9-12</sup> The impact of the STOP trial on pediatric stroke mortality rates has not been assessed.

We hypothesized that the ethnic disparity in childhood stroke mortality has diminished since the publication of the STOP trial in 1998. Because childhood strokes in the setting of sickle cell disease are ischemic 75% to 95% of the time, we would expect the STOP trial to have a greater impact on ethnic disparities in ischemic than hemorrhagic stroke.<sup>6,7,9,13</sup> To test this hypothesis, we evaluated the demographics and secular trends in mortality from ischemic and hemorrhagic stroke in US children younger than 20 years using death certificate data from the National Center for Health Statistics (NCHS) from 1988 to 2007.

## Methods

Our study cohort included all US children from 1988, 1 decade prior to the publication of the STOP trial, through 2007, the most recent year for which NCHS mortality data were available at the time of the study. Because the NCHS database groups 15- to 19-year-olds together, we defined childhood as younger than 20 years. Within this cohort, we identified childhood stroke deaths by searching the mortality database of the NCHS using *International Classification of Diseases, Ninth Revision (ICD-9)* (eTable 1

in Supplement) and *ICD-10* (eTable 2 in Supplement) codes for ischemic and hemorrhagic stroke.<sup>14</sup> The database used *ICD-9* codes from 1988 to 1998 and *ICD-10* codes from 1999 to 2007. We used stroke *ICD-9* codes published in a prior article on childhood stroke deaths in the United States and the equivalent *ICD-10* codes.<sup>4,15</sup> Hemorrhagic stroke included both subarachnoid and intracerebral hemorrhage while ischemic stroke included both venous sinus thrombosis and arterial ischemic stroke.

We used NCHS methods for determining mortality rates.<sup>16</sup> In general, the NCHS calculates crude annualized mortality rates as the number of deaths reported each calendar year divided by the estimated number of people in the population; the rates are expressed as deaths per 100 000 person-years. When a rate is calculated for multiple years, the total number of deaths during that epoch is divided by the sum of the population estimates for each individual year. From 1980 to 1998, the NCHS calculated annualized mortality rates for infants (<1 year) as the number of infant deaths (children <1 year at the time of death) divided by the number of live births during a given period; from 1999 through 2007, they calculated mortality rates as the number of infant deaths divided by the estimated number of infants in the population.<sup>17</sup> When the NCHS compared mortality rates using live births compared with population estimation, there was only a slight difference in rates.<sup>16</sup> The NCHS database classified race into 3 mutually exclusive categories from 1988 to 1998, which included black, white, and other, while from 1999 to 2007, the NCHS database classified race into 4 mutually exclusive groups, black, white, American Indian or Alaska native, and Asian or Pacific islander.<sup>18</sup> For our analysis, which is a comparison of black and white children, we combined the latter 2 groups into the "other" category.

Our primary analysis included all children younger than 20 years for consistency with the previously published report on US childhood stroke mortality.<sup>4</sup> Since the recommendations from the STOP trial do not apply to children younger than 2 years, we performed a secondary analysis excluding infants (<1 year). The NCHS mortality database used in our analyses categorizes age as follows: younger than 1 year, 1 to 4 years, 5 to 9 years, 10 to 14 years, and 15 to 19 years. Hence, we could not isolate 1- and 2-year-olds.

For our analyses of temporal trends in stroke mortality, we used the direct method of standardization to age adjust mortality rates to the 1990 US population to be consistent with previous publication.<sup>4</sup> For graphical purposes only, the mortality rates were smoothed using a 3-point moving average and averaging end points with nearest neighbors. To compare mortality rates, we calculated incidence rate ratios as a measure of relative risk. Because our study cohort included the entire population of US children, rather than a sample of this population, confidence intervals may be superfluous but were calculated out of convention. All statistical analyses were done using Stata (version 11; StataCorp).

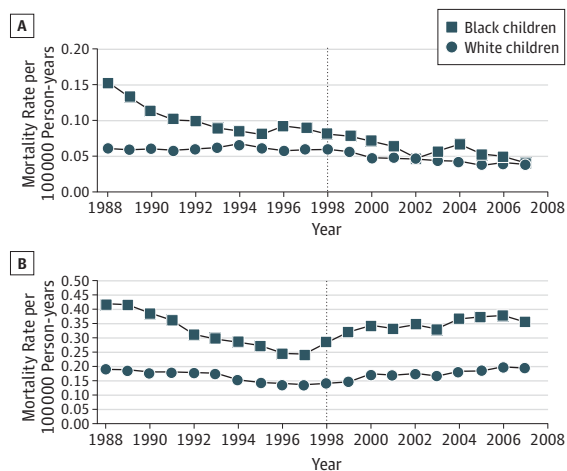
## Results

Our study cohort included a total of 1 555 045 537 person-years of US children. Black children accounted for 16% of the

Table 1. Study Population of All US Children, 1988 Through 2007

Characteristic	Person-years	%
Race		
Black	248 547 617	16
White	1 224 001 441	79
Other	82 496 479	5
Sex		
F	758 405 904	49
M	796 639 633	51
Age, y		
<1	80 094 608	5
1-4	311 128 987	20
5-9	387 876 812	25
10-14	389 043 279	25
15-19	386 901 851	25

Figure 1. Time Trends in US Childhood Stroke Mortality Rates From 1988 Through 2007 in Black Children vs White Children



A, Ischemic stroke. B, Hemorrhagic stroke. A vertical line is drawn to represent when the Stroke Prevention Trial in Sickle Cell Anemia was published.

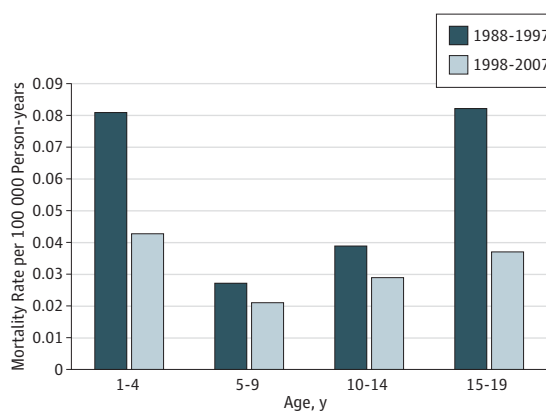
population and sex was distributed evenly (Table 1). Within this cohort, childhood stroke was named as the primary cause of death in 4425 children in the United States from 1988 through 2007, averaging 221 stroke deaths per year. Ischemic stroke accounted for 20% of deaths; hemorrhagic strokes accounted for 67%; and 12% were unspecified. Average annual mortality rates were 0.285 per 100 000 person-years for all stroke types; 0.058, for ischemic stroke; and 0.181, for hemorrhagic stroke.

While the ethnic disparity in hemorrhagic stroke mortality has remained relatively stable over the study period, ischemic stroke mortality rates in black vs white children appear to be converging (Figure 1). The excess risk of ischemic stroke mortality in black vs white children decreased by almost two-thirds, from 74% (1988-1997) to 27% (1998-2007); the excess risk of hemorrhagic stroke mortality remained unchanged (Table 2). In our secondary analysis in which we excluded children younger than 1 year, the relative risk of ischemic stroke mortality for black vs white children was 1.72 (95%

Table 2. Ischemic and Hemorrhagic Stroke Mortality in US Black vs White Children, 0 to 19 Years of Age, 1988 Through 1997 and 1998 Through 2007

Stroke Type	Stroke Mortality per 100 000		
	Black	White	Relative Risk (95% CI)
1988-1997			
Ischemic	0.106	0.061	1.74 (1.42-2.13)
Hemorrhagic	0.317	0.167	1.90 (1.68-2.14)
1998-2007			
Ischemic	0.058	0.045	1.27 (0.99-1.64)
Hemorrhagic	0.332	0.168	1.97 (1.76-2.20)

Figure 2. Ischemic Stroke Mortality Rates in US Black Children From 1988 Through 1997 Compared With 1998 Through 2007, Stratified by Age at the Time of Death



CI, 1.27-2.29) from 1988 through 1997 and 1.09 (95% CI, 0.75-1.54) from 1998 through 2007. The relative risk of hemorrhagic stroke mortality for black vs white children was 1.39 (95% CI, 1.18-1.63) from 1988 through 1997 and 1.67 (95% CI, 1.42-1.96) from 1998 through 2007. To determine whether the decline in ischemic stroke mortality in black children differed by age group, we calculated the average annual mortality rates before and after 1998, stratified by age; all age groups showed a decline, even the younger than 1 year group, who had a pre-1998 stroke mortality rate of 0.93 per 100 000 person-years and post-1998 rate of 0.55 per 100 000 person-years. We compared the age groups that should be affected by the STOP trial and found the greatest change in older adolescents (Figure 2).

### Discussion

The excess risk of death from ischemic, but not hemorrhagic, stroke in US black children has decreased over the past decade. The only major change in childhood stroke care during this period was the initiation of long-term blood transfusion therapy for primary stroke prevention in sickle cell disease. The STOP trial randomized children with sickle cell disease, aged 2 to 18 years, identified as high risk for stroke based on transcranial Doppler ultrasonography, to long-term blood transfusion therapy or standard care. The trial demonstrated that treat-

ing high-risk children with transfusion therapy decreased the risk of stroke by more than 90%.<sup>8</sup> The impact of the intervention occurred quickly: the stroke-free survival curves of the transfusion group vs the standard-care group diverged after 6 months.<sup>8</sup> A Clinical Alert by the National Heart, Lung, and Blood Institute made the STOP trial results public in 1997 and the results were published in 1998.<sup>19</sup>

To determine whether the observed decline in stroke deaths in US black children could be attributed to the STOP trial, we used published rates of the prevalence of sickle cell disease, the incidence of stroke in children with sickle cell disease, and the case fatality of childhood stroke to estimate the absolute number of stroke deaths that the STOP trial could prevent per year. There are approximately 12.8 million black children younger than 20 years in the United States. Newborn screening results in California found that 1 in 396 black children have sickle cell disease; hence, there are approximately 32 300 black children younger than 20 years with sickle cell disease.<sup>20</sup> Prior to the STOP trial, the rate of stroke in children with sickle cell disease was 285 per 100 000 person-years; hence, there would be approximately 92 sickle cell disease-related ischemic strokes per year.<sup>21</sup> If the STOP trial recommendations have been completely implemented, incident strokes should be reduced by 90%, meaning that 83 strokes would be prevented per year. Based on a 4% case fatality rate for childhood stroke, the STOP trial should prevent 3 stroke deaths per year.<sup>22</sup> The absolute number of ischemic stroke deaths among US black children was 11 in 1990, and 8 in 2007, corresponding with the estimated impact of the STOP trial.

In our study, the ethnic disparity in ischemic stroke mortality in US children began to diminish even prior to 1998, when the STOP trial results were published. It is possible that clinical practice changed while the STOP trial was under way. In 1992, a publication by the STOP trial investigators demonstrated that screening with transcranial Doppler ultrasonography could identify those children at extremely high risk of first stroke; at that time, blood transfusion therapy was already the standard treatment for secondary stroke prevention.<sup>23</sup> The hematology community was highly aware of the trial; it is possible that some began screening and treating patients even before the STOP trial results were formally announced. However, other literature suggests that transcranial Doppler ultrasonography screening increased after the publication of the STOP trial, from 1.8 per 100 000 person-years pre-1998 in California, to 5.0 per 100 000 person-years from 1998 through 1999, and 11.4 per 100 000 person-years after 1999.<sup>12</sup> A decrease in stroke admissions in children with sickle cell disease was also seen in California starting in 1999.<sup>9</sup> Therefore, application of the STOP trial recommendations likely played a role in the narrowing ethnic disparity in ischemic stroke mortality in US children over the past decade.

We hypothesized that we would observe a greater change in ethnic disparities in ischemic stroke than hemorrhagic stroke. Although the STOP trial included both ischemic and hemorrhagic strokes as outcomes, 11 of the 12 observed strokes were ischemic, the most common stroke type among children with sickle cell disease.<sup>6-9,13</sup> Hence, the anticipated impact of the trial was primarily on childhood ischemic stroke,

and we indeed found declining ethnic disparities in mortality from ischemic, but not hemorrhagic, stroke.

Our observation of declining ischemic stroke mortality among black children crossed the full age range included in the STOP trial. Prior to 1998, the highest ischemic stroke mortality rate in the US pediatric black population was in children aged 15 to 19 years. This group also had the largest decrease in stroke mortality after 1998. These results correlate with a natural history study that demonstrated that the majority of pediatric patients with sickle cell disease who died of stroke were between 10 and 19 years of age.<sup>24</sup>

Several retrospective studies have demonstrated a decline in the incidence of first-time stroke in children with sickle cell disease since 1998.<sup>9-12</sup> Furthermore, a recent prospective study demonstrated that the implementation of the STOP protocol in a sickle cell population decreases the cumulative risk of stroke. The study examined a cohort of patients in France with sickle cell disease who were diagnosed by newborn screen, followed with transcranial Doppler ultrasonography screening, and treated with long-term transfusion according to the STOP protocol. They were found to have a cumulative stroke risk of 1.9% by the age of 18 years, a notable difference from the historical natural history data: 10% cumulative risk of stroke by the age of 20 years.<sup>6,25</sup> These results demonstrate that stroke risk can be decreased in a population as well as in the setting of a trial. If the STOP trial has made an impact on the incidence of stroke in children with sickle cell disease, it follows that it would impact stroke mortality, explaining our observed narrowing in ethnic disparity in ischemic stroke mortality.

However, several findings suggest that the STOP trial may not have been the only change to impact the ethnic disparities in childhood ischemic stroke mortality. As mentioned earlier, the disparity began to decline even prior to the publication of the STOP trial in 1998. In addition, we observed a decline in the ethnic disparity in stroke mortality in infants, an age group that should not be impacted by the STOP trial. Other data suggest that sickle cell disease may not be the sole explanation for ethnic disparities in childhood stroke. A California study examining childhood stroke admissions from 1991 through 2000 found that, compared with white children, black children were at 2.6-fold increased risk of ischemic stroke and 1.6-fold increased risk of hemorrhagic stroke. Among black children admitted with ischemic stroke, 38% had a diagnosis of sickle cell disease; when cases with sickle cell disease were excluded, black children still had a 61% increased risk of stroke compared with white children.<sup>3</sup> Adult studies have shown that black individuals have a higher incidence of, and mortality from, both hemorrhagic and ischemic stroke compared with white individuals.<sup>26-29</sup> These disparities have largely been attributed to higher rates and poorer control of hypertension, diabetes, and smoking, which are uncommon risk factors for childhood stroke.<sup>30,31</sup> Other genetic or environmental factors may contribute to the ethnic disparities in stroke incidence and mortality in both black adults and children. However, sickle cell disease likely played a major role in the ethnic disparity for ischemic stroke in the young, and we are not aware of other changes in clinical care that could explain the declining disparity in stroke mortality.

Our study had several limitations. Because the NCHS mortality database does not provide information on secondary diagnoses, like sickle cell disease, we could not determine whether stroke deaths within this particular subgroup changed. We were unable to determine whether the changes in stroke mortality were due to a decrease in case fatality or a decrease in the incidence of childhood stroke. Furthermore, as in any administrative study using *ICD-9* and *ICD-10* codes, there is always the possibility of coding error. Death certificate diagnosis of adult stroke using *ICD-8* and *ICD-9* codes has been shown to have both high specificity and high predictive value, and a recent comparabil-

ity study demonstrated that *ICD-9* and *ICD-10* codes for adult cerebrovascular mortality were similar, with a comparability ratio of 1.0588.<sup>15,32</sup> However, the NCHS mortality database switched from *ICD-9* to *ICD-10* codes in 1999, the year after the publication of the STOP trial, which raises the possibility that our findings were related to a change in coding. It seems unlikely, though, that such change would be different for black children compared with white children. Despite these limitations, this study provides indirect evidence that National Institutes of Health investment in sickle cell disease stroke research has narrowed the ethnic gap in childhood ischemic stroke mortality.

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Critical revision of the manuscript for important intellectual content: Fullerton.

Statistical analysis: Lehman.

Study supervision: Fullerton.

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