Low Birth Weights Contribute to the High Rates of Early-Onset Chronic Renal Failure in the Southeastern United States

Daniel T. Lackland, DrPH; Holly E. Bendall, MSc; Clive Osmond, PhD; Brent M. Egan, MD; David J. P. Barker, MD, PhD

Background: The southeastern United States is a region in which rates of cardiovascular and renal diseases are excessive. Within the Southeast, South Carolina has unusually high rates of end-stage renal disease (ESRD) in young people, with more than 70% of cases attributed to hypertension and diabetes.

Objective: To determine whether the increased vulnerability to early-onset ESRD might originate through impaired renal development in utero as measured by low birth weight.

Methods: Patients who were diagnosed with renal failure and undergoing dialysis from 1991 through 1996 were identified from the ESRD registry maintained by the Southeastern Kidney Council, Raleigh, NC. Birth weights reported on birth certificates were selected for the ESRD cases and non-ESRD controls who were born in South Carolina in 1950 and later. Birth weights were compared for 1230 cases and 2460 controls who were matched for age, sex, and race.

Results: Low birth weight was associated with ESRD among men and women as well as blacks and whites. Among people whose birth weight was less than 2.5 kg, the odds ratio for ESRD was 1.4 (95% confidence interval, 1.1-1.8) compared with people who weighed 3 to 3.5 kg. This association was present for renal failure resulting from diabetes, hypertension, and other causes.

Conclusions: Low birth weights, which reflect adverse effects on development in utero, contribute to the early onset of ESRD in South Carolina. Since low birth weight increases the risk of ESRD from multiple causes, the data suggest that an adverse environment in utero impairs kidney development and makes it more vulnerable to damage from a range of pathological processes.

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SUBJECTS AND METHODS

The Southeast Kidney Council (Network 6 of the United States Renal Data System, Raleigh, NC) maintains a registry of all people receiving dialysis for chronic renal failure in the states of South Carolina, North Carolina, and Georgia. The network implements and maintains a database collection and management system that includes quality assurance and monitoring to assure complete case ascertainment. The database includes the name, race, sex, and date of birth of each subject, as well as the nephrologist’s diagnosis of the primary cause of renal failure. The primary disease causing renal failure for each patient with ESRD is identified from the nephrologist’s diagnosis, which is recorded during the application and certification process for Medicare benefits. For the analyses in this study, the primary diagnoses were categorized in 3 groupings: hypertension, diabetes, and other.

Birth weight was determined from the weight reported on the South Carolina birth certificate. Since 1990, the birth weight of babies born in South Carolina has been recorded on the birth certificate, which also records the race of each child’s mother.

The years 1991 through 1996 constitute the most recent period for which ESRD data were available. The ESRD registry identified 2446 South Carolina residents (1377 men and 1072 women) who had renal dialysis during these years. The identification data on the dialysis record were sent to the Office of Vital Records at the South Carolina Department of Health and Environmental Control in Columbia. Visual matching on name and birth date followed initial computer matching. The second phase of the matching process was a manual search for the birth certificates of the successful computer matches. Birth certificates were identified and located for 1345 (55%) of the 2446 subjects. Birth weight was recorded on 1230 of the 1345 birth certificates, including 892 men and 338 women. In most cases, nonmatches were probably the result of individuals who were born outside South Carolina and who changed their surnames with marriage.

The birth weights were recorded in pounds and ounces and converted to grams for analyses. Subjects were categorized according to birth weight (ie, $<2500$, $2500-2999$, $3000-3499$, $3500-3999$, or $=4000$ g). Two controls matched for sex and race were selected for each of these 1230 cases. Since birth certificates are registered in sequential order, the next 2 certificates with the same sex and race were selected. This procedure controlled for age. When a birth weight was not reported on a selected control certificate, the next certificate in sequence was selected. Age was calculated in completed years as of January 1, 1994. The Mann-Whitney test was used to compare the ages of case subjects according to sex, race, and cause of ESRD. Matching was preserved during the analysis of the data using conditional logistic regression in STATA, release 5 (STATA Corp, College Station, Tex). Odds ratios for renal failure were calculated for each birth weight category. The most common birth weight group, 3000 to 3499 g, was chosen as the reference interval to provide stable odds ratio estimates.

RESULTS

Of the 1230 cases with ESRD, 70% of patients (858) were black, 72% (892) were male, 19% (233) had diabetes, 29% (359) had hypertension, and 46% (371) were “other.” For only 67 (5%), the cause of renal failure was unknown. The comorbid conditions and/or primary diagnoses were based on the reports from the nephrologist at the time of first dialysis. A substantial racial difference in the cause of ESRD was found in this study population, with 53% of ESRD cases among blacks caused by hypertension or diabetes vs 36% among whites.

The mean birth weight was 3210 g for black and 3361 g for white case subjects, and it was higher in men (3295 g) than women (3149 g). Table 1 shows the odds ratios for renal failure from all causes of ESRD according to birth weight in men and women. Among all cases, the highest odds ratio is in the lowest birth weight group (ie, $<2500$ g). However, there is evidence of a U-shaped trend (quadratic trend), with elevated odds ratios at either end of the birth weight distribution ($P = .02$ for quadratic trend). The pattern is similar in men and women when analyzed separately.

Table 2 shows the odds ratios for renal failure according to cause of ESRD. For hypertension, diabetes, and other causes, there are elevated odds ratios among those with birth weights of 2500 g or less. In addition, the U-shaped trend is evident among case subjects with diabetes ($P = .02$ for quadratic trend). The quadratic trend is less evident in case subjects with hypertension or other causes of renal failure, in which case the trends are more linear. The Figure, which omits the small number of cases of unknown cause, illustrates these patterns.

Table 3 shows that high odds ratios in association with low birth weight are seen in black and white case subjects. In separate models, for quadratic trends $P = .03$.
for white and $P=.19$ for black case subjects. However, the quadratic trends for the 2 races did not differ significantly.

**Table 1. Odds Ratios for Renal Failure by Sex and Birth Weight Group**

<table>
<thead>
<tr>
<th>Birth Weight Group, g</th>
<th>No. of Controls</th>
<th>No. of Cases</th>
<th>Odds Ratio (95% CI)</th>
<th>No. of Controls</th>
<th>No. of Cases</th>
<th>Odds Ratio (95% CI)</th>
<th>No. of Controls</th>
<th>No. of Cases</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2500</td>
<td>222</td>
<td>147</td>
<td>1.4 (1.1-1.8)</td>
<td>160</td>
<td>96</td>
<td>1.2 (0.9-1.6)</td>
<td>62</td>
<td>51</td>
<td>1.9 (1.2-3.0)</td>
</tr>
<tr>
<td>2500-2999</td>
<td>505</td>
<td>256</td>
<td>1.0 (0.9-1.3)</td>
<td>330</td>
<td>166</td>
<td>1.0 (0.8-1.3)</td>
<td>175</td>
<td>90</td>
<td>1.2 (0.8-1.6)</td>
</tr>
<tr>
<td>3000-3499</td>
<td>882</td>
<td>435</td>
<td>1.0</td>
<td>622</td>
<td>318</td>
<td>1.0</td>
<td>260</td>
<td>117</td>
<td>1.0</td>
</tr>
<tr>
<td>3500-3999</td>
<td>623</td>
<td>268</td>
<td>0.9 (0.7-1.0)</td>
<td>479</td>
<td>210</td>
<td>0.9 (0.7-1.1)</td>
<td>144</td>
<td>58</td>
<td>0.9 (0.6-1.3)</td>
</tr>
<tr>
<td>≥4000</td>
<td>228</td>
<td>124</td>
<td>1.1 (0.9-1.4)</td>
<td>193</td>
<td>102</td>
<td>1.0 (0.8-1.4)</td>
<td>35</td>
<td>22</td>
<td>1.4 (0.8-2.4)</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval.

**Table 2. Odds Ratios for Renal Failure by Primary Cause and Birth Weight Group**

<table>
<thead>
<tr>
<th>Birth Weight Group, g</th>
<th>Diabetes</th>
<th>Hypertension</th>
<th>Other</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Controls</td>
<td>No. of Cases</td>
<td>Odds Ratio (95% CI)</td>
<td>No. of Controls</td>
</tr>
<tr>
<td>&lt;2500</td>
<td>35</td>
<td>19</td>
<td>1.3 (0.7-2.4)</td>
<td>69</td>
</tr>
<tr>
<td>2500-2999</td>
<td>105</td>
<td>45</td>
<td>1.0 (0.6-1.6)</td>
<td>140</td>
</tr>
<tr>
<td>3000-3499</td>
<td>172</td>
<td>72</td>
<td>1.0</td>
<td>261</td>
</tr>
<tr>
<td>3500-3999</td>
<td>123</td>
<td>66</td>
<td>1.3 (0.8-2.0)</td>
<td>176</td>
</tr>
<tr>
<td>≥4000</td>
<td>31</td>
<td>31</td>
<td>2.4 (1.3-4.2)</td>
<td>72</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval.

Among men and women as well as among blacks and whites, chronic renal failure was significantly associated with low birth weight. One of the strengths of this study was the inclusion of black and white case subjects with ESRD in the southeastern United States. The analyses involved 1230 people who were born in South Carolina, developed chronic renal failure at a young age (<50 years), and required dialysis. This study was possible because a registry of all patients on dialysis has been maintained. Moreover, birth weight has been routinely recorded on birth certificates since 1950. Birth weights were ascertained for 65% of men receiving dialysis for ESRD. Based on our previous study of birthplace and stroke deaths in South Carolina, most of the remaining 35% were probably born outside the state.20 Birth weights were obtained for only 32% of women, which reflects the difficulty encountered when attempting to trace women, who usually change surnames at marriage. This would only introduce bias and limit extrapolations if associations between birth weight and ESRD were different in men and women who were born outside South Carolina or between women who were married or single. In our case-control study, we were able to match for sex, age, and race but not for socioeconomic status. The association of ESRD with low birth weight could, therefore, reflect associations with other aspects of low socioeconomic status. However, the links between low birth weight and both hypertension and NIDDM are independent of socioeconomic status.13-17 Another limitation of the study was the inability to determine the level of blood pressure and glycemic control as well as the duration of hypertension and diabetes for the cases. However, the significant association with low birth weight was consistent for all causes of ESRD.

Low birth weight was found to be associated with cases of ESRD that were attributed to a range of causes, including those cases for which no cause was identified. One possible explanation for this was that reduced fetal growth is associated with defects in the development of the kidney that make it more vulnerable to a number of pathological processes. Brenner and colleagues20-23 have proposed that chronic renal failure is associated with a
than those who had normal birth weights. Animal and human studies have shown that low rates of intrauterine growth are associated with reduced numbers of nephrons. Brenner and Mackenzie have suggested that retarded fetal growth leads to a reduced number of nephrons, which in turn leads to increased hydrostatic pressure in the glomerular capillaries, glomerular hyperfiltration, and the development of glomerular sclerosis. This sclerosis could in turn lead to further loss of nephrons as the glomerular hypertension and hyperfiltration worsen.

The association between birth weight and diabetic ESRD was U-shaped and may reflect a mixture of insulin-dependent childhood-onset diabetes and NIDDM. These data do not distinguish between these forms of diabetes. The risk of ESRD is 4 times greater in patients with insulin-dependent diabetes, which is associated with high birth weight. In a large study of children in Sweden, the relative risk of insulin-dependent diabetes rose progressively from 0.81 to 1.20 across the range of birth weight, after adjusting for gestational age. Likewise, an association between maternal undernutrition, retarded fetal growth, and the subsequent development of NIDDM has been demonstrated. Since this study involves the early onset of ESRD, maturity-onset diabetes of the young may be a significant contributor. This syndrome is defined clinically by the early onset of NIDDM. While somewhat different in physical and demographic characteristics from the black-white population in our study, an investigation of Japanese patients with early-onset NIDDM (diagnosed before age 30 years) found a high incidence of diabetic nephropathy consistent with rates among Pima Indian patients with NIDDM and white patients with insulin-dependent diabetes mellitus. A U-shaped association between birth weights and elevated urinary albumin excretion was identified in Pima Indians with NIDDM.

The results of this study suggest that the high rates of ESRD among young people in South Carolina originate through an adverse environment in utero, which may impair the development of the kidney and make it more vulnerable to damage by a range of pathological processes. While the association between low birth weight and ESRD extends across race and sex, the high rates of ESRD in South Carolina are concentrated in the black population. Low birth weight is more common in South Carolina and the Southeast than in other states and regions, and it is more common among blacks than whites. Thus, the results of these analyses could provide one explanation for the high rates of chronic renal failure in the southeastern region of the United States as well as the excessive rates of ESRD among the black population. The earlier age of onset of renal failure in blacks with diabetes and hypertension compared with whites may reflect an accelerated progression of these diseases in blacks and/or a greater vulnerability of the kidney to their effects. The number of people who will be treated with long-term dialysis is predicted to increase over the next 40 years. The economic burden to Medicare, which covers the costs of ESRD, will continue to grow with an increasing disease rate and aging population. This economic drain may be reduced by the implementation of programs to improve perinatal health.

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