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# Early-Life Antecedents of Atrial Fibrillation: Place of Birth and Atrial Fibrillation-Related Mortality

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**PURPOSE:** Recent evidence suggests early-life factors correlate with atrial fibrillation (AF). We hypothesized that AF-related mortality, similar to stroke mortality, is elevated for individuals born in the southeastern United States.

**METHODS:** We estimated 3-year (1999–2001) average AF-related mortality rates by using U.S. vital statistics for 55- to 89-year-old white (136,573 AF-related deaths) and black subjects (8,288 AF-related deaths). We estimated age- and sex-adjusted odds of AF-related (contributing cause) mortality associated with birth state, and birth within the U.S. stroke belt (SB), stratified by race. SB results were replicated with the use of 1989–1991 data.

**RESULTS:** Among black subjects, four contiguous birth states were associated with statistically significant odds ratios ⩾1.25 compared with the national average AF-related mortality. The four highest-risk birth states for blacks also predicted elevated AF-related mortality among white subjects, but patterns were attenuated. The odds ratio for AF-related mortality associated with SB birth was 1.19 (confidence interval 1.13–1.25) for black and 1.09 (CI 1.07–1.12) for white subjects when we adjusted for SB adult residence.

**CONCLUSIONS:** Place of birth predicted AF-related mortality, after we adjusted for place of adult residence. The association of AF-related mortality and SB birth parallels that of other cardiovascular diseases and may likewise indicate an importance of early life factors in the development of AF.

*Ann Epidemiol 2011;21:732–738.* 

KEY WORDS: Atrial Fibrillation, Geographic, Lifecourse Mortality, Residence.

## INTRODUCTION

Accumulated epidemiologic data link early-life risk factors such as low birth weight and childhood socioeconomic status to a range of cardiovascular outcomes, including heart failure, myocardial infarction, stroke, and overall mortality (1–6). However, little is known regarding the relationship between early environmental factors and the later development of arrhythmias. Recently, an association between greater birth weight and increased risk of atrial fibrillation (AF) has been reported, implicating a role for early life factors in the causal pathway for this most common and morbid arrhythmia (7).

The possible role of early-life conditions in the etiology of AF is a challenge to study because there are few data sources; AF is transient and often asymptomatic, making

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This study was supported with a pilot project grant from the Harvard Program on Global Demography and Aging, which is supported by the National Institute on Aging, and by National Institute on Aging grant R21AG03438501.

Dr. Glymour has received honoraria for lectures or educational activities not funded by industry and received research support from the NIH, the Robert Wood Johnson Foundation Health and Society Scholars Programs at Columbia and Harvard Universities, and the MacArthur Foundation Network on Socioeconomic Status and Health, the American Heart Association, the Harvard School of Public Health, and the Harvard Center for Population and Development Studies.

Ms. Kosheleva receives/has received research support as a programmer from the NIH (#1R01AG027122–01A2, NIOSH #1R03OH009338–01, and #1R03CA137666–01A1), the Program on Global Demography of Aging (Harvard School of Public Health), and from the MacArthur Foundation Network on Socioeconomic Status and Health.

Dr. Benjamin receives research support from 1RC1 HL101056; 1R01HL092577; 1R01HL102214; 1 R01 AG028321; and N01-HC 25195.

Analyses are based on data from the National Center for Health Statistics (NCHS), but NCHS is not responsible for any analyses, interpretations, or conclusions presented here.

Received March 24, 2011. Accepted June 3, 2011. Published online July 27, 2011.


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1047-2797/$ - see front matter
doi:10.1016/j.annepidem.2011.06.003

**Selected Abbreviations and Acronyms**

AF = atrial fibrillation
SB = stroke belt
DC = District of Columbia
OR = odds ratio
CI = confidence interval

assessment of the outcome difficult. Similarly, childhood social conditions are difficult to assess, which has led to the use of place of birth as a powerful proxy. Birthplace is a nonspecific marker for a host of early life exposures and therefore especially valuable when little is known about specific risk factors. Birth in the southeastern United States is associated with elevated risk of stroke incidence and mortality (8, 9). Because of the strong association between AF and stroke (10), we hypothesized that AF and stroke exhibit similar geographic patterns, with elevations among people born in the "stroke belt" (SB, ie, North Carolina, South Carolina, Georgia, Tennessee, Arkansas, Mississippi, or Alabama). Because AF is a well-described independent risk factor for stroke (11), investigating whether geographic variation also exists in AF and the relationship of these patterns to those of stroke may reveal clues to the underlying mechanism of these unexplained patterns. Environmental factors that influence cardiovascular pathology leading to stroke also may influence risk of developing AF, or AF may even play a mediating role for cerebrovascular disease in the SB.

To examine the possibility of geographic variation in the epidemiology of AF, we used national census and mortality data from 1989 to 1991 and 1999 to 2001 to assess the risk of AF-related mortality across the United States by individual state of birth or state of adult residence and by residence in the SB. To rule out the possibility that geographic patterns were explained by differences in cause of death coding, we assessed whether geographic patterns of AF-related mortality persisted in out-migrants, who were born in the SB but lived elsewhere in adulthood.

## METHODS

### Data Sources

The 1990 and 2000 U.S. Census Public Use Microsamples were examined to define the at-risk populations in 1990 and 2000, respectively (12). These are 5% samples from the full census data, upweighted to represent the eligible U.S. population in each year. Samples were restricted to individuals who were born in any of the 49 U.S. states (excluding Hawaii) or the District of Columbia (DC), who resided in a U.S. state or DC at ages 55–89 years on the census date and who self-reported their race as black or white. Mortality records for 1989–1991 and 1999–2001 were obtained from the National Center for Health Statistics cause of death files (13). We pooled mortality records across 3-year periods to increase the stability of estimated mortality rates. The rates for 1990 were calculated by the use of the deaths recorded in 1989–1991 (divided by three) as the numerator and the population at risk in the 1990 census as the denominator. The rates for 2000 were calculated by the use of deaths recorded in 1999–2001 (divided by three) as the numerator and the population at risk in the 2000 census as the denominator. AF-related deaths were identified as those mortality records with contributing cause of death ICD-9 code 427.3 for 1990 and ICD-10 code I48 for 2000. In each analysis, mortality records and census data were used to calculate AF-related mortality rates for each combination of covariates and exposures: race, sex, and birth year and (depending on the analysis), state of birth, state of adult residence, SB birth, or SB adult residence.

It was determined by the Human Subjects Committee of the Harvard School of Public Health that the present research, consisting of secondary analyses of publicly available data sets, did not constitute human subjects research.

### Data Collection and Measurements

Exposures were defined on the basis of state of birth or state of adult residence. Our definition of the SB comprised seven states (North Carolina, South Carolina, Georgia, Tennessee, Arkansas, Mississippi, or Alabama), corresponding to the U.S. Department of Health & Human Services Stroke Belt Elimination Initiative and our own previous work (6, 14, 15). We considered four SB exposure categories: born in the SB and residing in the SB during adulthood (individuals who were "doubly exposed"); the out-migrants, who were born in the SB but did not live there in adulthood (ie, at census date); the in-migrants, who were born outside the SB but resided in the SB in adulthood; or neither born in the SB nor lived there in adulthood.

### Analyses

Mortality rates were calculated by linking mortality and population data within each stratum defined by the exposure and covariates. We first used logistic regressions with random effects (SAS proc glimmix) for each state to estimate the odds of AF-related mortality for adult residents of each state (regardless of state of birth), adjusted for sex, age, and age-squared. We next repeated these models, estimating the odds of AF-related mortality for individuals who were born in each state (regardless of place of adult residence). Models were stratified by race. Empirical Bayes (shrinkage) estimates of the odds ratios (OR) associated with each state of adult residence and each state of birth were mapped. We used the Bayes estimates to account for