Birth Weight Is a Significant Risk Factor for Incident Atrial Fibrillation

David Conen, MD, MPH; Usha B. Tedrow, MD, MSc; Nancy R. Cook, ScD; Julie E. Buring, ScD; Christine M. Albert, MD, MPH

Background—Few if any studies have assessed the relationship between birth weight and incident atrial fibrillation (AF).

Methods and Results—From 1993 to 2009, we prospectively followed 27,982 women who were >45 years of age and free of cardiovascular disease and AF at baseline. Information on birth weight was categorized into 5 different categories: <2.5, 2.5 to 3.2, 3.2 to 3.9, 3.9 to 4.5, and >4.5 kg. The primary outcome was time to incident AF. During 14.5 years of follow-up, 735 AF events occurred. Age-adjusted incidence rates for incident AF from the lowest to the highest birth weight category were 1.45, 1.82, 1.88, 2.57, and 2.55 events per 1000 person-years of follow-up. After multivariable adjustment, hazard ratios for incident AF across increasing birth weight categories were 1.0, 1.30 (95% confidence interval [CI], 0.96 to 1.75), 1.28 (95% CI, 0.96 to 1.69), 1.70 (95% CI, 1.23 to 2.37), and 1.71 (95% CI, 1.12 to 2.61) (P for linear trend=0.002). Adding body mass index, blood pressure, and diabetes mellitus at study entry did not have a large effect on these estimates (P for linear trend=0.004). In contrast, including height in the multivariable model substantially attenuated the relationship between birth weight and AF (P for linear trend=0.17), and additional adjustment for maximum weight in young adulthood further attenuated this association (multivariable-adjusted hazard ratio across birth weight categories, 1.0, 1.27 [95% CI, 0.94 to 1.71], 1.10 [95% CI, 0.83 to 1.46], 1.41 [95% CI, 1.01 to 1.96], and 1.29 [95% CI, 0.84 to 1.98]; P for linear trend=0.23).

Conclusions—Birth weight is significantly associated with incident AF among women, suggesting that early life determinants may play an important role in the pathogenesis of AF.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00000479.

Key Words: atrial fibrillation ■ birth weight ■ epidemiology ■ fetal development ■ women

In 1989, Barker et al1 described an inverse association between birth weight and the risk of dying from ischemic heart disease during adulthood. Since this early report, multiple studies have confirmed an increased risk of cardiovascular disease among individuals with a low birth weight.2,3 In addition, birth weight has been related to the incidence of several cardiovascular risk factors such as obesity, hypertension, and type 2 diabetes mellitus.4–8 Thus, accumulating evidence suggests that early life determinants may be important in the pathogenesis of adult disease.

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However, despite this large body of evidence for the association between birth weight and cardiovascular disease, few if any studies have addressed a potential relationship between birth weight and atrial fibrillation (AF), the most common sustained cardiac arrhythmia in the general population and a major risk factor for total mortality, congestive heart failure, and stroke.11–15 Unfortunately, treatment strategies aimed at the elimination of established AF have limited long-term success rates and significant risks,16,17 making further investigations into the pathophysiology of AF an important priority to define more efficient prevention targets or novel mechanisms for drug development.

Elevated blood pressure and obesity are among the most important risk factors for the occurrence of AF,18,19 and both have been associated with birth weight.5–8 We therefore hypothesized that birth weight would be a risk factor for incident AF during adulthood and prospectively assessed this relationship in a large cohort of initially healthy women.

Methods

Study Participants

All study subjects were participants of the Women’s Health Study, a completed randomized trial evaluating the effects of low-dose aspirin
and vitamin E in the primary prevention of cardiovascular disease and cancer. Details of the study design have been given previously.20,21 Briefly, beginning in 1993, 39,876 female health professionals in the United States who were ≥45 years of age and free of cardiovascular disease, cancer, or other major illnesses were randomized to receive 100 mg aspirin every other day, 600 IU vitamin E every other day, both agents, or placebo. Randomized treatment ended on March 31, 2004, and women were invited to participate in continued observational follow-up, which for the present study was truncated on March 2, 2009. Of the original cohort, 4324 opted out of the observational follow-up. These women were excluded from this analysis because their AF could not be reliably confirmed. However, very similar results were obtained when we repeated our analyses using self-reported AF events among all women as the main outcome variable (data not shown).

For the present analysis, we further excluded 785 women with a history of AF at study entry, 6146 women with missing birth weight information, 632 women because they were part of a multiple birth, and 7 women because of cardiovascular events that occurred before randomization. The final study population consisted of 27,982 women, and the median follow-up was 14.5 years (interquartile range, 13.9 to 14.8 years). Written informed consent was obtained from all participants. The study was approved by the institutional review board of Brigham and Women’s Hospital, Boston.

Birth Weight Ascertainment

Information on baseline variables was collected with mailed questionnaires. Follow-up questionnaires asking participants about study outcomes and other information were sent every 6 months during the first year and every 12 months thereafter. Information on birth weight was obtained at study entry using the following categories: <5.5 lb (<2.5 kg), 5.6 to 6.9 lb (2.5 to 3.2 kg), 7.0 to 8.5 lb (3.2 to 3.9 kg), 8.6 to 9.9 lb (3.9 to 4.5 kg), or ≥10 lb (>4.5 kg). At the same time, women were also asked whether they were part of a multiple birth. The validity of self-reported birth weight has been assessed in the Nurses’ Health Study, in which 70% of participants reported the same birth weight category as that listed on their birth certificate.22 The Spearman correlation coefficient between categories of self-reported and certificate-derived birth weight was 0.74. Very similar validation results have been found in the Health Professionals Follow-up Study.8 Other covariates of interest that were assessed at study entry included age, body mass index (weight in kilograms divided by the square of height in meters), body surface area (square root (weight×height)/3600)),23 history of hypertension, history of hypercholesterolemia (self-reported cholesterol of at least 240 mg/dL [6.22 mmol/L]), smoking, diabetes mellitus, exercise, alcohol consumption, highest education level achieved, and race/ethnicity. To better assess cumulative lifetime exposure to increased body size, we included in the analyses maximum body weight between 18 and 30 years of age in addition to the body size variables assessed at study entry.

Ascertainment of Incident AF

Details about the confirmation of AF in the Women’s Health Study have been reported previously.18,24 In brief, women enrolled in the continued observational follow-up who reported an incident AF event on at least 1 yearly questionnaire were sent an additional questionnaire to confirm the episode and to collect additional information. They were also asked for permission to review their medical records. For all deceased participants who reported AF during the trial and extended follow-up period, we contacted family members to obtain consent and additional relevant information. An end-point committee of physicians reviewed medical records for reported events according to predefined criteria. An incident AF event was confirmed if there was ECG evidence of AF or if a medical report clearly indicated a personal history of AF. Of the 169 potential events reviewed for the present study, 735 (84.6%) could be confirmed and occurred after study entry.

Statistical Analysis

Baseline characteristics across birth weight categories were compared with Kruskal-Wallis tests for continuous variables and χ² tests for categorical variables. Cox proportional-hazards models were used to calculate relative risks and to compare hazard ratios and 95% confidence intervals (CIs) for incident AF across birth weight categories. For each woman, person-years of follow-up were calculated from the date of return of the run-in questionnaire to date of first end point, death, loss to follow-up, or March 2, 2009, whichever came first. All analyses used the lowest birth weight category (<2.5 kg) as the reference group.

Age-adjusted models were further adjusted for hypercholesterolemia, smoking, exercise, alcohol consumption, education, race/ethnicity, and hormone replacement therapy. Subsequently, a series of Cox models were constructed to gain further insights into the relationship between birth weight and incident AF and to identify variables that may potentially mediate such an association. In a first step, we added body mass index, systolic and diastolic blood pressures, and history of diabetes mellitus to the multivariable model described above. Because of recent findings of a strong association between height and incident AF among men,23 we included height at study entry in the next model. We then added maximum body weight between 18 and 30 years of age to the final model. We also assessed the individual effect of various body size variables on the risk of incident AF, including body weight in young adulthood, adult height, and adult body surface area.

Because newborns with a birth weight ≥4.5 kg are usually considered macrosomic,26 we repeated our main analyses among women with birth weights <4.5 kg. We also assessed the relationship between premature birth and incident AF among the 27,265 women with information on this variable. To minimize the possibility that the effect of birth weight on the risk of incident AF could be due to intercurrent cardiovascular events, we refitted our Cox models after censoring women with an intercurrent cardiovascular event (confirmed myocardial infarction, stroke, or coronary revascularization) at the date of the event.

To assess linear trends across categories, each birth weight category was assigned a representative value in an ordinal variable (2.1, 2.8, 3.5, 4.2, and 4.7 kg). The proportional-hazards assumption was examined by including birth weight by logarithm of time interaction terms in the model.27 The assumption was found to be met for all models. All analyses were carried out with SAS version 9.1 (SAS Institute Inc, Cary, NC). A 2-tailed value of P<0.05 was considered to indicate statistical significance.

Results

Baseline characteristics according to birth weight categories are shown in Table 1. The majority of women indicated a birth weight between 3.2 and 3.9 kg (n=14,214, 50.8%), followed by the birth weight categories 2.5 to 3.2 kg (n=7,228, 25.8%), <2.5 kg (n=2,962, 10.6%), 3.9 to 4.5 kg (n=2,785, 10.0%), and >4.5 kg (n=793, 2.8%). Age and body size variables gradually increased across increasing birth weight categories. For hypertension, diabetes mellitus, hypercholesterolemia, and smoking, we found U-shaped relationships across birth weight categories. Compared with the highest category, women in the lowest birth weight category had a higher prevalence of diabetes mellitus, a lower prevalence of hypertension, and a lower prevalence of regular alcohol consumption (Table 1).

During a median follow-up of 14.5 years (13.9 to 14.8 years), a confirmed first episode of AF occurred in 735 women. Age-adjusted incidence rates for AF across increasing birth weight categories were 1.45, 1.82, 1.88, 2.57, and 2.55 events per 1000 person-years of follow-up (Table 2). A strong risk gradient across birth weight categories persisted.
Table 1. Baseline Characteristics According to Birth Weight Categories

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>&lt;2.5 (n = 2962)</th>
<th>2.5–3.2 (n = 7228)</th>
<th>3.2–3.9 (n = 14214)</th>
<th>3.9–4.5 (n = 2785)</th>
<th>≥4.5 (n = 793)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>52 (49–58)</td>
<td>52 (48–57)</td>
<td>52 (49–58)</td>
<td>53 (49–58)</td>
<td>56 (51–61)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index at study entry, kg/m²</td>
<td>25.0 (22.3–28.9)</td>
<td>24.6 (22.2–28.2)</td>
<td>25.0 (22.6–28.3)</td>
<td>25.1 (22.8–29.2)</td>
<td>25.8 (23.0–30.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight at study entry, kg</td>
<td>66 (58–76)</td>
<td>66 (59–75)</td>
<td>68 (61–78)</td>
<td>70 (63–82)</td>
<td>73 (64–84)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adult height, cm</td>
<td>163 (157–168)</td>
<td>163 (157–168)</td>
<td>165 (160–170)</td>
<td>168 (163–170)</td>
<td>168 (163–170)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Maximum weight between 18 and 30 y of age, kg</td>
<td>59 (54–67)</td>
<td>59 (56–66)</td>
<td>61 (57–68)</td>
<td>64 (59–73)</td>
<td>64 (59–73)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>2768 (94.4)</td>
<td>6806 (95.1)</td>
<td>13 694 (97.0)</td>
<td>2660 (96.6)</td>
<td>755 (95.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>806 (27.2)</td>
<td>1742 (24.1)</td>
<td>3338 (23.5)</td>
<td>648 (23.3)</td>
<td>236 (30.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>120 (4.1)</td>
<td>176 (2.4)</td>
<td>340 (2.4)</td>
<td>81 (2.9)</td>
<td>22 (2.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of hypercholesterolemia, n (%)</td>
<td>891 (30.1)</td>
<td>2007 (27.8)</td>
<td>3887 (27.4)</td>
<td>762 (27.4)</td>
<td>249 (31.4)</td>
<td>0.006</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>443 (15.0)</td>
<td>881 (12.2)</td>
<td>1707 (12.0)</td>
<td>355 (12.8)</td>
<td>117 (14.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Exercise, n (%)</td>
<td>955 (32.3)</td>
<td>2508 (34.7)</td>
<td>5211 (36.7)</td>
<td>1079 (38.7)</td>
<td>345 (43.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adult height, cm</td>
<td>1562 (52.8)</td>
<td>3836 (53.1)</td>
<td>7286 (51.3)</td>
<td>1351 (48.5)</td>
<td>331 (41.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Maximum weight between 18 and 30 y of age, kg</td>
<td>2981 (41.3)</td>
<td>5835 (41.1)</td>
<td>1066 (38.4)</td>
<td>363 (45.8)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Hormone replacement therapy, n (%)</td>
<td>12 340 (42.0)</td>
<td>2981 (41.3)</td>
<td>5835 (41.1)</td>
<td>1066 (38.4)</td>
<td>363 (45.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Alcohol consumption, n (%)</td>
<td>434 (16.7)</td>
<td>1314 (34.3)</td>
<td>6080 (36.1)</td>
<td>1091 (39.2)</td>
<td>347 (43.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rarely/never</td>
<td>1079 (36.4)</td>
<td>2621 (36.3)</td>
<td>5134 (36.1)</td>
<td>1091 (39.2)</td>
<td>347 (43.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt;1 times/wk</td>
<td>610 (20.6)</td>
<td>1469 (20.3)</td>
<td>2908 (20.5)</td>
<td>551 (19.8)</td>
<td>146 (18.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1–3 times/wk</td>
<td>981 (33.1)</td>
<td>2322 (32.2)</td>
<td>4635 (32.6)</td>
<td>867 (31.2)</td>
<td>211 (26.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥3 times/wk</td>
<td>292 (9.9)</td>
<td>811 (11.2)</td>
<td>1532 (10.8)</td>
<td>274 (9.9)</td>
<td>89 (11.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Never</td>
<td>1384 (46.7)</td>
<td>3114 (43.1)</td>
<td>6080 (42.8)</td>
<td>1222 (43.9)</td>
<td>395 (49.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rarely/never</td>
<td>383 (12.9)</td>
<td>976 (13.9)</td>
<td>1892 (13.3)</td>
<td>389 (14.0)</td>
<td>86 (10.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1–3 drinks/mo</td>
<td>920 (31.1)</td>
<td>2420 (33.5)</td>
<td>4740 (33.4)</td>
<td>885 (31.8)</td>
<td>221 (27.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥1 drink/d</td>
<td>274 (9.3)</td>
<td>715 (9.9)</td>
<td>1500 (10.6)</td>
<td>287 (10.3)</td>
<td>90 (11.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Highest education level, n (%)</td>
<td>1581 (54.5)</td>
<td>3833 (54.1)</td>
<td>7661 (54.8)</td>
<td>1589 (57.9)</td>
<td>477 (61.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Less than a bachelor’s degree</td>
<td>1793 (57.9)</td>
<td>4143 (57.9)</td>
<td>8227 (57.9)</td>
<td>1803 (62.9)</td>
<td>527 (65.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bachelor’s degree</td>
<td>679 (23.4)</td>
<td>1728 (24.4)</td>
<td>3434 (24.6)</td>
<td>640 (23.3)</td>
<td>171 (22.1)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Master’s degree or doctorate</td>
<td>639 (22.0)</td>
<td>1523 (21.5)</td>
<td>2895 (20.7)</td>
<td>517 (18.8)</td>
<td>127 (16.4)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are medians (interquartile ranges) or counts (percentages). Number of events across categories may not sum to the given number because of missing data.

*Based on Kruskal-Wallis tests for continuous variables and χ² tests for categorical variables.

after multivariable adjustment for potential confounders but excluding biological processes such as obesity, hypertension, and diabetes mellitus potentially within the causal pathway (Table 2, multivariable model 1). In this model, women in the second, third, fourth, and fifth birth weight categories had a hazard ratio for incident AF of 1.30 (95% CI, 0.95 to 1.75), 1.28 (95% CI, 0.96 to 1.69), 1.70 (95% CI, 1.23 to 2.37), and 1.71 (95% CI, 1.12 to 2.61) compared with women in the lowest birth weight category (P for linear trend = 0.002). Adding a measure of body size in young adulthood (maximum body weight between 18 and 30 years of age) to the multivariable model including adult height and body mass index further attenuated the relationship between birth weight and AF (multivariable model 4). The relationship between birth weight and AF was similarly attenuated when adult body surface area at study entry was used as an alternative to adult height as a measure of body size (P for linear trend over birth weight categories = 0.11). Each of these potentially mediating body size variables was strongly associated with incident AF after adjustment for age, birth weight, adult body mass index, diabetes mellitus, smoking, exercise, alcohol consumption, education, race/ethnicity, hormone replacement therapy, systolic and diastolic blood pressures, and diabetes mellitus. The multivariable-adjusted hazard ratios for adult height, adult body surface area, and maximum body weight at 18 to 30 years of age were 1.05 per 1 cm (95% CI, 1.04 to 1.06), 1.71
Table 2. Risk of Incident AF According to Birth Weight Categories

<table>
<thead>
<tr>
<th>Birth Weight Category, kg</th>
<th>Events, n</th>
<th>Age-adjusted incidence rate</th>
<th>Age-adjusted relative risk</th>
<th>Multivariable model 1*</th>
<th>Multivariable model 2†</th>
<th>Multivariable model 3‡</th>
<th>Multivariable model 4§</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.5 (n=2962)</td>
<td>59</td>
<td>1.45</td>
<td>1.27 (0.95–1.71)</td>
<td>1.30 (0.96–1.75)</td>
<td>1.31 (0.97–1.77)</td>
<td>1.28 (0.94–1.73)</td>
<td>1.27 (0.94–1.71)</td>
</tr>
<tr>
<td>2.5–3.2 (n=7228)</td>
<td>172</td>
<td>1.82</td>
<td>1.31 (1.00–1.72)</td>
<td>1.28 (0.96–1.69)</td>
<td>1.27 (0.96–1.68)</td>
<td>1.13 (0.85–1.50)</td>
<td>1.10 (0.83–1.46)</td>
</tr>
<tr>
<td>3.2–3.9 (n=14,214)</td>
<td>369</td>
<td>1.88</td>
<td>1.75 (1.27–2.41)</td>
<td>1.70 (1.23–2.37)</td>
<td>1.68 (1.21–2.34)</td>
<td>1.43 (1.02–1.99)</td>
<td>1.41 (1.01–1.96)</td>
</tr>
<tr>
<td>3.9–4.5 (n=2785)</td>
<td>100</td>
<td>2.57</td>
<td>1.76 (1.16–2.67)</td>
<td>1.71 (1.12–2.61)</td>
<td>1.63 (1.07–2.50)</td>
<td>1.34 (0.87–2.05)</td>
<td>1.29 (0.84–1.98)</td>
</tr>
<tr>
<td>≥4.5 (n=793)</td>
<td>35</td>
<td>2.55</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are counts, rates per 1000 person-years of follow-up, or hazard ratios (95% CIs) as appropriate.

*Adjusted for age, hypercholesterolemia, smoking, exercise, alcohol consumption, education, race/ethnicity, and hormone replacement therapy. Because of missing covariates, the multivariable model was based on 715 events in 27,174 women.
†Additionally adjusted for body mass index, systolic blood pressure, diastolic blood pressure, and diabetes mellitus. Because of missing covariates, the multivariable model was based on 696 events in 26,368 women.
‡Additionally adjusted for adult height. Because of missing covariates, the multivariable model was based on 696 events in 26,368 women.
§Additionally adjusted for maximum body weight between 18 and 30 years of age. Because of missing covariates, the multivariable model was based on 689 events in 25,992 women.

per 1 SD (95% CI, 1.50 to 1.96), and 1.02 per 1 kg (95% CI, 1.02 to 1.03), respectively.

In sensitivity analyses excluding women with a macrosomic birth weight of >4.5 kg, a significant risk gradient persisted between birth weight and AF (P for linear trend=0.011) after controlling for confounding variables according to multivariable model 2 (see the legend in Table 2). Birth weight also remained a significant predictor of incident AF when we additionally adjusted for preterm birth (P for linear trend across birth weight categories=0.017). Preterm birth compared with full-term birth was not significantly related to incident AF (multivariable hazard ratio, 0.71; 95% CI, 0.45 to 1.11).

Table 3. Risk of Incident AF According to Birth Weight Categories, Censoring Women at Their First Cardiovascular Event

<table>
<thead>
<tr>
<th>Birth Weight Category, kg</th>
<th>No. of events</th>
<th>Age-adjusted incidence rate</th>
<th>Age-adjusted relative risk</th>
<th>Multivariable model 1*</th>
<th>Multivariable model 2†</th>
<th>Multivariable model 3‡</th>
<th>Multivariable model 4§</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.5 (n=2962)</td>
<td>52</td>
<td>1.32</td>
<td>1.34 (0.98–1.83)</td>
<td>1.34 (0.98–1.84)</td>
<td>1.33 (0.97–1.83)</td>
<td>1.30 (0.94–1.78)</td>
<td>1.28 (0.93–1.76)</td>
</tr>
<tr>
<td>2.5–3.2 (n=7228)</td>
<td>161</td>
<td>1.74</td>
<td>1.38 (1.03–1.85)</td>
<td>1.32 (0.98–1.77)</td>
<td>1.29 (0.96–1.74)</td>
<td>1.15 (0.85–1.55)</td>
<td>1.12 (0.83–1.50)</td>
</tr>
<tr>
<td>3.2–3.9 (n=14,214)</td>
<td>348</td>
<td>1.81</td>
<td>1.89 (1.35–2.65)</td>
<td>1.81 (1.29–2.55)</td>
<td>1.77 (1.26–2.50)</td>
<td>1.49 (1.05–2.11)</td>
<td>1.47 (1.04–2.08)</td>
</tr>
<tr>
<td>3.9–4.5 (n=2785)</td>
<td>96</td>
<td>2.53</td>
<td>1.83 (1.17–2.84)</td>
<td>1.75 (1.12–2.73)</td>
<td>1.65 (1.06–2.58)</td>
<td>1.34 (0.86–2.10)</td>
<td>1.29 (0.82–2.02)</td>
</tr>
<tr>
<td>≥4.5 (n=793)</td>
<td>32</td>
<td>2.43</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are counts, rates per 1000 person-years of follow-up, or hazard ratios (95% CIs) as appropriate.

*Adjusted for age, hypercholesterolemia, smoking, exercise, alcohol consumption, education, race/ethnicity, and hormone replacement therapy. Because of missing covariates, the multivariable model was based on 670 events in 27,174 women.
†Additionally adjusted for body mass index, systolic blood pressure, diastolic blood pressure, and diabetes mellitus. Because of missing covariates, the multivariable model was based on 651 events in 26,368 women.
‡Additionally adjusted for adult height. Because of missing covariates, the multivariable model was based on 651 events in 26,368 women.
§Additionally adjusted for maximum body weight between 18 and 30 years of age. Because of missing covariates, the multivariable model was based on 644 events in 25,992 women.

Discussion

To the best of our knowledge, this is the first large prospective assessment of the relationship between birth weight and the occurrence or AF during adulthood. After multivariable adjustment, we found a significant, direct linear relationship between birth weight and incident AF (P=0.002) such that women in the highest birth weight category had a significant 71% increased risk of incident AF compared with women in the lowest category. Taking into account the effect of adult body mass index, blood pressure, and diabetes mellitus had a

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small effect on this association. In contrast, substantial attenuation was observed when adult height and weight in young adulthood were added to these models, suggesting that adult height and/or cumulative lifetime exposure to elevated body mass were more important mediators of the association between birth weight and incident AF than body mass index, a measure of adiposity, in adulthood.

The direct association observed in this study between birth weight and incident AF stands in direct contrast to the previously reported inverse associations between birth weight and cardiovascular disease and diabetes mellitus,\textsuperscript{1,2,4} both risk factors for the development of AF.\textsuperscript{28,29} As in our study, confounding by socioeconomic status does not appear to account for the association between birth weight and these outcomes,\textsuperscript{2,4} and the underlying mechanism is unknown. It has been hypothesized that adverse prenatal environmental factors might retard intrauterine growth and confer permanent changes in organ development and metabolism, leading to future adult disease.\textsuperscript{30} Our data on AF risk suggest that these potential negative prenatal influences that adversely affect other types of cardiovascular disease may be offset by the relative protection that lower birth weight confers on the susceptibility of the atria to fibrillation in adulthood.

Prior studies, including our own, have demonstrated the important influence of adult obesity, measured as body mass index, on the development of AF.\textsuperscript{19,31–33} Our findings add to this literature by showing that birth weight confers an increased risk of developing AF later in life that is independent of adult body mass index. Furthermore, recent data have highlighted the importance of other body size measures in determining AF risk, and our study suggests that much of the association between birth weight and AF appears to be mediated through adult height and body mass. Adult height has been associated with incident AF in prior studies,\textsuperscript{25,32} and body surface area measured in young adulthood has also been recently associated with subsequent AF among Swedish men.\textsuperscript{25} Our data not only confirm these findings in a female population but also might raise some potential interesting pathogenic insights.

Given the relationship between birth weight and adult body size measures,\textsuperscript{7,8,34} genetic or environmental intrauterine factors may partially "program" adult body mass and, as a result, subsequent AF risk. Adult body mass may subsequently determine left atrial size,\textsuperscript{19,29,35} which directly influences AF risk. The association between birth weight and AF raises the possibility that there also may be other yet-to-be-discovered early life determinants. Recent findings from large-scale genome-wide association studies of AF provide further support for the importance of early developmental factors in the pathogenesis of AF. The strongest signal in these studies was found on chromosome 4q25 near \textit{PITX2}, a gene that is important in the development of the left atrium and other cardiac structures involved in the pathogenesis of AF.\textsuperscript{36} Interestingly, the other genetic locus that has been consistently related to incident AF (\textit{ZFHX3}) is also involved in growth regulation of several tissues and may even interact with \textit{PITX2}.\textsuperscript{37} In this context, it is possible that birth weight is an indirect marker of underlying genetic factors that modulate the risk of developing AF during adulthood.

Although height is highly heritable and influenced by prenatal factors,\textsuperscript{38,39} postnatal factors such as childhood nutrition also influence adult height.\textsuperscript{40} Therefore, if adult height is the proximate causal factor, it is possible that the relationship between birth weight and incident AF may just be a consequence of the correlation between birth weight and adult height.\textsuperscript{34} The risk estimates for height remained highly significant after controlling for birth weight, which seems to support this possibility. However, it is difficult to evaluate independent associations of 2 correlated variables that may lie within the same causal pathway, especially when one is more subject to measurement error. Adult height is known to be self-reported with great precision in health professionals, the correlation coefficients with measured height being between 0.96 and 0.98.\textsuperscript{38} This greater precision in measurement could also account for the stronger association observed for adult height as opposed to birth weight, which was also reported in categories.

**Strengths and Limitations**

Strengths of the present study include the prospective design, sample size, and long-term follow-up with a large number of confirmed events. The following potential study limitations also require discussion. First, the inclusion of initially healthy, middle-aged female health professionals, most of them white, may limit the generalizability of the results to men or other female populations. Given the inverse associations between birth weight and other forms of cardiovascular disease, the relationship may differ in older populations or in those with a higher prevalence of cardiovascular disease, in whom a greater proportion of AF is secondary to established cardiac disease. Second, as described above, birth weight was based on recall by study participants and was reported in categories limiting the precision of the measurement, and such nondifferential misclassification may have biased our results toward the null. The latter also precluded an assessment of whether extreme birth weights would have a differential impact on incident AF. Third, screening ECGs are not systematically available in this cohort, and some asymptomatic cases of AF may have gone undetected. However, in this cohort of health professionals, who are medically sophisticated and have access to health care, underdetection is less likely. In support of this contention, we found that the number of asymptomatic AF cases in this cohort (n = 73, 9.9%) was similar to that detected by screening ECGs in other cohorts.\textsuperscript{29,41} Fourth, defining the initial episode of AF accurately may be challenging, especially when 8% to 10% of women are asymptomatic at the time of diagnosis. Misspecification of the time of incidence may have introduced some bias toward the null into the time-to-event analysis. Finally, we were unable to take into account important maternal factors that may influence birth weight and its impact on cardiovascular outcomes such as maternal smoking or socioeconomic status.

**Conclusions**

Birth weight is significantly associated with incident AF, suggesting that early life determinants may play an important role in the pathogenesis of AF. Our findings also suggest that
a significant part of the association between birth weight and AF is mediated through height and overall body mass. If the relationship described in the present study is found to be causal in future studies, the increasing number of newborns with elevated birth weight may at least in part be responsible for the increasing burden of AF in the general population.42

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Disclosures
None.

References
CLINICAL PERSPECTIVE

Although birth weight has been associated with the risk of coronary disease and stroke, few if any studies have assessed the influence of birth weight on the risk of developing atrial fibrillation. We prospectively followed up 27,982 women who were >45 years of age and free of cardiovascular disease and atrial fibrillation at baseline. Birth weight was categorized into 5 different categories: <2.5, 2.5 to 3.2, 3.2 to 3.9, 3.9 to 4.5, and >4.5 kg. We found that higher birth weight was associated with an increased risk of atrial fibrillation during adulthood. The 2 highest categories were associated with a 70% and 71% increased risk after multivariable adjustment. Further adjustment for adult height and maximum body weight in young adulthood substantially attenuated these findings. Our results therefore demonstrate that birth weight is significantly associated with incident atrial fibrillation among women. We believe that our findings also suggest that early life determinants may play an important role in the pathogenesis of atrial fibrillation. Most of this effect seems to be mediated through height and cumulative lifetime exposure to elevated body mass. In this context, the increasing prevalence of newborns with an elevated birth weight over the last decades might provide one explanation for the increasing AF burden in Western societies.
Birth Weight Is a Significant Risk Factor for Incident Atrial Fibrillation
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