Epidemiology and Prevention

Absolute and Attributable Risks of Atrial Fibrillation in Relation to Optimal and Borderline Risk Factors
The Atherosclerosis Risk in Communities (ARIC) Study

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Background—Atrial fibrillation (AF) is an important risk factor for stroke and overall mortality, but information about the preventable burden of AF is lacking. The aim of this study was to determine what proportion of the burden of AF in blacks and whites could theoretically be avoided by the maintenance of an optimal risk profile.

Methods and Results—This study included 14,598 middle-aged Atherosclerosis Risk in Communities (ARIC) Study cohort members. Previously established AF risk factors, namely high blood pressure, elevated body mass index, diabetes mellitus, cigarette smoking, and prior cardiac disease, were categorized into optimal, borderline, and elevated levels. On the basis of their risk factor levels, individuals were classified into 1 of these 3 groups. The population-attributable fraction of AF resulting from having a nonoptimal risk profile was estimated separately for black and white men and women. During a mean follow-up of 17.1 years, 1520 cases of incident AF were identified. The age-adjusted incidence rates were highest in white men and lowest in black women (7.45 and 3.67 per 1000 person-years, respectively). The overall prevalence of an optimal risk profile was 5.4% but varied according to race and gender: 10% in white women versus 1.6% in black men. Overall, 56.5% of AF cases could be explained by having ≥1 borderline or elevated risk factors, of which elevated blood pressure was the most important contributor.

Conclusion—As with other forms of cardiovascular disease, more than half of the AF burden is potentially avoidable through the optimization of cardiovascular risk factors levels. (Circulation. 2011;123:1501-1508.)

Key Words: arrhythmias, cardiac ■ body mass index ■ diabetes mellitus ■ epidemiology ■ risk factors

Atrial fibrillation (AF) is one of the most commonly diagnosed cardiac arrhythmias in clinical practice, affecting 2.3 million people in the United States. Individuals with AF are at substantially increased risk of stroke and have twice the mortality rate from cardiovascular disease and overall mortality compared with those with normal sinus rhythm. Moreover, AF is responsible for one third of all hospitalizations for cardiac rhythm disturbances and consequently is associated with significant healthcare costs that in the United States alone exceed $6 billion annually.
Methods

Study Design and Subjects

The ARIC Study is a prospective cohort study of atherosclerotic diseases within 4 communities in the United States: Forsyth County, NC; Jackson, MS; Washington County, MD; and the northwest suburbs of Minneapolis, MN. The recruitment of study participants is described in detail elsewhere. Briefly, the cohort at baseline in 1987 to 1989 was comprised of 15,792 men and women 45 to 64 years of age who were selected by list of area probability sampling. The baseline home interview and clinic examination measured various risk factors and cardiovascular conditions. Three triennial study visits occurred subsequently, with the last visit in 1996 to 1998. Additionally, participants or their proxies were contacted annually by telephone to ascertain hospitalizations and death. The ARIC Study protocol was approved by the institutional review board of each participating university, and informed consent was obtained from each study participant.

Definition of Exposure Categories

On the basis of previous evidence, we categorized individuals as having an optimal AF risk factor profile if at baseline they met the following criteria: no history of cardiac disease (HF or CHD); systolic BP <120 mm Hg, diastolic BP <80 mm Hg, and no use of antihypertensive medication; body mass index (BMI) <25 kg/m²; fasting serum glucose <100 mg/dL, no use of antidiabetic medication, and no history of physician-diagnosed diabetes mellitus; and never smoker. A borderline risk factor profile was defined as having any of the following criteria and no elevated risk factor profile characteristics (see below); systolic BP of 120 to 139 mm Hg and/or diastolic BP of 80 to 89 mm Hg and no use of antihypertensive medication; BMI of 25 to <30 kg/m²; fasting serum glucose 100 to 125 mg/dL and no history of diabetes mellitus; and former smoker. An elevated risk factor profile was defined as having any of the following criteria: history of cardiac disease (HF or CHD); systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, or use of antihypertensive medication; BMI ≥30 kg/m²; fasting serum glucose ≥126 mg/dL, use of antidiabetic medication, or history of physician-diagnosed diabetes mellitus; or current smoker.

Baseline Examination

Blood collection and processing techniques have previously been described. In brief, serum glucose was measured by a hexokinase/glucose-6-phosphate dehydrogenase method. Sitting BP was measured 3 times with a random-zero sphygmomanometer after 5 minutes of rest. The mean of the last 2 measurements was used for the analysis. Self-reported use of antihypertensive medications within the past 2 weeks was collected at baseline. Smoking status (current, former, or never smokers) was derived from interviews.
BMI was computed from weight in a scrub suit and standing height. The primary analysis was conducted in all individuals without a history of AF, and a secondary analysis was conducted after exclusion of individuals with prevalent CHD and HF at baseline. Prevalent CHD included individuals with a history of myocardial infarction, myocardial infarction adjudicated from the baseline ECG, or history of coronary bypass or angioplasty. Prevalent HF cases were identified if either of the 2 following conditions was true: a “yes” in response to the question, “Were any of the medications you took during the last 2 weeks for heart failure?” or the presence of stage 3, or “manifest HF,” as defined by the Gothenburg criteria. All current medications (taken within the preceding 2 weeks) were brought into the clinic and documented.

### Outcome Ascertainment

Individuals with evidence of AF or atrial flutter on an ECG at study baseline were excluded from this analysis. Diagnoses of incident AF and atrial flutter were obtained through the end of 2007 from 3 sources: ECGs done at study visits (visits 2 to 4); presence of an International Classification of Disease, ninth revision, code for AF (427.31 or 427.32) in a hospital discharge, or AF listed as any cause of death on a death certificate. Hospitalizations with AF associated with open cardiac surgery were not considered events. Date of AF occurrence was the earliest of any AF diagnosis. All ARIC examination ECGs were recorded with MAC PC Personal Cardiographs (Marquette Electronics, Inc, Milwaukee, WI). A standard supine 12-lead resting ECG was recorded at each clinic visit and was transmitted by modem to the ARIC ECG Reading Center for automatic reading and coding. All AF cases that were automatically detected from the study ECGs were visually rechecked by a cardiologist. Prior analysis within the ARIC cohort to determine the validity of hospital discharge diagnoses for AF reported 84% sensitivity and 98% specificity in the ascertainment of AF events.

### Statistical Analysis

Of the 15,792 initial ARIC participants, 1194 were excluded for the following reasons: nonwhite and nonblack (n = 274), means and SDs for the baseline continuous variables and percentages for the categorical variables were calculated separately for men and women and for whites and blacks. Age- and gender-standardized prevalence of optimal, borderline, and elevated risk factors were determined at study baseline (1987 to 1989). The age- and gender-adjusted incidence of AF by levels of optimal risk factors was estimated separately in whites and blacks through the use of Poisson regression. Person-years of follow-up were derived from the baseline examination until a first diagnosis of AF, loss to follow-up, death, or December 31, 2007. Associations of risk factor profile at baseline with the incidence of AF were estimated with Cox proportional hazards models that were adjusted for age, study site, education, income, and height. Race- and gender-specific analyses were conducted. The assumption of proportional hazards was examined by adding to the model an interaction term between follow-up time and exposure of interest, computing Schoenfeld residuals, and inspecting the log(−log[survival function]) curves. A SAS macro developed by Zhang and colleagues was used to estimate direct adjusted survival curves for each race/gender category on the basis of a stratified Cox model.

Population-attributable fractions (PAFs) were calculated to determine the possible impact of altering risk profiles on AF occurrence. PAFs were computed according to the following formula:

$$ PAF = \frac{\text{pdi} \times (\text{RR}_i - 1)}{\text{RR}_i}, $$

where pdi is the proportion of cases falling into ith exposure level and RR is the relative risk of changing exposure level with unexposed group (i = 0). Poisson models were used to obtain the RR. To estimate the PAFs for each of the 5 risk factors, models were adjusted for age, study site, education, income, and height, and additionally for each of the other risk factors under investigation (ie, systolic BP, BMI, diabetes mellitus, and smoking).

One thousand bootstrap samples were created to obtain the 95% confidence intervals (CIs) for PAFs.

### Results

#### Prevalence of Risk Categories by Race and Gender

At baseline, the mean age of the 14,598 (55% women, 25% black) participants included in this analysis was 54.2 years (SD, 5.8 years). Table 1 shows both the race- and gender-specific prevalences of optimal, borderline, and elevated levels of BP, BMI, diabetes mellitus, smoking, and prior cardiac disease at study baseline. Overall, just over 5% of the cohort had optimal risk factor levels, just over one quarter had ≥1 borderline risk factor levels, and two thirds of the cohort had ≥1 elevated risk factors at study baseline (Table 2). More than 80% of blacks had ≥1 elevated risk factors compared with ≈60% of whites.

#### Incidence of AF

During a mean follow-up of 17.1 years, there were 1,520 cases of incident AF. Of these, 98.8% were identified from hospi-
talizations, 7.8% from study ECGs, and 5.5% from death certificates (some cases were identified by a method). The age-adjusted incidence rates were 7.45, 4.59, 5.27, and 3.67 per 1000 person-years in white men, white women, black men, and black women, respectively. Compared with those with no risk factors, the age-adjusted incidence rates were 3 times higher in those with elevated risk factors: 2.19 versus 6.59 per 1000 person-years, respectively (Table 3). Individuals with ≥1 borderline risk factor levels had intermediate incidence rates. For any category of risk factor levels, white men had the highest rates and black women the lowest rates (Table 3). Overall, among individuals exhibiting an optimal risk factor profile, the multiple-adjusted relative hazard of AF was 0.33 (95% CI, 0.23 to 0.47), and in those with ≥1 borderline risk factors, it was 0.50 (95% CI, 0.44 to 0.57) compared with those with ≥1 elevated risk factors. These estimates were comparable across the 4 race and gender groups (Table 3). The gender- and race-specific survival curves for the time spent free from AF according to risk factor profile are shown in the Figure. In a sensitivity analysis that included only those individuals who had AF diagnosed at a study visit (n=119), 25 cases of AF occurred among those with a borderline risk factor profile, and 94 occurred in those with an elevated risk factor profile (no events occurred in the optimal risk profile group). The relative hazard for having a borderline risk factor profile compared with having an elevated risk profile was 0.56 (95% CI, 0.36 to 0.87).

Overall, the PAF estimates indicated that having ≥1 elevated risk factor levels could explain 50% (95% CI, 37.5 to 58.5) of AF events (Table 3). In whites, the PAF estimates were comparable in women and men: 50% and 38.2%, respectively. In blacks, the PAF estimates associated with having ≥1 elevated risk factors were 94% and 91% in women and men, respectively. However, this PAF estimate is subject to considerable variability because of small numbers in the optimal risk factor category (n=83), and an alternative estimate based on the RR in the total population of whites and blacks and the risk factor prevalence in blacks yielded a PAF of 49.4% in black men and 59.5% in women (Table 3). Borderline levels of risk factors explained an additional 6.5% of all AF cases. Thus, the proportion of all AF cases that could be attributed to ≥1 elevated and borderline risk factors was reduced to 59.8%,

### Table 3. Incidence Rate, Relative Hazard (95% Confidence Intervals), and Population-Attributable Fraction for Atrial Fibrillation by Race and Gender in the Atherosclerosis Risk in Communities Study, 1987 to 2007

<table>
<thead>
<tr>
<th>Risk Profile</th>
<th>At Risk, n</th>
<th>Incident AF, n</th>
<th>Incidence Rate*</th>
<th>RH (95% CI)†</th>
<th>PAF % 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimal RFs</td>
<td>794</td>
<td>31</td>
<td>2.19</td>
<td>0.33 (0.23–0.47)</td>
<td>0.00</td>
</tr>
<tr>
<td>Borderline RFs only</td>
<td>4064</td>
<td>288</td>
<td>3.68</td>
<td>0.50 (0.44–0.57)</td>
<td>6.53</td>
</tr>
<tr>
<td>Elevated RFs</td>
<td>9740</td>
<td>1201</td>
<td>6.59</td>
<td>1 (Reference)</td>
<td>50.0</td>
</tr>
<tr>
<td>White women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimal RFs</td>
<td>578</td>
<td>21</td>
<td>2.02</td>
<td>0.33 (0.21–0.52)</td>
<td>0.00</td>
</tr>
<tr>
<td>Borderline RFs only</td>
<td>1704</td>
<td>89</td>
<td>2.68</td>
<td>0.45 (0.36–0.56)</td>
<td>4.29</td>
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<tr>
<td>Elevated RFs</td>
<td>3506</td>
<td>415</td>
<td>6.04</td>
<td>1 (Reference)</td>
<td>50.0</td>
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<tr>
<td>White men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimal RFs</td>
<td>140</td>
<td>10</td>
<td>3.95</td>
<td>0.40 (0.21–0.75)</td>
<td>0.00</td>
</tr>
<tr>
<td>Borderline RFs only</td>
<td>1789</td>
<td>179</td>
<td>5.17</td>
<td>0.55 (0.46–0.65)</td>
<td>5.85</td>
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<tr>
<td>Elevated RFs</td>
<td>3216</td>
<td>538</td>
<td>9.07</td>
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<tr>
<td>Black women‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimal</td>
<td>53</td>
<td>0</td>
<td>0.00</td>
<td>...</td>
<td>0.00</td>
</tr>
<tr>
<td>Borderline RFs</td>
<td>324</td>
<td>9</td>
<td>1.69</td>
<td>0.42 (0.21–0.83)</td>
<td>1.57</td>
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<tr>
<td>Elevated RFs</td>
<td>1889</td>
<td>141</td>
<td>4.10</td>
<td>1 (Reference)</td>
<td>59.5</td>
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<tr>
<td>Black men‡</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimal</td>
<td>23</td>
<td>0</td>
<td>0.00</td>
<td>...</td>
<td>0.00</td>
</tr>
<tr>
<td>Borderline RFs</td>
<td>247</td>
<td>11</td>
<td>2.63</td>
<td>0.41 (0.22–0.76)</td>
<td>2.63</td>
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<tr>
<td>Elevated RFs</td>
<td>1129</td>
<td>107</td>
<td>6.04</td>
<td>1 (Reference)</td>
<td>49.4</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; RH, relative hazard; CI, confidence interval; PAF, population-attributable fraction; and RF, risk factor.

*The incidence rate of AF per 1000 person-years adjusted for age (mean age, 54.2 years).
†Adjusted for age, study site, education, income, and height.
‡Black women and men did not have any incident cases of AF in the optimal group, so optimal and borderline were combined and the relative risk from the whole population was applied to obtain their PAF.
46.6%, 49.7%, and 36.6% in black women, black men, white women, and white men, respectively.

Examination of the PAFs associated with each of the 5 risk factors in turn indicated that elevated BP, which affected 38.7% of the entire cohort, was the most important contributor, accounting for 21.6% (95% CI, 16.8 to 26.7) of incident AF cases. This rose to 24.5% if borderline levels of BP, which affected another 22.7% of the cohort, were also included (Table 4). Obesity and overweight explained 17.9% of all AF cases, and diabetes mellitus and impaired glucose tolerance combined accounted for the smallest fraction of the AF burden in this cohort (3.9%; Table 4).

Discussion

Overall, in this US cohort of middle-aged adults who had been followed up prospectively for, on average, 17 years, 57% of incident AF (95% CI, 38 to 70) could be attributed to elevated or borderline levels of risk factors for AF, namely elevated BP, overweight/obesity, diabetes mellitus, smoking, and prior cardiac disease. The PAF estimates were broadly consistent across the race and gender groups, although they were slightly higher for blacks than for whites, in part reflecting the greater prevalence of underlying risk factors in blacks. It is also possible that the PAF in blacks was underestimated. As explained previously, if the race-specific estimates had been used, then all of the AF burden in blacks would have been explained by having ≥1 borderline or elevated risk factors. But, given that there were no events within those blacks with an optimal risk profile, the variability around this estimate was considered to be too substantial to be meaningful. Hence, it was considered more appropriate to use risk estimates from the total population as opposed to race-specific risk estimates.

This is only the second study to attempt to quantify the burden of AF resulting from major and modifiable risk factors. The previous study, based on the Framingham cohort, reported that cigarette smoking, diabetes mellitus, hypertension, and prevalent CHD combined explained 44% of the burden in men and 58% in women.13 These estimates are broadly comparable to those in the present study, which also sought to quantify the burden of AF resulting from having borderline, rather than elevated, levels of risk factors. This is an important consideration, given that a significant proportion of the population has suboptimal levels of BMI, BP, and blood glucose. In addition, we provide estimates for both whites and blacks.

Elevated BP was the most important contributor to the burden of AF. It explained more than one fifth of all AF cases, nearly one quarter if borderline BP was also included. In comparison, only 3% of AF cases were attributable to diabetes mellitus, which in part reflects the much higher prevalence of elevated BP in the study cohort (38.7%) compared with diabetes mellitus (10.1%). The present finding that elevated levels of risk factors explained 50% of the overall incidence of AF in the ARIC cohort is lower than previously reported ARIC estimates of the PAF for HF and CHD and stroke (63.6% and 70.2% caused by nonoptimal risk factor levels, respectively), suggesting that other factors, possibly genetic, may have a greater role in the etiology...
Indeed, studies have indicated that the heritability component of AF is larger than it is for either HF or coronary artery disease (62% versus 28% versus 50%, respectively). It is also possible that the PAFs estimated in the present study may actually have underestimated the contribution of individual risk factors, such as obesity to the incidence of AF. Obesity may increase the risk of AF through several different physiological pathways, eg, by increasing the risk of diabetes mellitus or hypertension, which in turn increases the risk of AF. However, the model used in the present study estimated only the direct and independent contribution of obesity on subsequent risk of AF and did not take into account the possible indirect pathways by which obesity may affect future risk of AF.

**Potential for Primary Prevention**
From a public health perspective, our data highlight the substantial potential for AF risk reduction through primary prevention strategies that target modification and improvement in behavioral (eg, cigarette smoking, sedentary lifestyle) and dietary (eg, salt intake, excess calorie consumption) risk factors. Moreover, because improvement in these behaviors would also favorably affect other AF risk factors, such as diabetes mellitus or hypertension, which in turn increases the risk of AF. However, the model used in the present study estimated only the direct and independent contribution of obesity on subsequent risk of AF and did not take into account the possible indirect pathways by which obesity may affect future risk of AF.

**Possible Explanations for Racial Disparity in Incidence Rates of AF**
Individuals exhibiting an optimal risk profile had one third the incidence rate of AF compared with those with elevated risk factors. The rates at each risk profile were markedly lower in blacks than in whites, especially men. The reasons for this racial difference are unknown, but unlikely to be explained by differences in risk factor levels, particularly because levels of hypertension and obesity were higher in blacks compared with whites. As discussed in a previous publication, the racial difference is also unlikely to be due to lower case ascertainment or poorer access to medical care in blacks compared with whites. Hence, these data imply that among otherwise healthy white individuals, there are unknown risk factors, possibly genetic or other as-yet unknown factors, that are important determinants of AF risk.

**Strengths and Limitations**
In addition to the 20-year follow-up, strengths of the study include information on a wide range of variables to allow...
adjustment, although as with any observational study, it is not possible to fully exclude the possibility of residual confounding. There are, however, some important limitations. First, we were unable to differentiate subtypes of AF and hence assumed that the associations between risk factors and outcome are consistent across AF subtypes. This assumption is not unreasonable, given that some studies that have been able to differentiate AF subtypes have not reported any difference in the magnitude of the associations. For example, Dublin and colleagues observed no significant difference in the positive relationship between diabetes mellitus and AF according to whether it was paroxysmal, persistent, or permanent. Second, as discussed in a previous ARIC publication, the ascertainment of cases of AF mainly through hospital discharge codes may have led to the underascertainment of cases that perhaps were not severe enough to warrant hospitalization. The third major limitation relates to possible misclassification of study participants over the course of the follow-up period. For example, in an extreme-case scenario, a participant with AF may have had an optimal risk profile at baseline but over time may have become obese, hypertensive, and diabetic, resulting in an elevated risk factor profile. However, the fact that this individual would have been classified as having an optimal profile (at baseline) would have resulted in an underestimation of the impact of these risk factors on subsequent risk of AF. Third, as is common in this type of analysis, we assumed censoring to be ignorable; i.e., we took into account the fact that some individuals may have died of CHD before developing AF by adopting the common solution to this problem, which was to adjust for all factors that are likely causes of both AF and CHD, namely hypertension, diabetes mellitus, smoking, obesity, and HF, as well as age, gender, and race. For this reason, we believe our assumption that censoring is ignorable is correct to a reasonable approximation, although it is also possible that we did not adjust for all possible factors.

Finally, because >98% of AF cases were diagnosed through hospital discharge forms, the PAFs may be more indicative of only the severest forms of AF that require hospitalization. For example, individuals with hypertension and diabetes mellitus require more frequent medical contact and hence may be more likely to have their AF detected compared with those without these conditions who may be asymptomatic for AF. However, in a sensitivity analysis that included only those cases of AF diagnosed by ECG at a study visit, the results were highly comparable with the results from the overall population. Further evidence to support the generalizability of the study findings comes from a comparison of AF incidence rates in ARIC with those from other population-based cohorts that were less reliant on hospitalized records for diagnosis of AF. For example, in Framingham, the incidence rates for AF per 1000 person-years in men and women 55 to 64 years of age were 6.2 and 3.8, respectively, which are compatible with the incidence rates reported here. Moreover, and importantly, the population diversity in ARIC is greater than in previous cohorts in that it includes individuals from 4 states in the United States and a significant proportion of blacks.

Conclusions
Findings from this well-characterized cohort of middle-aged men and women indicate that maintaining an optimal risk profile would theoretically avoid more than half of the overall burden of AF. This study further reinforces the need for successful primary prevention strategies that enable individuals to adopt and maintain healthy diet and behavioral patterns as a means of reducing future cardiovascular risk.

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Disclosures
None.

References


**CLINICAL PERSPECTIVE**

This study, which is based on >17 years of follow-up of >14 500 men and women, represents an important contribution to the literature on the major and modifiable causes of atrial fibrillation (AF). Atrial fibrillation is an important risk factor for stroke and overall mortality and affects between 0.4% and 1.0% of the US population. Unlike other forms of cardiovascular disease, information about the preventable burden of AF is lacking. Therefore, the aim of this study was to determine what proportion of the burden of AF in blacks and whites could theoretically be avoided by the maintenance of an optimal risk profile. Previously established modifiable AF risk factors, namely high blood pressure, elevated body mass index, diabetes mellitus, cigarette smoking, and prior cardiac disease, were categorized into optimal, borderline, and elevated levels. On the basis of their risk factor levels, individuals were classified into 1 of these 3 groups. Overall, 57% of AF cases could be explained by having ≥1 borderline or elevated risk factors, of which suboptimal blood pressure was the most important contributor, accounting for one quarter of the burden of AF. In comparison, only 3% of AF cases were attributable to diabetes mellitus. These findings illustrate that, as with other forms of cardiovascular disease, more than half of the AF burden is potentially avoidable through the maintenance of optimal levels of classic cardiovascular risk factors, further reinforcing the need for effective primary prevention strategies that enable individuals to adopt and maintain healthy diet and behavioral patterns.
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