

ORIGINAL RESEARCH ARTICLE

Genetic Predisposition, Clinical Risk Factor Burden, and Lifetime Risk of Atrial Fibrillation

BACKGROUND: The long-term probability of developing atrial fibrillation (AF) considering genetic predisposition and clinical risk factor burden is unknown.

METHODS: We estimated the lifetime risk of AF in individuals from the community-based Framingham Heart Study. Polygenic risk for AF was derived using a score of ≈ 1000 AF-associated single-nucleotide polymorphisms. Clinical risk factor burden was calculated for each individual using a validated risk score for incident AF comprised of height, weight, systolic and diastolic blood pressure, current smoking status, antihypertensive medication use, diabetes mellitus, history of myocardial infarction, and history of heart failure. We estimated the lifetime risk of AF within tertiles of polygenic and clinical risk.

RESULTS: Among 4606 participants without AF at 55 years of age, 580 developed incident AF (median follow-up, 9.4 years; 25th–75th percentile, 4.4–14.3 years). The lifetime risk of AF >55 years of age was 37.1% and was substantially influenced by both polygenic and clinical risk factor burden. Among individuals free of AF at 55 years of age, those in low-polygenic and clinical risk tertiles had a lifetime risk of AF of 22.3% (95% confidence interval, 15.4–29.1), whereas those in high-risk tertiles had a risk of 48.2% (95% confidence interval, 41.3–55.1). A lower clinical risk factor burden was associated with later AF onset after adjusting for genetic predisposition ($P < 0.001$).

CONCLUSIONS: In our community-based cohort, the lifetime risk of AF was 37%. Estimation of polygenic AF risk is feasible and together with clinical risk factor burden explains a substantial gradient in long-term AF risk.

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Clinical Perspective

What Is New?

- The lifetime risk of developing atrial fibrillation is about 37% after 55 years of age, which is considerably greater than prior estimates.
- The lifetime risk of atrial fibrillation varies substantially according to genetic predisposition and clinical risk factor burden.
- Atrial fibrillation develops at an older age among individuals with a favorable clinical risk factor profile regardless of genetic predisposition.
- Nevertheless, the lifetime risk of atrial fibrillation in individuals with high genetic predisposition was substantial, even when the clinical risk factor burden was low.

What Are the Clinical Implications?

- Individualized projections of lifetime atrial fibrillation risk may be refined by accounting for genetic predisposition and clinical risk factor burden.
- Robust estimation of genetic predisposition to atrial fibrillation is feasible with genome-wide single-nucleotide polymorphism data.
- Addressing modifiable clinical risk factors might attenuate long-term risk of developing atrial fibrillation or delay the onset of disease.

The probability of developing atrial fibrillation (AF) is influenced by both inherited and acquired risk factors.^{1–3} Genetic association studies of common genetic variants have confirmed a polygenic basis for AF.^{4,5} Well-validated clinical risk factors such as anthropometrics and cardiovascular disease components can stratify short-term AF risk.³ Although both genetic predisposition and clinical risk factor burden are associated with AF risk, the contribution of these well-established risk factors to the long-term probability of developing AF is unknown.

By accounting for competing causes of death, lifetime risk estimates provide accurate assessments of long-term disease probabilities within populations.⁶ For AF in particular, such estimates can serve as practical risk approximations for both clinicians and patients because the short-term risks of AF are generally small.³ Previous lifetime risk estimates for AF have typically reflected average risks in entire study samples rather than within specific risk factor strata.^{7–12}

Comprehensive genomic assessment is currently feasible and accessible as is evidenced by direct-to-consumer availability of genetic tests, yet it remains of uncertain utility partly owing to the lack of valid associations with long-term disease risks.¹³ Simultaneously, increasing emphasis is being placed on addressing modifiable risk factors to potentially prevent AF given morbidity associ-

ated with the disease.^{14,15} Thus, there is a critical need to understand the joint relations between established risk factors and the probability of developing AF.

We therefore aimed to characterize the degree to which inherited predisposition and clinical risk factor burden influence the long-term probability of developing AF. With longitudinal follow-up, genome-wide genotyping information, and detailed assessment of clinical risk factors, the community-based Framingham Heart Study is well suited for the examination of associations between inherited predisposition and clinical risk factor burden in relation to lifetime risk of developing AF.

METHODS

Summary-level genetic association results cited in this article are available in the Cardiovascular Disease Knowledge Portal (<http://broadcvdi.org>).¹⁶ Individual-level data from samples described are available through application to the respective repositories.^{17,18}

STUDY SAMPLE

We calculated lifetime risks of AF in the Framingham Heart Study, a community-based observational cohort study designed to investigate cardiovascular disease risk factors.^{19–21} The Original cohort was comprised of 5209 men and women from Framingham, Massachusetts, 30 to 62 years of age in 1948 during their first round of standardized examinations. Participants returned for detailed medical histories, physical examinations, and laboratory tests every 2 years. Beginning in 1971, spouses and children of the Original cohort participants (n=5124) were recruited in the Offspring cohort with similar examinations every 4 to 8 years. Participants from the Third Generation cohort (ie, grandchildren of the Original cohort) were enrolled in 2002 and examined every 6 to 8 years. All participants signed informed consents at each examination cycle, and the Boston University Medical Center Institutional Review Board approved study protocols.

For the present analysis, we derived 3 samples based on participants who attended a study examination in ≤ 5 years of each of the attained ages of 55 (n=10239), 65 (n=7909), and 75 (n=5047) years. We selected 55 years of age as the initial age to maximize the sample of participants in whom DNA was ascertained before an index attained age. Participants could be included in >1 sample. From these samples, we excluded participants if they lacked follow-up after the attained age, did not participate in DNA collection, had prevalent AF at the study examination or DNA collection, had DNA collected >95 years of age, or lacked complete single-nucleotide polymorphism (SNP) or risk factor data (see the following text for further description and sample selection flowcharts in [Figure I through IV in the online-only Data Supplement](#)). In sensitivity analyses, we also estimated the lifetime risk of AF in individuals without available DNA.

AF ASCERTAINMENT

AF was ascertained in the Framingham Heart Study as previously described.²² Briefly, at each study examina-

tion, participants' medical histories, physical examinations, and electrocardiograms were obtained. Records of all interim outpatient appointments and hospitalizations for cardiovascular disease were sought for manual review by mailings and telephone calls via health history updates every 24 months. Participants were classified as having AF if the arrhythmia was present on an ECG obtained at a study visit or encounter with external clinicians, Holter monitoring, or noted in hospital records. Study investigators reviewed all available records, regardless of symptoms, to determine the dates of AF. Two physicians adjudicated first-detected AF events.

GENOTYPING AND IMPUTATION

Details of genotyping, imputation, and quality control have been previously described²³ and are summarized in the [online-only Data Supplement Methods](#).

POLYGENIC RISK FOR AF

Full methods of the approach to estimating genetic predisposition to AF are described in the [online-only Data Supplement Methods](#) and are briefly summarized here. Our approach was motivated by the concept that complex genetic trait liability may be explained by the cumulative effects of hundreds or thousands of common genetic variants, many of which are associated with traits at levels that do not exceed the stringent genome-wide significance threshold (ie, $P < 5 \times 10^{-8}$).^{24–27} We therefore created 30 candidate SNP groups using association results from a prior genome-wide association study of AF (133 073 individuals overall, 17 931 with AF)⁴ by selecting SNPs across a preselected range of 6 increasingly liberal degrees of association with AF (ie, from P value $< 5 \times 10^{-8}$ to < 0.001) and 5 linkage disequilibrium thresholds (ie, from $r^2 \geq 0.1$ to ≥ 0.9). The derived groups were comprised of between 58 and 10 751 SNPs.

We then constructed polygenic risk scores from the candidate SNP groups and independently validated scores by testing each for association with AF in 120 286 individuals of European ancestry in the population-based UK Biobank¹⁷ (described in the [online-only Data Supplement Methods](#)) using multivariable logistic regression. We calculated scores by summing the dosage of each AF risk allele carried by an individual (ranging from 0 to 2 for each SNP) weighted by the natural logarithm of the relative risk for each SNP from the prior analysis⁴ to yield a single continuous value for each individual. Models were adjusted for age, sex, genotyping array, and 1 principal component of ancestry. We considered the most informative score the 1 with the best model fit, as measured by the lowest Akaike information criterion.²⁸

Polygenic risk scores were strongly associated with AF in the UK Biobank, with P values ranging from 3.1×10^{-55} to 1.5×10^{-146} . The best-fitting score (Figure 1) was derived from a candidate group of 1168 SNPs (of which 835 were imputed with high quality in the UK Biobank) ([Table 1 in the online-only Data Supplement](#)). Regions tagged by the optimal SNP score accounted for a greater proportion of variance in AF susceptibility in the UK Biobank as measured by SNP heritability²⁹ (7.4%; 95% confidence interval [CI], 6.1–8.8) than those tagged by genome-wide significant loci alone (3.0%; 95% CI, 2.2–3.8) (see [online-only Data Supplement Methods](#) for details). We therefore calculated polygenic risk scores for AF in the Framingham Heart Study participants on the basis of the same candidate SNP group (of which 986 SNPs were genotyped or imputed with high confidence in Framingham) using the same approach defined earlier. Further description of our approach is provided in the [online-only Data Supplement Methods](#).

All participants in the UK Biobank provided written informed consent to participate in research as previously described,¹⁷ and the UK Biobank was approved by the UK Biobank Research Ethics Committee (reference number 11/NW/0382). Use of UK Biobank data were approved by the local Partners Healthcare Institutional Review Board.

CLINICAL RISK FOR AF

We estimated clinical risk factor burden in each Framingham Heart Study participant by using a validated composite 5-year clinical risk score for AF (CHARGE-AF Score [Cohorts for Heart and Aging Research in Genomic Epidemiology AF]).^{3,30–33} For each sample at the attained ages of 55, 65, and 75 years, we measured clinical risk factors for each individual in ≤ 5 years of the attained age and calculated the clinical composite score as a weighted sum of clinical risk factors that included height, weight, systolic and diastolic blood pressure, current smoking status, use of antihypertensive medication, diabetes mellitus, and history of myocardial infarction and heart failure. Weights for each component are provided in the [online-only Data Supplement Methods](#). Ascertainment of these clinical risk factors has previously been described.²² Because we assessed the residual lifetime risk of AF within strata of attained age, we omitted age from the composite score.

STATISTICAL ANALYSIS

We performed lifetime risk analyses in each of 3 samples from the Framingham Heart Study based on a person's index or attained age free of AF. The 3 samples were defined at 55, 65, and 75 years of age. Participants were

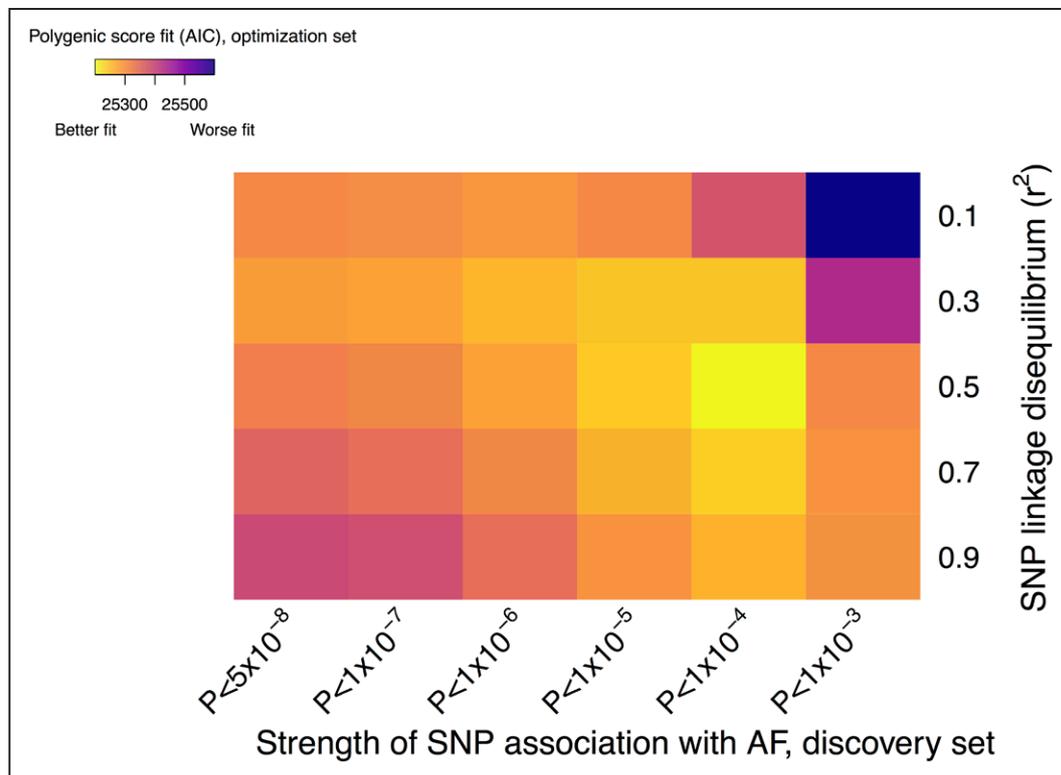


Figure 1. Defining polygenic risk for atrial fibrillation (AF).

We derived 30 candidate polygenic risk scores from the results of a prior genetic association study of AF.⁴ Each risk score was comprised of candidate single-nucleotide polymorphisms (SNPs) selected based on a varying strength of SNP association with AF in the prior analysis (x axis) and the degree of linkage disequilibrium between each SNP (y axis). Polygenic risk scores were then created as outlined in the Methods section using a linear weighted approach and tested for association with AF in an independent sample from the UK Biobank (N=120 286 individuals of European ancestry total, 2987 with AF). The most informative or optimal polygenic risk score was considered that with the best model fit as defined by the lowest Akaike's information criterion (AIC). Colors correspond to model fit, with yellow indicating a better fit. All scores were highly associated with AF in the optimization sample (P value range 3.1×10^{-55} to 1.5×10^{-146}). The optimal score was comprised of 1168 SNPs.

followed from the later of the date of their index age free of AF or their date of DNA collection until their first AF event, death, last available date known to be free of AF based on a Framingham examination or medical records, 95 years of age, or December 31, 2014, whichever occurred first. The multiple-decrement life-table approach was applied to calculate the lifetime risk of AF, adjusting for the competing risk of death.⁶ Adjustment for the competing risk of death avoids overinflation of cumulative incidence estimates that may occur if the competing risk is not taken into account.

We first calculated lifetime risk estimates for each attained age overall. We then performed the same life-table approach stratified by tertiles of the AF polygenic risk score and the clinical risk factor score separately. Tertiles were derived based on the distributions in the overall sample specific to each index age. Tertile 1 was considered low risk, tertile 2 was considered intermediate risk, and tertile 3 was considered high risk. We then assessed the joint contributions of genetic predisposition and clinical risk factor burden by calculating lifetime risks of AF within cross-tabulated tertiles of both

the polygenic risk score and clinical risk score, resulting in 9 risk strata. In secondary analyses, we calculated the cumulative incidences of AF at 10-, 20-, and 30-year time horizons. We also performed an exploratory analysis in which we regressed AF on continuous genetic predisposition and clinical risk factor burden in the 55 years of age sample, and we introduced a multiplicative interaction term. Models were fit using proportional hazards regression with and without adjustment for the competing risk of death.³⁴

To assess whether a favorable cardiovascular risk profile was associated with a later age of AF onset after accounting for genetic predisposition, we regressed the age of AF onset on the clinical risk factor burden both within tertiles of polygenic risk scores and separately and adjusted for tertiles of polygenic risk among individuals who developed AF using linear regression. Analyses were performed in the sample of individuals with an attained age of 55 years without AF. Two-sided P values < 0.05 were considered statistically significant. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute), PLINK v1.9,³⁵ and R version 3.2.2.³⁶

RESULTS

In total, 5131 unique individuals were included in the analyses for the 3 samples defined by attained ages of 55 ($n=4606$), 65 ($n=3271$), and 75 ($n=1887$) years without AF (Table). Among participants alive and free of AF at 55 years of age, 580 developed AF during the observed follow-up period. The median (25th–75th percentile) follow-up durations for the attained 55, 65, and 75 years of age samples were 9.4 years (4.4–14.3 years), 7.4 years (3.2–12.7 years), and 5.6 years (2.1–9.1 years), respectively. As expected, the proportions with comorbid medical illnesses were generally greater among older participants. Participants with DNA who were included in the study were generally ascertained in a more contemporary era than those without DNA (Table II in the online-only Data Supplement).

Estimates of lifetime risk of AF are displayed in Figure 2 and Table II in the online-only Data Supplement. At 55 years of age, the overall residual lifetime risk of AF was 37.1% (95% CI, 34.6–39.6) and was similar at older attained ages. The participant characteristics stratified by tertile of AF genetic predisposition and clinical

Table. Characteristics of the 5131 Participants According to Attained Age

Variable	Attained Age Free of Atrial Fibrillation, y		
	55 (N=4606)	65 (N=3271)	75 (N=1887)
Framingham Heart Study cohort			
Original	378 (8.2)	542 (16.6)	638 (33.8)
Offspring	3124 (67.8)	2584 (79.0)	1242 (65.8)
Third Generation	1104 (24.0)	145 (4.4)	7 (0.4)
Years of follow-up, median (25th–75th percentile)	9.4 (4.4–14.3)	7.4 (3.2–12.7)	5.6 (2.1–9.1)
Age at covariate measurement, y	55.0±1.9	65.0±1.7	74.9±1.6
Age at DNA collection, y	59.6±11.3	65.9±10.4	73.4±8.6
Women	2492 (54.1)	1869 (57.1)	1120 (59.4)
Current smoker	915 (19.9)	422 (12.9)	124 (6.6)
Systolic blood pressure, mm Hg	125±17	131±18	137±20
Diastolic blood pressure, mm Hg	78±10	76±10	72±10
Hypertension treatment	1031 (22.4)	1299 (39.7)	1015 (53.8)
Height, cm	168±9	166±9	163±10
Weight, kg	78.3±17.5	77.0±16.6	73.6±15.2
Diabetes mellitus	270 (5.9)	350 (10.7)	246 (13.0)
History of heart failure	15 (0.3)	20 (0.61)	21 (1.1)
History of myocardial infarction	74 (1.6)	126 (3.9)	101 (5.4)

Values are n (%) or means±standard deviation, unless otherwise noted. Participants can appear in >1 attained age group.

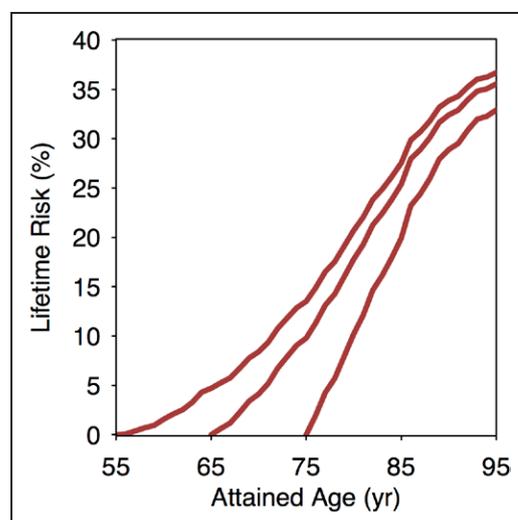


Figure 2. Lifetime risk of atrial fibrillation (AF) at selected attained ages, adjusted for the competing risk of death.

Lifetime risk of AF in Framingham Heart Study participants for a given attained age is cumulative through 95 years of age.

ical risk factor burden are displayed in Tables III and IV in the online-only Data Supplement. The lifetime risk of AF was higher among individuals with greater genetic predisposition to AF. For example, among individuals free of AF at 55 years of age, those in the highest tertile of polygenic risk had an estimated lifetime risk of AF of 46.9% (95% CI, 42.7–51.2), whereas those in the lowest tertile had a risk of 25.8% (95% CI, 21.8–29.9) (Figure 3 and Table V in the online-only Data Supplement). Similar graded patterns of AF risk according to genetic predisposition were observed at different attained ages and with shorter time horizons.

Comparable to analyses of polygenic risk factor burden, the lifetime risk of AF was highest among individuals with a greater burden of clinical AF risk factors. For example, individuals within the highest tertile of clinical AF risk factor burden at 55 years of age had a lifetime risk of developing AF of 43.1% (95% CI, 38.9–47.3), whereas those in the lowest tertile had a risk of 32.6% (95% CI, 28.2–37.0) (Figure 3 and Table VI in the online-only Data Supplement). However, the lifetime risk of AF was similar between those with intermediate and low clinical risk factor profiles. Analogous patterns were observed at different attained ages and with time horizons of 10, 20, and 30 years of follow-up (Table VI in the online-only Data Supplement).

To assess the joint contributions of genetic predisposition and clinical risk factor burden to the lifetime risk of developing AF, we estimated AF risks by tertiles of both polygenic and clinical risk. Among individuals free of AF at 55 years of age, those in the lowest polygenic and clinical risk strata had a lifetime risk of AF of 22.3% (95% CI, 15.4–29.1), whereas those in the highest

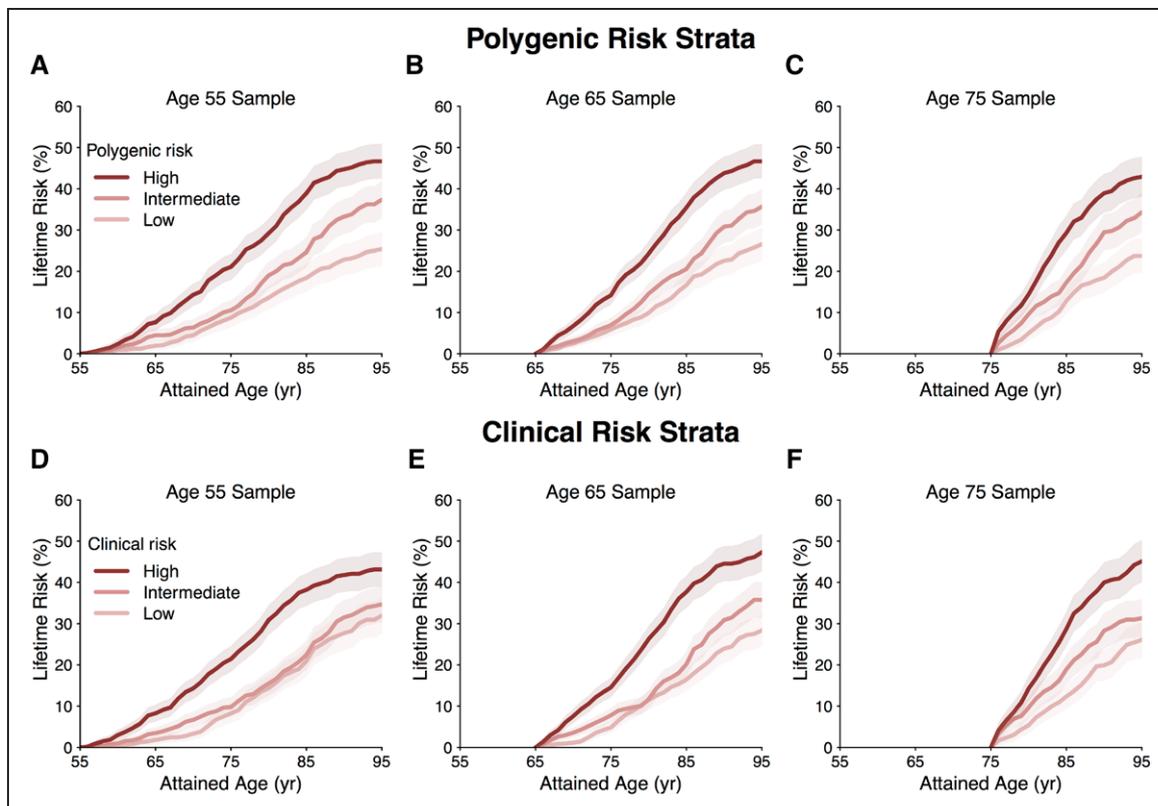


Figure 3. Lifetime risk of atrial fibrillation (AF) stratified by polygenic risk or clinical risk factor burden tertiles adjusted for the competing risk of death.

A through **F**, Lifetime risk of AF in Framingham Heart Study participants stratified by low-, intermediate-, and high-polygenic risk (**A** through **C**) or clinical risk factor burden (**D** through **F**) at attained ages of 55, 65, and 75 years free of AF.

polygenic and clinical risk tertiles had lifetime risks of AF as high as 48.2% (95% CI, 41.3–55.1) (Figure 4). For individuals with low clinical risk factor burden but high genetic predisposition to AF, the lifetime risk was 43.6% (95% CI, 35.6–51.6), a value comparable to that in other high clinical risk factor burden strata. Substantial gradients of AF risk were consistently observed within strata of polygenic and clinical risk regardless of the attained age and follow-up time horizons (Tables VII through IX in the online-only Data Supplement). We did not observe an interaction between genetic predisposition and clinical risk factor burden in exploratory models in which both were treated as continuous covariates (Table X in the online-only Data Supplement), but our power to detect an interaction was modest. Among individuals who developed AF, we observed that a lower clinical risk factor burden was associated with a later age of AF onset, regardless of genetic predisposition ($P < 0.001$ within each tertile of polygenic risk) (Figure 5). We observed an ≈ 7 -year gradient in the age of AF onset across tertiles of clinical risk factor burden when adjusted for polygenic predisposition to AF (age \pm standard error; 73.2 \pm 0.6 years, 78.6 \pm 0.7 years, 80.6 \pm 0.7 years, for high, intermediate, and low clinical risk factor burden, respectively).

DISCUSSION

Our findings illustrate the high lifetime risk of AF and contributions of both genetic and clinical factors in determining long-term AF risk. In the community-based Framingham Heart Study sample comprised of 5,131 individuals with contemporary follow-up, we observed that the lifetime risk of AF was 37.1% after 55 years of age. Marked variability in the lifetime risk of AF can be accounted for by both polygenic predisposition and clinical risk factor burden. The lifetime risk of AF ranged from $\approx 20\%$ among individuals in the lowest tertiles of both polygenic and clinical risk to $\approx 50\%$ among individuals in the highest tertiles of both. On average, a favorable clinical risk profile was associated with later onset of AF regardless of polygenic predisposition to AF.

Our findings have 3 major implications. First, the observed stratification of AF risk by a score comprised of ≈ 1000 SNPs highlights the feasibility of comprehensive polygenic risk profiling for AF and estimation of lifetime risk based on inherited predisposition. In contrast to the traditional method of creating scores comprised only of the top variant at each disease susceptibility locus,^{37,38} we estimated polygenic risk by including many SNPs

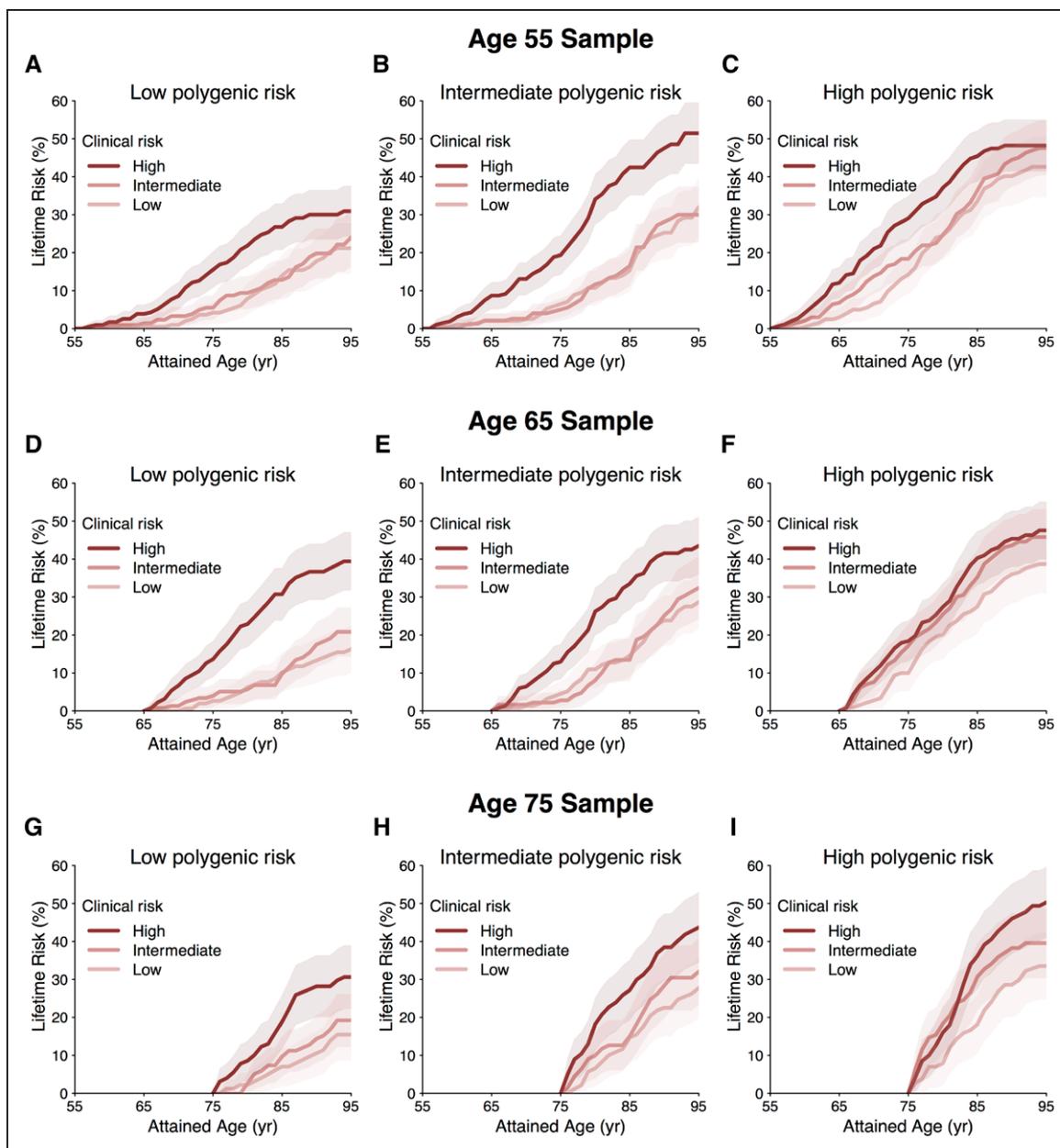


Figure 4. Lifetime risk of atrial fibrillation (AF) stratified by polygenic risk within clinical risk factor burden tertiles adjusted for the competing risk of death.

A through **I**, Lifetime risk of AF in Framingham Heart Study participants stratified by low-, intermediate-, and high-polygenic risk and clinical risk factor burden at attained ages of 55 years (**A** through **C**), 65 years (**D** through **F**), and 75 years (**G** through **I**).

that did not exceed stringent genome-wide significance thresholds, an approach that likely contributed to the considerable degree of risk stratification observed. Our study provides absolute AF risk estimates associated with comprehensively ascertained polygenic risk, and demonstrates that genomic risk profiles can be incorporated into lifetime risk models. Given the increasing ubiquity of genomic data in the clinical setting and through direct-to-consumer testing, epidemiologically derived estimates are necessary for generating accurate personalized risk assessments.

Second, our observation that individuals with a lower burden of clinical risk factors had a reduced probability of developing AF within polygenic risk strata underscores the potential importance of risk factor modification for attenuating AF risk regardless of inherited predisposition, similar to a recent analysis of coronary heart disease.³⁹ Among individuals who developed AF, a more favorable clinical risk profile was associated with postponement of disease onset, indicating that optimal cardiovascular health may compress the period of exposure to AF. Nevertheless, the fact that individu-

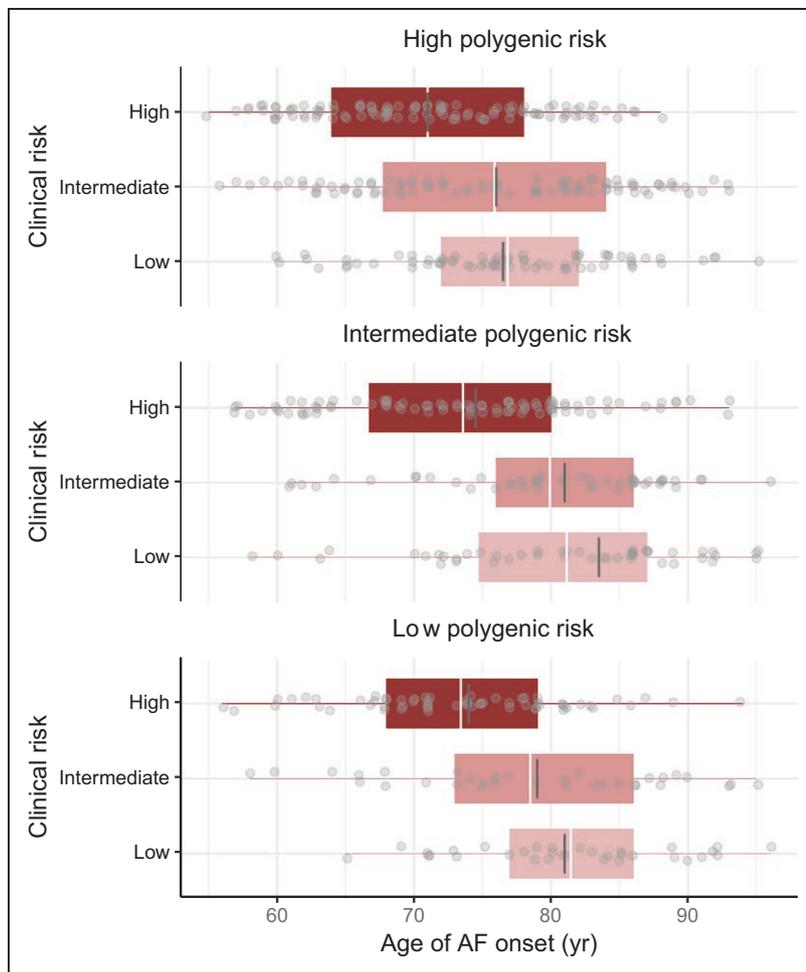


Figure 5. Age of atrial fibrillation (AF) onset stratified by clinical and polygenic risk.

Gray dots indicate the age of AF onset in Framingham Heart Study participants free of AF at 55 years of age who subsequently developed AF. The white and dark gray lines represent the mean and median age of AF onset, respectively; boxes represent the interquartile range; and whiskers correspond to range of age of AF onset. The 2-sided P values were <0.001 for the associations between clinical risk factor burden and age of AF onset within each tertile of polygenic risk score.

als with few clinical risk factors but high polygenic risk had an $\approx 40\%$ lifetime probability of developing AF underscores the independent contribution of an inherited predisposition to disease risk.

Modifiable AF risk factors include hypertension, obesity, smoking, diabetes mellitus, and obstructive sleep apnea,^{3,40} the first 4 of which were included in our assessment of clinical risk factor burden. Risk factor management through lifestyle modification reduces AF burden and severity.^{41,42} Future analyses are warranted to determine the extent to which dedicated risk factor modification will prevent AF, delay onset, reduce arrhythmia burden, and minimize overall attributable morbidity and mortality across the spectrum of polygenic risk.

Third, the $\approx 37\%$ average lifetime risk of AF estimated in our study emphasizes the immense public health impact presented by AF. Prevention of AF is an important goal, particularly when considering the clinical and economic impacts of the arrhythmia, limitations of antiarrhythmic and anticoagulant therapy, and increasing prevalence of AF in an era of greater longevity.^{43–45} Whereas prior reports have suggested that the lifetime risk of AF is about 1 in 4,^{7–12} the higher lifetime risk estimates in our study may be related to diminished mortality from competing

causes of death, greater follow-up during older ages of life when AF risk is greatest, or enhanced surveillance for AF owing to increased awareness of the arrhythmia.⁴⁶ We anticipate that the true lifetime risk of AF and attributable morbidity are currently underestimated because undiagnosed AF is common.^{47,48} Utilization of increasingly available mobile cardiac rhythm monitoring technology and wearable sensors is likely to provide refined estimates of the lifetime risk of AF in the future.^{49,50}

In contrast with prior reports demonstrating that AF genetic risk does not add substantively to short-term AF discrimination beyond clinical risk factors,^{51,52} our current report has several important differences. First, the present article is focused on residual lifetime probabilities of AF conditional on survival to specified ages, rather than short-term improvements in discrimination of disease risk in pooled samples. Second, the comprehensive approach for determining AF genetic predisposition we used is based on a larger and better-powered discovery sample and relaxed assumptions about both SNP association with AF and linkage disequilibrium, which resulted in a score comprised of ≈ 1000 variants. In aggregate, the findings highlight the high lifetime risk of developing AF and the substantial contributions of genetic predis-

position and clinical risk factor burden to variability in long-term AF risk. Nevertheless, the clinical utility and cost-effectiveness of genomic profiling remain unclear.

Our study should be interpreted in the context of the study design. The Framingham Heart Study is principally composed of individuals of European ancestry, consequently limiting the generalizability of our findings to other ethnic/racial groups particularly because AF is more prevalent in such individuals.³ The polygenic risk score utilized in our analysis was based on a linear combination of common and low-frequency variants selected using summary-level data from a prior genome-wide association study. The fact that the optimal score utilized in our analysis included many subgenome-wide threshold SNPs highlights both the polygenic nature of AF and the importance of larger, well-powered, multi-ancestry studies to identify the genetic determinants of AF. Future scores based on larger samples that include rare genetic variants and utilize different methods for variant selection or weighting may improve the specificity of scores used to summarize genetic predisposition to AF. We cannot establish causal relations between the specific SNPs and clinical risk factors included in our score and risk of AF. Further refinement of polygenic risk or clinical risk algorithms, and application to larger samples, may further enhance short, intermediate, and lifetime risk estimation for AF. Additional clinical risk factors, such as echocardiographic measurements, may be important determinants of disease risk and were not included.

In conclusion, the contributions of genetic predisposition and clinical risk to the development of AF are substantial. Our findings demonstrate the feasibility of assessing AF risk within genetic and clinical risk factor strata and provide epidemiological estimates of long-term AF risk. Future studies are warranted to further refine polygenic and clinical risk estimates in additional races and populations.

ARTICLE INFORMATION

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