Response to Editor and Reviewer Comments

Dear Drs. Kwaku and Ovbiagele,

We are thankful for the thoughtful and constructive comments, and appreciative of the time you’ve taken to review our manuscript titled “*Association Between Family History and Early-Onset Atrial Flutter Across Racial and Ethnic Groups*”. We have outlined our revisions to the paper based on these comments below. You will find the original comments in bold, followed by our response and extracts from the manuscript in red.

## Reviewer #1

**This paper adds to the justification for earlier case finding and intervention for atrial flutter which has clearly not received as much attention as has atrial fibrillation. It is a provocative study in its demonstration that “in those without familial risk, Black race was most strongly associated with AFL”. The conclusions of this study, if reproduced, may make genetic counselling appropriate for those with early onset atrial flutter.**

***Response***: We are thankful for the comments, and hope that our general and specific revisions will further strength the findings of the study.

## Reviewer #2

**This is an interesting, well written manuscript reporting important study findings evaluating the role of race, ethnicity, and family history of atrial tachyarrhythmias to determine the OR of developing early-onset atrial flutter (EOAFL) over late onset AFL in an ethnically diverse cohort. Primary outcome was positive family history of : AFL, AFib and other tachyarrhythmias, and ischemic stroke. Secondary outcome was self-reported race/ethnicity and sex. The results found a positive family history was strongly associated with EOAFL compared to late onset AFL in Whites. But Black race, increased BMI, alcohol use, were associated with EOAFL regardless of family history. And use of cardioselective beta- or calcium channel blockers had an almost 3-fold decrease in odds of EOAFL.**

**Specific Comments**:

1. **Page 2, Abstract under Design, Settings, and Participants, the authors state they used “adjudicated baseline questionnaires”, but there is no mention of questionnaires in the manuscript Methods.**

* ***Response***: We have now included this in the methods section, as well as adding the appropriate citation from prior work using this questionnaire.
* Page 3, Lines 37-39: “Family history was assessed through adjudicated baseline questionnaires and direct family interviews about the diagnosis of atrial tachyarrhythmias, stroke, and cardiomyopathy.”
* Pages 6-7, Lines 116-122: “The study team contacted, via in-person or telephone interview, the FDRs of individual participants with positive family history by initial baseline questionnaire to identify individual cardiac diagnoses of AFL, AF, suspected cardio-embolic strokes, and cardiomyopathy[1](#ref-Alzahrani2018).”

1. **Page 2, Abstract under Exposure, “FDR” needs to be spelled out before abbreviation is 1st used in both Abstract & manuscript.**

* ***Response***: FDR stands for first-degree relative. We have ensured that abbreviations throughout have been spelled out appropriately at first usage.
* Page 3, Lines 32: “…atrial tachyarrhythmias in first-degree relatives (FDR)”
* Page 5, Lines 73: “…first-degree relatives (FDR)”

1. **Page 2, Abstract under Exposure, the primary exposure includes stroke, but only see that discussed as a sensitivity analysis in Methods & Results in manuscript.**

* ***Response***: We have corrected the terminology. We analyzed stroke and heart failure as part of a sensitivity analysis after looking primarily at the risk of EOAFL when only evaluating those with a family history of atrial tachyarrhythmias.
* Page 3, Lines 41: “The primary independent variable was a positive family history in FDR of AFL, atrial fibrillation (or other atrial tachyarrythmias).”
* Page 8, Lines 145: “Our primary independent variable was family history of AFL, AF, or other atrial tachyarrhythmias.”
* Page 8, Lines 150-151: “In sensitivity analyses, we expanded the definition of family history to include cardioembolic stroke or CHF as objective and downstream sequelae of atrial tachyarrhythmias.”

1. **Page 2, Abstract under Conclusions, direction of associations needs to be indicated in 2nd sentence. ie., instead of stating “weight”, should indicate either increased or decreased weight, or use another term such as obesity or increased BMI. Same thing for “alcohol use”. It also seems like the findings about “certain anti-hypertensive agents” should be in a separate sentence to emphasize those important findings demonstrating a large decrease in EOAFL risk when taken by subjects in your study.**

* ***Response***: We found this comment to be particularly helpful at highlighting the importance of these findings within our study. We have adjusted the conclusion to match this (and have made minor changes throughout the paper to help clarify).
* Page 4, Lines 59-61: “Black race, obesity, and increased alcohol use were also associated with EOAFL, regardless of familial factors Certain anti-hypertensive agents (cardioselective beta- and calcium channel-blockers) were associated with a decreased risk of EOAFL.”
* Pages 13-14, Lines 281-283: “Third, given that increased BMI, increased alcohol use, and obstructive sleep apnea play an important role in the development of EOAFL, aggressive risk factor screening and modification, along with lifestyle changes, is warranted.”

1. **Page 5, in Methods section, under Atrial Tachyarrhythmias, with the 12-leads and other recording data collected, was there any indication of the type of Aflutter and whether one type was more significantly linked to occurrence of EOAFL?**

* ***Response***: This is a very interesting perspective to consider if abnormalities in right atrial activation in new-onset of AFL may be associated, one way or the other, with certain risk factors. We unfortunately excluded those with atypical flutter from the onset to help maintain a population with “similar” characteristics. We did confirm a diagnosis of typical AFL by ECG criteria through manual review, which allowed us to create a large, well-phenotyped cohort, although intriniscally limited to evaluating the effects of typical (vs. atypical) AFL. We have added this to the methods section and marked it as a limitation of this study.
* Page 4, Lines 104-107: “AFL was defined as those with typical AFL, characterized by a continuous undulation or ”sawtooth” pattern with dominant negative deflections in inferior leads suggesting a counterclockwise rotation,[2](#ref-Cosio2017) with atrial rates greater than approximately 240 beats per minute (cycle lengths approximately 250 ms, or faster). Only ECGs that were consistent with typical AFL were considered for study inclusion.”
* Page 14, Lines 285-289: “First, the diagnoses of AFL and AF tend to be concomitant, and although a diagnosis of AFL was presumed, we cannot ascertain if other concealed or occult arrhythmias were present prior. We did confirm a diagnosis of typical AFL by ECG criteria through manual review, which allowed us to create a large, well-phenotyped cohort, although intrinsically limited to evaluating the effects of typical (vs. atypical) AFL.”

1. **Page 5, in Methods section, important point to note that the study personnel included bilingual research coordinators when recruiting subjects in a study focused on subjects with different ethnicities.**

* ***Response***: We agree with this statement and have emphasized that, particularly as it highlights the effect of language-barrier biases on data collection. We have specified this in the methods.
* Page 6, Lines 97-99: “Experienced English and Spanish speaking research coordinators screened for family history to identify those with a history of cardiovascular conditions in FDRs using a adjudicated, baseline questionnaire.[1](#ref-Alzahrani2018)”
* Page 6, Lines 119-122: “Spanish bilingual research staff were used to interview primarily Spanish speaking participants and FDRs.”

1. **Page 16-26. You have added in Legend for Table 1 what bold font indicates, but that is missing from notation for Tables 2-4 and Supplemental Tables 1 and 3.**

* ***Response***: We agree that refinement to the table legends and annotations would improve legibility and interpretation of our findings. We have revised the tables. The revised tables are in the manuscript for reference. Tables 1-4, Pages 16-19

## Reviewer #3

**Shah and colleagues present an analysis of risk factors for early as compared with late onset atrial flutter. The authors report that history of atrial arrhythmias in first degree relatives is associated with EOAF in White/Hispanic /Latinx patients but not in Black patients. This study is unique in that it focuses on atrial flutter in the absence of any history of atrial fibrillation.**

**I congratulate the authors for attempting to identify the contribution of family history to EOAF in a fairly sizable population. However I do have questions and concerns.**

1. **The authors approach atrial flutter as a distinct genetic and arrhythmia entity with specific potential risk factors, however they include first degree relative atrial fibrillation (as well as cardioembolic stroke and heart failure) in the definition of family history. This seems inconsistent.**

* ***Response***: We have used this definition in our previous studies,[1](#ref-Alzahrani2018),[3](#ref-Chalazan2021) although we do agree that the difference between AFL and AF may be more of a spectrum than distinct entities. As such, considering surrogates for AF may shed light into both similarities and differences between the two arrhythmias. We have reported that AF and AFL are often asymptomatic and difficult to accurately report in family members, thus more objective findings (such as cardioembolic strokes) that are downstream sequelae are important both clinically and for research purposes.[1](#ref-Alzahrani2018) However, we believe that distinguishing between factors that are perhaps more commonly associated with AF should be analyzed separately. In our initial submission, we had separated the analyses for those with family histories of atrial tachyarrhythmias (primary) from the combined family histories that included cardiomyopathy and cardioembolic stroke (sensitivity). We have modified the text such that it is now hopefully clear our approach accounts for this potential confounding. To be specific, there were no significant changes to effect sizes based on expanding the definition of family history.
* Page 3, Lines 41: “The primary independent variable was a positive family history in FDR of AFL, atrial fibrillation (or other atrial tachyarrythmias).”
* Page 8, Lines 145: “Our primary independent variable was a family history of atrial tachyarrhythmias.”
* Page 8, Lines 147-148: “A positive family history was defined as having a diagnosis of atrial flutter, atrial fibrillation, or atrial tachycardia in a FDR.”
* Page 10, Lines 200-201: “In all models, expanding the definition of a positive family history to include CHF or cardioembolic stroke did not significantly change the estimates.”
* Pages 11-12, Lines 233-235: “As subjective histories are prone to recall bias, we allowed for several potential risks of underlying arrhythmia as part of the screening (AFL, AF, cardiomyopathy, and strokes), and found similar sensitivity for the association with EOAFL regardless of definition of a positive family history.”

1. **While the authors sought to confirm all tracings of arrhythmia in the proband, the association between atrial flutter and fibrillation is well-described, and there is a body of literature that suggests one cannot have atrial flutter without left atrial arrhythmia and/or fibrillation. It is unclear to me how the diagnosis was reached in this cohort and how occult fibrillation was excluded. As such, the distinction of this cohort as “flutter only” is questionable and it might be of value to subject patients with “fibrillation only” to the same analysis to see if there are any differences in the associations found.**

* ***Response***: We agree with the reviewer that a strong relationship does exist between AFL and AF, and it would not be surprising if a percentage of individuals with EOAFL in fact did have occult AF. We were unable to rule out occult AF however, although we did attempt to look for signs of other atrial tachyarrhythmias prior to the first diagnosis of typical AFL. In those cases, when AF was identified, we did consider them in the LOAFL category, although unmonitored AF remains possible. We agree that a “fibrillation only” cohort is worthy of studying - although that data is not available within this cohort, in our previous work we have more directly evaluated EOAF.[1](#ref-Alzahrani2018),[3](#ref-Chalazan2021) We have listed this as a limitation of the study and its interpretation.
* Page 14, Lines 285-287: First, the diagnoses of AFL and AF tend to be concomitant, and although a diagnosis of AFL was presumed, we cannot ascertain if other concealed or occult arrhythmias were present prior.

1. **The authors state that all first-degree relatives of the proband that reported a family history were contacted. However, FDR of those without a stated family history do not appear to have been contacted. This seems to be a very significant limitation to this study, as many patients are unaware of family medical history. Without confirming the absence of arrhythmia history in all patients in this study, the associations found are likely exaggerated.**

* ***Response***: We agree that patients are frequently unaware of a family history, but from a clinical perspective we have found that the yield can be quite low for contacting FDRs who did not indicate a family history, particularly when using a rigorous family history questionnaire, as we have previously reported.[1](#ref-Alzahrani2018),[3](#ref-Chalazan2021) We have included this as a limitation in the study but believe it also reflects current clinical practice and thus may be somewhat more pragmatic.
* Page 8, Lines 298-303: “Fifth, only FDRs in participants that indicated a positive family history were evaluated with a confirmatory interview, and there may be limitations in participant recall and unawareness of family member’s health status. This may confound our findings, although this is similar to clinical practice patterns on interrogation of family history of disease.”

1. **Please provide the definition used for atrial flutter (atrial rate, flutter wave morphology, typical vs atypical, etc). Also please define “social drinking”.**

* ***Response***: For this study, we used typical AFL as the major inclusion criteria, as reviewed by an experienced cardiologist on 12-lead ECG, with other macro-reentrant and micro-reentrant atrial tachycardias being excluded. We have specified the definition of typical AFL in the methods. We have also included the definition of social drinking (those with greater than 1-2 drinks per day) in the methods.
* Page 6, Lines 104-107: “AFL was defined as those with typical AFL, characterized by a continuous undulation or ”sawtooth” pattern with dominant negative deflections in inferior leads suggesting a counterclockwise rotation,[2](#ref-Cosio2017) with atrial rates greater than approximately 240 beats per minute (cycle lengths approximately 250 ms, or faster).”
* Page 7, Lines 126-127: “Alcohol use was defined as alcohol consumption greater than that of social drinking, defined as less than 2 drinks per day for men, and less than 1 drink per day for women),[4](#ref-Grant2015) as reported by participants.”

1. **Did any of the patients approached refuse to participate in the study? Is this what is meant by “no patients excluded”?**

* ***Response***: We did not record individuals who declined participation. As we had designed this as an observational cohort, we intended to include all-comers that met inclusion criteria. We have modified the word choice to be clearer of our intent, with exclusion criteria being otherwise primarily age-related.
* Page 6, Lines 94-96: Individuals were asked to participate if they were older than 17 years of age, were able and willing to provide consent for study participation, and had a documented history of typical AFL. There were no other exclusion criteria for enrollment.”

1. **It is counter-intuitive that hypertension had an inverse relation with EOAF aside from treatment with calcium channel or beta blockers. Please propose a mechanism for this in the discussion.**

* ***Response***: We appreciate the reviewers interest in this somewhat surprising finding. We evaluated interaction between hypertension and the primary variables of interest as well as beta/calcium channel blockers, which showed no statistical interaction. However, when evaluating why this counter-intuitive finding occurred, we found that there was statistical, multiplicative cross-over interaction between sex and hypertension. However, the combined main effects and interaction terms approached 1, suggesting that although there was statistical significance, it was may not necessarily be interpretable. We contended full-disclosure of our terms were the most appropriate to understand the balance of risk factors in this cohort, with understanding that interpretation may be difficult in certain situations (such as with interaction). We have attempted to display these findings and contextualize this result.
* Page 10, Lines 195-196: There was multiplicative cross-over interaction between hypertension and sex, however the main effects were not significant.
* Page 13, Lines 265-267: “We surprisingly found that the risk of EOAFL due to hypertension was secondary to multiplicative interaction with female sex, suggesting that although the overall effect size was small, there may be potential sex differences in risk profiles.”

1. **The authors make the argument for eliciting a family history of atrial arrhythmias in determining patient risk of EOAF. However, it is not clear that the diagnoses of atrial arrhythmias in the first degree relatives preceded that in the probands. Please clarify.**

* ***Response***: We were not able to identify the onset of AFL or other atrial tachyarrhythmias in a majority of family members due to limited recall of time of diagnosis. We have included this as a limitation.
* Page 14, Lines 303-309: “Fourth, the study design designated cohorts based on age, thus limiting our ability to directly assess the relationship of age with AFL. We were also unable to assess the effect of age on diagnosis in FDRs of probands, as a majority of family members had limited recall of the time of their own diagnosis.”

## EDI Reviewer

**In “Association Between Family History And Early-Onset Atrial Flutter Across Racial And Ethnic Groups,” Shah and colleagues sought to examine the role of race, ethnicity and history of atrial tachyarrhythmias in first-degree relatives (FDR) in the odds of developing early onset atrial flutter. The following should be considered:**

**Major Comments:**

1. **Please provide what was the hypothesis for why race would affect development of EOAFL? Is there a conceptual model the authors can include to explain how they chose their variables of interest?**

* ***Response***: We chose to evaluate race particularly due to the paradoxical relationship between race and atrial fibrillation, and noted that this had not yet been evaluated in atrial flutter. It is not clear from this study if social determinants of health modify this relationship or if racial factors are the primary driver. We now include references to several studies that highlight the importance of exploring racial differences in arrhythmia research.
* Page 5, Lines 73-75: “In contrast to the well-defined clinical features, characteristics, and genetic basis for AF,[5](#ref-Kornej2020) current understanding of risk factors and role of family history of atrial tachyarrhythmias in first-degree relatives (FDR) towards the development of early-onset (EO) AFL.[6](#ref-Halligan2004) Similarly, the role race-ethnicity is unknown, which is particularly important in the context of the paradoxically lower rate of AF seen in Black individuals despite similar or increased burden of clinical risk factors.[7](#ref-Stamos2016)–[9](#ref-Magnani2016)”

1. **Please confirm how family history of arrhythmia was determined. Self-report? Chart review?**

* ***Response***: We first used patient recollection based on a adjudicated baseline questionnaire. We confirmed these findings by direct phone interview with first-degree relatives (although not every family member could be reached, and we relied in part on the recollection of other family members as well).
* Page 6, Lines 97-99: “Experienced English and Spanish speaking research coordinators screened for family history to identify those with a history of cardiovascular conditions in FDRs using a adjudicated, baseline questionnaire.[1](#ref-Alzahrani2018)”
* Page 7, Lines 119-122: “Spanish bilingual research staff were used to interview primarily Spanish speaking participants and FDRs. Clinical records were additionally reviewed for each FDR to confirm diagnoses, and family pedigrees were constructed for these probands.”

1. **According to Table 1 there appears to be 19.3% of individuals missing race/ ethnicity in this analysis. Please describe how those with missing race were addressed. Do the findings persist with these individuals included / excluded?**

* ***Response***: We apologize for the confusion. We display the race-ethnicity groups in Table 1 however we did not clearly state how the participants were aggregated. To simplify and maintain power for our analyses, we chose to compare Black versus non-Black. We combined the White, Mixed, and Hispanic populations into a non-Black category (after excluding Asians, <3% of the population) due to a high degree of overlap in the communities in this metropolitan-based (Chicago) study. We did not perform race-ethnicity sensitivity analyses using the small subgroups due to power issues, as only ~10% of the population had a positive family history.
* Page 8, Lines 154-159: “To maintain power for our analyses, we chose to compare Black versus non-Black. We combined the White, Mixed, and Hispanic populations into a non-Black category (after excluding Asians, which were <3% of the population) due to a high degree of overlap in the communities in this metropolitan-based (Chicago) study. We did not perform race-ethnicity sensitivity analyses using the small subgroups due to limited power, as only ~10% of the population had a positive family history. Thus, race-ethnicity was dichotomized as Black vs. non-Black participants in all analyses.”

1. **There are 2 paragraphs in the Discussion that start to address the reasons why the racial differences observed in this analysis were found. The authors note, “This may partially be due to the concomitant diagnosis of AFL with AF, and the difficulty in differentiating the two diagnoses clinically.” I’m not sure how this explains the difference between white and Black individuals developing AF. Please provide further mechanisms for why this difference was observed as this was a key finding. Similarly for the findings that alcohol use / OSA were more commonly seen as risk factors in Black individuals.**

* ***Response***: We find this point to be very salient and important to emphasize. We have included an additional context in the discussion focusing on the differences in race and arrhythmia associations, including previous paradoxes found particularly in atrial fibrillation. Importantly, these findings may also reflect unmeasured confounders, particularly that symptoms of palpitations and arrhythmias may be under-reported based on cultural differences.
* Page 12, Lines 248-256: “Several studies have shown that there is a lower incidence of AF in Black than in White individuals,[10](#ref-Rodriguez2015),[11](#ref-Borzecki2008) even though established risk factors for AF are more common in Black individuals.[7](#ref-Stamos2016),[12](#ref-Andrade2014) This paradox is poorly understood and suggests underlying racial and socioeconomic disparities along with inherit bias in study design.[8](#ref-Roberts2016),[13](#ref-Soliman2014) In striking contrast to observations of AF incidence, our findings demonstrate that that Black participants had a higher odds of EOAFL than that of Non-Black participants.[7](#ref-Stamos2016) This may partially be due to the concomitant diagnosis of AFL with AF and the difficulty in differentiating the two diagnoses clinically, as well as differences in symptom reporting and intensity of monitoring.[14](#ref-Shiyovich2010),[15](#ref-Granada2000) However, identifying and diagnosing AF in Black participants may be more difficult due to differences in symptom recognition, as well as social determinants that are not yet well understood.[16](#ref-Norby2021)”
* Page 12-13, Lines 258-263: “Alcohol use, which has a known association for AFL,[17](#ref-Marcus2008) as well as obstructive sleep apnea, was only associated with an increased risk of EOAFL in Black participants vs. non-Black participants. While there is not clear evidence to highlight the reason for these differences, both alcohol use and sleep apnea may lead to higher adrenergic tone which may trigger episodes of AFL. The reason why individuals of Black race are more affected however remains unknown.”

**Additional Comments:**

1. **Please avoid the use of “Whites” and “Blacks” in the manuscript. These should be changed to White/Black individuals, patients, etc.**

* ***Response***: We have standardized the terminology to reflect this. We appreciate the feedback to write in a more equitable and inclusive manner. These revisions occur throughout the manuscript, and will not be listed here.

1. **Abstract: the Results state that, “participants with EOAFL were younger…more Black, or White” Please advise which is correct?**

* ***Response***: We have corrected the abstract phrasing to be more clear. Participants with EOAFL were more often Black participants.
* Page 3, Lines 46-47: “Of 909 patients enrolled, participants with EOAFL were predominantly of Black race-ethnicity, more often men, had higher body-mass index, and had higher burden of comorbidities as compared to LOAFL.”

1. **Methods: is the definition of “EOAFL” as a diagnosis of AFL before 66 years of age a validated definition? Please confirm / provide citation.**

* ***Response***: This is a commonly used definition when describing atrial fibrillation. We have modified that definition from our own previous work for this study.[1](#ref-Alzahrani2018)
* Page 6, Lines 110-112: “We defined EOAFL as a diagnosis of AFL before 66 years of age, without prior atrial tachyarrhythmias, including AF, anti-arrhythmic drug (AAD) use, or evidence of structural heart disease,[6](#ref-Halligan2004) similar to previous approaches used to define EOAF.[3](#ref-Chalazan2021),[18](#ref-Yoneda2021),[19](#ref-Yoneda2022)”

1. **Statistical Analysis: what social factors were included in this analysis?**

* ***Response***: We included alcohol usage and smoking as social factors, however we see the confusion in this terminology. We will modify this to be behavioral factors in the manuscript.
* Page 7, Lines 140-141: “We first present participant characteristics including demographic factors, clinical comorbidities, and behavioral factors.”

1. **Results: please advise why White or Hispanic/Latinx were combined in a single analysis (Page 8).**

* ***Response***: We chose to combine White/Hispanic/Mixed populations mainly due to limited power and the overlap between the White/Caucasian and Hispanic populations in the local metropolitan community (Chicago). Please see response to #3 above.

1. **Discussion (Page 9): the Results did not show an analysis comparing EOAFL to LOAFL. Please advise.**

* ***Response***: We have clarified the result terminology. The paper was a cross-sectional analysis that compared the rates of covariates between those with EOAFL and LOAFL. We have revised Table 1 to compare the groups and thus be more informative. Table 1, Page 16:

1. **Discussion (Page 9): the second paragraph of this section notes that, “The importance of family history in our study supports the known genetic predisposition to atrial flutter in those of European ancestry.” Please advise if this finding was described in the Results. It seems that many of the individuals with a family history had a history of conditions other than atrial flutter, including AF.**

* ***Response***: We agree that this phrasing is confusing. We have removed the direct references to ancestry. We believe that a family history of atrial tachyarrhythmias is overall a potential genetic/familial risk for the development of atrial flutter. We have clarified this in the methods and results.
* Page 8, Lines 147-148: “A positive family history was defined as having a diagnosis of AFL, AF, or atrial tachycardia in a FDR.”
* Page 10, Lines 205-206: “In all models, expanding the definition of a positive family history to include CHF or cardioembolic stroke did not significantly change the estimates.”
* Pages 11-12, Lines 238-240: “As subjective histories are prone to recall bias, we allowed for several potential risks of underlying arrhythmia as part of the screening (AFL, AF, cardiomyopathy, and strokes), and found similar sensitivity for the association with EOAFL regardless of definition of a positive family history.”

1. **Discussion:” we identified 31 kindreds with a history of atrial arrhythmias and showed for the first time that family members of probands with EOAFL” – again, this is the first time to my knowledge these results were described. Please advise.**

* ***Response***: This observation was made in Table 1, but not effectively demonstrated in the results section. We have taken care to also state this in the main results to ensure consistency.
* Page 9, Lines 178: “Of the families with a history of atrial tachyarrhythmias, 31 probands had EOAFL.”

# Additional References for Response to Reviewer Comments

1. Alzahrani Z, Ornelas-Loredo A, Darbar SD, Farooqui A, Mol D, Chalazan B, et al. Association Between Family History and Early-Onset Atrial Fibrillation Across Racial and Ethnic Groups. JAMA Network Open 2018;1:e182497. doi:[10.1001/jamanetworkopen.2018.2497](https://doi.org/10.1001/jamanetworkopen.2018.2497).

2. Cosío FG. Atrial Flutter, Typical and Atypical: A Review. Arrhythmia & Electrophysiology Review 2017;6:55. doi:[10.15420/aer.2017.5.2](https://doi.org/10.15420/aer.2017.5.2).

3. Chalazan B, Mol D, Darbar FA, Ornelas-Loredo A, Al-Azzam B, Chen Y, et al. Association of Rare Genetic Variants and Early-Onset Atrial Fibrillation in Ethnic Minority Individuals. JAMA Cardiology 2021;6:811–819. doi:[10.1001/jamacardio.2021.0994](https://doi.org/10.1001/jamacardio.2021.0994).

4. Grant BF, Goldstein RB, Saha TD, Chou SP, Jung J, Zhang H, et al. Epidemiology of DSM-5 Alcohol Use Disorder: Results From the National Epidemiologic Survey on Alcohol and Related Conditions III. JAMA Psychiatry 2015;72:757–766. doi:[10.1001/jamapsychiatry.2015.0584](https://doi.org/10.1001/jamapsychiatry.2015.0584).

5. Kornej J, Börschel CS, Benjamin EJ, Schnabel RB. Epidemiology of Atrial Fibrillation in the 21st Century: Novel Methods and New Insights. Circulation Research 2020;127:4–20. doi:[10.1161/CIRCRESAHA.120.316340](https://doi.org/10.1161/CIRCRESAHA.120.316340).

6. Halligan SC, Gersh BJ, Brown RD, Rosales AG, Munger TM, Shen WK, et al. The Natural History of Lone Atrial Flutter. Annals of Internal Medicine 2004;140:265–269. doi:[10.7326/0003-4819-140-4-200402170-00008](https://doi.org/10.7326/0003-4819-140-4-200402170-00008).

7. Stamos TD, Darbar D. The "Double" Paradox of Atrial Fibrillation in Black Individuals. JAMA Cardiol 2016;1:377–379. doi:[10.1001/jamacardio.2016.1259](https://doi.org/10.1001/jamacardio.2016.1259).

8. Roberts JD, Hu D, Heckbert SR, Alonso A, Dewland TA, Vittinghoff E, et al. Genetic Investigation Into the Differential Risk of Atrial Fibrillation Among Black and White Individuals. JAMA Cardiol 2016;1:442–450. doi:[10.1001/jamacardio.2016.1185](https://doi.org/10.1001/jamacardio.2016.1185).

9. Magnani JW, Norby FL, Agarwal SK, Soliman EZ, Chen LY, Loehr LR, et al. Racial Differences in Atrial Fibrillation-Related Cardiovascular Disease and Mortality: The Atherosclerosis Risk in Communities (ARIC) Study. JAMA Cardiol 2016;1:433–441. doi:[10.1001/jamacardio.2016.1025](https://doi.org/10.1001/jamacardio.2016.1025).

10. Rodriguez CJ, Soliman EZ, Alonso A, Swett K, Okin PM, Goff DC, et al. Atrial fibrillation incidence and risk factors in relation to race-ethnicity and the population attributable fraction of atrial fibrillation risk factors: The Multi-Ethnic Study of Atherosclerosis. Annals of Epidemiology 2015;25:71–76, 76.e1. doi:[10.1016/j.annepidem.2014.11.024](https://doi.org/10.1016/j.annepidem.2014.11.024).

11. Borzecki AM, Bridgers DK, Liebschutz JM, Kader B, Kazis LE, Berlowitz DR. Racial differences in the prevalence of atrial fibrillation among males. Journal of the National Medical Association 2008;100:237–245. doi:[10.1016/s0027-9684(15)31212-8](https://doi.org/10.1016/s0027-9684(15)31212-8).

12. Andrade J, Khairy P, Dobrev D, Nattel S. The clinical profile and pathophysiology of atrial fibrillation: Relationships among clinical features, epidemiology, and mechanisms. Circulation Research 2014;114:1453–1468. doi:[10.1161/CIRCRESAHA.114.303211](https://doi.org/10.1161/CIRCRESAHA.114.303211).

13. Soliman EZ, Prineas RJ. The paradox of atrial fibrillation in African Americans. Journal of Electrocardiology 2014;47:804–808. doi:[10.1016/j.jelectrocard.2014.07.010](https://doi.org/10.1016/j.jelectrocard.2014.07.010).

14. Shiyovich A, Wolak A, Yacobovich L, Grosbard A, Katz A. Accuracy of Diagnosing Atrial Flutter and Atrial Fibrillation From a Surface Electrocardiogram by Hospital Physicians: Analysis of Data From Internal Medicine Departments. The American Journal of the Medical Sciences 2010;340:271–275. doi:[10.1097/MAJ.0b013e3181e73fcf](https://doi.org/10.1097/MAJ.0b013e3181e73fcf).

15. Granada J, Uribe W, Chyou PH, Maassen K, Vierkant R, Smith PN, et al. Incidence and predictors of atrial flutter in the general population. Journal of the American College of Cardiology 2000;36:2242–2246. doi:[10.1016/S0735-1097(00)00982-7](https://doi.org/10.1016/S0735-1097(00)00982-7).

16. Norby FL, Benjamin EJ, Alonso A, Chugh SS. Racial and Ethnic Considerations in Patients with Atrial Fibrillation: JACC Focus Seminar. J Am Coll Cardiol 2021;78:2563–2572. doi:[10.1016/j.jacc.2021.04.110](https://doi.org/10.1016/j.jacc.2021.04.110).

17. Marcus GM, Smith LM, Whiteman D, Tseng ZH, Badhwar N, Lee BK, et al. Alcohol intake is significantly associated with atrial flutter in patients under 60 years of age and a shorter right atrial effective refractory period. PACE - Pacing and Clinical Electrophysiology 2008;31:266–272. doi:[10.1111/j.1540-8159.2008.00985.x](https://doi.org/10.1111/j.1540-8159.2008.00985.x).

18. Yoneda ZT, Anderson KC, Quintana JA, O’Neill MJ, Sims RA, Glazer AM, et al. Early-Onset Atrial Fibrillation and the Prevalence of Rare Variants in Cardiomyopathy and Arrhythmia Genes. JAMA Cardiology 2021;6:1371–1379. doi:[10.1001/jamacardio.2021.3370](https://doi.org/10.1001/jamacardio.2021.3370).

19. Yoneda ZT, Anderson KC, Ye F, Quintana JA, O’Neill MJ, Sims RA, et al. Mortality Among Patients With Early-Onset Atrial Fibrillation and Rare Variants in Cardiomyopathy and Arrhythmia Genes. JAMA Cardiology 2022. doi:[10.1001/JAMACARDIO.2022.0810](https://doi.org/10.1001/JAMACARDIO.2022.0810).