# Accepted Manuscript


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PII: S1547-5271(19)30099-2

DOI: https://doi.org/10.1016/j.hrthm.2019.01.027

Reference: HRTHM 7892

To appear in: *Heart Rhythm*

Received Date: 16 November 2018

Please cite this article as: Groh CA, Faulkner M, Getabecha S, Taffe V, Nah G, Sigona K, McCall D, Hills MT, Sciarappa K, Pletcher MJ, Olgin JE, Marcus GM, Patient-Reported Triggers of Paroxysmal Atrial Fibrillation, *Heart Rhythm* (2019), doi: https://doi.org/10.1016/j.hrthm.2019.01.027.

# Patient-Reported Triggers of Paroxysmal Atrial Fibrillation

**Short Title:** Paroxysmal Atrial Fibrillation Triggers

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**Funding**

This work was supported by the Patient Centered Outcomes Research Institute (PCORI). The Health eHeart Alliance is a Patient-Powered Research Network in PCORnet®, the National Patient-Centered Clinical Research Network, an initiative funded by PCORI. The Health eHeart Alliance's participation in the development of PCORnet® was partially funded through a PCORI Award [137480].

**Disclosures**

Dr. Marcus receives research funding from Medtronic and Jawbone, is a consultant for Johnson and Johnson and InCarda, and holds equity in InCarda. Dr. Olgin receives research funding from ZOLL, Myia, and iBeat, is a consultant for Novartis and VivaLink, and holds equity in Context AI. Ms. McCall receives speakers bureau from Janssen, SentreHeart, and the CardioVascular Clinical Trialists Forum and serves as a patient principal investigator on PCORI and AHRQ funded grants. Ms. Victoria Taffe previously worked as a part-time employee for the American Heart Association, Western States Affiliate. Other authors: None.

**Total word count:** 4,208

## ABSTRACT

**BACKGROUND:** Triggers for discrete atrial fibrillation (AF) events remain poorly studied and incompletely characterized.

**OBJECTIVE:** The present study describes common triggers for AF and their relationships with patient characteristics.

**METHODS:** We invited symptomatic, paroxysmal AF patients enrolled in the Health eHeart Study and through the patient-centered advocacy organization StopAfib.org to complete a questionnaire regarding their AF triggers and cardiovascular risk factors.

**RESULTS:** Of 1,295 participants with symptomatic AF, 957 (74%) reported triggers for episodes of AF. In comparison to those without triggers and after multivariate adjustment, those reporting triggers had a 71% lower odds of congestive heart failure (odds ratio [OR] 0.29, 95% CI 0.14 to 0.60, p=0.001) and over a two-fold greater odds of a family history of AF (OR 2.04, 95% CI 1.21 to 3.47, p=0.008). The most commonly reported triggers were alcohol (in 35%), caffeine (in 28%), exercise (in 23%), and lack of sleep (in 21%). Multivariable models revealed that younger patients, women, and those with an AF family history more commonly experienced various triggers. Patients reported a median of two different triggers (interquartile range 1-3); female sex, Hispanic ethnicity, obstructive sleep apnea, and a family history of AF were each associated with a greater number of AF triggers. Vagally-mediated triggers tended to cluster together within individuals.

**CONCLUSION:** The majority of patient-reported triggers are modifiable, potentially identifying accessible means to prevent and reduce AF episodes. Exploring the interactions between AF patient type, including underlying genetic differences, and common exposures may be fruitful areas of investigation.

**KEYWORDS:** Atrial fibrillation, atrial flutter, triggers, alcohol, caffeine

## INTRODUCTION

Atrial fibrillation (AF) is increasing in prevalence and expected to affect 16 million Americans by 2050.[1] Studies have focused on predictors for the development of incident AF (specifically, predictors of the first diagnosis of the disease), identifying older age, male sex, white race, multiple cardiovascular comorbidities, and lifestyle factors such as alcohol consumption and smoking as important.[1–5] However, little is known about acute exposures that influence the development of a discrete AF episode. Previous studies have demonstrated that the majority of AF patients describe situations that trigger their episodes.[6] In a small, single-center study restricted to patients seeking medical care, stress, physical exertion, and fatigue were the leading factors preceding AF events.[7] While the mechanisms for which these triggers may precipitate AF remain unknown, experimental studies in animal models and humans have shown alterations in autonomic tone, either exaggerated vagal or sympathetic stimulation, can initiate AF.[8–10] We previously showed that patients more often reported vagal behaviors as triggers for AF in comparison to patients with other supraventricular tachycardias (SVTs), suggesting that categorizing potential AF triggers as sympathetic or vagal may be a clinically useful construct.[11]

Characterizing the frequency of various AF triggers and identifying specific populations more prone to report specific triggers (or types of triggers) may help identify behavioral interventions effective in preventing AF episodes and reducing AF burden. Better understanding individual-level triggers idiosyncratic to a given individual may help empower the patient, representing a novel approach to improving quality of life and reducing healthcare utilization for AF. We therefore sought to describe the triggers of AF most commonly reported by patients and how those triggers, individually and categorized by autonomic category, relate to patient characteristics and one another.

## METHODS

### Patient Population

The current study arose as part of the preparation and design of the Patient Centered Outcomes Research Institute (PCORI)-funded Individualized Studies of Triggers of Paroxysmal Atrial Fibrillation (I-STOP-AFib) randomized trial (ClinicalTrials.gov Identifier: NCT03323099). The study was approved by the University of California, San Francisco Institutional Review Board. With the goal of identifying the most common AF triggers to test in an interventional trial, two senior board-certified electrophysiologists (JEO and GMM) developed an initial list of commonly-reported triggers based on the available literature and their experience treating AF patients. This list was then modified based on input from 8 AF patients (4 AF patients treated locally at UCSF and 4 AF patients selected from the national, PCORI-funded Health eHeart Alliance).

On March 8, 2017, a single email invitation was sent to what was then all of the 2,426 AF patients in the Health eHeart Study (a worldwide internet-based, longitudinal, cardiovascular cohort study) who reported paroxysmal AF (paroxysmal AF defined as AF that “comes and goes on its own” to participants) to complete an online survey. On March 14, 2017, a separate weblink was electronically sent to subscribers to the StopAfib.org newsletter (StopAfib.org is a non-profit patient advocacy and resource organization for those living with AF) inviting those who perceive AF triggers to participate in the online survey. Finally, an AF patient advocate and Health eHeart alliance patient principal investigator (DM) posted the survey link to online social media sources. Participants were initially asked about AF symptoms and, if they reported symptomatic AF, were

then queried about triggers for AF episodes. Those patients were then asked questions about their specific triggers (Supplemental **eMethods**). Patients without AF symptoms were excluded.

**Definition of Specific Triggers and Comorbid Conditions**

The following specific triggers were queried: alcohol, caffeine, lack of sleep, exercise, not exercising, consuming cold beverages, consuming cold foods, high sodium diet, consuming large meals, dehydration, and lying on one's left side. An affirmative response was considered present if the patient selected either that a given exposure resulted in AF "all of the time" or "some of the time."

Participants were also given the opportunity to enter other specific triggers aside from the 11 previously listed using free text. These were reviewed and categorized individually by one of the authors (CAG) (Supplemental **eTable 1**). Manually entered triggers were included in trigger frequency tabulations but not included for other comparison analyses.

Participants who reported symptomatic AF and triggers for AF episodes were asked about general demographics and their known risk factors for AF and cardiovascular disease. For those without AF triggers that were also Health eHeart Study participants, linked data to previously ascertained demographic and medical history information was used.

In order to analyze triggers categorized by their influence on autonomic tone, caffeine, exercise, and dehydration were grouped into a "sympathetic" category while a cold beverage, cold food, and large meals were grouped into a "vagal" category. The remainder were categorized as "unknown" in regards to their effect on autonomic tone.

**Statistical Analysis**

Continuous and ordinal variables are expressed as means and standard deviations or median and interquartile ranges (IQR), respectively. Normally distributed continuous variables were compared using the Student's t-tests, and variables with either a skewed distribution or that were ordinal were compared using the Wilcoxon rank sum test. The $\chi^2$ test was used to compare categorical variables. Both bivariate and multivariate logistic regression were used to measure associations between triggers and patient characteristics. Participants had the opportunity to report multiple triggers. Triggers were reported and analyzed individually even if a given participant reported multiple triggers. All queried patient characteristics were included as covariates in the multivariable models. To assess for a possible association between "autonomic-categorized" triggers, a probability matrix for the odds of reporting one trigger versus another trigger was generated. A two-tailed p-value of $<0.05$ was considered statistically significant. Analyses were performed using STATA version 15 (STATA Corp., College Station, TX).

## RESULTS

After including only those who initiated the online surveys and met the inclusion criteria, 1,295 AF patients were included in the study (**Figure 1**). Of the 1,295 patients with symptomatic AF, 957 (74%) reported perceiving triggers for AF episodes. Characteristics of the queried populations are listed in **Table 1**. Participants tended to be middle-aged, equally distributed by sex, and predominately Caucasian. AF patients with triggers less often had congestive heart failure (CHF) and more often had a family history of AF.

After multivariable adjustment, heart failure patients exhibited a 71% lower odds of reporting any AF triggers whereas those with a family history of AF had over twice the odds of experiencing triggers of their AF (**Table 2**).

Alcohol, caffeine, and exercise were the most commonly reported triggers (**Figure 2**). Participants reported a median of 2 triggers (IQR 1-3). Females, those of Hispanic ethnicity, those with a history of sleep apnea, and those with a family history of AF reported a larger number of triggers (**Figure 3**).

Relationships between specific triggers and patient characteristics are shown in **Table 3**. Younger individuals and females exhibited statistically significant relationships with several triggers, while a family history of AF was associated with an increased odds of reporting alcohol and caffeine as triggers. Hispanic ethnicity was also strongly associated with caffeine as a trigger.

Those with one vagal trigger tended to report other vagal triggers, but no other clear co-occurrence of triggers by autonomic type was observed within individuals (**Figure 4**). There were no differences in relationships with different autonomic categories and patient characteristics (Supplemental **eFigure 1**).

## DISCUSSION

Our findings demonstrate that symptomatic participants commonly report triggers for AF episodes. Alcohol consumption, caffeine, and exercise were the most frequently reported triggers of AF. Compared to those without a family history of AF, participants with a family history of AF were more likely to report any trigger, to have a greater number of different AF triggers, and to identify alcohol and caffeine as specific triggers for their AF. Similarly, women were more likely to report a greater number of triggers and identify with several queried triggers. Conversely, those with CHF were less likely to have any AF triggers. Finally, it appears that various triggers related to enhanced vagal tone may cluster together within individuals.

182

183 **Alcohol and AF Triggers**

184 Current epidemiologic studies regarding risk factors for AF focus on predictors of the
185 development of the first diagnosis of AF in large cohort studies. There is a paucity of literature
186 regarding acute predictors for AF episodes in those who already carry the diagnosis. We
187 previously performed a smaller study querying participants scheduled for electrophysiologic
188 procedures, demonstrating that alcohol and vagal activity were associated with a greater odds of
189 precipitating symptomatic arrhythmia episodes in AF patients compared to participants with
190 SVT.[11] Moreover, one study specifically surveying subjects with paroxysmal AF found that 34%
191 of participants reported alcohol consumption preceding their episodes.[7] These observations may
192 yet be explained by chance given ubiquitous and frequent use of alcohol and potentially random
193 timing of AF.

194

195 **Autonomic Tone and AF Triggers**

196 Changes in autonomic tone have been implicated in the onset of a discrete AF episode, most
197 commonly attributed to increases in vagal tone among AF patients with structurally normal
198 hearts.[8–10,12] Our previous work restricted to AF patients presenting for electrophysiology
199 procedures at a single center suggested that up to 38% of AF patients report vagal triggers
200 (sleeping, eating, resting).[11] Our current study, now representing a larger remote cohort, is
201 consistent with these findings in that one vagal trigger appears to be more commonly associated
202 with other vagal triggers. Our study did not find those susceptible to “vagal” influences to be of a
203 younger age or with a family history of AF as in previous studies.[11] In fact, there was no
204 association between patient characteristics and autonomic category of triggers.

205

206 **Women and AF Triggers**

207 Among those that reported triggers, women were more likely to have a greater number of
208 triggers. Women experience symptomatic AF more often than men, and therefore may be better
209 equipped (or more apt to) identify some behavioral or environmental influence relevant to AF
210 episodes.[13–15] Interestingly, despite reporting a larger number of triggers, women did not exhibit
211 a statistically greater likelihood of reporting any trigger when compared to men. We cannot
212 exclude insufficient power as an explanation for this negative result, although it is also possible
213 that the nature of triggers differs by gender only among those with trigger-prone AF.

214

215 **CHF and AF Triggers**

216 Those with CHF were less likely to have AF triggers. It is known that those with asymptomatic
217 AF have a lower incidence of CHF.[16] Moreover, CHF increases the likelihood of having AF, and
218 more severe CHF symptoms are associated with a higher prevalence of AF.[17] Given this link
219 between CHF and AF symptoms, it is possible that the severity of CHF morbidity overwhelms
220 observed triggers for AF alone. Alternatively, because AF in the setting of CHF more likely
221 involves abnormalities in the physical substrate of the atria, CHF-related AF may be less prone
222 to functional changes related to the dynamic nature of environmental triggers.

223

224 **Family History of AF and Triggers**

225 A family history of AF was strongly associated with having triggers for AF. A family history
226 appears to be genetically mediated and is known to occur more commonly among those with AF
227 in the absence of conventional risk factors (or "lone AF").[18,19] Our findings suggest there may be

a heritable component of AF trigger sensitivity or that inherited AF is particularly susceptible to environmental exposures.

**Limitations**

Several limitations of our study should be acknowledged. Primarily, our study is limited by questionnaires relying on self-report, and we cannot verify the occurrence of AF episodes with specific triggers. However, this is the only practical means to at least begin to understand the various triggers that may be important to patients and indeed the study deliberately focuses on patient-reported events. We also previously validated the diagnosis of AF using this same survey in the Health eHeart Study.[20] This is not a study comparing patients with and without AF, making biases related to the accuracy of an AF diagnosis potentially less relevant. We only queried patients with symptomatic AF and indeed were interested in triggers of episodes known to the patients. It is possible that some or all of these triggers do not initiate AF itself, but potentially are more likely to enhance symptoms of AF when it occurs (for example by changing conduction properties of the atrioventricular node). Our study group may not be representative of the larger paroxysmal AF population due to selection bias. Moreover, the participants were self-selected and may be more interested and in-tune with their own health than non-responding patients with paroxysmal AF; therefore, the prevalence of triggers overall is particularly subject to potential bias from this selection factor. Our study participants were required to have internet and computer access to answer the questionnaires, possibly limiting our accessibility to specific socioeconomic groups. Finally, as with any observational study, we cannot exclude residual confounding or confounding related to unmeasured covariates.

## CONCLUSIONS

The majority of AF patients reported at least one identifiable trigger for their discrete AF episodes, alcohol, caffeine, and exercise being the most common. Triggers were more commonly associated with a family history of AF and less so with a history of CHF, and patients with one vagal trigger were more likely to report additional vagal triggers. Given the increasing prevalence of AF and the resultant burden on the healthcare system, identifying modifiable triggers may help to empower patients. Influencing exposures that trigger AF may help improve quality of life and reduce healthcare utilization. The particular relevance of triggers among those with a family history of AF suggests that better understanding gene-environment interactions may reveal novel mechanisms and ultimately help to counsel patients regarding appropriate lifestyle interventions.

## APPENDIX

### Supplementary Data

Supplementary data associated with this article can be found in the online version.

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335 **FIGURE LEGENDS**

336

337 **Figure 1.** Consort Diagram for Study Inclusion

338 AF, atrial fibrillation**.**

339

340 **Figure 2.** Frequency of Specific Triggers (N=957). All triggers were included, such that the

341 same participant could have reported more than one.

342 AF, atrial fibrillation.

343

344 **Figure 3.** Scatter Density Plot of Total Number of Reported Triggers by Sex (Figure 3A),

345 Ethnicity (Figure 3B), OSA History (Figure 3C), and Family History of AF (Figure 3D). The

346 width of each horizontal line for a given number of triggers represents the relative proportions

347 among all participants reporting in each category. Medians are shown by the black circles

348 (connected by the sold black lines), and interquartile ranges are represented by the dashed lines.

349 OSA, obstructive sleep apnea; AF, atrial fibrillation.

350

351 **Figure 4. Heat Map for Specific Triggers.**

352 Heat map constructed based on odds ratios (OR) for relationship between each specific trigger

353 grouped in autonomic categories. The color gradients highlight the strength of associations using

354 conditional formatting. Included odds ratios exhibited significance at $p<0.05$. White cells

355 represent no relevant value.

356

## TABLES

**Table 1. Demographics of Queried Population**

| | All Participants with Triggers† (N=957) | Health eHeart Only‡ | | |
|---|---|---|---|---|
| | | With Triggers (N=312) | Without Triggers (N=187) | p value |
| Age (years) - Mean (SD) | 63 (52-74) | 62 (51-73) | 64 (53-75) | 0.35 |
| Female Sex | 317 (50%) | 142 (46%) | 92 (50 %) | 0.37 |
| Caucasian - n (%) | 612 (97%) | 288 (95%) | 172 (98%) | 0.15 |
| Hispanic Ethnicity - n (%) | 21 (3%) | 10 (3%) | 12 (7%) | 0.09 |
| HTN - n (%) | 315 (49%) | 158 (51%) | 96 (52%) | 0.82 |
| Diabetes - n (%) | 54 (8%) | 26 (8%) | 23 (12%) | 0.15 |
| CHF - n (%) | 38 (6%) | 19 (6%) | 24 (13%) | **0.008** |
| CAD - n (%) | 91 (14%) | 58 (19%) | 39 (21%) | 0.54 |
| OSA - n (%) | 166 (27%) | 85 (29%) | 44 (26%) | 0.44 |
| AF Family History- n (%) | 215 (36%) | 86 (30%) | 30 (19%) | **0.009** |

† 64-69% reportable data

‡90-100% reportable data

SD, standard deviation; HTN, hypertension; CHF, congestive heart failure; CAD, coronary artery disease; OSA, obstructive sleep apnea; AF, atrial fibrillation.

**Table 2. Association of Triggers with Comorbid Conditions in the Health eHeart Study Population (N=499)†**

| | Triggers versus No Triggers | | | | | |
|---|---|---|---|---|---|---|
| | Crude OR | 95% CI | p value | Adjusted OR | 95% CI | p value |
| 10-yr Age Increase | 0.93 | 0.79-1.10 | 0.38 | 0.90 | 0.73-1.10 | 0.30 |
| Female Sex | 0.84 | 0.59-1.22 | 0.36 | 0.72 | 0.47-1.11 | 0.14 |
| Caucasian Race | 0.44 | 0.14-1.36 | 0.15 | 0.43 | 0.13-1.41 | 0.13 |
| Hispanic Ethnicity | 0.48 | 0.20-1.14 | 0.10 | 0.34 | 0.11-1.14 | 0.08 |
| HTN | 0.94 | 0.65-1.35 | 0.73 | 0.97 | 0.62-1.54 | 0.91 |
| Diabetes | 0.66 | 0.36-1.19 | 0.17 | 0.65 | 0.31-1.36 | 0.25 |
| CHF | 0.42 | 0.22-0.78 | **0.006** | 0.29 | 0.14-0.60 | **0.001** |
| CAD | 0.84 | 0.53-1.33 | 0.45 | 1.16 | 0.64-2.13 | 0.63 |
| OSA | 1.21 | 0.79-1.86 | 0.38 | 1.36 | 0.81-2.27 | 0.25 |
| AF Family History | 1.87 | 1.17-3.00 | **0.009** | 2.04 | 1.21-3.47 | **0.008** |

† StopAfib.org participants did not receive additional questions if they did not report a trigger, hence these data are only available from previously ascertained information from Health eHeart Participants. Multivariable adjustment included all listed covariates.

HTN, hypertension; CHF, congestive heart failure; CAD, coronary artery disease; OSA, obstructive sleep apnea; AF, atrial fibrillation; CI, confidence interval; OR, odds ratio

375 **Table 3. Adjusted Odds Ratio for Specific Triggers**

376

| | 10-Year Age Increase | Female Sex | Caucasian | Hispanic Ethnicity | HTN | Diabetes | CHF | CAD | OSA | AF Family History |
|---|---|---|---|---|---|---|---|---|---|---|
| **Alcohol** | **0.83†** | 0.77 | 1.88 | 1.09 | 1.04 | 1.16 | 1.22 | 1.28 | 1.12 | **2.03*** |
| **Caffeine** | 0.92 | **2.02*** | 0.34 | **4.30*** | 0.74 | 1.73 | 0.60 | 1.22 | 1.56 | **1.56*** |
| **Exercise** | **0.82†** | 0.85 | 0.56 | 1.68 | 1.01 | 1.02 | 0.93 | 1.07 | 1.19 | 1.17 |
| **Lack of Sleep** | **0.76†** | **2.09*** | 0.83 | 1.45 | 1.09 | 0.82 | 0.97 | 0.80 | **1.77*** | 1.23 |
| **Dehydration** | **0.76†** | **2.03*** | 5.42 | 0.60 | 1.10 | 0.67 | 0.76 | 0.86 | 1.31 | 1.04 |
| **Large Meal** | **0.81†** | 0.98 | 1.17 | 1.33 | 1.05 | 1.87 | 0.58 | 0.94 | 1.09 | 1.13 |
| **Lying on Left Side** | **0.78†** | **2.83*** | 1.83 | 1.28 | 0.75 | 1.69 | 2.04 | 1.39 | 1.40 | 0.92 |
| **Cold Beverage** | 0.86 | 1.46 | 1.30 | 1.53 | 0.91 | 1.37 | 0.89 | 1.12 | 1.79 | 1.27 |
| **High Salt Diet** | 0.74 | 1.11 | 1.12 | 0.94 | 1.28 | 1.85 | 2.95 | 0.65 | 1.50 | 1.04 |
| **Cold Food** | 1.21 | **2.70*** | 0.58 | 3.28 | 0.64 | 1.05 | 0.62 | 0.96 | 1.28 | 1.90 |
| **No Exercise** | 0.77 | 0.80 | 1.00 | 1.00 | 0.78 | 0.96 | 1.00 | 1.37 | 1.02 | 2.33 |

377 Multivariable adjustment included all listed covariates. An * highlights statistically significant
378 OR>1 and † highlights statistically significant OR<1. Statistical significance set at $p<0.05$.
379 HTN, hypertension; CHF, congestive heart failure; CAD, coronary artery disease; OSA,
380 obstructive sleep apnea; AF, atrial fibrillation; OR, odds ratio

381

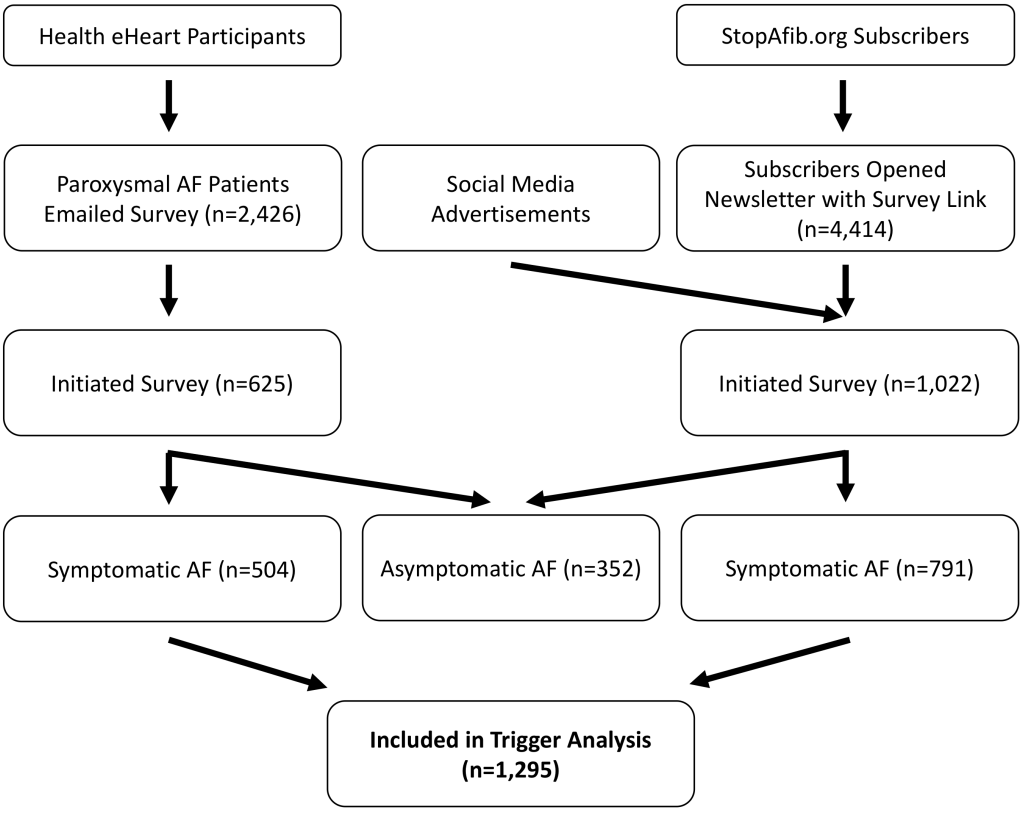


**Figure 1**

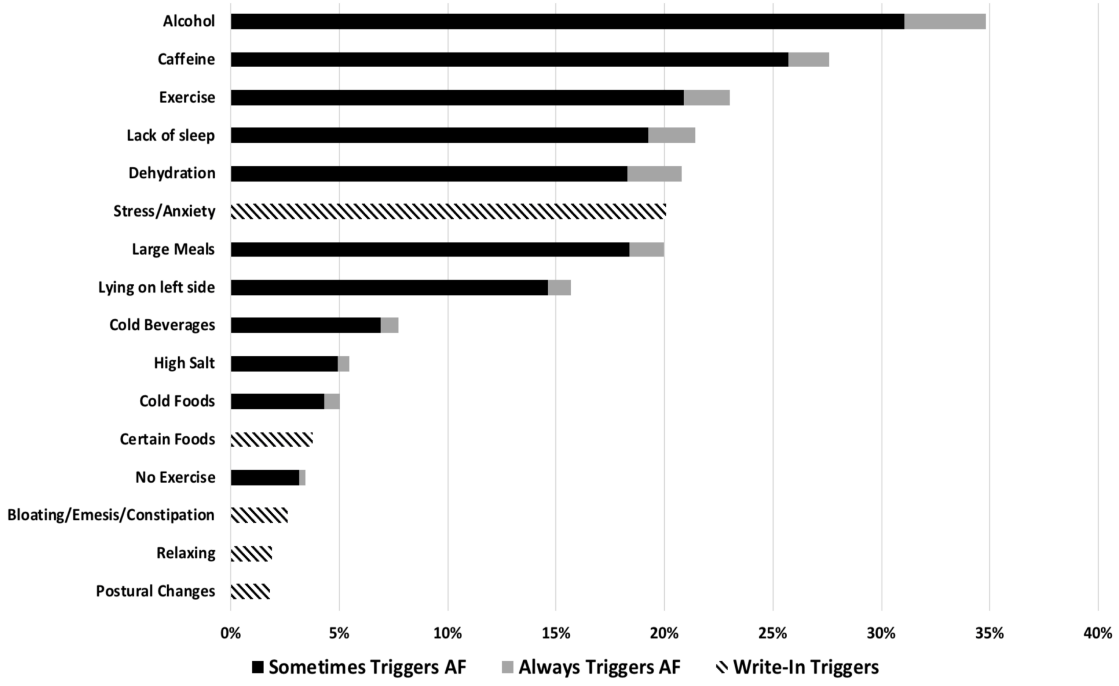


**Figure 2**

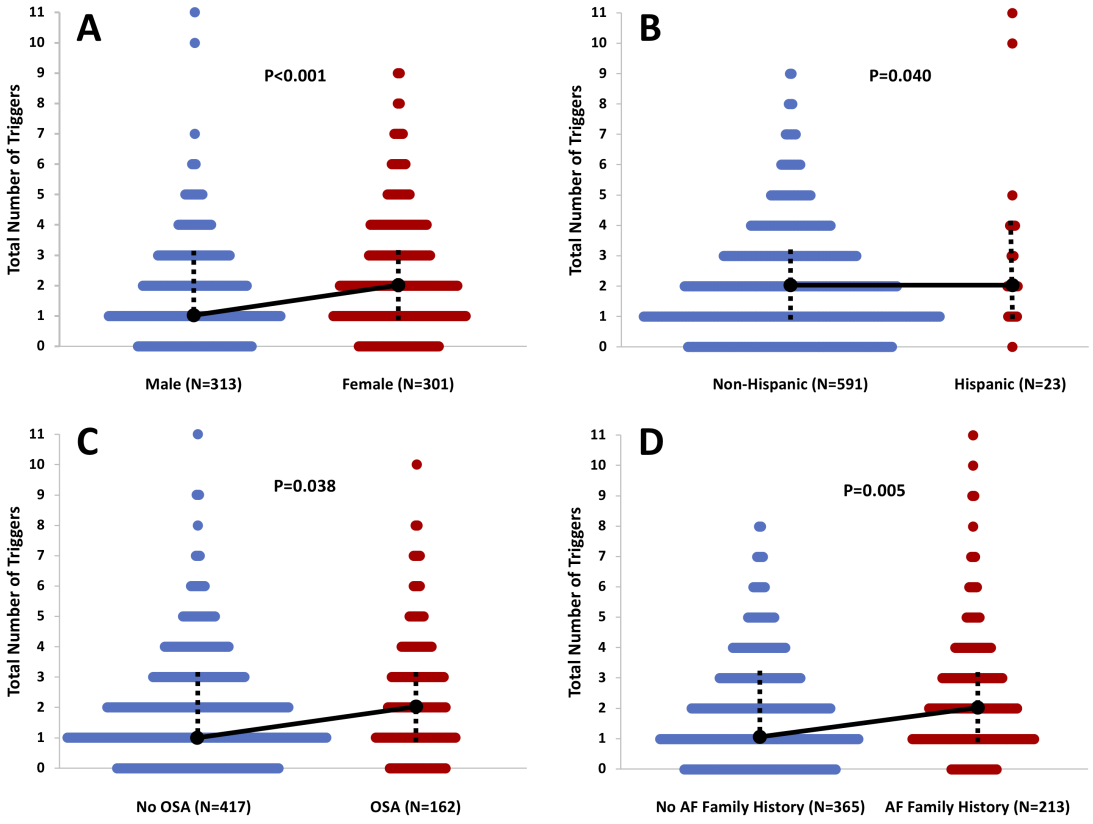


**Figure 3**

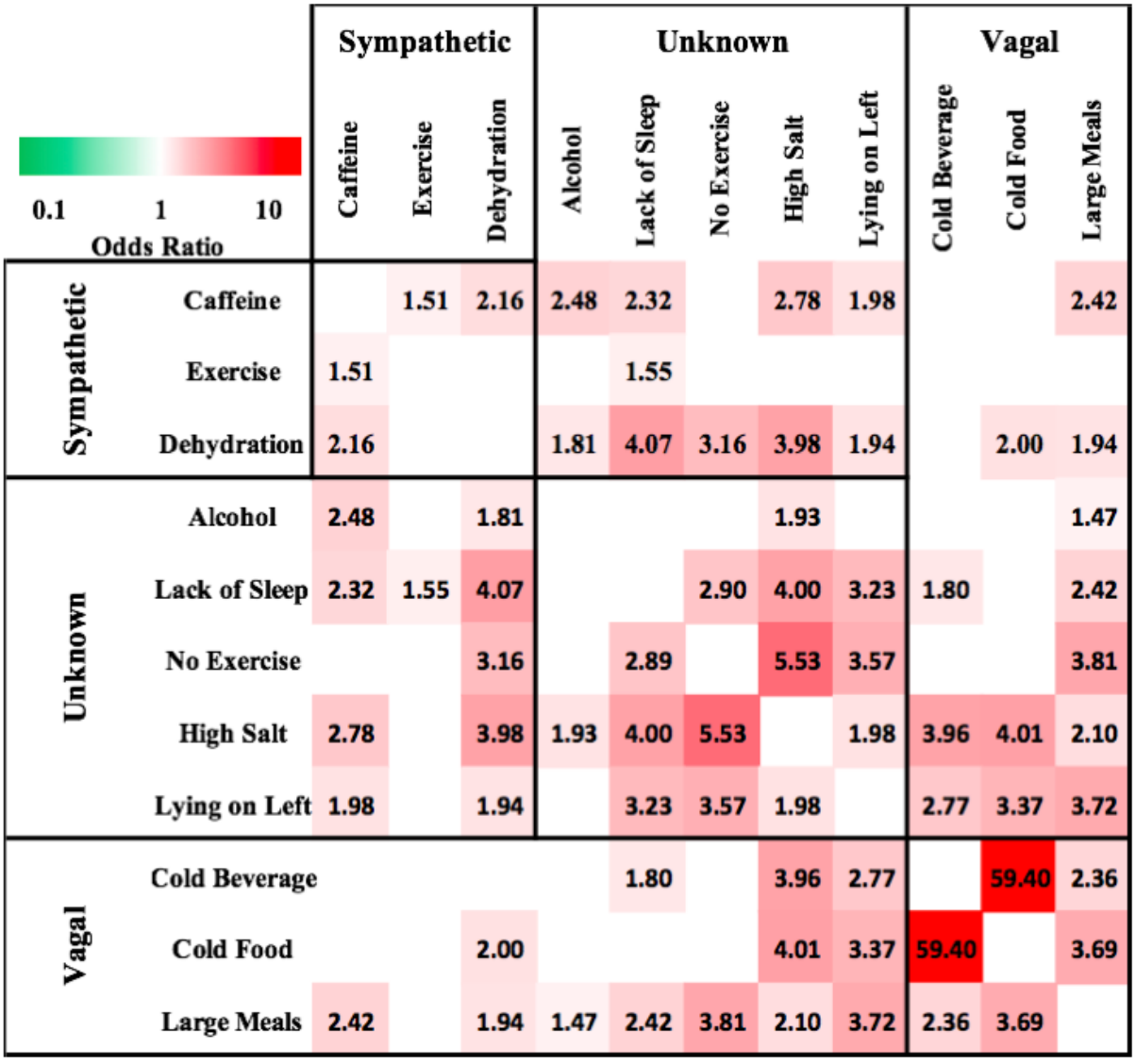
0.1
1
10
Odds Ratio
Sympathetic
Unknown
Vagal
Caffeine
Exercise
Dehydration
Alcohol
Lack of Sleep
No Exercise
High Salt
Lying on Left
Cold Beverage
Cold Food
Large Meals
Sympathetic
Caffeine 1.51 2.16 2.48 2.32 2.78 1.98 2.42
Exercise 1.51 1.55
Dehydration 2.16 1.81 4.07 3.16 3.98 1.94 2.00 1.94
Unknown
Alcohol 2.48 1.81 1.93 1.47
Lack of Sleep 2.32 1.55 4.07 2.90 4.00 3.23 1.80 2.42
No Exercise 3.16 2.89 5.53 3.57 3.81
High Salt 2.78 3.98 1.93 4.00 5.53 1.98 3.96 4.01 2.10
Lying on Left 1.98 1.94 3.23 3.57 1.98 2.77 3.37 3.72
Vagal
Cold Beverage 1.80 3.96 2.77 59.40 2.36
Cold Food 2.00 4.01 3.37 59.40 3.69
Large Meals 2.42 1.94 1.47 2.42 3.81 2.10 3.72 2.36 3.69

**Figure 4**