A Literature Review Investigating the Role of Sex and Gender in Atrial Fibrillation Outcomes

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Abstract

Atrial fibrillation (AF), the most common cardiac arrhythmia, presents distinct challenges influenced by sex and gender. To preface, *sex* refers to biological attributes (chromosomal, hormonal, and physiological), while *gender* involves a set of sociocultural roles, behaviours, and expectations prescribed to individuals according to their attributed-at-birth sex. While men exhibit higher AF prevalence, women face disproportionately severe outcomes, including increased stroke risk, hospitalizations, and mortality. This review explores the interplay of genetic, hormonal, physiological, and environmental factors driving these disparities. Sex-specific genetic pathways, such as mutations in KCN1 and KCNE5, alongside hormonal influences like estrogen's dual effects on cardioprotection and arrhythmogenesis, contribute to variations in AF risk. Additionally, structural and functional differences in the heart, such as ventricular wall thickness and cardiac output, further differentiate AF presentations between sexes. Environmental and sociocultural factors, including chronic stress and underutilization of anticoagulation therapies, exacerbate gender-based inequities, particularly among women. Recognizing these multifaceted influences is crucial for developing personalized prevention, diagnosis, and management strategies. This literature review advocates for integrating sex and gender considerations into clinical guidelines to improve outcomes for all individuals affected by AF.

Keywords: Atrial Fibrillation, Sex, Gender, Health, Social Determinants of Health

Introduction

Atrial fibrillation (AF) is the most common type of heart arrhythmia, which is when the heart beats in an irregular rhythm (NHS, 2017). Normally, the electrical signals within the heart are coordinated to allow the atria and the ventricles to contract in a synchronized manner, however, in AF, the electrical signals in the atria are disorganized, leading to chaotic contractions of the atria (NHS, 2017). As a result, the atria quiver or fibrillate instead of contracting effectively, leading to an irregular heartbeat.

Each year in the United States, over 454,000 hospitalizations occur with AF as the primary diagnosis, and the condition is associated with approximately 158,000 deaths annually (Centers for Disease Control and Prevention, 2022). Furthermore, the death rate attributed to AF, either as the primary cause or as a contributing factor, has been steadily increasing over the past two decades. Common symptoms of AF include heart palpitations, light-headedness, extreme fatigue, shortness of breath, and chest pain (Centers for Disease Control and Prevention, 2022). Although the main cause of AF may vary from person to person, some of the most common risk factors are advancing age, high blood pressure, obesity, European ancestry, diabetes, heart failure, ischemic heart disease, hyperthyroidism, chronic kidney disease, moderate to heavy alcohol use, smoking, and enlargement of the chambers on the left side of the heart (Centers for Disease Control and Prevention, 2022).

Studies have shown that AF is more prevalent in men compared to women (Ko et al., 2016). Specifically, the Global Burden of Disease reported an estimated age-adjusted prevalence of 12.6 million women and 20.9 million men living with AF globally in 2010 (Chugh et al., 2014). However, research shows that women with AF tend to have poorer outcomes compared to men, including higher rates of stroke, hospitalization, and mortality (Ko et al., 2016). This

difference can be attributed to varying major risk factors by sex and differences in symptom presentation. For example, certain risk factors for AF may affect men and women differently. For instance, obesity may be a stronger risk factor for AF in women compared to men (Ko et al., 2016). Additionally, women experience different symptoms than men, with some experiencing symptoms that are considered to be less typical such as fatigue, shortness of breath, and fainting, rather than the more typical palpitations experienced by men (Ball et al., 2013; Scheuermeyer et al., 2015). This can exacerbate treatment disparities, as physicians may question the severity of the condition (Paquette et al., 2000).

Although there is a vast amount of literature on AF as well as its demographics, there is a scarcity of attention given to the sex and gender differences that are associated with AF. In this case study, we will explore how the interaction of physiological, environmental, and sociocultural factors surrounding sex and gender affect AF.

Methodology

This review aimed to explore the relationship between sex, gender, hormones, and atrial fibrillation (AF), with a focus on how environmental and sociocultural influences impact the development and progression of the condition. To achieve this, we conducted a comprehensive search of the relevant literature using key terms such as "atrial fibrillation," "sex," "gender," "hormones," "organs and body," "environmental influences," and "sociocultural influences."

Search Strategy

A systematic search was conducted in PubMed to identify articles that were relevant to the topic. We focused on studies published in peer-reviewed journals from 1994 onwards to capture the most recent developments in the field.

Inclusion Criteria

The articles included in this review met the following criteria:

- Focused on atrial fibrillation and its relation to sex, gender, hormones, and environmental or sociocultural influences
- Included primary research studies, systematic reviews, meta-analyses, or other review articles
- Studies involving human participants
- Articles published from 1994 onward

Exclusion Criteria

Articles were excluded if they met the following criteria:

- Focused on animal studies or non-human subjects
- Did not specifically address atrial fibrillation or the specified influencing factors
- Were not available in full text
- Studies that were not peer-reviewed (e.g., conference abstracts, opinion pieces)

Screening and Selection Process

The initial search yielded 80 articles. These articles were then screened for relevance based on their titles and abstracts. After removing duplicates and articles that did not meet the inclusion criteria, we selected 31 articles for full-text review. These included a mix of systematic reviews, meta-analyses, and primary research studies. Each article was assessed for its relevance and

quality, ensuring that only studies with rigorous methodology and strong evidence were included in the final review.

Genes

Genetic changes within an individual's genome may directly cause AF, and may also affect a person's risk for developing AF. With increasing research being done to map the entire human genome, new genetic loci that are associated with AF are constantly being found (Vinciguerra et al., 2024). These genes tend to be associated most commonly with European ancestry. When there is a hereditary gene that causes AF, this is known as familial AF. An article by Vinciguerra and colleagues examined genes that are known to directly cause AF, and also genes that make an individual more predisposed to certain risk factors for AF such as electrical irregularities, structural remodelling of the heart and vasculature, and increased inflammation. The most common gene that directly causes AF is a mutation in a gene called KCNQ1 which gives instructions for building ion channels within heart muscle. This directly affects the electrical rhythm of the heart as the channel transports potassium (positive electrical charge) out of the cells (Chen et al., 2003). This effectively shortens action potential duration in the heart, and the refractory period. This genetic mutation is much more common in women that in men (Lorca et al., 2020). Further research is needed to fully determine why the prevalence differs, but initial hypotheses suggest hormonal influences, differences in ion channel function, and other genetic and environmental factors (Lorca et al., 2020). There are also sex-linked genes that play a role in influencing AF risk, such as KCNE5 at Xq23 and EMD at Xq28, although there is little research on this topic (Wren & Davies, 2022). Sex-linked traits are most often connected to the larger X-chromosome since it contain more genes than the Y-chromosome (Basta & Pandya, 2023). Since males only have 1 X chromosome, they are more likely to develop AF if there is

genetic variance found on the X chromosome. However, when we examine individuals older than 75 years of age, we see a higher incidence in the female population, likely due to the increased longevity observed in the female populations (Westerman & Wenger, 2019). This indicates that predisposition to the development of AF is clearly not solely due to genetic influence, and likely is modulated by a unique blend of environmental, social, and physiological factors.

Hormones

The disparities that can be observed in the incidence and severity of AF between males and females may be related to the sex hormone, estrogen. Although estrogen is known to be cardioprotective, recent evidence suggests that it may play a role in hindering ion channel function, elevating the severity of certain arrhythmias (Erlandstodder et al., 2023). A recent review found that many reproductive health factors can increase a woman's risk for developing AF, indicating that sex hormones play a role in risk modulation for this disease. A study by Lu et al in 2022 found that abnormally early or late onset of menstruation, irregular cycles, or the early or late onset of menopause all increased women's risk of developing AF. Having less than 30 "reproductive" years (described as the time between the onset of menarche and menopause) was also associated with an increased risk of AF. This increased risk may be due to a shorter lifetime exposure to endogenous estrogen, which as mentioned above, is established to have cardioprotective effects (Lu et al., 2022). When we examine the role of exogenous estrogen and progestin as used in hormone replacement therapy and its effect on AF risk, this relationship becomes even more complicated. Users of estradiol-only HRT showed no significant elevated risk for AF, while users of all other HRTs did show elevated risk for the development of AF (Lee et al., 2021). When examining past users of HRT, estradiol plus progestin users actually showed

a significantly decreased risk for AF. In comparison, looking at the use of oral contraceptives (OCs), the literature shows that OCs are not associated with an increased risk of AF. Rather, there is evidence of a decrease in risk associated with the prolonged use of OCs (Dou et al., 2023). Although some of these results are confounding, it is important to establish that it is relatively unknown whether exogenous sex hormones (such as those used in HRT and OCs) have the same mechanism of action, and the same effect on our body's cells, as endogenous sex hormones.

Exploring stress and stress hormones such as cortisol, we see that there is a connection with the risk of developing AF. A literature review highlights that chronic stress as well as high levels of cortisol are associated with an increased risk for the development of AF. While both men and women experience stress, the manifestation and consequences of this stress often differ. Women are more likely to experience chronic stress, which often stems from multiple factors such as playing roles of caregiving, career, and societal expectations (American Psychological Association, 2023). This chronic stress can lead to dysregulation of the stress hormones through the autonomic nervous system, contributing to physiological changes that increase the risk of cardiovascular diseases such as AF. Lastly, women may be more likely to internalize stress due to societal norms, leading to behaviours like emotional eating or sedentary habits, which further exacerbate cardiovascular risks. Further insights of stress through the lens of environmental influences are discussed later in this paper.

Finally, another biological difference between males and females is the process of pregnancy. Although studies on AF and pregnancy are limited, there is an association observed between pregnancy and significant hemodynamic changes, including increased blood volume which leads to four-chamber cardiac dilatation, and up to 50% increased cardiac output by the

seventh month of pregnancy (O'Neal et al., 2014). Furthermore, the elevated levels of different catecholamines and hormones present during pregnancy contribute to the different risk factors associated with AF. Studies report that AF usually happens during the third trimester or within 24 hours of postpartum. These significant physiological changes during pregnancy may also help to explain the disparities between males and females for the onset of AF.

Organs and Body

A primary effect of AF is that it increases an individual's risk for blood clots in the heart, creating an elevated risk of stroke (Cove et al., 2013). Even though women are less likely to develop AF, when they do they have a higher risk of stroke and other thromboembolic events (Marzona et al., 2018). This may be due to the under-utilization of certain pharmacotherapies such as anticoagulants for females, but there is also evidence to suggest a more physiological basis for these trends (Cove et al., 2013). Males and females each have differences in vasculature and hemodynamics. As women become older, they go through physiological changes at a greater rate than men such as increased pulse pressure, increased arterial stiffness, and thickened left ventricle that predispose them to increased risk for cardiovascular complications (Cove et al., 2013). This may explain why women with AF are more likely to experience stroke, with more severe complications. A systematic review also explored adverse clinical events in almost 1,000,000 patients with AF and found that in general women were at a significantly higher risk for stroke than men (Marzona et al., 2018). Interestingly, when taking into account ethnicity, Asian women with AF were found to not be at higher risk for stroke. Although there was no mechanism provided for this difference, it does indicate that race and sex together may play a role in the differences observed in stroke risk for AF patients and should be further explored.

Looking further at physiological differences, the female heart tends to beat at a faster rate, and has a greater ejection fraction, but generates a smaller cardiac output compared to an average male (St Pierre et al., 2022). If we apply allometric scaling, which is looking at the different inputs and outputs of the heart and comparing it to the different sizes of males and females, while controlling for lean body mass and other factors, we see that the female heart is still much different in physiology compared to the male heart (St Pierre et al., 2022). This demonstrates that the female heart is not just a smaller-sized male heart, but is subject to many different variables that contribute to its physiology as well as the diseases associated with its structure. The smaller, faster, beating heart of females may be associated with worse outcomes of AF but may provide a preventative measure for the onset of AF. Furthermore, muscle composition and wall thickness of the heart's chambers may be an important contributing factor for AF. Studies have shown an association between the larger left atria, as well as increased left ventricular wall thickness and the risk of AF (Vaziri et al., 1994). On average, in absolute terms, men tend to have a greater left ventricular wall thickness and larger left atria which may explain the higher rates of AF in men compared to women (Kishi et al., 2015). These studies show a clear trend, as the independent anatomy of the heart in males and females directly correlates to its physiology as well as the risks of AF that may be associated with it.

Exploring the interaction of comorbidities and the risk of AF, we may observe another one of the most common heart conditions - myocardial infarction (MI). Research shows a connection between AF and MI (Soliman et al., 2014). Specifically, it was found that women experience a higher association between AF and MI compared to their male counterparts. Furthermore, there is a higher association of AF and contracting coronary heart disease within females compared to men, when looking at a study in older adults (O'Neal et al., 2014). These

studies show that AF is more associated with other diseases and co-morbidities in females, compared to males, and this association should be further explored.

Environmental Influences

Environmental and community factors may also contribute to the onset and an individual's susceptibility to AF. There is extensive research on social determinants that contribute to the onset of AF, including stress, ethnicity, gender, sex, socioeconomic status, social support, and healthcare treatment (Essien et al., 2021). Literature shows that the lack of social support is a major factor in the increased development of AF (Essien et al., 2021). Social support is a key factor in quality of life but is often not encouraged adequately in younger, male demographics (O'Neil et al., 2018). From a young age, boys are not typically forced into social settings and therefore may develop antisocial behaviours that can lead to deficits in strong, intimate friendships/relationships and ultimately emotional dysregulation (O'Neil et al., 2018). Masculinity and gender roles can play a role in causing this maladaptive stress response that may come off as anger, which can manifest into symptoms of AF (O'Neil et al., 2018).

Another environmental factor that can lead to the manifestation of AF is the social reliability and act of drinking caffeine in the form of coffee (Coppi et al., 2023). Coffee consumption is a large part of many lifestyles, often related to the act of getting coffee with friends, family, and coworkers (Coppi et al., 2023). Since caffeine is a stimulant, it increases blood pressure, and heart rate, and can temporarily block adenosine receptors - which are important in sustaining heart rhythm - leading to the onset of AF (Coppi et al., 2023). One study found that men who drank fewer cups of coffee per day (1-3 cups) had a lower risk of developing AF (Vijaykumar Bodar et al., 2019). However, a study on women found that they were 36% more likely to develop AF with only slightly more caffeine consumption, specifically 2-4 cups

per day (Conen et al., 2010). This may mean that women are more likely to develop AF from increased caffeine consumption compared to men.

Acute stress and anxiety is other environmental factors that can lead to the onset of AF, due to the role stress plays on the heart through the autonomic nervous system and the hypothalamus pituitary adrenal axis (Svensson et al., 2017). Stress can produce electrophysiological changes to the sinoatrial (SA) node and the atrioventricular (AV) node, which are responsible for regulating heart rhythm, potentially leading to altered heart rhythm and the onset of AF. One study found that women were more likely to develop stress-induced AF, whereas men did not develop AF from stress (Svensson et al., 2017). This may mean that women who experience acute stress at a high degree are at an increased risk of developing AF. Acute stress and anxiety can lead to increased caffeine consumption and lifestyle/dietary changes that can therefore lead to a cycle of behaviours that increase the risk for the manifestation of AF (Coppi et al., 2023). This calls for action by physicians to equally treat, prescribe, and refer everyone with symptoms of AF, regardless of sex or gender. Physicians should also consider all possible environmental factors including lifestyle, diet, and social determinants while triaging patients for common AF symptoms. It is not only physical symptoms, genetics, and cell-related, but AF can also be brought on by environmental and community influences.

Sociocultural Influences

Healthcare & Treatment Discrepancies:

Societal and cultural norms have significantly influenced healthcare system biases regarding gender, affecting the delivery of healthcare for AF. Access to healthcare is another key social determinant that might prevent people from getting proper treatment for AF (Bhave et al.,

2015). For many new diagnoses, receiving treatment from a specialist elicits the best improvements in symptoms, but women are significantly less likely to receive the same treatment or see a specialist at all, when compared to men (Bhave et al., 2015). In regards to treatment options like catheter ablation, anticoagulant prescription, and rhythm control medications, women are also significantly less likely to receive a catheter ablation or be prescribed anticoagulants compared to men (Bhave et al., 2015). Research shows, that women are more likely to be older, experience worse symptoms, and have more comorbidities at the time of diagnosis, which leads to a lower quality of life with AF (Kostopoulou et al., 2019). Since women are less likely to be prescribed anticoagulants and are less likely to be taken seriously by medical professionals, there have been more instances and risk of stroke in females with AF compared to males (Kostopoulou et al., 2019). Research suggests that women are less likely to receive referral to a specialist, and their perceived symptoms are taken less seriously compared to men (Kostopoulou et al., 2019).

Symptom Presentation Discrepancy:

The reason for the healthcare and treatment discrepancies may be attributed to the difference in presentation of symptoms between men and women. Research indicates that the clinical presentation of AF significantly varies between men and women, with women experiencing more symptoms such as weakness and fatigue instead of common symptoms of AF experienced by men (Ball et al., 2013; Scheuermeyer et al., 2015). This is significant as it contributes to the perceived gender stereotypes in healthcare that women may exacerbate their symptoms, resulting in the delay of their treatment and care by healthcare workers (Ball et al., 2013b; Paquette et al., 2000). Furthermore, these differences in symptom presentation also influence how doctors and nurses may manage rate and rhythm control for AF. An ORBIT-AF

registry found that women were less likely to receive beta-blocker therapy, with 62% compared to 65.5% in men, and were more likely to receive digoxin, with 24.6% in men compared to 22.6% in women (Piccini et al., 2016). In addition, research highlights that women were found to be more likely to be prescribed digoxin compared to men, increasing all-cause mortality, vascular death, and sudden death in women (Washam et al., 2015). The consistent preference of healthcare workers to treat women with digoxin at a higher rate than men as a rate control agent for AF may be worsening their health outcomes. Current literature demonstrates a clear systemic gender bias in favour of men within the healthcare field. Due to traditional gender stereotypes and roles, women's pain and symptoms from AF are often taken less seriously by healthcare practitioners, influencing their treatment, outcomes, and overall quality of life compared to men. Furthermore, the gender bias extends beyond the management of AF, also influencing the systemic trust women have in the healthcare system. Women's concerns who healthcare practitioners downplay may lead to them not seeking medical attention in the future, further endangering their health.

Racial Disparities

Societal and cultural norms also play a prominent role in exacerbating racial and ethnic disparities in the delivery of healthcare for AF. These disparities arise from implicit biases, social determinants of health, health literacy and systemic trust in the healthcare system. Research has shown that black and Hispanic patients with low incomes were found to be associated with lower use of rhythm control and cathartic ablation respectively (Eberly et al., 2021). The lower use of these treatment interventions arguably equates to a delivery of suboptimal care for these populations as it was observed in another study that private insurance and higher household income were associated with an increased likelihood of undergoing ablation (Kummer et al.,

2015). This is significant because it portrays how income levels create an implicit bias for these healthcare workers to treat individuals and groups differently for AF. Furthermore, there is a disparity in health literacy regarding AF among ethnic groups. Research has indicated that non-white patients with lower education levels have been shown to be less likely to receive care from cardiologists for AF (O'Neal et al., 2018). There is a clear implicit bias among healthcare practitioners to treat individuals with lower education differently, resulting in the minority population receiving less information, suboptimal care, and experiencing poorer health outcomes. Finally, societal and cultural norms rooted in systemic mistrust of the healthcare system exacerbate racial disparities observed in the treatment of many Indigenous communities. Data from the PINNACLE/NCDR registry found that American Indian and Alaskan Native patients were less likely to be treated with rhythm-control interventions for AF compared to non-American patients (Khalid et al., 2020). This discrepancy can be attributed to the historical injustices faced by these indigenous communities regarding unethical practices and research being conducted without their consent. As a result, there is a deeply rooted mistrust in Western medicine, resulting in the reluctance to try newer therapies for AF. Furthermore, many of these communities prioritize traditional holistic practices to health and healing compared to the reductionist approach of symptom prevention in Western medicine (Koithan & Farrell, 2010). This avoidance of Western medicine in Indigenous communities contributes to poorer outcomes in AF, highlighting the importance of incorporating their cultural perspectives into treatment strategies (Howard et al., 1999)

Conclusion

In conclusion, addressing AF within the healthcare field requires a holistic approach that considers the interactions between: genes, hormones, organs, body, and environment and

sociocultural influences. Throughout this paper, we explored how sex and gender disparities can influence the severity and the risk of developing AF and how these factors are often more complex than perceived due to a myriad of factors. The onset of AF is more prevalent in men compared to women. Still, women who do develop AF tend to experience poorer outcomes compared to men, including higher rates of stroke, hospitalization, and mortality. The current notion amongst healthcare workers in Western medicine is to consistently treat diseases such as AF with reductionist thinking, whereby the role of sex and gender disparities is not considered. This approach falls short as it does not recognize the complexity of AF. There is an urgency to foster greater awareness among healthcare professionals of promoting inclusivity for all individuals, regardless of their gender, in addressing different conditions including AF. As a result, future research needs to be tailored towards prevention centred on patients, emphasizing a systemic view of the interconnected aspects to achieve inclusive and equitable delivery of AF care. By doing this, we can strive towards optimizing maximal patient care and enhancing overall cardiovascular health for individuals of all genders.

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