

**Obesity, self-reported symptom severity, and quality of life in people with atrial
fibrillation: a community-based cross-sectional survey**

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Abstract

Background and Aims: Intentional weight loss may reduce symptom severity of atrial fibrillation (AF) in relatively young patients with overweight. We examined whether symptom severity and quality of life (QoL) are associated with weight status in the general population with AF.

Methods and Results: Patients with electrocardiogram-confirmed AF completed validated questionnaires: the EuroQol 5 Dimensions QoL questionnaire and the Toronto Atrial Fibrillation Severity Scale (AFSS). The AFSS assessed the AF burden scoring on AF-related symptoms and the total AF burden measured as a combination of duration, frequency, and severity of an irregular heartbeat. Generalized liner models examined the association of body mass index (BMI) with AF severity and QoL adjusting for confounders. Between 2018 and 2019, 882 of 1901 (46%) mailed questionnaires were returned completed. Participants had a mean (SD) age of 74 (10) years old and a BMI of 27.4 (5.6) kg/m². Sixteen percent reported having never experienced an irregular heartbeat. A 5kg/m² higher BMI was associated with a 0.65 (95%CI: 0.25 to 1.06) higher symptom score, where 3 points represent a clinically relevant change in state. A 5kg/m² higher BMI was associated with a -1.61 (95%CI: -2.72 to -0.50) lower QoL score. The coefficient of the total AF burden for a 5kg/m² higher BMI was 0.17 (95% CI: -0.01 to 0.68).

Conclusion: BMI was positively associated with symptoms and negatively associated with one of the two measures of QoL, but not with the total AF burden. However, the strength of association was small and not clinically meaningful.

Keywords: obesity, atrial fibrillation, symptoms, quality of life

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia affecting about 33.5 million people worldwide [1]. It is a risk factor for stroke, dementia, heart failure, and mortality, and its growing prevalence poses an increasing disease burden to patients and economic burden to healthcare systems.

Overweight, obesity and weight gain itself have all been linked with an increased risk of incident AF [2]. Body mass index (BMI), along with hypertension, is one of the two strongest independent modifiable factors associated with incident AF in cohort studies and Mendelian randomization analysis suggests this relationship is causal [3].

On top of incidence, BMI is also associated in a U-shape fashion with AF recurrence post ablation [4]. However, the relationship of BMI with the total AF burden (a composite of the frequency, duration, and severity of AF episodes) and severity of common AF symptoms, such as palpitations, fatigue, and dyspnea, that patients experience is less clear. A randomized trial showed that intentional weight loss in people with AF and overweight reduced the components of the total AF burden and the severity of AF symptoms and improved wellbeing [5]. One cross-sectional study including 1,382 patients with AF found a positive correlation between BMI and AF symptom severity in patients receiving rhythm-control treatment, but no evidence of a significant association in patients receiving other forms of AF treatment or between BMI and total AF burden [6]. However, a study of 110 people undergoing a first AF ablation found that pericardial fat, but not BMI, was strongly associated with AF symptom severity [7]. Another cross-sectional study found that BMI was positively associated with AF symptom severity, but not significantly so after adjusting for physical activity and depression [8]. Moreover, the aforementioned studies did not examine if specific symptoms tended to drive the demonstrated associations.

The majority of patients with AF at some point experience symptoms related to the disease [9]. The severity of these symptoms has been associated with poorer quality of life (QoL). Symptom severity has also been associated with cardiovascular morbidity and mortality in a secondary analysis of a trial of pharmacological heart rate control in people

with permanent AF [10]. However, whether BMI is independently associated with AF-related healthcare utilization or QoL in this population has not been previously examined. Understanding these associations may help inform whether weight loss interventions might be considered as a treatment for some symptomatic patients with AF to reduce symptom burden and improve QoL. Therefore, this study aimed to examine the association between weight status, AF burden and symptom severity, and QoL.

Methods

Study design, setting and participants

In this cross-sectional survey, 10 general practices in central England searched their electronic databases and mailed questionnaires to all eligible participants. All adults with an electrocardiogram-confirmed diagnosis of AF (persistent, permanent, or paroxysmal) were included unless their AF was resolved, based on the standard Quality Outcome Framework database codes for AF [11]. Participants were also excluded if they had a significant cognitive impairment or disability that rendered them unable to complete the questionnaire, they were unable to understand sufficient written English, or they were at the end of life. Participants provided consent by completing and returning the survey in a pre-paid envelope. The study was approved by the National Health Service London - Bloomsbury Research Ethics Committee (Ref: 18/LO/0429).

Measures

The Self-Administered Comorbidity Questionnaire assessed the presence of 12 defined medical conditions and 3 open-ended items, the treatment for each condition, and related functional limitations. The questionnaire has previously shown acceptable test-retest reliability and validity [12]. Each individual questionnaire could score between 0 to 45, with higher scores indicating higher comorbidity burden.

The University of Toronto Atrial Fibrillation Severity Scale (AFSS) assessed the following categories: (a) the total AF burden as the sum of the frequency, duration, and severity of the first and most recent AF episodes with higher scores indicating greater

burden (range 3-30), (b) global well-being as a visual analogue scale, with higher scores indicating higher well-being (range 0-10), (c) a symptom score as the sum of five symptoms at rest (palpitations, dyspnea, fatigue or weakness, dizziness, and chest pain) and two symptoms during exercise (fatigue, dyspnea), each coded in a 5-point Likert-scale from “not having had this symptom in the past 4 weeks” to “a great deal” with higher scores indicating higher symptom severity (range 0-35), and (d) the health care utilization as a sum of the number of cardioversions, ablations, Accident and Emergency (A&E) visits, AF-related hospitalizations, and specialist appointments [13]. The symptom score is a measure of symptom severity in AF patients validated against a clinician-reported measure of QoL in AF, with a 3-point change indicating a clinically significant difference [14, 15].

Participants recorded their QoL using the reliable and validated EuroQol 5 Dimensions questionnaire (EQ-5D-5L). The EQ-5D index score was calculated using the reference values for England scored 0-1 and the overall health rating on the day of the survey was calculated as a score ranging from 0-100 in a visual analogue scale with higher scores indicating better health. A 0.08-point change in the index score and an 8-point change in the visual analogue scale score are regarded as minimally clinically significant differences [16, 17].

Participants reported standard demographic characteristics including their weight and height from which BMI was calculated. Obesity was defined as $BMI \geq 30 \text{ kg/m}^2$. Participants were classified into four treatment groups based on their self-reported prescribed medication: no AF treatment, rate-control (β -blockers, digoxin, verapamil, or diltiazem), rhythm-control if they were prescribed at least one rhythm-control medication (sotalol, flecainide, amiodarone, or disopyramide) with or without rate-control treatment, or ablation if they had an ablation irrespective of medication [6]. Questionnaires are available in Appendix 1.

Statistical analysis

Continuous data are presented as means (standard deviations) and categorical data as counts (percentages). Differences in demographic characteristics by the type of treatment

were assessed with chi-square test or analysis of variance and Tukey post-hoc test. Generalized linear regression models in complete cases examined the association of BMI with AF severity, namely total AF burden, symptom score, healthcare utilization, and global well-being, as well as QoL based on the EQ-5D visual analogue scale and the EQ-5D index score. BMI was modelled as a continuous 1kg/m² increase and the yielded estimate was multiplied by 5 to aid clinical interpretation of the findings. All models were adjusted for age, sex, comorbidity score, treatment modality (with no treatment as reference), and smoking status (current/former vs. never) on the basis of a theoretical analysis via a directed acyclic graph [18]. We ran sensitivity analyses (a) splitting the total AF burden, regressing BMI against the severity of AF symptoms and separately against the frequency and duration of symptoms (b) by including only participants reporting symptoms and AF burden (i.e. symptom score ≥ 1 and total AF burden ≥ 3). Statistical significance was set at $p < 0.05$. All analysis was conducted in RStudio, v1.1.463.

Results

Between October 2018 and June 2019, 882 (46.4%) of the 1901 sent surveys were returned. Table 1 presents the demographic characteristics. Participants had a mean (SD) age of 74.3 (10.2) years old, had a BMI of 27.4 (5.4), 24% were affected by obesity, 4% were currently smoking and 44.3% had previously smoked. Most were male (64.2%), white (98.1%), and married (70.6%).

Regarding AF treatment, 21.7% were receiving no AF-specific medication, 7.1% were prescribed rhythm-control treatment, 45.4% were prescribed rate-control treatment, and 17.9% had received an ablation, with missing treatment data for 7.9% of participants. Those who received either rhythm control or ablation were significantly younger than those receiving no treatment (-5.9 years (95% CI: -9.6 to -2.3) and -2.8 years (95% CI: -5.5 to -0.01), respectively). Furthermore, significantly more males than females reported receiving no treatment for AF (71.4% vs. 60.9%, $p = 0.01$). There was no evidence that the treatment groups differed on other demographic characteristics. Back pain was the most common

reported co-morbidity (442, 50.1%), followed by hypertension (313, 35.5%) and heart disease (297, 33.7%) with relatively few people suffering from respiratory disease (Table 2).

On average, participants were taking 5 (SD: 3) prescribed medications with other types of cardiovascular disease and type 2 diabetes being the most common treatment indications.

Disease severity and QoL characteristics are presented in Table 2 and Figure 1.

Most participants reported symptomatic AF (74.3%) and both the mean total AF burden (16.1, SD: 6.5) and the mean total symptom score (7.5, SD: 6.5) were categorized as moderate. The symptom score was primarily driven by dyspnea during exercise closely followed by fatigue. There were 145 participants (16.4%) reporting asymptomatic AF (data on AF symptoms were missing for 9.3% of participants). Compared with asymptomatic patients, patients with symptoms were more likely to report receiving treatment for AF (78.3% vs. 63.8%, $p<0.001$), were more likely to be female (37.2% vs. 26.7%, $p=0.04$), and were younger (73.2 vs. 79.3 years, $p<0.001$). BMI and smoking status did not differ between these groups.

After adjustment for confounders, a 5kg/m² higher BMI was positively associated with a 0.65-point (95% CI: 0.25 to 1.06, $t=3.14$, $p=0.002$) higher symptom score (Figure 2). It was also negatively associated with QoL in the EQ-5D visual analogue scale (-1.61 points, 95% CI: -2.72 to -0.50, $t=-2.85$, $p=0.005$, for 5kg/m² higher BMI). However, the magnitude of both of these associations did not approach clinical significance. Furthermore, BMI was not independently associated with QoL assessed by the EQ-5D index score (-0.01 points, 95% CI: -0.02 to 0.0001, $t=-1.76$, $p=0.08$) or with the global well-being score (-0.08 points, 95% CI: -0.19 to 0.001, $t=-1.34$, $p=0.18$). The magnitude of the association with AF-related healthcare utilization (-0.17 points, 95% CI: -0.33 to -0.01, $t=-2.04$, $p=0.04$) or total AF burden (0.17 points, 95% CI: -0.01 to 0.68, $t=0.65$, $p=0.52$) was also small. In the sensitivity analysis, regression of total AF burden on BMI showed no evidence of an association with frequency and duration of AF (0.16 points, 95% CI: -0.012 to 0.7, $t=0.80$, $p=-0.43$) or with severity of AF symptoms (-0.12 points, 95% CI: -0.30 to 0.002, $t=-1.45$, $p=0.15$). Full details of the models are provided in the Table S1. In a sensitivity analysis including only

participants experiencing symptoms, the effect estimates did not materially change (Table S2).

Discussion

In this community-based cross-sectional survey, most participants with AF were symptomatic. Mean total AF burden and symptom severity score were both classified as moderate. BMI was positively associated with symptom burden and negatively associated with one of the two measures of QoL in people with AF. We observed a weak negative association of BMI with AF-related healthcare utilization but no independent associations of BMI with total AF burden, the EQ-5D index score, or global well-being.

Our findings are in line with previous studies showing that asymptomatic AF is associated with older age and male gender [19]. The AFSS symptom score was also similar to that in previous studies of people with permanent AF, e.g. the RACE II study where the mean was 7.8 ± 6.3 [10], though lower than other studies that recruited people with recurrent persistent AF [20].

In our study, BMI was not associated with the perceived AF frequency, duration, or severity of episodes (total AF burden). This is consistent with another cross-sectional analysis [6] and a non-randomized study showing no change in these parameters following significant weight loss [21]. However, the subjective nature of reporting might have underestimated the total AF burden and diluted the association with the actual AF burden. As BMI is generally positively associated with higher healthcare utilization, the negative observed association between BMI and AF-related healthcare utilization was unexpected, but the association was weak and of unclear clinical significance.

Reporting of QoL in people with AF has varied across previous research. Some studies suggest that whilst QoL is initially impacted after a new AF diagnosis, this soon recovered to baseline level and remained unchanged over subsequent follow-up [22]. In the general population, elevated BMI has been negatively associated with the presence of some of the perceived problems in the EQ-5D index score but it is unclear whether it is

associated with the total index score [23]. This is the first study to evaluate the relationship between BMI and QoL in people with AF using a widely-used standardized QoL, showing similar QoL scores with the general population in this age group [24]. Although the association between BMI with EQ-5D index and global well-being in our study was not significant, the direction of the association was similar with the association between BMI and the EQ-5D visual analogue scale. This discrepancy between the two EQ-5D measures might exist because the visual analogue scale measures the participant's views on their overall health more broadly which may lead to an assessment of overall health closer aligned to the participant's perspective [25].

Previous research has demonstrated that intentional weight loss in people with obesity using either a very low calorie diet or structured weight management program can reduce AF symptom burden in a dose-response manner over long-term follow-up [5, 26, 27]. This may not be surprising. Common symptoms associated with AF, such as dyspnea and fatigue, may be related to obesity itself and be particularly severe in people who are sarcopenic [28]. If so, weight loss may alleviate these symptoms [29] independently of any effect on AF itself. This may explain why losing weight reduces symptom burden in people with symptomatic AF while our findings indicate minimal association between obesity and total AF burden. Therefore, obesity doesn't seem to substantially increase the symptom burden of AF. Future research should aim to verify these potential explanations.

Our results suggest that there are likely to be significant numbers of people in the community with symptomatic AF and co-occurring obesity who therefore might benefit from weight loss interventions to reduce symptoms and improve QoL. However, the feasibility, safety, and effectiveness of these types of weight loss interventions still need to be tested in community samples of older people with AF, as published trials have recruited relatively young participants with AF [5, 26, 27]. This is particularly important given other data show an association between higher BMI and waist circumference and reduced risk of stroke, thromboembolism, and all-cause mortality among people with AF – the so called 'obesity paradox'[30]. Further research is, therefore, needed to determine what degree of weight loss

should be recommended and to which patients to improve symptom burden and QoL without negatively impacting prognosis. The interactions between obesity, cardiorespiratory fitness, physical activity, and diet warrant further investigation when considering potential interventions to reduce AF symptom severity [8, 31]. Rate control was the most commonly reported treatment reflecting current practice and guidance for first-line medication. Of note, only a small minority of people were treated with rhythm-control medication, despite the fact most reported being symptomatic on rate control. An opportunity for improvement in care exists for better symptom management.

Strengths of the study include the high response rate and the fact that our sample might be more representative of people living with AF in the community than in previous studies that enrolled participants from secondary care or clinical trials with stringent eligibility criteria [10]. Purposive sampling was used to select practices with a range of demographic characteristics, meaning the results have external validity regionally. The response rate was similar to that of other surveys in populations with obesity-related disease [32]. We used three validated questionnaires to capture key outcome data, including symptom score and QoL. Self-reporting of symptoms may be more accurate than primary care coding for categorizing AF as paroxysmal, persistent, or permanent but still relies on patients to be aware of changes in heart rhythm, which is not always the case.

The study has some limitations. The cross-sectional design does not allow for causal inference. The sample was predominantly of white ethnicity which is typical of the population aged at least 65 years in the recruitment area. The recruitment strategy aimed to achieve regional validity, however, these findings may not be generalizable to the wider population with AF. For example, rate of comorbidities, such as hypertension, were low which might be due to self-report or because healthier volunteers might be more likely to take part in epidemiological research. Weight and height were also self-reported but these data have been found to be valid for epidemiological analyses in a cohort from the same region despite some over-estimation of height and under-estimation of weight [33]. BMI is limited as a measure of obesity at the individual level, but it provides an accurate and valid measure in

cohort studies [34]. We did not collect data on intentional weight loss attempts and although it is plausible that some people might have intentionally lost weight and improved their symptom score prior to the study, the proportion of weight loss attempts in the general population with similar demographics is limited. Given the self-report nature of the study, we only collected data on some of the components of the CHA₂DS₂-VASc score, but not data on heart failure, so the risk of stroke and thromboembolism in this study remains unclear [35]. We did not validate the self-reported information against primary care or hospital records, and it is possible patients were inaccurate in recording measures and treatment or healthcare utilization. These measures may be subject to recall bias which may reduce the strength of observed associations. Data were collected at a single time point and although participants were asked about historical symptoms, this too may be subject to recall bias. Furthermore, it was not possible to collect data on disease onset and therefore we could not estimate AF duration and changes in AF severity over time. It was not possible to confirm the proportion of participants with paroxysmal, persistent or permanent AF. Symptom scores were analyzed in relation to type of medication but not dose, which may impact on the effectiveness of treatment. Although we aimed to adjust for the most important confounders, residual confounding cannot be ruled out.

Conclusions

In conclusion, we found a high proportion of people with AF in the community living with symptoms attributable to AF. Overall, the total burden and severity of symptoms were moderate. BMI was positively associated with symptoms and negatively associated with one but not both measures of QoL and not with total AF burden. However, the magnitude of the associations was modest, and these associations were not clinically meaningful.

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Acknowledgements

We would like to thank all the staff at the GP practices for technical support, the NIHR Clinical Research Network for facilitating study recruitment, and the study participants for completing the survey.

Funding

This study was funded by the NIHR Oxford Biomedical Research Centre. PA is an NIHR Senior Investigator and funded by the NIHR Oxford Biomedical Research Centre and Applied Research Collaboration. BC is funded by the British Heart Foundation. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Conflicts of interest

DAK, PA, and SAJ report being investigators in a NIHR-funded trial where the weight loss intervention was donated by Nestle Health Sciences to the University of Oxford outside the submitted work. PA reports grants from Cambridge Weight Plan Ltd to the University of Oxford outside the submitted work. PA did half a day's consultancy for WW outside the submitted work and WW reimbursed his time to the University of Oxford. None of these association led to payments to them personally. The other authors report no conflicts of interest.

Figure Legends

Figure 1 Means (SD) of each of the constructs of AF disease severity by BMI category.

Figure 2 Adjusted regression models of the association between BMI and each of the constructs of AF disease severity. Shaded areas represent 95% CIs. Each tick at the top of the x axis indicates the BMI of each participant.