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Christensen, Signe Westh; Berg, Selina Kikkenborg; Rod, Naja Hulvej; Zwisler, Ann Dorthe Olsen; Thygesen, Lau Caspar; Risom, Signe Stelling

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Physical activity and serious adverse events in patients with atrial fibrillation and/or atrial flutter treated with catheter ablation

Signe Westh Christensen, MSc, Selina Kikkenborg Berg, PhD, Naja Hulvej Rod, DMSc, Ann-Dorthe Olsen Zwisler PhD, Lau Caspar Thygesen PhD, Signe Stelling Risom PhD.

a Centre for Cardiac, Vascular, Pulmonary and Infectious Diseases, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen O, Denmark.

b National Institute of Public Health, University of Southern Denmark, Studiestræde 6, 1455 Copenhagen K, Denmark.

c Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Blegdamsvej 3B, 2100 Copenhagen N, Denmark.

d Department of Public Health, Section of Epidemiology, University of Copenhagen, Øster Farimagsgade 5, 1353 Copenhagen K, Denmark.

e Knowledge Centre for Rehabilitation and Palliative Care, University of Southern Denmark and Odense University Hospital, Vestergade 17, 5800 Nyborg, Denmark.

f University College Copenhagen, Institute for Nursing and Nutrition, Tagensvej 86, 2200 Copenhagen N, Denmark.

Corresponding author:
Signe Westh Christensen, MSc in Public Health
Centre for Cardiac, Vascular, Pulmonary and Infectious Diseases, Unit 2151, Rigshospitalet, Copenhagen University Hospital, Denmark.
Blegdamsvej 9, 2100 Copenhagen O
signe.westh.christensen@regionh.dk
+45 23657764
E-mail addresses of authors:

Signe Westh Christensen: signe.westh.christensen@regionh.dk

Selina Kikkenborg Berg: selina@rh.dk

Naja Hulvej Rod: nahuro@sund.ku.dk

Ann Dorthe Olsen Zwisler: Ann.Dorthe.Olsen.Zwisler@rsyd.dk

Lau Caspar Thygesen: lct@sdu.dk

Signe Stelling Risom: signe.stelling.risom@regionh.dk

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ABSTRACT

**Background:** Atrial fibrillation (AF) and atrial flutter (AFL) are cardiac arrhythmias associated with cardiovascular morbidity. Physical activity (PA) can trigger AF and AFL recurrence, but can also improve physical functional capacity in this patient group. Guidelines do not include concrete recommendations regarding PA for this patient group.

**Objective:** To assess the impact of the level of PA on risk of serious adverse events (SAEs) in patients with AF and/or AFL treated with catheter ablation.

**Methods:** A prospective cohort study including 462 patients with AF and/or AFL treated with catheter ablation from the CopenHeart Survey. The International Physical Activity Questionnaire (IPAQ) was used to explore patients’ self-reported level of PA. SAEs were identified in the Danish National Patient Register and the Danish Civil Registration System one year after study onset. Cox regression analysis was carried out to assess the risks of SAE.

**Results:** During the one-year follow-up period, 98 patients (21.8%) experienced at least one SAE. Patients with a moderate-high PA level had a 36% lower risk of experiencing SAEs during the follow-up period, compared to patients in the low PA group, after adjusting for confounders.

**Conclusion:** A moderate-high vs. low level of PA was found to be associated with a lower incidence of SAEs in patients undergoing AF and/or AFL ablation.
**Keywords:** Atrial Fibrillation, Atrial Flutter, Catheter Ablation, Exercise, Patient Readmission, Lifestyle Interventions.

**ABBREVIATIONS LIST**

AF: Atrial Fibrillation

AFL: Atrial Flutter

CRS: Danish Civil Registration System

DNPR: Danish National Patient Register

HR: Hazard Ratio

IPAQ: International Physical Activity Questionnaire

MET: The Metabolic Equivalent of Task

RCT: Randomized Controlled Trial
INTRODUCTION

Clinical research indicates a positive effect of physical activity in patients with atrial fibrillation (AF) in reducing the progression of established AF and increasing physical capacity (1–3). However, some patients experience episodes of AF when being physically active. Therefore, they become reluctant to be physically active (4). Atrial flutter (AFL) differs from AF in terms of mechanism and management but has many similar clinical characteristics (5). Heart diseases represent a major public health concern and have serious implications for individuals and societies (1). Symptoms for patients with AF or AFL include palpitations, fatigue, dyspnea, dizziness, syncope and reduced exercise capacity (6). AF and AFL are associated with an increased risk of stroke and other thromboembolic events (6). Contact with the health care system and hospital admissions caused by the arrhythmias, such as rhythm control treatments, are frequent in patients with AF and/or AFL (6,7). The guidelines report that 10–40% of patients with AF are hospitalized each year and in the United States, AF accounts for more than 450,000 hospitalizations yearly (6,8). AF and AFL have an impact on patients’ daily life, causing poor social and physical functioning and a decreased quality of life (6,9,10).

As a result of an increasing life expectancy, better detection of arrhythmias and improved survival from cardiovascular disease, the burden of AF and/or AFL is further expected to increase in the coming decades (6,11).

Catheter ablation is an invasive rhythm control strategy that is widely used for treating symptomatic patients with AF and/or AFL and the number of patients treated with it has increased rapidly in recent years (6). Ablated patients describe that it is more challenging than expected to return to their everyday lives after AF ablation procedures and report significantly lower quality of life and physical activity levels compared to a population without long-standing disease (9,12).
Today, international guidelines do not include concrete recommendations for physical activity for patients with AF or AFL treated with catheter ablation (6,7,13). A randomized controlled trial (RCT) found a positive effect of cardiac rehabilitation on physical capacity in patients ablated for AF (14). However, few studies have explored whether the intensity of physical activity can make a difference in outcomes like AF/AFL recurrence, quality of life, hospitalization or mortality in patients ablated for AF/AFL. A RCT composed of 76 patients with paroxysmal/persistent AF without ablation treatment, found a difference between the intervention group and control group in the number of hospitalizations with more patients in the low-intensity group admitted due to recurrent AF (n=17), compared to the high-intensity group (n=13) (15). A register-based prospective cohort study also showed lower rates of adverse events in AF patients (all types of AF without ablation treatment) who reported occasional, regular and intense physical activity compared to the group that reported no physical activity. The patients who reported no physical activity had a statistically significant higher, all-cause mortality (16).

The objective of this observational study is to assess if the level of physical activity has an impact on the risk of serious adverse events in patients with AF and/or AFL treated with catheter ablation.

**METHODS**

**STUDY DESIGN:** This prospective cohort study includes data from the CopenHeart Survey, which is a nationwide survey with linkage and follow-up in Danish national registers. The survey was investigating patient-reported outcomes, readmission, and mortality in various patient groups (17–20). The patients who could participate in the survey were those who had been hospitalized for heart valve surgery, endocarditis, implantable cardioverter defibrillator or ablation for either AF and/or AFL (21). In the period between January 1 and June 30 of 2011 all patients who had been hospitalized with these diseases discharged or transferred from one of the five heart centres in
Denmark were invited to participate in the survey. The present study includes patients with AF and/or AFL treated with catheter ablation.

**PARTICIPANTS:** Patients treated with radiofrequency ablation for AF or AFL between January 1, 2011 and June 30, 2011 in one of the five heart centres in Denmark, Danish residents and 18 years or older. Exclusion criteria were research-protected address, emigration or death between the ablation procedure and survey delivery.

**PROCEDURE:** The CopenHeart Survey was mailed out in December 2011 (Figure 1). Eligible patients received the survey by post with a prepaid envelope, and a reminder was sent four weeks later. All adults treated with radiofrequency ablation for AF or AFL were identified from the Danish National Patient Register (DNPR) (22) using the Danish procedure codes: BFFB03 and BFFB04 (23).

**VARIABLES AND MEASURES**

**Physical activity level:** In the CopenHeart Survey the responders’ level of physical activity was assessed by the validated, self-reported International Physical Activity Questionnaire (IPAQ) short form (24,25). Studies find that reliable and valid physical activity data can be collected by IPAQ, that the specificity of the questionnaire is acceptable though its sensitivity is found to be low (24,26). The physical activity level was reported 6–12 months after patients' index ablation procedure (Figure 1). The questionnaire measures the different levels of physical activity during the day, the duration of the activity in hours and minutes, and the number of days the activity was performed in the last seven days. The IPAQ covers four different domains of physical activity: vigorous, moderate, walking and sitting (24). A vigorous level of physical activity comprehends activities that require physical efforts such as strength training and aerobics whereas moderate physical activity implies bicycling at a regular pace or playing tennis.
The responders’ answers in the survey were categorized following the IPAQ protocol (27). However, small adjustments were made to avoid a number of responders with missing values on the IPAQ items. Some of the responders reported physical activity that lasted less than ten minutes on items regarding the IPAQ and according to the IPAQ manual, the answers indicating an activity less than ten minutes (1-7 days a week) should not be included in the respondents total time of physical activity and be removed from further analyses (27). These patients were not removed, as even short periods of physical activity that last less than the recommended 30 minutes per day, could have had a positive effect on the patients’ health (28–31). The IPAQ data were used to create a categorical variable with three different levels of physical activity: low, moderate, and high, as indicated by the IPAQ scoring manual (27). The moderate and high physical activity groups were merged (moderate-high) to obtain statistical power for the analyses. The low category is defined as physical activity not included in the moderate or high category. The moderate category is equivalent to 30 minutes of moderate-intensity physical activity on most days, five or more days of moderate-intensity activity and/or walking of at least 30 min/day or 600 Metabolic Equivalent of Task (MET) min/week and represents the World Health Organization’s (WHO) internationally accepted recommendation of 30 minutes of physical activity-per day. The high category is equivalent to at least one hour or more of moderate-intensity physical activity per day, 7 days of moderate or vigorous physical activity of 3000 MET-min/week or 3 days of vigorous physical activity of 1500 MET-min/week (27).

**Serious adverse events:** To obtain data regarding serious adverse events, the responders were followed in the DNPR and the Danish Civil Registration System (CRS) for a 12-month follow-up period, from December 31, 2011 to December 31, 2012 (22,32). A serious adverse event was defined as any admission registered in the DNPR or a registration of death in the CRS. In this study, a serious adverse event covers all acute or planned admissions, visits to the emergency room as well
as medical and surgical treatments. The study onset was chosen to be from the time where the responders’ level of physical activity was obtained. The fixed time frame comprehends a one-year follow-up period from study onset and 18 to 24 months from the patients’ index admissions for ablation (Figure 1). The DNPR and CRS have national coverage with complete follow-up and DNPR is internationally known to be one of the most comprehensive registers of its kind (22,32). The outcome variable, including admissions and death, was dichotomized for further analyses and the variable distinguished between patients who experienced any serious adverse events and patients who did not, during the one-year follow-up period.

The variables: age, gender, marital status, comorbidities, and procedures were derived from the DNPR and the CRS, while time from ablation procedure to survey response, educational level and smoking were derived from the CopenHeart Survey. The rationale for using these covariates was established and identified using a directed acyclic graph (DAG) (e-Component file 1).

**Ethics approval**

All patients gave consent for participation when replying to the survey, and for using the register follow-up. The CopenHeart Survey was approved by the Institutional Review Board and the Danish Data Protection Agency (2013-41-1643). The study complies with the Declaration of Helsinki.

**STATISTICAL METHODS**

Two-sided p-values were considered statistically significant at a 5% level, with a 95% confidence interval presenting the variation in the estimates. The baseline characteristics for the responders and non-responders as well as the responders’ variables and their level of physical activity were analyzed with a chi-square test. Kaplan–Meier analysis, log-rank test, and Cox proportional hazards regression were used in the analysis of the level of physical activity and serious adverse events. The
assumption of proportional hazards was tested graphically by plotting the logarithm-transformed cumulated hazard function against time and deemed acceptable.

Prior knowledge and the method of DAG were used to identify covariates and potential confounders appropriate for adjustment in the analysis of the association between the exposure and the outcome. The DAG aims to visually illustrate the assumptions behind the relations between the exposure, outcome, and covariates (33). The covariates included in the DAG were selected based on their clinical meaningfulness and by previous literature indicating their possible impact on the association between physical activity and serious adverse events (e-Component file 1). The identified confounders were: age, gender, marital status, educational level, time from ablation to survey, smoking, diet, alcohol consumption, comorbidities (chronic obstructive pulmonary disease, thyroid diseases, cardiovascular diseases) and previous heart surgery (e-Component file 1). The diet and alcohol consumption variables were found to be possible confounders for the association. These variables were not obtained in the survey, which is why it was not possible to adjust for them in the Cox regression model.

Two analytical models were used: first, a model adjusting for age and gender (model 1); and second, a fully adjusted model including age, gender, marital status, educational level, time from ablation to survey, smoking, comorbidities (chronic obstructive pulmonary disease, thyroid diseases, cardiovascular diseases) and previous heart surgery (model 2). Statistical analyses were performed in SPSS for Windows, version 25.0.

RESULTS

A total of 714 patients underwent catheter ablation procedures for AF and/or AFL in the five heart centers in Denmark between January and June 2011. In total, 627 patients were eligible for the study and 462 patients responded to the survey (response rate of 73.7%) (Figure 2).
CHARACTERISTICS OF THE STUDY POPULATION

The patients included were predominately male (73.2%), mean age 61 years, married (75.3%) with comorbidities such as hypertension (32.0%) and ischemic heart disease (18.0%). More responders had previously experienced myocardial infarction and thyroid diseases, whereas the non-responders were more likely to suffer from chronic obstructive pulmonary disease. The results indicate that the responders, in general, were older and suffered from more comorbidities than the non-responders (e-Component file 2).

Out of the 462 responders of the survey, 450 (97.4%) of them answered the IPAQ. Of these 155 (34.4%) reported low physical activity, 189 (42.0%) moderate physical activity and 106 (23.6%) reported high physical activity following the IPAQ manual criteria (27). A higher number of females than males were represented in the low physical activity category (Females: 36.1% (44/122) vs. males: 33.8% (111/328)). This was however not statistically significant.

A statistically significant difference (p=0.05) between the two physical activity categories for the variable educational level was found. A higher proportion of patients with no or a low (<3 years) level of education was represented in the low physical activity category, whereas there were more patients with medium (3-4 years) and high (>4 years) level of education in the moderate-high physical activity group. The time from the patients’ index admissions to answering the survey differed statistically significantly from each other in the two activity groups (p=0.02). Responders categorized in the low physical activity group had a higher burden of comorbidities compared to the responders in the moderate-high physical activity group (Table 1).

PHYSICAL ACTIVITY AND SERIOUS ADVERSE EVENTS
Out of the 450 responders, 98 (21.8%) of them experienced a serious adverse event during the follow-up period. Out of these 98 patients, 92 were admitted to a hospital and six of them died. Four of the dead responders were categorized in the low physical activity group (2.6%) and two in the moderate-high physical activity group (0.7%). In total, 41 patients (26.5%) in the low physical activity group and 57 patients (19.3%) in the moderate-high physical activity group experienced a serious adverse event during the follow-up period. The patients were primarily hospitalized due to AF and/or AFL, cardiovascular diagnoses (e.g. ischemic heart disease), heart failure, DC conversion, ablation, and pacemaker implantation.

The Kaplan-Meier estimates for serious adverse events did not differ statistically in terms of physical activity level (p=0.07). A statistically significant difference was found in the Cox regression Model 2 (Table 2). The hazard ratio (HR) for serious adverse events in the given time period was found to be 36% lower (CI 0.42-0.98) for the individuals in the moderate-high physical activity group, compared to individuals in the low physical activity group after adjusting for age, gender, marital status, educational level, time from ablation to survey, smoking, chronic obstructive pulmonary disease, thyroid diseases, cardiovascular diseases and previous heart surgery (Table 2). The possible effect modification of gender and age was tested in the fully adjusted model and none was found.

**DISCUSSION**

The results of this study indicate that a self-reported moderate or high physical activity level 6-12 months after catheter ablation for AF and/or AFL is associated with a lower risk of serious adverse events when adjusting for potential confounders. However, there is also a risk that the patients’ answers in the survey were influenced by their general health status and that their general health was, therefore, the true predictor for the progression of AF and/or AFL.
We found that a moderate-high physical activity level was associated with lower number of serious adverse events, which is in accordance with previous studies. Skielboe and colleagues reported a higher number of hospitalizations due to recurrent AF in the patient group randomized to low physical activity (89.5%) vs. moderate-high physical activity (68.4%) during the one-year follow-up (15). Furthermore, the results is in accordance with the findings in the observational study by Proietti et al. in which the results are inclined to favor occasional (OR=0.48; p<0.0001), regular (OR=0.40; p<0.0001) and intense (OR=0.29; p=0.011) physical activity over low or no physical activity in terms of serious adverse events in patients with AF (16). However, in these two studies, AF patients were not treated with catheter ablation.

The RCT study by Risom et al. including patients ablated for AF, found a different trend since two patients (2%) in the intervention group with physical activity experienced serious adverse events (AF in relation to exercise and death unrelated to the intervention) and only one patient (1%) in the control group experienced a serious adverse event (unrelated to the intervention) (14). The serious adverse events occurred during the 12-week study period and only one of the events was directly related to the physical activity intervention (14). However, the number of events was so low that no final conclusion can be based on the findings related to serious adverse events.

As the two categories of physical activity (moderate and high) were merged into one category in the analyses it is assumed that the moderate and high level of physical activity have the same effect on patients with AF and/or AFL (34). Nevertheless, this assumption is yet to be confirmed. Working with two groups of physical activity levels that are below or equal to the WHO’s recommendations would make it easier and be more useful in implementing future recommendations in clinical settings in future studies with a larger population.
It has been found that physical inactivity is negatively associated with survival in patients with coronary heart disease, whereas regular physical activity has a preventive effect (35). Additionally, benefits of long-term physical activity are found in patients with heart diseases, like heart failure and coronary heart disease (36). Nevertheless, the preventive effect of physical activity may not be the same among patients with AF and/or AFL treated with catheter ablation and this has yet received little attention in the medical literature.

Knowledge about the possible mechanisms connecting physical activity and patients with AF/AFL is sparse, but several possible explanations exist. It has been found that regular physical activity reduces the risk of developing AF compared to a sedentary lifestyle (37), and moderate regular physical activity has been recommended to prevent the development of AF (1,6). However, high-intensity physical activity has been reported to increase the risk of AF and AFL, especially in athletes (38–41). A recent review from 2019 examining the effects and safety of exercise in patients with AF concludes that this patient group should exercise regularly after evaluation of possible underlying conditions and that physical activity recommendations should be individualized for patients with AF (42).

Current research indicates a J-shaped association between AF and physical activity. This has led to the hypothesis that different mechanisms could explain the reduced risk of AF with moderate physical activity and the increased risk of AF with intensive exercise (34,41). The extent of cardiac adaptations with light and moderate physical activity is not fully known. However, some studies suggest that the lower risk of AF often seen with moderate physical activity could be linked to cardiovascular risk factors (34). Risk factors such as obesity, hypertension and diabetes increase the risk of AF and physical activity can modify these risk factors (1,43). A vigorous physical activity level includes cardiac adaptations such as an increased vagal tone, lower resting heart rate, increased stroke volume, chamber dilation and better systolic and diastolic function (34). These alterations
have been shown to possibly increase the risk of AF (34). Potential mechanisms explaining the increased risk of AF with a vigorous level of physical activity have been proposed, but the exact mechanisms behind are still yet to be clarified (34).

One physiological reason for the fewer incidences in the moderate-high physical activity group could be that physical activity can lower the heart rate during exercise. This can have a reverse effect on the autonomic balance and contribute towards a stronger parasympathetic tone. This could lead to more time in sinus rhythm and less AF and/or AFL (44–47).

The results indicated that patients in the low physical activity group suffered from a higher burden of comorbidities, compared to those in the moderate-high physical activity group. Therefore, it is reasonable to believe that their underlying general health could confound the results. Furthermore, the time from responders’ index admission to answering the survey seems to influence the reported physical activity level. Ablation treatment frequently results in temporary increased arrhythmias and worsened symptoms in the first three to six months after the procedure (7,8). A longer period of time after ablation treatment seems to encourage the level of physical activity patients engage in (12).

However, there is also a risk that the patients’ answers in the survey are influenced by their general health status and their underlying general health, therefore, is the true predictor for the progression of AF and/or AFL.

**STUDY LIMITATIONS**

The patients’ physical activity level was obtained 6-12 months after their ablation procedure through the IPAQ. The patients were not followed from their index ablation admissions but for a fixed period of time, representing a one-year follow-up period. This is a main limitation as ablation treatment can result in temporary increased arrhythmias in the first months after the procedure and
therefore the period where the risk of serious adverse events in relation to arrhythmias is the highest (7,8). Thus, the patients’ levels of physical activity are unknown prior to and during the period right after their ablation procedure. Some patients may have already suffered from serious adverse events due to physical activity before they answered the survey. This may have led to an overestimation of the positive effects of physical activity on the risk of serious adverse events in this study.

This study also lacks statistical power as only 98 responders (21.8%), who answered the IPAQ, experienced a serious adverse event during the one-year follow-up period. The use of self-reported data creates a possibility of misclassification of the patients’ physical activity level. Addressing lifestyle factors such as physical activity is an issue because responders may answer according to what they believe is socially acceptable (48).

Another concern relates to the variables possibly confounding the relation between the level of physical activity and the risk of serious adverse events. The variables possibly confounding the relation were identified using a DAG. It was not possible to adjust for all confounders in the Cox regression model. Information regarding e.g. diet, weight, and alcohol consumption was not collected in the CopenHeart Survey. There is also a risk of residual confounding from other underlying health conditions and comorbidities. Furthermore, the generalizability of the results is limited as catheter ablation patients do not represent well the general population of AF and/or AFL patients. The lack of information regarding AF/AFL recurrence is also a considerable limitation as it is possible that AF/AFL recurrence would affect the level of physical activity that the patients would and could engage in.

Finally, data from national registers can be biased due to wrong or incomplete coding. The specific diagnosis codes can change over time, and specific codes may be used more in some periods due to awareness of a specific disease in society. Since the responders deal with a range of comorbidities simultaneously with AF and/or AFL, it can be challenging to register them with one primary
diagnosis code in the DNPR and therefore misclassification may occur. However, the DNPR is internationally known to be one of the most comprehensive registers of its kind (22). Although the results of this study are in line with the majority of previous research, its design is not solid enough to allow a confirmation of a causal relation between the level of physical activity and the risk of serious adverse events in patients with AF and/or AFL treated with catheter ablation.

One of the key strengths of the study is the use of data from a nationwide cohort with wide inclusion of AF and/or AFL patients treated with catheter ablation, complete follow-up through registers, and also a relatively high response rate (73.7%).

CONCLUSIONS

In conclusion, an association was found between the level of physical activity and the risk of serious adverse events in patients with AF and/or AFL treated with catheter ablation. A moderate-high vs. low level of physical activity was associated with a lower incidence of serious adverse events. Whether this is due to an actual beneficial effect of physical activity or because those who chose to perform physical activity are generally in better health, is yet to be confirmed in future studies.

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We thank all the patients who participated in the CopenHeart Survey. Furthermore, the entire CopenHeart group for distributing the surveys, and for supporting the patients who telephoned to ask questions or add information apart from the answers provided in the survey.

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**DECLARATION OF CONFLICTING INTERESTS**

The authors declare that there is no conflict of interest.
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FIGURE TITLES

Figure 1: Time frame of the study.

Figure 2: Flowchart of the study population.
**Table 1:** Characteristics of the study population according to the level of physical activity level among patients with atrial fibrillation and/or atrial flutter treated with catheter ablation, the CopenHeart Survey 2011 (n=450).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low physical activity level (n=155)</th>
<th>Moderate-high physical activity level (n=295)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Age^a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-49 years (n=44)</td>
<td>17 (11.0)</td>
<td>27 (9.1)</td>
<td></td>
</tr>
<tr>
<td>50-65 years (n=255)</td>
<td>82 (52.9)</td>
<td>173 (58.6)</td>
<td>0.52</td>
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<tr>
<td>66-75 years (n=134)</td>
<td>48 (31.0)</td>
<td>86 (29.2)</td>
<td></td>
</tr>
<tr>
<td>≥76 years (n=17)</td>
<td>8 (5.1)</td>
<td>9 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Gender^a</td>
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<td></td>
</tr>
<tr>
<td>Female (n=122)</td>
<td>44 (28.4)</td>
<td>78 (26.4)</td>
<td>0.66</td>
</tr>
<tr>
<td>Male (n=328)</td>
<td>111 (71.6)</td>
<td>217 (73.6)</td>
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</tr>
<tr>
<td>Marital status^a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married (n=342)</td>
<td>114 (73.5)</td>
<td>228 (77.3)</td>
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</tr>
<tr>
<td>Unmarried (n=108)</td>
<td>41 (26.5)</td>
<td>67 (22.7)</td>
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<tr>
<td>Educational level^b</td>
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<td></td>
<td></td>
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<tr>
<td>No education (n=68)</td>
<td>31 (20.9)</td>
<td>37 (12.7)</td>
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<td>Low level (n=187)</td>
<td>66 (44.6)</td>
<td>121 (41.6)</td>
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<td>86 (29.6)</td>
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<td>High level (n=67)</td>
<td>20 (13.5)</td>
<td>47 (16.2)</td>
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<tr>
<td>Smoking^b</td>
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<td>Non-smoker (n=361)</td>
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<td>244 (84.1)</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>Smoker (n=79)</td>
<td>Atrial arrhythmia type&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Time from ablation to survey&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>-----------------------------</td>
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<td>----------------------------------</td>
<td>----------------------------------------</td>
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<tr>
<td></td>
<td></td>
<td>Persistent (n=26)</td>
<td>6-7 months (n=128)</td>
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<td></td>
<td></td>
<td>10 (6.5)</td>
<td>35 (22.6)</td>
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<td></td>
<td>Paroxysmal (n=128)</td>
<td>8-9 months (n=156)</td>
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<td>38 (24.5)</td>
<td>67 (43.2)</td>
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<tr>
<td></td>
<td></td>
<td>AFL (n=150)</td>
<td>10-12 months (n=166)</td>
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<tr>
<td></td>
<td></td>
<td>53 (34.2)</td>
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</table>

<sup>a</sup>The variables were obtained from the Danish National Patient Register (DNPR) and each corresponds to 450 patients.

<sup>b</sup>The variables: educational level (n=439) and smoking (n= 440) were obtained from the CopenHeart Survey and therefore missing values occurred.
Table 2: Cox regression model for serious adverse events (admissions and mortality) for respondents \((n=98)\).

<table>
<thead>
<tr>
<th>Physical activity level</th>
<th>Crude model HR (95% CI)</th>
<th>Model 1&lt;sup&gt;a&lt;/sup&gt; HR (95% CI)</th>
<th>Model 2&lt;sup&gt;b&lt;/sup&gt; HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Moderate-high</td>
<td>0.69 (0.46-1.03)</td>
<td>0.70 (0.47-1.04)</td>
<td>0.64 (0.42-0.98)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Model 1 is adjusted for two covariates: gender and age.

<sup>b</sup> Model 2 is adjusted for ten covariates: age, gender, marital status, educational level, time from ablation to survey, smoking, chronic obstructive pulmonary disease, thyroid diseases, cardiovascular diseases and previous heart surgery.
A directed acyclic graph (DAG) was used to identify covariates and potential confounders appropriate for adjustment in the analysis for the association between the exposure, level of physical activity, and the outcome, any serious adverse events. The DAG aims to visually illustrate the assumptions behind the relations between the exposure, outcome and covariates (1). In the following section, the variables that could affect the association between the exposure and outcome, are examined.

Age is a risk factor for serious adverse events in patients with atrial fibrillation (AF) and/or atrial flutter (AFL) and it can affect the level of physical activity patients engage in (2). Elderly patients often engage less in physical activity compared to younger individuals (3). A study by Bauman et al. that examined the correlating factors affiliated to physical activity, reported that age and overall physical activity are negatively associated (4).

The level of physical activity may differ between genders with AF and/or AFL. It has been found that overall physical activity and male gender are positively associated (4). The risk of serious adverse events does also differs between genders, as it is reported that the risk of death in women with AF is higher than in men (5–7).

It is assumed that the health awareness of patients with AF and/or AFL can affect the engagement in physical activity. Furthermore, the patients’ health behavior such as smoking or alcohol consumption affect the level of physical activity the individual engage in, as well as the risk of serious adverse events (8,9). In the literature, it is however also found that physical activity can affect individuals’ alcohol consumption (10). In this DAG the arrow is chosen to go from the alcohol variable to the exposure variable because it is more likely that the alcohol consumption in patients with AF and/or AFL affect the level of physical activity and not the other way around. Smoking and physical activity are incongruent behaviors, and it is found that smoking can reduce individuals’ ability to engage in physical activities (11). It has also been found that patients with AF whose body mass index (BMI) is above 25 (overweight or obese), have an increased risk of stroke and death whereas the BMI depends on the level of physical activity the individual engage in (9).

The marital status of the patients may also influence the outcome since marriage has a protective effect on mortality (12). Moreover, it is likely that individuals’ marital status also can affect their engagement in physical activity. Marital status is negatively associated with overall physical activity, where married individuals are more physically active than unmarried individuals (4). It is well known that low educational attainment is a risk factor for serious adverse events. Education is positively associated with overall physical activity because the level of education affects the amount of physical activity that the individual engage in (4,13). It is possible that individuals’ educational level affects the individuals’ health awareness and thereby also their health behavior such as smoking, alcohol consumption and BMI (9).
The patients’ genetics might also affect the risk of serious adverse events. It is found that AF has a strong heritable component (14,15). The amount of time between the patients’ ablation procedure and the survey may also alter the patients’ reported level of physical activity. This elapsed time period also influences the outcome, given that the patients were going to be older, and age increases the risk of serious adverse events in patients with AF and/or AFL (2).

Cardiovascular diseases such as ventricular arrhythmia, ischemic heart disease, heart failure, myocardium infarction and hypertension can affect the incidence of any serious adverse events in patients with AF and/or AFL (8,16). The cardiovascular diseases are associated with AF and AFL, and the exposure of interest can be a risk factor in the development of the diseases (8). However, cardiovascular diseases can also affect the level of physical activity the patient engage in. It is likely that patients with cardiovascular disease engage less in physical activity, compared to healthy individuals. However, in this DAG an arrow is drawn from cardiovascular diseases to the exposure because it is more likely that patients with AF and/AFL also suffer from cardiovascular diseases and therefore do not engage in physical activity than the physical activity has led to the development of the cardiovascular diseases.

In addition to the cardiovascular diseases, patients with AF and/or AFL often have other comorbidities that can affect the incidence of serious adverse events (8). Furthermore, the level of comorbidities also has an impact on the level of physical activity that patients engage in (3). Thyroid diseases and type 2 diabetes are associated with AF and/or AFL and they can affect the exposure and the outcome of interest (8,17). A study from 2017 found that women with diabetes and AF had an increase in hospitalization (18). COPD is also a risk factor for the development of AF and AFL and can affect the exposure as well as the outcome (8,19).

Previous heart surgery can also contribute to the development of AF and/or AFL (8). The structural changes of the cardiac structure that result from surgery scars, can increase the risk of serious adverse events in the patient group (8,20). Furthermore, it is likely that previous heart surgery also can have an impact on the patients’ willingness or ability to engage in physical activity.

The assumptions presented in the previous sections are based on prior knowledge and literature about the causal web underlying the relation between the exposure and outcome. A possible relation between physical activity and serious adverse events in patients with AF and/or AFL are presented in the DAG in the figure below.
AF: Atrial fibrillation, AFL: Atrial flutter, BMI: Body Mass Index, Cardiovascular diseases cover the following diagnosis codes: previous heart failure (DI50), ischemic heart disease DI20-DI25, ventricular arrhythmia (DI49), myocardium infarction (DI21) and hypertension (DI10), COPD: Chronic obstructive pulmonary disease.
References for supplementary file 1


10. Leasure JL, Neighbors C, Henderson CE, Young CM. Exercise and Alcohol Consumption: What We Know, What We Need to Know, and Why it is Important. Front psychiatry. 2015;6:156.


Supplementary file 2

Baseline characteristics for the non-respondent and respondent patients with atrial fibrillation and/or atrial flutter treated with catheter ablation, the CopenHeart Survey 2011 (n=627).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-responders (n=165)</th>
<th>Responders (n=462)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-49 years</td>
<td>26 (15.7)</td>
<td>44 (9.5)</td>
<td>0.18</td>
</tr>
<tr>
<td>50-65 years</td>
<td>89 (53.9)</td>
<td>263 (56.9)</td>
<td></td>
</tr>
<tr>
<td>66-75 years</td>
<td>45 (27.3)</td>
<td>137 (29.7)</td>
<td></td>
</tr>
<tr>
<td>≥76 years</td>
<td>5 (3.1)</td>
<td>18 (3.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>37 (22.4)</td>
<td>124 (26.8)</td>
<td>0.27</td>
</tr>
<tr>
<td>Male</td>
<td>128 (77.6)</td>
<td>338 (73.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>111 (67.3)</td>
<td>348 (75.3)</td>
<td>0.19</td>
</tr>
<tr>
<td>Unmarried</td>
<td>54 (32.7)</td>
<td>114 (24.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Atrial arrhythmia type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent</td>
<td>9 (5.5)</td>
<td>26 (5.6)</td>
<td>0.93</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>38 (23)</td>
<td>132 (28.6)</td>
<td>0.17</td>
</tr>
<tr>
<td>AFL</td>
<td>59 (35.8)</td>
<td>152 (32.9)</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>Time from ablation to survey</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-7 months</td>
<td>58 (35.2)</td>
<td>130 (28.1)</td>
<td></td>
</tr>
<tr>
<td>8-9 months</td>
<td>50 (30.3)</td>
<td>162 (35.1)</td>
<td>0.64</td>
</tr>
<tr>
<td>10-12 months</td>
<td>57 (34.5)</td>
<td>170 (36.8)</td>
<td></td>
</tr>
</tbody>
</table>
## Comorbidities

<table>
<thead>
<tr>
<th>Condition</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes type 2</td>
<td>12 (7.3)</td>
<td>36 (7.8)</td>
<td>0.83</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary</td>
<td>12 (7.3)</td>
<td>16 (3.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Thyroid diseases</td>
<td>1 (0.6 )</td>
<td>19 (4.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Previous heart surgery</td>
<td>5 (3.0 )</td>
<td>14 (3.0)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

## Cardiovascular diseases

<table>
<thead>
<tr>
<th>Condition</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular arrhythmia</td>
<td>3 (1.8 )</td>
<td>3 (0.7 )</td>
<td>0.19</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>29 (17.6)</td>
<td>83 (18.0)</td>
<td>0.91</td>
</tr>
<tr>
<td>Heart failure</td>
<td>24 (14.6)</td>
<td>55 (11.9)</td>
<td>0.38</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3 (1.8 )</td>
<td>27 (5.8 )</td>
<td>0.04</td>
</tr>
<tr>
<td>Hypertension</td>
<td>52 (31.5)</td>
<td>148 (32.0)</td>
<td>0.90</td>
</tr>
</tbody>
</table>