Physical activity modifies the risk of atrial fibrillation in obese individuals: the HUNT3 study

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Abstract

Background
Atrial fibrillation (AF) is the most common heart rhythm disorder and high body mass index (BMI) is a well-established risk factor for AF. The objective was to examine the associations of physical activity (PA) and body mass index (BMI) and risk of atrial fibrillation (AF), and the modifying role of PA on the association between BMI and AF.

Design
Prospective cohort study

Methods
This study followed 43,602 men and women from the HUNT3 study in 2006-2008 until first AF diagnosis or end of follow up in 2015. AF diagnoses were collected from hospital registers and validated by medical doctors. Cox proportional hazard regression analysis was performed to assess the association between PA, BMI and AF.

Results
During a mean follow up of 8.1 years (352,770 person-years), 1459 cases of AF were detected (4.1 events per 1000 person-years). Increasing levels of PA were associated with gradually lower risk of AF ($p$ trend 0.069). Overweight and obesity were associated with an 18% (HR 1.18, 95% CI 1.03-1.35) and 59% (HR 1.59, 95% CI 1.37-1.84) increased risk of AF, respectively. High levels of PA attenuated some of the higher AF risk in obese (HR 1.53, 95% CI 1.03-2.28 in active and 1.96, 95% CI 1.44-2.67 in inactive) compared to normal weight individuals.

Conclusion
Overweight and obesity were associated with increased risk of AF. PA offsets some, but not all AF risk associated with obesity.

Word count: 234

Keywords: Atrial fibrillation, physical activity, body mass index, obesity.
Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with increased morbidity and mortality.\textsuperscript{1} The risk of AF rises exponentially after 70 years of age and the AF prevalence is therefore expected to rise substantially in the years to come due to the aging of the population.\textsuperscript{2}

High body mass index (BMI) is a well-established risk factor for AF\textsuperscript{3}. Considering that overweight and obesity has reached pandemic proportions, with an estimated prevalence of 2.1 billion in 2013\textsuperscript{4}, identifying potential modifiers of the association between high BMI and AF is important.

Physical activity (PA) protects against many cardiovascular risk factors related to overweight and obesity. Moreover, a recent review suggests that moderate levels of PA is also beneficial for AF prevention\textsuperscript{5}. However, it is not clear whether PA modifies the risk of AF associated with high BMI. One study showed that PA attenuated the risk of AF in postmenopausal obese women,\textsuperscript{6} whereas another study found similar results in obese men, but not in obese women.\textsuperscript{7} Furthermore, the literature on PA and incident AF has shown divergent results. While numerous studies have shown that moderate to high levels of PA is associated with lower risk of AF,\textsuperscript{8, 9} some report increased risk of AF with vigorous leisure time PA\textsuperscript{10, 11} or with high levels of occupational PA\textsuperscript{12}. Therefore, it has been suggested that there is a U- or J-shaped association between PA and AF.\textsuperscript{5}

In this study, we investigate the role of PA and BMI on incident AF in men and women from a general population, and further examine whether PA modifies the association between BMI and AF. We hypothesized that PA and BMI are both associated with risk of AF, and that PA attenuates some of the AF risk conferred by overweight and obesity.

Methods

Study population and design

The third wave of the HUNT study (HUNT3), was carried out between October 2006 and June 2008 in Nord-Trøndelag County, Norway. All residents aged 18 years or older (n=93 860) were invited, of whom 50 803 (54.1%) participated. Details about study procedures and methods have previously been described\textsuperscript{13}. We included 43 602 participants after excluding participants with AF diagnosed before baseline (n=1438), underweight (<18.5 kg/m\textsuperscript{2}) (n=303) or missing
baseline data (n=5460). All participants signed a written informed consent before participating in the study. The regional committee for medical and health research ethics approved the study.

Assessment of physical activity

Participants reported their average leisure-time PA by answering three questions concerning frequency, intensity and duration; 1: “How often do you exercise?” with the response alternatives “never” [0], “less than once a week” [0], “once a week” [1], “two to three times per week” [2.5], and “almost every day” [5]. 2: “If you do such exercise as frequently as once or more times a week, how hard do you push yourself?” with the response alternatives “I take it easy, I don’t get out of breath or break a sweat” [1], “I push myself until I’m out of breath and break into a sweat” [2] and “I practically exhaust myself” [3]. Question 3: “How long does each session last?” with the response alternatives “less than 15 min” [0.1], “15-29 min” [0.38], “30 min to 1 h” [0.75], and “more than 1 h” [1.0]. We calculated a PA summary score by multiplying each participant’s response (i.e., numbers in brackets) to the three questions. The PA score have previously been found to be reliable and valid\(^{14}\). Those who responded “never” or “less than once a week” were given a score of 0 and classified as inactive. The remaining participants were classified into tertiles based on the distribution of their score values, where “low PA” had an index score from 0.05 to 1.88, “medium PA” from 1.89 to 3.75 and “high PA” from 3.76 to 15.00.

Clinical and questionnaire-based information

Trained nurses conducted standardized measurements of height, weight, and blood pressure. Height and weight were measured to the nearest centimeter and half kilogram, respectively, with participants wearing light clothes without shoes. BMI was calculated as weight divided by the square of the height (kg/m\(^2\)). Participants were classified as normal weight (18.5-25.9 kg/m\(^2\)), overweight (25-29.9 kg/m\(^2\)) and obese (≥30 kg/m\(^2\)) according to World Health Organization’s standard classification. Blood pressure was measured three times using a Dinamap 845XT (Citikon, Tampa, USA), with the mean values of the second and third measurement used. Obese participants were classified as metabolically unhealthy if they had two or more of the following criteria: nonfasting triglycerides >1.7 mmol/l, nonfasting glucose ≥11.1 mmol/l, high-density lipoprotein <1.03 mmol/l for men and <1.29 mmol/l for women, blood pressure ≥130/85 mm Hg or use of hypertension medication, or self-reported diabetes diagnosis.
From a self-administered questionnaire, we obtained information on current smoking, alcohol use in the past two weeks, self-reported cardiovascular disease (CVD), diabetes, and occupational status according to international standard classification of occupations.

Follow up and ascertainment of AF
We followed the participants from the date of examination until first onset of validated AF or atrial flutter diagnosis or the end of follow-up in November 2015, whichever came first. To identify persons with AF, information on ICD-10 code I48 atrial fibrillation/atrial flutter was retrieved from diagnosis registers at the two hospitals in the county. All AF diagnoses were validated by medical doctors using recorded ECGs according to standard criteria. In cases where the ECG was unavailable, medical records were reviewed and AF was verified when a physician had described the ECG as AF or atrial flutter according standard criteria. A study validating hospital-diagnoses of AF in this population has been published elsewhere.

Statistical analysis
Descriptive data are presented as means ± standard deviations for continuous variables and percentages for categorical variables. We used Cox proportional hazard regression with 95% confidence intervals, using attained age as time scale, to assess the association between physical activity, BMI and AF. We tested the proportional hazard assumptions by using Schoenfeld residuals and found evidence of non-proportionally by sex. Therefore, we used a stratified Cox regression analysis conditioning on sex. We developed sex- and age-adjusted models and multivariable models adjusting for potential confounding factors, including current smoking, alcohol use, self-reported CVD and occupational status. In order to obtain a valid estimate of the causal effect of physical activity and BMI on incident AF, we did not adjust for potential mediators in the multivariable models, such as hypertension and diabetes, because conditioning on intermediate variables within the causal path are likely to give biased estimates.

To study the interaction between physical activity and BMI on AF risk, we performed analysis on the combined association between physical activity and AF across 9 subgroups of BMI and PA with highest PA levels and normal BMI as reference. Further, we did stratified analysis of PA and AF risk by level of BMI. In addition, we stratified obese individuals into metabolically healthy and unhealthy individuals and examined whether the association between PA and AF were different between the groups. Finally, we used a method described by Andersson et al. to calculate relative excess risk due to interaction (also known as interaction contrast ratio)
between physical inactivity and obesity with 95% confidence intervals, with the following formula:\(^8\):

\[
\text{Relative excess risk due to interaction} = \text{RR}_{11} - \text{RR}_{10} - \text{RR}_{01} + 1
\]

Where \(\text{RR}_{11}\) = the relative risk when physical inactivity and obesity is present; \(\text{RR}_{10}\) = the relative risk when physical inactivity is present but obesity is absent; \(\text{RR}_{01}\) = the relative risk when obesity is present but physical inactivity is absent.

**Results**

In total 20,016 (45.9%) men and 23,586 (54.1%) women with a mean age at baseline of 52.1±15.0 and 50.9±15.5 years, respectively, were included. Further baseline characteristics according to sex and physical activity levels are shown in Table 1. During a mean follow up of 8.1 years (352,770 total person-years), 1459 new cases of AF were documented, corresponding to an incidence rate of 4.1 events per 1000 person-years.

Higher levels of PA were associated with a gradually lower risk of AF (Table 2, \(p\)-trend 0.061). After multivariable adjustment, participants with the highest levels of PA had 14% lower risk of AF compared to inactive participants (HR 0.86, 95% CI 0.72-1.02). Additional adjustment for baseline BMI weakened the association.

Hazard ratios for incident AF associated with BMI is shown in Table 3. In the multivariable model, overweight and obesity were associated with an 18% and 59% higher risk of AF, respectively, compared to normal BMI (HR 1.18, 95% CI 1.03-1.35 and 1.59, 95% CI 1.37-1.84). Further adjustment for PA did not influence the estimates.

The combined analysis showed that obesity was associated with increased risk of AF, compared to the normal weight group across all PA categories (Figure 1 and Supplemental Table 1). However, higher levels of PA attenuated the AF risk in the obese group and inactive obese had HR of 1.96 (95% CI 1.44-2.67) compared to active normal weight participants, while the corresponding HR for active obese were 1.53 (95% CI 1.03-2.28). Stratified analyses showed similar results with a 22% lower risk of AF in active versus inactive obese participants (HR 0.78, 95% CI 0.55-1.09) and no apparent association between PA and AF in normal and overweight individuals (\(p\)-trend 0.76 and 0.96, respectively, Supplemental table 2). There were neither any differences in risk reduction in metabolically healthy versus unhealthy obese individuals.
Finally, the relative excess risk due to interaction between physical inactivity and obesity were calculated. Obesity and inactivity alone was associated with 32.2% and 6% higher risk of AF, respectively. When both risk factors were present, i.e., being obese and inactive, there was an additional 25.6% increased risk of AF beyond the effect of these factors alone (RERI 0.256, 95% CI -0.08-0.59).

Discussion
In this prospective cohort study of 43 602 men and women, overweight and obesity were both associated with increased risk of developing AF. Higher PA levels attenuated some of the AF risk in obese individuals, with a lower risk in highly active compared to inactive counterparts. Overall, higher levels of PA were associated with a moderate, gradually lower risk of AF, although not statistically significant.

Our results are in agreement with two previous studies suggesting that PA reduces the risk of AF in obesity. In a study of ~80 000 postmenopausal women, the risk of AF was greater for sedentary obese women than for physical active obese women. Moreover, Huxley et al. found a similar reduction in AF risk with increasing levels of PA in obese men, but not in obese women.

We found no association between PA and AF in the normal and overweight group. Although the normal BMI group showed a trend towards increased risk of AF with low to moderate PA, the low precision of the estimates precludes any firm conclusions. Our results suggest that obese individuals are likely to benefit the most from being physically active concerning AF risk.

The pathophysiology behind obesity and AF risk is likely to be multifactorial, including changes in hemodynamics, cardiac structural remodeling, autonomic dysfunction and inflammation, as well as an increased prevalence of AF risk factors such as hypertension, type 2 diabetes, dyslipidemia and cardiovascular disease. PA may reduce AF occurrence in obesity directly by its ability to reduce these major AF risk factors. Moreover, PA possesses anti-inflammatory properties which may potentially influence AF risk conferred by obesity. Indeed, both systemic inflammation and local inflammation in pericardial fat has been shown to be associated with the development of AF. In a Korean cohort of ~ 390 000 adults, metabolically unhealthy obese individuals had greater risk for AF than their metabolically healthy counterparts. A greater risk reduction would be expected among metabolically unhealthy obese individuals if PA mediates some of its beneficial effects by reducing metabolic
risk factors. However, we found no particular difference in risk reduction associated with PA for metabolically healthy versus unhealthy obese individuals.

Further, PA may protect against AF development by improving cardiorespiratory fitness. Qureshi et al. showed that each metabolic equivalent higher fitness was associated with a 7% reduced risk of AF, and this association was even stronger for obese than for non-obese individuals. In addition, Grundvold et al. reported that unfit men had higher risk of AF with increasing BMI, compared to physically fit men where no such association were found.

The relation between PA and AF is complex and not fully understood. It has consistently been shown that long-term participation in endurance sports is associated with increased prevalence of AF. The pathophysiology behind arrhythmogenesis in healthy athletes with few CVD risk factors is, however, likely to be different from AF development in nonathletic individuals and most evidence points towards a protective effect of moderate to high levels of PA on AF incidence. Our results, although not compelling, indicate that the protective effect of PA on AF risk is more pronounced in obese individuals and that the combination of obesity and an inactive lifestyle confers a higher risk than either risk factor alone.

There are both strengths and limitations in this study that warrant mention. This study cohort consisted of a large population sample including both men and women, and complement the few other studies conducted on this topic. Further, we consider the use of validated diagnosis as a major advantage of this study that ensures high specificity. Still, about one third of AF cases may be asymptomatic and undetected which cause lower sensitivity. However, imperfect specificity is generally a greater threat to validity than imperfect sensitivity in epidemiological studies. The assessment of PA was based on a self-reported questionnaire, which is a limitation. However, the questionnaire used has previously been validated and shown to be reproducible. Lastly, we cannot exclude the possibility of residual confounding in both measured and unmeasured covariates.

**Conclusion**

In a large cohort of men and women, overweight and obesity were strongly associated with increased risk of developing AF. PA attenuated some of the AF risk associated with obesity. Hence, increasing PA levels should be considered as a strategy for prevention of AF in this high-risk group.
Acknowledgement
We would like to thank all the participants and technicians of the HUNT study for their contributions.

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Conflict of interest
None declared

Author contributions
LEG, BMN, JPL and VM contributed to conception or design of the work. LEG and BMN acquired data and did the analyses, and IJ and UW contributed to interpretation. LEG and BMN drafted the manuscript and all authors critically revised it and gave final approval.
References


### Table 1 Baseline characteristics according to sex and physical activity level

<table>
<thead>
<tr>
<th></th>
<th>Men (n=20,016)</th>
<th></th>
<th></th>
<th>Women (n=23,586)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inactive (n=5415)</td>
<td>Low (n=5332)</td>
<td>Medium (n=5116)</td>
<td>High (n=4153)</td>
<td>Inactive (n=3937)</td>
<td>Low (n=7793)</td>
</tr>
<tr>
<td><strong>Age, mean (SD), y</strong></td>
<td>50.5 (14.6)</td>
<td>54.4 (14.6)</td>
<td>52.8 (14.5)</td>
<td>50.4 (16.2)</td>
<td>51.8 (16.6)</td>
<td>53.1 (15.3)</td>
</tr>
<tr>
<td><strong>Height, mean (SD), cm</strong></td>
<td>177.8 (6.6)</td>
<td>177.5 (6.7)</td>
<td>178.4 (6.6)</td>
<td>178.5 (6.6)</td>
<td>164.4 (6.3)</td>
<td>164.4 (6.4)</td>
</tr>
<tr>
<td><strong>Weight, mean (SD), kg</strong></td>
<td>88.8 (14.3)</td>
<td>87.1 (12.9)</td>
<td>86.8 (12.5)</td>
<td>85.3 (12.1)</td>
<td>75.6 (15.6)</td>
<td>74.0 (13.7)</td>
</tr>
<tr>
<td><strong>BMI, mean (SD), kg/m²</strong></td>
<td>28.1 (4.1)</td>
<td>27.6 (3.7)</td>
<td>27.3 (3.5)</td>
<td>26.7 (3.4)</td>
<td>28.0 (5.5)</td>
<td>27.3 (4.8)</td>
</tr>
<tr>
<td><strong>SBP, mean (SD), mmHg</strong></td>
<td>133.0 (16.3)</td>
<td>134.3 (16.9)</td>
<td>133.5 (16.6)</td>
<td>132.6 (16.3)</td>
<td>128.4 (19.6)</td>
<td>128.6 (19.4)</td>
</tr>
<tr>
<td><strong>DBP, mean (SD), mmHg</strong></td>
<td>76.7 (10.9)</td>
<td>77.3 (10.9)</td>
<td>76.6 (10.7)</td>
<td>74.6 (11.2)</td>
<td>70.9 (11.0)</td>
<td>71.1 (10.7)</td>
</tr>
<tr>
<td><strong>Antihypertensive medication, %</strong></td>
<td>19.0</td>
<td>23.8</td>
<td>20.4</td>
<td>17.2</td>
<td>16.1</td>
<td>13.9</td>
</tr>
<tr>
<td><strong>Hypertension</strong>, %</td>
<td>41.0</td>
<td>46.9</td>
<td>41.9</td>
<td>38.0</td>
<td>37.7</td>
<td>37.7</td>
</tr>
<tr>
<td><strong>CVD</strong>, %</td>
<td>10.4</td>
<td>12.7</td>
<td>11.1</td>
<td>9.6</td>
<td>8.6</td>
<td>7.6</td>
</tr>
<tr>
<td><strong>MI</strong>, %</td>
<td>4.0</td>
<td>5.4</td>
<td>4.2</td>
<td>3.8</td>
<td>2.0</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>HF</strong>, %</td>
<td>0.8</td>
<td>1.0</td>
<td>0.7</td>
<td>0.7</td>
<td>0.9</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>AP</strong>, %</td>
<td>4.1</td>
<td>5.0</td>
<td>4.1</td>
<td>3.5</td>
<td>3.1</td>
<td>2.7</td>
</tr>
<tr>
<td><strong>Stroke</strong>, %</td>
<td>2.5</td>
<td>2.9</td>
<td>2.6</td>
<td>2.0</td>
<td>2.6</td>
<td>2.2</td>
</tr>
<tr>
<td><strong>Diabetes, %</strong></td>
<td>4.6</td>
<td>5.1</td>
<td>4.3</td>
<td>4.1</td>
<td>4.6</td>
<td>3.8</td>
</tr>
<tr>
<td><strong>Current smoking, %</strong></td>
<td>33.4</td>
<td>23.3</td>
<td>18.4</td>
<td>16.1</td>
<td>38.5</td>
<td>26.6</td>
</tr>
<tr>
<td><strong>Alcohol use</strong>, %</td>
<td>83.8</td>
<td>85.4</td>
<td>87.0</td>
<td>86.3</td>
<td>64.0</td>
<td>70.8</td>
</tr>
</tbody>
</table>

Data are presented as means (SD) or percentages. BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; mmHg, millimeter of mercury; CVD, cardiovascular disease; MI, myocardial infarction; HF, heart failure; AP, angina pectoris.

a Systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or self-reported use of antihypertensive medication.

b Comprises self-reported MI, HF, stroke, AP and/or other CVD.

c Alcohol use 2 weeks before examination.
Table 2: Hazard ratios of incident atrial fibrillation according to physical activity level

<table>
<thead>
<tr>
<th>PA-I</th>
<th>N</th>
<th>AF events</th>
<th>Person-Years</th>
<th>Model 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Model 2&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Model 3&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive</td>
<td>9352</td>
<td>362</td>
<td>75 556</td>
<td>1.0 (Reference)</td>
<td>1.0 (Reference)</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>Low</td>
<td>13 125</td>
<td>506</td>
<td>106 111</td>
<td>0.90 (0.79-1.04)</td>
<td>0.92 (0.80-1.05)</td>
<td>0.94 (0.82-1.08)</td>
</tr>
<tr>
<td>Medium</td>
<td>12 426</td>
<td>371</td>
<td>100 662</td>
<td>0.87 (0.75-1.0)</td>
<td>0.89 (0.77-1.03)</td>
<td>0.93 (0.81-1.08)</td>
</tr>
<tr>
<td>High</td>
<td>8699</td>
<td>220</td>
<td>70 441</td>
<td>0.82 (0.69-0.97)</td>
<td>0.86 (0.72-1.02)</td>
<td>0.91 (0.77-1.09)</td>
</tr>
</tbody>
</table>

P-trend 0.015  P-trend 0.061  P-trend 0.305

Data are presented as hazard ratios (95% confidence intervals). PA-I indicates physical activity index score; low equals an index score from 0.05 to 1.88, medium from 1.89 to 3.75 and high from 3.76 to 15.00. AF, atrial fibrillation.

<sup>a</sup> Adjusted for sex and age.

<sup>b</sup> Adjusted for sex, age, current smoking, alcohol use, self-reported CVD and occupational status.

<sup>c</sup> Adjusted for model 2 + BMI
<table>
<thead>
<tr>
<th>BMI, kg/m²</th>
<th>N</th>
<th>AF events</th>
<th>Person-Years</th>
<th>Model 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Model 2&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Model 3&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5-24.9</td>
<td>14 323</td>
<td>312</td>
<td>116 308</td>
<td>1.0 (Reference)</td>
<td>1.0 (Reference)</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>25-29.9</td>
<td>19 488</td>
<td>701</td>
<td>157 567</td>
<td>1.19 (1.04-1.36)</td>
<td>1.18 (1.03-1.35)</td>
<td>1.18 (1.03-1.35)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>9791</td>
<td>446</td>
<td>78 895</td>
<td>1.62 (1.40-1.88)</td>
<td>1.59 (1.37-1.84)</td>
<td>1.58 (1.36-1.83)</td>
</tr>
</tbody>
</table>

P-trend <0.001 P-trend <0.001 P-trend <0.001

Data are presented as hazard ratios (95% confidence intervals). BMI indicates body mass index, AF, atrial fibrillation.

<sup>a</sup>Adjusted for sex and age.

<sup>b</sup>Adjusted for sex, age, current smoking, alcohol use, self-reported CVD and occupational status.

<sup>c</sup>Adjusted for model 2 + physical activity
Figure legend Figure 1

Hazard ratios of incident atrial fibrillation according to category of physical activity index score and BMI. High physical activity and normal BMI is used as reference group. Hazard ratios are adjusted for sex, age, current smoking, alcohol use, self-reported CVD and occupational status. P for trend <0.001.

Figure 1

Physical activity, body mass index and risk of atrial fibrillation