The Relationship Between Physical Activity and Heart Failure Risk in Women

Rahman et al: Physical Activity and Heart Failure Risk

Iffat Rahman, PhD1; Andrea Bellavia, MSc1; Alicja Wolk, DrMedSci1

1Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

Correspondence to
Iffat Rahman
Unit of Nutritional Epidemiology
Institute of Environmental Medicine
Karolinska Institutet
Box 210
17177 Stockholm, Sweden
Tel: 0046-8-52487256
Fax: 0046-8-336981
Email: Iffat.Rahman@ki.se

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Abstract

**Background**—Physical activity is a modifiable health-related behaviour shown to be associated with reduced risk of coronary heart disease and stroke. There is some evidence that this could also be the case for heart failure. We investigated if total physical activity, as well as different domains of physical activity, was associated with heart failure risk.

**Methods and Results**—The Swedish Mammography Cohort was utilized in which 27,895 women were followed from 1997 through 2011. First event of heart failure was ascertained through the Swedish National Patient Register and Cause of Death Register. Cox proportional hazards regression analyses were conducted to estimate multivariable-adjusted hazard ratios and 95% confidence intervals. We also analyzed survival percentiles by applying Laplace regression. During an average follow-up time of 13 years (369,207 person-years) we ascertained 2,402 first events of heart failure hospitalizations and deaths. We found that moderate to high levels of total physical activity were associated with a reduced risk of future heart failure. When looking into different domains of physical activity, walking/bicycling more than 20 minutes/day was associated with 29% lower risk of heart failure (95% CI, -36% to -21%), when investigating survival percentiles this could be translated into 18 months longer heart failure free survival.

**Conclusions**—Our study shows that physical activity could protect against heart failure in women. When looking closer into different domains of physical activity, walking or biking at least 20 minutes every day was associated with the largest risk reduction of heart failure.

**Key Words:** epidemiology, physical activity, heart failure
Heart failure (HF) has a large impact on the disease burden in westernized countries, especially among those above 65 years of age. More than 5.8 million people in the United States and 23 million people worldwide suffer from HF. Around 1 in 5 people will be affected by HF at some point in their life. In Sweden, heart failure is a major cause for hospitalization. Moreover, HF patients are at high risk for mortality. It is thus of utmost importance to identify behavioral and lifestyle factors that could prevent HF incidence.

Physical activity (PA) is a modifiable health-related behaviour shown to be associated with reduced risks of coronary heart disease and stroke. There is some evidence that this could also be the case for HF. To the best of our knowledge, no study has investigated the dose-response relationship between total PA and HF modeling the exposure as a continuous variable. Only one previous study investigated the association between different types of PA and risk of heart failure, examining only three domains of PA.

Moreover, all previous studies presented their results in terms of relative risks. It could be valuable to complement current knowledge by adding a time-dimension to the association by evaluating the percentiles of survival. Modeling survival percentiles provides a direct measurement of differences in time (i.e. days, months) by which a certain percentage of the population has suffered from HF according to PA levels, facilitating both interpretation and communication of the results. A novel method to estimate survival percentiles, Laplace regression, has been introduced by Bottai and Zhang.

We therefore sought out to investigate how total PA and five different domains of PA (walking/bicycling, exercise, work occupation, household work, and reading/watching TV) affect the development of HF in a population-based prospective cohort study of women, by analyzing both relative risks and survival percentiles.
Methods

Study population

The study participants belonged to the Swedish Mammography Cohort (SMC), a population-based cohort established between 1987 and 1990. All women residing in Uppsala and Västmanland counties in Sweden (n=90,303) born between 1914 and 1948 were asked to complete an extensive questionnaire concerning diet, anthropometric traits, reproductive factors and lifestyle factors (response rate 74%). A second questionnaire was sent out in 1997 (n=56,030) which comprised of additional questions such as smoking and alcohol consumption, presence of hypertension, and family history of myocardial infarction (response rate 70%). More variables on HF risk factors were collected in the second questionnaire, hence 1997 served as baseline for the current study. In total, 38,984 women completed the questionnaires.

We excluded individuals with prevalent HF, myocardial infarction, or cancer (except non-melanoma skin cancer) (n=2,672) from the baseline population, based on linkage of the cohort to the Swedish National Patient Register and the Swedish Cancer Register. This effort was made since the above mentioned diseases might affect both traditional HF risk factors and HF development. Individuals with missing information on total PA (n=5,179), were also excluded from the study sample. The final study population consisted of 27,895 women.

The questionnaire also included information on participant’s educational attainment, diagnosis of diabetes (which was complemented with information from the diabetes register and the Swedish National Patient Register), weight, height, and waist circumference.

Information on history of stroke and angina was obtained from the Swedish National Patient Register.

Assessment of physical activity

Participants reported their level of activity at work, home/housework, walking/bicycling, and
exercise in the year before study enrollment. Questions regarding inactivity (watching television or reading) and hours per day of sleeping and sitting or lying down were also asked for. Each type of physical activity was assigned an intensity score defined as metabolic equivalents (MET) hours/day, the intensity score was based on the compendium of physical activities. The mean MET values assigned for the different types of physical activities were as follows: walking/bicycling ~ 3.6 MET; exercise ~ 5.0 MET; work occupation ~ 1.3 MET for mostly sitting down to 3.9 for heavy manual work; home/household work ~ 2.5 MET; watching TV/reading ~ 1.2 MET; sleep ~ 0.9 MET. Total daily physical activity score (TPA) was then estimated by multiplying the intensity score of each type of physical activity for its reported duration and then adding all specific activities together. Work occupation contributed to 50% of the TPA, the rest of the specific types of activities contributed with 10% each to TPA. The questions on TPA during the past year in SMC have been validated by a previous study on a sub-population of SMC. They found that the correlation comparing self-reported TPA with accelerometers and records were 0.38 (95% CI, 0.22–0.54) and 0.64 (95% CI, 0.45–0.83), respectively, which suggest that TPA was measured with reasonable validity.

HF ascertainment

Dates of the first registered incident HF hospitalization as well as dates of deaths from HF were ascertained from September 15, 1997 to December 31, 2011 through linkage of the cohort to the Swedish National Patient Register and the Causes of Death Register. The Swedish National Patient Register represents the inpatient register, which includes all hospital admissions that entailed at least one overnight stay, and the outpatient register which includes diagnoses registered during non-private specialized care. To identify incident HF events we used International Classification of Diseases-10 codes I50 (HF) and I11.0 (hypertensive heart disease with HF). We included the first HF event recorded in the registers listed as either the primary or secondary diagnosis of hospitalizations or deaths.
The study has been approved by the Regional Ethical Review Board at Karolinska Institutet.

Statistical analyses

Data handling and generation of descriptive statistics were performed in SAS (version 9.2; SAS Institute, Inc, Cary, NC). Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using Cox proportional hazards regression models with days since beginning of follow-up time as the underlying time scale. Start of follow-up was 15 September, 1997. Follow-up was censored at the date of first event of HF, death or December 31, 2011, whichever occurred first.

We first evaluated the effect of physical activity on HF incidence by considering quartiles of TPA with the lowest quartile as the reference group. Potential interactions between TPA quartiles and the other covariates in the model were also investigated. Subsequently, TPA was modeled as a continuous variable by means of restricted cubic splines with three knots of the distribution (at 37, 42, and 49 MET hours/day) using the median level of 42 MET hours/day as the reference value. Linearity of the dose-response was examined by testing the null hypothesis that the coefficient of the second spline was equal to zero. We then graphed the dose-response association between TPA and HF incidence.

Additionally, the exposure variables of interest were different types of physical activity, namely walking/bicycling, exercise, work occupation, home/household work, and leisure-time inactivity. To examine if the results were influenced by reverse causality, we conducted a sensitivity analysis in which study participants who developed HF during the three first years of follow-up time were excluded. We also conducted a sensitivity analysis where we excluded all study participants diagnosed with stroke or angina at baseline.

Secondly, Laplace regression was conducted. Given a percentile of survival, this method estimates differences in HF free survival according to levels of the exposure and adjusts for potential confounders. In the study cohort, 8.5% of the participants experienced an HF
event during the follow-up period. We therefore focused on the 8th percentile and estimated multivariable-adjusted differences in survival between women who were active and inactive on the different domains of PA (walking/bicycling, exercise, work occupation, household work, and reading/watching TV). The measure of association was defined as 8th percentile difference (PD) i.e. the difference in time by which 8% of the population experienced an HF event during the follow-up time. To evaluate if the results were influenced by the choice of the 8th percentile, we also conducted a sensitivity analysis, focusing on 5th survival PDs. Covariates included in the multivariable-adjusted model were; educational attainment (primary school, high school, university), smoking (never, past, current [<10, >10 cigarettes/d]), alcohol consumption (never/past/current [<5, >5 g/d]), family history of myocardial infarction, history of stroke, history of angina, hypertension, diabetes, body mass index (BMI) (<18.5, 18.5-24.9, 25-29.9, >30 kg/m²), and waist circumference (<80, 80-88, >88 cm). The proportional hazards assumption was confirmed by investigating Schoenfeld’s residuals. STATA software version 12.1 (StataCorp) was used to calculate Cox proportional hazards regression and Laplace regression.

Results

During an average follow-up time of 13 years (369,207 person-years), we ascertained a total of 2,402 HF events including 2,124 first events of HF hospitalizations and 278 HF deaths. The average age at study entry was 61.1 years (the age range was 47.7 - 83.7). Baseline characteristics by quartiles of TPA are provided in Table 1. Women who were at the bottom quartile of TPA in the previous year had higher prevalence of stroke and angina compared to women who had been more physically active. Highly educated women had a lower frequency of an active lifestyle.
We first evaluated how different quartiles of TPA are associated with HF development. The results from the analyses are shown in Table 2. Comparing to women in the bottom quartile of TPA, women in the second quartile had a lower risk of HF, in the multivariable-adjusted model (HR=0.88; 95% CI, 0.79-0.98). The third and the fourth quartiles of TPA were significantly associated with a HF risk reduction of similar magnitude (HR=0.76, 95% CI; 0.68-0.85 for the third quartile) and (HR=0.73, 95% CI; 0.65-0.82 for the fourth quartile) in the multivariable-adjusted model. No statistically significant interaction was found between TPA quartiles and any of the covariates in the model (all p>0.05).

When modeling TPA as a continuous exposure variable using restricted cubic splines we found evidence for non-linearity from the restricted cubic spline analysis (p=0.009). There was a steep negative association between TPA and incident HF for women who had the lowest level of physical activity (30 MET hours/day) (HR=1.70; 95% CI, 1.42-2.07). Above the median level of TPA (42 MET hours/day), there remained almost no association between TPA and HF (Figure).

When looking into the different domains of activities that constituted TPA we found that only certain types of PA were associated with a reduced risk of HF (Table 3). Walking/bicycling at least 20 minutes/day was associated with lower risk of HF with an HR of 0.71 (95% CI, 0.64 to 0.80). Furthermore, exercising more than 1 hour per week and engaging in household work more than 1 hour per day were associated with a lower HF risk with an HR of 0.83 (95% CI, 0.75 to 0.92), and an HR of 0.82 (95% CI, 0.70 to 0.97), respectively, in the multivariable-adjusted model. An active work occupation was associated with lower risk of HF with an HR of 0.82 compared to more sedentary work occupations, however, after adjusting for the other types of PA the association was no longer significant.

The sensitivity analysis where we excluded study participants that developed HF in the three first years of follow-up (N=204) to account for potential reverse causality showed results
which were very similar to the main analysis. For example, the HR for walking/bicycling changed from 0.71 in the main analysis to 0.73 (95% CI, 0.65 to 0.82) in the sensitivity analysis.

In the analysis where we excluded study participants with history of stroke (N=326) or angina (N=486) at baseline in order to further restrict influences from those diseases the results were very similar to the main analysis (the largest effect was found for walking/bicycling, HR=0.68), with the exception that household work was no longer significantly associated with HF risk (HR=0.85, 95% CI, 0.71-1.02).

Table 4 shows the absolute difference in days of HF free survival between groups of moderate to high versus low levels of PA obtained from the Laplace regression. After adjustment for potential confounders, high levels of walking/bicycling and exercise were significantly associated with longer HF free survival compared to low levels of the corresponding PA types. The largest difference was detected for walking/bicycling. Based on the first 8% of participants who developed HF, women who engaged in walking or bicycling less than 20 minutes per day suffered from HF event 18 months earlier than women who walked or biked at least 20 minutes per day (PD=547 days, 95% CI, 288-805).

The sensitivity analysis in which we measured the association at 5th PD showed negligible differences compared to the main Laplace analysis, with walking/bicycling showing the biggest PD followed by exercise (data not shown).

**Discussion**

We found that moderate to high levels of TPA were associated with a reduced risk of future HF. When examining which domains of PA were associated with a reduced risk of HF, we found walking/bicycling more than 20 minutes a day, exercising more than 1 hour per week and engaging in more than 1 hour household work per day to be inversely associated with HF.
development. Each of these types of activity reduced HF risk statistically significantly and independently of each other. Active daily walking or bicycling had the largest impact, reducing the risk of HF with 29%. Further, women with a low score on certain domains of physical activity, particularly on walking/bicycling, developed HF 18 months earlier than women who were more active.

Our findings on the association between TPA and HF risk are in line with previous studies\textsuperscript{11, 13, 14}. However we noticed a non-linear trend; after moderate levels of TPA there was no further association with a reduced risk of HF. None of the above mentioned studies evaluated the dose response association with flexible models such as splines. Our study is in line with a previous meta-analysis investigating the dose-response relationship between TPA and coronary heart disease which detected a risk reduction with moderate levels of TPA but only a modest further risk reduction at higher levels of TPA\textsuperscript{6}.

A former study investigating the effect of different types of PA on HF risk found occupational activity and leisure-time physical activity to be associated with HF\textsuperscript{12}. We observed the largest effect from walking/bicycling, followed by exercise and household work. Our findings are to some extent similar since walking and bicycling was part of the PA domain of “leisure-time activity” in that study.

The cardio-protective biological mechanisms exerted by PA are poorly understood. Nevertheless, some explanations have been proposed. For instance, it has been suggested that the beneficial effects of PA on CVD risk is mediated by reductions in mainly inflammatory and hemostatic biomarkers, and to some extent blood pressure, lipids, and BMI\textsuperscript{20}. Moreover in a study by deFilippi et al it was shown that moderate levels of PA was associated with lower levels of the CVD biomarkers sensitive troponin T and N-terminal pro-B-type natriuretic peptide and subsequently also lower risk of HF\textsuperscript{21}. 


Strengths of our study include the large size of the population-based cohort. The study had a long follow-up time and we were able to identify a large number of incident HF events. The outcome definition was based on clinical diagnoses and not self-reports. A validation study on primary HF diagnoses in the Swedish National Patient Register has shown that the validity for a primary HF diagnosis is high (95%) 22. To avoid misclassification of HF outcome, we also included HF diagnoses at the second position where the validity has been shown to be 76%. The validity for HF diagnosis in positions three to six has been reported to be 63% 22. We therefore limited our HF definition to include diagnoses only at the first and second positions. Furthermore, we could not capture outpatient cases who were admitted to a private specialized health care setting. Misclassification of HF outcome could have afflicted this study possibly contributing to attenuation of the associations with HF risk.

PA was examined according to MET hours per day of TPA, considering various domains of PA. It is a well validated construct of PA intensity which takes into account the multidimensional nature of PA18. In addition, we also modeled the different domains of TPA separately (e.g. walking, occupational activity, leisure-time inactivity). These estimates are more accessible and can easily be conveyed to society for public health improvements.

In addition to presenting the results in hazard ratios, we complemented our analyses using Laplace regression to provide an absolute estimate of differences in HF free survival according to levels of PA. Laplace regression models the percentiles of survival expressing results directly in terms of time differences across levels of the exposure (i.e. years, months, days) 16. The estimates of Laplace regression are not dependent on the baseline risk and on the length of follow-up. Moreover, by using this method we were able to present the results in an intuitive way that is easily accessible to the general public.

A potential limitation to this study is that the measurements of PA were based on self-reports of the study participants’ habitual PA level in the past year, hence a certain degree of
misclassification of PA cannot be ruled out. This could particularly have been a problem for TPA since a previous validation study on a sub-sample of SMC showed that the correlation between self-reported TPA and PA measured with accelerometers was 0.38\(^1\). Moreover, TPA was self-reported for a one year period prior to baseline, therefore it is possible that TPA changed during the follow-up time. Due to the prospective design of the SMC we do not expect that a potential misclassification is dependent on the outcome, hence a potential misclassification of TPA could have led to an underestimation of the association with HF risk.

It should be emphasized that we cannot infer on causality based on our study results. The association between PA and risk of future HF could for instance be due to unmeasured confounders or residual confounding both at baseline and during follow-up time. For example, we could not identify study participants with sub-clinical diabetes at baseline since we did not administer an oral glucose tolerance test, therefore sub-clinical diabetes could potentially have confounded the associations between PA and HF risk.

There may also be some concerns regarding the generalizability of this study. We investigated the association between PA and HF in a population consisting of middle-aged and elderly Caucasian women, thus we might not be able to extrapolate our findings to other ethnicities, younger age groups, or men.

**Conclusions**

Our study shows that moderate to high levels of PA could protect against HF in women. When looking closer into different domains of PA, walking or biking at least 20 minutes every day was associated with the largest risk reduction of HF. Public awareness of the beneficial effect of physical activity could potentially contribute to reducing the HF burden in society. Further investigations are therefore warranted.
Sources of Funding

This work was supported by the Swedish Research Council Committee for Medicine and the Swedish Research Council Committee for infrastructure.

Disclosures

None.

References


Table 1. Age-standardized descriptive statistics of 27,895 women from the Swedish Mammography Cohort

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Quartiles of total physical activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total physical activity, MET hours/day</td>
<td>&lt;39</td>
</tr>
<tr>
<td>No of participants</td>
<td>7171</td>
</tr>
<tr>
<td>Age at baseline, years</td>
<td>61.0</td>
</tr>
<tr>
<td>University education (%)</td>
<td>23.9</td>
</tr>
<tr>
<td>Ever smokers (%)</td>
<td>50.3</td>
</tr>
<tr>
<td>Current drinkers (%)</td>
<td>86.4</td>
</tr>
<tr>
<td>History of stroke (%)</td>
<td>1.8</td>
</tr>
<tr>
<td>History of angina (%)</td>
<td>2.5</td>
</tr>
<tr>
<td>Family history of MI (%)</td>
<td>30.6</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>22.1</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>3.9</td>
</tr>
<tr>
<td>BMI&gt;30 kg/m2 (%)</td>
<td>34.1</td>
</tr>
<tr>
<td>HF cases (%)</td>
<td>10.3</td>
</tr>
</tbody>
</table>

The descriptive statistics are expressed as means unless otherwise stated.
Table 2. Association between quartiles of TPA and risk of HF

<table>
<thead>
<tr>
<th>Model</th>
<th>Quartiles of total physical activity (MET hours/day)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;39</td>
<td>39-42</td>
<td>43-46</td>
<td>&gt;46</td>
</tr>
<tr>
<td>Age-adjusted HR (95% CI)</td>
<td>1.0 (ref)</td>
<td>0.80 (0.71-0.89)</td>
<td>0.67 (0.61-0.75)</td>
<td>0.64 (0.58-0.72)</td>
</tr>
<tr>
<td>Multivariable-adjusted HR (95% CI)'</td>
<td>1.0 (ref)</td>
<td>0.88 (0.79-0.98)</td>
<td>0.76 (0.68-0.85)</td>
<td>0.73 (0.65-0.82)</td>
</tr>
</tbody>
</table>

*Adjusted for educational attainment (primary school, high school, university), smoking (never, past, current [≤10, >10 cigarettes/d]), alcohol consumption (never/past/current [<5, ≥5 g/d]), family history of myocardial infarction, history of stroke, history of angina, hypertension, diabetes, BMI (<18.5, 18.5-24.9, 25-29.9, ≥30kg/m^2), and waist circumference (<80, 80-88, >88 cm).
Table 3. Association between different types of physical activity and risk of HF

<table>
<thead>
<tr>
<th>Type of physical activity</th>
<th>Hazard ratio (95% CI)*</th>
<th>Hazard ratio (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walking/bicycling</td>
<td>0.65 (0.59-0.73)</td>
<td>0.71 (0.64-0.80)</td>
</tr>
<tr>
<td>≥20 minutes/day versus &lt;20 minutes/ day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td>0.73 (0.67-0.80)</td>
<td>0.83 (0.75-0.92)</td>
</tr>
<tr>
<td>≥1 h/week versus &lt; 1 h/week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work occupation</td>
<td>0.82 (0.74-0.90)</td>
<td>0.93 (0.83-1.03)</td>
</tr>
<tr>
<td>Active versus mostly sitting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home/household work</td>
<td>0.73 (0.62-0.85)</td>
<td>0.82 (0.70-0.97)</td>
</tr>
<tr>
<td>≥1 h/day versus &lt; 1 h/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactivity (Watching TV/reading)</td>
<td>1.00 (0.83-1.19)</td>
<td>0.99 (0.83-1.18)</td>
</tr>
<tr>
<td>&lt;3 h/day versus ≥ 3 h/day</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for educational attainment (primary school, high school, university), smoking (never, past, current [≤10, >10 cigarettes/d]), alcohol consumption (never/past/current [<5, ≥5 g/d]), family history of myocardial infarction, history of stroke, history of angina, hypertension, diabetes, BMI (<18.5, 18.5-24.9, 25-29.9, ≥30kg/m²), and waist circumference (<80, 80-88, >88 cm).

† Additionally adjusted for all types of physical activity.
Table 4. 8th HF free survival percentile differences (PD) in days by specific types of physical activity

<table>
<thead>
<tr>
<th>Type of physical activity</th>
<th>PD (95% CI), days *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walking/bicycling ≥20 minutes/day versus &lt;20 minutes/day</td>
<td>547 (288-805)</td>
</tr>
<tr>
<td>Exercise ≥1 h/week versus &lt; 1 h/week</td>
<td>349 (192-506)</td>
</tr>
<tr>
<td>Work occupation Active versus mostly sitting</td>
<td>-7 (-161-148)</td>
</tr>
<tr>
<td>Home/household work ≥1 h/day versus &lt; 1 h/day</td>
<td>231 (-102-564)</td>
</tr>
<tr>
<td>Inactivity (Watching TV/reading) &lt;3 h/day versus ≥3 h/day</td>
<td>-109 (-321-102)</td>
</tr>
</tbody>
</table>

* Adjusted for educational attainment (primary school, high school, university), smoking (never, past, current [≤10, >10 cigarettes/d]), alcohol consumption (never/past/current [<5, ≥5 g/d]), family history of myocardial infarction, history of stroke, history of angina, hypertension, diabetes, BMI (<18.5, 18.5-24.9, 25-29.9, ≥30kg/m²), and waist circumference (<80, 80-88, >88 cm). All types of physical activity were mutually adjusted for.
Figure Legend

Figure. Multivariable-adjusted HRs for incident HF depending on daily total physical activity.

HRs were adjusted for educational attainment (primary school, high school, university), smoking (never, past, current [≤10, >10 cigarettes/d]), alcohol consumption (never/past/current [<5, ≥5 g/dl]), family history of myocardial infarction, history of stroke, history of angina, hypertension, diabetes, BMI (<18.5, 18.5-24.9, 25-29.9, ≥30kg/m²), and waist circumference (<80, 80-88, >88 cm). Solid curve represents the restricted cubic spline and dashed-dotted line represents the 95% CI.