Relationship Between Physical Activity and Heart Failure Risk in Women

Iffat Rahman, PhD; Andrea Bellavia, MSc; Alicja Wolk, DrMedSci

**Background**—Physical activity is a modifiable health-related behavior 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 whether 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 used in which 27,895 women were followed up from 1997 to 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 >20 minutes/d was associated with 29% lower risk of heart failure (95% confidence interval, −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 ≥20 minutes every day was associated with the largest risk reduction of heart failure. (*Circ Heart Fail*. 2014;7:877-881.)

**Key Words:** epidemiology ■ heart failure

Heart failure (HF) has a large effect on the disease burden in westernized countries, especially among those aged >65 years. More than 5.8 million people in the United States and 23 million people worldwide have 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, patients with HF are at high risk for mortality. It is thus of utmost importance to identify behavioral and lifestyle factors that could prevent HF incidence.

**Clinical Perspective on p 881**

Physical activity (PA) is a modifiable health-related behavior 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 1 previous study investigated the association between different types of PA and risk of heart failure, examining only 3 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 provide a direct measurement of differences in time (ie, days and months) by which a certain percentage of the population has 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.

Therefore, we sought out to investigate how total PA and 5 different domains of PA (walking/bicycling, exercise, work occupation, household work, and reading/watching television) 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 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.

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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 nonmelanoma skin cancer; n=2,672) from the baseline population, based on linkage to the Swedish National Patient Register and the Swedish Cancer Register. This effort was made because the above-mentioned diseases might affect both traditional HF risk factors and HF development. Individuals with missing information on total PA (n=5179) 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 mellitus (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 PA

Participants reported their level of activity at work, home/housework, walking/bicycling, and exercise in the year before study enrollment. Questions on inactivity (watching television or reading) and hours per day of sleeping and sitting or lying down were also asked for. Each type of PA was assigned an intensity score defined as metabolic equivalents (MET) hours/d, the intensity score was based on the compendium of physical activities.18 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 television/reading ≈1.2 MET; sleep ≈0.9 MET. Total daily PA score (TPA) was then estimated by multiplying the intensity score of each type of PA 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 subpopulation of SMC. They found that the correlation comparing self-reported TPA with accelerometers and records was 0.38 (95% confidence interval [CI], 0.22–0.54) and 0.64 (95% CI, 0.45–0.83), respectively, which suggest that TPA was measured with reasonable validity.19

HF Ascertainment

Dates of the first registered incident HF hospitalization and 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 entitled ≥1 overnight stay, and the outpatient register that includes diagnoses registered during nonprivate specialized care. To identify incident HF events we used International Classification of Diseases-Tenth Revision codes 150 (HF) and 111.0 (hypertensive heart disease with HF). We included the first HF event recorded in the registers listed as either the primary or the 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% 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 September 15, 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 PA 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 3 knots of the distribution (at 37, 42, and 49 MET hours/d) using the median level of 42 MET hours/d 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.

In addition, the exposure variables of interest were different types of PA, namely walking/bicycling, exercise, work occupation, home/household work, and leisure-time inactivity. To examine whether the results were influenced by reverse causality, we conducted a sensitivity analysis in which study participants who developed HF during the first 3 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.

Second, 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.20 In the study cohort, 8.5% of the participants experienced an HF event during the follow-up period. Therefore, we focused on the eighth 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 television). The measure of association was defined as eighth percentile difference (PD; ie, the difference in time by which 8% of the population experienced an HF event during the follow-up time). To evaluate whether the results were influenced by the choice of the eighth percentile, we also conducted a sensitivity analysis, focusing on fifth survival PDs.

Covariates included in the multivariable-adjusted model were education, attained highest school, age, body mass index, waist circumference, smoking (never, past, and current [≤10 and >10 cigarettes/d]), alcohol consumption (never/past/current [<5 and ≥5 g/d]), family history of myocardial infarction, history of stroke, history of angina, hypertension, diabetes mellitus, body mass index (<18.5, 18.5–24.9, 25–29.9, and ≥30 kg/m²), and waist circumference (<80, 80–88, and >88 cm). The proportional hazards assumption were 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 2402 HF events, including 2124 first events of HF hospitalizations and 278 HF deaths. The average age at study entry was 61.1 years (the age range, 47.7–83.7 years). 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 with 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. Compared with 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 PA (30 MET...
Table 1. Age-Standardized Descriptive Statistics of 27895 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 h/d</td>
<td>&lt;39  39–42  43–46  &gt;46</td>
</tr>
<tr>
<td>No. of participants</td>
<td>7171  6439  7519  6766</td>
</tr>
<tr>
<td>Age at baseline, y</td>
<td>61.0  61.1  61.5  61.5</td>
</tr>
<tr>
<td>University education, %</td>
<td>23.9  25.2  20.5  10.5</td>
</tr>
<tr>
<td>Ever smokers, %</td>
<td>50.3  45.7  43.6  43.7</td>
</tr>
<tr>
<td>Current drinkers, %</td>
<td>86.4  85.7  84.2  81.5</td>
</tr>
<tr>
<td>History of stroke, %</td>
<td>1.8   1.0   1.0   0.5</td>
</tr>
<tr>
<td>History of angina, %</td>
<td>2.5   1.6   1.7   1.4</td>
</tr>
<tr>
<td>Family history of MI, %</td>
<td>30.6  30.0  30.6  33.3</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>22.1  20.4  19.4  19.2</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>4.0   3.2   3.0   3.1</td>
</tr>
<tr>
<td>BMI (kg/m²) &gt;18.5 &lt;25</td>
<td>34.1  31.6  32.4  32.9</td>
</tr>
<tr>
<td>MET, hazard ratio</td>
<td>1.00  0.91  0.84  0.76</td>
</tr>
</tbody>
</table>

The descriptive statistics are expressed as means unless otherwise stated. BMI indicates body mass index; HF, heart failure; MET, metabolic equivalents; and MI, myocardial infarction.

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hours/d; HR, 1.70; 95% CI, 1.42–2.07). Above the median level of TPA (42 MET hours/d), 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 for ≥20 minutes/d was associated with lower risk of HF with an HR of 0.71 (95% CI, 0.64–0.80). Furthermore, exercising ≥1 hour/wk and engaging in household work for >1 hour/d were associated with a lower HF risk with an HR of 0.82 (95% CI, 0.70–0.97), respectively, in the multivariable-adjusted model. An active work occupation was associated with lower risk of HF with an HR of 0.82 when compared with 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 who developed HF in the first 3 years of follow-up (n=204) to account for potential reverse causality showed results, which were 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, 0.65–0.82) in the sensitivity analysis.

In the analysis where we excluded study participants with history of stroke (n=326) or angina (n=486) at baseline to restrict influences from those diseases further, the results were 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 3 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

Table 2. Association Between Quartiles of Total Daily Physical Activity Score and Risk of Heart Failure

<table>
<thead>
<tr>
<th>Model</th>
<th>Quartiles of Total Physical Activity (MET h/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>&lt;39  39–42  43–46  &gt;46</td>
</tr>
<tr>
<td>Age-adjusted HR (95% CI)</td>
<td>0.65 (0.59–0.73)  0.71 (0.64–0.80)</td>
</tr>
<tr>
<td>Multivariable-adjusted HR (95% CI)</td>
<td>0.65 (0.59–0.73)  0.71 (0.64–0.80)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HR, hazard ratio; and MET, metabolic equivalents.

*Adjusted for educational attainment (primary school, high school, and university), smoking (never, past, and current ≤10 and >10 cigarettes/dl), alcohol consumption (never/past/current ≤5 and >5 g/dl), family history of myocardial infarction, history of stroke, history of angina, hypertension, diabetes mellitus, body mass index (<18.5, 18.5–24.9, 25–29.9, and ≥30 kg/m²), and waist circumference (<80, 80–88, and >88 cm).
survival when compared with low levels of the corresponding PA types. The largest difference was detected for walking/bicycling. On the basis of the first 8% of participants who developed HF, women who engaged in walking or bicycling for <20 minutes/d had HF event 18 months earlier than women who walked or biked for ≥20 minutes/d (PD=547 days; 95% CI, 288–805).

The sensitivity analysis in which we measured the association at fifth PD showed negligible differences when compared with 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 for >20 minutes a day, exercising for >1 hour/wk, and engaging in >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 effect, reducing the risk of HF with 29%. Furthermore, women with a low score on certain domains of PA, 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. However, we noticed a nonlinear 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.

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

The cardioprotective 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 cardiovascular disease risk are mediated by reductions in mainly inflammatory and hematostatic biomarkers, and to some extent blood pressure, lipids, and body mass index. Moreover in a study by deFilippi et al, it was shown that moderate levels of PA were associated with lower levels of the cardiovascular disease biomarker-sensitive troponin T and N-terminal pro-B-type natriuretic peptide and subsequently also lower risk of HF.

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%). 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 3 to 6 has been reported to be 63%. Therefore, we 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 healthcare 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 PA. In addition, we also modeled the different domains of TPA separately (eg, walking, occupational activity, and 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 HRs, 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 (ie, years, months, and days). 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 because a previous validation study on a subsample of SMC showed that the correlation between self-reported TPA and PA measured with accelerometers was 0.38. Moreover, TPA was self-reported for a 1-year period before baseline; therefore, it is possible that TPA changed during the follow-up time. Because of 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 be, for instance, because of unmeasured confounders or residual confounding both at baseline
and during follow-up time. For example, we could not identify study participants with subclinical diabetes mellitus at baseline because we did not administer an oral glucose tolerance test; therefore, subclinical diabetes mellitus could potentially have confounded the associations between PA and HF risk. There may also be some concerns on the generalizability of this study. We investigated the association between PA and HF in a population consisting of middle-aged and elderly white 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 for ≥20 minutes every day was associated with the largest risk reduction of HF. Public awareness of the beneficial effect of PA could potentially contribute to reducing the HF burden in society. Additional investigations are, therefore, warranted.

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Disclosures
None.

References
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