PHYSICAL ACTIVITY AND HEART FAILURE INCIDENCE IN POSTMENOPAUSAL WOMEN

Results from the Women’s Health Initiative

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• Heart Failure (HF) total direct medical costs $30B in 2012 … $70B projected by 2030

• HF disproportionately affects older adults … 1 in 5 lifetime risk at age 60
  ➢ ≈80% of cases occur after age 65.

• HF with preserved (HFpEF) and reduced (HFrEF) ejection fraction:
  ➢ Different etiologies … different contributions of major risk factors
  ➢ HFrEF worse prognosis
  ➢ HFpEF more common in elderly, women, minorities … fewer therapy options
### Table 2. Crude, Age-Adjusted, and Age-Specific Rates of Hospitalized Heart Failure by Race/Ethnicity (per 100,000 Person-Years)

<table>
<thead>
<tr>
<th></th>
<th>Whites</th>
<th>Blacks</th>
<th>Hispanics</th>
<th>Asian/Pacific Islanders</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crude</strong></td>
<td>293.0</td>
<td>364.9</td>
<td>176.6</td>
<td>118.3</td>
<td>290.4</td>
</tr>
<tr>
<td><strong>Age-adjusted</strong></td>
<td>274.0</td>
<td>380.0</td>
<td>193.1</td>
<td>103.2</td>
<td>271.1</td>
</tr>
<tr>
<td>Age &lt;50–59 y</td>
<td>88.6</td>
<td>203.4</td>
<td>113.2</td>
<td>35.2</td>
<td>101.2</td>
</tr>
<tr>
<td>Age 60–69 y</td>
<td>258.8</td>
<td>408.8</td>
<td>178.9</td>
<td>107.4</td>
<td>265.0</td>
</tr>
<tr>
<td>Age 70–≥79 y</td>
<td>674.2</td>
<td>721.0</td>
<td>490.6</td>
<td>275.9</td>
<td>662.8</td>
</tr>
</tbody>
</table>

156,143 women followed through 2005 (mean 7.8 yr)
Risk Factors for Incident Hospitalized Heart Failure With Preserved Versus Reduced Ejection Fraction in a Multiracial Cohort of Postmenopausal Women

42,170 women followed through 2015 (mean 13.6 yr)

Proportion of Incident HF classified as HFpEF, HFrEF, HFuEF

Numbers on bars = cases

Age-adjusted Annualized Incidence (%)

<table>
<thead>
<tr>
<th></th>
<th>HFpEF</th>
<th>HFrEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>0.20</td>
<td>0.10</td>
</tr>
<tr>
<td>Black</td>
<td>0.15</td>
<td>0.10</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.08</td>
<td>0.05</td>
</tr>
</tbody>
</table>
The prevention of heart failure (HF) is an urgent public health need with national and global implications.

Currently, we have limited understanding of the pathophysiological basis of HF in patients with preserved left ventricular systolic function and management techniques to prevent it.
• **Exercise training** is becoming an established component of **HF management**.

  - HF-ACTION landmark RCT exercise training (mostly walking) in stable advanced HF patients (O'Connor CM et al. *JAMA*, 2009;301:1439)

• Role of **usual physical activity** in **HF prevention** less clear, especially in older women.
Physical Activity and Heart Failure: Taking Steps to Control a Major Public Health Burden

- Published literature between 2000-2017 (PubMed, Google Scholar, SportDiscus)
- **28 studies** evaluating HF incidence
  - 25 primary studies: 18 on PA; 1 on sedentary behavior; 6 on fitness
  - 3 pooled/meta-analysis
- **Cohort size**: 1,142 – 137,303
- **Follow-up**: ≥15 years (9 studies), 10-15 years (12 studies), <10 years (4 studies)
- **HF cases**: 88 – 4,652
- **Results in women**: 8
- **Results in non-Caucasians**: 4
- **HFpEF and HFrEF**: 1
- **No data on older (>65 years) women from diverse racial-ethnic backgrounds**
WHI Studies* on Physical Activity and HF Incidence

Among ambulatory community-living women, ages 50-79, at WHI enrollment:

1. Examine the association of self-reported PA with incidence of HF, HFpEF and HFrEF.
2. Examine self-reported walking amount and speed with HF, HFpEF, and HFrEF.
3. Examine self-reported sedentary behavior with overall HF.

* We have begun evaluating overall HF risk in relation to accelerometer-measured PA and SB in OPACH. Will not have time to summarize these findings today.
Heart Failure Surveillance in WHI

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Main Study</td>
<td>Extension 1</td>
<td>Extension 2</td>
<td>Extension 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Emphasis on CVD (HF, AF)</td>
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</tbody>
</table>

- **Enrollment → April, 2005:** N = 161,808
  - Overall HF based upon self-reported HF, MI or CHD (Form 33), adjudicated (HT, centrally; non-HT CT & OS, locally)

- **April 2005 → present:** UNC Subcohort: N = 44,174
  - MRC: all HT women, and all black and Hispanic women in Extension 2. (N=22,315)
  - Additional women from SRC. (N=21,859)
  - All central or local confirmed HF cases; non-confirmed HF w/ CHD Hx and essential records.
  - All cases during main WHI and Extension 1 (retrospectively); Extensions 2 & 3 ongoing.
  - HFpEF (≥45% [50%] EF) and HFrEF (<45% [50%] EF) … using clinical records, biomarkers, imaging results
Among ambulatory community-living women, ages 50-79, at WHI enrollment:

1. Examine the association of **self-reported PA** with incidence of HF, HFrEF and HFrEF.

**Excluded from this analysis:** HF history at enrollment, inability to walk one block unassisted

- **137,303** women (**35,272** EF subcohort) followed for a **mean 14 years**
- **2,523** (1.8%) overall HF cases, **734** (2.1%) HFrEF, **451** (1.3%) HFrEF cases

- **Cox regression** adjusting for study arm, age, race-ethnicity, sociodemographic and HF risk factors.

- **Controlled for time-varying CHD** (MI, revascularization) interim to HF diagnosis.

- **Time-varying PA** exposures explored in secondary analyses

- **Today, presenting results for walking amount** (MET-hr/wk)
# Overall HF (2,523 cases)

<table>
<thead>
<tr>
<th>Walking Amount (MET-hr/wk)</th>
<th>None (0)</th>
<th>&gt;0-3.5</th>
<th>3.6-7.5</th>
<th>&gt;7.5</th>
<th>Trend P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>18,992</td>
<td>39,736</td>
<td>38,577</td>
<td>38,998</td>
<td></td>
</tr>
<tr>
<td>Cases (rate*)</td>
<td>840 (2.6)</td>
<td>609 (2.8)</td>
<td>706 (2.4)</td>
<td>368 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Model 1 (covariates)</td>
<td>1.00 ref</td>
<td>0.98 (0.89, 1.09)</td>
<td>0.93 (0.83, 1.03)</td>
<td>0.72 (0.63, 0.81)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Model 2 (plus nonwalking PA)</td>
<td>1.00 ref</td>
<td>0.99 (0.89, 1.10)</td>
<td>0.95 (0.86, 1.05)</td>
<td>0.74 (0.65, 0.84)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Model 3 (time-varying walking)</td>
<td>1.00 ref</td>
<td>0.88 (0.81, 0.98)</td>
<td>0.69 (0.62, 0.67)</td>
<td>0.58 (0.50, 0.66)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Data are HR (95% CI). *Crude rate per 1000 person-years.

**Model 1**: adjusted for study arm, age, race-ethnicity, education, income, smoking, alcohol use, BMI, diabetes, hypertension, systolic and diastolic BP, A-Fib, hormone therapy use, hysterectomy status, and **time-varying CHD**.

**Model 2**: above plus non-walking physical activity.

**Model 3**: **time-varying walking** adjusted for all of the above.
## HFpEF (734 cases)

<table>
<thead>
<tr>
<th>Walking Amount (MET-hr/wk)</th>
<th>Trend P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (0)</td>
<td></td>
</tr>
<tr>
<td>&gt;0-3.5</td>
<td></td>
</tr>
<tr>
<td>3.6-7.5</td>
<td></td>
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<tr>
<td>&gt;7.5</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td></td>
</tr>
<tr>
<td>6,446</td>
<td></td>
</tr>
<tr>
<td>11,579</td>
<td></td>
</tr>
<tr>
<td>9,108</td>
<td></td>
</tr>
<tr>
<td>8,139</td>
<td></td>
</tr>
<tr>
<td>Cases (rate*)</td>
<td></td>
</tr>
<tr>
<td>279 (1.7)</td>
<td></td>
</tr>
<tr>
<td>184 (1.9)</td>
<td></td>
</tr>
<tr>
<td>179 (1.5)</td>
<td></td>
</tr>
<tr>
<td>92 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Model 1 (covariates)</td>
<td></td>
</tr>
<tr>
<td>1.00 ref</td>
<td></td>
</tr>
<tr>
<td>0.98 (0.81, 1.18)</td>
<td></td>
</tr>
<tr>
<td>0.87 (0.72, 1.06)</td>
<td></td>
</tr>
<tr>
<td>0.67 (0.53, 0.85)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Model 2 (plus nonwalking PA)</td>
<td></td>
</tr>
<tr>
<td>1.00 ref</td>
<td></td>
</tr>
<tr>
<td>0.98 (0.81, 1.18)</td>
<td></td>
</tr>
<tr>
<td>0.88 (0.72, 1.06)</td>
<td></td>
</tr>
<tr>
<td>0.68 (0.53, 0.87)</td>
<td>.001</td>
</tr>
<tr>
<td>Model 3 (time-varying walking)</td>
<td></td>
</tr>
<tr>
<td>1.00 ref</td>
<td></td>
</tr>
<tr>
<td>0.93 (0.78, 1.11)</td>
<td></td>
</tr>
<tr>
<td>0.68 (0.55, 0.83)</td>
<td></td>
</tr>
<tr>
<td>0.69 (0.53, 0.89)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Data are HR (95% CI). *Crude rate per 1000 person-years.

**Model 1:** adjusted for study arm, age, race-ethnicity, education, income, smoking, alcohol use, BMI, diabetes, hypertension, systolic and diastolic BP, A-Fib, hormone therapy use, hysterectomy status, and time-varying CHD.

**Model 2:** above plus non-walking physical activity.

**Model 3:** **time-varying walking** adjusted for all of the above.
## HFrEF (451 cases)

<table>
<thead>
<tr>
<th>Walking Amount (MET-hr/wk)</th>
<th>None (0)</th>
<th>&gt;0-3.5</th>
<th>3.6-7.5</th>
<th>&gt;7.5</th>
<th>Trend P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>6,446</td>
<td>11,579</td>
<td>9,108</td>
<td>8,139</td>
<td></td>
</tr>
<tr>
<td>Cases (rate*)</td>
<td>183 (1.1)</td>
<td>92 (0.9)</td>
<td>110 (0.9)</td>
<td>66 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Model 1 (covariates)</td>
<td>1.00 ref</td>
<td>0.75 (0.58, 0.97)</td>
<td>0.78 (0.62, 0.99)</td>
<td>0.67 (0.51, 0.90)</td>
<td>.01</td>
</tr>
<tr>
<td>Model 2 (plus nonwalking PA)</td>
<td>1.00 ref</td>
<td>0.76 (0.59, 0.92)</td>
<td>0.79 (0.62, 0.99)</td>
<td>0.69 (0.51, 0.92)</td>
<td>.02</td>
</tr>
<tr>
<td>Model 3 (time-varying walking)</td>
<td>1.00 ref</td>
<td>1.01 (0.81, 1.27)</td>
<td>0.82 (0.64, 1.05)</td>
<td>0.61 (0.43, 0.86)</td>
<td>.002</td>
</tr>
</tbody>
</table>

Data are HR (95% CI). *Crude rate per 1000 person-years.

**Model 1**: adjusted for study arm, age, race-ethnicity, education, income, smoking, alcohol use, BMI, diabetes, hypertension, systolic and diastolic BP, A-Fib, hormone therapy use, hysterectomy status, and **time-varying CHD**.

**Model 2**: above plus non-walking physical activity.

**Model 3**: **time-varying walking** adjusted for all of the above.
Additional Results

- Patterns of inverse association for total PA and walking with overall HF, HFrEF, HFrEF consistent across subgroups of age, race-ethnicity, physical functioning

- Findings persisted after discarding:
  - the first 2 years of follow-up
  - women with low physical functioning (RAND <60) and low ADL scores

- No greater benefit seen for vigorous intensity PA than for walking

- **NOTE**: 7.5 MET-hr/wk of walking *meets current guideline* recommendation

Published in: *JACC Heart Failure*. 2018;6(12):983-995
1,142 adults (65% women), mean age 76.

10-year follow-up, men and women combined:
HF, 250 total
HFrEF, 108 (43%)
HFrEF, 106 (42%)
(remainder uEF)

Adjusted for age, sex, alcohol, systolic BP, hypertension, diabetes, valvular disease, LV hypertrophy, and BMI.
Among ambulatory community-living women, ages 50-79, at WHI enrollment:

2. Examine the association of self-reported walking pace with incidence of HF, HFP EF and HFrEF.

- **Excluded from this analysis:** History of HF, cancer at enrollment, inability to walk one block

- **25,479 EF subcohort** followed for a mean 14 years

- **1,377** overall HF cases; 753 HFP EF, 409 HFrEF cases, 215 unknown EF

- **Cox regression** adjusting for study arm, age, race-ethnicity, sociodemographic and HF risk factors.

Xiaochen Lin, PhD (Brown University) et al.
Walking Speed and HF Risks in 25,479 Women Followed 14 Years

Adjusted for age, OS/CT indicator, race, region, education, income, smoking, alcohol, BMI, hormone therapy use, diet quality score, family history of MI, hysterectomy status, history of diabetes, hypertension and CHD, and walking amount (hr/d).
Risk of HFpEF According to Categories of Walking Speed and Amount

Error bars are 95% CI
Numbers on bars = cases

Guideline Recommendation
Among ambulatory community-living women, ages 50-79, at WHI enrollment:

3. Examine the association of **self-reported sedentary time** with incidence of overall HF.

- **Excluded from this analysis:** History of HF, inability to walk one block
- **Sedentary time** = hours/day sitting or laying down, not asleep…(asked only in WHI-OS)
- 81,217 **WHI-OS cohort** followed for a **mean 14 years**
- 1,406 overall HF cases.
- **Cox regression** adjusting for study arm, age, race-ethnicity, sociodemographic and HF risk factors.
### Sedentary Time and Overall HF Risk in 81,217 Women Followed 14 Years

<table>
<thead>
<tr>
<th>Sedentary Time (hr/d)</th>
<th>N</th>
<th>Cases (rate*)</th>
<th>Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤5</td>
<td>6-9</td>
<td>≥10</td>
</tr>
<tr>
<td>N</td>
<td>6,446</td>
<td>11,579</td>
<td>9,108</td>
</tr>
<tr>
<td>Cases (rate*)</td>
<td>489 (2.2)</td>
<td>601 (2.0)</td>
<td>316 (2.3)</td>
</tr>
<tr>
<td>Model 1 (covariates)</td>
<td>1.00</td>
<td>1.02</td>
<td>1.17</td>
</tr>
<tr>
<td></td>
<td>ref</td>
<td>(0.90, 1.15)</td>
<td>(1.02, 1.35)</td>
</tr>
<tr>
<td>Model 2 (plus time-varying CHD)</td>
<td>1.00</td>
<td>1.01</td>
<td>1.16</td>
</tr>
<tr>
<td></td>
<td>ref</td>
<td>(0.90, 1.14)</td>
<td>(1.01, 1.34)</td>
</tr>
<tr>
<td>Model 3 (plus total PA)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.12</td>
</tr>
<tr>
<td></td>
<td>ref</td>
<td>(0.88, 1.12)</td>
<td>(0.97, 1.30)</td>
</tr>
</tbody>
</table>

Data are HR (95% CI). *Crude rate per 1000 person-years.

**Model 1**: adjusted for study arm, age, race-ethnicity, education, income, smoking, alcohol use, BMI, diabetes, hypertension, systolic and diastolic BP, A-Fib, hormone therapy use, hysterectomy status.

**Model 2**: above plus **time-varying CHD**.

**Model 3**: above plus **total recreational physical activity**.
California Men’s Study
82,695 men, ≥45 years, followed 10 years (3,473 HF cases), Kaiser Permanente data.

Effects of Physical Activity and Sedentary Time on the Risk of Heart Failure

Adjusted for age, race, education, income, BMI, smoking, hypertension, diabetes, BP medication, HDL-C, glucose, dietary intake, alcohol, prevalent CHD, total physical activity.
**Atherosclerosis**
- Improve risk factors
- Improve arterial dilation
- Reduce platelet adhesion
- Improve fibrinolysis
- Reduce inflammation
- Improve antioxidant system

**Comorbidity**
Reduce risk of obesity, diabetes, hypertension, CHD

**Neurohormonal Activity**
- Reduce sympathetic tone
- Increase parasympathetic tone
- Reduce angiotensin
- Reduce BNP, troponin
- Improve renal function

**Cardiac**
- Improve balance between oxygen supply and demand
- Favorable remodeling
- Reduce fibrosis
- Improve cross-bridge cycling
- Improve contractility
- Improve myocardial relaxation
- Improve compliance
- Improve stroke work
- Reduce apoptosis
- Improve aerobic fitness

**Skeletal Muscle**
- Improve capillarization
- Reduced fibrosis
- Improve oxygen extraction/utilization
- Improve contractility
- Improved aerobic fitness
- Reduce apoptosis

**Aerobic Physical Activity**

**POTENTIAL MECHANISMS**
Bolded are likely major pathways
Skeletal Muscle Myopathy in Heart Failure

**HFrEF**
- Systolic Heart Failure

**Muscle Myopathy**
- Impaired Energetics
- Morphologic Changes
- Reduced Function

**Biological muscle alterations**:
- %Lean mass: ↓↓
- Intramuscular fat: ↑
- Interfascicle fibrosis: ↑
- Mitochondrial density: ↓
- Mitochondrial oxidative capacity: ↓

**Functional muscle impairments**:
- Fiber atrophy: ↑↑↑
- % Fast twitch fibers: ↓↓
- Capillary/Fiber ratio: ↓
- Alpha motor units: ↓
- Force production: ↓

**HFpEF**
- Diastolic Heart Failure

**Muscle Myopathy**
- %Lean mass: ↓
- Intramuscular fat: ↑↑
- Interfascicle fibrosis: ↑↑
- Mitochondrial density: ↓↓
- Mitochondrial oxidative capacity: ↓

- Fiber atrophy: ↑
- % Fast twitch fibers: ↓
- Capillary/Fiber ratio: ↓↓
- Alpha motor units: ↓
- Force production: ↓

(Adapted from source: Current Cardiology Reports. 2018;20:116.)
Why are these findings relevant to public health and clinical medicine?

- **Review of published studies on PA and HF (LaMonte 2018)**
  - No study focusing exclusively on older postmenopausal women
  - Only 1 study on HFpEF and HFrEF risk (underpowered)
  - Only 1 study on sedentary behavior and HF risk

- **2008 and 2018 Physical Activity Guidelines for Americans**
  - Insufficient evidence for a conclusive recommendation on primary HF prevention

- **2017 ACC/AHA Clinical Guidelines for HF management**
  - Fewer available therapies for effective HFpEF management, compared to HFrEF

- **Improved HF prevention is key to reducing the population burden of HF**
  - Walking is the most commonly reported recreational activity among U.S adults
  - A community-based **RCT testing the hypothesis** that increasing PA and reducing SB will lower HF incidence is ongoing: *WHISH-2-Prevent HF* (PI: Eaton)