# Objectively Measured Vigorous-Intensity Physical Activity is Related to Endothelial Function in Midlife and Older Men but not in Estrogen-Deficient Postmenopausal Women

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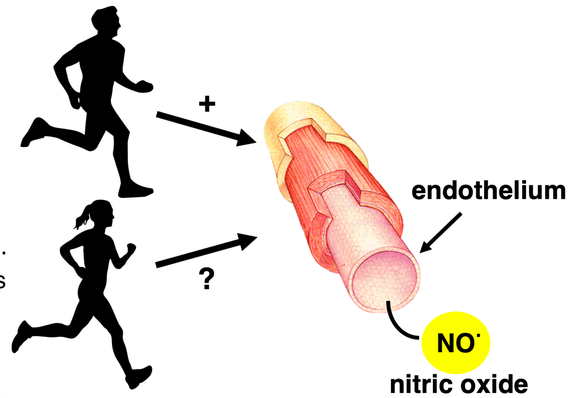
## Abstract

**Background.** Aerobic exercise training is consistently associated with enhanced vascular endothelial function via suppression of oxidative stress in midlife/older (ML/O; ≥50 years) men but not in estrogen-deficient postmenopausal women (E-PMW). It is unclear if chronic physical activity (PA) patterns assessed under free-living conditions, including sedentary behavior and vigorous exercise, are related to endothelial function among ML/O men or E-PMW. We investigated if objectively measured PA patterns were associated with endothelial function in ML/O adults and the potential mechanisms involved. **Methods.** 172 ML/O adults were included for analysis (67 ± 7 years; 85M/87W). Endothelium-dependent dilation was assessed via brachial artery flow-mediated dilation ($FMD_{BA}$), a bioassay of endothelial function. PA was assessed over 3-7 days via wrist-worn accelerometers (GENEActiv), which measured sedentary time and light, moderate, and vigorous activity. The relations between endothelial function and PA were examined using simple and stepwise linear regression. Multiple linear regression was used to examine the correlation between endothelial function and PA when controlling for conventional cardiovascular disease risk factors. Plasma oxidized low-density lipoprotein (OxLDL) concentrations and total antioxidant status were used as markers of oxidative stress and antioxidant defenses, respectively. Interleukin-6, tumor necrosis factor-α, and C-reactive protein concentrations were examined to assess chronic low-grade inflammation. Mediation analysis was used to determine the potential for changes in oxidative stress, antioxidant defenses, and inflammation as mechanisms mediating the relation between PA and endothelial function. **Results.** In the entire cohort of subjects, $FMD_{BA}$ was negatively associated with sedentary time ($R^2$=0.04; p=0.01), not associated with light PA ($R^2$=0.02; p=0.09), and positively associated with moderate ($R^2$=0.03; p=0.04) and vigorous ($R^2$=0.06; p<0.01) PA. Only sedentary time ($R^2$=0.06; p=0.02) and vigorous PA ($R^2$=0.11; p<0.01) were associated with $FMD_{BA}$ in ML/O men. No PA parameters were associated with $FMD_{BA}$ in E-PMW (all p>0.05). Stepwise linear regression revealed vigorous PA primarily mediated the effects of PA on $FMD_{BA}$ in ML/O men ($R^2$=0.10; p<0.01). When controlling for age, blood pressure, body mass index, triglycerides, high-density lipoprotein, low-density lipoprotein, and fasting glucose, vigorous PA independently predicted $FMD_{BA}$ in ML/O men ($R^2$=0.05; p=0.05) but not in E-PMW ($R^2$=0.03; p=0.18). Plasma OxLDL concentrations mediated 13.5% of the group effect of vigorous PA on $FMD_{BA}$ (p<0.01); no other plasma markers had a mediating effect (all p>0.05). **Conclusions.** Objectively measured PA, primarily vigorous PA, is positively associated with endothelial function in ML/O men but not in E-PMW. This relation is mediated, in part, by oxidative stress. These associations are consistent with findings that aerobic exercise training does not improve endothelial function in E-PMW. Alternative strategies to improve endothelial function in E-PMW are needed. **Program Number: 953.19**

## Introduction

- Aging is associated with vascular endothelial dysfunction, which increases risk for cardiovascular diseases (CVD).
- A sedentary lifestyle exacerbates age-related vascular endothelial dysfunction.
- In men, regular aerobic exercise:
  - Reverses age-related vascular endothelial dysfunction.
  - Preserves nitric oxide bioavailability and reduces oxidative stress.
- Regular aerobic exercise does not consistently improve endothelial function in estrogen-deficient postmenopausal women.
- It is unclear if physical activity (PA) patterns assessed under free-living conditions are related to endothelial function among midlife/older (ML/O; ≥50 years) men or estrogen-deficient postmenopausal women.

**<u>Purpose</u>: To determine whether objectively measured PA is associated with vascular endothelial function in ML/O adults, and whether this association is partially mediated by oxidative stress or inflammation.**




## Methods

### PARTICIPANTS

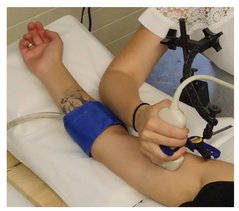
- 172 ML/O adults were included for analysis (85 men / 87 women).

### PRIMARY MEASUREMENTS

- **Endothelium-Dependent Dilation:** Brachial Artery Flow-Mediated Dilation ($FMD_{BA}$)
- **Physical Activity:** Wrist-worn GENEActiv accelerometers collected the percentage of time spent sedentary and in light, moderate, and vigorous intensity PA (3-7 day recordings)

### SECONDARY MEASUREMENTS

- **Oxidative Stress:** Plasma oxidized low-density lipoprotein (OxLDL)
- **Antioxidant Defenses:** Plasma total antioxidant status
- **Inflammation:** Plasma interleukin-6, tumor necrosis factor-α, and C-reactive protein



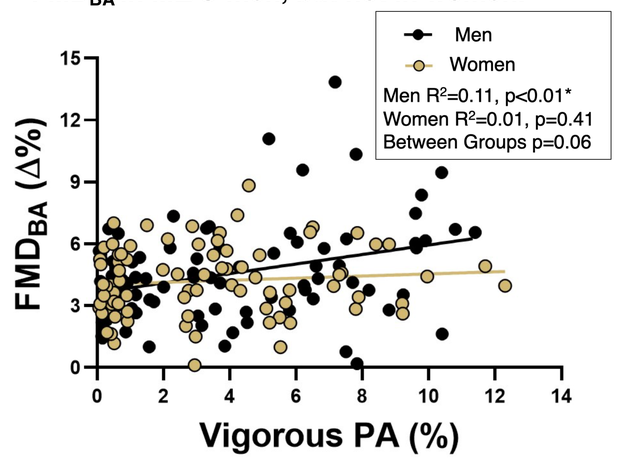
## Results

### 1. Subject characteristics

| | Group | Men | Women |
|---|---|---|---|
| ***n*** | 172 | 85 | 87 |
| **Age (years)** | 67 ± 1 | 66 ± 1 | 68 ± 1* |
| **SBP (mmHg)** | 125 ± 1 | 127 ± 1 | 123 ± 2 |
| **DBP (mmHg)** | 75 ± 1 | 77 ± 1 | 73 ± 1* |
| **MAP (mmHg)** | 92 ± 1 | 94 ± 1 | 90 ± 1* |
| **BMI (kg/m²)** | 25.7 ± 0.3 | 26.8 ± 0.4 | 24.6 ± 0.4* |
| **Total cholesterol (mg/dL)** | 181 ± 3 | 170 ± 4 | 190 ± 4* |
| **HDL cholesterol(mg/dL)** | 59 ± 2 | 51 ± 2 | 67 ± 3* |
| **LDL cholesterol(mg/dL)** | 106 ± 2 | 104 ± 4 | 108 ± 2 |
| **Triglycerides (mg/dL)** | 102 ± 4 | 107 ± 6 | 97 ± 5 |
| **Glucose (mg/dL)** | 91 ± 1 | 93 ± 1 | 89 ± 1 |

Values are mean ± SE; * p<0.05 vs. men.

### 2. Vigorous PA was positively associated with $FMD_{BA}$ in ML/O men, but not in women.

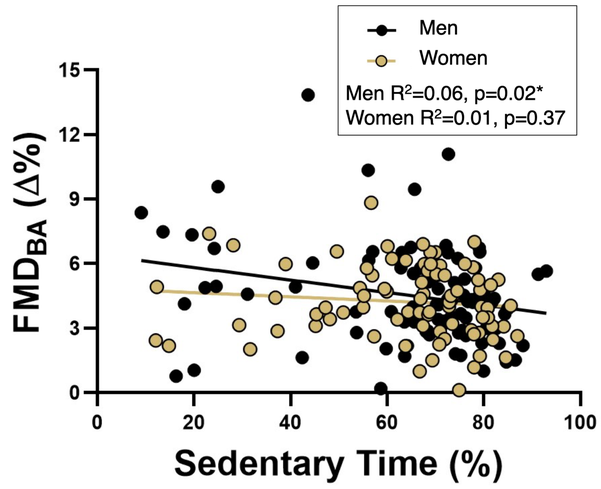



### 3. In men, the relation between vigorous PA and $FMD_{BA}$ remained after controlling for CVD risk factors (men $R^2$=0.05, p=0.05*; women $R^2$=0.03, p=0.18).

### 4. Plasma OxLDL mediated 13.5% of the relation between vigorous PA and $FMD_{BA}$ (p<0.01*).

- Markers of antioxidant defenses and inflammation had no mediating effect.

### 5. Sedentary time was negatively associated with $FMD_{BA}$ in men, but not in women.




### 6. Light and moderate PA were not associated with $FMD_{BA}$ in men or women.

| | Men (n=85) | | Women (n=87) | |
|---|---|---|---|---|
| | $R^2$ | p-value | $R^2$ | p-value |
| **Light PA (%)** | 0.04 | 0.08 | <0.01 | 0.78 |
| **Moderate PA (%)** | 0.03 | 0.10 | 0.03 | 0.15 |

## Conclusions

1. Objectively measured vigorous-intensity PA was associated with vascular endothelial function in ML/O men, but not in estrogen-deficient postmenopausal women.
2. Plasma OxLDL mediated part of the relation between vigorous-intensity PA and vascular endothelial function, which suggests oxidative stress contributed to this relation.
3. These results are consistent with previous cross-sectional and exercise intervention findings that PA is associated with vascular endothelial function in ML/O men, but not in estrogen-deficient postmenopausal women.
4. Identifying alternative lifestyle interventions that can improve vascular endothelial function in estrogen-deficient postmenopausal women is a biomedical research priority.

## Acknowledgements

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