Supplemental material

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BMJ Open Sp Ex Med

Low But Not High Exercise Systolic Blood Pressure is Associated with Long-Term All-Cause Mortality

Supplementary data

Kristofer Hedman, Leonard A Kaminsky, Ahmad Sabbahi, Ross Arena, Jonathan Myers

1. Supplementary Methods

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DATA SUPPLEMENT

Supplementary methods S1.

Details on exercise testing and exercise capacity estimation

Each subject underwent a standardized treadmill exercise test using an individualized ramp protocol. The choice of protocol was individualized based on estimated exercise capacity and a targeted 8-12 min exercise duration, using the one-page Veterans Specific Activity Questionnaire. Subjects were encouraged to exercise without handrail support until volitional fatigue in absence of any indication for stopping the test (see below). Age-predicted maximal heart rate was not used as a target endpoint. The degree of effort was quantified using the Borg scale of perceived exertion.

Standard criteria for termination were used, including signs of inducible cardiac ischemia (i.e >2.0 mm horizontal/downsloping ST depression, moderately severe angina, a sustained drop in systolic blood pressure (SBP) or serious rhythm disturbances). A SBP >250 mmHg or a diastolic BP >115 mmHg were relative indications for test termination.

Peak exercise capacity was estimated as metabolic equivalents of task (METs), which is a surrogate measure of peak oxygen uptake, expressed as multiples of an assumed oxygen uptake (VO_2) at rest of 3.5 mL/kg/min. Thus, a peak exercise capacity of 10 METs corresponds to an estimated peak VO_2 of 35 mL/kg/min. Standard American College of Sports Medicine (ACSM) equations were used for calculating peak METs:

a) Walking $VO_2 = (S \times 0.1) + (S \times G \times 1.8) + 3.5$
b) Running $VO_2 = (S \times 0.2) + (S \times G \times 0.9) + 3.5$

where S is treadmill speed (in m/min) and G is grade (%, in decimal form). A treadmill speed >5.0 miles per hour (>134 m/min) were used to define running vs. walking VO_2.

Age-predicted peak METs was calculated using a population-specific equation as: 18 - [0.15 × Age].

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Supplementary Methods S2.

Definitions of cardiovascular comorbidities and risk factors

We used the following definitions in determining the presence of cardiovascular comorbidities and risk factors at baseline exercise testing:

- **Previous coronary artery disease (CAD)**; previous myocardial infarction, cardiac procedures/interventions and/or coronary artery stenosis >50% at imaging.
- **Hypertension**; previous diagnosis of hypertension and/or use of any anti-hypertensive medication (not including beta-blockers).
- **Smoking**; Current smoker or previous smoker with history of >10 pack-years of smoking.
- **Hypercholesterolemia**; Total cholesterol >220 mg/dL, statin use, or both.
- **Diabetes mellitus**; a diagnosis at time of test per medical records.

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Table S1. Relative risk of all-cause mortality over 20 years per 5th and 95th reference percentiles for peak systolic blood pressure and delta systolic blood pressure, respectively.

	Unadjusted	Model 1	Model 2	Model 3
	Adjusted for			
	-	Age	Age, exercise capacity, SBP at rest	As model 2 plus risk factors* and beta-blocker med
Peak systolic blood pressure category				
<5th percentile (n=903)	**1.23** (1.11-1.36)	**1.40** (1.27-1.56)	**1.14** (1.02-1.28)	1.04 (0.92-1.16)
5-95th percentile (n=6083)	Reference	Reference	Reference	Reference
>95th percentile (n=178)	**0.75** (0.59-0.96)	1.09 (0.85-1.39)	1.13 (0.88-1.45)	1.21 (0.94-1.57)
Delta systolic blood pressure category				
<5th percentile (n=1151)	**1.29** (1.18-1.42)	**1.42** (1.29-1.55)	**1.20** (1.09-1.32)	**1.14** (1.03-1.25)
5-95th percentile (n=5905)	Reference	Reference	Reference	Reference
>95th percentile (n=108)	**0.67** (0.48-0.93)	0.86 (0.62-1.20)	0.96 (0.69-1.34)	1.01 (0.73-1.41)

*, risk factors include body mass index, current smoking, diabetes mellitus, hypertension, hyperlipidemia or a previous diagnosis of coronary artery disease. Model 3 also adjusted for use of beta-blocker medication. SBP, systolic blood pressure. Reference values from FRIEND (Fitness Registry and the Importance of Exercise: A National Database) published in Sabbahi et al. Hypertension. 2018;71:229-236. DOI: 10.1161/HYPERTENSIONAHA.117.10116.

DATA SUPPLEMENT
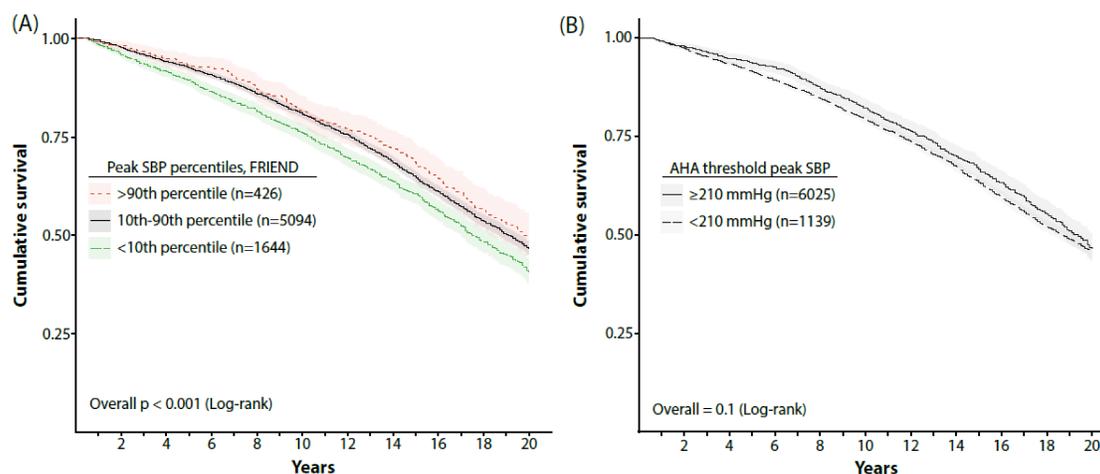
Figure S1. Survival over 20-years per peak systolic blood pressure categorized by FRIEND reference percentiles (panel A) or the AHA threshold (B).
AHA, The American Heart Association; SBP, systolic blood pressure.
Reference categories in panel A from FRIEND (Fitness Registry and the Importance of Exercise: A National Database) published in Sabbahi et al. Hypertension. 2018;71:229-236. DOI:10.1161/HYPERTENSIONAHA.117.10116. The AHA threshold from Exercise Standards for Testing and Training: A Scientific Statement From the American Heart Association, published by in Fletcher et al. Circulation. 2013; 128:873-934.