The exaggerated systolic hypertensive response to exercise associates cardiovascular events: a systematic review and meta-analysis

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Article type: Original article

Received: August 15, 2019.

Accepted: September 25, 2019.

Published online: October 2, 2019.

ISSN: 1897-9483

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The exaggerated systolic hypertensive response to exercise associates cardiovascular events: A systematic review and meta-analysis

Short title: Systolic hypertensive response at exercise and cardiovascular events

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Word count: 2035

Conflict of interest: none to declare.

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What’s new?

The clinical relevance of exaggerated systolic hypertensive response to exercise (SHRE) and its predictive value of cardiovascular events are not ascertained. This meta-analysis answers those uncertainties. In a sample of 47,188 participants from eight studies who were followed up for 19.3 years, higher SHRE was found in subjects with composite events - cardiovascular mortality and coronary artery disease compared to individuals with normal response. An exercise systolic blood pressure of 196 mmHg predicted CV events with sensitivity of 62% and specificity of 75% with positive likelihood ratio <3 and strong correlation (r=-0.71). These findings highlight the importance of identifying normal individuals with exaggerated SHRE as pre-hypertensives. They also pave the way for future studies that could propose optimum means of controlling blood pressure of those individuals who would otherwise be discharged from clinics based on normal office blood pressure readings, but in essence they are at serious cardiovascular risks.

Abstract

Introduction. The pathophysiology of exaggerated systolic hypertensive response to exercise (SHRE) is not fully understood and its role in predicting cardiovascular (CV) events is contradictory.

Objectives. The aim of this review with meta-analysis was to analyze the association of SHRE with CV clinical outcomes in healthy normotensive subjects.

Patients and methods. We searched Pubmed-MEDLINE, Cochrane Library, Refworks and Google Scholar aiming to find clinical studies which reported data on CV event rate and outcomes (coronary artery events, CV mortality and composite outcomes), for patients who underwent exercise testing and had SHRE. Sensitivity and specificity (with 95% CI) analysis for
assessing the diagnostic accuracy of SHRE cut-off associated with CV events was estimated using hierarchical summary receiver operating characteristic analysis.

**Results.** Eight studies with 47,188 participants were included with a median follow-up duration of 19.3 years. Higher SHRE was found in patients with composite events - CV mortality and coronary artery disease (HR = 1.363 [1.135-1.604]; p<0.001), in those who developed coronary artery events (HR = 1.532 [1.240-1.893]; p<0.001) and CV mortality (HR = 1.286 [1.075-1.539]; p=0.006) compared to normal response individuals. An exercise systolic blood pressure of 196 mmHg predicted CV events with sensitivity of 62% (54–69%) and specificity of 75% (60–86%) with positive likelihood ratio (LR+) <3 and strong correlation (r=–0.71).

**Conclusions:** This meta-analysis supports the clinical relevance of exaggerated SHRE as an associate of composite and individual CV clinical outcome. These findings should be taken as a thought-provoking evidence for identifying better stratification of such patients and consequently for optimum management of this, high risk, group.

**Key words:** Cardiovascular events, exercise hypertension, stress test, systolic hypertensive response to exercise.

**Introduction**

Exercise stress testing is mainly used for the assessment of coronary artery disease (CAD), with blood pressure (BP) measurements obtained as integral part of the test [1]. In healthy individuals, the increased cardiac output with exercise is associated with perpetual increase in systolic BP (SBP), but diastolic BP (DBP) remains unchanged or may slightly fall. The prevalence of exaggerated systolic hypertensive response to exercise (SHRE) has previously been suggested to be 5–40 % [2, 3]. However, there is no available consensus for an exact definition or validated
cut-off value for SHRE. In most publications, the SHRE is defined as 60 mmHg difference between baseline and peak SBP for men and 50 mmHg for women, or SBP at peak exercise exceeding the 90th percentile (>210 mmHg for men and >190 mmHg for women) or diastolic >110 mmHg in either gender [4-7]. Respective values at moderate exercise (100 Watt) are SBP of 160 mmHg and 170 mmHg [8]. The pathophysiology of SHRE is not fully understood, with various mechanisms proposed, including endothelial dysfunction; reduced compliance/increased stiffness of great arteries, and high neurohormonal (mainly Angiotensin II) stress induced activation [9-15]. Although may be clinically ignored, SHRE has been reported to be associated with systolic and diastolic left ventricular (LV) dysfunction [16-22], and can lead to target organ damage, i.e. LV hypertrophy, carotid atherosclerosis [17-21] and significant CAD [21], irrespective of resting BP [22, 23], but its predictive value of those events remains contradictory [24-27].

The aim of this review with meta-analysis therefore, was to determine the role of SHRE in predicting CV clinical outcomes in healthy, normotensive subjects.

Patients and methods

The research methodology used in this study was according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement for reporting systematic reviews and meta-analyses of observational studies (Figure 1, MOOSE checklist) [28]. The literature search was undertaken independently by two reviewers (LP and GB) and comprised results of the most commonly used online databases (Pubmed-MEDLINE; Cochrane Library; Refworks and Google Scholar), with the main focus on published studies which reported data on CV event rate and outcomes (including mortality), up till July 2017, in patients who underwent exercise
testing and had SHRE. Disagreements, between reviewers, were resolved by discussion with a third party (MYH). The included search terms were “exercise” or "stress test"; "exercise-induced hypertension” or "hypertensive response to exercise" or "exercise-related blood pressure" or "Exercise Blood Pressure" or "Exercise exaggerated systolic Blood Pressure" or “exercise” and "cardiovascular event" or "cardiovascular disease" or "cerebrovascular event" or "cerebrovascular disease" or “stroke” or “mortality” or "myocardial infarction" and “outcome” or “follow-up” or “predict”. Search filters or “limits” to English language, human studies and adults (≥ 18 years) were applied according to availabilities. In addition, relevant articles from reference lists were also included in the revision.

Criteria for study inclusion

Studies were included in the meta-analysis if they met the following criteria: (1) published in a peer reviewed, English language journal; (2) a human study involving adults > 18 years of age; (3) reporting office BP; (4) reporting exercise BP (measured during, at submaximal (moderate) workload and maximal workload; (5) reporting CV outcomes; (6) having a population that included subjects with a clinical indication for exercise stress testing or who were otherwise healthy and normotensive. From this meta-analysis we excluded studies which included: (1) Patients with history of any CV disease; (2) Patients with end-target organ damage (severe renal or liver disease); and (3) Patients in whom exercise BP was only measured during recovery periods (not during exercise). Only studies reporting categorical data comparing SHRE and non-SHRE were included, while continuous data were not analyzed due to the heterogeneous way of reporting. No restrictions were applied to the duration of follow up, including the new diagnosed type 2 diabetes. After individual analysis, the final studies included in this systematic review and
meta-analysis was unanimously accepted by the two reviewers (LP and GB). The outcomes investigated in this meta-analysis were: 1) coronary artery events, in the form of acute coronary syndrome and/or myocardial infarction; 2) CV mortality; and 3) composite outcomes (CV mortality and coronary artery disease).

Literature search overview

The literature search and selection process of articles included in the systematic review and meta-analysis is presented Figure 1. Initially, four online databases were used resulting in 8,419 articles. After excluding 8341 studies, 78 full articles were assessed. Further on, out of these 78 articles, 67 had to be excluded as per the diagram (Figure 1). A final critical search based on the eligibility criteria qualified only 11 articles to be included in the analysis [29-39]. Of these 11 articles, 3 were again not meta-analyzed: one article did not report CI [29], one lacked adjustment for office BP [31], and the third relied on continuous parameters only [33], leaving 8 studies finally included in the meta-analysis.

Data extraction

Two reviewers (LP and GB) independently extracted the relevant data, reviewing and resolving the discrepancies by consensus. Data extracted for the systematic review consisted of follow-up duration, gender, age of subjects, BP measurement type, details of exercise test and mode (treadmill, cycle and energy per time), clinical outcomes (events or mortality), analysis type, reference group (subjects with no SHRE), SHRE (scores), and multivariate variables (Table 1).

Statistical analysis
Statistical analysis was performed using standard software package (Comprehensive Meta-Analysis version 3 software; Biostat inc., Englewood, NJ, USA). A two-tailed P values less than 0.05 was considered significant. The baseline characteristics are reported in median and range. Mean and standard deviation (SD) values were estimated using the method described by Hozo et al [40]. For pooled analysis, risk ratio (RR) was also considered as hazard ratio (HR). The multivariable models (including age, sex, office BP and CV risk factors) were included in the meta-analysis. Forest plots were used to illustrate the individual results and meta-analyses. Hazard ratios with 95% confidence interval are presented as summary statistics for moderate and maximal exercise subgroups and also for the overall analysis. Heterogeneity between studies was tested by Cochran's test and means of $I^2$ statistics [41]. To assess the additive (between-study) component of variance, the reduced maximum likelihood method (tau2) took into analysis the occurrence of residual heterogeneity [42]. Studies were combined using random effect model, because of heterogeneity among studies in particular variation regarding cut off points and outcomes. Publication bias was assessed using funnel plots and Egger's test. When there were three or more studies included, we tested the subgroups for potential publication bias.

*Diagnostic accuracy*

To evaluate the diagnostic accuracy of SHRE cut-off that predicts CV events we used the hierarchical summary receiver operating characteristic (ROC) analysis. Sensitivity and specificity with 95% CI for individual studies were computed based on a diagnostic random-effects model [43]. To obtain summary points that take into account within-study variability and between-study variability (heterogeneity), we performed hierarchical summary ROC analysis using the Rutter and Gatsonis model [44]. Summary point from the hierarchical summary ROC analysis was then used to calculate positive likelihood ratio (LR+). Separate analyses were
performed for different SHRE cut-offs. In studies which did not provide optimal cut-offs, we created the ROC curve and identified the optimal cut-off as the point on the ROC curve closest to (0,1 on x-y coordinate). Statistical software OpenMetaAnalyst, Yosemite (software 12) for Windows (64-bit version; Microsoft) was used for statistical analysis including graphic presentations of forest plots of sensitivity and specificity and hierarchical summary ROC curves (HROC curve).

**Ethics**

In case of our study, ethics approval is unnecessary, as it is a meta-analysis.

**Results**

The total number of participants from the 11 studies [33-43] included for qualitative synthesis was 53,264 with a mean follow-up period of 18 years. Eight studies were eligible for the meta-analysis [34, 36; 38-43] with 47,188 participants with a mean follow-up of 19.3 years.

**SHRE associate of composite clinical outcomes**

The included eight studies reported composite outcomes: CV mortality and coronary artery disease. Patients with SHRE had higher rate of composite events (HR = 1.363 [1.158-1.606]; p<0.001; Figure 2) compared to those who did not have SHRE, in all included studies. The composite events rate did not differ between patients who achieved SHRE at maximal workload and those who did not achieve SHRE at maximal workload (p=0.118), whereas the composite
events rate was higher in patients who achieved SHRE at moderate workload, compared to those who did not achieve SHRE at moderate workload (HR = 1.349 [1.135-1.604]; p=0.001; Figure 2). There was no heterogeneity between the included studies (Q value 12.24, $I^2 = 34.6\%$, P = 0.14) and there was no publication bias, neither for moderate nor for maximal exercise subgroups, p=0.21 and p=0.77, respectively.

**SHRE associate of coronary events**

Four of the eight included studies reported coronary artery events, in the form of acute coronary syndrome and/or myocardial infarction, during the follow-up period. Of all included subjects, patients with SHRE had higher rate of coronary artery events during the follow-up (HR = 1.532 [1.240-1.893]; p<0.001; Figure 3) compared to those who did not have SHRE. Only one study had data of patients who achieved SHRE at maximal workload, in which the coronary artery events rate was higher in patients who had SHRE (HR = 2.470 [1.460-4.179]; p=0.001), compared to subjects that had not SHRE. The reported data from three other studies showed that in patients who achieved SHRE at moderate workload had higher rate of coronary artery events (HR = 1.397 [1.109-1.760]; p=0.005; Figure 3), compared to those who had not SHRE. There was moderate heterogeneity between the included studies (Q value 6.19, $I^2 = 51.5\%$, P = 0.1) neither there was a publication bias (p=0.80).

**SHRE associate of CV mortality**
Five of the eight included studies reported CV mortality during the follow-up period. In all included subjects, CV mortality rate was significantly higher in patients with SHRE (HR = 1.286 [1.075-1.539]; p=0.006; Figure 4) compared to subjects with no SHRE. The CV mortality did not differ between subjects who achieved SHRE at maximal workload and those who did not achieve SHRE at maximal workload (p=0.397), whereas the CV mortality rate was higher in patients who achieved SHRE at moderate workload (HR = 1.343 [1.085-1.661]; p=0.007; Figure 4), compared to those who did not achieved SHRE at moderate workload. There was no heterogeneity across the included studies (Q value 0.79, I^2 = 0%, P = 0.93) and there was no publication bias (p=0.31).

*Diagnostic accuracy of SHRE for composite CV events*

From the ROC analysis, systolic blood pressure cut-off value of 196 mmHg predicted composite CV events with summary sensitivity of 62% (54-69%) and specificity of 75% (60-86%) with positive likelihood ratio (LR+) <3 and strong correlation (r=-0.71) (Figure 5).

*Discussion*

This meta-analysis, based on data collected from eight eligible studies which included 47,188 participants followed-up for a mean of 19.3 years, showed that SHRE, particularly at moderate exercise was associated with serious composite clinical outcome in the form of coronary events and CV mortality. In addition, a cut off value of 196 mmHg and above for exercise systolic BP had a strong association and correlation with those clinical outcome.
Hypertension is the most dynamic CV measurement [45]. While resting values could be entirely normal (according to set guidelines) they may significantly fluctuate, up to seriously high values that could justify hospital admission, in some cases. Although this is difficult to predict and to manage, exercise related changes in BP is a feasible and reproducible investigation of such phenomenon, hence our interest in assessing the relationship between SHRE and clinical outcome. Indeed, our analysis shows that SHRE is related to serious clinical outcomes including CV mortality and life-threatening coronary artery events in patients with satisfactory acceptable resting or clinic measured BP. These findings are alarming and highlight the potential drawback of ignoring exercise related hypertension. Having established these findings, the difficulty remains as how to manage such individuals since no guidelines exist to recommend a particular treatment for them, for the level of SHRE when treatment should be commenced neither the nature of that treatment. In addition, apart from the general healthy life style recommended for all CV patients, no particular pattern is advisable for these individuals, as means of controlling the unsteady BP. Of concern could be unmonitored cardio-exercise training in these individuals with expected systolic blood pressure exceeding 200 mmHg that goes unnoticed. Our results propose a value of 196 mmHg for systolic SHRE as an associate of worse clinical outcome, hence the need for retesting this value prospectively in a large population.

Fluctuating blood pressure is known for its drastic effect on arterial health including endothelial dysfunction and arterial stiffness. If the combination of the two, as pressure afterload, is ignored they are bound to affect LV diastolic function and later on cavity compliance, even if systolic function remains preserved [46]. In addition, subendocardial ischemia with its risk of arrhythmia is an inevitable complication, in patients with persistently raised pressure afterload [47]. Finally,
with perpetual increase of LV stiffness, the left atrium enlarges and its pressure rises with its known complications in the form of arrhythmia and thromboembolism. These consequences could explain diastolic dysfunction in middle aged normotensive individuals with no other underlying cardiac pathology [23]. Hence the need for critical determination of physiologically acceptable BP changes with stress opposite to SHRE.

Limitations: Although eight studies were eligible for this analysis, sub-analyses according to the reported clinical outcome brought them down to small numbers, hence potentially limited impact. We had no hand in the design of individual studies, which is a known limitation for meta-analyses; an example of such limitation was the higher prevalence of male gender in some studies which might limit the applicability of our findings to both genders. Despite differences in study design between cohorts our findings showed no heterogeneity or bias between publications. Our findings support the importance of assessing SHRE during stress tests but lack providing any particular recommendation with regards to the best means of managing it. The workloads were increased with different protocols in different included studies. However, the target SHRE were achieved in all studies and we believe that the increased SBP did not differ at the same workload of different studies.

Conclusion: The current meta-analysis supports the clinical relevance of exaggerated systolic blood pressure response to exercise as an associate of serious composite and cardiovascular clinical outcome. These findings should be taken as a thought-provoking evidence for finding better stratification of such individuals and then optimum management for this, at risk, group.
Contribution statement:

LP and GB conceived the concept of the study. GB and PI contributed to the design of the study. LP, GB, HJ, and PI were involved in the data collection by literature search. HJ and IB analyzed the data. LP and HJ wrote the first draft of the manuscript. GB and MH supervised the design, data collection, and writing of the paper. All authors edited and approved the final version of the manuscript.

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80.


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systolic blood pressure response and left ventricular mass: The Framingham Heart study. 


Figure 1. Meta-analysis of Observational Studies in Epidemiology flowchart
Figure 2. Prediction of composite outcome by systolic hypertensive response to exercise

The last line box is red.
Heterogeneity: Chi²=12.24, df=8 (p=0.14) I²=34.6%

Test for overall effect: p<0.001
Figure 3. Prediction of coronary heart disease by systolic hypertensive response to exercise

The last line box is red.

Heterogeneity: $\text{Chi}^2=6.19$, df=2 (p=0.10) $I^2=50.4\%$

Test for overall effect: p=0.001
Figure 4. Prediction of cardiovascular mortality by systolic hypertensive response to exercise

The last line box is red.

Heterogeneity: $\chi^2=0.79$, df=4 (p=0.93) $I^2=0.0\%$

Test for overall effect: p=0.006
Figure 5. Diagnostic accuracy of systolic hypertensive response to exercise:

a) Individual studies, diagnostic 2x2 data (true positive, false positive, false negative, true negative, and corresponding values of sensitivity and specificity with 95% CI are described. Summary heterogeneity is described by $I^2$ statistic.
b) The Rutter and Gatsonis hierarchical summary receiver operating characteristic analysis for systolic hypertensive response to exercise (summary cut-off) to identify cardiac events. Summary sensitivity, summary specificity with 95% CI, and corresponding positive likelihood ratio are depicted.

Hierarchical summary receiver operating characteristic curve; Sensitivity: 0.62 (0.54-0.69), Specificity: 0.75 [0.60-0.86], LR+2.58, r=-0.71
Table 1. Overview of studies included in systematic review and meta-analysis

<table>
<thead>
<tr>
<th>No.</th>
<th>Study, Year, Reference</th>
<th>Subject s (n)</th>
<th>Follow-up (years)</th>
<th>Gender: M, F (%)</th>
<th>Age (years)</th>
<th>BP measure</th>
<th>Workload</th>
<th>Exercise test (mode)</th>
<th>Outcomes: event or mortality</th>
<th>Analysis type</th>
<th>Reference group</th>
<th>HRE</th>
<th>Variables included in multivariate models</th>
<th>Meta-analysed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Filipovsky et al. 1992 [29]</td>
<td>4,907</td>
<td>17</td>
<td>M (100%)</td>
<td>Range: 47±2</td>
<td>Noninvasive</td>
<td>Moderate</td>
<td>Bicycle (85-191W)</td>
<td>146 composite CV events</td>
<td>Categorical</td>
<td>Moderate SBP&lt;190mmHg</td>
<td>Moderate SBP&gt;230 mmHg</td>
<td>Age, Office SBP, BMI, Exercise SBP, Baseline HR, LVH, Smoking, Total cholesterol and Sports activities.</td>
<td>No (no CI reported)</td>
</tr>
<tr>
<td>2</td>
<td>Mundal et al. 1996 [30]</td>
<td>1,999</td>
<td>16</td>
<td>M (100%)</td>
<td>Range: 40-59</td>
<td>Mercury sphygmomanometer</td>
<td>Moderate</td>
<td>Bicycle (600 kpm/min)</td>
<td>255 CV deaths</td>
<td>Categorical</td>
<td>Moderate SBP&lt;200mmHg</td>
<td>Moderate SBP&gt;200mmHg</td>
<td>Age, office BP, Exercise capacity, Smoking, HR, BMI, Cholesterol, Triglycerides, Glucose.</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Fagard et al. 1996 [31]</td>
<td>143</td>
<td>16.2</td>
<td>M (100%)</td>
<td>Range: 35±12</td>
<td>Brachial artery cannulation/Maximal</td>
<td>Moderate</td>
<td>Bicycle 30W/4min.</td>
<td>38 composite CV events</td>
<td>Continuous</td>
<td>Continuous only</td>
<td>Continuous only</td>
<td>Age, Age squared, Office BP.</td>
<td>No (continuous only) parameters</td>
</tr>
<tr>
<td>4</td>
<td>Kohi et al. 1996 [32]</td>
<td>26,621</td>
<td>8.1</td>
<td>M (76%)</td>
<td>Mean: 42</td>
<td>Auscultation/ sphygm.</td>
<td>Maximal</td>
<td>Balke treadmill</td>
<td>105 CV composite events</td>
<td>Categorical</td>
<td>Continuous</td>
<td>Moderate SBP&lt;200mmHg</td>
<td>Age, BMI, Office BP. Treadmill time, Cholesterol, Glucose, CV family history, ECG changes, Smoking.</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Kurl et al. 2001 [33]</td>
<td>1,026</td>
<td>10.4</td>
<td>M (100%)</td>
<td>Mean: 52±5</td>
<td>Mercury sphygmomanometer/Maximal</td>
<td>Moderate</td>
<td>Bicycle 20W/min.</td>
<td>46 Cerebrovascular events</td>
<td>Continuous</td>
<td>Continuous only</td>
<td>Continuous only</td>
<td>Age, Examination years, Alcohol consumption, Smoking, LDL, T2DM, BMI.</td>
<td>No (not adjusted for office BP; continuous only)</td>
</tr>
<tr>
<td>6</td>
<td>Laukanen et al. 2006 [34]</td>
<td>1,731</td>
<td>12.7</td>
<td>M (100%)</td>
<td>Mean: 52±5</td>
<td>Mercury sphygmomanometer</td>
<td>Maximal</td>
<td>Bicycle (20W/3 min)</td>
<td>188 AMI</td>
<td>Categorical</td>
<td>Maximal SBP&lt;230mmHg</td>
<td>Maximal SBP&gt;230mmHg</td>
<td>Age, Office BP, year, Antihypertensives, Alcohol, Smoking, LDL, HDL, T2DM, BMI. Exercise ischaemia LVH.</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>Lewis et al. 2008 [35]</td>
<td>3,045</td>
<td>20</td>
<td>M (47%)</td>
<td>Mean: 43</td>
<td>Mercury sphygmomanometer</td>
<td>Moderate</td>
<td>Bruce treadmill</td>
<td>240 CV events</td>
<td>Categorical</td>
<td>Moderate &lt;80th percentile SBP&lt;180mmHg</td>
<td>Moderate &gt;80th percentile SBP&gt;180mmHg</td>
<td>Age, Sex, Office BP, BMI, T2DM, Current smoking, Total H DL, VHD, ECG LVH, Exercise test variables.</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>Hietanen et al. 2010 [36]</td>
<td>3,808</td>
<td>15</td>
<td>M (66%)</td>
<td>Mean: 50±10</td>
<td>Mercury sphygmomanometer</td>
<td>Moderate</td>
<td>Bicycle (20w/5min.)</td>
<td>170 Coronary events</td>
<td>Categorical</td>
<td>Moderate SBP&lt;215mmHg</td>
<td>Moderate SBP&gt;215mmHg</td>
<td>Age, Sex, BMI, Smoking, Family history, Physical work capacity, Self-reported elevated cholesterol and abnormal glucose.</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>Weiss et al. 2010 [37]</td>
<td>6,578</td>
<td>20.1 ± 4</td>
<td>M (55%)</td>
<td>Mean: 46</td>
<td>Cuff technique</td>
<td>Sub-maximal</td>
<td>Bruce treadmill</td>
<td>385 CV deaths</td>
<td>Categorical</td>
<td>Moderate SBP&lt;146mmHg</td>
<td>Moderate SBP&gt;180 mmHg</td>
<td>Age, Sex, Office BP, T2DM, LDL, HDL, Triglycerides, Smoking, BMI, Family history.</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>Skretteberg et al. 2013 [38]</td>
<td>1,392</td>
<td>28</td>
<td>M (100%)</td>
<td>Mean: 49.2</td>
<td>Mercury sphygmomanometer</td>
<td>Moderate</td>
<td>Bicycle (100W/6min.)</td>
<td>186 CHD deaths 292 CV events</td>
<td>Categorical</td>
<td>Moderate SBP&lt;160mmHg</td>
<td>Moderate SBP&gt;185 mmHg</td>
<td>Family history, Age, Resting SBP, Total cholesterol, Smoking, BMI, SBP100W, Maximal SBP, PF, Resting DBP, Resting HR, Fasting BG.</td>
<td>Yes</td>
</tr>
<tr>
<td>11</td>
<td>Mariampilla et al. 2017 [39]</td>
<td>2,014</td>
<td>35</td>
<td>M (100%)</td>
<td>Range: 40-59</td>
<td>Mercury sphygmomanometer</td>
<td>Moderate</td>
<td>Bicycle (100W/6min.)</td>
<td>226 CV events 309 CV deaths</td>
<td>Categorical</td>
<td>Moderate SBP=100-160 mmHg</td>
<td>Moderate SBP=200-275 mmHg</td>
<td>Age, resting SBP, current smokers, Total cholesterol, Family history, BMI, SBP 100W, Maximal SBP, PF, Resting DBP, Resting HR, Fasting BG.</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Abbreviations:** CV: cardiovascular; CHD: Coronary heart disease; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; PF: physical fitness, T2DM: Type 2 Diabetes mellitus; LDL: Low density lipoprotein; HDL: High density lipoprotein; BMI: Body mass index; SD: Standard deviation; AMI: Acute myocardial infarction; ECG: Electrocardiogram, LVH: Left ventricular hypertrophy; HR: Heart rate; BG: Blood glucose, W: Watt