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Screening Asymptomatic Adults With Resting or Exercise Electrocardiography: A Review of the Evidence for the U.S. Preventive Services Task Force

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Background: Coronary heart disease is the leading cause of death in adults. Screening for abnormalities by using resting or exercise electrocardiography (ECG) might help identify persons who would benefit from interventions to reduce cardiovascular risk.

Purpose: To update the 2004 U.S. Preventive Services Task Force evidence review on screening for resting or exercise ECG abnormalities in asymptomatic adults.

Data Sources: MEDLINE (2002 through January 2011), the Cochrane Library database (through the fourth quarter of 2010), and reference lists.

Study Selection: Randomized, controlled trials and prospective cohort studies.

Data Extraction: Investigators abstracted details about the study population, study design, data analysis, follow-up, and results and assessed quality by using predefined criteria.

Data Synthesis: No study evaluated clinical outcomes or use of risk-reducing therapies after screening versus no screening. No study estimated how accurately resting or exercise electrocardiography classified participants into high-, intermediate-, or low-risk groups, compared with traditional risk factor assessment alone. Sixty-three prospective cohort studies evaluated abnormalities on resting or exercise ECG as predictors of cardiovascular events after adjustment for traditional risk factors. Abnormalities on resting ECG (ST-segment or T-wave abnormalities, left ventricular hypertrophy, bundle branch block, or left-axis deviation) or exercise ECG (ST-segment depression with exercise, chronotropic incompetence, abnormal heart rate recovery, or decreased exercise capacity) were associated with increased risk (pooled hazard ratio estimates, 1.4 to 2.1). Evidence on harms was limited, but direct harms seemed minimal (for resting ECG) or small (for exercise ECG). No study estimated harms from subsequent testing or interventions, although rates of angiography after exercise ECG ranged from 0.6% to 2.9%.

Limitations: Only English-language studies were included. Statistical heterogeneity was present in several of the pooled analyses.

Conclusion: Abnormalities on resting or exercise ECG are associated with an increased risk for subsequent cardiovascular events after adjustment for traditional risk factors, but the clinical implications of these findings are unclear.

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Coronary heart disease (CHD) is the leading cause of death in U.S. adults (1, 2). Many persons do not experience symptoms before a major first CHD event, such as sudden cardiac arrest, myocardial infarction, congestive heart failure, or unstable angina (3). Traditional Framingham risk factors (age, sex, blood pressure, serum total or low-density lipoprotein cholesterol concentration, high-density lipoprotein cholesterol concentration, cigarette smoking, and diabetes) can help predict future CHD events but do not explain all of the excess risk (4, 5). Supplementing traditional risk factor assessment with other methods, including resting or exercise electrocardiography (ECG), might help better guide use of risk-reduction therapies in asymptomatic persons without known CHD (6).

In 2004, the U.S. Preventive Services Task Force (USPSTF) recommended against screening with resting or exercise ECG in adults at low risk for CHD (D recommendation) and found insufficient evidence for a recommendation in adults at increased risk (I recommendation) (7). To update its recommendations, the USPSTF commissioned a new evidence review in 2009 to systematically evaluate the current evidence on screening with resting or exercise ECG. Our report differs from earlier USPSTF reviews because we focused on studies that adjusted for traditional cardiovascular risk factors, performed meta-analysis, and evaluated whether screening with ECG in improves risk reclassification. The key questions, analytic framework (**Appendix Figure**, available at www.annals.org), and scope were developed in accordance with previously published USPSTF processes and methods. The key questions were as follows:

1. What are the benefits of screening for abnormalities on resting or exercise electrocardiography compared with no screening on coronary heart disease outcomes?

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Context

What are the potential benefits of screening electrocardiography (ECG)?

Contribution

Studies included in this systematic review showed that some abnormalities found on resting or exercise ECG were independent predictors of future cardiovascular events. No study compared clinical outcomes or use of risk-reducing therapies between persons who did and did not receive screening ECG. No studies assessed whether ECG findings better classified patients into meaningful risk groups than did traditional risk factor assessment alone.

Implication

Some abnormalities on ECG are risk factors for cardiovascular events, but the benefits and clinical implications of routine ECG screening are not clear.

—The Editors

2. How does the identification of high-risk persons via resting or exercise electrocardiography affect use of treatments to reduce cardiovascular risk?

3. What is the accuracy of resting or exercise electrocardiography for stratifying persons into high-, intermediate- and low-risk groups?

4. What are the harms of screening with resting or exercise electrocardiography?

METHODS

We followed a standard protocol for this review. Detailed search strategies, selection criteria, evidence tables, quality assessments, and forest plots are available in a technical report available at the Agency for Healthcare Research and Quality (AHRQ) Web site (8).

Data Sources

We searched MEDLINE from 2002 through January 2011 and the Cochrane Library database through the fourth quarter of 2010 to identify relevant English-language articles. We also reviewed reference lists of relevant articles and included studies from the previous USPSTF review that met inclusion criteria.

Study Selection

We included studies that evaluated persons without symptoms of CHD, reported results separately for asymptomatic persons, or had fewer than 10% of participants with symptoms. Randomized, controlled trials and controlled observational studies were included if they evaluated the effects of screening with resting or exercise ECG versus no screening on clinical outcomes (benefits or harms) or the use of lipid-lowering therapy or aspirin (interventions for which recommended use varies by assessed cardiovascular risk). Prospective cohort studies that reported rates of cardiovascular outcomes and controlled for at least 5 of the 7 Framingham cardiovascular risk factors (male sex, age, tobacco use, diabetes, hypertension, total or low-density lipoprotein cholesterol concentration, and high-density lipoprotein cholesterol concentration) by means of restriction (such as by enrolling only male participants) or adjustment were also included. Two reviewers independently evaluated each study to determine inclusion eligibility. Only published studies were included.

Data Extraction and Quality Assessment

One investigator abstracted details about the population, study design, analysis, and duration of follow-up; the Framingham risk factors and other adjusted confounding factors; and results. A second investigator reviewed the data abstraction for accuracy. Two investigators independently applied criteria developed by the USPSTF (9) to rate the quality of each study as good, fair, or poor. Discrepancies in quality ratings were resolved by consensus.

Data Synthesis and Analysis

Using methods developed by the USPSTF, we assessed the aggregate internal validity (quality) of the body of evidence for each key question as good, fair, or poor, on the basis of the number, quality, and size of the studies; consistency of results between studies; and directness of evidence (9).

To evaluate the benefits of screening for asymptomatic CHD, we focused on (in order of preference) death from CHD, death from cardiovascular disease, nonfatal myocardial infarction, all-cause mortality, stroke, other cardiovascular outcomes (such as congestive heart failure), and composite cardiovascular outcomes. The accuracy of screening with ECG for identifying the presence or degree of asymptomatic atherosclerosis was not evaluated because of its unclear clinical implications. Participant anxiety, labeling, and rates and consequences of subsequent tests and procedures were evaluated to assess the harms of screening. Other USPSTF reviews (10, 11) have evaluated adverse outcomes associated with lipid-lowering therapy and aspirin.

Several methods were used to assess the incremental value of resting or exercise ECG (12). We evaluated how adding screening with ECG to traditional risk factor assessment affects reclassification of persons as being at high (10-year risk for CHD events >20%), medium (10% to 20%), or low (<10%) risk compared with classification on the basis of traditional risk factors alone (13). The recent literature (13–16) has emphasized understanding the frequency and accuracy by which people are reclassified into different risk categories, which can have an important effect on clinical decisions (6, 17). We also evaluated how adding resting or exercise ECG to traditional risk factor assessment changed the c-statistic (which measures how accurately a risk assessment method separates persons with from those without a disease or outcome [18]), when this was reported, and whether screening with ECG improves calibration (the degree to which predicted and observed risk estimates agree [15]).

Most studies did not provide sufficient data to estimate the degree and accuracy of reclassification. They instead provided an estimate of risk associated with the presence (vs. the absence) of abnormalities on ECG after adjustment for traditional risk factors. We used Stata/IC, version 11.1 (StataCorp, College Station, Texas), to conduct meta-analyses of abnormalities on ECG that were evaluated by at least 3 studies of (in order of preference) adjusted estimates of risk for CHD death, death from cardiovascular disease, nonfatal myocardial infarction, all-cause mortality, or composite cardiovascular outcomes, using the Dersimonian–Laird random-effects model (19). Heterogeneity was estimated by using the I^2 statistic (20). If at least 5 studies evaluated an electrocardiographic abnormality, potential sources of heterogeneity were assessed by stratifying studies according to the outcome evaluated, study quality, and use of different definitions for the abnormality being evaluated. Sensitivity analyses were performed that excluded outlier studies, if present. Meta-regression was also performed on the proportion of men enrolled in the study, the number of traditional risk factors adjusted for (range, 5 to 7), and the duration of follow-up.

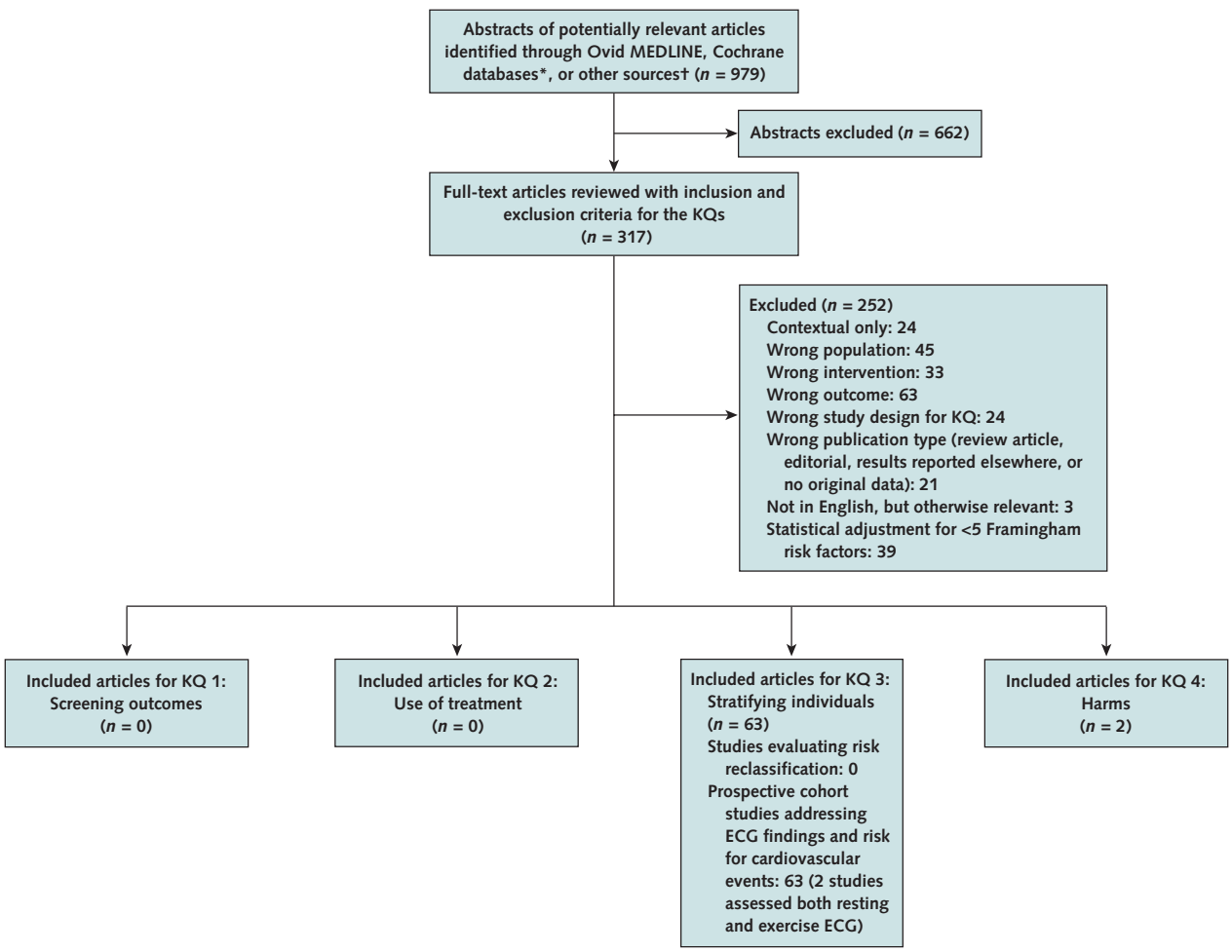
Role of the Funding Source

Our study was funded by AHRQ under a contract to support the work of the USPSTF. Staff at AHRQ and members of the USPSTF helped to develop the scope of the work and reviewed draft manuscripts. Approval from AHRQ was required before manuscript could be submitted for publication, but the authors are solely responsible for the content and the decision to submit it for publication.

RESULTS

The **Figure** shows the results of the evidence search and selection process.

Figure. **Summary of evidence search and selection.**



ECG = electrocardiography; KQ = key question.
* Includes the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
† Includes studies identified from reference lists or suggested by experts.

Table 1. **Summary of Pooled Risk Estimates for Subsequent Cardiovascular Events With Abnormalities on Resting or Exercise ECG**

Type of ECG and Abnormality	Studies (References), *n*	Pooled Adjusted HR (95% CI)	I^2 Value, %
Resting ECG			
ST-segment abnormalities	5 (27, 29, 33, 36, 39)	1.9 (1.4–2.5)	62
T-wave abnormalities	6 (27, 29, 33, 39, 45)	1.6 (1.3–1.8)	56
ST-segment or T-wave abnormalities	7 (28, 31, 33, 41, 42, 49, 50)	1.9 (1.6–2.4)	50
Left ventricular hypertrophy	8 (24, 25, 29, 35, 36, 39, 41, 50)	1.6 (1.3–2.0)	46
Bundle branch block	4 (29, 39, 41, 42, 67, 68, 69)	1.5 (0.98–2.3)	46
Left-axis deviation	3 (29, 41, 50)	1.5 (1.1–1.9)	0
Exercise ECG			
ST-segment depression with exercise	12 (23, 24, 52, 55, 56, 58, 59, 63, 69, 72, 76, 81)	2.1 (1.6–2.9)	71
Chronotropic incompetence	4 (51, 52, 66, 72)	1.4 (1.3–1.6)	0
Abnormal heart rate recovery*	3 (23, 54, 74)	1.5 (1.3–1.9)	0
Decreased exercise capacity or fitness	6 (23, 53, 61, 69, 77, 85)	Range, 1.7–3.1 (could not be pooled)	–

ECG = electrocardiography; HR = hazard ratio.
* Estimate is for all-cause mortality; cardiovascular-specific outcomes could not be pooled.

Key Question 1

What are the benefits of screening for abnormalities on resting or exercise electrocardiography compared with no screening on coronary heart disease outcomes?

Similar to the previous USPSTF reviewers (21), we found no randomized, controlled trials or prospective cohort studies on the effects of screening asymptomatic adults with resting or exercise ECG versus no screening on clinical outcomes.

Key Question 2

How does the identification of high-risk persons via resting or exercise electrocardiography affect use of treatments to reduce cardiovascular risk?

Like the previous USPSTF reviewers (21), we identified no studies that evaluated how screening affects use of lipid-lowering therapy or aspirin.

Key Question 3

What is the accuracy of resting or exercise electrocardiography for stratifying persons into high-, intermediate- and low-risk groups?

No study estimated how accurately resting or exercise electrocardiography classified participants into high-, intermediate-, or low-risk groups compared with traditional risk factor assessment alone, or provided sufficient data for constructing risk-stratification tables (13). One study in women (22) found that adding resting ECG findings to the Framingham risk score increased the c-statistic for prediction of future CHD events from 0.69 to 0.74, but the CIs for the estimates overlapped substantially. Another study in men and women (23) reported a c-statistic of 0.73 for traditional risk factor assessment by using the European Systematic Coronary Risk Evaluation (SCORE) alone versus 0.76 for SCORE plus exercise ECG variables (CIs not reported).

Twenty-seven prospective cohort studies of resting ECG, reported in 28 publications (22, 24–50), and 38 prospective cohort studies of exercise ECG (23, 24, 34, 51–85) evaluated abnormalities on baseline ECG and risk for subsequent cardiovascular events; 2 studies (24, 34) evaluated both resting and exercise ECG (**Supplement Tables 1** and **2**, available at www.annals.org). Excluding double-counted populations, we evaluated resting ECG in 173 710 participants and exercise ECG in 91 746 participants. Duration of follow-up ranged from 3 years (31, 79) to 56 years (27). Ten studies of resting ECG (22, 24, 29, 30, 32, 34, 36, 44, 45, 50) and 19 studies of exercise ECG (24, 34, 51, 52, 54–58, 60, 63, 67–69, 72, 75, 78, 80, 83) were rated good-quality; the rest were rated fair-quality. The most common methodological shortcomings were no description of handling of participants with uninterpretable ECG results (43 of 62 studies), loss to follow-up (39 of 62 studies), or race in reports of baseline demographic characteristics (31 of 62 studies). Three studies (70, 71, 79), discussed separately, only enrolled persons with diabetes mellitus or impaired fasting glucose.

Several abnormalities on resting ECG were associated with an increased risk for subsequent cardiovascular events (**Table 1**). The pooled adjusted hazard ratio (HR) was 1.9 (95% CI, 1.4 to 2.5; I^2 = 62%) for persons with resting ST-segment abnormalities (5 studies [27, 29, 33, 36, 39]), 1.6 (CI, 1.3 to 1.8; I^2 = 56%) for those with T-wave abnormalities (6 studies [27, 29, 33, 36, 39, 45]), and 1.9 (CI, 1.6 to 2.4; I^2 = 50%) for those with either ST-segment or T-wave abnormalities (7 studies [28, 31, 33, 41, 42, 49, 50]).

Left ventricular hypertrophy (LVH), left-axis deviation, and bundle branch block on resting ECG were each associated with a similar risk for subsequent cardiovascular events. The pooled adjusted HR was 1.6 (CI, 1.3 to 2.0; I^2 = 46%) for LVH (8 studies [24, 25, 29, 35, 36, 39, 41, 50]), 1.5 (CI, 1.1 to 1.9; I^2 = 0%) for left-axis deviation (3 studies [29, 41, 50]), and 1.5 (CI, 0.98 to 2.3; I^2 = 46%) for bundle branch block (4 studies [29, 39, 41, 42]).

Six studies (22, 29, 37, 38, 41, 50) evaluated major or minor abnormalities on resting ECG and subsequent cardiovascular events, but the results could not be pooled

because the definitions of major and minor varied (**Table 2**). Two studies (29, 41) reported an association between presence of a major abnormality on resting ECG and CHD death over 10 years (HR, 2.3 [CI, 1.5 to 3.7] and 3.1 [CI, 1.9 to 5.1], respectively), and a third (22) reported an association with CHD events over 5 years (HR, 3.0 [CI, 2.0 to 4.5]). In each study, the risk estimate for minor abnormalities was weaker than the estimate for major abnormalities. For example, 1 study (41) reported HRs of 1.8 (CI, 1.3 to 2.5) for minor abnormalities and subsequent CHD death and 3.1 (CI, 1.9 to 5.1) for major abnormalities. In some studies (29, 50), the association between minor abnormalities and subsequent CHD events did not reach statistical significance.

Other abnormalities on resting ECG have been evaluated, including prolonged QT interval, ischemic changes, atrial fibrillation, right-axis deviation, Q waves, ventricular premature contractions, and high resting heart rate (26, 32, 34, 38–40, 42, 46–48, 86), but these were evaluated in too few studies or were too variably defined to draw firm conclusions about their usefulness as predictors. Several studies were not included in the meta-analyses because they evaluated nonpooled outcomes or electrocardiographic abnormalities. One study (43) found ST-segment abnormalities (but not T-wave abnormalities or LVH) associated with increased risk for stroke over 0 to 30 years of follow-up (HR, 3.4 [CI, 2.1 to 5.4]), and another (32) found an association between ST-segment or T-wave abnormalities and incident congestive heart failure (HR, 1.6 [CI, 1.3 to 2.1]). In 1 study, incomplete bundle branch block (HR, 1.4 [CI, 1.0 to 2.0]) and complete bundle branch block (HR, 1.7 [CI, 1.3 to 2.4]) were associated

Table 2. **Major and Minor Abnormalities on ECG as Predictors of Cardiovascular Events**

Study, Year (Reference)	Study Name	Sample Size, *n*	Mean Age (Range), *y*	Men, %	Mean Duration of Follow-up, *y*	Definition (Prevalence) of ECG Abnormalities		HR for Events With Major or Minor ECG Abnormalities Compared With No Abnormalities (95% CI)
						Major	Minor	
De Bacquer et al, 1998 (29)	Belgian Inter-University Research on Nutrition and Health	9954	48 (25–74)	52	10	Minnesota code 4.1, 4.2, 5.1, 5.2, 6.1, 6.2, 7.1, 7.2, 8.1, or 8.3 (29%)	Minnesota code 1.3, 2.1, 2.2, 3.1, 3.2, 4.3, 5.3, or 9.1 (3.6%)	CHD death: major, 2.3 (1.5–3.7); minor, 1.1 (0.77–1.7)
Denes et al, 2007 (22)	Women's Health Initiative	14 749	63 (50–79)	0	5.2	Novacode 1.4, 1.5, 1.7, 1.8, 1.9, 2.3.1, 2.3.2, 2.4, 3.1.0, 3.1.1, 3.2.0, 3.3.0, 3.3.1, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 6.1.1, 6.1.4, 6.1.7, or 6.1.8 (6.2%)	Novacode 2.1, 2.2.1, 3.4.1, 3.4.2, 4.1.1, 4.1.2, 5.7, 5.8, 6.1.0, 7.1, 8.1, 10.1, or 10.2 (28%)	CHD events: major, 3.0 (2.0–4.5); minor, 1.6 (1.1–2.1) CVD events: major, 2.3 (1.8–3.0); minor, 1.4 (1.1–1.7)
Liao et al, 1988 (37)	The Chicago Heart Association Detection Project in Industry	17 633	51	55	11.5	Minnesota code 6.1 or 6.2; 7.1, 7.2, or 7.4; 8.3; 8.1; 4.1; or 5.1 or 5.2 (11.1%)	Minnesota code 1.3, 2.1 or 2.2, 3.1, 3.2, 4.3, 5.3, 6.3, or 9.1 (6%)	CHD death: major, 3.7 for men and 1.9 for women; minor, 2.1 for men and 1.5 for women CVD death: major, 3.4 for men and 2.1 for women; minor, 2.1 for men and 1.5 for women All-cause mortality: major, 2.4 for men and 1.4 for women; minor, 1.7 for men and 1.2 for women*
Macfarlane et al, 2007 (38)	West of Scotland Coronary Prevention Study	5835	55	100	4.9	Not assessed	Minnesota code 4.2, 4.3, 5.2, 5.3 (8%)	CHD death or nonfatal myocardial infarction: minor, 1.7 (1.3–2.3) All-cause mortality: minor, 2.2 (1.5–3.1)
Menotti et al, 2001 (41), and Menotti and Seccareccia, 1997 (42)	The FINE Study	1785	Not reported (65–84)	100	10	Minnesota code 1.1, 4.1, 5.1, 6.8, 7.1, 7.4, or 8.3 (8%)	Minnesota code 1.2, 1.3, 2.1, 4.2–4.4, 5.2–5.3, 6.4, 7.2, 7.3, or 8.1 (39%)	CHD death: major, 3.1 (1.9–5.1); minor, 1.8 (1.3–2.5)†
Sutherland et al, 1993 (50)	Charleston Heart Study	993	48 (35–74)	100	30	Minnesota code 4.1, 4.2, 5.1, 5.2, 7.1, 7.2, 7.4, 8.1, or 8.3 (9%)	Minnesota code 1.3, 2.1, 2.2, 3.1, 4.3, 5.3, 6.3, or 9.1 (14%)	CHD death: major, 2.7 (1.5–5.0) for white men and 2.0 (0.93–4.1) for black men; minor, 1.3 (0.74–2.1) for white men and 0.58 (0.24–1.4) for black men All-cause mortality: major, 2.1 (1.4–3.1) for white men and 1.4 (0.91–2.1) for black men; minor, 1.2 (0.92–1.7) for white men and 0.79 (0.52–1.2) for black men

CHD = coronary heart disease; CVD = cardiovascular disease; ECG = electrocardiography; FINE = Finland, Italy, and the Netherlands; HR = hazard ratio.
* No CIs were reported.
† Compared with absent or marginal abnormalities.

with greater risk for congestive heart failure than no bundle branch block (30). Another study (44) found new or incident LVH on 6-year follow-up ECG to be associated with increased risk for CHD death.

Several abnormalities on exercise ECG were also associated with an increased risk for subsequent cardiovascular events (**Table 1**). The most frequently evaluated abnormality, ST-segment depression with exercise (12 studies [23, 24, 52, 55, 56, 58, 59, 63, 69, 72, 76, 81]), was associated with an adjusted pooled HR of 2.1 (CI, 1.6 to 2.9).

In 4 studies (51, 52, 66, 72), chronotropic incompetence on exercise ECG (defined as inability to reach 85% or 90% of maximum predicted heart rate) was associated with a pooled adjusted HR of 1.4 (CI, 1.3 to 1.6; I^2 = 0%) for subsequent cardiovascular events. Abnormal heart rate recovery (defined as a decrease of <12 beats/min from peak heart rate 1 minute into recovery or of <42 beats/min after 2 minutes) was associated with a pooled adjusted HR for all-cause mortality of 1.5 (CI, 1.3 to 1.9; I^2 = 0%) in 3 studies (23, 54, 74). Studies that were excluded from the meta-analysis because they evaluated ECG findings as multicategory or continuous variables also found that lower maximum heart rate (24, 34, 84) and slower return to baseline heart rate were associated with increased risk (34).

Decreased exercise capacity or fitness (on the basis of metabolic equivalents or watts achieved or exercise duration) was consistently associated with increased risk for subsequent cardiovascular events or mortality in 9 studies (23, 53, 60, 61, 69, 77, 81, 82, 85), but results could not be pooled because of the different methods of measurement and analysis. In 6 studies (23, 53, 61, 69, 77, 85), adjusted HRs for subsequent cardiovascular events or all-cause mortality ranged from 1.7 to 3.1 for lower versus higher exercise capacity categories. In 5 studies (23, 60, 69, 81, 82), lower exercise capacity was also predictive when analyzed as a continuous variable.

Two studies (63, 72) found ventricular ectopy during or after exercise ECG to be associated with increased risk for cardiovascular events (HR, 2.5 [CI, 1.6 to 3.9] and 1.7 [CI, 1.1 to 2.6], respectively). One study each found decreased peak oxygen pulse (53), lower Duke treadmill score (60), and "abnormal" (undefined) exercise ECG (53) associated with increased risk for cardiovascular events. Finally, 1 study (73) found that having both low heart rate recovery and low metabolic equivalents was a stronger predictor of death from cardiovascular disease than having either abnormality alone.

Stratifying the studies in the meta-analyses by type of cardiovascular outcome assessed, study quality, or restriction to men resulted in estimates that were similar to the overall pooled estimates and did not reduce observed statistical heterogeneity. An exception was LVH on resting ECG, for which estimates were lower for the 4 studies rated good-quality (HR, 1.2 [CI, 0.9 to 1.7]; I^2 = 31%) (24, 29, 36, 50) than for the 4 rated fair-quality (HR, 2.0 [CI, 1.6 to 2.5]; I^2 = 0%; P for difference = 0.03) (25, 35, 39, 41). Variability in the proportion of men, duration of follow-up, or number of traditional risk factors adjusted for also did not explain the between-study variance in estimates. Excluding the outlier trials (23, 72) from the meta-analysis of ST-segment depression on exercise ECG did not reduce statistical heterogeneity or result in different estimates. In studies that stratified results by sex (26, 29, 33, 37, 39, 42, 52, 53, 73, 85), estimates of risk associated with various abnormalities in resting and exercise ECG were either similar for men and women or had overlapping CIs.

Two studies (70, 79) evaluated exercise ECG in diabetic participants. One study (70) found that 1-mm ST-segment depression or elevation with exercise was associated with increased risk for CHD death (HR, 2.1 [CI, 1.3 to 3.3]). The second study (79) also found that exercise-induced ST-segment depression was associated with increased risk for CHD events, but the sample size was small (86 participants) and the CI was very wide (HR, 21 [CI, 2 to 204]). One other study (71) found higher fitness on exercise ECG (on the basis of maximum exercise duration and metabolic equivalents) was associated with a lower risk for all-cause mortality than low fitness (HR, about 0.65 for either moderate or high fitness) in women with impaired fasting glucose or undiagnosed diabetes.

Key Question 4

What are the harms of screening with resting or exercise electrocardiography testing?

Direct Harms

No studies reported harms directly associated with resting ECG. For exercise ECG, 1 study with 377 participants (87), included in the previous USPSTF review, reported no complications as a direct result of screening. Survey data that included symptomatic participants undergoing exercise ECG reported arrhythmia in fewer than 0.2%, acute myocardial infarction in 0.04%, and sudden cardiac death in 0.01% (88). The overall risk for experiencing sudden death or an event that requires hospitalization has been estimated to be 1 per 10 000 tests (88).

Harms Associated With Subsequent Tests or Interventions

We identified no studies on harms associated with follow-up testing or interventions after a screening resting or exercise ECG. In 9 studies (87, 89–96), summarized in the previous USPSTF evidence review (97), rates of subsequent angiography in primarily asymptomatic participants after an abnormal exercise ECG ranged from 0.6% to 2.9%, excluding an outlier study of hypertensive veterans (94) with a 13% angiography rate. Two subsequent studies of screening exercise ECG (23, 55), comprising 4605 participants, found that 0.6% and 1.7% of the total sample subsequently had angiography, and 0.1% (4 of 3554) and

Table 3. **Summary of Evidence**

Key Question	Studies, *n*	Overall Quality Rating	Summary of Findings
1. What are the benefits of screening for abnormalities on resting or exercise electrocardiography compared with no screening on coronary heart disease outcomes?	None	–	No randomized, controlled trials or controlled observational studies of screening asymptomatic adults for CHD with resting or exercise ECG versus no screening were identified.
2. How does the identification of high-risk persons via resting or exercise electrocardiography affect use of treatments to reduce cardiovascular risk?	None	–	No studies were identified that evaluated how screening patients for CHD by using resting or exercise ECG affects use of interventions to reduce cardiovascular risk.
3. What is the accuracy of resting or exercise electrocardiography for stratifying persons into high-, intermediate- and low-risk groups?	None on risk reclassification, 2 on changes in the c-statistic, and 63 on risk associated with abnormalities on ECG	Fair	No study estimated how accurately resting or exercise ECG plus traditional risk factor assessment classified patients into high-, intermediate-, or low-risk groups compared with classification on the basis of traditional risk factor assessment alone, or provided sufficient data for risk stratification tables to estimate risk reclassification rates. Two studies found resting or exercise ECG findings plus traditional risk factor assessment resulted in a slight increase in the c-statistic compared with traditional risk factor assessment alone. Pooled analyses showed that abnormalities on resting ECG (ST-segment or T-wave abnormalities, left ventricular hypertrophy, bundle branch block, or left-axis deviation) or exercise ECG (ST-segment depression with exercise, failure to reach maximum target heart rate, or low exercise capacity) are associated with an increased risk (pooled hazard ratio estimates from 1.4 to 2.1) for subsequent cardiovascular events, after adjustment for traditional risk factors.
4. What are the harms of screening with resting or exercise electrocardiography?	2 studies	Poor	No studies reported harms directly associated with screening with resting ECG. One study (included in the previous report) found no complications in 377 patients who had screening with exercise ECG. No studies reported downstream harms associated with follow-up testing or interventions after screening with resting or exercise ECG.

CHD = coronary heart disease; ECG = electrocardiography.

0.5% (5 of 1051), respectively, had a subsequent revascularization procedure.

None of these studies estimated complications associated with angiography or revascularization procedures. On the basis of large, population-based registries that include symptomatic persons (98), the risk for any serious adverse event as a result of angiography is about 1.7%; this includes risk for death (0.1%), myocardial infarction (0.05%), stroke (0.07%), and arrhythmia (0.4%).

Coronary angiography, computed tomography angiography, and myocardial perfusion imaging are associated with radiation exposure that could increase cancer risk. Coronary angiography is associated with an average effective radiation dose of 7 mSv and myocardial perfusion imaging with a dose of 15.6 mSv (99).

Persons who have an abnormal screening result and undergo additional testing, but do not have coronary artery disease, are subjected to potential harms without the possibility of benefit. One study included in the previous USPSTF review (96) found severe coronary artery disease in 15% of participants who had angiography; another (89) found that 55% of participants who underwent angiography had greater than 50% occlusion and 37% had greater than 70% occlusion in at least 1 coronary artery. A recent, large (nearly 400 000 participants) study (100) of a primarily symptomatic population (70%) who had angiography found that 39% had no coronary artery disease (defined as <20% stenosis).

DISCUSSION

Table 3 summarizes our results. Like the previous USPSTF reviewers, we found no studies that evaluated clinical outcomes or use of lipid-lowering therapy or aspirin after screening with resting or exercise ECG compared with no screening. Another critical research gap is that no studies directly evaluated the incremental value of adding screening with ECG to traditional risk factor assessment for accurately classifying persons into different risk categories. The lack of information on reclassification is critical from a clinical perspective because decisions regarding therapies for reducing cardiovascular risk are often based on whether a person is classified as having low (<10% risk over the next 10 years), intermediate, or high (>20%) risk for future CHD events. On the basis of current data, we cannot determine the degree to which resting or exercise ECG accurately moves a person from one risk category to another, rather than yielding a more precise estimate in a risk category (which is less clinically useful). For example, in populations at very low (<5%) risk for CHD events,

such as most young adults, even a doubling of risk would not move a person from a lower to a higher risk category. Similarly, abnormalities on resting or exercise ECG are unlikely to change management decisions for persons who are already at high risk on the basis of traditional risk factor assessment. The greatest potential benefits of screening with ECG would be for intermediate-risk persons, because the presence of abnormalities would shift such persons into a high-risk group for whom additional interventions might be warranted. Two studies (22, 23) evaluated the effect on the *c*-statistic of adding resting or exercise ECG findings to traditional risk factor assessment compared with traditional risk factor assessment alone, but this measure is of limited clinical usefulness because it does not provide information about the actual predicted risks in an individual patient or the proportion of patients who are classified (or reclassified) as high-, intermediate-, or low-risk (13).

Most of the available evidence evaluated the association between abnormalities on resting ECG (ST-segment abnormalities, T-wave abnormalities, LVH, left-axis deviation, or bundle branch block) or exercise ECG (ST-segment depression with exercise, chronotropic incompetence, impaired heart rate recovery, or decreased exercise capacity) and risk for subsequent cardiovascular events, after adjustment for traditional Framingham risk factors. The adjusted pooled HRs ranged from around 1.4 to around 2.1 for various abnormalities on resting or exercise ECG. Despite strong evidence that such abnormalities are associated with increased risk beyond that accounted for by assessment of traditional risk factors, understanding the usefulness of screening requires additional information on the reclassification that would result and on whether such reclassification would lead to clinical actions that improve patient outcomes (6).

Evidence on harms associated with screening ECG is limited. However, serious direct harms seem to be minimal with resting ECG (other than possible anxiety or labeling) and small or rare with exercise ECG (for example, ischemia or injuries associated with exercise), assuming appropriate attention to contraindications to exercise testing and adherence to standard safety precautions. However, the potential downstream harms from additional testing or interventions that result from screening could be of greater concern. Some patients have angiography after a screening ECG and are therefore exposed to the potential harms related to that procedure, which include bleeding, radiation exposure, and contrast allergy or nephropathy. Patients who receive lipid-lowering therapy or aspirin because of screening ECG are exposed to the harms related to those interventions. Evidence on downstream harms associated with screening is not available, although data indicate that 0.6% to 1.7% of patients subsequently have angiography. A small proportion (<1%) of patients have revascularization with coronary artery bypass graft surgery or a percutaneous coronary intervention after screening exercise ECG, despite the risks of these interventions and their lack of benefits in asymptomatic persons (23, 55).

Our evidence review has limitations. We included only English-language studies, which could have resulted in language bias. A random-effects model was used to perform meta-analysis, because studies that evaluated the risk associated with various rest or exercise ECG abnormalities varied in quality and duration of follow-up, assessed different patient populations and cardiovascular outcomes, and used different methods to define the abnormalities. Although statistical heterogeneity was present in several of the meta-analyses, stratified analyses and meta-regression had little effect on estimates and conclusions. Referral bias could have resulted in underestimates of risk if identification of electrocardiographic abnormalities led to increased use of treatments effective at reducing cardiovascular risk.

Studies are needed to directly evaluate how screening with resting or exercise ECG affects clinical outcomes compared with no screening. Any screening study should also evaluate harms, including downstream harms related to additional testing and therapies. Although randomized trials would be desirable, well-conducted, nonrandomized prospective studies could also be informative. In the absence of direct evidence on the clinical effects of screening, data from future studies on risk prediction should enable estimates of reclassification, from which potential benefits of screening might be extrapolated on the basis of the known efficacy of interventions in high-risk populations. Decisions to allocate resources to update this or similar reviews on the usefulness of screening ECG might be predicated on the availability of such evidence, identified by using literature scans or other methods. Many of the studies included in our review evaluated large sample sizes over long periods, and the information needed to assess reclassification rates in these databases probably already exists. Reanalyzing preexisting databases would therefore be a more efficient method for obtaining information on reclassification than would initiating new studies.

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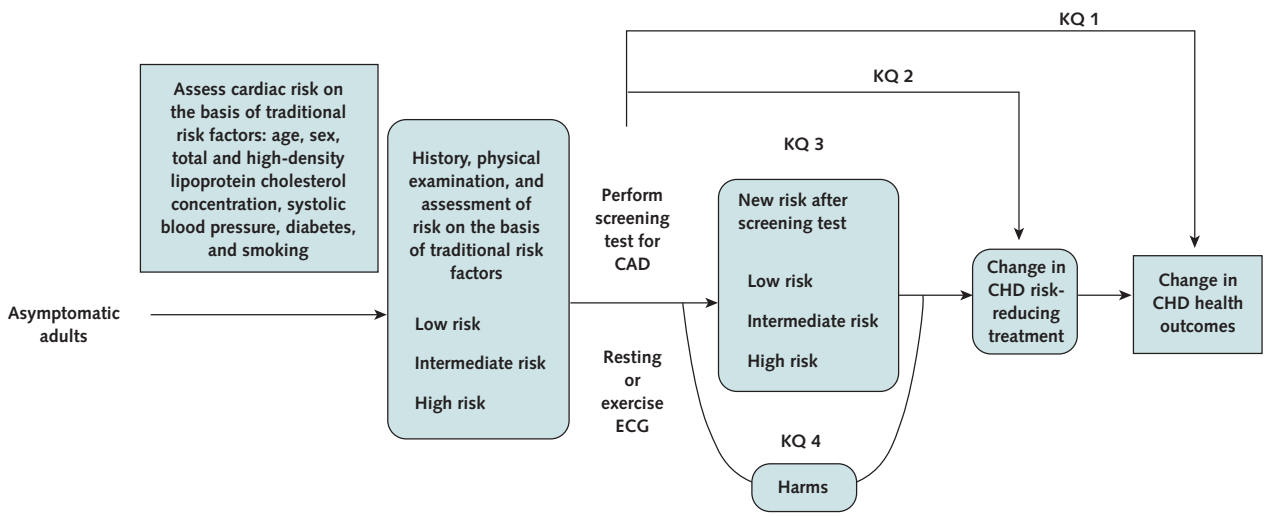
Appendix Figure. **Analytic framework and key questions.**



CAD = coronary artery disease; CHD = coronary heart disease; ECG = electrocardiography; KQ = key question.

Supplement Table 1. Cohort studies of resting electrocardiogram abnormalities as predictors of cardiovascular events

Author, year	Study name and country Population	Sample size and demographics	ECG abnormalities evaluated: prevalence	Mean follow-up (years)	Framingham risk factor adjusted for	All-cause mortality and incident CV events	Quality
Bodegard et al, 2004 (24)	Study not named Norway Work volunteers	n=2,014 Mean age: 50 years (range 40-59 years) 100% male Race NR	LVH: 5.3%	22	Age, sex, smoking, SBP, total cholesterol	CHD death: 15% All cause mortality: 37% Acute MI: 19% Coronary artery bypass graft surgery: 6.0% Stroke: 7.7%	Good
Brown et al, 2000 (25)	Second National Health and Nutrition Examination Survey (NHANES II) United States General community	n=7,924 Mean age: 49 years (range 25-74) 48% male 90% white 10% black	LVH: 1.9%	15	Sex, smoking, diabetes, SBP, total cholesterol	CHD death: 3.7% Heart disease death: 5.3%	Fair
Crow et al, 2003 (26)	Atherosclerosis Risk in Community (ARIC) Study	n=14,696 Mean age: 54 years (range 45- 64)	QTc: Continuous variable JTc: Continuous variable Wide QRS complex: 3.1%	13	Age, sex, smoking, diabetes, SBP, HDL, LDL	Incident MI or fatal CHD event: 5.6%	Fair

	United States General community	43% male 73% white					
Cuddy et al, 2006 (27) Other sources: www.mfus.ca	The Manitoba Follow-Up Study Canada Royal Canadian Air Force recruits	n=3,983 Mean age: 31 years (range 20-39) 100% male Race NR	Atrial fibrillation: 7% VPCs: 23% Atrioventricular block: 12% Right bundle branch block: 5% Left bundle branch block: 2% LVH: 12% ST and T-wave abnormalities: 22% (ST); 37% (T-wave)	56	Age, sex (100% male), smoking, diabetes, SBP, DBP	Sudden unexpected cardiac death: 4.3%	Fair
Daviglus et al, 1999 (28) Other publications: Oglesby, 1963 (101)	The Chicago Western Electric study United States Male electric company workers	n=1,673 Mean age: 47 years (range 40-55) 100% male Race NR	Minor ST-T abnormalities: 10.3%	29	Age, sex (100% male), smoking, SBP, total cholesterol	CHD death: 21% MI death: 14% CVD death: 28% All cause mortality: 53%	Fair
De Bacquer et al, 1998 (29)	Belgian Inter-University Research on Nutrition and Health (BIRNH) study Belgium General	n=9,954 Mean age: 48 years (range 25-74) 52% male Race NR	Any ECG abnormality: 29% Major ECG abnormality: 29% Minor ECG abnormality: 3.6% Ischemic ECG abnormality: 10% ST depression: 2%	10	Age, sex, smoking, diabetes, SBP, HDL, LDL, total cholesterol	CHD death: 1.3% CVD death: 2.4% All cause mortality: 7.9%	Good

	community		Abnormal T wave: 8% Arrhythmias: 6% Bundle branch blocks: 1% LVH: 0.6% Left axis deviation: 4%				
Denes et al, 2007 (22)	Women's Health Initiative United States Clinical trial enrollees	n=14,749 Mean age: 63 yrs (range 50-79) 0% male 84% white	Major ECG abnormality: 6.2% Minor ECG abnormality: 28%	5.2	Age, sex (100% female), smoking, diabetes, hypertension, statin use	CHD events: 4.0% CVD events: 1.7%	Good
Diercks et al, 2002 (31)	Prevention of Renal and Vascular End-stage Disease study The Netherlands General community	n=7,330 Mean age: 48 years (range 28-75) 50% male Race NR	ST-T changes: 17%	3	Age, sex, smoking, diabetes, hypertension, total cholesterol	CVD death: 0.3% All cause mortality: 1.2%	Fair
Dhingra et al, 2006 (30)	Framingham Heart Study United States General community	n=1,759 Mean age: 70 years (SD 7) 37% male Race NR	QRS duration 100-119 ms (incomplete bundle branch block): 17% QRS duration ≥120 ms (complete bundle branch block): 6%	12.7	Age, sex, smoking, diabetes, hypertension, HDL, total cholesterol	CHF: 18% (men 18%; women 19%)	Good
Gottdiener et al, 2000 (32)	Cardiovascular Health Study United States	n=4,652 (analyzed group with no	Major Q/QS waves: 5.2% LVH: 4.2% Isolated major ST-T wave	6.3	Age, sex, smoking, diabetes,	CHF: 8.5%	Good

Other publications: Furberg et al, 1992 (102)	General community	prevalent CHD) Mean age: 73 years (range 65-100 yrs; entire cohort, including prevalent CHD) 40% male 85% non-black	abnormalities: 6.3% Atrial fibrillation: 3.2% Atrioventricular block: 5.3% Ventricular conduction defects: 8.7% (Prevalences based on entire Cardiovascular Study cohort)		hypertension, HDL, LDL, total cholesterol		
Greenland et al, 2003 (33)	The Chicago Heart Association Detection Project in Industry United States Work-based	n=17,615 Mean age: 50 years (range 40-64) 55% male 95% white	Any ST changes: 3.6% men; 5.4% women Minor T-wave abnormality: 1.6% men; 1.9% women Minor ST depression: 1.2% men; 1.5% women	22	Age, sex, smoking, blood glucose, SBP, total cholesterol	CHD death: 7.1% CVD death: 9.9%	Fair
Jouven et al, 2005 (34)	Paris Protective Study I France Civil servants	n=5,713 Mean age: 48 years (range 42-53 years) 100% male Race not reported	High (>75 beats per minute) resting heart rate: 8%	23	Age, sex (100% male), smoking, diabetes, SBP, cholesterol	Fatal MI (sudden death): 1.4% Fatal MI (nonsudden death): 2.3% All-cause mortality: 27%	Good
Kahn et al, 1996 (35)	Bronx Longitudinal Aging Study United States	n=459 Mean age: 79 years (range 75-85)	LVH: 9.2%	10	Age, sex, smoking, hypertension,	CVD death: 19% MI death: 16% All cause mortality: 34%	Fair

	General community	35% male >95% white			total cholesterol	Cerebrovascular accident mortality: 3.3% All cardiovascular disease: 56% Fatal or non-fatal MI: 14% Fatal or non-fatal cerebrovascular accident: 7.6%	
Larsen et al, 2002 (36)	The Copenhagen City Heart Study Denmark General community	n=10.982 Mean age: 54 years (range 35-74) 45% male >98% white	Left ventricular hypertrophy: 11% T-wave inversion: 3.4% ST-T depression and T-wave inversion: 0.7% LVH + T-wave inversion: 0.8% LVH + ST-T depression + T-wave inversion: 0.7%	21	Age, sex, smoking, diabetes, SBP, total cholesterol	CVD death: 18% Fatal or non-fatal MI: 10% Fatal or non-fatal CHD events: 19%	Good
Liao et al, 1988 (37)	The Chicago Heart Association Detection Project in Industry United States Work-based	n=17,633 Mean age: 51 years 55% male 100% white	Major abnormality: 11.1% Minor abnormality: 6% Any abnormality: 17.5%	11.5	Age, sex, smoking, diabetes, DBP, total cholesterol	CHD death: 2.9% Cardiovascular death: 3.8% All cause mortality: 7.8%	Fair
MacFarlane et al, 2007 (38)	West of Scotland Coronary	n=5,835 Mean age 55 yrs	Left axis deviation MN code 2.1: 2.7% Right axis deviation	4.9 yrs	Age, sex (100% male), smoking, diabetes,	Definite MI: 5.4% Suspected MI:1.5% All-cause	Fair

	Prevention Study (WOSCOPS) United Kingdom	100% male Race NR	MN code 2.2 or 2.3: 0.5% High voltage left ventricular leads MN code 3.1: 5.1% High voltage right ventricular leads MN code 3.2: 0.06% ST abnormalities MN code 4.2 or 4.3: 2.3% T-wave abnormalities MN code 5.2 or 5.3: 7.9% Right bundle branch block MN code 7.2.1 or 7.8: 1% Definite or probable LVH MN code 3.1 + ST or T wave abnormalities: 0.6%; 0.3% Possible LVH MN code 3.1 or 3.3: 7.3% Minor ECG abnormality MN code 4.2, 4.3, 5.2, or 5.3: 7.7% T-wave inversion T-wave amplitude <0 mV: 2.6%		hypertension, HDL, total cholesterol	mortality: NR	
Machado et al, 2006 (39) Other publications: ARIC Investigators, 1989	Atherosclerosis Risk in Communities Study (ARIC) United States General	n=12,987 Mean age: 54 years (range 45-64) 43% male	Minor Q wave: 2% Prolonged QTc interval: 9% LVH (Cornell): 2% LVH (ST-T strain pattern): 2% Major ventricular conduction	11.6	Age, sex, smoking, diabetes, SBP, DBP, HDL, LDL	Incident CHD: 5.6%	Fair

(103)	community	74% white	defects: 2% Major ST depression: <1% Minor ST depression: 1% ST elevation: 1% Major T-wave findings: 4% Any ECG abnormality: 18.1%				
Massing et al, 2006 (40)	Atherosclerosis Risk in Communities Study (ARIC) United States General community	n=15,070 Mean age: 54 years (range 45-64) 45% male 74% white	Ventricular premature contractions: 6.2%	>10 (11.6 in other ARIC publications)	Age, sex, smoking, diabetes, hypertension, HDL, LDL	Asymptomatic population CHD death: 1.6% CHD events: 9.6% All cause mortality: 10.5%	Fair
Menotti et al, 1997 (42) Other publications: RIFLE Research Group, 1993 (104)	RIsk Factors and Life Expectancy (RIFLE) study Italy General community	n=22,553 Mean age: NR; 50% 50-69 years 54% male Race NR	Q-QS wave: 0.8% ST-T changes: 5.7% High R wave: 4.7% Arrhythmia: 1.2% Bundle branch blocks: 1.2%	6	Age, sex, smoking, SBP, total cholesterol	All-cause mortality (by subgroup) Q-QS: 1.6% ST-T: 1.6% High R wave: 0.9% Arrythmia:1.5% Blocks: 1.3%	Fair
Menotti et al, 2001 (41) Other publications: Menotti et al, 1997 (42)	The FINE Study Finland, the Netherlands and Italy General community	n=1,785 Mean age: Not reported (range 65-84 years) 100% male Race NR	Q-QS wave: 6.8% ST-T abnormality: 22% High R wave: 15% Left axis deviation: 13% Arrhythmia: 8.5% Bundle branch blocks: 7.3% Major abnormalities: 8.3% Minor abnormalities: 39%	10	Age, sex (100% male), smoking hypertension, total cholesterol	CHD death: 9%	Fair

Moller et al, 2007 (43)	Uppsala Longitudinal Study of Adult Men Sweden General community	n=2,322 Age 50 years (all participants were age 50 at enrollment) 100% male Race NR	Q/QS wave pattern: 1.3% LVH: 1.2% ST-segment depression: 2.3% T-wave abnormality: 5.9% Atrial fibrillation: 0.3%	Mean NR; follow-up >20 with max 32	Age, sex (100% male), smoking, diabetes, hypertension, HDL, LDL	Fatal and nonfatal stroke: 15% Fatal and nonfatal ischemic stroke: 10%	Fair
Prineas et al, 2001 (44)	Multiple Risk Factor Intervention Trial (MRFIT) United States Clinical trial enrollees	n=12,866 Mean age 46 years* (range 35-57), based on entire MRFIT cohort 100% male 93% white	New (incident) LVH on 6-year follow-up ECG based on various criteria: Sokolow-Lyon: 6% Cornell voltage: 1% Cornell Product: 2% Novacode: 5% MN code 3.1 or 3.3 + 5.1, 5.2 or 5.3: 4% Significant increase in LVH on 6-year follow-up ECG based on various criteria: Sokolow-Lyon: 0.5% Cornell voltage: 3.5% Cornell product: 2.8% Novacode: 1.4% □□ 12 product (sum of peak to-peak amplitudes of QRS complexes except lead avR, x QRS duration): 0.8%	16	Age, sex (100% male), DBP, total cholesterol, smoking	CHD death: 4.8% CVD death: 6.6%	Good
Prineas et al, 2002 (45)	Multiple Risk Factor	n=12,866 Mean age: 46	Minor T-wave abnormalities: 7.1%	18	Age, sex (100% male), smoking,	CHD death: 7.3% CVD death: 10%	Good

	Intervention Trial (MRFIT) United States Clinical trial enrollees	years (range 35-57), based on entire MRFIT cohort 100% male 93% white			diabetes, DBP, HDL, LDL	All cause mortality: 23%	
Rautaharju et al, 2006a and 2006b (47, 48)	Women's Health Initiative (WHI) United States Clinical trial enrollees	n=35,715 Mean age: 62 years (range 50-79) 0% male 82% white	QRS/T angle STV5 TV1 TV5 QTrr STV5 gradient Myocardial infarction by ECG Cornell voltage QRS non-dipolar voltage Ultrashort heart rate variability	6.2	Age, sex (100% female), smoking, diabetes, SBP	CHD death: 0.3% Incident CHF: 1.0% All cause mortality: 2.4% Nonfatal and fatal CHD events: 1.4%	Fair
Rautaharju et al, 2006c (46)	Cardiovascular Health Study United States General community	n=4,085 Mean age: 73 years (inclusion criteria age ≥65 years) 37% male 85% non-black	ST-depression: Continuous variable ECG-Left ventricular mass: Continuous variable QRS/T angle: Continuous variable	9.1	Age, sex, smoking, diabetes, SBP (hypertensive status or use of anti-hypertensives)	CHD death: 7.2% All cause mortality: 35%	Fair
Sigurdsson et al, 1996 (49)	The Reykjavik Study Iceland General	n=8,340 Mean age: 52 years (range 35-60 years)	ST-T changes: 5%	4 to 24	Age, sex (100% male), smoking, fasting blood glucose,	Silent ST-T segment group Angina: 9% MI: 5%	Fair

	community	100% male Race NR			hypertension (SBP and DBP), total cholesterol	All cause mortality: 12%	
Sutherland et al, 1993 (50)	Charleston Heart Study United States General community	n=993 Mean age: 48 years (range 35-74) 100% male 66% white	Major ECG abnormality: 9% Minor ECG abnormality: 14% Left axis deviation: 8% Early repolarization: 23% Nonspecific ST-T changes: 16% LVH: 4%	30	Age, sex (100% male), smoking, diabetes, SBP, total cholesterol	CHD death: 19%	Good

Abbreviations: ARIC=Atherosclerosis risk in community , BIRNH=Belgian inter-university research on nutrition and health, CHD=Coronary heart disease, CHF=Congestive heart failure, CVD=Cardiovascular disease, DBP=Diastolic blood pressure, ECG=Electrocardiography, HDL=High-density lipoprotein, LDL=Low=density lipoprotein, LVH=Left ventricular hypertrophy, MRFIT=Multiple risk factor intervention trial, MI=Myocardial infarction, NHANES=National health and nutrition examination survey, NR=Not reported, RIFLE=Risk factors and life expectancy study, SBP=Systolic blood pressure, VPC=Ventricular premature complexes, WHI=Women's health initiative, WOSCOPS=West of Scotland coronary prevention study

Supplement Table 2. Cohort studies of exercise electrocardiogram abnormalities as predictors of cardiovascular events

Author, year	Study name Exercise test Country Population	Sample size Demographics	Exercise ECG abnormality: Prevalence	Mean follow-up (years)	Framingham risk factor adjusted for	All-cause mortality and incident CV events	Quality
Adabag et al, 2008 (51)	Multiple Risk Factor Intervention Trial (MRFIT) Treadmill/standard Bruce protocol United States Clinical trial enrollees	n=12,555 Mean age: 46 years (range 35 to 57 years) 100% male 7% black; other races NR	Failure to reach target heart rate: 19%	25: CHD death and all-cause mortality 7: sudden death and fatal/nonfatal MI	Age, sex, smoking, fasting glucose, SBP, HDL, LDL	CHD death (25 years): 13% All-cause mortality (25 years): 37% 7 yr follow-up Sudden death: 1.2% Fatal or nonfatal MI: 6.6%	Good
Aktas et al, 2004 (23)	Study not named Treadmill/primarily Bruce or modified Bruce protocols United States Self-referred, consecutive adults undergoing routine executive physical	n=3554 Mean age: 57 years (range 50-75 years) 81% male 1.8% black; other races not reported	ST segment changes 1 to <2mm: 6% ≥2mm: 4.4% Any change: 10.4% Abnormal heart rate recovery 15.4% (549/3554)	8	Age, sex, smoking, TC, HDL, SBP, diabetes	All-cause mortality: 3.2% (114/3554)	Fair
Balady et al, 2004 (52)	Framingham Heart Study Treadmill/standard	n=3,043 Mean age: 45 years (range	ST segment depression: 4.3% Failure to reach	18	Age, sex, smoking, diabetes, SBP, DBP, HDL, total	Any CHD event (angina, coronary insufficiency, MI,	Good

Other publications: Framingham Study (105)	Bruce protocol United States General community	30-70 years) 47% male Race NR	target heart rate: 9.0%		cholesterol	or CHD death): 10%	
Blair et al, 1996 (53) Other publications: Wei et al, 1999 (106)	Aerobics Center Longitudinal Study Treadmill/Maximal Balke protocol United States General community	n=32,421 Mean age: 43 years (range 20-88 years) 79% male Race NR	Abnormal ECG (not defined): 6.8%	8.2 (8.4 men; 7.5 women)	Age, sex (results stratified by gender), smoking, SBP, total cholesterol, fasting glucose	CVD death: 0.8% All cause mortality: 2.1%	Fair
Bodegard et al, 2004 (24)	Study not named Bicycle/Maximal Norway Work volunteers	n=2,014 Mean age: 50 years (range 40-59 years) 100% male Race NR	ST segment depression: 14%	22	Age, sex, smoking, SBP, total cholesterol	CHD death: 15% All cause mortality: 37% Acute MI: 19% Coronary artery bypass graft surgery: 6.0% Stroke: 7.7%	Good
Cole et al, 2000 (54)	Lipid Research Clinics Prevalence Study Treadmill/Standard or modified Bruce United States General population	n=5,234 Mean age: 44 years 61% male 96% white (other races NR)	Heart rate recovery at 2 minutes <42 bpm: 33%	12	Age, sex, SBP, smoking, diabetes, lipid profiles (cholesterol)	CVD death: 2.2% All cause mortality: 6.2%	Good
Cournot et al, 2006 (55)	Study not named Exercise method nod described/submaximal	n=1,051 Mean age: 52 years (range	ST segment depression: 5.3%	6	Age, sex, smoking, diabetes, SBP, HDL,	CHD or CVD death: 0.6% Any coronary	Good

	France Cardiology clinic attendees	18-79 yrs) 64% male Race NR			total cholesterol	event (cardiac death, sudden death, MI, and angina): 3.2% All cause mortality: 1.7% CHD or CVD death: 0.6% Stable or unstable angina: 1.2% Nonfatal MI: 1.4%	
Ekelund et al, 1989 (56)	Lipid Research Clinics Coronary Primary Prevention Trial Treadmill/submaximal Bruce protocol United States Clinical trial enrollees	n=3,775 Mean age: 47 years (range 35-59 years) 100% male Race NR	ST segment depression or elevation: 8.2%	7.4	Age, sex, smoking, diabetes, SBP, HDL, LDL	CHD death: 1.8% Nonfatal MI: 7.6% All cause mortality: 3.7%	Good
Fleg et al, 1990 (57)	Baltimore Longitudinal Study of Aging Treadmill/modified Balke United States General community	n=407 Mean age: 60 years (range 40 years and older) 71% male 97% white	ST segment depression: 16%	4.6	Age, sex, smoking, diabetes, hypertension, total cholesterol	CVD death: 1.7% Non-fatal MI: 3.2% Angina: 4.9% Any coronary event: 9.8%	Good
Giagnoni et al, 1983 (58)	Study not named Supine Ergometer/submaximal Italy	n=514 Age: 44% 46-65 years (range 18-65 years)	ST segment depression: 1.2%	6.0	Age, sex, smoking, SBP, total cholesterol	Any coronary event (angina, myocardial infarction, or	Good

	Factory workers	73% male Race NR				sudden death): 6.6% All cause mortality: 3.1%	
Gordon et al, 1986 (59)	Lipid Research Clinics Mortality Follow-Up study Treadmill/submaximal modified Bruce protocol United States Lipid clinic attendees	n=3,640 Age: 35% 50-79 years (range 30-79 years) 100% male 100% white	ST segment depression or elevation: 18%	8.1	Age, sex (100% male), smoking, hyperglycemia; hypertension; HDL, LDL	CHD death: 1.4% CVD death: 1.8% All cause mortality: 4.1%	Fair
Gulati et al, 2003 (61)	St. James Women Take Heart Treadmill/maximal Bruce protocol United States General community	n=5,271 Mean age: 52 years (range NR, standard deviation 11 years) 0% male 86% white	Exercise capacity: Mean 8.0 METs	8.4	Age, sex (100% female), smoking, SBP, DBP, HDL, total cholesterol	All cause mortality: 3.2%	Fair
Gulati et al, 2005 (60) Same population as Gulati et al, 2003 (61)	St. James Women Take Heart Treadmill/maximal Bruce protocol United States General community	n=5,636 Mean age: 52 years (range NR, standard deviation 11 years) 0% male 86% white	Duke Treadmill Score: Mean score 8	9	Age, sex, smoking, diabetes, SBP, DBP, HDL, total cholesterol	CHD death: 0.9% All cause mortality: 3.0%	Good

Josephson et al, 1990 (62)	Baltimore Longitudinal Study of Aging Treadmill/submaximal modified Balke protocol United States General population	n=726 Mean age: 55 years (range 22-84 years) 63-87% male (varied by group) Race NR	ST segment depression: 12% on initial test, 13% on follow-up test	6.4-7.7	Age, sex, smoking, hypertension, cholesterol	Cardiac events (angina, nonfatal MI, or cardiac death): 8.8%	Fair
Jouven et al, 2000 (63) Other publications: Filipovsky, et al, 1992 (107)	Paris Protective Study Bicycle/standardized graded exercise test France Civil servants	n=6,101 Mean age: 48 years (range 42-52 years) 100% male Race NR	ST segment depression: 4.4% Frequent premature ventricular contractions: 2.8%	23	Age, sex (100% male), smoking, diabetes, SBP, total cholesterol	CHD death: 7.1% All cause mortality: 27%	Good
Jouven et al, 2005 (34)	Paris Protective Study I Bicycle/standardized graded exercise test France Civil servants	n=5,713 Mean age: 48 years (range 42-53 years) 100% male Race NR	Abnormal (<89 beats per minute) heart rate increase during exercise: 8% Abnormal heart rate recovery (heart rate decrease at 1 min after cessation of exercise <25 beats per minute): 6%	23	Age, sex (100% male), smoking, diabetes, SBP, cholesterol	Fatal MI (sudden death): 1.4% Fatal MI (nonsudden death): 2.3% All cause mortality: 27%	Good

Kurl et al, 2003 (64)	Kuopio Ischemic Heart Disease Risk Factor Study Bicycle/maximal symptom-limited exercise test Finland General population	n=1,726 Mean age: 52 years (range 42-60 years) 100% male Race NR	ST segment depression: 7.1%	10	Age, sex (100% male), smoking, diabetes, SBP, LDL	CHD death: 5.0% Stroke: 4.2%	Fair
Kurl et al, 2009 (65)	Kuopio Ischemic Heart Disease Risk Factor Study Bicycle/maximal symptom-limited exercise test Finland General population	n=1,639 Mean age: 52 years (range 42-60 years) 100% male Race NR	ST segment depression: 6.7%	16	Age, sex, smoking, diabetes, SBP, HDL, total cholesterol	Stroke: 5.9%	Fair
Lauer et al, 1996 (66)	Framingham Offspring Study Treadmill/Submaximal Bruce protocol United States Offspring and spouses of Framingham Heart Study participants	n=1,575 Mean age: 43 years (range NR) 100% male Race NR	Failure to reach target heart rate: 21% Increase in heart rate from rest to peak exercise: Continuous outcome Ratio of heart rate to metabolic reserve used by stage 2 (7.1 METs) of exercise:	7.7	Age, sex, smoking, hypertension, diabetes, cholesterol	CHD events (MI, angina, or sudden cardiac death): 6.0% All cause mortality: 3.5%	Fair

			Continuous outcome				
Laukkanen et al, 2001 (67)	Kuopio Ischemic Heart Disease Risk Factor Study Bicycle/maximal symptom-limited exercise test Finland General population	n=1,769 Mean age: 52 years (range 42-60 years) 100% male Race NR	ST segment depression During exercise: 10.7% After exercise: 3.1%	10	Age, sex (100% male), smoking, SBP, diabetes, LDL, HDL	CHD death: 3.0% CVD death: 4.4% Nonfatal coronary events (MI or typical angina): 9.8%	Good
Laukkanen et al, 2006 (68)	Kuopio Ischemic Heart Disease Risk Factor Study Bicycle/maximal symptom-limited exercise test Finland General population	n=1,596 Mean age: 52 years (range 42-61 years) 100% male Race NR	Peak oxygen pulse (V_{o2max}/maximum heart beat): Continuous variable ST segment depression: 6.8%	14	Age, sex (100% male), smoking, diabetes, SBP, DBP, HDL, LDL	CHD death: 4.2% All cause mortality: 17%	Good
Laukkanen et al, 2008 (69)	Kuopio Ischemic Heart Disease Risk Factor Study Bicycle ergometer/maximal symptom-limited exercise test Finland General population	n=1,639 Mean age: 52 years (range 42-60 years) 100% male Race NR	Exercise capacity measured as highest workload achieved during exercise test in watts: Continuous outcome, also categorized into quartiles (>230 W; 196-230 W; 162-195 W; <162	16.6	Age, sex (100% male), smoking, diabetes, SBP, DBP, total cholesterol, HDL (Framingham risk score) or age, sex (100% male), total cholesterol, SBP, smoking (European SCORE)	CVD death: 7.1% Major CVD event: 21% All cause mortality: 19%	Good

			W) Exercise-induced ST depression: horizontal or downsloping ST depression 1.0 mm 80 ms after the J-point: 6.5%				
Lyerly et al, 2008 (70)	Aerobics Center Longitudinal Study Treadmill/maximal modified Balke protocol United States General population (subgroup of diabetic persons)	n=2854 Mean age: 50 years (range 21-84 years) 100% male Race NR	ST segment depression or elevation ≥1 mm ≥0.08 second from the J-point: 11% ST segment depression 0.5-1.0 mm at least 0.08 seconds: 11%	16	Age, sex (all male), smoking, fasting glucose, hypertension, hypercholesterolemia	CHD death: 11% CVD death: 7.4% All cause mortality: 15%	Fair
Lyerly et al, 2009 (71)	Aerobic Center Longitudinal Study Treadmill/Maximal United States Impaired fasting glucose or undiagnosed diabetes mellitus population	n=3044 Mean age: 47.4 years (range 20-79 years) 100% female Mostly white (details NR)	Cardiorespiratory fitness: Low 17% (517/3044) Moderate 34% (1041/3044) High 49% (1486/3044)	15.6	Age, sex (all female), smoking, alcohol, hypertension, hypercholesterolemia, family history of diabetes	CVD death: 1.6% All cause mortality: 5.6%	Fair

Mora et al, 2003 (72)	Lipid Research Clinics Prevalence Study Treadmill/Maximal Bruce protocol United States General population	n=2,994 Mean age: 47 years 100% female 94% white (other races NR)	ST segment depression: 37% Ventricular premature contractions or tachycardia: 7.6% Failure to reach target heart rate: 37%	20.3	Age, sex (all female), smoking, diabetes, LDL, HDL, hypertension	CVD death: 4.9% All cause mortality: 14%	Good
Mora et al, 2005 (73)	Lipid Research Clinics Prevalence Study Treadmill/standard Bruce protocol United States General population	n=6126 Mean age 45 years (SD 10; range not reported) 54% male 96% White; other races not reported	HRR + METs categorized into "high" or "low" based on sex-specific medians - High HRR and High METs: 28% Low HRR or METs: 41% Low HRR and Low METs: 31%	20	Age, sex, smoking, TC, HDL, hypertension	10-year follow-up - CVD death: 1.3% 20-year follow-up - CVD death: 4%	Fair
Morshedi-Meibodi et al, 2002 (74)	Framingham Offspring Study Treadmill/Bruce protocol United States General population	n=2,967 Mean age: 43 years (range NR, standard deviation 10 years) 47% male Race NR	Heart rate recovery: Continuous variable Heart rate recovery at 1 minute <12 bpm: Prevalence NR	15	Age, sex, smoking, diabetes, SBP, DBP, HDL, total cholesterol	CHD events: 7.2% CVD events: 10% All cause mortality: 5.6%	Fair

			Heart rate recovery at 2 minutes <42 bpm: Prevalence NR				
Okin et al, 1991 (75)	Framingham Offspring Study Treadmill/standard Bruce protocol United States General population	n=3,168 Mean age: 44 years (rage 17 to 70 years, standard deviation 10 years) 48% male Race NR	Heart rate adjusted ST segment depression index ≥1.6 μV bpm: 8.7% Abnormal rate-recovery loop: 6.0%	4.3	Age, sex, smoking, diabetes (fasting blood glucose), hypertension (DBP), total cholesterol	CHD events (angina, ischemic chest pain, fatal or nonfatal MI, sudden or nonsudden coronary death): 2.1% (65/3168)	Good
Okin et al, 1996 (76)	Multiple Risk Factor Intervention Trial Treadmill/standard Bruce protocol United States Clinical trial enrollees	n=5,940 Mean age: NR (range 35-57 years) 100% male Race NR	ST segment depression: 3.1% Heart rate adjusted ST segment depression index ≥1.60 μV bpm: 12%	7	Ages, sex (100% male), DBP, total cholesterol, smoking	CHD death: 1.8% (109/5940)	Fair
Peters et al, 1983 (77)	Study not named Bicycle ergometer/20-minute heart-rate-controlled graded exercise test United States Men employed in fire or law enforcement	n=2,779 Median age: 41 years (mean not reported; range 35-53 years) 100% male	Low physical work capacity, defined as below the median for each age group (median for entire cohort was	4.8	Age, sex (100% male), total cholesterol, smoking, hypertension	Fatal MI: 0.2% Nonfatal MI: 1.1%	Fair

	departments	Race NR	140 watts)				
Rautaharju et al, 1986 (78)	Multiple Risk Factor Intervention Trial Treadmill/standard Bruce protocol United States Clinical trial enrollees	n=6,150 Mean age: 46 years (range 35-57 years) 100% male 93% white 7% black	ST segment depression: 12%	7	Age, sex (100% male), smoking, DBP, total cholesterol	CHD death: 1.8% CVD death: 2.1% All cause mortality: 3.8% Silent MI: 2.4% Clinical MI: 3.5%	Good
Rutter et al, 2002 (79) Other publications: Rutter et al, 1999 (108)	Study not named Treadmill United Kingdom Diabetes clinic patients	n=86 Mean age: 62 years (range 45-75 years) 72% male Race NR	ST segment depression (>1mm horizontal or downsloping ST-segment depression at 80 ms after the J-point for 3 consecutive beats): 52%	2.8	Age, sex, smoking, hemoglobin a1c, clinic and 24 hour ambulatory blood pressure, total cholesterol (Framingham Risk Score also entered as a separate variable)	Any CHD event (cardiac death, MI, or new-onset angina): 17%	Fair
Rywik et al, 1998 (80)	Baltimore Longitudinal Study of Aging Treadmill/submaximal modified Balke protocol United States General population	n=825 Mean age: 51 years (range 22-89 years) 60% male Race NR	ST segment depression: 18% during exercise, 7.6% during recovery	9	Age, sex, smoking, cholesterol, hypertension, diabetes (fasting glucose)	Coronary events (angina, MI, or coronary death): 6.7% (55/825)	Good
Rywik et al,	Baltimore Longitudinal Study of	n=1083 Mean age 52	>=1 mm horizontal or	7.9	Age, sex, total cholesterol, glucose,	Any coronary event: 7%	Fair

2002 (81)	Aging Treadmill/modified Balke protocol United States General population volunteers	years (SD 18) 57% male Race not reported	downsloping ST segment depression (MN code 11.1): 16% >=1 mm horizontal or downsloping ST segment depression (MN code 11.1), 0.5-1 mm horizontal or downsloping ST segment depression (MN code 11.2), <0.5 mm ST segment depression but downsloping ST segment and ST segment or T nadir <0.5 mm below baseline (MN code 11.3), or ST segment depression <0.5 mm at rest or induced by postural shift or hyperventilation, worsened to type 11.1 response during or after	hypertension	Specific events- Angina: 3% MI: 2% CHD death: 2%

			exercise (MN code 11.1): 44% Duration of exercise: Continuous variable (minutes)				
Savonen et al, 2007 (82)	Kuopio Ischemic Heart Disease Risk Factor Study Bicycle/maximal symptom-limited exercise test Finland General population	n=1,314 Mean age: 52 years (range 42-61 years) 100% male Race NR	ST segment depression: 14% Workload (chronotropic index at heart rate 100/bpm): Continuous variable	12	Age, sex (100% male), smoking, diabetes, SBP, DBP, HDL, LDL	CHD death: 2.7% CVD death: 3.9% All cause mortality: 10%	Fair
Siscovick et al, 1991 (83) Other publications: Lipid Research Clinics Program 1984 (109)	Lipid Research Clinics Coronary Primary Prevention Trial Treadmill/submaximal Bruce protocol United States Men with hypercholesterolemia	n=3,617 Mean age: NR (range 35-59 years) 100% male 100% white	ST depression or elevation ≥1mm or 10μV-sec	7.4	Age, sex (100% male), LDL, HDL, smoking, SBP	Acute cardiac events (nonfatal MI and CHD death): 1.8% (51/2893)	Good
Slattery et al, 1988 (84)	US Railroad Study Treadmill/submaximal 3-minute exercise test United States Men employed in the	n=2,431 Mean age not reported (range 22-79 years) 100% male	Heart rate following 3-minute submaximal exercise test,	Not reported, maximum duration 20 years	Age, sex (100% male), SBP, total cholesterol, smoking	CHD death: 11% All cause mortality: 27%	Fair

	US railroad industry	100% white	categorized into quartiles				
Sui et al, 2007 (85)	Aerobics Center Longitudinal Study Treadmill/modified Balke protocol United States General population	n=26637 Mean age NR; range 18-83 years 78% male Race NR	Fitness level, based on duration of maximal treadmill exercise test Low: lowest quintile Moderate: 2nd and 3rd quintiles High: upper two quintiles	10	Age, smoking, hypertension, diabetes, dyslipidemia	Any CVD event (MI, revascularization, or stroke): 5.7% MI: 1.8% Revascularization: 2.8% Stroke: 1.1%	Fair

Abbreviations: bpm=Beats per minute, CHD=Coronary heart disease, CVD=Cardiovascular disease, DBP=Diastolic blood pressure, ECG=Electrocardiogram, HDL=High-density lipoprotein, LDL=Low-density lipoprotein, LVH=Left ventricle hypertrophy, METs=Metabolic equivalents, MI=Myocardial infarction, MRFIT=Multiple risk factor intervention trial, NR=Not reported, SBP=Systolic blood pressure

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