

**Kaiser Permanente Research Affiliates Evidence-based Practice Center
Kaiser Permanente Center for Health Research**

Expert Review Form

Nontraditional Risk Factors in Cardiovascular Disease Risk Assessment: A systematic Evidence
Report for the US Preventive Services Task Force

Name of Reviewer Matthew Budoff

May we acknowledge you in our final report and manuscript? Yes No

Instructions:

Thank you for taking the time to review this report. We are particularly interested in hearing from you about anything in this report that you believe is inaccurate or confusing. In addition, we have specific questions about each section. Finally, we are interested in hearing any additional comments you have, either of a detailed or general nature. If applicable, specification of page and line numbers from the draft report are extremely helpful.

A. Introduction

1. Are there any additional issues you think we should cover in the introduction?

No

2. Do you see anything inaccurate, superfluous, or unclear?

No

3. Any additional comments on the Introduction?

No

B. Methods

1. Do you see any problems with our methods?

There were a large number of pertinent papers that were not included in the report, reasons of which is unclear based on methods, these should have been discoverable and included.

2. Any additional comments about the Methods section?

No

C. Results/Key Questions

[For general comments regarding key questions, please preface your comment with the key question number (i.e. KQ2: text)]

1. Are there any studies you believe we may have missed?

The subgroup analysis that most approximates the study in question (key q4), was studied in the original Arad publication as CAC >400, demonstrating a 42% reduction in events - calcium score >400 (8.7% vs. 15.0%, $p = 0.046$). This should at least be listed as data related to randomized trials with CAC, as a subgroup. Furthermore, another analysis of that study (Blaha et al J Am Coll Cardiol Img 2012;5;252-60) also demonstrated 7.2% of the treated individuals with a positive family history had a cardiovascular event versus 12.5% of the placebo group (hazard ratio [HR]: 0.55; 95% confidence intervals [CI]: 0.31 to 0.97; $p = 0.040$). This should be mentioned under key Q4 and again in the discussion as demonstrating a significant 45% reduction in events with CAC screening. It is understood that subgroups are not as robust as the primary study, but given the difficulty in ethically randomizing patients with atherosclerosis to no therapy, the studies cannot be repeated, so we must be informed by subgroups and further analysis of existing data. It is considered unethical by the NIH to randomize patients with coronary artery calcium (established atherosclerosis) to no therapy.

In regard to net reclassification, there are a number of population based prospective studies not included. The Framingham offspring study (3,529 persons) (Preis, Am J Cardiol 2009;103:1710 – 5.), Dallas Heart Study (2,084 patients)(Paixao, Am Coll Cardiol Img 2015;8:1285–93), and St Francis heart study (parent study Arad J Am Coll Cardiol 2005;46:158–65), along with McClelland for multiple cohorts (J Am Coll Cardiol. 2015 Oct 13;66(15):1643-53.)

Table 23 and 24 – population based outcome studies with CAC – missing Dallas Heart Study (multiple papers including Paixao), Cardia (Carr et al JAMA Cardiology), St Francis Heart Study (n=4903) (Arad J Am Coll Cardiol 2005;46:158–65), MESA (Budoff J Am Coll Cardiol 2009;53:345-52). Also, the PACC study reported long term outcomes (Taylor J Am Coll Cardiol 2005;46:807–14). This latter study also reported on costs, which may be informative for other parts of the discussion. Page 37, line 13 – states largest cohort was 6603, but that is not correct, as Budoff reported on MESA (n=6814 and Lamonte reported on Cooper clinic, n>10,000, and McClelland 2015 reported on multiple cohorts with n=11,498). Cooper Clinic Study is one of the largest studies that looked at hard events (MI and CVD Death), with >10,000 patients – (Lamonte MJ, Fitzgerald SJ, Church TS, et al. Coronary artery calcium score and coronary heart disease events in a large cohort of asymptomatic men and women. Am J Epidemiol 2005;162:421–9).

2. Are there studies that you believe we should have excluded?

no

3. Do you believe we have inaccurately described any studies?

Yes – the South Bay Heart Watch was an NIH funded prospective population based study, not a “asymptomatic people getting a CAC scan (i.e., South Bay Heart Watch)” p27, line 18.

You stated " Only two cohorts (South Bay Heart Watch, MESA) reported including any non-White participants."(Line 25, page 27) which is not correct - Cardia, Dallas Heart, PACC (Taylor (J Am Coll Cardiol 2005;46:807–14) also reported on non-white cohorts. "Two studies (South Bay Heart Watch,90 MESA83) explicitly excluded participants with diabetes" is not correct, MESA had 881 persons with Diabetes included prospectively, and McClelland did not exclude them from her analysis (ref above), nor did Budoff (ref above).

The statement that only two studies had 10 year follow up and only MESA reported on >100 events is incorrect. Heinz Nixdorff Recall study reported in Mahabadi et al JACC CI 2016 (During a mean follow-up of 9.9 +/- 2.6 years, 241 subjects (6.6%) developed a hard cardiovascular event. This included 138 subjects with fatal or nonfatal myocardial infarction, 86 fatal or nonfatal strokes (6 subjects with myocardial infarction and stroke); additional 23 cardiovascular deaths occurred.). While technically 9.9 is <10, probably not a fair characterization of the study. Certainly 241 hard events is >100. Furthermore, the follow-up paper by Mahabadi in JACC CI 2017 demonstrated “During 10.4 +/- 2.0 years of follow-up, 131 myocardial infarctions occurred”. The Cardia study reported on 12.5 year follow up -CARR Jama Cardiology 2017 (The mean follow-up period for incident events was 12.5 Years, with 57 incident CHD events and 108 incident CVD events observed). Dallas Heart reported on 5933 individuals with 161 CVD events during a mean follow-up of 7.3 years (Radford JACC CI 2016). Geisel et al also looked at 10.3 year follow up of both ABI and CAC in Heinz Nixdorff Recall study, reporting on 223 events (Geisel EHJ 2017).

4. Any additional comments about the Results?

The language regarding the conclusions for CAC predicting outcomes and reclassification would be stronger for CAC if the missing studies were included. The larger cohorts and larger event samples were not included, weakening the associations and conclusions for CAC testing. There are numerous long (>10 year) and large (>100 events) studies that were not mentioned in the discussion or results section.

D. Discussion

1. Do you think we missed any important points?

The paper by McClelland (J Am Coll Cardiol 2015;66:1643–53) demonstrated “Inclusion of CAC in the MESA risk score offered significant improvements in risk prediction (C-statistic 0.80vs.0.75; $p < 0.0001$). External validation in both the HNR and DHS studies provided evidence of very good discrimination and calibration. Harrell’s C-statistic was 0.779 in HNR and 0.816 in DHS. Additionally, the difference in estimated 10-year risk between events and nonevents was approximately 8%to9%, indicating excellent discrimination. Mean calibration, or calibration-in-the large, was excellent for both studies, with average predicted 10-year risk within one-half of a percent of the observed event rate”. All of this would change the tone of the discussion, for calibration, discrimination, good quality studies and improvement in C Statistic. This paper included 6726 patients from MESA (including those with diabetes) with no exclusions, no imputation, with external validation in TWO population based cohorts (Dallas Heart and HNR). It represents true 10 year event rates in a total multi-study population of 11, 498 patients with hundreds of events, and is widely deemed ‘excellent’ quality paper, further refining the discussion/conclusion that only fair quality papers exist with coronary calcium.

2. Do you disagree with any of the discussion items?

Yes, see above. Discussion of only “fair quality studies”, “inadequate follow up” and “long and large cohorts”, are all incorrect and key studies demonstrating improvement in discrimination and calibration with CAC were not included.

4. Any additional comments about the Discussion?

The conclusion that “While CAC appears to be the most promising nontraditional risk factor to improve discrimination and reclassification, it is based on a much smaller body of evidence which lacks pooled analyses and longer-term followup.” is incorrect and once the missing studies are added, will result in a different conclusion altogether. The body of evidence is robust with CAC, there are ample longer term follow up studies and pooled analysis already exist (ie – McClelland 2015, Budoff JCCT 2013).

E. Other Sections

Please comment on the structured abstract, conclusions, figures, tables and appendices.

F. General Comments

1. Is the report clearly written, adequately detailed and of an appropriate length?

Excellent analysis, missing a few key papers on the topic, not surprising since there are >1000 papers on CAC alone, and >300 from MESA related to coronary calcium. I am glad to provide every manuscript that I referenced as missing in the different sections and glad to re-review once the conclusions are changed to reflect the complete available literature.

2. Please make any additional comments you feel would help us improve the report.

An excellent report, whose conclusions will undoubtedly change once all the aforementioned studies are included and revised, but I would HIGHLY recommend that this be reviewed by Michael Blaha at Johns Hopkins as an external reviewer, as he has done a large amount of the research evaluating the performance of both CAC and CRP in his career, and has a great grasp of both NRI, AUC and calibration for risk prediction. He can better address whether some of the additional papers would change the conclusions in a meaningful way.