Identifying High-Value Lifestyle Interventions for Cardiovascular Disease Prevention

Identifying high-value lifestyle interventions for cardiovascular disease prevention

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Paula Ning-Tze Chu

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Abstract

This dissertation evaluates lifestyle strategies for the management of cardiovascular risk factors and prevention of cardiovascular disease (CVD).

In Chapter 1, I systematically review and summarize the evidence of the effect of yoga, a popular mind-body practice, on cardiovascular disease and metabolic syndrome risk factors. I perform a narrative systematic review and a random-effects meta-analysis of randomized controlled trials (RCTs) of posture-based yoga practice. I find that yoga showed significant improvement in a variety of risk factors for CVD and metabolic syndrome, including body mass index, systolic blood pressure, and total cholesterol when compared to no or minimal intervention control groups. When compared to active exercise controls, yoga produced similar risk factor level reduction. Promising evidence supports yoga's role in improving cardio-metabolic health. Findings are limited, however, by small trial sample sizes, heterogeneity, and moderate RCT quality.

In Chapter 2, I evaluate the comparative effectiveness of four different lifestyle strategies for reducing 10-year CVD risk. I used published literature on risk factor reductions associated with group therapy for smoking cessation, Mediterranean diet, aerobic exercise (walking), and yoga together with the Pooled Cohort risk algorithms to calculate a personalized optimal strategy for risk reduction based on different risk profiles. I find that for smokers, successful smoking cessation is an optimal strategy for reducing risk whereas for non-smokers or for smokers who do not quit successfully, stress reduction through yoga produces the greatest risk reductions.

In Chapter 3, I examine the cost-effectiveness of aerobic exercise and yoga compared to current medical practice for primary prevention of CVD in US adults. I use a subset of RCTs from Chapter 1, along with published literature on utilities, costs, and other parameters as inputs into a validated disease

microsimulation model. I calculate the costs per quality-adjusted life year ($/QALY) of aerobic exercise and yoga with an exercise on prescription approach from the societal and healthcare perspective as well as if the activities were reimbursed. Results suggest that both interventions are not cost-effective using a threshold of $100,000/QALY due to high patient time costs in the societal perspective; when the activities are reimbursed and gains in quality of life are taken into account, then the activities can be cost-effective. Future research can explore patient preference and adherence and utility gains from physical activity.

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DISSERTATION INTRODUCTION

Cardiovascular disease and metabolic disorders are leading causes of morbidity and mortality worldwide and are associated with large health and financial costs.[1] Atherosclerotic cardiovascular disease (CVD), a disease of the arteries that supply the heart and brain, is responsible for approximately 30% of total global mortality.[2] The total direct and indirect costs of CVD and stroke in the US in 2010 are estimated at $315.4 billion and costs are projected to grow to $804 billion by 2020 and $1208 billion by 2030.[1]

Multiple risk factors can contribute to development of CVD and metabolic syndrome, including hyperlipidemia and hypertension. It is estimated that about one third of adults in the US have elevated blood cholesterol, a third have high blood pressure, and another third are pre-hypertensive or at high risk of developing high blood pressure.[2] Some of the risk factors for CVD can be modified through behavior and changes in lifestyle like increasing physical activity, eating a healthy diet, and quitting smoking.[3]

In a recent statement, the American Heart Association has expanded its focus from the traditional medical model focusing on treatment of established CVD toward a public health model promoting positive cardiovascular health.[4] This new model highlights healthy behaviors like healthy dietary pattern, nonsmoking, and physical activity in all segments of the population.

Considerable research has been done on the benefits of physical activity,[5-8] a healthy dietary pattern,[9-14] in particular the Mediterranean diet pattern,[15-18] and smoking cessation [19-22] on cardiovascular disease risk factors and outcomes. Another intervention that has shown promise in promoting positive cardiovascular health is yoga. According to the National Center for Complementary and Integrative Health (NCCIH), yoga is a mind and body practice that combined physical postures, breathing techniques, and meditation or relaxation.[23] In 2012, it is estimated that 9.5% of US adults (21 million) practiced yoga in the previous year, up more than 6 million from the previous survey cycle in 2007.[24] Studies have shown that yoga is effective against stress,[25-26] hypertension,[27-29] and other cardiovascular risk factors.[30-32]

In Chapter 1 I systematically evaluate the evidence on the effectiveness of yoga for modifying risk factors for cardiovascular disease and metabolic syndrome in adult populations using published RCTs. I quantitatively summarize the effectiveness of yoga versus both non-active controls and active exercise controls.

In Chapter 2 I utilize the results from Chapter 1 in combination with evidence on three other lifestyle interventions to assess the comparative effectiveness of the strategies for reducing cardiovascular disease risk. To align with the trend of personalized medicine and more shared decision making between patient and provider, I calculate the potential 10-year CVD risk reduction from group therapy for smoking cessation, Mediterranean diet, walking for aerobic exercise, and yoga for an array of patient profiles to identify the optimal tailored intervention.

Lastly, in Chapter 3 I expand on the health and economic implications of select interventions included in the previous chapters. I assess the cost-effectiveness of two forms of physical activity – aerobic exercise and yoga – versus current medical practice for primary prevention of CVD in US adults. Given the large, growing health and economic burden of CVD, the findings in this dissertation could contribute to the renewed efforts and emphasis on CVD prevention through lifestyle change.

REFERENCES

1. Go AS, Mozaffarian D, Roger VL et al. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. Circulation 2014;129:e28-e292.

2. Lozano R, Naghavi M, Foreman K et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2095-128.

3. Lim SS, Vos T, Flaxman AD et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2224-60.

4. Mozaffarian D, Benjamin EJ, Go AS et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation 2015;131:e29-322.

5. Thompson PD, Buchner D, Pina IL et al. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). Circulation 2003;107:3109-16.

6. Thompson PD, Franklin BA, Balady GJ et al. Exercise and acute cardiovascular events placing the risks into perspective: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism and the Council on Clinical Cardiology. Circulation 2007;115:2358-68.

7. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 2006;174:801-9.

8. Haskell WL, Lee IM, Pate RR et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Medicine and science in sports and exercise 2007;39:1423-34.

9. Perk J, De Backer G, Gohlke H et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). European heart journal 2012;33:1635-701.

10. Ness AR, Powles JW. Fruit and vegetables, and cardiovascular disease: a review. International journal of epidemiology 1997;26:1-13.

11. Sacks FM, Svetkey LP, Vollmer WM et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. The New England journal of medicine 2001;344:3-10.

12. Bazzano LA, Serdula MK, Liu S. Dietary intake of fruits and vegetables and risk of cardiovascular disease. Current atherosclerosis reports 2003;5:492-9.

13. Kromhout D, Menotti A, Kesteloot H, Sans S. Prevention of coronary heart disease by diet and lifestyle: evidence from prospective cross-cultural, cohort, and intervention studies. Circulation 2002;105:893-8.

14. Kris-Etherton P, Eckel RH, Howard BV, St Jeor S, Bazzarre TL. AHA Science Advisory: Lyon Diet Heart Study. Benefits of a Mediterranean-style, National Cholesterol Education Program/American Heart Association Step I Dietary Pattern on Cardiovascular Disease. Circulation 2001;103:1823-5.

15. Estruch R, Ros E, Salas-Salvado J et al. Primary prevention of cardiovascular disease with a Mediterranean diet. The New England journal of medicine 2013;368:1279-90.

16. Panagiotakos DB, Pitsavos C, Stefanadis C. Dietary patterns: a Mediterranean diet score and its relation to clinical and biological markers of cardiovascular disease risk. Nutrition, metabolism, and cardiovascular diseases : NMCD 2006;16:559-68.

17. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation 1999;99:779-85.

18. Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. BMJ 2008;337:a1344.

19. Lubin JH, Couper D, Lutsey PL, Woodward M, Yatsuya H, Huxley RR. Risk of cardiovascular disease from cumulative cigarette use and the impact of smoking intensity. Epidemiology 2016.

20. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. Journal of the American College of Cardiology 2004;43:1731-7.

21. Bazzano LA, He J, Muntner P, Vupputuri S, Whelton PK. Relationship between cigarette smoking and novel risk factors for cardiovascular disease in the United States. Annals of internal medicine 2003;138:891-7.

22. Ockene IS, Miller NH. Cigarette smoking, cardiovascular disease, and stroke: a statement for healthcare professionals from the American Heart Association. American Heart Association Task Force on Risk Reduction. Circulation 1997;96:3243-7.

23. National Center for Complementary and Integrative Medicine. Yoga. 2015. Available at: https://nccih.nih.gov/health/yoga. Accessed 1 March 2016.

24. Clarke T, Black, LI, Stussman, BJ. Trends in the use of complementary health approaches among adults: United States, 2002-2012. National Health Statistics Reports. Hyattsville, MD: National Center for Health Statistics, 2015.

25. Kirkwood G, Rampes H, Tuffrey V, Richardson J, Pilkington K. Yoga for anxiety: a systematic review of the research evidence. British journal of sports medicine 2005;39:884-91; discussion 891.

26. Chong CS, Tsunaka M, Tsang HW, Chan EP, Cheung WM. Effects of yoga on stress management in healthy adults: A systematic review. Alternative therapies in health and medicine 2011;17:32-8.

27. Raub JA. Psychophysiologic effects of Hatha Yoga on musculoskeletal and cardiopulmonary function: a literature review. J Altern Complement Med 2002;8:797-812.

28. Hagins M, States R, Selfe T, Innes K. Effectiveness of yoga for hypertension: systematic review and meta-analysis. Evidence-based complementary and alternative medicine: eCAM 2013;2013:649836.

29. Wolff M, Sundquist K, Larsson Lonn S, Midlov P. Impact of yoga on blood pressure and quality of life in patients with hypertension - a controlled trial in primary care, matched for systolic blood pressure. BMC cardiovascular disorders 2013;13:111.

30. Innes KE, Bourguignon C, Taylor AG. Risk indices associated with the insulin resistance syndrome, cardiovascular disease, and possible protection with yoga: a systematic review. The Journal of the American Board of Family Practice / American Board of Family Practice 2005;18:491-519.

31. Jayasinghe SR. Yoga in cardiac health (a review). European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology 2004;11:369-75.

32. Yadav RK, Magan D, Yadav R, Sarvottam K, Netam R. High-density lipoprotein cholesterol increases following a short-term yoga-based lifestyle intervention: a non-pharmacological modulation. Acta Cardiologica 2014;69:543-9.

CHAPTER 1

The effectiveness of yoga in modifying risk factors for cardiovascular disease and metabolic syndrome: a systematic review and meta-analysis of randomized controlled trials

Paula Chu MS[1,4], Rinske A. Gotink MSc[2,5], Gloria Y. Yeh MD, MPH[3], Sue J. Goldie MD, MPH[4,6], M.G. Myriam Hunink MD, PhD[2,5,6]

[1] Department of Health Policy, Harvard University, Cambridge, MA USA
[2] Department of Epidemiology, Erasmus MC, Rotterdam, the Netherlands
[3] Division of General Medicine and Primary Care, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA USA
[4] Center for Health Decision Science, Harvard School of Public Health, Boston, MA USA
[5] Department of Radiology, Erasmus MC, Rotterdam, the Netherlands
[6] Department of Health Policy and Management, Harvard School of Public Health, Boston, MA USA

ABSTRACT

Background: Yoga, a popular mind-body practice, may produce changes in cardiovascular disease (CVD) and metabolic syndrome risk factors.

Design: This was a systematic review and random-effects meta-analysis of randomized controlled trials (RCTs).

Methods: Electronic searches of MEDLINE, EMBASE, CINAHL, PsycINFO, and The Cochrane Central Register of Controlled Trials were performed for systematic reviews and RCTs through December 2013. Studies were included if they were English, peer-reviewed, focused on asana-based yoga in adults, and reported relevant outcomes. Two reviewers independently selected articles and assessed quality using Cochrane's Risk of Bias tool.

Results: Out of 1404 records, 37 RCTs were included in the systematic review and 32 in the meta-analysis. Compared to non-exercise controls, yoga showed significant improvement for body mass index (-0.77 kg/m^2 [95% CI, -1.09 to -0.44]), systolic blood pressure (-5.21 mmHg [-8.01 to -2.42]), low-density lipoprotein cholesterol (-12.14 mg/dL [-21.80 to -2.48]), and high-density lipoprotein cholesterol (3.20 mg/dL [1.86 to 4.54]). Significant changes were seen in body weight (-2.32 kg [-4.33 to -0.37]), diastolic blood pressure (-4.98 mmHg [-7.17 to -2.80]), total cholesterol (-18.48 mg/dl [-29.16 to -7.80]), triglycerides (-25.89 mg/dl [-36.19 to -15.60), and heart rate (-5.27 beats/min [-9.55 to -1.00]), but not fasting blood glucose (-5.91 mg/dL [-16.32 to 4.50]) nor glycosylated hemoglobin (-0.06% Hb [-0.24 to 0.11]). No significant difference was found between yoga and exercise. One study found an impact on smoking abstinence.

Conclusions: There is promising evidence of yoga on improving cardio-metabolic health. Findings are limited by small trial sample sizes, heterogeneity, and moderate quality of RCTs.

Key words: Yoga, cardiovascular disease, metabolic syndrome, systematic review, meta-analysis

INTRODUCTION

Background

Cardiovascular disease (CVD) and metabolic syndrome are major public health problems in the United States and worldwide.[1,2] Metabolic syndrome is defined as having at least three metabolic risk factors – increased blood pressure, high blood sugar level, excess body fat, and abnormal cholesterol levels – and greatly increases the chance of future cardiovascular problems.[3] Lifetime risk of CVD is substantial as estimated through risk functions like those from the Framingham Heart Study,[4] underlining the need for prevention and control of risk factors.

CVD and metabolic syndrome share many of the same modifiable risk factors. Several guidelines name physical inactivity, the fourth leading risk factor of global mortality,[5] as an important modifiable risk factor for CVD and metabolic syndrome.[6-8] They state that regular and adequate levels of physical activity in adults can reduce the risk of hypertension, coronary heart disease, stroke, diabetes, and can help maintain a healthy weight. Yoga, an ancient practice from India that incorporates physical, mental, and spiritual elements, may be an effective form of physical activity.

Yoga therapy

In recent years, clinical literature has reported cardiovascular health benefits from mind-body therapies.[9-11] Yoga, one type of mind-body therapy, has been increasing in popularity in the US and in many parts of the world. Yoga, meaning "union" in Sanskrit, incorporates physical, mental, and spiritual elements. In the West, Hatha yoga, one style of yoga, has been most commonly practiced. Hatha yoga consists of a series of physical exercises that focus on stretching and stimulating the spine and muscles in coordination with breath control, thought to stabilize the hypothalamic-pituary-adrenal axis and sympathoadrenal activity.[12-14] According to the 2007 National Health Interview Survey, about 20% of the US population used some form of mind-body practice.[15] Another study estimates that about 15 million

adults in America report having practiced yoga at least once in their life, [16] seeking wellness or treatment for specific health conditions.

Rationale

A 2005 Cochrane study reviewed the evidence of yoga for secondary prevention of coronary heart disease on mortality, cardiovascular events, hospital admissions, and quality of life and found no randomized controlled trials (RCTs) meeting its inclusion criteria.[17] Another review done in 2005 examined CVD clinical endpoints and insulin resistance with observational studies, uncontrolled trials, and nonrandomized controlled trials and found improvements in insulin resistance syndrome with yoga.[13] Other reviews have shown yoga to be beneficial in treatment of coronary heart disease, post-myocardial infarction rehabilitation, and hypertension.[11 13 18-22] Since this time, several new RCTs have been published. We sought to comprehensively review recent RCT evidence of the effectiveness of yoga on these risk factors and provide a pooled quantitative measure.

Objectives

Our objectives were a) to identify and systematically evaluate the evidence on the effectiveness of yoga for modifying risk factors for cardiovascular disease and metabolic syndrome in adult populations using published systematic reviews, b) to update the evidence by conducting a systematic review of recent RCTs and c) to estimate a summary measure of effectiveness by conducting a meta-analysis of the evidence of yoga's effectiveness versus no-exercise and exercise controls.

METHODS

Data sources and search terms

The protocol for this review has been published on the PROSPERO website (http://www.crd.york.ac.uk/PROSPERO) with the registration number CRD42013006375. An amendment was added to the protocol including an exercise control group and published in an online revision note. Articles in this review were identified by accessing the following biomedical electronic

databases with the assistance of a medical librarian: MEDLINE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, EMBASE, and PsycINFO. Using existing published systematic reviews (SRs) as a starting point for gathering evidence, SRs and/or meta-analyses were searched through December 2013. To collect any recent data that may have been missed, we supplemented the search by searching for RCTs published in the last three years through December 2013. Citations were also retrieved by manually searching reference lists of relevant articles. The databases were searched using the keywords "yoga" and "systematic review" for published SRs and "yoga" and "randomized controlled trials" for recent RCTs (see Appendix Table 1.2 for search strategies).

Study selection and inclusion process

Records were pooled from the various databases. Titles and abstracts of SRs that appeared to meet the inclusion criteria were retrieved for further evaluation. Systematic reviews were defined as articles that included an explicit and repeatable literature search method and had explicit and repeatable inclusion and exclusion criteria for studies. RCTs included in the SRs were then retrieved. The process was repeated for the supplementary search of RCTs.

For inclusion in our SR, the studies had to be published in English in a peer-reviewed journal, be conducted in adults (18+ years) who were either healthy, at risk, or with a history of cardiovascular disease or metabolic syndrome and no other major comorbidities, test an asana- (or posture-) based intervention, and report relevant outcomes. We focused only on SRs that included at least one randomized controlled trial with yoga therapy as a trial arm. No restrictions were placed on style of yoga practiced, frequency, or duration. Articles were excluded if we were unable to isolate the effect of yoga (i.e. yoga was part of a multimodal intervention whose non-yoga components were given to the active intervention group but not to the control group), outcomes reported only psychosocial risk factors or psychological outcomes like stress and anxiety, and the population treated focused on other conditions or comorbidities (e.g. women with breast cancer, populations with renal disease). Two investigators (PC and RG) independently selected studies for inclusion; disagreements were resolved by discussion.

Outcomes

The outcomes of interest were changes in the levels of modifiable risk factors for cardiovascular disease and metabolic syndrome. Particularly, we were interested in measures of body composition, blood pressure, lipid panel, glycemic control, heart rate, and smoking status. Primary outcomes include body mass index (BMI), systolic blood pressure (SBP), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). Other outcomes – body weight, diastolic blood pressure (DBP), total cholesterol (TC), triglycerides (TG), fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), heart rate, and smoking status – were considered secondary outcomes. Outcomes were kept in their natural units.

Data extraction and quality assessment

From each eligible study we extracted the characteristics of the participants, intervention description (type, length of session, frequency), control group description, duration of follow-up, number of patients randomized at baseline and number at follow-up, and effect measures (pre- and post-mean and standard deviations in intervention and control arms, mean change scores and standard deviations if reported). Data from the longest follow-up was extracted. Data extraction was performed by one investigator (PC) and checked for accuracy and completeness by a second reviewer (RG). Any discrepancies were resolved by discussion.

RCTs were appraised using the Cochrane Collaboration's Risk of Bias (ROB) tool, a commonly used tool to assess risk of bias.[23] Trial quality was evaluated by using categories of high, low, or unclear risk in regards to randomization method, allocation concealment, blinding of study personnel and outcomes assessment, attrition, and reporting methods. Two reviewers (PC and RG) independently evaluated RCT quality and resolved any discrepancies by discussion.

Statistical analysis

Change scores, mean differences (MDs) between treatment arms, and sample sizes reported were on an intention-to-treat basis. MDs were calculated by subtracting the change score in the control group from the change score in the yoga group. Where MDs and standard deviations were not reported, standard deviations were calculated using a conservative correlation coefficient of 0.5 for within-patient correlation from baseline to follow-up. MDs between groups and 95% confidence intervals (CIs) were calculated for each outcome.

The magnitude of heterogeneity was evaluated using the I^2 statistic testing the null hypothesis that all studies are evaluating the same effect.[24] I^2 values of 25%, 50%, and 75% correspond to low, moderate, and high heterogeneity, respectively. Because meta-analysis pools studies that are clinically and methodologically diverse, data on MDs from trials were statistically pooled using a random effects model.[25] We also categorized patients into four subgroups based on patient conditions – healthy, with CVD risk factors, with diabetes or metabolic syndrome, and diagnosed with coronary artery disease (CAD) – to depict heterogeneity in the populations included and their response to treatment. Healthy patients are those free of clinical manifestations of any medical or psychiatric illness including clinically significant cardiovascular disease and diabetes mellitus. Those with CVD risk factors included patients with hypertension, high cholesterol levels, obesity, and current smokers. Diabetes and metabolic syndrome were diagnosed through medical examination or history, and CAD was confirmed through angiography.

Controls were separated into aerobic exercise (physical training, aerobic exercise, cycling, running, brisk walking) and non-aerobic exercise groups. Yoga was compared to these two control groups separately to obtain an estimate of its effectiveness versus active controls and versus non-active controls (details published in protocol amendment. Reference Manager (RevMan) Version 5.2 software from the Cochrane Collaboration was used for data analysis.[26]

Publication bias

Publication bias was assessed for each of the primary outcomes by visual inspection of funnel plots generated using RevMan software. The MDs were plotted on the x-axis and the standard errors, a measure of study size, on the y-axis. In the absence of bias, the scatterplot should be approximately symmetrical; the more asymmetry, the more bias is present.

RESULTS

Literature search

We identified 643 studies from the SR search and 761 studies from the RCT search for a total of 1404 records (Figure 1.1). After removal of duplicates, a total of 880 titles and abstracts were screened. A total of 37 RCTs (24 RCTs from 18 SRs and 13 additional RCTs) met our criteria for inclusion in the review. Although 37 studies met criteria, five studies did not report exact numbers for our primary or secondary outcomes and could not be included in the meta-analysis,[27-31] leaving 32 studies for statistical analysis.

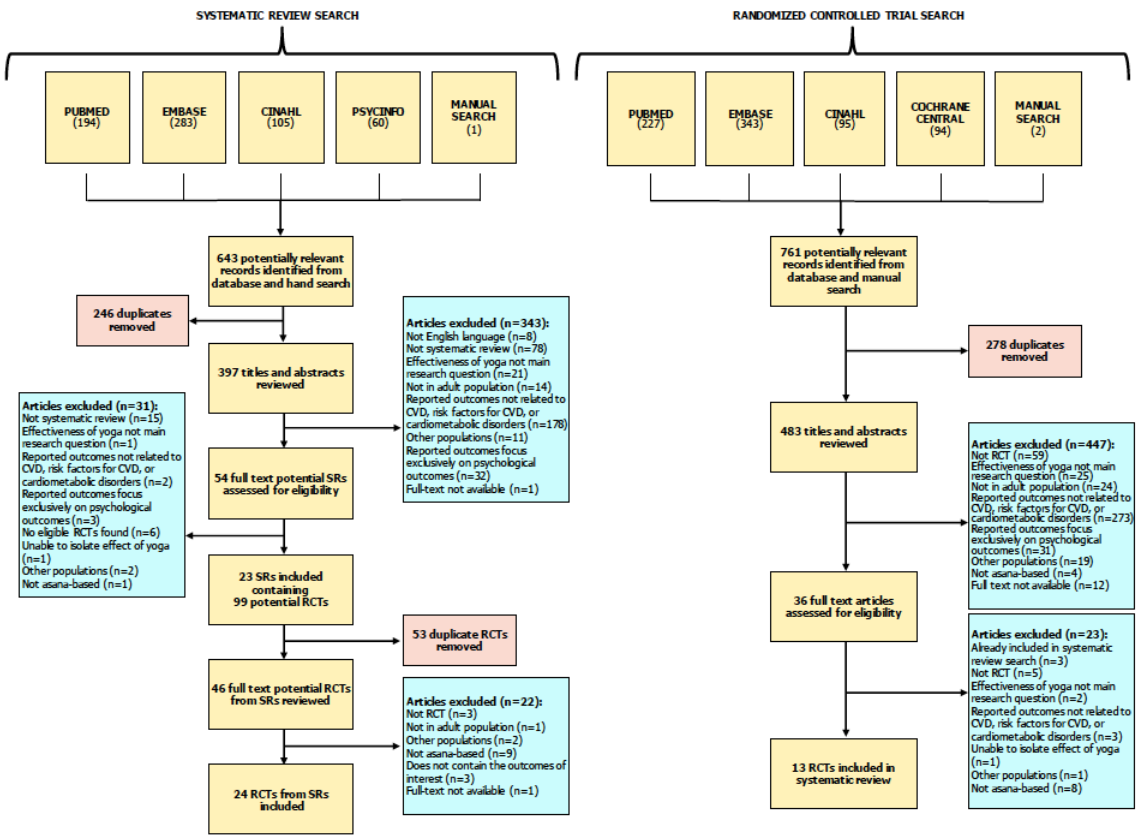


Figure 1.1. Flowchart depicting the search and screening process of systematic reviews and randomized controlled trials (RCTs). CVD: cardiovascular disease

Study quality

Study quality and description of methodology varied amongst the included studies (Table 1.1). Thirteen studies [32-43] provided details on the specific randomization method that was used in the RCT and four [31,35,37,38] described treatment assignment. Due to the nature of the intervention, all studies had high risk of bias for blinding of participants; however, 3 studies reported blinding of the personnel, indicating that technicians were blinded to treatment assignment of individuals.[34,44,45] Almost all studies except one [34] had unclear risk for blinding of outcome assessment. However, there was generally low risk of bias for incomplete reporting of outcomes and selective reporting of outcomes. A summary of study quality can be seen in Appendix Figure 1.7.

Table 1.1. Included randomized controlled trial study characteristics by population.

Study	From SR	Total no. randomized (yoga/ control) Total no. at follow-up (yoga/control)	Treatment group	Mean age±SD Age range	% female	Intervention Time per session	Control	Frequency Duration	Outcome measures	Study quality[b] No. of domains at low/ unclear/ high risk
HEALTHY ADULTS										
Blumenthal et al. (1989)[27a]	Patel et al. (2012),[60] Roland et al. (2011)[61]	101 (34/33/34) 97 (34/31/32)	Community dwelling elderly with no CAD	Yoga 67.8±5.9, control 66.5±4.3 (1), 66.8±4.3 (2) Range: 60-83	50	Yoga and flexibility 60 min	1) Aerobic exercise (warm up, cycle, brisk walking/jogging, cool down) 60 min 2) Waiting list	2x/wk 16 weeks	BW, SBP, DBP, TC, LDL-C, HDL-C	2/3/1
Cusumano et al. (1993)[12]	Innes et al. (2005)[13]	90 (45/45) 90 (45/45)	Female Japanese under-graduates	Range: 18-20	100	Hatha yoga 80 min	Jacobsen progressive muscle relaxation	1x/wk 3 weeks	HR	2/3/1
Bowman et al. (1997)[46]	Innes et al. (2005),[13] Patel et al. (2012),[60] Roland et al. (2011),[61] Ross et al. (2010)[22]	40 (20/20) 26 (12/14)	Healthy sedentary elderly	68 Range: 62-81	38	Hatha yoga 90 min	Aerobic training (10 min warm up, 20 min stationary cycling, 10 min warm down) 40 min	2x/wk 6 weeks	SBP, HR	0/3/3
Stachenfeld et al. (1998)[47]	Patel et al. (2012),[60] Yang (2007)[62]	17 (8/9) 15 (8/7)	Healthy older women	Yoga: 73±3, control 71±2 Range: >65	100	Yoga exercises 60 min	Aerobic training (treadmill 30 min or trampoline walking 40-50 min)	3-4x/wk 12 weeks	BW, SBP, DBP, HR	1/3/2

Table 1.1 (Continued).

Ray et al. (2001a)[41]	Jayasinghe (2004)[11]	40 (20/20) 28 (17/11)	Healthy men from Indian army	Yoga 21.9±1.5, control 22.7±2.0 Range: 19-23	0	Hatha yoga 60 min	Physical army training (slow running, body flexibility, pull-ups) 60 min	6x/wk 24 weeks	BW, HR	2/2/2
Ray et al. (2001b)[56]	Innes et al. (2005)[13]	54 (28/26) 54 (28/26)	Healthy adults	Yoga 23.4±4.0, control 22.2±5.1 Range: 20-25	19	Hatha yoga 60 min	No intervention	3x/wk 20 weeks	SBP, DBP, HR	2/3/1
Fields et al. (2002)[34]	Innes et al. (2005)[28]	15 (6/3/6) 15 (6/3/6)	Healthy seniors	Yoga 74±6, control 76±10 (1), control 77±7 (2) Range: >65	NR	Mahrishi Vedic Medicine (meditation, herbal supplement, meetings, yoga asana, walking, diet) 60 min	1) Modern medicine (conventional dietary, exercise (walking, stretching), and multivitamin approaches); 2) Usual care	7x/wk 52 weeks	SBP, DBP, TC, LDL-C, HDL-C TG, FBG, HbA1c	4/1/1
Harinath et al. (2004)[42]	Abel et al. (2012),[63] Innes et al. (2005)[13]	30 (15/15) 30 (15/15)	Healthy army soldiers	29.6±4.9 Range: 25-35	0	Hatha yoga 60 min	Routine physical army training (slow running, body flexibility)	7x/wk 12 weeks	SBP, DBP, HR	3/2/1

Table 1.1 (Continued).

Chen et al. (2008)[28 a]	Patel et al. (2012),[60] Roland et al. (2011)[61]	204 (67/65/72) 176 (57/53/66)	Seniors in a community activity center	69±6.3 Range: 60-75	73	1) Silver yoga (yoga, stretching, meditation) 70 min 2) Silver yoga (no meditation) 55 min	Waiting list	3x/wk 24 weeks	BW, BMI, SBP	1/3/2
Vogler et al. (2011)[29 a]		40 (20/20) 38 (19/19)	Physically inactive older adults	Yoga 76, control 72 Range: 56-94	NR	Iyengar yoga 90 min Home practice 15-20 min	Usual daily routine	2x/wk 3x/wk (home practice) 8 weeks	SBP, DBP	2/3/1
Kanojia et al. (2013)[64]		50 (25/25) 50 (25/25)	Young healthy females	Yoga 18.6±1.1, control 18.1±0.8 Range: 18-20	100	Yoga 40 min	No intervention	6x/wk	BW, SBP, DBP, HR	2/3/1
Kim et al. (2012)[65]		47 (27/20) 34 (16/18)	Normal premeno-pausal women	Yoga 45.7±5.2, control 43.2±4.5 Range: 35-50	100	Ashtanga yoga 60 min	Normal daily lifestyles	2x/wk 32 weeks	SBP, DBP, HR	1/4/1

Table 1.1 (Continued).

Wolever et al. (2012)[66]		239 (90/96/53) 205 (76/82/47)	Employees of a national insurance carrier	Yoga 41.6± 10.1, control 44.3±9.4 (1), 42.7±9.7 (2)	77	Viniyoga stress reduction program 60 min	1) Mindfulness at Work program 2) List of resources	1x/wk 12 weeks	SBP, DBP	2/3/1
Tracy et al. (2013)[30 a]		32 (21/11) 21 (10/11)	Young healthy adults	Yoga 29±6, control 26±7 Range: 21-39	52	Bikram yoga 90 min	Normal lifestyle	3x/wk 8 weeks	SBP, HR	0/3/3
ADULTS WITH CVD RISK FACTORS										
van Montfrans et al. (1990)[67]	Innes et al. (2005),[13] Hagins et al. (2013)[19]	42 (23/19) 35 (18/17)	Adults with mild un-complicated hypertension	Yoga 40, control 43 Range: 24-60	49	Hatha yoga + progressive muscle relaxation + stress management 60 min	Passive relaxation	1x/wk; 2x/wk (home practice) 52 weeks	BW, SBP, DBP, TC	2/3/1
Mahajan et al. (1999)[54]	Innes et al. (2005),[13] Jayasinghe (2004),[11] Yang (2007),[62] Patel et al. (2012)[60]	93 (52/41) 93 (52/41)	Angina patients and asymptomatic participants with CAD risk factors	Range: 56-59	0	4d yoga camp + diet; yoga practice + lifestyle advice 60 min	Conventional therapy (diet control, moderate aerobic exercise as prescribed) + lifestyle advice	4 days + 7x/wk 14 weeks	BW, TC, LDL-C, HDL-C, TG	1/4/1

Table 1.1 (Continued).

Murugesan et al. (2000)[53]	Innes et al. (2005),[13] Jayasinghe (2004),[11] Nicolson et al. (2004),[68] Innes et al. (2007),[14] Patel et al. (2012),[60] Hagins et al. (2013),[19] Wang et al. (2013)[69]	33 (11/11/11) 33 (11/11/11)	Hypertensive patients	Range: 35-65	NR	Yoga 60 min	1) Daily medical treatment with antihypertensives 2) No intervention	7x/wk 11 weeks	BW, SBP, DBP	2/3/1
McCaffrey et al. (2005)[39]	Hagins et al. (2013),[19] Rioux et al. (2013),[70] Wang et al. (2013)[69]	61 (32/29) 54 (27/27)	Adults with diagnosed hypertension not currently taking medication	Yoga 56.7, control 56.2	65	Yoga practice with instructional booklet and tape 63 min	General education about hypertension	3x/wk 8 weeks	BMI, SBP, DBP, HR	2/2/2
Cohen et al. (2011)[71]	Wang et al. (2013),[69] Hagins et al. (2013)[19]	78 (46/32) 57 (26/31)	Adults with untreated pre-hypertension or Stage 1 hypertension not taking anti-hypertensive medication	Yoga 48.2±1.6, control 48.3±2.4 Range: 22-69	50	Iyengar yoga 70min (classes all weeks, 25 min home practice weeks 6-12)	Enhanced usual care with dietary education	2x/wk first 6 weeks; 1x/wk next 6 weeks 12 weeks	BW, SBP, DBP, HR	1/3/2

Table 1.1 (Continued).

Subramanian et al. (2011)[48]	Hagins et al. (2013)[19]	100 (25/25/25/25) 94 (25/25/23/21)	Young adults with pre-hypertension and hypertension not taking anti-hypertensive medication	Yoga 23, control 23.3 (1), 23.7 (2), 23.7 (3)	33	Yoga 30-45 min	1) No intervention, 2) physical exercise (brisk walking) 50-60min, 3) Salt intake reduction to at least half previous intake	5x/wk 8 weeks	SBP, DBP	2/3/1
Bock et al. (2012)[32]	Carim-Todd et al. (2013)[72]	55 (32/23) 55 (32/23)	Middle age female smokers that intended to quit smoking	45.6±8.3	100	Vinyasa yoga + CBT	Wellness sessions for health education + CBT	2x/wk 8 weeks	7-day point-prevalence smoking abstinence	3/2/1
Lee et al. (2012)[73]		16 (8/8) 16 (8/8)	Obese postmenopausal women Yoga 54.5±2.8, control 54.3±2.9 100%			Yoga 60 min	No exercise	3x/wk 16 weeks	BW, BMI, TC, LDL-C, HDL-C, TG, FBG	2/3/1
ADULTS WITH DIABETES OR METABOLIC SYNDROME										
Monro et al. (1992)[52]	Innes et al. (2005),[13] Aljasir et al. (2010),[74] Innes et al. (2007),[14] Pilkington et al. (2007)[75]	21 (11/10) 21 (11/10)	Patients with non-insulin-dependent DM controlled with medication or diet	Yoga 53, control 57	NR	Yoga + normal medication and diet 90 min	Usual care (continuation of medication, diet)	2-4x/wk 12 weeks	FBG, HbA1c	1/3/2

Table 1.1 (Continued).

Kerr et al. (2002)[31 a]	Innes et al. (2007),[14] Pilkington et al. (2007)[75]	37 (17/20) 33 (17/16)	Patients with poorly controlled type 1 and 2 DM	Yoga 60.3±7.8, control 61.4±10.7	NR	Hatha yoga + education + continued insulin 90 min	Education + simple exercises + continued insulin	2x/wk 16 weeks	BW, BMI, TC, LDL-C, HDL-C, TG, HbA1c	1/2/3
Cohen et al. (2008)[33]	Anderson et al. (2011),[57] Sharma et al. (2012),[76] Hagins et al. (2013)[19]	26 (14/12) 24 (12/12)	Underactive, overweight adult men and women with metabolic syndrome not taking medication	Yoga 52±9, control 52±8 Range: 30-65	85	Yoga 90 min + 3 hr intro	Waiting list	2x/wk for 5 wks, then 1x/wk for 5 weeks; 3x/week (home practice) 10 weeks	BW, BMI, SBP, DBP, TC, LDL-C, HDL-C, TG, FBG	3/2/1
Gordon et al. (2008)[45]	Patel et al. (2012),[60] Ross et al. (2010),[22] Sharma et al. (2012)[76]	231 (77/77/77) 231 (77/77/77)	Elderly patients with type 2 DM	Yoga 64, control 63.9 (1), 63.6 (2)	81	Hatha yoga + continued diet and medication 120 min	1) Conventional physical aerobic exercise (180 min) + continued diet and medication 2) No intervention/continued diet and medication	1x/wk; 3-4x/wk (home practice) 24 weeks	TC, LDL-C, HDL-C, TG, FBG	3/3/0

Table 1.1 (Continued).

Saptharishi et al. (2009)[40]	Hagins et al. (2013)[19]	120 (30/30/30/30) 102 (21/29/27/25)	Young adults with hypertension and pre-hypertension not taking anti-hypertensive medication	Yoga: 22.5±1.36, control 22.5±1.4 (1), 22.4±1.3 (2), 22.5±1.47 (3)	33	Yoga 30-45 min	1) No intervention 2) Brisk walking 50-60 min 3) Salt intake reduction to at least half previous intake	5x/wk 8 weeks	SBP, DBP	3/2/1
Skoro-Kondza et al. (2009)[37]	Sharma et al. (2012)[48]	59 (29/30) 59 (29/30)	Patients with type 2 DM not taking insulin	60±10	61	Yoga + advice 90 min	Waiting list + advice	2x/wk 12 weeks	HbA1c	2/2/2
Yang et al. (2011)[77]	Sharma et al. (2012),[74] Patel et al. (2012)[60]	25 (13/12) 23 (12/11)	Patients with metabolic syndrome not taking cholesterol, BP, or glucose-lowering medication	51.7±4.9 Range:45-65	91	Vinyasa style yoga 60 min	General health education materials every 2 weeks	2x/wk 12 weeks	BW, SBP, DBP, TC, LDL-C, HDL-C, TG, FBG	2/3/1
Vaishali et al. (2012)[38]		60 (30/30) 57 (27/30)	Elderly subjects with type 2 DM more than 15 years on antidiabetic drugs	Yoga 65.8±3.2, control 64.4±3.8 Range: >60	37	Yoga + education + medication as in control 45-60 min	Education + conventional hypoglycemic medications	6x/wk 12 weeks	TC, LDL-C, HDL-C, TG, FBG, HbA1c	4/1/1

Table 1.1 (Continued).

Hegde et al. (2013)[78]		29 (14/15) 29 (14/15)	Prediabetic subjects	Yoga 46.5±13.0, control 44.7±9.6 Range: 30-75	52	Yoga 75-90 min	Waiting list	7x/wk 12 weeks (one wknd break)	BMI, SBP, DBP, FBG, HbA1c	3/2/1
Shantakumari et al. (2013)[51]		100 (50/50) 100 (50/50)	Patients with type 2 DM and dyslipidemia, mean duration DM 5-10 years Yoga 45.5±8, control 44.5±11 48%			Yoga + drugs as in control 60 min	Oral hypoglycemic drugs	7x/wk 12 weeks	BW, BMI, TC, LDL-C, HDL-C, TG	2/3/1
ADULTS WITH DIAGNOSED CORONARY ARTERY DISEASE (CAD)										
Manchanda et al. (2000)[49]	Innes et al. (2005),[13] Jayasinghe (2004),[11] Yang et al. (2007),[62] Patel et al. (2012)[60]	42 (21/21) 42 (21/21)	Male patients with CAD and chronic stable angina	Yoga 51±9, control 52±10 Range: 32-72	0	Yoga + medication for angina as in control 90 min	Conventional medical therapy (risk factor control and AHA step I diet) + medication for angina (no lipid-lowering drugs)	7x/wk 4 days training + 1 year follow-up	BW, TC, LDL-C, HDL-C, TG	3/3/0
Jatuporn et al. (2003)[55]	Innes et al. (2005)[13]	44 (22/22) 44 (22/22)	Adults with CAD without prior therapeutic intervention	Yoga 61.5 ±4.7, control 56.8±7.6	20	Intensive lifestyle modification without lipid-lowering drugs (yoga, support, dietary advice, relaxation) 60 min	Conventional treatment with lipid-lowering drugs	3x/wk 16 weeks	BMI, TC, LDL-C, HDL-C, TG	2/3/1

Table 1.1 (Continued).

Ades et al. (2005)[43]	Patel et al. (2012)[60]	51 (25/26) 42 (21/21)	Community-dwelling women with established CAD for at least 6 months	Yoga: 71.5±4.8, control 72.9±6.1 Range: >65	100	Light yoga + continued medication as in control 30-40 min	Resistance exercise training + continued medication (aspirin, β-adrenergic blockers, nitrates, calcium-blockers)	3x/wk 24 weeks	BW, BMI	3/2/1
Pal et al. (2011)[35]		160 (85/85) 154 (80/74)	Patients diagnosed with CAD	Yoga 58.9±9.4, control 58.6±10.5	16	Yoga + medication as in control 35-40 min	Medication only (metoprolol/atenolol, aspirin, clopidopril, atorvastatin/rosuvastatin, ramipril/losartan/telmisartan)	5x/wk 24 weeks	BMI, SBP, DBP, TC, LDL-C, HDL-C, TG, HR	4/1/1
Pal et al. (2013)[36]		258 (129/129) 208 (105/103)	Patients diagnosed with CAD	Yoga 59.1±9.9, control 56.4±10.9	20	Yoga + medication as in control 35-40 min	Medication only (metoprolol/atenolol, aspirin, clopidopril, atorvastatin/rosuvastatin, ramipril/losartan/telmisartan)	5x/wk 72 weeks	BMI, SBP, DBP, HR	2/3/1

[a] Findings only described in text, numbers not reported

[b] Based on the Cochrane Collaboration's risk of bias tool, numbers correspond to number rated low risk, unclear risk, and high risk on 6 domains

Unless otherwise noted, the yoga group also received usual care in addition to the listed interventions.

Abbreviations: NR=not reported, SD=standard deviation, CAD=coronary artery disease, DM=diabetes mellitus, CBT=cognitive behavioral therapy, AHA=American Heart Association, SBP=systolic blood pressure, DBP=diastolic blood pressure, BW=body weight, BMI=body mass index, LDL-C=low-density lipoprotein cholesterol, HDL-C=high-density lipoprotein cholesterol, TC=total cholesterol, TG=triglycerides, FBG=fasting blood glucose, HbA1c=glycosylated hemoglobin

Study characteristics

Characteristics of the included studies are listed in Table 1.1. The included studies comprised a total of 2768 participants, with about an equal mix of men (47%) and women (53%). RCTs included participants of all ages with an average age of 50. 1287 (47%) were assigned to receive the yoga intervention and 1461 (53%) assigned to the control arm. 1094 (85%) of yoga participants completed the study while 1301 (89%) of control participants made it to follow-up. Duration of studies varied, with follow-up times ranging from 3 weeks to 52 weeks, with a median of 12 weeks. Dividing into subgroups, 38% (14/37) of studies were conducted in healthy populations, and 22% (8/32) of studies in populations with CVD risk factors, 27% (10/32) in populations with diabetes or metabolic syndrome, and 13% (5/32) in populations with CAD.

Control arms included usual care or conventional medical therapy (23%), a form of relaxation (6%), education (11%), diet alone (4%), waiting list or no intervention (32%), cognitive-based therapy (2%), and exercise (21%). Five two-arm RCTs,[41-43,46,47] 3 three-arm RCTs,[27,40,45] and 1 four-arm RCT [48] used exercise as one of the comparator strategies. Exercise controls consisted of physical training, cycling, running, brisk walking, or resistance training [43]. One exercise trial [27] was excluded from the meta-analysis due to incomplete reporting of effect measures.

Risk factor outcomes

Yoga versus non-exercise controls

Yoga showed significant improvement of risk factors versus non-exercise controls for each of the primary outcomes: BMI (-0.77 kg/m^2 [-1.09 to -0.44]), SBP (-5.21 mmHg [-8.01 to -2.42]), LDL-C (-12.14 mg/dL [-21.80 to -2.48]), and HDL-C (3.20 mg/dL [1.86 to 4.54]) (Figures 1.2-1.5). For the secondary outcomes, significant improvement was seen in all risk factors except FBG (-5.91 mg/dL [-16.32 to 4.50]) and HbA1c (-0.06 %Hb [-0.43 to 0.31]) (Appendix Figure 1.8).

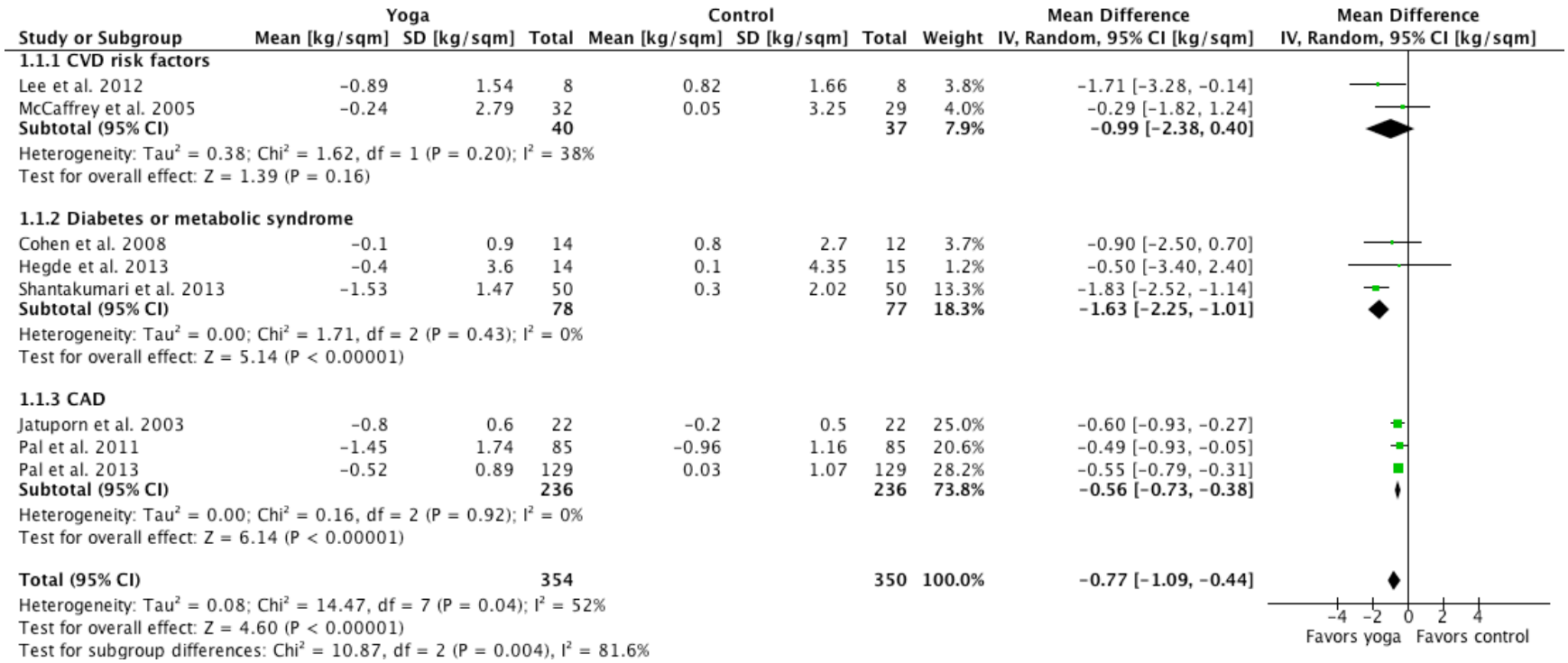


Figure 1.2. Forest plot of body mass index results. Negative mean differences between groups favor the yoga intervention, positive mean differences favor control.

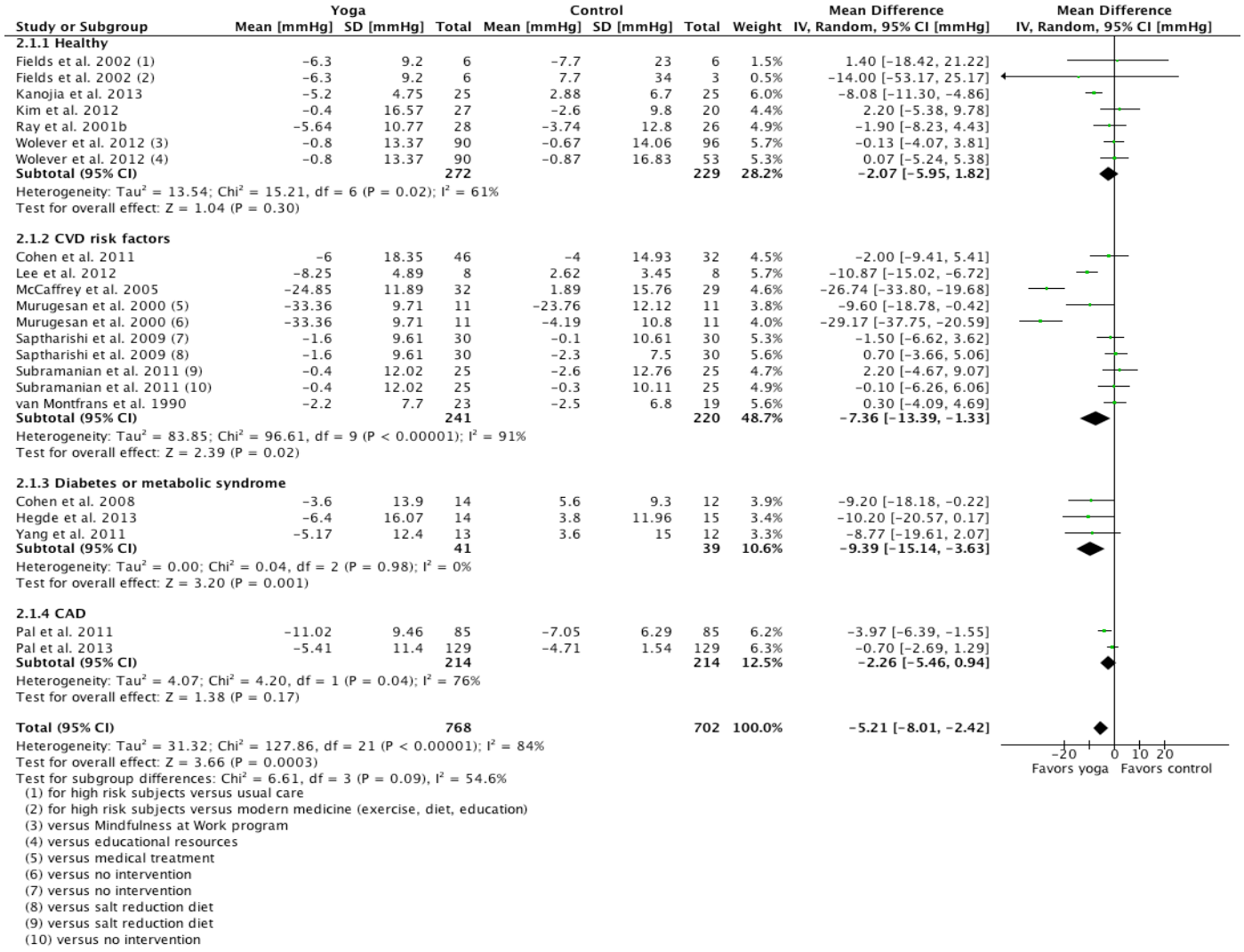


Figure 1.3. Forest plot of systolic blood pressure (mmHg) results. Negative mean differences between groups favor the yoga intervention, positive mean differences favor control.

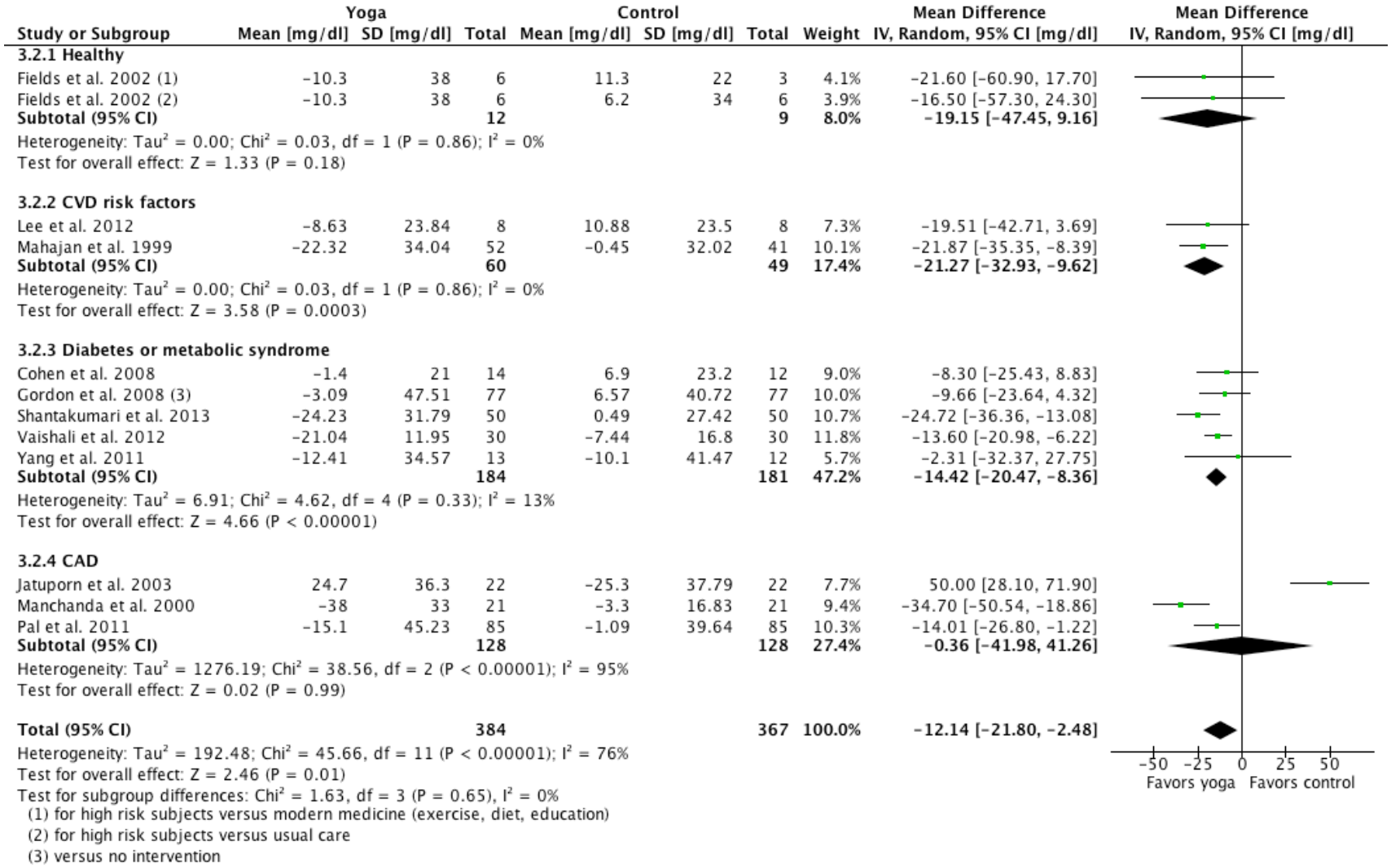


Figure 1.4. Forest plot of low-density lipoprotein cholesterol (mg/dl) results. Negative mean differences between groups favor the yoga intervention, positive mean differences favor control.

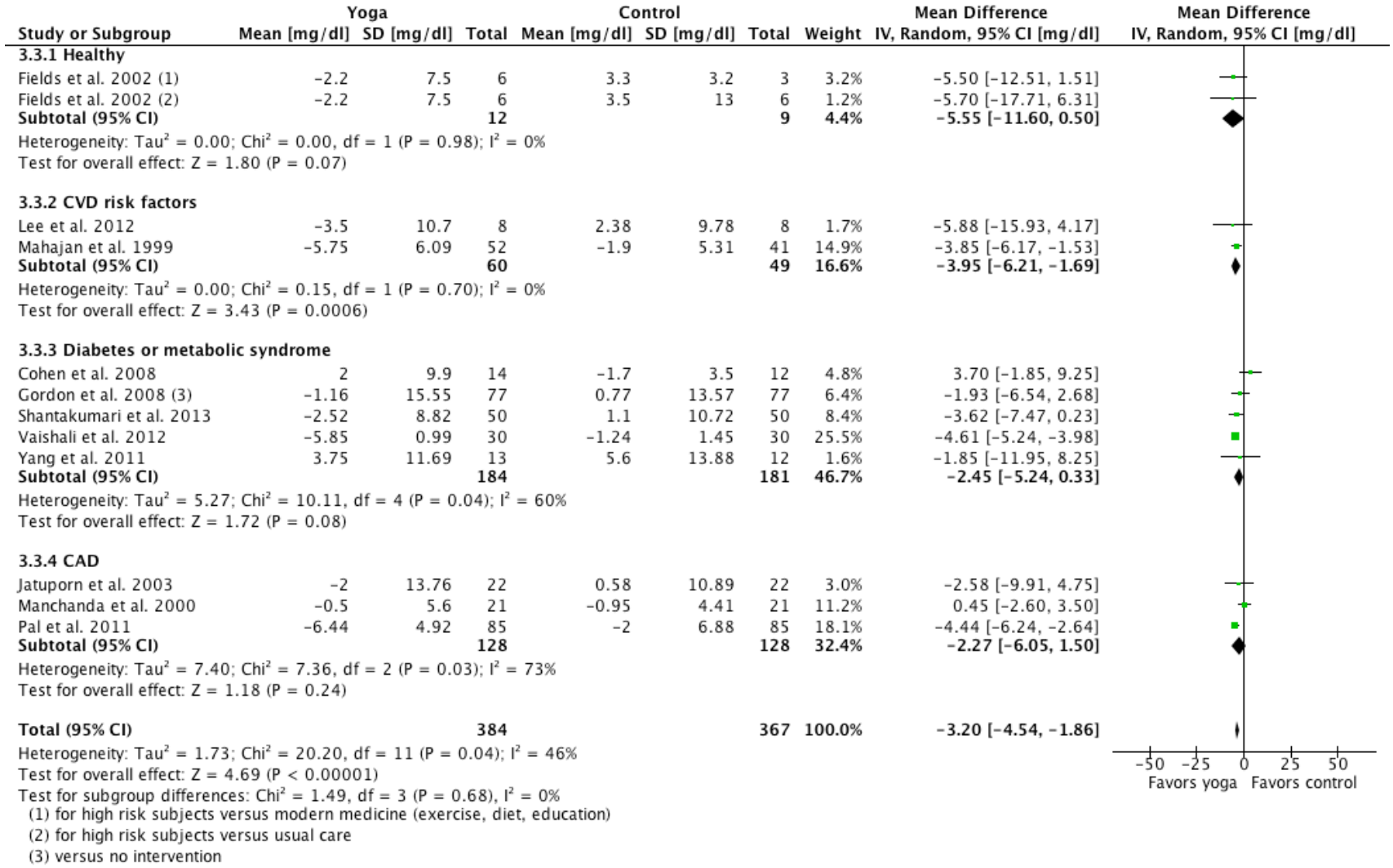


Figure 1.5. Forest plot of high-density lipoprotein cholesterol (mg/dl) results. Note: signs are reversed so axis stay consistent with other forest plots even though an increase in HDL-C levels reflects clinical improvement.

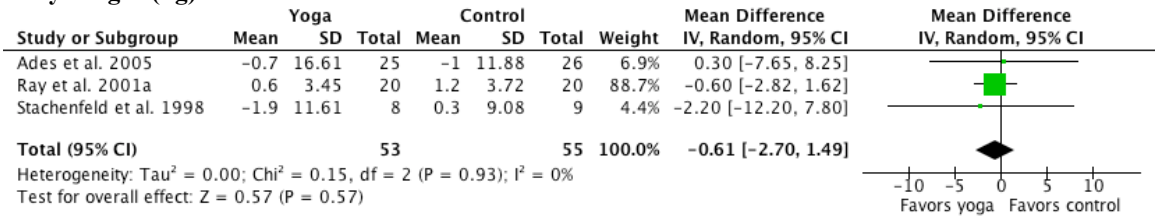
Improvements reported in secondary outcomes include reductions of body weight (-2.35 kg [-4.33 to -0.37]), DBP (-4.98 mmHg [-7.17 to -2.80]), TC (-18.48 [-29.16 to -7.80), TG (-25.89 mg/dL [-36.19 to -15.60]), and heart rate (-5.27 beats/min [-9.55 to -1.00]) (Appendix Figure 1.8).

Only one trial was found which evaluated the impact of yoga on smoking status.[32] When twice-weekly Vinyasa-style yoga was added in addition to cognitive behavioral therapy (CBT) for smoking cessation, smokers in the intervention group had higher odds of 7-day and 24-hour abstinence compared to a control group receiving CBT and education at the end of the 8-week study period (7-day quit OR 4.56 [95% CI 1.12 to 18.57], 24-hr quit OR 4.19 [1.16 to 15.11]. These results did not last, however, when abstinence was measured at 6-month follow-up (7-day quit OR 1.54 [0.34 to 6.92], 24-hr quit OR 1.87 [0.43 to 8.16]).

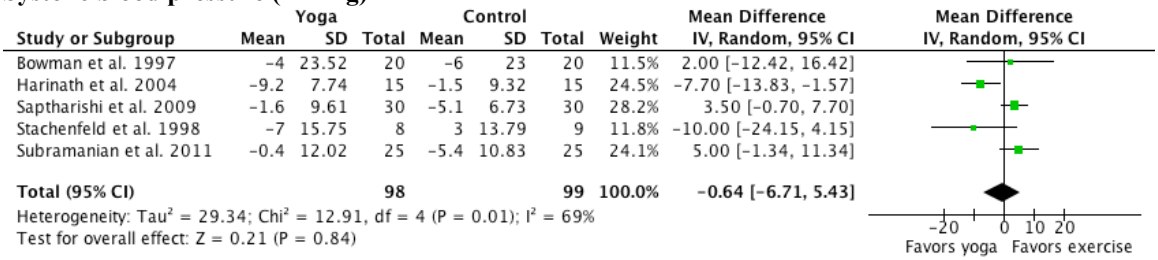
When yoga is used in addition to medication, significant improvement was found in body weight,[49] BMI, [35,36] blood pressure,[20,50] lipid levels,[35,38,49,51] FBG,[38,52] HbA1c,[38,52] and heart rate [36] in patients with type 2 diabetes or CAD. As a substitute for medical therapy, results are less definitive. Two RCTs found yoga more effective than drug therapy in controlling blood pressure [53] and body weight.[53,54] In a three-arm trial in which yoga was directly compared to a group that received antihypertensive treatment and a group receiving no treatment in patients at high risk for CVD, yoga reduced SBP almost three times more than the antihypertensive therapy (MD -29.17 mmHg, [-37.75, -20.59] and -9.60 mmHg, [-18.78, -0.42], respectively. [53] When yoga was included in addition to continued medication in CAD patients, an additional benefit, although smaller, is still observed. [35,36] Among CAD patients, yoga is less effective as a substitute for medication such as statins and lipid-lowering drugs in lowering LDL-C;[55] however, as an adjunct treatment to medication, yoga provides an additional statistically significant benefit. [35,49]

Yoga versus exercise

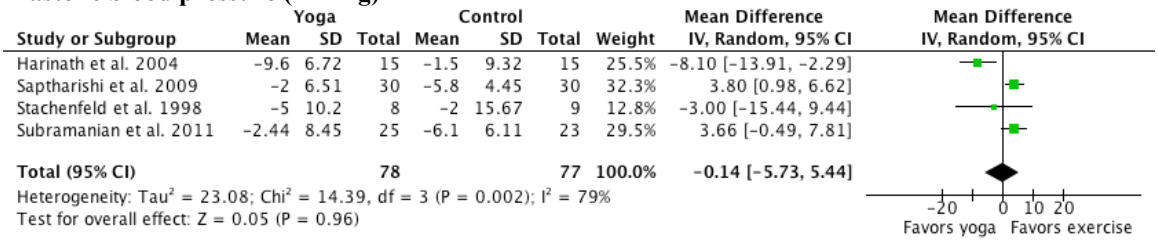
Body weight (kg)



Systolic blood pressure (mmHg)



Diastolic blood pressure (mmHg)



Heart rate (beats/min)

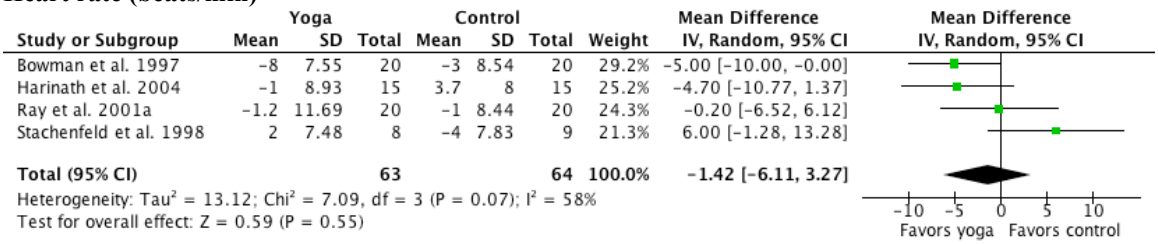


Figure 1.6. Forest plots of yoga versus physical exercise results for body weight, systolic blood pressure, diastolic blood pressure, and heart rate.

Five out of nine trials comparing yoga to exercise were conducted in healthy populations [27,41,42,46,47,56] and the remaining were conducted in young patient populations with hypertension,[40,48] an elderly female population with CAD,[43] and a population with type 2 diabetes mellitus.[45]

Among the outcomes that were reported by more than one study, there was no significant difference in the effectiveness of yoga versus aerobic exercise in modifying body weight (MD: -0.61kg, 95% CI [-2.70, 1.49]),[41,43,47] SBP (MD: -0.64mmHg, 95% CI [-6.71, 5.43]),[40,42,46-48] DBP (MD: -0.14mmHg, 95% CI [-5.73, 5.44]),[40,42,47,48] and heart rate (MD: -1.42 beats/min, 95% CI [-6.11,

3.27])[41,42,46,47,56] (Figure 1.6). In addition, there was also no difference comparing the two strategies for BMI,[43] LDL-C,[45] HDL-C,[45] TC,[45] TG,[45] or FBG.[45]

When all studies were pooled together, all trends remained irrespective of controls. Mean differences in risk factor reductions changed only slightly (Appendix Table 1.3).

Publication bias

Funnel plots assessing publication bias of the primary outcomes are shown in Appendix Figure 1.9. As the funnel plots are mostly symmetrical, we do not find evidence of strong publication bias.

DISCUSSION

The review shows that the practice of yoga may be beneficial to managing and improving risk factors associated with cardiovascular disease and metabolic syndrome. This finding, however, should be cautiously interpreted as the RCTs included were of limited sample size, heterogeneous, and had unclear or high risk of bias on several domains. When trials were pooled, all but two of the outcomes examined in this review showed improvement after a yoga intervention when compared to non-exercise controls.

Compared to traditional aerobic exercise controls, there was no significant difference in how exercise or yoga changed risk factors, suggesting similar effectiveness of the two forms of physical activity and possibly similar underlying mechanisms. The mechanism behind the therapeutic effect of yoga for cardiovascular disease is still unclear; studies have suggested that yoga may modulate autonomic function and beneficially alter markers of sympathetic and parasympathetic activity.[12-14] Through practicing yoga, the effects of stress can be reduced, leading to positive impacts on neuroendocrine status, metabolic and cardio-vagal function, and related inflammatory responses. [12-14] The similarity in effectiveness on risk factors between the two forms of exercise suggest that there could be comparable working mechanisms, with some possible physiological aerobic benefits occurring with yoga practice, and some stress-reducing, relaxation effect occurring with aerobic exercise.

This review helps strengthen the evidence base for yoga as a potentially effective therapy for cardiovascular and metabolic health. Our results support earlier reviews on the positive benefits of yoga on primary and secondary prevention of cardiovascular disease and metabolic syndrome.[11,13,18-20,22,50,57] Two systematic reviews that were recently published find that there is some evidence for yoga having favorable effects on cardiovascular disease risk factors.[58,59] One review, conducted by the Cochrane Collaboration, included 11 trials with its more restrictive inclusion criteria and found significant improvement in DBP, TG, and HDL.[59] The second review, with broad inclusion criteria and a wider list of outcomes, included 44 trials and found that yoga improves SBP, DBP, heart rate, respiratory rate, waist circumference, waist/hip ratio, TC, HDL, very low density lipoprotein, HbA1c, and insulin resistance.[58] All studies find that published RCTs on yoga are small, of short duration, and heterogeneous, precluding any strong conclusions on the effectiveness of yoga.

Yoga may provide the same benefits in risk factor reduction as traditional physical activity such as cycling or brisk walking, supporting a previous narrative review.[22] This finding is significant as individuals who cannot or prefer not to perform traditional aerobic exercise might still achieve similar benefits in cardiovascular disease risk reduction. Evidence supports yoga's accessibility and acceptability to patients with lower physical tolerance like those with preexisting cardiac conditions, the elderly, or those with musculoskeletal or joint pain.[28]

Lastly, in addition to CVD risk factor improvements, other benefits may result from practicing yoga. For example, yoga may provide health-related quality of life improvements such as reductions in stress and anxiety and better coping mechanisms distinct from other forms of exercise. Yoga may also be practiced in a variety of settings with no special equipment needed, potentially increasing the frequency and ease of practice. These benefits may produce greater willingness to engage in a form of physical activity, better adherence and sustainability, ultimately facilitating greater long-term individual- and population-level CVD and metabolic risk reductions.

Limitations

There are potential limitations of this review. First, we included only English language articles and articles published in peer-reviewed journals. Second, several outcomes are related to cardiovascular and metabolic health; we focused on the major risk factors and surrogate markers for these conditions, as they are predictive of CVD risk [4] and concrete outcomes such as cardiac death and myocardial infarction were not reported in the RCTs. As with all RCTs, findings are applicable to the patient population in which the study was conducted and wide generalizations should be avoided.

There was a great deal of heterogeneity across included studies. Because part of the appeal and feasibility of yoga is the customizability of the practice to individual practitioners, a wide variety of yoga interventions, frequencies and lengths of practice and follow-up were included. To deal with some of this variation, we used random effects in the meta-analysis and divided patient populations into subgroups. Although I^2 values did drop within subgroups compared to overall, heterogeneity was still present. As more studies are undertaken and published, further division by yoga tradition, duration of follow-up, and other factors can be performed.

Lastly, study quality and assessment could be improved. Many studies had small sample sizes and did not fully report all methods and outcomes, leading to high or unclear ratings in the risk of bias on several domains. On a related note, although the Cochrane Risk of Bias tool is widely used and applicable, the definitions and structure of the rating system can lead to inaccurate estimation of study quality. For example, blinding of participants is not possible in RCTs evaluating yoga, automatically leading to a high bias rating in the 'performance bias' domain, which assesses blinding of participants and personnel. Study quality could thus be underestimated in many cases. Nevertheless, more complete reporting of methodology and outcomes by authors can help enhance the usefulness of rigor of the trials.

Future research directions

Despite the growing evidence on the health implications of yoga, the physiological mechanisms behind the observed clinical effects of yoga on cardiovascular risk remains unclear. Inquiries into the minimum effective dose of yoga, and the dose-response relationship can help elucidate yoga's potential as a medical therapy. Research is also still lacking on the costs and economic implications; more research can be done comparing the relative costs and benefits of yoga versus traditional methods like exercise or medication. Yoga has the potential to be a cost-effective treatment and prevention strategy given its low cost, lack of expensive equipment or technology, potential greater adherence and health-related quality of life improvements, and possible accessibility to larger segments of the population.

CONCLUSION

Our review finds emerging evidence to support a role for yoga in improving common modifiable risk factors of cardiovascular disease and metabolic syndrome. Whereas previous reviews have looked at a single or a few risk factors, our review significantly updates the existing literature summary and encompasses numerous CVD and metabolic risk factors that can be used to calculate overall CVD risk. We believe that these findings have important implications for the acceptance of yoga as an effective therapeutic intervention. Given the growing popularity of yoga in the US and around the world, there is a need for larger randomized controlled studies that meet explicit, high quality methodological standards to ascertain the effects of yoga. This review demonstrates the potential of yoga to have an impact on concrete, physiological outcomes that represent some of the greatest health burdens today.

CONFLICTS OF INTEREST

None declared.

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REFERENCES

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2014 update: a report from the american heart association. Circulation 2014;129(3):e28-e292.

2. World Health Organization. Global status report on noncommunicable diseases 2010. Geneva: World Health Organization, 2011.

3. National Heart, Lung, and Blood Institute. What is metabolic syndrome, http://www.nhlbi.nih.gov/health/health-topics/topics/ms/ (2011, accessed 7 March 2014).

4. D'Agostino RB, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: The Framingham heart study. Circulation 2008;118(4):E86-E86.

5. World Health Organization. Global recommendations for physical activity for health, http://whqlibdoc.who.int/publications/2010/9789241599979_eng.pdf (2010, accessed 7 March 2014).

6. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63.

7. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2889-2934.

8. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J 2012;33(13):1635-701.

9. Younge JO, Gotink RA, Baena CP, et al. Mind-body practices for patients with cardiac disease: a systematic review and meta-analysis. European Journal of Preventive Cardiology 2015;11:1385-98.

10. Cramer H, Lauche R, Haller H, et al. A systematic review of yoga for heart disease. European Journal of Preventive Cardiology 2015;22:284-95.

11. Jayasinghe SR. Yoga in cardiac health (a review). Eur J Cardiovasc Prev Rehabil 2004;11(5):369-75.

12. Cusumano JA RS. The short-term psychophysiological effects of Hatha yoga and progressive relaxation on female Japanese students. Applied Psychology: An International Review 1993;42(1):77-90.

13. Innes KEB, C. Taylor, A. G. Risk indices associated with the insulin resistance syndrome, cardiovascular disease, and possible protection with yoga: a systematic review. J Am Board Fam Pract 2005;18(6):491-519.

14. Innes KEV, H. K. The influence of yoga-based programs on risk profiles in adults with type 2 diabetes mellitus: a systematic review. Evid Based Complement Alternat Med 2007;4(4):469-86.

15. Barnes PM BB, Nahin R. CDC National Health Statistics Report #12. Complementary and Alternative Medicine Use Among Adults and Children: United States, 2007, 2008.

16. Saper RB, Eisenberg DM, Davis RB, et al. Prevalence and patterns of adult yoga use in the United States: Results of a national survey. Alternative therapies in health and medicine 2004;10(2):44-49.

17. Lau HLK, J. S. Yeung, F. Chau, P. H. Woo, J. Yoga for secondary prevention of coronary heart disease. Cochrane Database Syst Rev 2012;12:CD009506.

18. Bussing A, Michalsen A, Khalsa SB, et al. Effects of yoga on mental and physical health: a short summary of reviews. Evid Based Complement Alternat Med 2012;2012:165410.

19. Hagins M, States R, Selfe T, et al. Effectiveness of yoga for hypertension: systematic review and meta-analysis. Evid Based Complement Alternat Med 2013;2013:649836.

20. Raub JA. Psychophysiologic effects of Hatha Yoga on musculoskeletal and cardiopulmonary function: a literature review. Journal of Alternative & Complementary Medicine 2002;8(6):797-812.

21. Hutchinson SC EE. Yoga therapy for coronary heart disease: a systematic review. Focus on Alternative and Complementary Therapies 2003;8:144.

22. Ross AT, S. The health benefits of yoga and exercise: a review of comparison studies. Journal of alternative and complementary medicine 2010;16(1):3-12.

23. Higgins JPT AD, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. Cochrane Handbook for Systematic Reviews of Interventions Version 510, 2011.

24. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557-60.

25. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7(3):177-88.

26. Review Manager (RevMan) [program]. 5.2 version. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

27. Blumenthal JA, Emery CF, Madden DJ, et al. Cardiovascular and behavioral effects of aerobic exercise training in healthy older men and women. J Gerontol 1989;44(5):M147-57.

28. Chen KM, Chen MH, Hong SM, et al. Physical fitness of older adults in senior activity centres after 24-week silver yoga exercises. J Clin Nurs 2008;17(19):2634-46.

29. Vogler J, O'Hara L, Gregg J, et al. The impact of a short-term iyengar yoga program on the health and well-being of physically inactive older adults. Int J Yoga Therap 2011(21):61-72.

30. Tracy BL, Hart CE. Bikram yoga training and physical fitness in healthy young adults. J Strength Cond Res 2013;27(3):822-30.

31. Kerr D GE, Ryder J, e tal. An Eastern art form for a Western disease: randomised controlled trial of yoga in patients with poorly controlled insulin-treated diabetes. Practical Diabetes Int 2002;19(6):164-66.

32. Bock BC, Fava JL, Gaskins R, et al. Yoga as a complementary treatment for smoking cessation in women. Journal of women's health (2002) 2012;21(2):240-48.

33. Cohen BE, Chang AA, Grady D, et al. Restorative yoga in adults with metabolic syndrome: a randomized, controlled pilot trial. Metab Syndr Relat Disord 2008;6(3):223-9.

34. Fields JZ, Walton KG, Schneider RH, et al. Effect of a multimodality natural medicine program on carotid atherosclerosis in older subjects: a pilot trial of Maharishi Vedic Medicine. Am J Cardiol 2002;89(8):952-8.

35. Pal A, Srivastava N, Tiwari S, et al. Effect of yogic practices on lipid profile and body fat composition in patients of coronary artery disease. Complementary therapies in medicine 2011;19(3):122-27.

36. Pal A, Srivastava N, Narain VS, et al. Effect of yogic intervention on the autonomic nervous system in the patients with coronary artery disease: A randomized controlled trial. Eastern Mediterranean Health Journal 2013;19(5):452-58.

37. Skoro-Kondza LT, S. S. Gadelrab, R. Drincevic, D. Greenhalgh, T. Community based yoga classes for type 2 diabetes: an exploratory randomised controlled trial. BMC Health Serv Res 2009;9:33.

38. Vaishali K, Kumar KV, Adhikari P, et al. Effects of Yoga-Based Program on Glycosylated Hemoglobin Level Serum Lipid Profile in Community Dwelling Elderly Subjects with Chronic Type 2 Diabetes Mellitus-A Randomized Controlled Trial. Physical & Occupational Therapy in Geriatrics 2012;30(1):22-30.

39. McCaffrey R, Ruknui P, Hatthakit U, et al. The effects of yoga on hypertensive persons in Thailand. Holistic nursing practice 2005;19(4):173-80.

40. Saptharishi L, Soudarssanane M, Thiruselvakumar D, et al. Community-based Randomized Controlled Trial of Non-pharmacological Interventions in Prevention and Control of Hypertension among Young Adults. Indian journal of community medicine : official publication of Indian Association of Preventive & Social Medicine 2009;34(4):329-34.

41. Ray US, Sinha B, Tomer OS, et al. Aerobic capacity & perceived exertion after practice of Hatha yogic exercises. The Indian journal of medical research 2001;114:215-21.

42. Harinath K, Malhotra AS, Pal K, et al. Effects of Hatha yoga and Omkar meditation on cardiorespiratory performance, psychologic profile, and melatonin secretion. Journal of alternative and complementary medicine 2004;10(2):261-8.

43. Ades PA, Savage PD, Brochu M, et al. Resistance training increases total daily energy expenditure in disabled older women with coronary heart disease. Journal of applied physiology 2005;98(4):1280-5.

44. Manchanda SC, Madan K. Yoga and meditation in cardiovascular disease. Clinical Research in Cardiology 2014:1-6.

45. Gordon LA, Morrison EY, McGrowder DA, et al. Effect of exercise therapy on lipid profile and oxidative stress indicators in patients with type 2 diabetes. BMC Complement Altern Med 2008;8:21.

46. Bowman AJ, Clayton RH, Murray A, et al. Effects of aerobic exercise training and yoga on the baroreflex in healthy elderly persons. European journal of clinical investigation 1997;27(5):443-9.

47. Stachenfeld NS, Mack GW, DiPietro L, et al. Regulation of blood volume during training in post-menopausal women. Medicine and science in sports and exercise 1998;30(1):92-8.

48. Subramanian H, Soudarssanane MB, Jayalakshmy R, et al. Non-pharmacological Interventions in Hypertension: A Community-based Cross-over Randomized Controlled Trial. Indian journal of community medicine : official publication of Indian Association of Preventive & Social Medicine 2011;36(3):191-6.

49. Manchanda SC, Narang R, Reddy KS, et al. Retardation of coronary atherosclerosis with yoga lifestyle intervention. J Assoc Physicians India 2000;48(7):687-94.

50. Field T. Yoga clinical research review. Complement Ther Clin Pract 2011;17(1):1-8.

51. Shantakumari N, Sequeira S, El Deeb R. Effects of a yoga intervention on lipid profiles of diabetes patients with dyslipidemia. Indian Heart Journal 2013;65(2):127-31.

52. Monroe R PJ, Kumar A, et al. Yoga therapy for NIDDM: a controlled trial. Complement Med Res 1992;6:66-8.

53. Murugesan R, Govindarajulu N, Bera TK. Effect of selected yogic practices on the management of hypertension. Indian J Physiol Pharmacol 2000;44(2):207-10.

54. Mahajan AS, Reddy KS, Sachdeva U. Lipid profile of coronary risk subjects following yogic lifestyle intervention. Indian Heart J 1999;51(1):37-40.

55. Jatuporn S, Sangwatanaroj S, Saengsiri AO, et al. Short-term effects of an intensive lifestyle modification program on lipid peroxidation and antioxidant systems in patients with coronary artery disease. Clin Hemorheol Microcirc 2003;29(3-4):429-36.

56. Ray US, Mukhopadhyaya S, Purkayastha SS, et al. Effect of yogic exercises on physical and mental health of young fellowship course trainees. Indian J Physiol Pharmacol 2001;45(1):37-53.

57. Anderson JGT, A. G. The metabolic syndrome and mind-body therapies: a systematic review. J Nutr Metab 2011;2011:276419.

58. Cramer H, Lauche R, Haller H, et al. Effects of yoga on cardiovascular disease risk factors: a systematic review and meta-analysis. International journal of cardiology 2014;173(2):170-83.

59. Hartley L, Dyakova M, Holmes J, et al. Yoga for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2014;5:CD010072.

60. Patel NK, Newstead AH, Ferrer RL. The effects of yoga on physical functioning and health related quality of life in older adults: a systematic review and meta-analysis. Journal of alternative and complementary medicine 2012;18(10):902-17.

61. Roland KPJ, J. M. Jones, G. R. Does yoga engender fitness in older adults? A critical review. J Aging Phys Act 2011;19(1):62-79.

62. Yang K. A review of yoga programs for four leading risk factors of chronic diseases. Evid Based Complement Alternat Med 2007;4(4):487-91.

63. Abel ANL, L. K. Williams, J. S. The Effects of Regular Yoga Practice on Pulmonary Function in Healthy Individuals: A Literature Review. Journal of alternative and complementary medicine 2012.

64. Kanojia S, Sharma VK, Gandhi A, et al. Effect of yoga on autonomic functions and psychological status during both phases of menstrual cycle in young healthy females. Journal of clinical and diagnostic research : JCDR 2013;7(10):2133-9.

65. Kim S, Bemben MG, Bemben DA. Effects of an 8-month yoga intervention on arterial compliance and muscle strength in premenopausal women. J Sports Sci Med 2012;11(2):322-30.

66. Wolever RQ, Bobinet KJ, McCabe K, et al. Effective and viable mind-body stress reduction in the workplace: A randomized controlled trial. Journal of Occupational Health Psychology 2012;17(2):246-58.

67. van Montfrans GA KJ, Wieling W et al. Relaxation therapy and continuous ambulatory blood pressure in mild hypertension: a controlled study. BMJ 1990;300:1368-72.

68. Nicolson DJD, H. O. Campbell, F. Mason, J. M. Lifestyle interventions or drugs for patients with essential hypertension: A systematic review. Journal of Hypertension 2004;22(11):2043-48.

69. Wang J, Xiong X, Liu W. Yoga for essential hypertension: a systematic review. PloS One 2013;8(10):e76357.

70. Rioux JG, Ritenbaugh C. Narrative review of yoga intervention clinical trials including weight-related outcomes. Alternative therapies in health and medicine 2013;19(3):32-46.

71. Cohen DL, Bloedon LT, Rothman RL, et al. Iyengar Yoga versus Enhanced Usual Care on Blood Pressure in Patients with Prehypertension to Stage I Hypertension: a Randomized Controlled Trial. Evidence-based Complementary and Alternative Medicine 2011:546428-28.

72. Carim-Todd L, Mitchell SH, Oken BS. Mind–body practices: An alternative, drug-free treatment for smoking cessation? A systematic review of the literature. Drug and Alcohol Dependence 2013;132(3):399-410.

73. Lee JA, Kim JW, Kim DY. Effects of yoga exercise on serum adiponectin and metabolic syndrome factors in obese postmenopausal women. Menopause 2012;19(3):296-301.

74. Aljasir BB, M. Al-Shehri, B. Yoga Practice for the Management of Type II Diabetes Mellitus in Adults: A systematic review. Evid Based Complement Alternat Med 2010;7(4):399-408.

75. Pilkington KS, E. Kirkwood, G. Richardson, J. Diabetes and complementary therapies: Mapping the evidence. Practical Diabetes International 2007;24(7):371-76.

76. Sharma MK, Adam P. Role of Yoga in Preventing and Controlling Type 2 Diabetes Mellitus. Journal of Evidence-Based Complementary & Alternative Medicine 2012;17(2):88-95.

77. Yang K, Bernardo LM, Sereika SM, et al. Utilization of 3-month yoga program for adults at high risk for type 2 diabetes: A pilot study. Evidence-based Complementary and Alternative Medicine 2011;2011.

78. Hegde SV, Adhikari P, Shetty S, et al. Effect of community-based yoga intervention on oxidative stress and glycemic parameters in prediabetes: a randomized controlled trial. Complementary therapies in medicine 2013;21(6):571-6.

CHAPTER 2

Comparative effectiveness of personalized lifestyle management strategies for cardiovascular disease risk reduction

Paula Chu, MS[1,2], Ankur Pandya, PhD[2,3], Joshua A. Salomon, PhD[2,5], Sue J. Goldie, MD, MPH[2,3], M.G. Myriam Hunink, MD, PhD[2,5,6]
[1] Department of Health Policy, Harvard University, Cambridge, MA USA
[2] Center for Health Decision Science, Harvard TH Chan School of Public Health, Boston, MA USA
[3] Department of Health Policy and Management, Harvard TH Chan School of Public Health, Boston, MA USA
[4] Department of Global Health and Population, Harvard TH Chan School of Public Health, USA
[5] Department of Epidemiology, Erasmus MC, Rotterdam, the Netherlands
[6] Department of Radiology, Erasmus MC, Rotterdam, the Netherlands

ABSTRACT

Background: Evidence shows that healthy diet, exercise, smoking interventions, and stress reduction reduce cardiovascular disease (CVD) risk. We aimed to compare the effectiveness of these lifestyle interventions for individual risk profiles and determine their rank order in reducing 10-year CVD risk.

Methods and Results: We computed risks using the American College of Cardiology/American Heart Association Pooled Cohort Equations for a variety of individual profiles. Using published literature on risk factor reductions through diverse lifestyle interventions – group therapy for stopping smoking, Mediterranean diet, aerobic exercise (walking), and yoga, we calculated the risk reduction through each of these interventions to determine the strategy associated with the maximum benefit for each profile. Sensitivity analyses were conducted to test the robustness of the results.

In the base-case analysis, yoga was associated with the largest 10-year CVD risk reductions (maximum absolute reduction 16.7% for the highest risk individuals). Walking generally ranked second (max 11.4%), followed by Mediterranean diet (max 9.2%) and group therapy for smoking (max 1.6%). If the individual was a current smoker and successfully quit smoking (i.e., achieved complete smoking cessation), then stopping smoking yielded the largest reduction. Probabilistic and one-way sensitivity analysis confirmed the demonstrated trend.

Conclusions: This study reports the comparative effectiveness of several forms of lifestyle modifications and found smoking cessation and yoga to be the most effective forms of CVD prevention. Future research should focus on patient adherence to personalized therapies, cost-effectiveness of these strategies, and the potential for enhanced benefit when interventions are performed simultaneously rather than as single measures.

Keywords: comparative effectiveness, lifestyle modification, cardiovascular risk reduction

INTRODUCTION

Consensus exists that lifestyle changes such as stopping smoking, higher levels of physical activity, and certain dietary patterns can lead to lower rates of cardiovascular disease (CVD) and other chronic diseases.[1-5] Current clinical guidelines in both the United States and Europe include such changes in their recommendations for reducing the risk of CVD.[1,6,7] For example, the 2013 American College of Cardiology (ACC) and American Heart Association (AHA) Guidelines to Reduce Cardiovascular Risk give a strong, Grade A recommendation for adults who need low-density lipoprotein (LDL-C) and blood pressure (BP) lowering to follow a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains and limit intake of sweets, sugar-sweetened beverages and red meats.[1]

Clinical guidelines for providers and patients rely on evidence that includes data analysis of individual studies, data synthesis that pools results from many studies, and models that use data to project future risk. An attractive feature of models and tools that predict risk is the ability to estimate the effectiveness of alternative strategies for different populations and subpopulations, and for individuals with specific characteristics. In fact, the ACC and AHA recently published a new set of equations that can be used to estimate 10-year and lifetime risk of a first hard atherosclerotic cardiovascular disease (CVD) event, or first occurrence of non-fatal myocardial infarction or death from coronary heart disease or fatal or nonfatal stroke.[8] These equations, known as the Pooled Cohort Equations, are based on data from diverse, community-based cohorts that represent both African-American and White men and women in the US. Full descriptions of the CVD risk equations and their development have been published elsewhere.[8,9]

With the introduction of the ACC/AHA guidelines and the accompanying debates on use of statin therapy, calls for more focus on personal lifestyle modification and behavior change have been made.[10-12] There has additionally been growing interest in using data and analytic tools to develop personalized recommendations that consider an individual's clinical risk profile.[13-15] Personalized recommendations utilizing comparative effectiveness research (CER) have been done previously using life expectancy gains

based on US Preventive Services Task Force (USPSTF) guidelines [16-18] with substantial gains in life expectancy shown with greater use of preventive services.[19]

The objective of this study is to estimate the risk reductions that can be expected from diverse lifestyle modifications for patients with specified clinical characteristics and establish the comparative effectiveness of these strategies depending on individual risk profiles. We calculated risk by inputting individual levels of key risk factors including age, blood pressure, lipid levels, hypertension treatment and smoking status into the Pooled Cohort Equations and then using the best available evidence on the effects of different interventions on each of these risk factors to establish the comparative effectiveness of interventions for individuals depending on their profiles. We considered the following lifestyle interventions: group therapy for stopping smoking, Mediterranean diet (a diet that emphasizes high intake of fruits, vegetables, whole grains, fatty fish, nuts, and olive oil),[1] aerobic exercise (specifically walking), and yoga (a popular form of exercise focusing on the mind-body connection).

These interventions were chosen to encompass a range of strategies that may be part of a lifestyle modification regime. For stopping smoking, already well-established as a main driver of cardiovascular risk, we chose group therapy counseling sessions rather than nicotine replacement therapy or medication to more closely align with the non-pharmacological nature of the other strategies. A healthy diet and aerobic exercise are regarded as mainstays in prevention of CVD, with accumulating evidence on the impact of the Mediterranean diet on cardiovascular risk.[5, 20, 21] Yoga, a form of physical activity that involves physical postures, breath work, and meditation or relaxation, is becoming more prevalent in the US; a 2012 National Center for Health Statistics survey showing that 9.5% of adults (21 million) used yoga in the previous 12 months.[22] Yoga is thought to reduce response to stress and affect the autonomic nervous system through relaxation techniques and breath control.[23, 24] Three recent systematic reviews and meta-analyses suggest that yoga may significantly improve risk factors for CVD like body weight, lipid profile, and blood pressure.[25-27]

METHODS

This study uses the Pooled Cohort Equations published by Goff et al. (2013) to calculate 10-year CVD risk separately for white and African-American individuals.[8] We focused on the non-diabetic white and African-American populations.

Risk factors in the equations are age, systolic blood pressure (SBP), whether the patient is treated for hypertension or not, total cholesterol (TC) and HDL-cholesterol (HDL-C), current smoking status, and history of diabetes. Levels of risk factors were entered in the Pooled Cohort Equations to calculate an individual's absolute 10-year atherosclerotic CVD risk. The potential improvement in each risk factor that could be achieved through the four lifestyle management strategies – group therapy for smoking (only for current smokers), the Mediterranean dietary pattern, walking, and yoga – were obtained from published literature (Table 1). The risk factor effect sizes were then translated into reductions in 10-year CVD risk for each intervention.

Table 2.1. Effectiveness of lifestyle interventions on reducing CVD risk through changes in risk factors

	Impact of Lifestyle Changes on Risk Factor due to Interventions			
Risk factor	**Group therapy for smoking**	**Mediterranean diet**	**Walking**	**Yoga**
Smoking (% quitting)	9.90* (8.00, 12.30) (28)	--	--	--
Systolic blood pressure (mmHg)	--	-1.70 (-3.35, -0.05) (29)	-3.80 (-5.90, -1.70) (30)	-4.45 (-6.99, -1.90) (27)
Total cholesterol (mg/dl)	--	-7.35 (-10.32, -4.39) (29)	-3.48 (-12.37, 5.80) (30)	-17.00 (-27.29, -6.71) (27)
HDL cholesterol (mg/dl)	--	0.94 (-1.93, 3.82) (29)	2.32 (0.46, 5.41) (30)	2.87 (1.47, 4.26) (27)

* Probability of quitting smoking with group therapy compared to 5% probability of quitting without intervention. The relative proportion of quitting (relative risk) is 1.98 for group therapy versus control (95% CI: 1.60-2.46)[28]

Interventions

Intervention effect sizes were obtained from meta-analyses of randomized controlled trials (RCTs). Published literature was searched and meta-analyses were selected if they included RCTs using intention-to-treat analysis, contained summary estimates of all relevant risk factors within a single report, and compared the treatment to a control group of no/minimal intervention or usual care. We used an alternate set of estimates in a sensitivity analysis.

For current smokers, group therapy for smoking cessation consisted of about 6-8 scheduled meetings led by professional facilitators for at least six months that included information, advice, and encouragement for quitting.[28] For Mediterranean diet, data were taken from a meta-analysis of RCTs in which patients followed a diet rich in fruit and vegetables, low in red meat, and moderate in fat from nuts and oils for at least six months with a follow-up of 2 years.[29] Evidence on change in risk factors from walking was obtained from a meta-analysis on pedometer use as a means to increase physical activity.[30] Specifically, participants were given a pedometer and encouraged to increase their daily steps (either with or without a daily step goal). This intervention resulted in an additional 2491 steps per day, roughly equivalent to 1 mile of walking. Walking was chosen to represent aerobic exercise as a low-impact form of aerobic activity that is accessible and suitable for most individuals. Mean duration of the intervention and follow-up was 18 weeks. Data on yoga came from the most recent meta-analysis of RCTs evaluating a variety of movement-based yoga styles including Hatha, Vinyasa, and Ashtanga and excluding breathing- or meditation-only styles.[27] Yoga was practiced 3-4 times per week on average, mean duration of the yoga interventions and follow-up was 18 weeks.

Data analysis

Calculations for risk factor changes as a result of lifestyle interventions were based on an intention-to-treat approach. The intervention effect estimates from Table 2.1 were added to the initial risk factor level for an individual with specific clinical characteristics to generate a new risk factor level. These new levels were then entered in the Pooled Cohort Equations to obtain a new CVD risk.

We calculated CVD risk with group therapy for smoking in two steps. First we calculated the CVD risk difference between a smoker and non-smoker, with all other risk factors unchanged to get the pure effect of group therapy on CVD risk. Then we multiplied this number by the probability a smoker would successfully quit with group therapy versus no group therapy to get the intention-to-treat estimate (see Appendix Chapter 2 supplemental data for details).

We calculated the absolute risk reduction of 10-year CVD risk across the 4 different interventions for the average patient in each risk subcategory. Base case results were displayed using heat maps, using color shading to represent gradation of risk across subgroups and strategies. Results were stratified by sex, smoking status and treatment for hypertension.

We included six risk factor profiles of hypothetical patients with varying levels of SBP, TC, and HDL-C with different combinations of smoking and hypertension treatment status to represent individuals with a wide range of CVD risk, extending from 1% to nearly 30%. The six profiles were created for both White and African American patients for a total of 12 different profiles. For each profile, we estimated the 10-year CVD risk in the absence of a lifestyle management intervention and with the addition of each of the four interventions.

Sensitivity analysis

We conducted several analyses to explore the impact of parameter uncertainty and the impact of alternative assumptions.

First, we conducted a deterministic sensitivity analysis using the published 95% confidence interval for the effect measure for each intervention. We conducted a 'worse case' scenario analysis using the smallest favorable change for all risk factors and a 'best case' scenario analysis using the largest favorable change for all risk factors.

Second, we conducted an analysis that explored the impact on CVD risk for an individual smoker who successfully quits. In contrast to the primary 'intention-to-treat' analysis explained above, this secondary analysis is more akin to a per protocol type of analysis. For example, a provider who is

considering options to recommend to a patient will discuss the relative benefits of those options based on evidence from study results analyzed by intention-to-treat. However, a patient might be interested in acquiring information for the 'benefit' they would obtain if they successfully stopped smoking. Therefore, we conducted an analysis in which we assumed a patient successfully quits and refer to this second analysis as 'successful smoking cessation'.

Third, we conducted a probabilistic sensitivity analysis to determine how often a strategy would be considered optimal for the twelve hypothetical patients. This analysis was done for both the base case analysis and the individual patient perspective. In each analysis one thousand random draws were performed in which we simultaneously varied the parameters in Table 2.1 – the effect size of the interventions for each risk factor and the probability of successfully quitting smoking with group therapy – according to its probability density function. Intervention parameters were drawn from a normal distribution and the probability of quitting smoking drawn from a beta distribution. Probability of successfully quitting was designated as 100% for the individual patient who successfully quits smoking. The base case intervention effect estimates were used as means and the 95% confidence intervals that were derived from published literature were used to inform the spread of the distribution.

Fourth, we used an alternative set of intervention effect estimates from published literature for the twelve hypothetical patient profiles to see if the ranking was sensitive to our choice of meta-analysis. We have presented the table of alternative estimates in the Appendix Table 2.5. For smoking cessation, we used another non-pharmaceutical intervention, physician advice for smoking cessation, to mimic the behavior change necessary to quit smoking.[31] Another meta-analysis on the Mediterranean dietary pattern for RCTs longer than three months from the Cochrane Database was selected for this sensitivity analysis [32]; however, only TC was pooled and reported and thus we varied only this parameter. To more broadly represent exercise as an intervention, we widened this intervention category to include more kinds of aerobic exercise including running, jogging, and cycling. For this, we used a recent meta-analysis of RCTs of lipid measurements (TC and HDL)[33] supplemented with a meta-analysis of the effect of aerobic exercise on SBP.[34] Both analyses used similar definitions of aerobic exercise, had similar patient

populations, and both had median durations of 12 weeks (range 2-3 weeks to 2 years). An alternate meta-analysis with similar inclusion criteria was employed for the yoga estimates.[25]

Lastly, we conducted a sensitivity analysis with the general Framingham risk score to examine if and how the relative rankings of the interventions would change with this commonly used risk algorithm.[35] This Framingham risk score closely matches the Pooled Cohort Equations used in the base case, assessing all the same cardiovascular disease events plus cardiac failure.

This study does not constitute human subjects research and thus did not require Institutional Review Board approval.

RESULTS

Figures 2.1-2.16 display heat maps of risk reductions from the 4 interventions for all hypothetical groups of patients, dichotomized by race, sex, smoking status, and treatment for hypertension. Axes represent the covariates – age, SBP, TC, and HDL – in the Pooled Cohort Equations. In the heatmaps, the colors vary from red (smallest risk reduction) to green (moderate risk reduction) to blue (largest risk reduction). Differences amongst the strategies for an individual patient can be observed by comparing the same cell across the 4 different interventions.

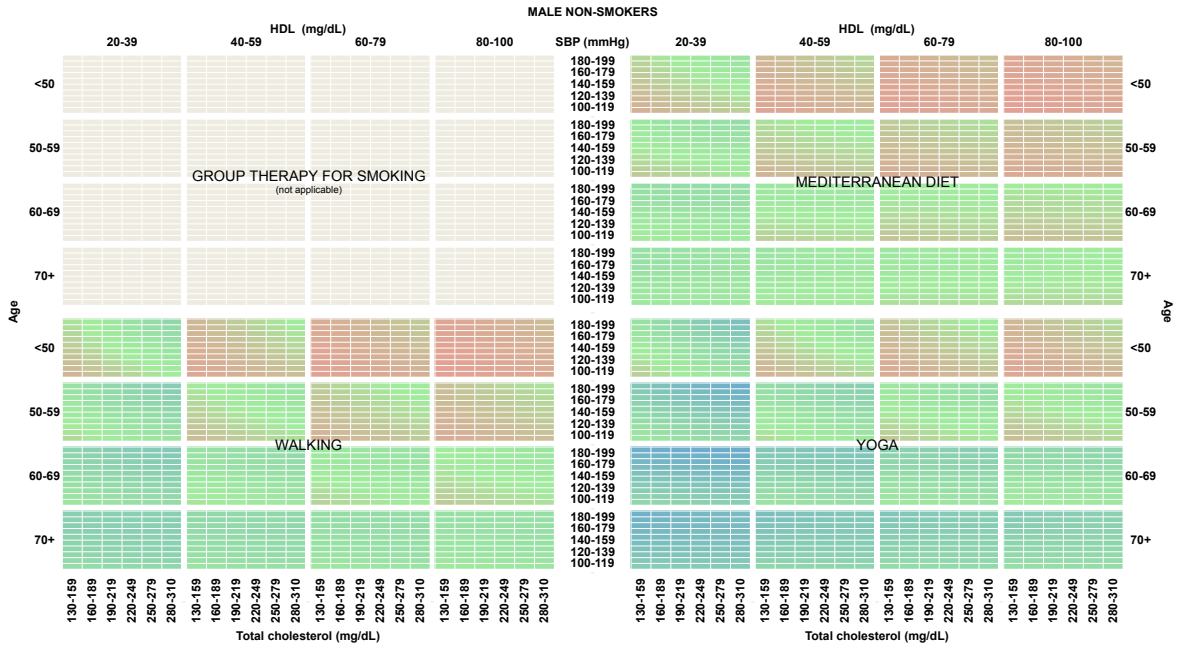

Figure 2.1. Risk reduction by intervention for white males, not treated for hypertension, non-smoker. Reductions range from smallest (red) to moderate (green) to largest (blue).

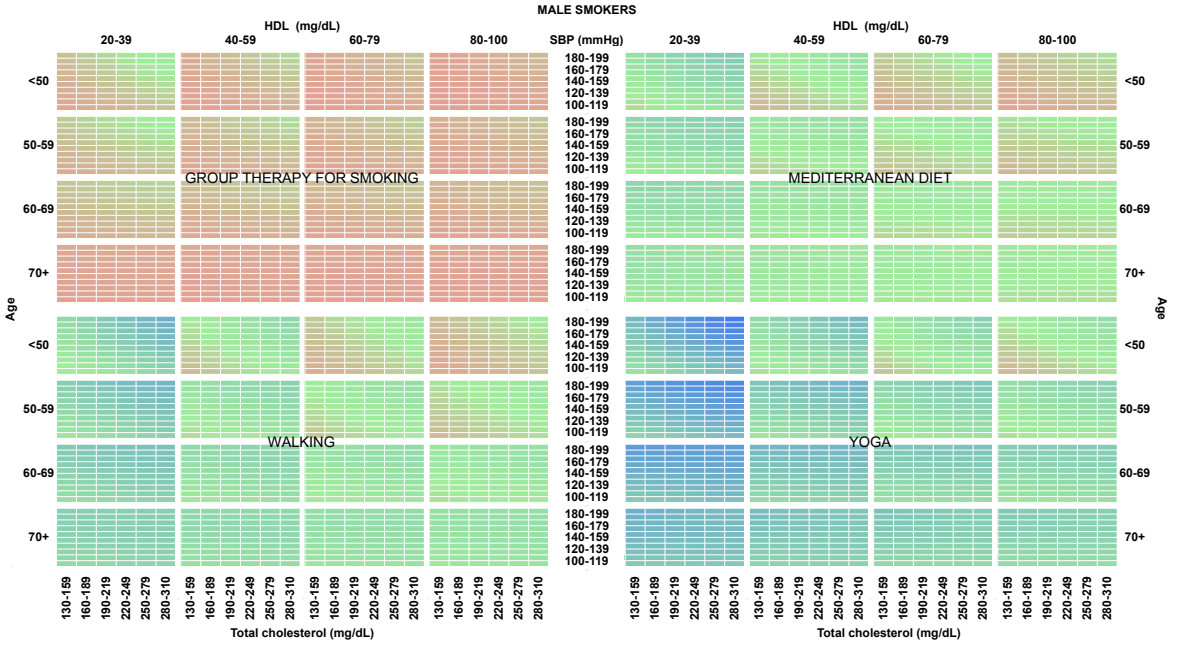

Figure 2.2. Risk reduction by intervention for white males, not treated for hypertension, smoker. Reductions range from smallest (red) to moderate (green) to largest (blue).

Key for figures:

Minimum reduction Maximum reduction

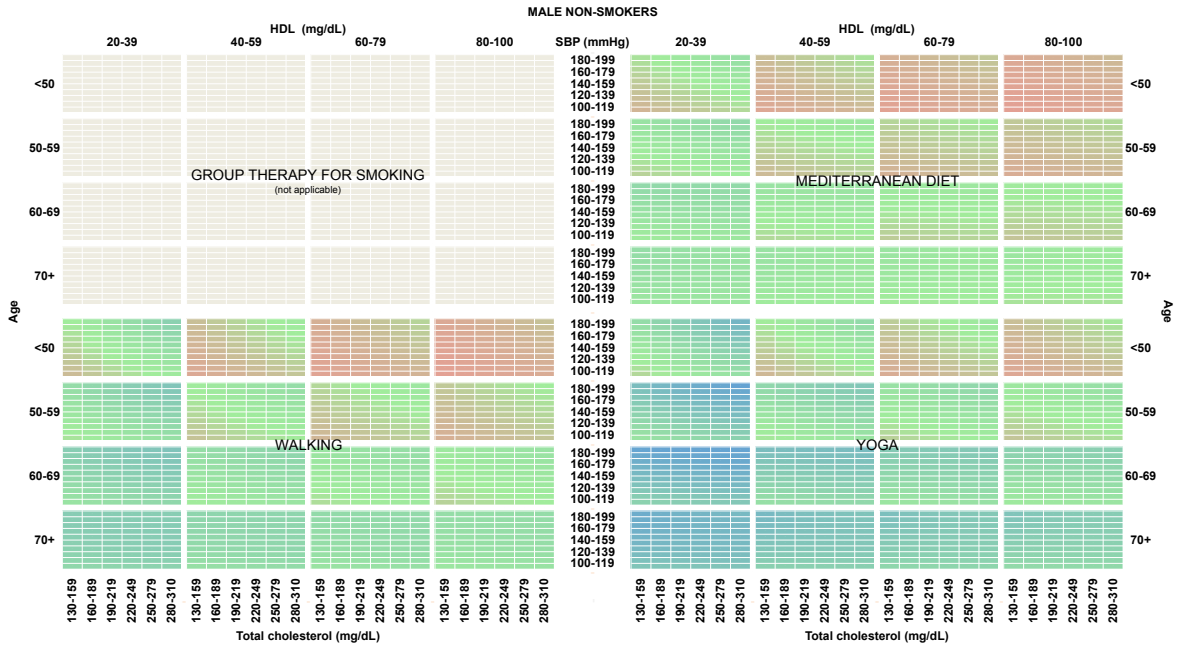

Figure 2.3. Risk reduction by intervention for white males, treated for hypertension, non-smoker. Reductions range from smallest (red) to moderate (green) to largest (blue).

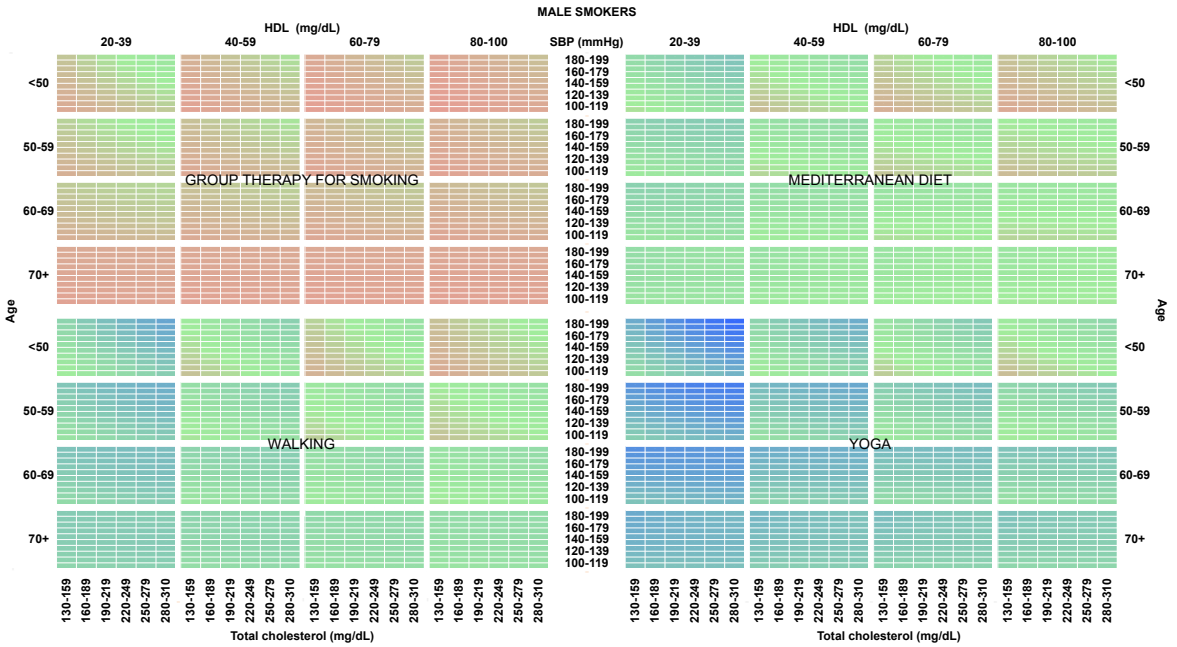

Figure 2.4. Risk reduction by intervention for white males, treated for hypertension, smoker. Reductions range from smallest (red) to moderate (green) to largest (blue).

Key for figures:

Minimum reduction Maximum reduction

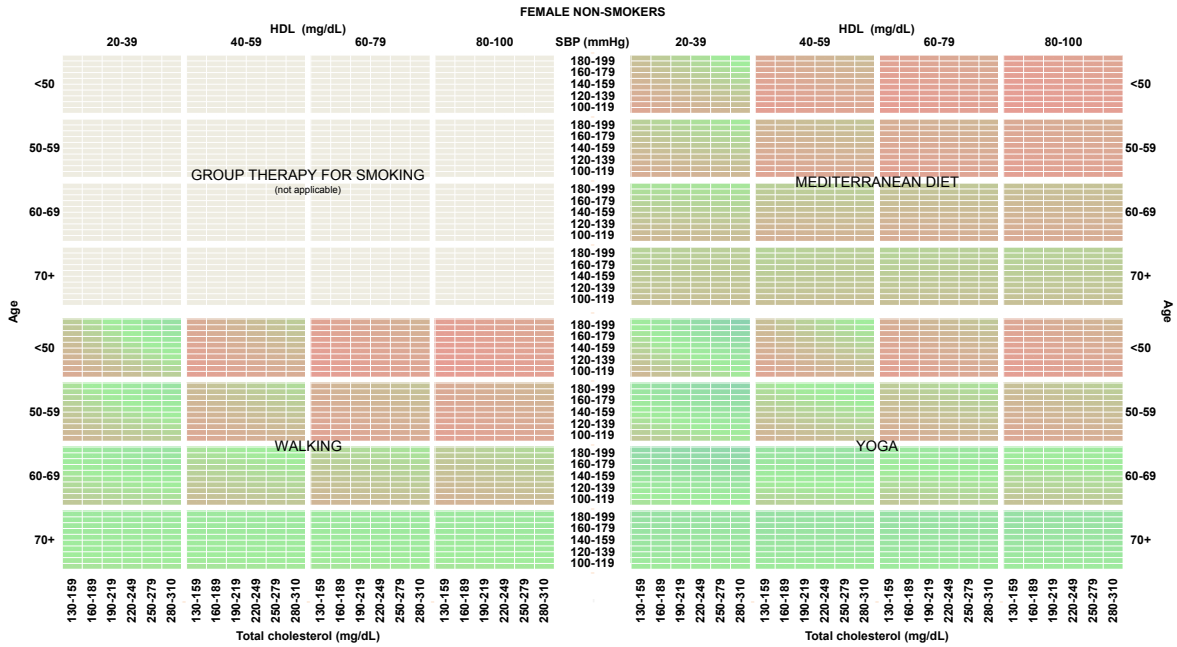

Figure 2.5. Risk reduction by intervention for white females, not treated for hypertension, non-smoker. Reductions range from smallest (red) to moderate (green) to largest (blue).

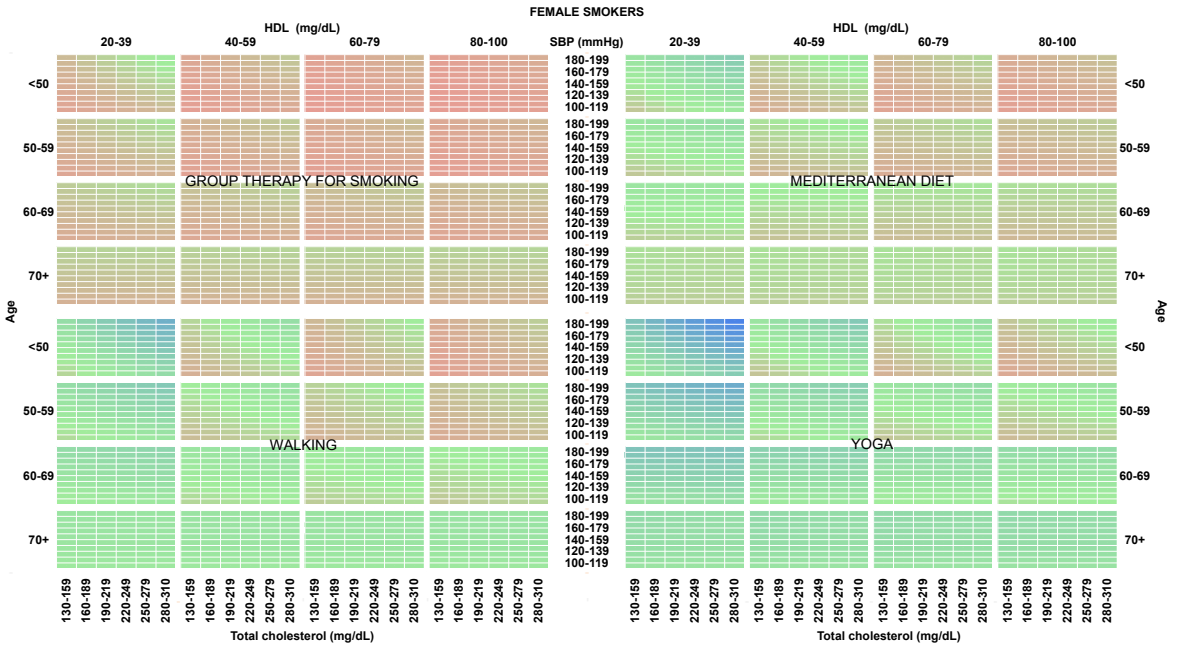

Figure 2.6. Risk reduction by intervention for white females, not treated for hypertension, smoker. Reductions range from smallest (red) to moderate (green) to largest (blue).

Key for figures:

Minimum reduction Maximum reduction

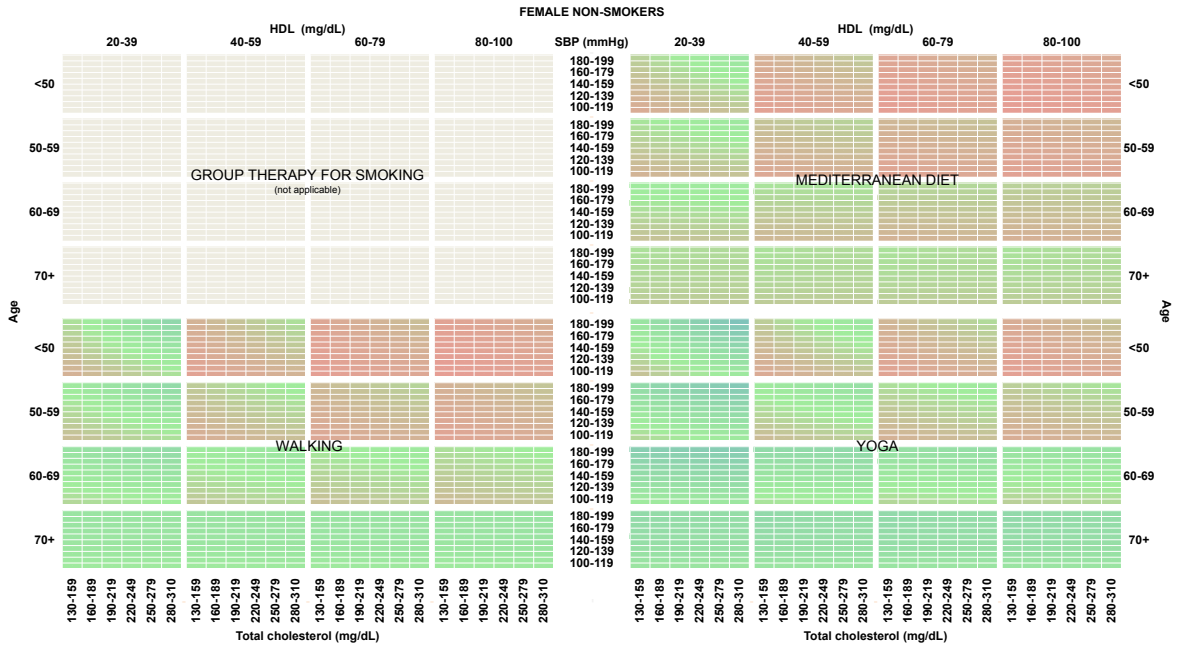

Figure 2.7. Risk reduction by intervention for white females, treated for hypertension, non-smoker. Reductions range from smallest (red) to moderate (green) to largest (blue).

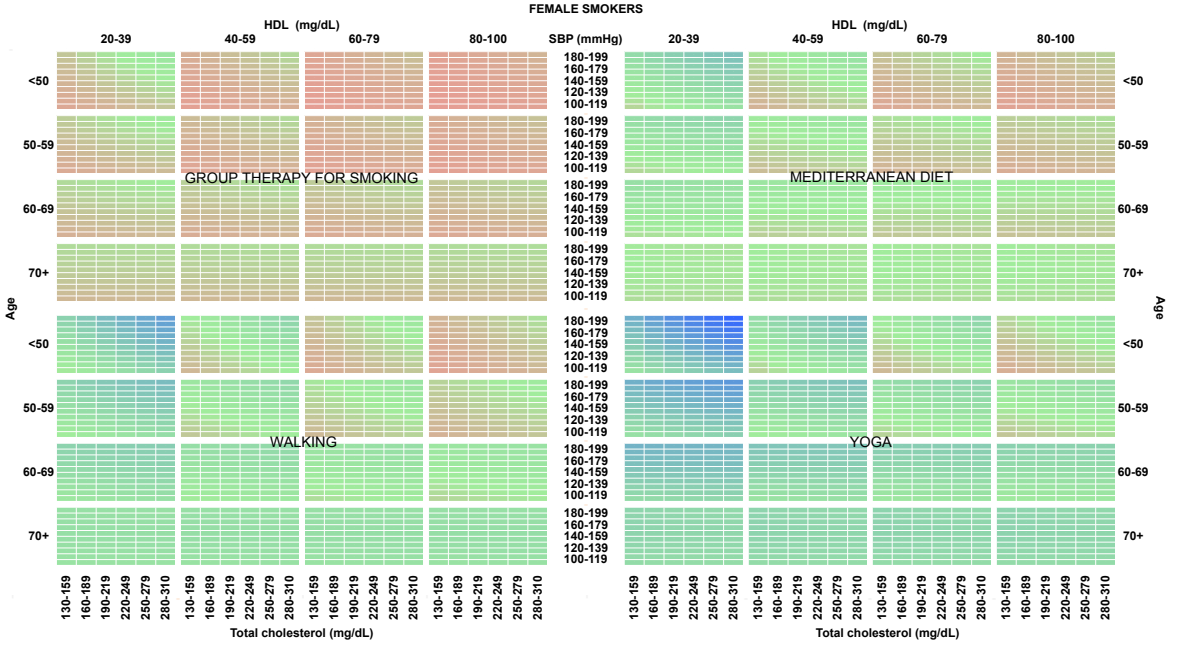

Figure 2.8. Risk reduction by intervention for white females, treated for hypertension, smoker. Reductions range from smallest (red) to moderate (green) to largest (blue).

Key for figures:

Minimum reduction Maximum reduction

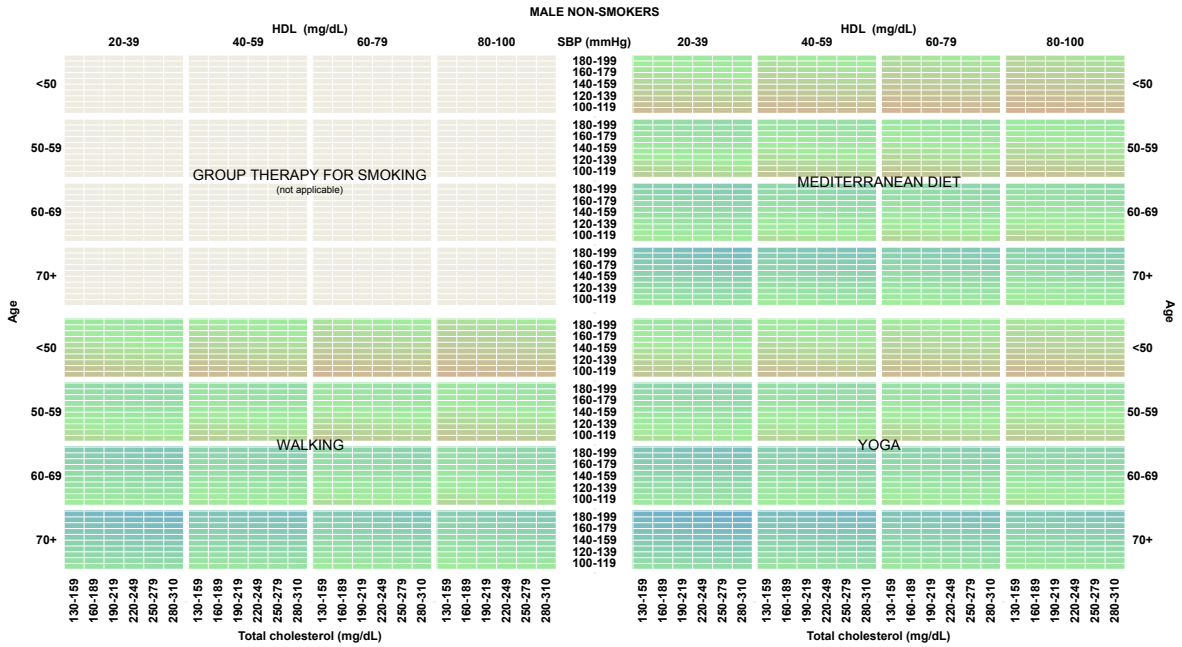

Figure 2.9. Risk reduction by intervention for African-American males, not treated for hypertension, non-smoker. Reductions range from smallest (red) to moderate (green) to largest (blue).

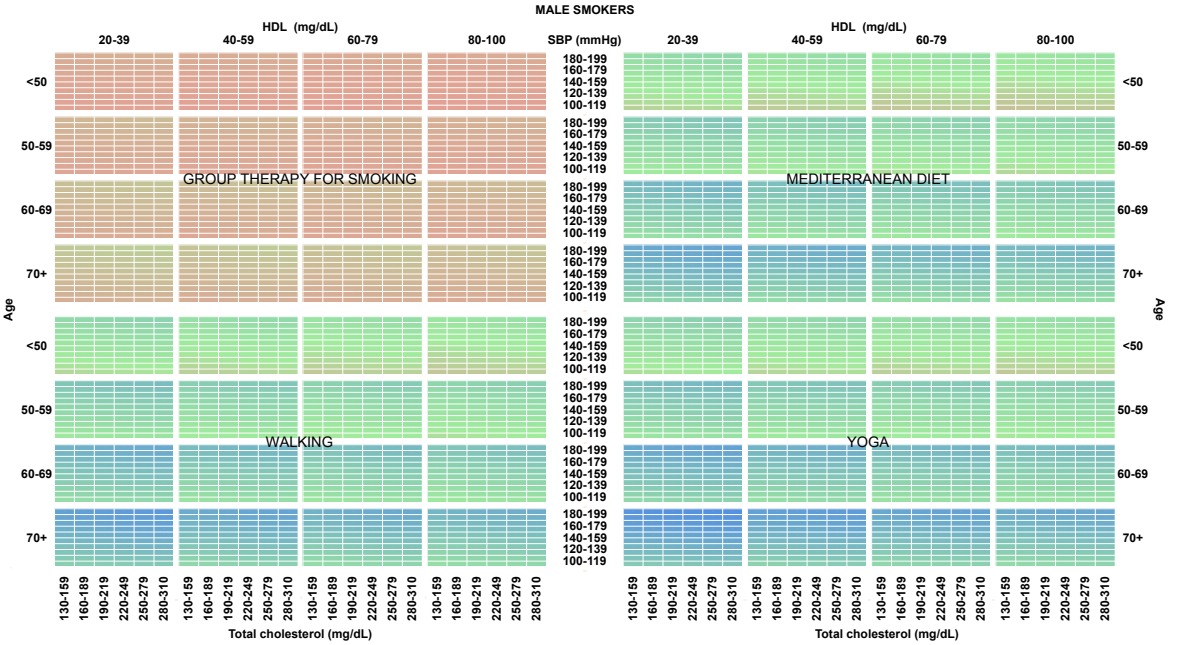

Figure 2.10. Risk reduction by intervention for African-American males, not treated for hypertension, smoker. Reductions range from smallest (red) to moderate (green) to largest (blue).

Key for figures:

Minimum reduction Maximum reduction

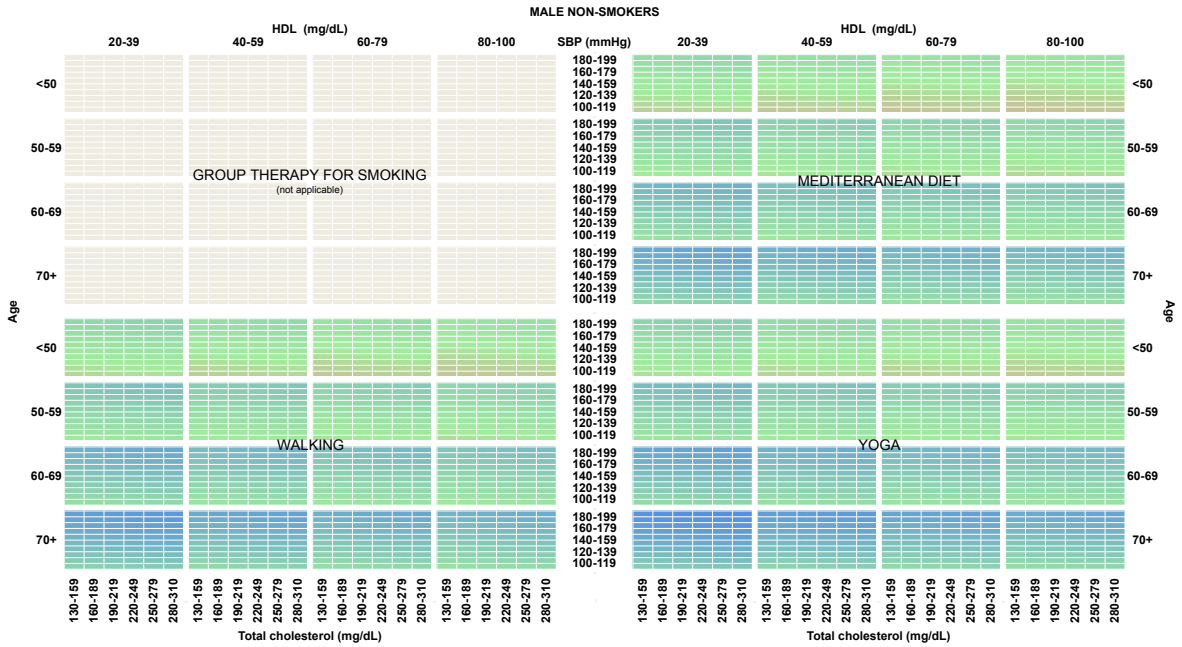

Figure 2.11. Risk reduction by intervention for African-American males, treated for hypertension, non-smoker. Reductions range from smallest (red) to moderate (green) to largest (blue).

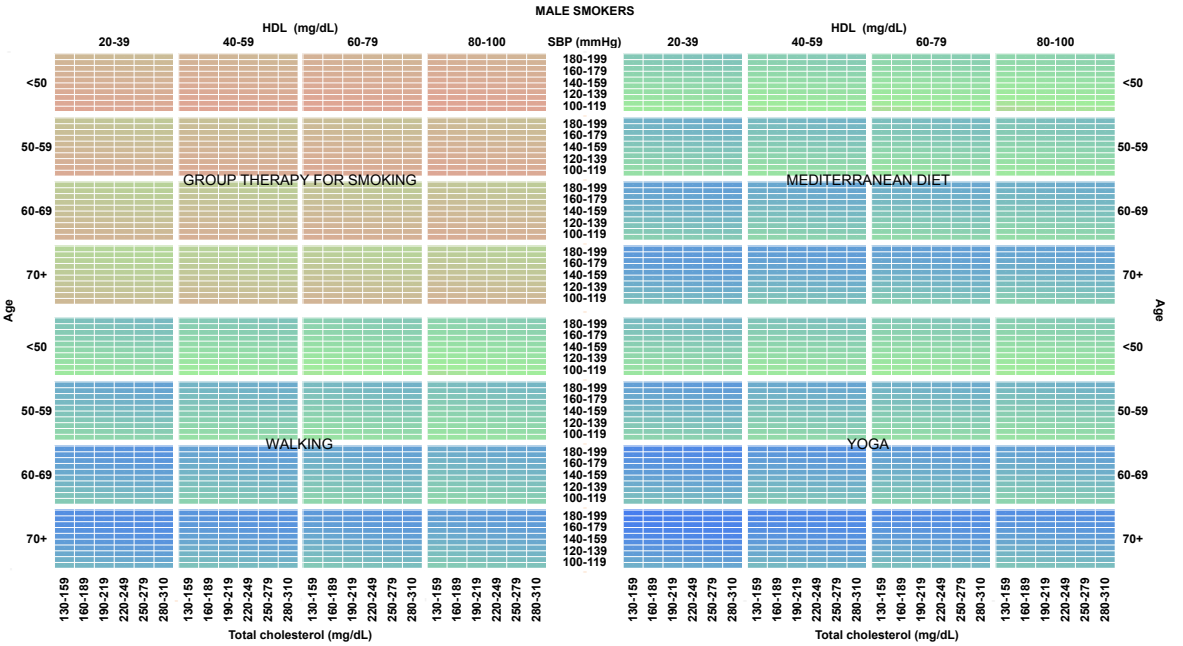

Figure 2.12. Risk reduction by intervention for African-American males, treated for hypertension, smoker. Reductions range from smallest (red) to moderate (green) to largest (blue).

Key for figures:

Minimum reduction Maximum reduction

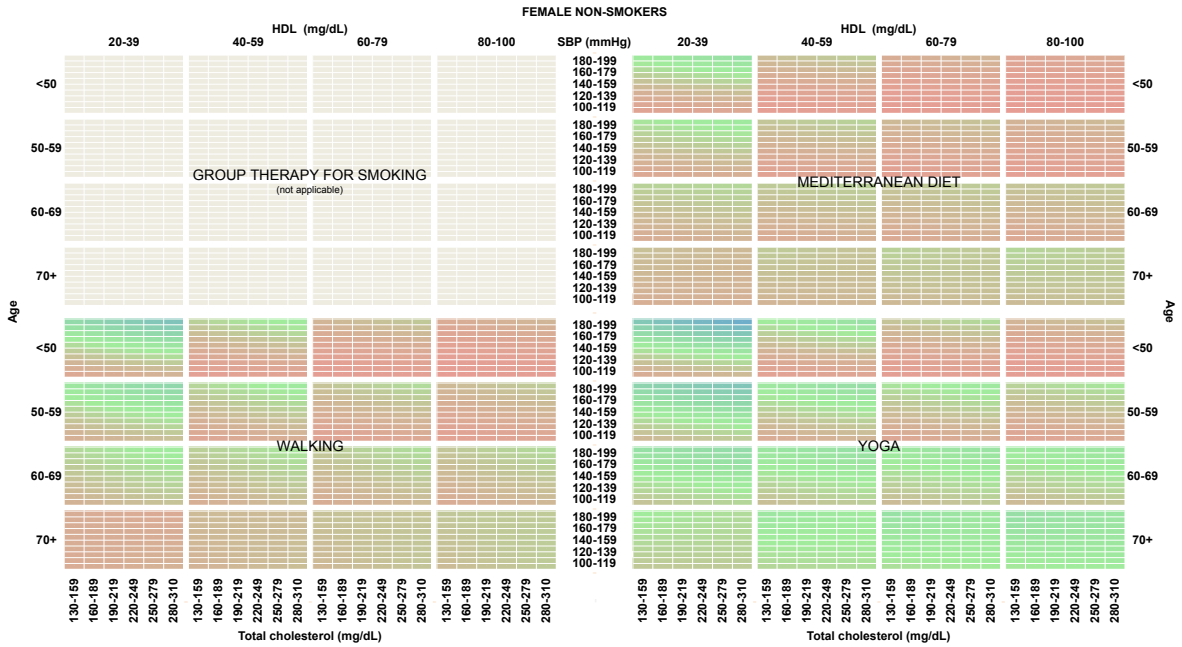

Figure 2.13. Risk reduction by intervention for African-American females, not treated for hypertension, non-smoker. Reductions range from smallest (red) to moderate (green) to largest (blue).

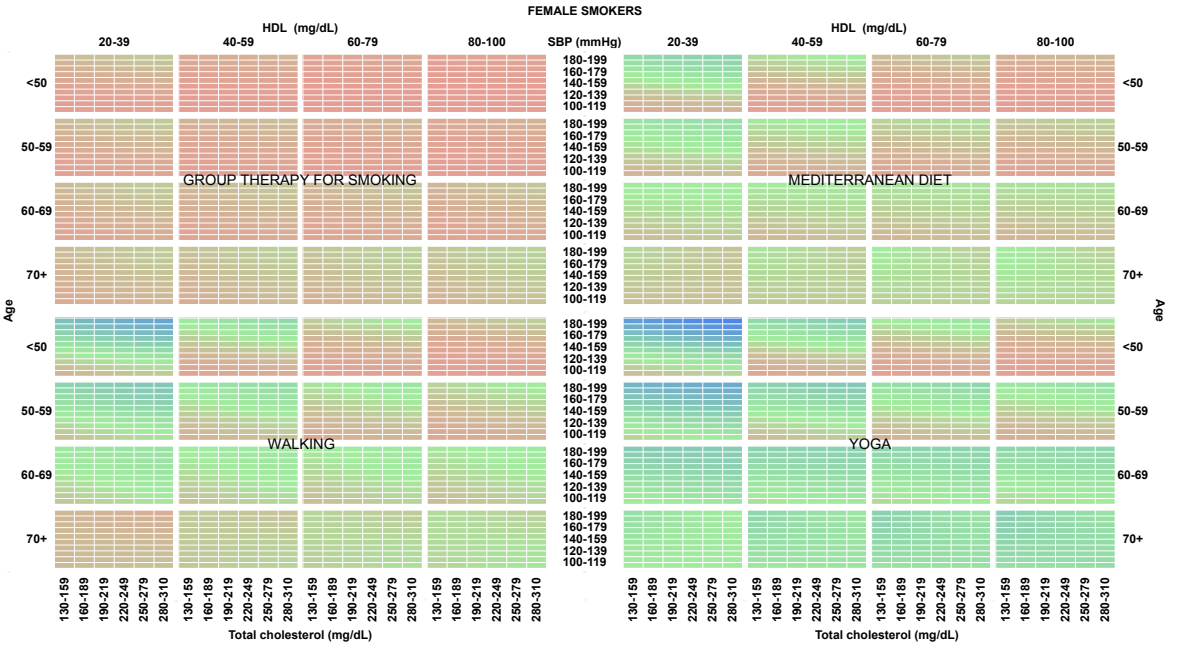

Figure 2.14. Risk reduction by intervention for African-American females, not treated for hypertension, smoker. Reductions range from smallest (red) to moderate (green) to largest (blue).

Key for figures:

Minimum reduction Maximum reduction

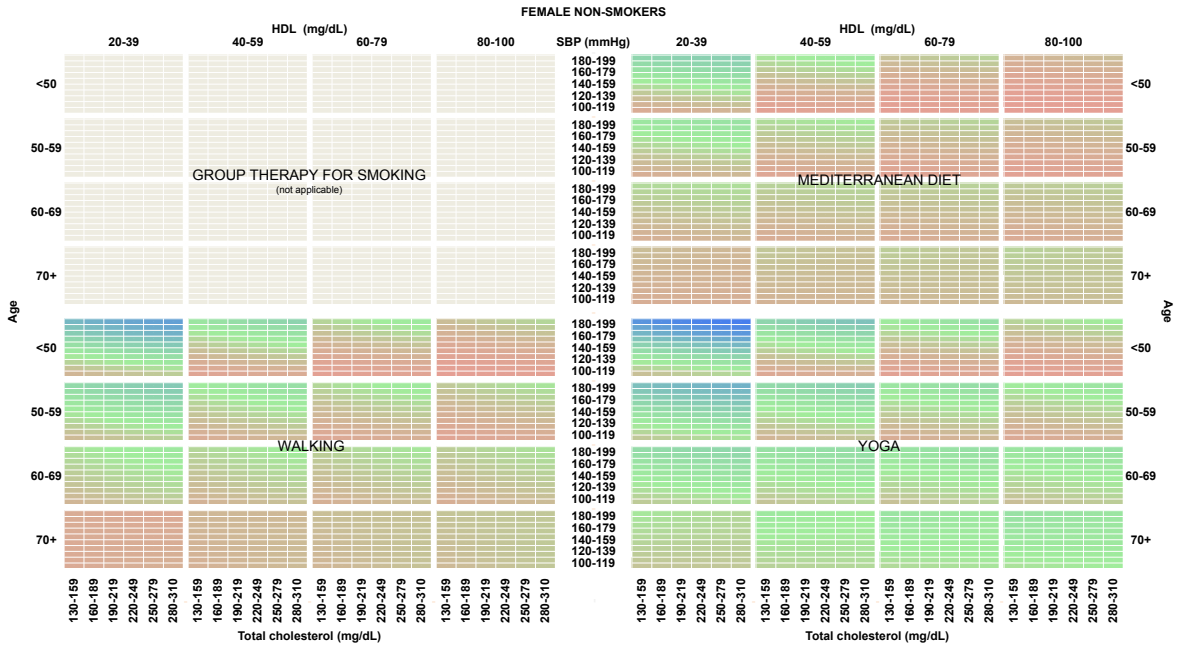

Figure 2.15. Risk reduction by intervention for African-American females, treated for hypertension, non-smoker. Reductions range from smallest (red) to moderate (green) to largest (blue).

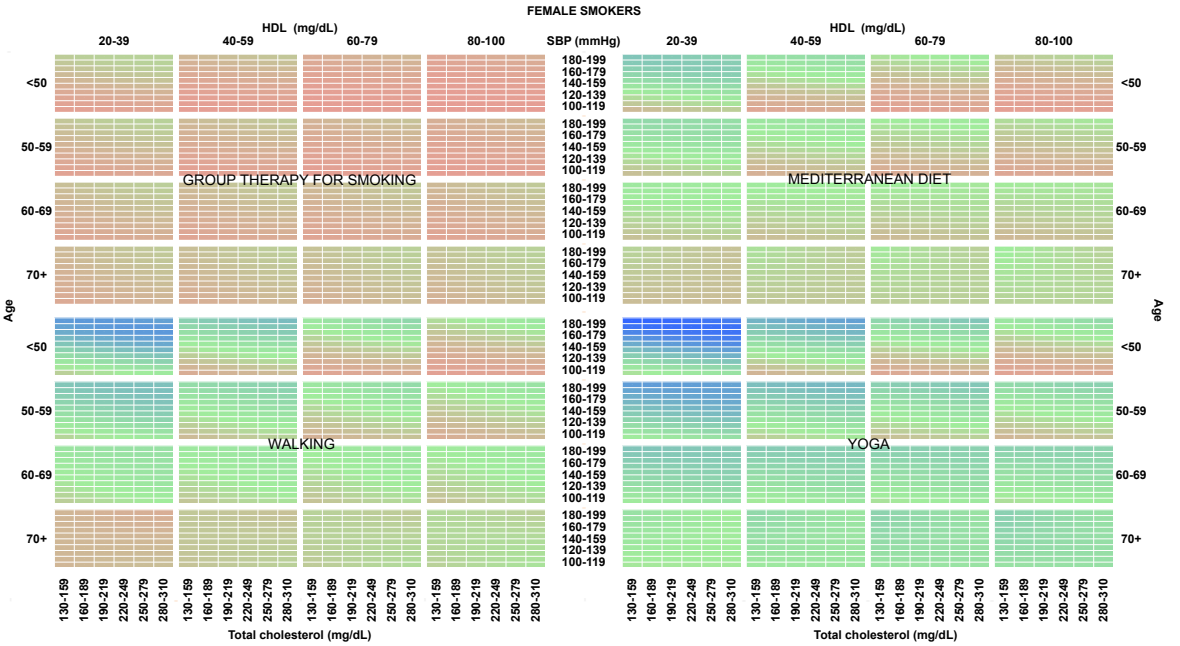

Figure 2.16. Risk reduction by intervention for African-American females, treated for hypertension, smoker. Reductions range from smallest (red) to moderate (green) to largest (blue).

Key for figures:

Minimum reduction Maximum reduction

Base case

In general across all profiles displayed in the heatmaps, the lowest risk reductions were with group therapy for smoking (red) and the highest reductions with yoga and walking exercise (blue). Although the results are heterogeneous across individual patients, the largest reductions on average were seen with yoga. The average risk reduction for all patients was 2.6% for yoga, compared to 1.9% for walking, 1.5% for Mediterranean diet, and 0.4% for smoking cessation counseling.

For the highest risk individuals who may experience the largest absolute reductions, the maximum reduction achieved with yoga was 16.7%. Walking typically fared second (max reduction 11.4%), followed by Mediterranean diet (max reduction 9.2%) and then group therapy for smoking if an individual was a current smoker (max reduction 1.6%). For some – white individuals with moderately low total cholesterol and high levels of HDL-cholesterol and elderly African-American women – Mediterranean diet outranked walking. African-American subjects generally achieved larger absolute risk reductions than white subjects.

Table 2.2 shows the risk reduction achieved through the various lifestyle modifications for the risk factor profiles representing twelve hypothetical individual patients.

Table 2.2 10-year CVD risk (%) for different risk factor profiles with and without lifestyle interventions with 95% credible intervals. Numbers with * represent the most effective CVD risk reduction strategy in the base case intention-to-treat analysis. Numbers with † represent the most effective strategy assuming successful cessation of smoking.

		10-year CVD risk (%) with intervention					
			Group therapy for smoking				
Risk profile		**None**	**BC‡**	**SC§**	**MED diet**	**Walking**	**Yoga**
1) 50-yr-old non-smoking woman, SBP 120 mmHg, not treated for hypertension, TC 160 mg/dL, HDL-C 50 mg/dL	White	0.9	N/A		0.8 (0.8, 0.9)	0.8 (0.7, 0.8)	0.7* (0.6, 0.8)
	AA‖	1.4			1.2 (1.1, 1.3)	1.1 (1.0, 1.2)	1.0* (0.9, 1.1)
2) 55-yr-old non-smoking man, SBP 140 mmHg, treated for hypertension, TC 170 mg/dL, HDL-C 45 mg/dL	White	7.0	N/A		6.4 (6.0, 6.8)	6.2 (5.8, 6.6)	5.5* (5.1, 6.0)
	AA	12.7			10.0 (9.7, 10.3)	9.7 (9.5, 9.9)	9.3* (9.0, 9.7)
3) 45-yr-old smoking man, SBP 160 mmHg, treated for hypertension, TC 200 mg/dL, HDL-C 40 mg/dL	White	12.2	11.8 (11.6, 12.0)	5.0†	11.0 (10.1, 12.0)	10.6 (9.8, 11.5)	9.3* (8.4, 10.2)
	AA	18.2	17.8 (17.6, 17.9)	9.4†	14.5 (14.1, 14.9)	14.1 (13.8, 14.4)	13.7* (13.2, 13.7)
4) 70-yr-old smoking woman, SBP 155 mmHg, not treated for hypertension, TC 145 mg/dL, HDL-C 70 mg/dL	White	18.6	18.3 (18.1, 18.4)	12.1†	18.0 (18.4, 17.6)	17.6 (17.2, 18.0)	17.0* (16.3, 17.6)
	AA	23.9	23.3 (23.1, 23.5)	13.3†	22.5 (21.9, 23.1)	22.5 (21.3, 23.6)	20.5* (19.1, 22.0)
5) 65-yr-old non-smoking man, SBP 180 mmHg, treated for hypertension, TC 200 mg/dL, HDL-C 60 mg/dL	White	23.2	N/A		22.1 (21.5, 22.8)	21.7 (21.0, 22.4)	20.5* (19.6, 21.5)
	AA	27.3			22.1 (21.6, 22.6)	21.6 (21.2, 22.0)	21.0* (20.4, 21.7)
6) 50-yr-old smoking man, SBP 170 mmHg, treated for hypertension, TC 260 mg/dL, HDL-C 35mg/dL	White	28.2	27.5 (27.2, 27.8)	14.4†	26.2 (24.4, 28.4)	25.3 (24.1, 26.6)	23.2* (21.7, 24.8)
	AA	28.1	27.5 (27.2, 27.7)	15.0†	22.8 (22.2, 23.4)	22.1 (21.8, 22.5)	21.6* (20.9, 22.3)

Abbreviations: ‡ base-case, § successful cessation, ‖ AA: African-American, SBP: systolic blood pressure, TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, N/A: not applicable

Sensitivity analysis

For both the best case and worse case scenarios trends were similar to those found in the base case, with the largest risk reductions achieved with yoga for all 12 profiles.

Results of our secondary sensitivity analyses assuming successful smoking cessation are shown in column "SC" in Table 2.2 with optimal strategies indicated with $^{+}$. If the patient is a smoker and successfully quits, then this lifestyle modification achieves the largest reductions in risk.

Probabilistic sensitivity analysis

Tables 2.3 & 2.4 show the results from the probabilistic sensitivity analysis based on 1,000 random draws for the base case and successful smoking cessation analyses. The highest-ranking strategy was yoga in over 88% of the simulations in the base case, with walking being the second most frequent optimal strategy. With successful cessation of smoking (i.e., complete smoking cessation), group therapy becomes the dominant strategy.

Table 2.3. Percentage of simulations that the strategy was ranked first (%) in the base case, by race-specific risk profile

	Risk profile					
Highest ranked strategy	**1**	**2**	**3**	**4**	**5**	**6**
White						
Group therapy for smoking	N/A	N/A	0.0	0.0	N/A	0.0
Mediterranean diet	0.3	0.3	0.3	0.0	0.1	0.6
Walking	2.5	2.2	2.5	6.6	3.6	3.7
Yoga	97.2	97.5	97.2	93.4	96.3	95.7
African-American						
Group therapy for smoking	N/A	N/A	0.0	0.0	N/A	0.0
Mediterranean diet	0.1	0.0	0.3	0.6	0.0	0.5
Walking	5.9	8.1	8.5	3.1	7.6	10.6
Yoga	93.9	91.9	91.2	96.3	92.4	88.9

Table 2.4. Percentage of simulations that the strategy was ranked first (%) in the secondary analysis assuming successful cessation of smoking, by race-specific risk profile

	Risk profile					
Highest ranked strategy	**1**	**2**	**3**	**4**	**5**	**6**
White						
Group therapy for smoking	N/A	N/A	100.0	100.0	N/A	100.0
Mediterranean diet	0.4	0.4	0.0	0.0	0.2	0.0
Walking	4.9	4.9	0.0	0.0	4.9	0.0
Yoga	94.7	94.7	0.0	0.0	94.9	0.0
African-American						
Group therapy for smoking	N/A	N/A	100.0	100.0	N/A	100.0
Mediterranean diet	0.2	0.0	0.0	0.0	0.0	0.0
Walking	7.8	10.3	0.0	0.0	9.6	0.0
Yoga	92.0	89.7	0.0	0.0	90.4	0.0

Alternative estimates

Appendix Figure 2.17 shows the comparison of the base-case estimates and alternative estimates for each hypothetical profile. As shown in the figure, the optimal strategy for each profile does not change, nor do the rankings among the interventions. In fact, some absolute risk reductions are lower with the alternate estimates compared to the base case.

When the Framingham algorithm is used (see Appendix Figure 2.18), the relative rankings among the interventions also remains the same. The absolute 10-year risk using the Framingham risk equations is higher in some cases, as the Framingham risk score includes both populations in a single score and also predicts risk of heart failure in addition to the outcomes predicted in the Pooled Cohort Equations.

DISCUSSION

We assessed the comparative effectiveness of four lifestyle management strategies on 10-year CVD risk. In the base-case intention-to-treat analysis, yoga resulted in the largest risk reduction out of the four interventions for non-smokers and smokers alike. Walking as a form of aerobic exercise generally placed after yoga, followed by Mediterranean diet. In both the deterministic and probabilistic sensitivity analyses, the same trend in the base case held for our twelve hypothetical patients (yoga, walking, diet, group therapy for smoking).

In the base case analysis, the impact of group therapy for stopping smoking on cardiac health was based on an intention-to-treat calculation, in order to be consistent across the four interventions; thus, only those who successfully quit realize reduced CVD risk. With the probability of successfully quitting being low, the benefits were correspondingly minimal. However, in a secondary analysis we demonstrated that for a current smoker, successful smoking cessation is the most effective of all lifestyle changes.

Our results are consistent with others who assessed the effect of CVD prevention. A simulation model by Kahn et al. (2008) that focuses specifically on cardiovascular disease interventions showed that

the greatest benefits in life expectancy would be achieved through the treatment of hypertension and elevated LDL-C.[31] On a population level, the large, multinational INTERHEART case-control study found that abnormal lipids was the most important risk factor with respect to population attributable risk for acute myocardial infarction (MI) across all age groups.[36] Accordingly, our study shows that yoga, which provides the largest improvements in systolic blood pressure and lipid levels, also provides the largest reduction in CVD risk.

In the analysis by Taksler et al. (2013), among USPSTF recommendations for preventive care, tobacco cessation, diabetes control, weight loss, and blood pressure reduction were consistently ranked among the top guidelines for increases in life expectancy across patients.[18] Tobacco cessation ranked high in their study as well as the INTERHEART study that demonstrated that the odds of an acute MI almost tripled for a current smoker versus a non-smoker.[37] Our finding that successful smoking cessation is the most effective of all lifestyle changes for current smokers is consistent with these studies.

Limitations

While risk assessment was based on recently published pooled cohort equations that allowed up-to-date, accurate, race-specific estimation, there are several limitations of this study. First, we focused changes in risk factors translated into CVD risk in the non-diabetic population. Although we evaluate diverse sets of patient characteristics, results may not generalize to different populations. The ACC/AHA report did not include any measures of adiposity in their algorithm, although the lifestyle interventions studied could impact those measures, further altering CVD risk.

Second, insufficient data precluded subgroup-specific pooled estimates of interventions on risk factors as well as any projections of future changes in disease outcomes. Future long-term studies could determine the effects of these interventions on CVD outcomes rather than on risk factors and model additional changes in risk factors and other disease processes using more complex microsimulation models.

Third, we chose to use the new ACC/AHA pooled cohort equations to calculate 10-year atherosclerotic CVD risk defined as a composite endpoint of first occurrence of non-fatal myocardial infarction, death from coronary heart disease, or fatal or nonfatal stroke. Other risk calculators – the Framingham Heart Study Coronary Heart Disease calculator,[38] the EURO-SCORE,[39] and the Adult Treatment Panel (ATP) III [40] to name a few – are also used to calculate risk scores for cardiovascular outcomes. While criticism over use of the ACC/AHA risk equations exists,[41-43] our model focuses on a change in risk amongst strategies, so would not be affected by choice of risk algorithm.

Fourth, results may be sensitive to model inputs. Our parameters are based on the best available published data, namely meta-analyses of controlled clinical trials. For example, data on the effectiveness of yoga on risk factors was obtained from a meta-analysis of RCTs of moderate quality and generally small sample size.[27] Other studies have, however, corroborated the results and found improvements of similar magnitude.[25, 26] Additionally, estimates for Mediterranean diet were obtained from a meta-analysis of RCTs involving overweight and obese patients which in some cases, have access to additional advice and counseling [29]; the actual benefit may differ based on individual characteristics and participation. As with all models, estimation is subject to the data available and results should be interpreted recognizing the limitations of the meta-analyses used.

Next, we recognize that patients have preferences for certain approaches and doctors may have prescribing preferences, including taking and prescribing medication, respectively. We have presented a rank order of strategies that do not include taking any pills or medication. As such, non-adherence with lifestyle change and other health behaviors, including pill-taking, is of concern and may dilute intervention effects. Our calculations are based on intention-to-treat rates from the clinical trials, which incorporate non-adherence. Additionally, personalized medicine may aid adherence to lifestyle changes.[44] Nonetheless, real-world adherence and associated risk improvement may differ from what we have presented.

Lastly, we report risk reductions based on a single intervention. It is possible that patients may try multiple interventions simultaneously (e.g. smoking cessation therapy and walking) and that these interventions would reduce CVD risk in a synergistic fashion. Furthermore, walking was chosen as a comparator intervention in this study as it is considered low-impact and widely accessible. More vigorous exercise such as jogging may confer even greater cardiovascular and fitness benefits and may change the rank order of strategies.

Clinical implications and policy relevance

Studies on personalized medicine for preventive care have found that some of the greatest gains in life expectancy come from services targeting cardiovascular disease.[18, 19, 36] Accurate, personalized recommendations regarding cardiovascular risk reduction can lead to better health and economic outcomes, reducing healthcare and patient time costs and increasing quality-of-life and productivity. Use of risk estimators has been shown to have significant, modest effects on prescribing preventive therapies and on risk factor levels.[9, 35, 45, 46]

Based on this model and available data, yoga to reduce CVD risk can be considered by physicians and patients as a preventive care strategy alongside smoking cessation, diet, and exercise. The potential benefit of yoga in lowering lipids, blood pressure, and body weight warrant further exploration of its health effects and dose-response relationship in future clinical trials.

The information presented in this paper has the potential to help inform clinicians and patients on which activities could be more effective at reducing long-term CVD risk based on their personal risk and preferences for interventions. These findings can be included in a decision aid used in the context of shared decision-making between clinician and patient. Additionally, the lifestyle management strategies analyzed in this study require little to no equipment, no expensive medication, and can be performed at home or at the convenience of patients. Further research can examine whether these low-cost strategies are cost-effective compared to other CVD management strategies and demonstrate whether tailored therapies do improve patient adherence and health outcomes.

CONCLUSION

This study reports the comparative effectiveness of several forms of lifestyle modifications – from the commonly advised smoking cessation, diet and exercise strategies to a more contemporary form of exercise, yoga, on 10-year CVD risk. For a current smoker, successfully quitting smoking is the most effective lifestyle change. Smoking cessation is, however, difficult to achieve and group therapy for stopping smoking has only a small probability of success. From an intention-to-treat perspective, if yoga is as effective as reported in currently published meta-analyses, then yoga could be considered among the strongest lifestyle interventions for reducing CVD risk. With more individualized estimates and recommendations, providers can better predict cardiovascular disease risk and manage prevention more effectively, particularly amongst different ethnic groups who may be at higher risk of CVD and can benefit from early CVD risk discussion.[47] Patients themselves can become more informed and involved in their own health and lifestyle choices.

Tailored recommendations for managing CVD risk has the potential to inform practice, improve care, and reduce health care expenditures. Our analysis supports the findings of several large-scale studies that CVD risk can be modified by lifestyle changes. Additional research can take into account adherence to management strategies as well as investigate the effects of multiple interventions. As the interventions we have included are relatively low cost, a priority for future research is to analyze the effect of these management strategies on quality of life, costs (i.e., affordability), and cost-effectiveness (i.e., value for money).

FUNDING

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DISCLOSURES

None.

REFERENCES

1. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2960-84.

2. Thompson PD, Buchner D, Pina IL, et al. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). Circulation. 2003;107:3109-16.

3. Lee IM, Shiroma EJ, Lobelo F, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet. 2012;380:219-29.

4. Berlin JA, Colditz GA. A meta-analysis of physical activity in the prevention of coronary heart disease. Am J Epidemiol. 1990;132:612-28.

5. Estruch R, Ros E, Salas-Salvado J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med. 2013;368:1279-90.

6. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2889-934.

7. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J. 2012;33:1635-701.

8. Goff DC, Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S49-73.

9. National Heart, Lung, and Blood Institute. Assessing cardiovascular risk: systematic evidence review from the Risk Assessment Work Group. Bethesda, MD: National Institutes of Health; 2013.

10. Kraus WE, Bittner V, Appel L, et al. The national physical activity plan: a call to action from the American Heart Association: a science advisory from the American Heart Association. Circulation. 2015;131:1932-40.

11. Lloyd-Jones DM, Goff D, Stone NJ. Statins, risk assessment, and the new American prevention guidelines. Lancet. 2014;383:600-2.

12. Mozaffarian D. The promise of lifestyle for cardiovascular health: time for implementation. J Am Coll Cardiol. 2014;64:1307-9.

13. Burke W, Psaty BM. Personalized medicine in the era of genomics. JAMA. 2007;298:1682-4.

14. Collins FS, Varmus H. A new initiative on precision medicine. N Engl J Med. 2015;372:793-5.

15. Hamburg MA, Collins FS. The path to personalized medicine. N Engl J Med. 2010;363:301-4.

16. Maciosek MV, Edwards NM, Coffield AB, et al. Priorities among effective clinical preventive services: methods. Am J Prev Med. 2006;31:90-6.

17. Taksler GB, Braithwaite RS. Personalized estimates of benefit from preventive care guidelines. Ann Intern Med. 2014;160:140.

18. Taksler GB, Keshner M, Fagerlin A, et al. Personalized estimates of benefit from preventive care guidelines: a proof of concept. Ann Intern Med. 2013;159:161-8.

19. Farley TA, Dalal MA, Mostashari F, Frieden TR. Deaths preventable in the U.S. by improvements in use of clinical preventive services. Am J Prev Med. 2010;38:600-9.

20. Domenech M, Roman P, Lapetra J, et al. Mediterranean diet reduces 24-hour ambulatory blood pressure, blood glucose, and lipids: one-year randomized, clinical trial. Hypertension. 2014;64:69-76.

21. Ruiz-Canela M, Estruch R, Corella D, et al. Association of Mediterranean diet with peripheral artery disease: the PREDIMED randomized trial. JAMA. 2014;311:415-7.

22. Clarke TC, Black LI, Stussman BJ, et al. Trends in the use of complementary health approaches among adults: United States. 2002-2012. Hyattsville, MD: National Center for Health Statistics; 2015.

23. Kiecolt-Glaser JK, Christian L, Preston H, et al. Stress, inflammation, and yoga practice. Psychosom Med. 2010;72:113-21.

24. Raub JA. Psychophysiologic effects of Hatha Yoga on musculoskeletal and cardiopulmonary function: a literature review. J Altern Complement Med. 2002;8:797-812.

25. Cramer H, Lauche R, Haller H, et al. Effects of yoga on cardiovascular disease risk factors: a systematic review and meta-analysis. Int J Cardiol. 2014;173:170-83.

26. Hartley L, Dyakova M, Holmes J, et al. Yoga for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2014;5:CD010072.

27. Chu P, Gotink RA, Yeh GY, et al. The effectiveness of yoga in modifying risk factors for cardiovascular disease and metabolic syndrome: A systematic review and meta-analysis of randomized controlled trials. Eur J Prev Cardiol. 2016;23:291-307.

28. Stead LF, Lancaster T. Group behaviour therapy programmes for smoking cessation. Cochrane Database Syst Rev. 2005;CD001007.

29. Nordmann AJ, Suter-Zimmermann K, Bucher HC, et al. Meta-analysis comparing Mediterranean to low-fat diets for modification of cardiovascular risk factors. Am J Med. 2011;124:841-51.

30. Bravata DM, Smith-Spangler C, Sundaram V, et al. Using pedometers to increase physical activity and improve health: a systematic review. JAMA. 2007;298:2296-304.

31. Stead LF, Buitrago D, Preciado N, et al. Physician advice for smoking cessation. Cochrane Database Syst Rev. 2013;5:CD000165.

32. Rees K, Hartley L, Flowers N, et al. 'Mediterranean' dietary pattern for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2013;8:CD009825.

33. Lin X, Zhang X, Guo J, et al. Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc. 2015;4:e002014.

34. Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. Ann Intern Med. 2002;136:493-503.

35. D'Agostino RB, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117:743-53.

36. Kahn R, Robertson RM, Smith R, Eddy D. The impact of prevention on reducing the burden of cardiovascular disease. Circulation. 2008;118:576-85.

37. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364:937-52.

38. Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97:1837-47.

39. Conroy RM, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24:987-1003.

40. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) Final Report. Circulation. 2002;106:3143-421.

41. Amin NP, Martin SS, Blaha MJ, et al. Headed in the right direction but at risk for miscalculation: a critical appraisal of the 2013 ACC/AHA risk assessment guidelines. J Am Coll Cardiol. 2014;63:2789-94.

42. DeFilippis AP, Young R, Carrubba CJ, et al. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. Ann Intern Med. 2015;162:266-75.

43. Ridker PM, Cook NR. Statins: new American guidelines for prevention of cardiovascular disease. Lancet. 2013;382:1762-5.

44. van der Leeuw J, Ridker PM, van der Graaf Y, Visseren FL. Personalized cardiovascular disease prevention by applying individualized prediction of treatment effects. Eur Heart J. 2014;35:837-43.

45. D'Agostino RB, Grundy S, Sullivan LM, Wilson P. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA. 2001;286:180-7.

46. Harle CA, Downs JS, Padman R. Effectiveness of personalized and interactive health risk calculators: a randomized trial. Med Decis Making. 2012;32:594-605.

47. Stuart-Shor EM, Berra KA, Kamau MW, Kumanyika SK. Behavioral strategies for cardiovascular risk reduction in diverse and underserved racial/ethnic groups. Circulation. 2012;125:171-84.

CHAPTER 3

Cost-effectiveness of aerobic exercise and yoga for primary prevention of cardiovascular disease

Paula Chu[1,2], Ankur Pandya[2,3], Thomas A. Gaziano[2,4], Stephen Sy[2], Joshua A. Salomon[2,5], Sue J. Goldie[1,3], M. G. Myriam Hunink[2,5,6]

[1] Department of Health Policy, Harvard University, Cambridge, MA USA
[2] Center for Health Decision Science, Harvard TH Chan School of Public Health, Boston, MA USA
[3] Department of Health Policy and Management, Harvard TH Chan School of Public Health, Boston, MA USA
[4] Brigham and Women's Hospital, Boston, MA
[5] Department of Global Health and Population, Harvard TH Chan School of Public Health, USA
[6] Department of Epidemiology, Erasmus MC, Rotterdam, the Netherlands
[7] Department of Radiology, Erasmus MC, Rotterdam, the Netherlands

ABSTRACT

Introduction: Physical inactivity is a major public health problem in the US that contributes to rising levels of cardiovascular (CVD) morbidity, mortality, and cost. Yoga, a form of physical activity focusing on breath, postures, and the mind-body connection may improve cardiovascular risk factors on a level comparable to aerobic exercise. The cost-effectiveness of these therapies on cardiovascular health, however, is unknown. The aim of this study is to assess the cost-effectiveness of aerobic exercise and yoga therapy compared to current medicine practice alone for primary prevention of cardiovascular disease in adult populations.

Methods: Using a validated cardiovascular disease microsimulation model, we calculated the costs and quality-adjusted life year (QALY) gains of aerobic exercise and yoga for cardiovascular disease prevention from the societal and healthcare perspective as an "exercise on prescription" intervention and as a reimbursed therapy. Impact of exercise and yoga on cardiovascular risk factors, relevant costs, injury rates, and health-related quality of life were estimated from published literature. Duration of benefit from activity was varied from 1 year, 3 years, 5 years, and 10 years. The parameters of intervention effectiveness and patient uptake and adherence were varied in sensitivity analyses. One-year cycle lengths and a lifetime horizon were used. Costs and QALYs were discounted by 3%.

Results: In the societal perspective including direct and indirect costs, both interventions were not cost-effective using a $100,000/QALY threshold in any scenario. In the healthcare perspective including only direct medical costs and costs of injury, aerobic exercise was cost-effective and yoga was cost-saving in all scenarios. If patients experience improvements in activity-related quality of life and have their fitness costs reimbursed, then the activities are cost-effective (1-year incremental cost-effectiveness ratio for exercise: $16,667/QALY, for yoga: $41,814/QALY).

Conclusion: Aerobic exercise and yoga were not cost-effective solely based on their impact on CVD from a societal perspective. If classes are free and individuals enjoy exercise, then both activities are good

buys for CVD prevention. Additional research can help determine longer-term benefits, activity-related quality of life effects, and patient adherence.

INTRODUCTION

Physical inactivity is a major public health problem in the US and worldwide. The Centers for Disease Control and Prevention (CDC) and American College of Sports Medicine (ACSM) recommend all healthy adults engage in at least 30 minutes of moderate-intensity aerobic physical activity five times per week or vigorous-intensity activity at least 20 minutes three times per week, or a mix, in addition to muscle strengthening exercises at least 2 days per week.[1] Data from 2011 indicates that more than half (52%) of US adults did not meet the recommendations for aerobic exercise and 76% did not meet the recommendations for muscle-strengthening activity.[1]

In the US about half (47%) of adults having at least one major risk factor for heart disease or stroke: uncontrolled high blood pressure, uncontrolled high LDL, or being a current smoker.[2] Evidence is clear on the benefits of physical activity for controlling risk factors that lead to chronic diseases like cardiovascular disease (CVD) and diabetes.[3-8] Compared to sedentary counterparts and those with low aerobic fitness, physically active or aerobically fit individuals have a 25% to 50% lower overall risk of developing cardiovascular disease.[5]

Yoga, a meditative movement practice that involves physical postures, breathing exercises, and relaxation to improve overall physical fitness, strength, and flexibility,[9] is a form of physical activity that is gaining popularity in the US. According to the National Center for Health Statistics Report in 2012, 9.5% of US adults (21 million) practiced yoga in the previous year.[10] A market research study that also estimated around 20 million Americans practiced yoga in 2012 found a variety of experience with yoga practice, with about 20% having practiced less than one year, 30% between 1 and 3 years, 30% between 3 and 5 years, and 20% over 5 years.[11] A national online survey of Iyengar yoga practitioners in the US conducted in 2011 found a longer average duration of practice of 11 years.[12] In terms of risk factor benefits, studies suggest yoga is effective against stress,[13] hypertension,[14,15] and other cardiovascular risk factors.[16-18]

Physical activities, including aerobic exercise and yoga, have the potential to modify risk factors and disease outcomes and their associated costs. Globally, physical inactivity contributes to between 1.5-3.0% of direct healthcare costs in developed countries.[19] In the US, healthcare costs related to physical inactivity in the US are staggering, estimated to be $8,600 per capita annually.[20] A recent study based on the National Health Interview Survey and Medical Expenditure Panel Survey estimated that physical inactivity accounts for roughly 9% of aggregate health care expenditures.[21]

With the large health and economic burden generated by physical inactivity and the limited resources available to combat it, cardiovascular care strategies must be evaluated not only for their effectiveness but also for their cost-effectiveness. Previous studies have focused on economic evaluations of exercise such as walking or jogging in primary and secondary CVD prevention populations and have found these activities to be an efficient use of resources that saves both lives and money.[22-25] No studies to date have examined the cost-effectiveness of yoga on cardiovascular health. The purpose of this study was to evaluate the cost-effectiveness of yoga and of aerobic exercise compared to traditional risk factor management for primary prevention of CVD in adults.

METHODS

Model

To evaluate cost-effectiveness, we used a previously validated cardiovascular disease policy computer-based simulation model.[26-28] We adapted the model to include the interventions of interest – current practice, aerobic exercise, and yoga – with US-based parameter inputs. All individuals in the model receive traditional risk factor management and optimal medical therapy as given in routine clinical practice. Current practice is used as the reference strategy in this analysis. Full details on current clinical practice are available elsewhere.[28]

The microsimulation model cycles individuals one at a time through a sequence of possible events and tracks their health outcomes and related costs. The model population is a hypothetical group of

one million individuals ages 40-75 whose characteristics are nationally representative of healthy US adults without a history of CVD. The population was formed using weighted sampling with replacement from the 2005-2006, 2007-2008, and 2009-2010 fasting data samples of the National Health and Nutrition Examination Survey. The model projects lifetime horizons using 1-year cycle lengths.

The possible health states and transitions individuals can experience are shown in the simplified schematic of the model in Figure 3.1. All individuals begin in the Disease Free state. From there, they can either stay disease free or transition to another health state (Coronary Heart Disease (CHD), Stroke, or Death). Transitions are governed by the following: Framingham risk functions for Coronary Heart Disease and Stroke,[29] published literature for acute (first year) and longer-term event recurrence and mortality,[30] and age- and sex-specific life tables[31] for non-CVD mortality. The Framingham risk functions use information on patient age, sex, systolic blood pressure, smoking status, diabetes status, treatment for hypertension, total cholesterol and high-density lipoprotein to predict CVD events. Transition probabilities are listed in Table 3.1.

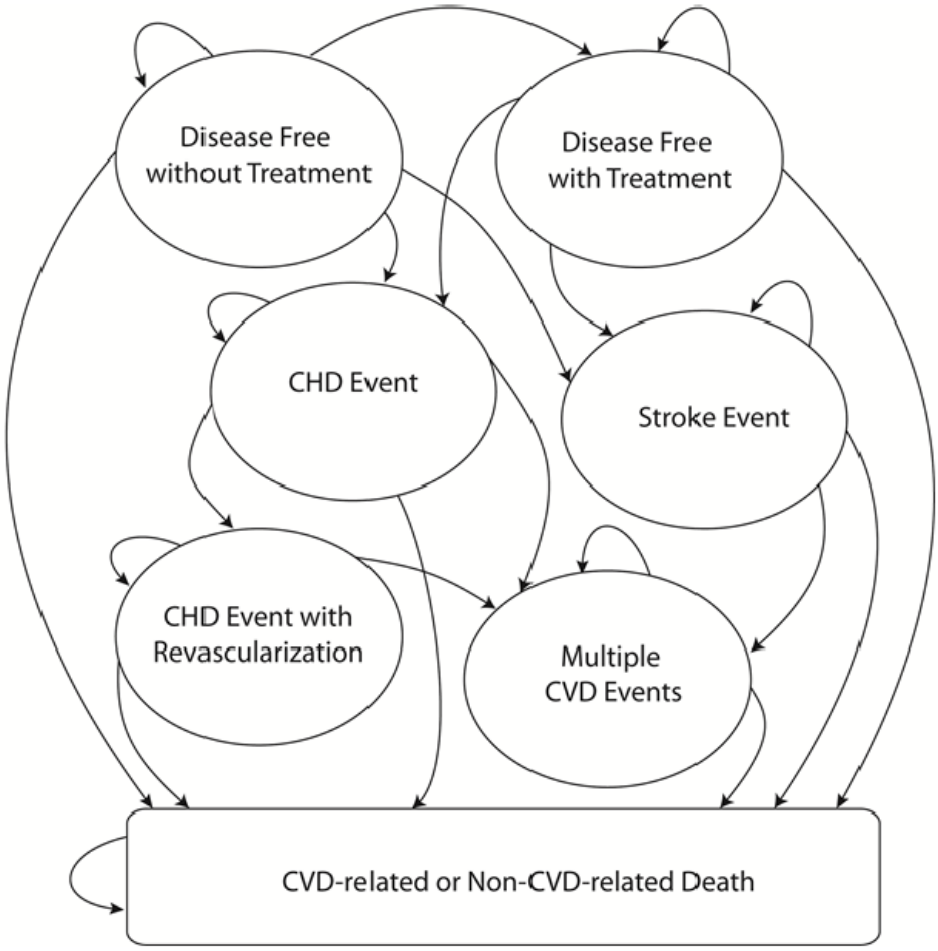


Figure 3.1. Health states in the cardiovascular disease simulation model.

Table 3.1. Disease progression inputs and health state utilities used in the cardiovascular disease simulation model.

Parameter	Value	Reference
Disease progression inputs		
From Disease Free State		
Non-CVD death	Age- and sex-specific table	(32)
CHD and stroke events	Risk factor-based equations	(33,34)
% Cardiac Arrest	Age- and sex-specific table	(35)
% MI (males)	0.35	(36)
% MI (females)	0.20	(36)
Chronic mortality (i.e., post-1st year) relative risks for CVD health states[+]		*(compared to life tables)*
Post-CHD, men <2 CHD events	1.6	(30)
Post-CHD, men ≥2 CHD events	3.4	(30)
Post-CHD, women <2 CHD events	2.1	(30)
Post-CHD, women ≥2 CHD events	2.5	(30)
Post-stroke	2.3	(37)
From Cardiac Arrest State		
Acute death*	0.954	(38)
MI event (within 1 year)	0.064	Assumption: same as MI
From MI State		
Immediate death (day 1-29)	0.15	(39)
Acute death (days 30-365)	Age- specific table	(35)
Acute CABG*	0.082	(40)
Acute PCI*	0.300	(40)
% Procedure death	0.009	(41)
Acute 2nd MI (no PCI)*	0.060	(42)
Acute 2nd MI (after PCI)*	0.052	(43)
Repeat MI (within 1 year)	0.064	(44)
From MI and CABG State		
Acute post-CABG death*	0.027	(45)
Acute 2nd MI (i.e., 2nd MI within one year after first MI)	0.051	(43)
Repeat MI (i.e., repeat MIs post 1st-year)	0.039	(44)
From Angina State		
Acute death*	0.045	(42)
Acute cardiac arrest*	0.006	(46)
Acute MI*	0.035	(47)
Acute CABG*	0.200	(48)
Acute PCI*	0.300	(48)
From Angina and CABG State		
Chronic (post 1st-year) death	0.018	(49)
MI event	0.021	(47)
From Stroke State		
Acute death*	0.140	(50)
Repeat stroke event	0.040	(51)
MI event	0.022	(52)

[+] Compared to the general population

*Acute refers to a 1-year timeframe

Abbreviations: CVD: cardiovascular disease, CHD: coronary heart disease, MI: myocardial infarction, CABG: coronary artery bypass grafting, PCI: percutaneous coronary intervention (includes percutaneous transluminal coronary angioplasty (PTCA) and stents)

Description of interventions

Two interventions – aerobic exercise and yoga – were compared to current practice. We defined aerobic exercise to be physical activity that increases heart rate and respiration and included activities such as jogging, brisk walking, and cycling. Yoga involved physical postures focusing on strengthening muscles in conjunction with breath control, relaxation, and meditation.[9]

Data

Intervention inputs are based on a meta-analysis of randomized controlled trials (RCTs) of yoga on cardiovascular and metabolic risk factors.[18] We identified trials in which aerobic exercise and yoga were compared head-to-head in populations without CVD and re-analyzed this subset of trials based on intention-to-treat analysis.[53-57] In these trials, participants in the randomized trials took part in 80-minute structured exercise classes or yoga classes under the guidance of a fitness instructor three times a week. Estimates of intervention effectiveness are shown in Table 3.2.

Table 3.2. Effectiveness of aerobic exercise and yoga interventions on major risk factors

	Change from Baseline Mean (95% CI)	
Risk factor	**Aerobic exercise**	**Yoga**
Systolic blood pressure	-4.31 (-6.91, -1.70)	-4.17 (-8.20, -0.14)
Total cholesterol	-1.93 (-16.41, 12.55)	-2.32 (-17.87, 13.23)
HDL-cholesterol	0.39 (-3.90, 4.68)	1.16 (-3.69, 6.01)

Abbreviations: HDL: high-density lipoprotein

Costs

We calculated costs due to resource use for all strategies from both a societal, health care system, and reimbursed healthcare system perspective. Costs associated with CVD events are listed in Table 3.

We took an "exercise on prescription" approach towards estimating intervention costs, mirroring a situation in which a clinician advises or prescribes a form of exercise in the base-case analysis. From the societal perspective, costs included direct medical costs, direct nonmedical costs, and indirect costs, including all out-of-pocket patient costs and patient time costs. In the health care system perspective

analysis, only direct medical costs were included. In the reimbursed health care system perspective analysis, costs included direct medical costs and class costs.

Intervention costs incremental to the reference current practice strategy are presented in Table 3.3. We assumed participants of all strategies – current practice, aerobic exercise, and yoga – received a routine doctor office visit during which an exercise program could be prescribed. For the societal perspective analysis, we included out-of-pocket costs for participating in these activities, including gym memberships, class fees, and equipment fees. We assumed apparel, shoes, and equipment costs (mat and props) are $100 per year for both aerobic exercise and yoga equipment.

For the societal perspective, we included time costs associated with travel and participation in the interventions. Travel distance and costs was based on online sources and was assumed to be equivalent for both interventions.[58,59] We assumed that individuals drove to and from their fitness classes.[60] Time costs were calculated as the weighted average of hourly wage data for those 40 years and older ($22.32) based on data from the Bureau of Labor Statistics.[59] We obtained an estimate of 10 minutes in travel time for one-way travel to and from fitness clubs, approximately 5 miles.[58] Transportation costs were based on an average price of gas per gallon of $2.29,[61] and an average fuel use of 25.2 miles per gallon.[62]

Although in the RCTs the exercise classes were provided free of charge, we included costs of classes in our analysis, which more realistically mimics current real-world conditions. The costs for aerobic exercise were based on the yearly cost of a gym membership (12 x $55),[63] which typically includes costs of unlimited structured group classes. Costs for yoga were estimated based on a $12 per class fee, [63] the predominant method of purchasing yoga classes. Costs for exercise memberships and classes were estimated from online sources.[63] These class fees were shifted to the healthcare system in the reimbursed healthcare system perspective, representing a situation in which a healthcare payer or insurance program subsidizes or reimburses the cost of fitness for its enrollees.

Injury rates and related costs were obtained from the 2005 US Consumer Product Safety Commission Hazard Screening Report, using the category “exercise activity and equipment” for aerobic exercise and “low impact sports” for yoga.[64] All costs are in 2015 US dollars.

Table 3.3. Costs and utilities for model inputs (2015$)

Description	Base case value	Reference
CVD event-related costs		
Acute costs for disease states		
Cardiac arrest	$19,607	(65)
MI	$59,801	(65)
Angina	$29,647	(65)
Stroke	$13,766	(65)
Acute costs for procedures		
CABG	$37,515	(65)
PCI	$35,347	(65)
Chronic annual costs for disease states		
All CHD states	$3,257	(66,67)
Stroke	$2,152	(68)
Yearly incremental activity costs		
Aerobic exercise		
Material/equipment*	$100	Assumption
Gym membership*	$660	(63)
Injuries	$138	(64)
Transport (fuel, roundtrip)*	$142	(58,61,62)
Transport (time, roundtrip)*	$1161	(58,59)
Time spent exercising*+(per person, number of days and time costs)		
1 year	8.6 days/$4,643	Calculation
3 years	26.0 days/$13,130	Calculation
5 years	43.3 days/$20,628	Calculation
10 years	86.7 days/$35,587	Calculation
Yoga		
Material/equipment*	$100	Assumption
Classes*	$1,872	(63)
Injuries	$31	(9)
Transport (fuel, roundtrip)*	$142	(58,61,62)
Transport (time, roundtrip)*	$1161	(58,59)
Time spent exercising*+(per person, number of days and time costs)		
1 year	8.6 days/$4,643	Calculation
3 years	26.0 days/$13,130	Calculation
5 years	43.3 days/$20,628	Calculation
10 years	86.7 days/$35,587	Calculation
Utilities		
Disease-free utilities by age and sex		
Males, ages		
40-49	0.887	(69)
50-59	0.861	(69)
60-69	0.840	(69)
70-79	0.802	(69)
80-89	0.782	(69)

Table 3.3 (Continued).

Females, ages		
40-49	0.863	(69)
50-59	0.837	(69)
60-69	0.811	(69)
70-79	0.771	(69)
80-89	0.724	(69)
Disease-state utilities		
Cardiac arrest	0.774	(70)
MI	0.704	(70)
Angina	0.695	(70)
Stroke	0.650	(70)
Disutilities for medication and repeat events		
On medication	-0.002	(71,72)
Repeat MI event	-0.049	(70)
Repeat stroke event	-0.052	(70)
Utilities for interventions in sensitivity analyses		
Aerobic exercise		
Scenario with decrease in utility	-0.0381	(73)
Scenario with increase in utility	+0.0388	(74)
Yoga	+0.0307	(73)

***** Cost items excluded from health system perspective

[+] Assuming full adherence to exercise regime and discounted at 3% annually

Abbreviations: CVD: cardiovascular disease, MI: myocardial infarction, CABG: coronary artery bypass grafting, PCI: percutaneous coronary intervention (includes percutaneous transluminal coronary angioplasty (PTCA) and stents), CHD: coronary heart disease

Utilities

The health-related quality of life used to describe the health states of individuals in this study are derived from a study of nationally representative US EuroQoL-5D (EQ-5D).[69] The EQ-5D is a commonly used preference-based quality of life score summarizing an individual's health regarding mobility, self-care, usual activities, pain, and anxiety/depression, with scores ranging from 0 (equivalent to death) to 1 (equivalent to perfect health).[75] Scores are stratified by age and sex and are listed in Table 3.

Intervention-specific utilities and CVD event-specific utilities are shown in Table 3. Utilities for the disease-free state are based on US nationally representative EQ-5D scores stratified by age and sex.[69] Utilities associated with events are also based on US nationally representative EQ-5D scores listed by condition.[70] The time spent in each health state along with the utility of that state are used to calculate

QALYs, or quality-adjusted life years. If in the rare case the disease-free utility was lower than the utility associated with the disease state, the lesser of the two was used.

Quality of life changes associated with the interventions were measured within the RCTs using the 36-item Short-Form Health Survey (SF-36). The SF-36 is a self-administered, standardized questionnaire that is a widely used generic measure of patient health-related quality of life.[76,77] It contains 36 items grouped into 8 domains: physical functioning, physical role, bodily gain, general health, vitality, social functioning, emotional role, and mental. Questionnaire responses were transformed into the EQ-5D using an algorithm published by Ara and Brazier 2008 that used the regression coefficients from the main prediction model to convert scores.[78]

Base-case analysis

Baseline values for costs, health state utilities, and expected cardiovascular benefit were evaluated in the base-case analysis from the three different perspectives.

Every year, participants doing exercise and yoga face a constant probability of injury due to their participation in the activity. If an individual is injured, they incur costs related to medical treatment for that injury and permanently drop out of the intervention. Once classes are stopped, the costs and benefits associated with the interventions cease. Risk factor levels of an individual in the intervention group return to those of the control group in the following cycle based on literature on the deconditioning effects after exercise training[79] and risk factors for the remainder of an individual's lifetime change according to the standard assumptions of the cardiovascular disease simulation model.

We multiplied certain costs and risk of injury influenced by participation in the interventions by an adjustment factor to account for limited compliance; this adjustment factor was the percentage of classes attended from an RCT comparing aerobic exercise and yoga.[73] The multiplier 0.69 was used for aerobic exercise to adjust the gas cost, travel time cost, class time cost, and risk of injury and 0.78 was used for yoga to the same costs plus the class fee costs. In sensitivity analysis we explored the effect of varying the multiplier value.

Due to the lack of long-term evidence, we conservatively assumed no change in quality of life from either intervention on the base-case analysis and tested this assumption in the sensitivity analysis.

The model calculates differences in events and costs with aerobic exercise and with yoga both compared to current practice. In this analysis the interventions are modeled not as mutually exclusive options but rather as program alternatives (e.g. a hospital working within a specified budget may choose to fund both activity programs for their patients to maximize health benefits).

The expected health benefit per dollar spent is indicated in the incremental cost-effectiveness ratio (ICER), defined as the incremental cost divided by the number of QALYs saved. A $100,000/QALY was used as a threshold for being cost-effective.[80] Strategies are dominated if they have higher incremental costs and lower QALYs than current practice, cost saving if they have lower incremental costs and comparable QALYs than current practice, and superior if they have lower incremental costs and higher QALYs than current practice. Costs and QALYs were discounted at 3% per annum as recommended by the Panel on Cost-effectiveness in Health and Medicine.[81]

Sensitivity analyses

We explored several alternative assumptions in the sensitivity analyses.

We ran the model under several durations of intervention effectiveness. We assumed the following lengths of participation in exercise and yoga classes: 1, 3, 5, and 10 years based on survey data of the duration of yoga practice.[11,12]

We also varied the following parameters to explore the effect on the cost-effectiveness: reduced adherence (effectiveness drops to 50% from base case of 100% of the estimates listed in Table 3.2 due to lower compliance with the exercise program, costs decreasing accordingly) and reduced uptake (the percentage of people initiating the intervention after prescription drops to 50% from the base case of 100%).

In addition, two utility scenarios were analyzed: one where quality of life improves with yoga but decreases with aerobic exercise as found in the RCT by Oken et al. 2006[73] and one where both interventions increase quality of life.[73,74]

RESULTS

Base case - Societal perspective

Base case results are shown in Table 3.4. In the base case from the societal perspective, both aerobic exercise and yoga have extremely high ICERs compared to current medical practice (5 year aerobic exercise ratio: $1,431,803/QALY gained, 5 year yoga ratio: $1,491,450/QALY gained), dramatically higher than the $100,000/QALY threshold. Total costs are high due to the high patient time costs associated with the interventions.

Base case - Healthcare perspective

From the healthcare perspective, total costs are lower compared to the societal perspective as time costs and out-of-pocket class costs contained in the societal perspective are excluded in each corresponding scenario. At 1 year, the ICER for aerobic exercise is $10,364; at 3 years, the ICER becomes $10,724/QALY due to the added exposure to risk of injury as the intervention duration increases. At 5 years, the ICER becomes $9,860 and at 10 years, $8,915 due to minor QALY gains. Yoga, for all intervention durations, is cost-saving and more effective due to the relatively lower injury rates (Table 3.5).

Base case analysis – Reimbursed healthcare perspective

In the case where fitness classes are reimbursed by an insurer or third-party payer, ICERs decrease considerably in most scenarios compared with the base-case analysis (Table 3.6). Total costs are lower than those in the societal perspective and higher than those in the healthcare perspective due to the added cost of class fees and memberships. In the case where all individuals are taking exercise or yoga

classes and experience the full health benefit in risk factor reduction, 5-year intervention ICERs are $202,854/QALY for aerobic exercise and $341,942/QALY for yoga.

Sensitivity analysis - Societal perspective

ICERs improved slightly as the number of years spent doing the intervention increase due to the increased number of QALYs from avoided CVD events despite the increased time and class costs; however, the cost-effectiveness profile remains very unfavorable (10-year aerobic exercise ICER: $1,320,889/QALY, 1 year yoga ICER: $1,298,805/QALY). For all intervention durations, the activities were not cost-effective using the $100,000/QALY cost-effectiveness threshold.

When adherence and the associated costs and injury risk were halved, the total costs dropped. Total QALYs also decreased along with costs, causing the ICERs to drop slightly compared to the base case. When percentage of participants dropped by half (only 50% of patients initiated exercise or yoga), the same result occurred in which total costs were reduced and total QALYs dropped compared to the base case. Similar ICERs are seen comparing the base case, reduced adherence, and reduced uptake scenarios.

Changes in quality of life due to the interventions considerably impacted ICERs but they remained over the $100,000/QALY cost-effectiveness threshold. The ICER for a 5-year exercise regimen drops from $1,431,803/QALY with base case adherence and uptake to $115,932/QALY with a quality of life improvement. The same holds true for yoga; the 5-year ICER drops from $1,491,450/QALY to $176,607/QALY. Conversely, when quality of life decreases with an intervention (i.e., disutility from going to the gym), the intervention becomes dominated (higher costs than current practice and less QALYs).

Sensitivity analysis - Healthcare perspective

Yoga remains superior in all scenarios. Aerobic exercise is cost-effective compared to current practice in all scenarios except when the quality of life decreases. When the quality of life with exercise increases, ICERs are below $800/QALY.

Sensitivity analysis – Reimbursed healthcare perspective

If patients experience increases in utility from physical activity, both interventions become cost-effective compared to the $100,000/QALY threshold, with a 5-year ICER for aerobic exercise of $16,425/QALY and a 1-year ICER for yoga of $40,490/QALY.

Table 3.4. One-, three-, five-, and ten-year per person quality-adjusted life years (QALYs), costs ($), and incremental cost-effectiveness ratios ($/QALY) for various scenarios evaluated from the societal perspective. Cost-effectiveness is color-coded with red being not cost-effective compared to current practice, yellow cost-effective using a $100,000/QALY threshold, and green cost saving or superior. Note: all strategies are compared to the reference strategy current practice.

Strategy	Total cost (2015$)	Total QALYs	ICER	Strategy	Total cost	Total QALYs	ICER
Current practice	$19,290	14.7467	--	Current practice	$19,290	14.7467	--
Base case (100% adherence and uptake, no HRQL change)							
Aerobic exercise				Yoga			
1 year	$24,155	14.7489	$2,211,273	1 year	$25,419	14.7494	$2,270,111
3 years	$33,333	14.7554	$1,614,149	3 years	$37,032	14.7576	$1,627,752
5 years	$41,769	14.7624	$1,431,803	5 years	$47,776	14.7658	$1,491,450
10 years	$59,841	14.7774	$1,320,889	10 years	$71,046	14.7837	$1,398,805
With reduced adherence (base case with 50% adherence)							
1 year	$21,727	14.7481	$1,740,571	1 year	$22,355	14.7483	$1,915,813
3 years	$26,337	14.7514	$1,499,319	3 years	$28,163	14.7526	$1,503,864
5 years	$30,594	14.7551	$1,345,726	5 years	$33,545	14.7568	$1,411,436
10 years	$29,774	14.7628	$1,272,311	10 years	$45,214	14.7664	$1,315,975
With quality of life changes (base case with HRQL decrease for exercise, increase for yoga)							
1 year	$24,155	14.7109	dominated	1 year	$25,419	14.7801	$183,512
3 years	$33,333	14.6461	dominated	3 years	$37,032	14.8462	$178,317
5 years	$41,769	14.5875	dominated	5 years	$47,776	14.9080	$176,607
10 years	$59,841	14.4619	dominated	10 years	$71,046	15.0423	$175,087
With quality of life changes (base case with HRQL increase for both)							
1 year	$24,155	14.7875	$119,235	1 year	$25,419	14.7801	$183,512
3 years	$33,333	14.8667	$117,026	3 years	$37,032	14.8462	$178,317
5 years	$41,769	14.9406	$115,932	5 years	$47,776	14.9080	$176,607
10 years	$59,841	15.0988	$115,170	10 years	$71,046	15.0423	$176,087
With reduced uptake (base case with 50% initiation)							
1 year	$21,719	14.7477	$2,429,400	1 year	$22,350	14.7480	$2,354,154
3 years	$26,302	14.7511	$1,593,727	3 years	$28,150	14.7521	$1,640,796
5 years	$30,512	14.7544	$1,457,455	5 years	$33,513	14.7562	$1,497,179
10 years	$39,534	14.7619	$1,331,875	10 years	$45,129	14.7652	$1,396,730

Abbreviations: HRQL: health-related quality of life

Table 3.5. One-, three-, five-, and ten-year per person quality-adjusted life years (QALYs), costs ($), and incremental cost-effectiveness ratios ($/QALY) for various scenarios evaluated from the healthcare perspective. Cost-effectiveness is color-coded with red being not cost-effective compared to current practice, yellow cost-effective using a $100,000/QALY threshold, and green cost saving or superior. Note: all strategies are compared to the reference strategy current practice.

Strategy	Total cost (2015$)	Total QALYs	ICER	Strategy	Total cost	Total QALYs	ICER
Current practice	$19,290	14.7467	--	Current practice	$19,290	14.7467	--
Base case (100% adherence and uptake, no HRQL change)							
	Aerobic exercise				Yoga		
1 year	$19,313	14.7489	$10,364	1 year	$19,228	14.7494	superior
3 years	$19,383	14.7554	$10,724	3 years	$19,139	14.7576	superior
5 years	$19,445	14.7624	$9,860	5 years	$19,054	14.7658	superior
10 years	$19,563	14.7774	$8,915	10 years	$18,848	14.7837	superior
With reduced adherence (base case with 50% adherence)							
1 year	$19,301	14.7481	$7,714	1 year	$19,258	14.7483	superior
3 years	$19,333	14.7514	$9,234	3 years	$19,207	14.7526	superior
5 years	$19,364	14.7551	$8,893	5 years	$19,164	14.7568	superior
10 years	$19,422	14.7628	$8,199	10 years	$19,056	14.7664	superior
With quality of life changes (base case with HRQL decrease for exercise, increase for yoga)							
1 year	$19,313	14.7109	dominated	1 year	$19,228	14.7801	superior
3 years	$19,383	14.6461	dominated	3 years	$19,139	14.8462	superior
5 years	$19,445	14.5875	dominated	5 years	$19,054	14.9080	superior
10 years	$19,563	14.4619	dominated	10 years	$18,848	15.0423	superior
With quality of life changes (base case with HRQL increase for both)							
1 year	$19,313	14.7875	$559	1 year	$19,228	14.7801	superior
3 years	$19,383	14.8667	$777	3 years	$19,139	14.8462	superior
5 years	$19,445	14.9406	$798	5 years	$19,054	14.9080	superior
10 years	$19,563	15.0988	$777	10 years	$18,848	15.0423	superior
With reduced uptake (base case with 50% initiation)							
1 year	$19,301	14.7477	$11,100	1 year	$19,258	14.7480	superior
3 years	$19,336	14.7511	$10,614	3 years	$19,215	14.7521	superior
5 years	$19,365	14.7544	$9,792	5 years	$19,172	14.7562	superior
10 years	$19,425	14.7619	$8,914	10 years	$19,069	14.7652	superior

Abbreviations: HRQL: health-related quality of life

Table 3.6. One-, three-, five-, and ten-year per person quality-adjusted life years (QALYs), costs ($), and incremental cost-effectiveness ratios ($/QALY) for various scenarios evaluated from the reimbursed therapy perspective. Cost-effectiveness is color-coded with red being not cost-effective compared to current practice, yellow cost-effective using a $100,000/QALY threshold, and green cost saving or superior. Note: all strategies are compared to the reference strategy current practice.

Strategy	Total cost (2015$)	Total QALYs	ICER	Strategy	Total cost	Total QALYs	ICER
Current practice	$19,290	14.7467	--	Current practice	$19,290	14.7467	--
Base case (100% adherence and uptake, no HRQL change)							
	Aerobic exercise				Yoga		
1 year	$19,970	14.7489	$309,091	1 year	$20,686	14.7494	$517,259
3 years	$21,276	14.7554	$228,356	3 years	$23,354	14.7578	$372,908
5 years	$22,475	14.7624	$202,854	5 years	$25,821	14.7658	$341,942
10 years	$25,030	14.7774	$186,987	10 years	$31,145	14.7837	$320,405
With reduced adherence (base case with 50% adherence)							
1 year	$19,630	14.7481	$242,857	1 year	$19,987	14.7483	$436,063
3 years	$20,284	14.7514	$211,468	3 years	$21,317	14.7526	$343,593
5 years	$20,889	14.7551	$190,333	5 years	$22,552	14.7568	$322,990
10 years	$22,184	14.7628	$179,776	10 years	$25,218	14.7664	$300,934
With quality of life changes (base case with HRQL decrease for exercise, increase for yoga)							
1 year	$19,970	14.7109	dominated	1 year	$20,686	14.7801	$41,814
3 years	$21,276	14.6461	dominated	3 years	$23,354	14.8462	$40,851
5 years	$25,030	14.4619	dominated	5 years	$25,821	14.9080	$40,490
10 years	$31,354	14.1536	dominated	10 years	$31,145	15.0423	$40,105
With quality of life changes (base case with HRQL increase for both)							
1 year	$19,970	14.7875	$16,667	1 year	$20,686	14.7801	$41,814
3 years	$21,276	14.8667	$16,556	3 years	$23,354	14.8462	$40,851
5 years	$22,475	14.9406	$16,425	5 years	$25,821	14.9080	$40,490
10 years	$25,030	15.0988	$16,304	10 years	$31,145	15.0423	$40,105
With reduced uptake (base case with 50% initiation)							
1 year	$19,629	14.7477	$339,400	1 year	$19,986	14.7480	$525,923
3 years	$20,282	14.7511	$225,477	3 years	$21,320	14.7521	$375,944
5 years	$20,878	14.7544	$206,286	5 years	$22,550	14.7562	$343,200
10 years	$22,155	14.7619	$188,474	10 years	$25,208	14.7652	$319,930

Abbreviations: HRQL: health-related quality of life

DISCUSSION

Whether aerobic exercise and yoga are cost-effective or not compared to current medical care depends on both the perspective taken in the analysis and the potential quality of life improvement from the intervention. From the societal perspective, regardless of the scenario, neither aerobic exercise nor yoga is cost-effective using a $100,000/QALY cost-effectiveness threshold due to the high costs of patient time. From the healthcare perspective, both strategies are cost-effective, sometimes even superior, compared to current practice as indirect costs (class fees and time costs) are excluded. In a system where participants are reimbursed for their fitness class fees and memberships, these physical activity interventions are only cost-effective if uptake and adherence are good and quality of life increases.

In the base case, the individual-level QALY gains from the interventions are modest, with gains of only a few additional days of healthy life with either exercise or yoga. Gains increase if individuals enjoy physical activity. The similar benefits derived from either activity suggest that if individuals are looking to improve their cardiovascular health and dislike aerobic exercise, they may consider yoga as an alternative and vice versa.

The results of the current analysis suggest that it is worth it for an individual to exercise to protect against CVD if classes/memberships are free or subsidized and activity improves his or her quality of life. For these individuals, the benefit and value derived from the activity is higher than the cost of the time spent exercising and the time spent traveling to a center or studio.

The finding that participant enjoyment is a key driver in cost-effectiveness corroborates a previous study by Hatziandreau et al[22] evaluating the cost-effectiveness of jogging as an intervention to lower CHD risk in a cohort of 35-year-old men followed for 30 years. The authors stated that the indirect cost spent doing exercise was the most important variable in determining whether the activity was cost saving or not. Indeed the cost/QALY gained was $11,313 (1995 US$) including direct and indirect time costs; while cost-effective, in a scenario in which the authors only included a subset of participants who

enjoyed the activity or in other words valued exercise as "no cost", results showed that exercise would be cost-saving.[22]

While we examined structured, center-based physical activity interventions, in the real world individuals may exercise at home, outside, or a variety of other settings. Garrett et al. (2011) published a systematic review of the cost-effectiveness of physical activity interventions in primary care and the community setting and showed that most interventions were cost-effective (ICERs ranged from $596 to $148,708 (inflated to 2015 US$) per QALY), particularly where no direct supervision or instruction was involved.[82] In a comparison of a structured exercise intervention versus an unstructured intervention in which individuals increased physical activity in their daily lives (e.g., taking the stairs instead of the elevator), the unstructured intervention was more cost-effective than the supervised exercise in improving cardiorespiratory fitness in healthy sedentary adults.[23] Our interventions included supervised, center-based classes; if participants were to do these activities at home without supervision (e.g. practicing yoga at home or doing exercise videos), it is likely that the interventions would be more cost-effective.

While we evaluated aerobic exercise and yoga for cardiovascular disease prevention, it is possible that individuals may pursue these activities for other health or wellness reasons and could experience other benefits beyond what we captured in the model. A qualitative study found that participants felt peaceful and upbeat after a yoga class, which also translated into self-reported improvements in exercise behaviors, stress management, and eating habits.[83] Similar feelings of well-being, such as "runner's high" or feelings of accomplishment could be achieved for some types of aerobic exercise. Such benefits could improve the adherence and the cost-effectiveness of the physical activity interventions.

Limitations

There are limitations of this study. First, because we used data from RCTs that directly compared yoga and aerobic exercise, the relevant number of trials was small and trials were of relatively short duration (median 12 weeks). In order to capture lifetime costs and benefits, certain assumptions were required for intervention duration and pattern. We assumed durations based on survey data and assumed

that individuals participated in these interventions continuously and thus received the benefits for that duration of time. In reality, individuals may start, stop, restart, etc. for different lengths of time. We did, however, use intervention effectiveness numbers based on intention-to-treat in the base case, which accounted for individual attrition and varied the intervention adherence in sensitivity analyses.

Adherence was obtained from an RCT that directly compared aerobic exercise and yoga.[73] Due to lack of more specific, long-term data, we assumed a constant rate for the duration of the intervention. Results remained robust after testing for the impact of adherence.

Next, the injuries included in the model are only those reported and medically treated, including trips to the emergency room. These injuries may be more costly than other injuries, and are only a subset of injuries that could afflict practitioners of these physical activities. Injuries not serious enough for medical attention and not reported may affect practice and stopping patterns.

Last, data is limited on quality of life change due to the interventions, particularly yoga. Few trials collect quality of life data using validated preference-based questionnaires. We used an estimate from Oken et al. (2006) in a healthy elderly population.[73] These changes in quality of life, along with the other inputs used in the model, may not be generalizable to other segments on the population. Although we performed analyses in which both aerobic exercise and yoga increase quality of life and one in which aerobic exercise decreases quality of life using utility estimates from another RCT,[74] the quality of life estimates are also based on a single study and the changes experienced by the study population may not translate to other populations.

CONCLUSION

The burden of CVD is large but is also preventable through changes in lifestyle and physical activity. This study shows that aerobic exercise and yoga were not cost-effective solely based on their impact on CVD from a societal perspective that considers patient time costs. For healthcare payers, aerobic exercise is cost-effective and yoga is cost-saving compared to current medical therapy. If payers fully subsidize the direct costs of exercise and yoga classes, then these activities would remain cost-

effective in individuals that also experience activity-related quality of life improvements. Additional research can help determine longer-term benefits in risk factors and outcomes, activity-related quality of life effects, and patient adherence.

REFERENCES

1. Centers for Disease Control and Prevention. Exercise or physical activity. CDC/National Center for Health Statistics, 2015.

2. Fryar CD CT, Li X. Prevalence of uncontrolled risk factors for cardiovascular disease: United States, 1999-2010. NCHS Data Brief. Hyattsville, MD: National Center for Health Statistics, Centers for Disease Control and Prevention, US Department of Health and Human Services, 2012.

3. Berlin JA, Colditz GA. A meta-analysis of physical activity in the prevention of coronary heart disease. American journal of epidemiology 1990;132:612-28.

4. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. CMAJ : Canadian Medical Association journal = Journal de l'Association Medicale Canadienne 2006;174:801-9.

5. Haskell WL, Lee IM, Pate RR et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Medicine and Science in Sports and Exercise 2007;39:1423-34.

6. Thompson PD, Franklin BA, Balady GJ et al. Exercise and acute cardiovascular events placing the risks into perspective: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism and the Council on Clinical Cardiology. Circulation 2007;115:2358-68.

7. Williams MA, Haskell WL, Ades PA et al. Resistance exercise in individuals with and without cardiovascular disease: 2007 update: a scientific statement from the American Heart Association Council on Clinical Cardiology and Council on Nutrition, Physical Activity, and Metabolism. Circulation 2007;116:572-84.

8. Thompson PD, Buchner D, Pina IL et al. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). Circulation 2003;107:3109-16.

9. National Center for Complementary and Integrative Medicine. Yoga. 2015. Available at: https://nccih.nih.gov/health/yoga. Accessed 1 March, 2016.

10. Clarke T, Black, LI, Stussman, BJ. Trends in the use of complementary health approaches among adults: United States, 2002-2012. National Health Statistics Reports. Hyattsville, MD: National Center for Health Statistics, 2015.

11. Yoga in America. Sports Marketing Surveys USA. Jupiter, FL, 2012.

12. Ross A, Friedmann E, Bevans M, Thomas S. Frequency of yoga practice predicts health: results of a national survey of yoga practitioners. Evidence-Based Complementary and Alternative Medicine : eCAM 2012;2012:983258.

13. Kirkwood G, Rampes H, Tuffrey V, Richardson J, Pilkington K. Yoga for anxiety: a systematic review of the research evidence. British Journal of Sports Medicine 2005;39:884-91.

14. Hagins M, States R, Selfe T, Innes K. Effectiveness of yoga for hypertension: systematic review and meta-analysis. Evidence-Based Complementary and Alternative Medicine : eCAM 2013;2013:649836.

15. Raub JA. Psychophysiologic effects of Hatha Yoga on musculoskeletal and cardiopulmonary function: a literature review. J Altern Complement Med 2002;8:797-812.

16. Innes KE, Bourguignon C, Taylor AG. Risk indices associated with the insulin resistance syndrome, cardiovascular disease, and possible protection with yoga: a systematic review. The Journal of the American Board of Family Practice / American Board of Family Practice 2005;18:491-519.

17. Jayasinghe SR. Yoga in cardiac health (a review). European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology 2004;11:369-75.

18. Chu P, Gotink RA, Yeh GY, Goldie SJ, Hunink MM. The effectiveness of yoga in modifying risk factors for cardiovascular disease and metabolic syndrome: A systematic review and meta-analysis of randomized controlled trials. European journal of preventive cardiology 2014.

19. Oldridge NB. Economic burden of physical inactivity: healthcare costs associated with cardiovascular disease. European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology 2008;15:130-9.

20. American Heart Association. The price of inactivity. American Heart Association, 2015. Available at: http://www.heart.org/HEARTORG/HealthyLiving/PhysicalActivity/FitnessBasics/The-Price-of-Inactivity_UCM_307974_Article.jsp#.VvMR9mQrK2w. Accessed 1 March 2016.

21. Carlson SA, Fulton JE, Pratt M, Yang Z, Adams EK. Inadequate physical activity and health care expenditures in the United States. Progress in Cardiovascular Diseases 2015;57:315-23.

22. Hatziandreu EI, Koplan JP, Weinstein MC, Caspersen CJ, Warner KE. A cost-effectiveness analysis of exercise as a health promotion activity. American Journal of Public Health 1988;78:1417-21.

23. Sevick MA, Dunn AL, Morrow MS, Marcus BH, Chen GJ, Blair SN. Cost-effectiveness of lifestyle and structured exercise interventions in sedentary adults: results of project ACTIVE. American Journal of Preventive Medicine 2000;19:1-8.

24. Georgiou D, Chen Y, Appadoo S et al. Cost-effectiveness analysis of long-term moderate exercise training in chronic heart failure. The American Journal of Cardiology 2001;87:984-8; A4.

25. Lowensteyn I, Coupal L, Zowall H, Grover SA. The cost-effectiveness of exercise training for the primary and secondary prevention of cardiovascular disease. Journal of Cardiopulmonary Rehabilitation 2000;20:147-55.

26. Gaziano TA, Steyn K, Cohen DJ, Weinstein MC, Opie LH. Cost-effectiveness analysis of hypertension guidelines in South Africa: absolute risk versus blood pressure level. Circulation 2005;112:3569-76.

27. Gaziano TA, Opie LH, Weinstein MC. Cardiovascular disease prevention with a multidrug regimen in the developing world: a cost-effectiveness analysis. Lancet 2006;368:679-86.

28. Pandya A, Sy S, Cho S, Weinstein MC, Gaziano TA. Cost-effectiveness of 10-Year Risk Thresholds for Initiation of Statin Therapy for Primary Prevention of Cardiovascular Disease. JAMA 2015;314:142-50.

29. D'Agostino RB, Sr., Vasan RS, Pencina MJ et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743-53.

30. Smolina K, Wright FL, Rayner M, Goldacre MJ. Long-term survival and recurrence after acute myocardial infarction in England, 2004 to 2010. Circulation Cardiovascular quality and outcomes 2012;5:532-40.

31. Heron M. Deaths: Leading Causes for 2006. National Vital Statistics Reports. Hyattsville, MD: National Center for Health Statistics, 2010.

32. Heron M. Deaths: Leading Causes for 2006. National Vital Statistics Reports. Hyattsville, MD: National Center for Health Statistics, 2010.

33. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. Stroke: a Journal of Cerebral Circulation 1991;22:312-8.

34. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. American Heart Journal 1991;121:293-8.

35. Weinstein MC, Coxson PG, Williams LW, Pass TM, Stason WB, Goldman L. Forecasting coronary heart disease incidence, mortality, and cost: the Coronary Heart Disease Policy Model. American Journal of Public Health 1987;77:1417-26.

36. National Heart Lung and Blood Institute (NHLBI). Incidence & Prevalence: 2006 Chart Book on Cardiovascular and Lung Diseases. National Institutes of Health 2006.

37. Dennis MS, Burn JP, Sandercock PA, Bamford JM, Wade DT, Warlow CP. Long-term survival after first-ever stroke: the Oxfordshire Community Stroke Project. Stroke; a journal of cerebral circulation 1993;24:796-800.

38. Nichol G, Thomas E, Callaway CW et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. JAMA : the Journal of the American Medical Association 2008;300:1423-31.

39. Go AS, Mozaffarian D, Roger VL et al. Executive summary: heart disease and stroke statistics--2014 update: a report from the American Heart Association. Circulation 2014;129:399-410.

40. Fang J, Alderman MH, Keenan NL, Ayala C. Acute myocardial infarction hospitalization in the United States, 1979 to 2005. The American Journal of Medicine 2010;123:259-66.

41. Dorros G, Cowley MJ, Janke L, Kelsey SF, Mullin SM, Van Raden M. In-hospital mortality rate in the National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. The American Journal of Cardiology 1984;53:17C-21C.

42. Capewell S, Murphy NF, MacIntyre K et al. Short-term and long-term outcomes in 133,429 emergency patients admitted with angina or myocardial infarction in Scotland, 1990-2000: population-based cohort study. Heart 2006;92:1563-70.

43. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. The New England Journal of Medicine 1996;335:217-25.

44. Jokhadar M, Jacobsen SJ, Reeder GS, Weston SA, Roger VL. Sudden death and recurrent ischemic events after myocardial infarction in the community. American Journal of Epidemiology 2004;159:1040-6.

45. Peterson ED, Coombs LP, DeLong ER, Haan CK, Ferguson TB. Procedural volume as a marker of quality for CABG surgery. JAMA : the Journal of the American Medical Association 2004;291:195-201.

46. Hsia J, Jablonski KA, Rice MM et al. Sudden cardiac death in patients with stable coronary artery disease and preserved left ventricular systolic function. The American Journal of Cardiology 2008;101:457-61.

47. Hemingway H, Shipley M, Britton A, Page M, Macfarlane P, Marmot M. Prognosis of angina with and without a diagnosis: 11 year follow up in the Whitehall II prospective cohort study. BMJ 2003;327:895.

48. Ford ES, Ajani UA, Croft JB et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. The New England Journal of Medicine 2007;356:2388-98.

49. Law MR, Watt HC, Wald NJ. The underlying risk of death after myocardial infarction in the absence of treatment. Archives of Internal Medicine 2002;162:2405-10.

50. Lee KK, Cipriano LE, Owens DK, Go AS, Hlatky MA. Cost-effectiveness of using high-sensitivity C-reactive protein to identify intermediate- and low-cardiovascular-risk individuals for statin therapy. Circulation 2010;122:1478-87.

51. Hardie K, Hankey GJ, Jamrozik K, Broadhurst RJ, Anderson C. Ten-year risk of first recurrent stroke and disability after first-ever stroke in the Perth Community Stroke Study. Stroke: a Journal of Cerebral Circulation 2004;35:731-5.

52. Touze E, Varenne O, Chatellier G, Peyrard S, Rothwell PM, Mas JL. Risk of myocardial infarction and vascular death after transient ischemic attack and ischemic stroke: a systematic review and meta-analysis. Stroke: a journal of Cerebral Circulation 2005;36:2748-55.

53. Saptharishi L, Soudarssanane M, Thiruselvakumar D et al. Community-based Randomized Controlled Trial of Non-pharmacological Interventions in Prevention and Control of Hypertension among Young Adults. Indian Journal of Community Medicine : official publication of Indian Association of Preventive & Social Medicine 2009;34:329-34.

54. Bowman AJ, Clayton RH, Murray A, Reed JW, Subhan MM, Ford GA. Effects of aerobic exercise training and yoga on the baroreflex in healthy elderly persons. European Journal of Clinical Investigation 1997;27:443-9.

55. Harinath K, Malhotra AS, Pal K et al. Effects of Hatha yoga and Omkar meditation on cardiorespiratory performance, psychologic profile, and melatonin secretion. J Altern Complement Med 2004;10:261-8.

56. Stachenfeld NS, Mack GW, DiPietro L, Morocco TS, Jozsi AC, Nadel ER. Regulation of blood volume during training in post-menopausal women. Medicine and Science in Sports and Exercise 1998;30:92-8.

57. Subramanian H, Soudarssanane MB, Jayalakshmy R et al. Non-pharmacological Interventions in Hypertension: A Community-based Cross-over Randomized Controlled Trial. Indian Journal of Community Medicine : official publication of Indian Association of Preventive & Social Medicine 2011;36:191-6.

58. International Health, Racquet & Sportsclub Association. Research. 2010. Available at: http://www.ihrsa.org/research-faqs/. Accessed 7 October 2015.

59. Bureau of Labor Statistics. Highlights of women's earnings in 2014. Bureau of Labor Statistics, 2015.

60. Santos AM, N.; Nakamoto, H.Y.; et al. Summary of Travel Trends: 2009 National Household Travel Survey. Washington, DC: U.S. Department of Transportation, 2011.

61. AAA. National Average Prices. AAA, 2015. Available at: http://www.fuelgaugereport.com/. Accessed 7 October 2015.

62. Autoblog. Average US mpg for September drops again. 2015. Available at: http://www.autoblog.com/2015/10/07/average-us-mpg-september-drops-again/. Accessed 7 October 2015.

63. World Lifestyle. Available at: http://www.worldlifestyle.com/health-fitness/how-much-does-fitness-cost. Accessed 7 October 2015.

64. Consumer Product Safety Commission. Hazard Screening Report, Sports Activities and Equipment (excluding Major Team Sports). Bethesda, MD: Consumer Product Safety Commission, 2005.

65. O'Sullivan AK, Sullivan J, Higuchi K, Montgomery AB. Health care utilization & costs for cystic fibrosis patients with pulmonary infections. Manag Care 2011;20:37-44.

66. Mark DB, Knight JD, Cowper PA, Davidson-Ray L, Anstrom KJ. Long-term economic outcomes associated with intensive versus moderate lipid-lowering therapy in coronary artery disease: results from the Treating to New Targets (TNT) Trial. American Heart Journal 2008;156:698-705.

67. Tsevat J, Kuntz KM, Orav EJ, Weinstein MC, Sacks FM, Goldman L. Cost-effectiveness of pravastatin therapy for survivors of myocardial infarction with average cholesterol levels. American Heart Journal 2001;141:727-34.

68. Pignone M, Earnshaw S, Tice JA, Pletcher MJ. Aspirin, statins, or both drugs for the primary prevention of coronary heart disease events in men: a cost-utility analysis. Annals of Internal Medicine 2006;144:326-36.

69. Hanmer J, Lawrence WF, Anderson JP, Kaplan RM, Fryback DG. Report of nationally representative values for the noninstitutionalized US adult population for 7 health-related quality-of-life scores. Medical decision making : an international journal of the Society for Medical Decision Making 2006;26:391-400.

70. Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. Medical decision making : an international journal of the Society for Medical Decision Making 2006;26:410-20.

71. Greving JP, Visseren FL, de Wit GA, Algra A. Statin treatment for primary prevention of vascular disease: whom to treat? Cost-effectiveness analysis. BMJ 2011;342:d1672.

72. Hutchins R, Viera AJ, Sheridan SL, Pignone MP. Quantifying the utility of taking pills for cardiovascular prevention. Circulation Cardiovascular quality and outcomes 2015;8:155-63.

73. Oken BS, Zajdel D, Kishiyama S et al. Randomized, controlled, six-month trial of yoga in healthy seniors: effects on cognition and quality of life. Alternative Therapies in Health and Medicine 2006;12:40-7.

74. Elley CR, Garrett S, Rose SB et al. Cost-effectiveness of exercise on prescription with telephone support among women in general practice over 2 years. British Journal of Sports Medicine 2011;45:1223-9.

75. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Annals of Medicine 2001;33:337-43.

76. Ware JE, Snow, K.K., Kolinski, M., Gandeck, B. SF-36 Health survey manual and interpretation guide. Boston, MA: The Health Institute, New England Medical Centre, 1993.

77. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. Journal of Health Economics 2002;21:271-92.

78. Ara R, Brazier J. Deriving an algorithm to convert the eight mean SF-36 dimension scores into a mean EQ-5D preference-based score from published studies (where patient level data are not available). Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2008;11:1131-43.

79. Mora-Rodriguez R, Ortega JF, Hamouti N et al. Time-course effects of aerobic interval training and detraining in patients with metabolic syndrome. Nutrition, Metabolism, and Cardiovascular Diseases : NMCD 2014;24:792-8.

80. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness--the curious resilience of the $50,000-per-QALY threshold. The New England Journal of Medicine 2014;371:796-7.

81. Gold M. Panel on cost-effectiveness in health and medicine: Medical Care, 1996.

82. Garrett S, Elley CR, Rose SB, O'Dea D, Lawton BA, Dowell AC. Are physical activity interventions in primary care and the community cost-effective? A systematic review of the evidence. The British Journal of General Practice : the Journal of the Royal College of General Practitioners 2011;61:e125-33.

83. Bryan S, Pinto Zipp G, Parasher R. The effects of yoga on psychosocial variables and exercise adherence: a randomized, controlled pilot study. Alternative Therapies in Health and Medicine 2012;18:50-9.

DISSERTATION CONCLUSION

CVD is a costly epidemic in the US and worldwide. Fortunately, many of the causal risk factors that underlie its pathophysiology are modifiable and substantial evidence exists on strategies for CVD prevention. These chapters evaluate the evidence and value of lifestyle strategies for CVD prevention.

Evidence on the beneficial effects of smoking cessation, exercise, and diet are well documented in published literature. Less, however, has been reported about yoga. I have shown in Chapters 1, 2 & 3 that yoga can be included in a broader discussion on interventions in preventive cardiology and the management of CVD risk factors. In Chapter 1, I presented what was known about the effectiveness of yoga on a variety of CVD risk factors and found that yoga does improve CVD risk factors like blood pressure and cholesterol. In Chapter 2, I showed the comparative effectiveness of four lifestyle strategies for reducing CVD risk and found that yoga, along with successful smoking cessation, were the best choices for reducing 10-year risk. In Chapter 3, I incorporated additional evidence on costs and changes in quality of life to assess the interventions on a societal and population level and found that yoga and aerobic exercise are not cost-effective from the societal perspective using a $100,00/QALY threshold but are cost-effective if the therapy is subsidized and individuals enjoy exercise.

Findings from this dissertation that can be used in clinical medicine to aid patient-provider discussions around CVD risk management. For the providers, knowledge of the comparative effectiveness of a wide array of preventive therapies that includes newer mind-body therapies like yoga can expand the clinical toolbox which they use to counsel patients. For patients, knowing they have non-pharmacological options for CVD risk management allows for more involvement and investment in their own medical decisions. If certain individuals are opposed to taking a pill like a statin or beta-blocker for risk factor improvement, they may be empowered and pleased to know that they have the option of going outside for a run or practicing yoga.

Research shows that when patients are given information and alternatives, they select strategies that are less invasive and less expensive than their physicians.[1] Importantly, these strategies can be

discussed between patient and provider at the primary care level, preventing possible costly expenditures at the secondary and tertiary care level. Simple, affordable tools primary care physicians have in their office like sphygmomanometers and risk charts can further promote inexpensive preventive care.

Additionally, the findings of the chapters can also be of value to healthcare providers and policymakers to consider in population-based guidelines and programs for CVD prevention. Small but clinically significant improvements in risk factors across the entire population can have greater impact than strategies targeting only higher risk patients. All risk groups can benefit from positive changes in diet, smoking status, and exercise.

While the evidence is strong and growing for these preventive interventions, barriers still exist for translation of this research into healthcare practice and policy guidelines.

First, one of the main reasons resistance remains may be due to dearth of evidence on the effectiveness of these strategies, particularly yoga. Although Chapter 1 synthesizes the available evidence for the effectiveness of yoga, there is only short-term data, which limits model conclusions and the strength with which a physician can prescribe this activity to a patient.

Yoga may not have gained as much traction as say, aerobic exercise and smoking cessation partly because it is a relatively new area of scientific study and partly because it is relatively difficult to assess methodologically. Trials cannot be blinded, participation can be low, and some of the psychosocial outcomes are challenging to measure. The variability and diversity in the practice of yoga makes it also difficult to compare across studies and generalize results.

Another barrier is that there is little data to take into account differences in patient population. There could be differing levels of uptake and adherence according to the patient characteristics, which could greatly impact the effectiveness. Findings from RCTs and meta-analyses may not be generalizable to other settings and populations.

Next, costs related to smoking cessation, exercise classes or yoga classes may be a barrier to access for patients who might benefit from such interventions. A finding from Chapter 3 was that if individuals experience an improvement in quality of life and are able to get reimbursed for their fitness

classes, then aerobic exercise and yoga are cost-effective options for improving cardiovascular health. Payers and employers who are interested in elective worksite wellness programs or reimbursable fitness policies should consider such initiatives based on the results of Chapter 3.

Lastly, incorporation of more specific parameters into cardiovascular health guidelines is needed as better evidence becomes available. For example, clear guidelines and recommendations exist on the proper "dosage" of exercise; the American College of Sports Medicine and the American Heart Association recommend 150 minutes per week of moderate intensity aerobic exercise, but do not give the recommended dosage of muscle strengthening activities, which includes yoga. Evidence is still lacking on the right dose or minimum effective dose of yoga to achieve cardiovascular benefits, which is further confounded by the various styles and components of yoga. These challenges, however, should not preclude yoga and other similar therapies from clinical conversations or guidelines but rather spur further research for better understanding of these preventive strategies.

FUTURE RESEARCH

Given limited evidence, further research is needed on the effectiveness of interventions, especially in the long-term, impact on quality of life, and mechanisms.

While this dissertation focused on how lifestyle interventions improved measurable clinical outcomes, more research is needed on their psychosocial outcomes and impact on quality of life. Research as shown that exercising and practicing yoga may have adjunctive benefits for other health behaviors and conditions such as healthy eating, better sleep quality, and better mental health measures.[2] Identification and assessment of this type of data that could boost health and well-being could be essential in the promotion of these lifestyle activities both in the public and amongst reimbursement agencies and payers.

Additionally, future studies and surveys should include a preference-based quality of life questionnaire to determine if the benefits of these activities do offset the associated monetary and time costs as presented in Chapter 3. This information on quality of life can spur further studies on the cost

effectiveness of exercise and yoga compared to other established practices. Additional evidence on cost-effectiveness can help support the interventions as complementary or stand-alone preventive care options and/or reimbursable expenses by third party payers.

Further research on the mechanism by which yoga conveys health benefits is needed. A recent systematic review states that yoga reduces sympathetic tone, increases parasympathetic tone, and improves cardiovagal function.[3] More research into the specific mechanisms and processes by which yoga confers health benefits could aid in increasing acceptance of yoga as a preventive therapy for CVD.

To conclude, despite some shortcomings of data, the clinical and economic case for yoga and other lifestyle interventions is encouraging. Clinical interventions and decisions can better align with the emerging evidence found in these chapters and other studies on which preventive interventions are most effective in improving cardiovascular health. The findings in this thesis support the incorporation of an array of lifestyle approaches in the management in CVD risk factors, with yoga among them.

REFERENCES

1. Wennberg JE. Outcomes research, cost containment, and the fear of health care rationing. The New England Journal of Medicine 1990;323:1202-4.

2. Ross A, Friedmann E, Bevans M, Thomas S. Frequency of yoga practice predicts health: results of a national survey of yoga practitioners. Evidence-based complementary and alternative medicine : eCAM 2012;2012:983258.

3. Innes KE, Bourguignon C, Taylor AG. Risk indices associated with the insulin resistance syndrome, cardiovascular disease, and possible protection with yoga: a systematic review. The Journal of the American Board of Family Practice / American Board of Family Practice 2005;18:491-519.

APPENDIX

Table 1.2. Search strategy for review

Database	Search terms
FOR SEARCH OF SYSTEMATIC REVIEWS	
PUBMED	(yoga[mesh] OR yoga[tiab]) AND systematic[sb]
EMBASE	('yoga'/de OR yoga:ab,ti) AND ([meta analysis]/lim OR [systematic review]/lim) OR ('yoga'/de OR yoga:ab,ti) AND (systematic OR systematically OR critical) AND (survey OR surveys OR overview OR overviews OR review OR reviews OR search OR searches searched OR searching OR handsearch OR hand NEAR/1 search* OR analysis OR critique OR appraisal)
CINAHL	MH "Yoga" OR AB yoga OR TI yoga Limiters: Publication Type: Meta Analysis, Systematic Review OR OR AB (systematic OR systematically OR critical) AND AB (survey OR surveys OR overview OR overviews OR review OR reviews OR search OR searches searched OR searching OR handsearch OR hand N1 search* OR analysis OR critique OR appraisal) AND (MH "Yoga" OR AB yoga OR TI yoga)
PSYCINFO	DE "Yoga" OR AB yoga OR TI yoga Methodology: systematic review OR TI (systematic OR systematically OR critical) AND TI (survey OR surveys OR overview OR overviews OR review OR reviews OR search OR searches searched OR searching OR handsearch OR hand N1 search* OR analysis OR critique OR appraisal) OR AB (systematic OR systematically OR critical) AND AB (survey OR surveys OR overview OR overviews OR review OR reviews OR search OR searches searched OR searching OR handsearch OR hand N1 search* OR analysis OR critique OR appraisal) AND DE "Yoga" OR AB yoga OR TI yoga
FOR SEARCH OF RANDOMIZED CONTROLLED TRIALS	
PUBMED	(yoga[mesh] OR yoga[tiab]) AND random*[tw] NOT systematic[sb] AND English[lang] AND ("2011/01/01"[PDAT] : "2013/12/31"[PDAT])
EMBASE	('yoga'/de OR yoga:ab,ti) AND random* NOT ([meta analysis]/lim OR [systematic review]/lim) AND [english]/lim AND [embase]/lim AND [1-1-2011]/sd
CINAHL	(MH "Yoga") OR TI yoga OR AB yoga AND random* [all fields]
COCHRANE CENTRAL	Yoga Limiters: Published Date: January 2011 – December 2013, Randomized Controlled Trials Language: English

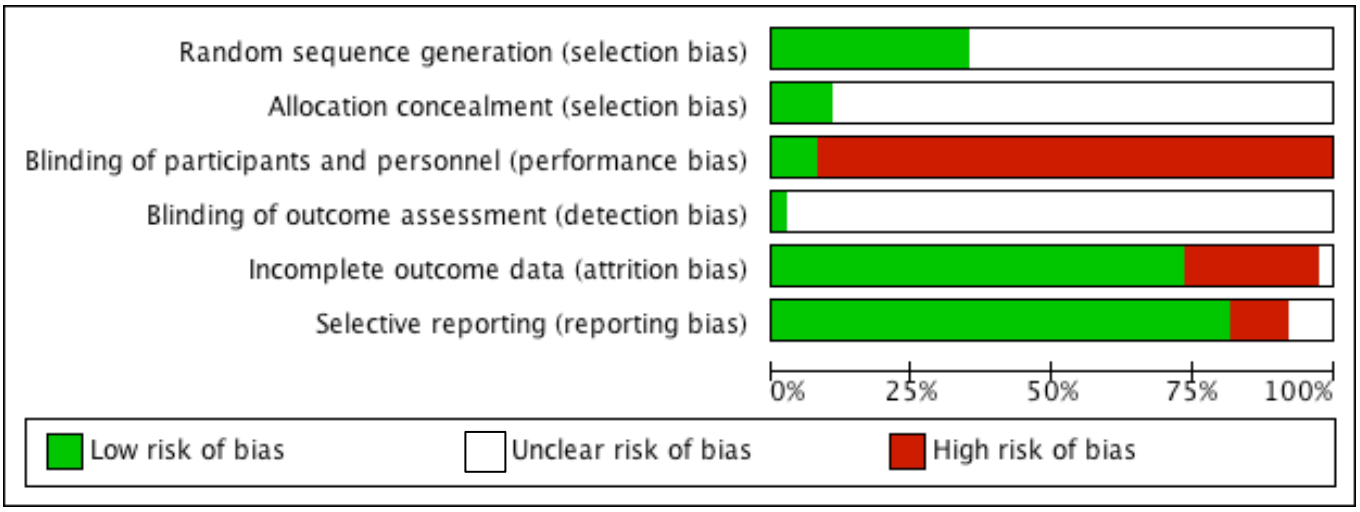


Figure 1.7 Risk of bias figure summarizing review authors' judgment of each risk of bias domain presented as percentages across all included studies.

Body weight (kg)

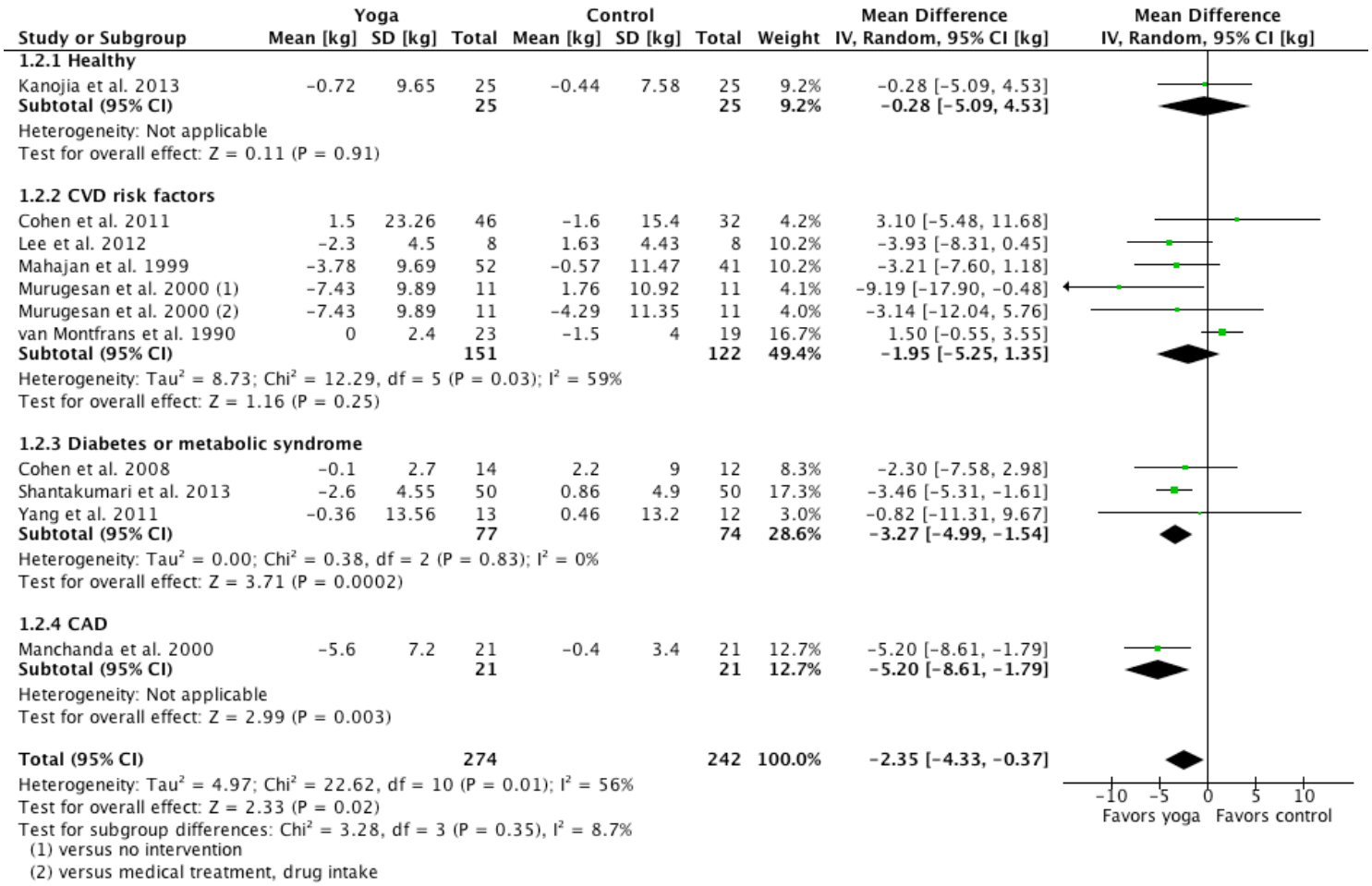
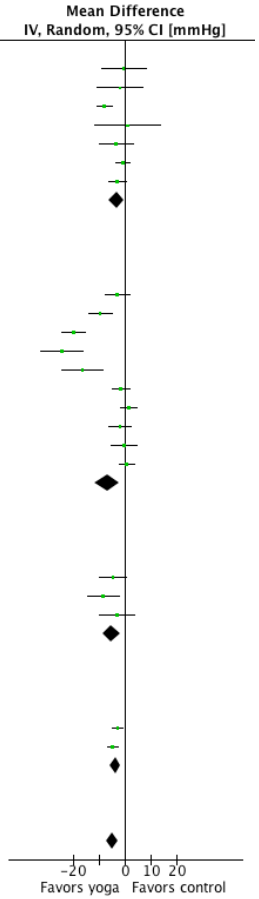


Figure 1.8. Forest plots of results of secondary outcomes – body weight, diastolic blood pressure, total cholesterol, triglycerides, fasting blood glucose, glycosylated hemoglobin, and heart rate.
Negative mean differences between groups favor the yoga intervention, positive mean differences favor control.

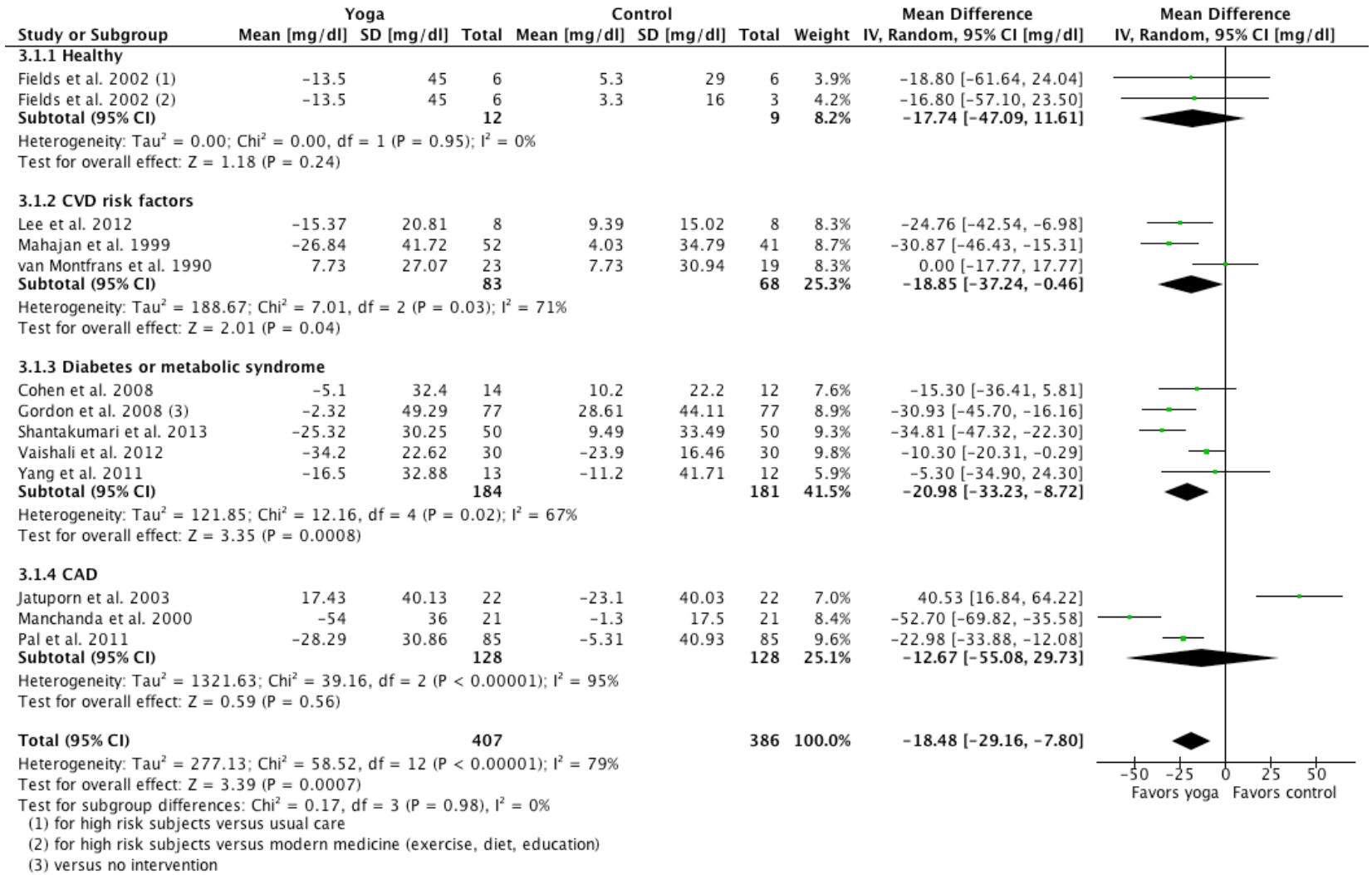
Diastolic blood pressure (mmHg)

Study or Subgroup	Yoga Mean [mmHg]	Yoga SD [mmHg]	Yoga Total	Control Mean [mmHg]	Control SD [mmHg]	Control Total	Weight	Mean Difference IV, Random, 95% CI [mmHg]
2.2.1 Healthy								
Fields et al. 2002 (1)	−7.5	7.8	6	−7	5.2	3	3.2%	−0.50 [−9.08, 8.08]
Fields et al. 2002	−7.5	7.8	6	−5.5	8.1	6	3.0%	−2.00 [−11.00, 7.00]
Kanojia et al. 2013	−1.44	4.7	25	6.56	5.67	25	5.6%	−8.00 [−10.89, −5.11]
Kim et al. 2012	0	10.2	27	−1	27.26	20	2.0%	1.00 [−11.55, 13.55]
Ray et al. 2001b	−4	11.85	28	−0.58	12.32	26	4.0%	−3.42 [−9.88, 3.04]
Wolever et al. 2012 (2)	−1.95	9.65	90	−1.17	9.69	96	5.6%	−0.78 [−3.56, 2.00]
Wolever et al. 2012 (3)	−1.95	9.65	90	1.03	11	53	5.3%	−2.98 [−6.55, 0.59]
Subtotal (95% CI)			**272**			**229**	**28.7%**	**−3.21 [−6.13, −0.29]**
Heterogeneity: $Tau^2 = 7.44$; $Chi^2 = 14.13$, df = 6 (P = 0.03); $I^2 = 58\%$								
Test for overall effect: Z = 2.16 (P = 0.03)								
2.2.2 CVD risk factors								
Cohen et al. 2011	−5	12.23	46	−2	9.8	32	4.7%	−3.00 [−7.90, 1.90]
Lee et al. 2012	−7.75	5.79	8	1.87	3.07	8	4.9%	−9.62 [−14.16, −5.08]
McCaffrey et al. 2005	−17.51	9.5	32	2.29	8.71	29	4.9%	−19.80 [−24.37, −15.23]
Murugesan et al. 2000 (4)	−26.27	9.55	11	−1.99	9.95	11	3.3%	−24.28 [−32.43, −16.13]
Murugesan et al. 2000 (5)	−26.27	9.55	11	−9.91	9.47	11	3.4%	−16.36 [−24.31, −8.41]
Saptharishi et al. 2009 (6)	−2	6.51	30	−0.4	6.79	30	5.4%	−1.60 [−4.97, 1.77]
Saptharishi et al. 2009 (7)	−2	6.51	30	−3.4	6.19	30	5.4%	1.40 [−1.81, 4.61]
Subramanian et al. 2011 (8)	−2.44	8.45	25	−0.5	7.2	25	4.9%	−1.94 [−6.29, 2.41]
Subramanian et al. 2011 (9)	−2.44	8.45	25	−2	9.9	25	4.6%	−0.44 [−5.54, 4.66]
van Montfrans et al. 1990	−2.4	4.7	23	−3.1	4.9	19	5.5%	0.70 [−2.22, 3.62]
Subtotal (95% CI)			**241**			**220**	**47.0%**	**−6.97 [−11.80, −2.13]**
Heterogeneity: $Tau^2 = 54.19$; $Chi^2 = 110.48$, df = 9 (P < 0.00001); $I^2 = 92\%$								
Test for overall effect: Z = 2.83 (P = 0.005)								
2.2.3 Diabetes or metabolic syndrome								
Cohen et al. 2008	−3	6.4	14	1.6	6.9	12	4.6%	−4.60 [−9.75, 0.55]
Hegde et al. 2013	−5.4	8.07	14	3	8.7	15	4.2%	−8.40 [−14.50, −2.30]
Yang et al. 2011	0.58	8.67	13	3.7	8.67	12	3.9%	−3.12 [−9.92, 3.68]
Subtotal (95% CI)			**41**			**39**	**12.6%**	**−5.41 [−8.82, −2.01]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.45$, df = 2 (P = 0.48); $I^2 = 0\%$								
Test for overall effect: Z = 3.11 (P = 0.002)								
2.2.4 CAD								
Pal et al. 2011	−8.85	7.92	85	−6.01	4.98	85	5.9%	−2.84 [−4.83, −0.85]
Pal et al. 2013	−3.27	8.01	129	1.51	8.69	129	5.8%	−4.78 [−6.82, −2.74]
Subtotal (95% CI)			**214**			**214**	**11.7%**	**−3.80 [−5.70, −1.90]**
Heterogeneity: $Tau^2 = 0.83$; $Chi^2 = 1.78$, df = 1 (P = 0.18); $I^2 = 44\%$								
Test for overall effect: Z = 3.91 (P < 0.0001)								
Total (95% CI)			**768**			**702**	**100.0%**	**−4.98 [−7.17, −2.80]**
Heterogeneity: $Tau^2 = 20.15$; $Chi^2 = 128.72$, df = 21 (P < 0.00001); $I^2 = 84\%$								
Test for overall effect: Z = 4.47 (P < 0.00001)								
Test for subgroup differences: $Chi^2 = 2.36$, df = 3 (P = 0.50), $I^2 = 0\%$								



(1) versus modern medicine
(2) versus Mindfulness at Work program
(3) versus educational resources
(4) versus no intervention
(5) versus medical treatment, drug intake
(6) versus control
(7) versus salt reduction diet
(8) versus no intervention
(9) versus salt reduction diet

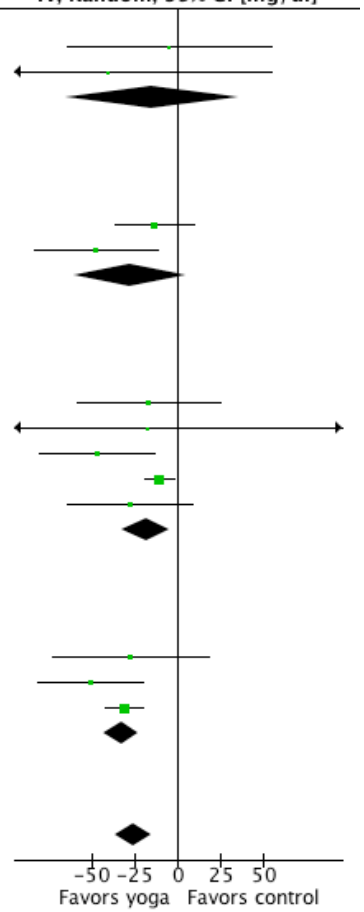
Total cholesterol (mg/dL)



(1) for high risk subjects versus usual care
(2) for high risk subjects versus modern medicine (exercise, diet, education)
(3) versus no intervention

Triglycerides (mg/dL)

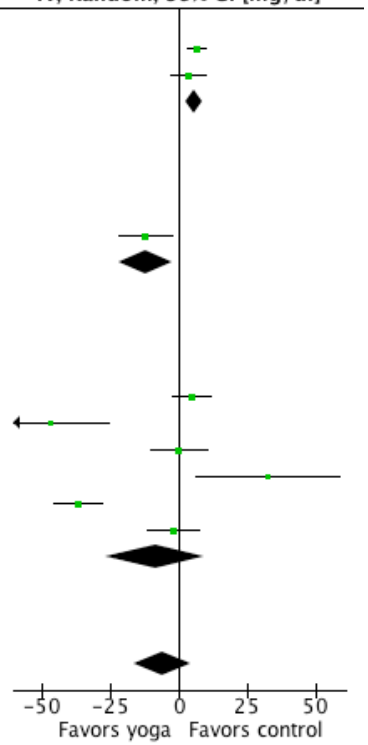
Study or Subgroup	Yoga Mean [mg/dl]	Yoga SD [mg/dl]	Yoga Total	Control Mean [mg/dl]	Control SD [mg/dl]	Control Total	Weight	Mean Difference IV, Random, 95% CI [mg/dl]
3.4.1 Healthy								
Fields et al. 2002 (1)	-26.5	73	6	-21.7	14	6	2.7%	-4.80 [-64.28, 54.68]
Fields et al. 2002 (2)	-26.5	73	6	14	66	3	1.1%	-40.50 [-135.31, 54.31]
Subtotal (95% CI)			**12**			**9**	**3.9%**	**-14.88 [-65.26, 35.50]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.39$, df = 1 (P = 0.53); $I^2 = 0\%$								
Test for overall effect: Z = 0.58 (P = 0.56)								
3.4.2 CVD risk factors								
Lee et al. 2012	-4.5	22.79	8	9	24.33	8	11.8%	-13.50 [-36.60, 9.60]
Mahajan et al. 1999	-51.26	90.38	52	-3.96	85.94	41	6.4%	-47.30 [-83.29, -11.31]
Subtotal (95% CI)			**60**			**49**	**18.2%**	**-27.47 [-60.09, 5.15]**
Heterogeneity: $Tau^2 = 333.15$; $Chi^2 = 2.40$, df = 1 (P = 0.12); $I^2 = 58\%$								
Test for overall effect: Z = 1.65 (P = 0.10)								
3.4.3 Diabetes or metabolic syndrome								
Cohen et al. 2008	-8.8	59.8	14	7.9	49.1	12	5.0%	-16.70 [-58.57, 25.17]
Gordon et al. 2008 (3)	-9.74	878.27	77	7.97	874.41	77	0.1%	-17.71 [-294.53, 259.11]
Shantakumari et al. 2013	-21.77	38.01	50	25.17	113.37	50	7.3%	-46.94 [-80.08, -13.80]
Vaishali et al. 2012	-18.6	14.21	30	-8.07	18.23	30	24.6%	-10.53 [-18.80, -2.26]
Yang et al. 2011	-11.5	44.19	13	16	48	12	6.3%	-27.50 [-63.76, 8.76]
Subtotal (95% CI)			**184**			**181**	**43.3%**	**-18.61 [-32.61, -4.60]**
Heterogeneity: $Tau^2 = 63.54$; $Chi^2 = 5.00$, df = 4 (P = 0.29); $I^2 = 20\%$								
Test for overall effect: Z = 2.60 (P = 0.009)								
3.4.4 CAD								
Jatuporn et al. 2003	-38.6	93.3	22	-11.4	57.23	22	4.3%	-27.20 [-72.94, 18.54]
Manchanda et al. 2000	-45.7	66	21	4.8	27.3	21	8.2%	-50.50 [-81.05, -19.95]
Pal et al. 2011	-38.04	37.39	85	-7.33	34.82	85	22.1%	-30.71 [-41.57, -19.85]
Subtotal (95% CI)			**128**			**128**	**34.6%**	**-32.66 [-42.64, -22.67]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.49$, df = 2 (P = 0.48); $I^2 = 0\%$								
Test for overall effect: Z = 6.41 (P < 0.00001)								
Total (95% CI)			**384**			**367**	**100.0%**	**-25.89 [-36.19, -15.60]**
Heterogeneity: $Tau^2 = 94.21$; $Chi^2 = 18.29$, df = 11 (P = 0.07); $I^2 = 40\%$								
Test for overall effect: Z = 4.93 (P < 0.00001)								
Test for subgroup differences: $Chi^2 = 2.82$, df = 3 (P = 0.42), $I^2 = 0\%$								



(1) for high risk subjects versus usual care
(2) for high risk subjects versus modern medicine (exercise, diet, education)
(3) versus no intervention

Fasting blood glucose (mg/dL)

Study or Subgroup	Yoga Mean [mg/dl]	Yoga SD [mg/dl]	Yoga Total	Control Mean [mg/dl]	Control SD [mg/dl]	Control Total	Weight	Mean Difference IV, Random, 95% CI [mg/dl]
4.1.2 Healthy								
Fields et al. 2002 (1)	1.3	3.6	6	-5	2	6	12.9%	6.30 [3.00, 9.60]
Fields et al. 2002 (2)	1.3	3.6	6	-2	5.2	3	12.4%	3.30 [-3.25, 9.85]
Subtotal (95% CI)			**12**			**9**	**25.3%**	**5.69 [2.75, 8.64]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.64$, df = 1 (P = 0.42); $I^2 = 0\%$								
Test for overall effect: Z = 3.79 (P = 0.0001)								
4.1.3 CVD risk factors								
Lee et al. 2012	-6.5	9.5	8	5.75	10.79	8	11.7%	-12.25 [-22.21, -2.29]
Subtotal (95% CI)			**8**			**8**	**11.7%**	**-12.25 [-22.21, -2.29]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.41 (P = 0.02)								
4.1.4 Diabetes or metabolic syndrome								
Cohen et al. 2008	2.6	9.3	14	-2	9.3	12	12.3%	4.60 [-2.57, 11.77]
Gordon et al. 2008 (3)	-62.82	70.3	77	-15.84	65.9	77	8.4%	-46.98 [-68.50, -25.46]
Hegde et al. 2013	-3.6	13.59	14	-3.6	14.73	15	11.6%	0.00 [-10.31, 10.31]
Monroe et al. 1992	10.8	28.8	11	-21.6	32.4	10	7.1%	32.40 [6.08, 58.72]
Vaishali et al. 2012	-47.83	14.28	30	-10.8	20.21	30	11.9%	-37.03 [-45.89, -28.17]
Yang et al. 2011	2.7	11.6	13	4.6	12.64	12	11.8%	-1.90 [-11.43, 7.63]
Subtotal (95% CI)			**159**			**156**	**63.0%**	**-8.77 [-26.77, 9.23]**
Heterogeneity: $Tau^2 = 448.69$; $Chi^2 = 78.68$, df = 5 (P < 0.00001); $I^2 = 94\%$								
Test for overall effect: Z = 0.96 (P = 0.34)								
Total (95% CI)			**179**			**173**	**100.0%**	**-5.91 [-16.32, 4.50]**
Heterogeneity: $Tau^2 = 216.25$; $Chi^2 = 113.74$, df = 8 (P < 0.00001); $I^2 = 93\%$								
Test for overall effect: Z = 1.11 (P = 0.27)								
Test for subgroup differences: $Chi^2 = 13.43$, df = 2 (P = 0.001), $I^2 = 85.1\%$								



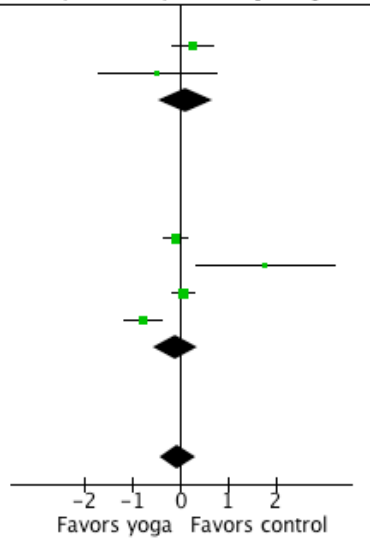
(1) for high risk subjects versus usual care
(2) for high risk subjects versus modern medicine (exercise, diet, education)
(3) versus no intervention

Glycosylated hemoglobin (HbA1c, %Hb)

Study or Subgroup	Yoga Mean [% Hb]	Yoga SD [% Hb]	Yoga Total	Control Mean [% Hb]	Control SD [% Hb]	Control Total	Weight	Mean Difference IV, Random, 95% CI [% Hb]
4.2.1 Healthy								
Fields et al. 2002 (1)	0.63	0.32	6	0.38	0.45	6	19.5%	0.25 [-0.19, 0.69]
Fields et al. 2002 (2)	0.63	0.32	6	1.13	1.07	3	6.7%	-0.50 [-1.74, 0.74]
Subtotal (95% CI)			**12**			**9**	**26.2%**	**0.11 [-0.47, 0.68]**
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 1.25$, df = 1 (P = 0.26); $I^2 = 20\%$								
Test for overall effect: Z = 0.36 (P = 0.72)								
4.2.2 Diabetes or metabolic syndrome								
Hegde et al. 2013	-0.1	0.4	14	0	0.3	15	23.8%	-0.10 [-0.36, 0.16]
Monroe et al. 1992	1.56	1.8	11	-0.2	1.6	10	5.2%	1.76 [0.31, 3.21]
Skoro-Kondza et al. 2009	-0.02	0.55	29	-0.07	0.3	30	24.4%	0.05 [-0.18, 0.28]
Vaishali et al. 2012	-1.16	0.75	30	-0.38	0.84	30	20.4%	-0.78 [-1.18, -0.38]
Subtotal (95% CI)			**84**			**85**	**73.8%**	**-0.09 [-0.56, 0.38]**
Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 18.88$, df = 3 (P = 0.0003); $I^2 = 84\%$								
Test for overall effect: Z = 0.38 (P = 0.70)								
Total (95% CI)			**96**			**94**	**100.0%**	**-0.06 [-0.43, 0.31]**
Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 21.61$, df = 5 (P = 0.0006); $I^2 = 77\%$								
Test for overall effect: Z = 0.34 (P = 0.74)								
Test for subgroup differences: $Chi^2 = 0.27$, df = 1 (P = 0.60), $I^2 = 0\%$								

(1) for high risk subjects versus usual care

(2) for high risk subjects versus modern medicine (exercise, diet, education)



Heart rate (beats/min)

Study or Subgroup	Yoga Mean [beats/min]	Yoga SD [beats/min]	Yoga Total	Control Mean [beats/min]	Control SD [beats/min]	Control Total	Weight	Mean Difference IV, Random, 95% CI [beats/min]
5.1.1 Healthy								
Cusumano et al. 1992	-3.22	9.6	45	-4.13	7.42	45	12.8%	0.91 [-2.64, 4.46]
Kanojia et al. 2013	-6.88	2.98	25	6.2	4.15	25	13.6%	-13.08 [-15.08, -11.08]
Kim et al. 2012	0	9.85	27	0.3	10.72	20	11.0%	-0.30 [-6.29, 5.69]
Ray et al. 2001b	-2.39	10.07	28	-0.86	9.54	26	11.6%	-1.53 [-6.76, 3.70]
Subtotal (95% CI)			**125**			**116**	**49.0%**	**-3.66 [-12.19, 4.87]**
Heterogeneity: $Tau^2 = 70.74$; $Chi^2 = 61.10$, df = 3 ($P < 0.00001$); $I^2 = 95\%$								
Test for overall effect: $Z = 0.84$ ($P = 0.40$)								
5.1.2 CVD risk factors								
Cohen et al. 2011	-2	12.23	46	-2	8.84	32	12.0%	0.00 [-4.68, 4.68]
McCaffrey et al. 2005	-11.85	8.88	32	4.22	8.87	29	12.2%	-16.07 [-20.53, -11.61]
Subtotal (95% CI)			**78**			**61**	**24.2%**	**-8.05 [-23.80, 7.70]**
Heterogeneity: $Tau^2 = 123.69$; $Chi^2 = 23.76$, df = 1 ($P < 0.00001$); $I^2 = 96\%$								
Test for overall effect: $Z = 1.00$ ($P = 0.32$)								
5.1.3 CAD								
Pal et al. 2011	-4.17	10.64	85	2.32	7.12	85	13.3%	-6.49 [-9.21, -3.77]
Pal et al. 2013	-2.5	8.79	129	1.78	9.13	129	13.5%	-4.28 [-6.47, -2.09]
Subtotal (95% CI)			**214**			**214**	**26.8%**	**-5.23 [-7.37, -3.09]**
Heterogeneity: $Tau^2 = 0.86$; $Chi^2 = 1.54$, df = 1 ($P = 0.21$); $I^2 = 35\%$								
Test for overall effect: $Z = 4.78$ ($P < 0.00001$)								
Total (95% CI)			**417**			**391**	**100.0%**	**-5.27 [-9.55, -1.00]**
Heterogeneity: $Tau^2 = 33.91$; $Chi^2 = 94.11$, df = 7 ($P < 0.00001$); $I^2 = 93\%$								
Test for overall effect: $Z = 2.42$ ($P = 0.02$)								
Test for subgroup differences: $Chi^2 = 0.25$, df = 2 ($P = 0.88$), $I^2 = 0\%$								

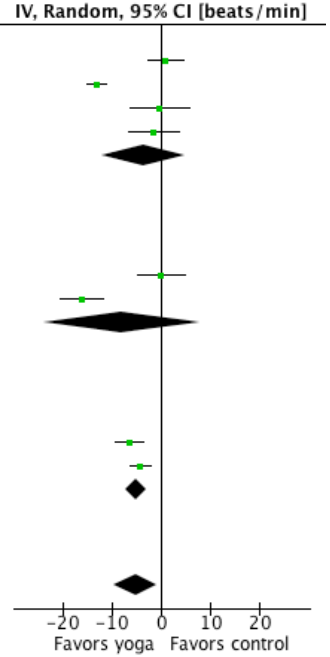
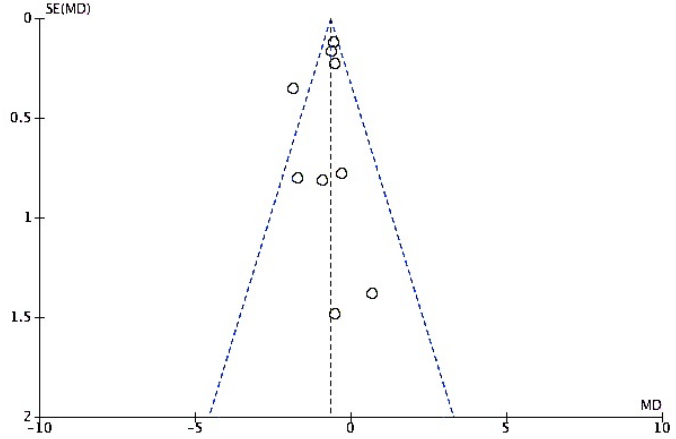


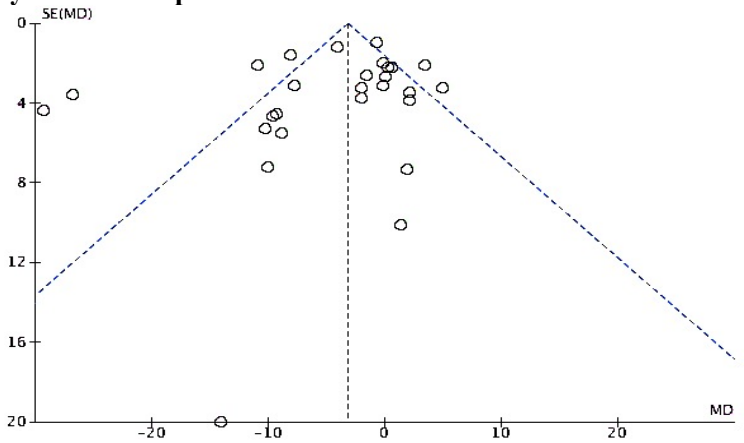
Table 1.3. Mean differences by control group

Outcome	Mean difference yoga v. control [95% CI] Non-exercise controls	All controls
Primary		
BMI (kg/m^2)	-0.77 [-1.09 to -0.44]	-0.75 [-1.07 to -0.42]
SBP (mmHg)	-5.21 [-8.01 to -2.42]	-4.45 [-6.99 to -1.90]
LDL-C (mg/dL)	-12.14 [-21.80 to -2.48]	-11.29 [-20.29 to -2.28]
HDL-C (mg/dL)	3.20 [1.86 to 4.54]	2.87 [1.47 to 4.26]
Secondary		
Body weight (kg)	-2.32 [-4.33 to -0.37]	-1.98 [-3.62 to -0.34]
DBP (mmHg)	-4.98 [-7.17 to -2.80]	-4.31 [-6.43 to -2.18]
TC (mg/dL)	-18.48 [-29.16 to -7.80]	-17.00 [-27.29 to -6.71]
TG (mg/dL)	-25.89 [-36.19 to -15.60]	-25.59 [-35.50 to -15.67]
FBG (mg/dL)	-5.91 [-16.32 to 4.50]	-5.82 [-15.64 to 4.00]
HbA1c (%Hb)	-0.06 [-0.24 to 0.11]	-0.06 [-0.24 to 0.11]
Heart rate (beats/min)	-5.27 [-9.55 to -1.00]	-4.05 [-7.56 to -0.54]

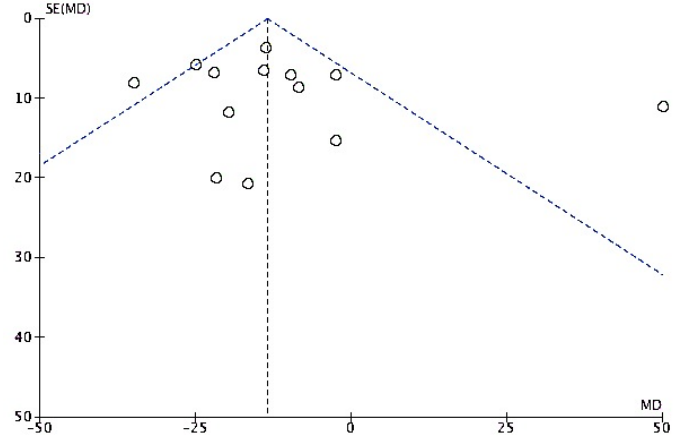
BMI



Systolic blood pressure



Low-density lipoprotein cholesterol



High-density lipoprotein cholesterol

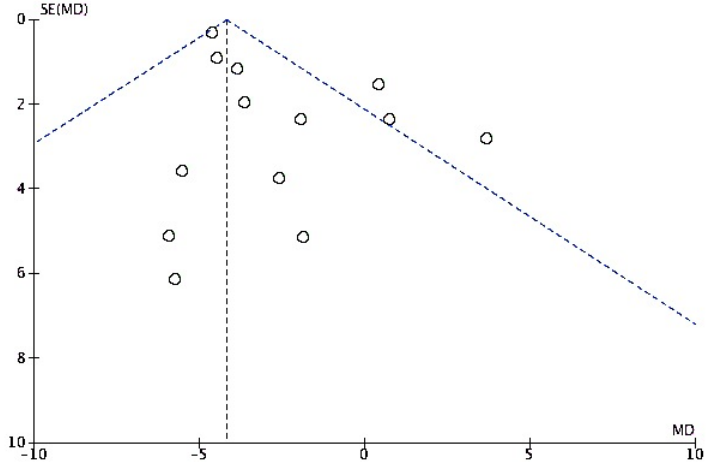


Figure 1.9. Funnel plots assessing publication bias.

CHAPTER 2

Supplemental data. Risk equation calculation

Example of individual 10 year CVD risk calculation with and without interventions
The hypothetical profile is profile 3 in Table 3, a white 45 year-old male with total cholesterol of 200 mg/dL, HDL-C of 40 mg/dL, and a treated systolic blood pressure of 160 mmHg. Regression coefficients are based on those published in Goff et al. (2013).

General equation without intervention for smokers:

$$1 - S_{10} * \exp\,[12.344\ln(age) + 1.797\ln(SBP) + 11.853\ln(TC) - 7.99\ln(HDL) + 7.837y \\ -2.664\ln(age)\ln(TC) + 1.769\ln(age)\ln(HDL) - 1.795\ln(age) - 61.18]$$

where S_{10} is the baseline survival rate at 10 years, or 0.9144 and y is 1 for smoking and 0 for not smoking

Plugging in numbers gives

$$1 - 0.9144 * \exp[12.344\,ln(45) + 1.797\,ln(160) + 11.853\,ln(200) - 7.99\,ln(40) + 7.837(1) \\ - 2.664\,ln(45)\,ln(200) + 1.769\,ln(45)\,ln(40) - 1.795\,ln(45) - 61.18] \\ = \ 12.17\%\ risk$$

This is the baseline 10-year CVD risk.

With group therapy smoking cessation:

$$1 - S_{10}\exp\,[12.344\ln(age) + 1.797\ln(SBP) + 11.853\ln(TC) - 7.99\ln(HDL) + 7.837y \\ -2.664\ln(age)\ln(TC) + 1.769\ln(age)\ln(HDL) - 1.795\ln(age) - 61.18]$$

Plugging in numbers gives

$$1 - S_{10}\exp\,[12.344\ln(45) + 1.797\ln(160) + 11.853\ln(200) - 7.99\ln(40) + 7.837(0) \\ -2.664\ln(45)\ln 200 + 1.769\ln(45)\ln(40) - 1.795\ln(45) - 61.18] \\ = 4.64\%\ risk$$

This is the baseline risk for a non-smoker with the same clinical profile. Note that the value 7.837 is multiplied by 0 for a non-smoker and disappears in the equation.

The potential gain in risk reduction from becoming a non-smoker is $12.17\% - 4.64\% = 7.53\%$

However, not everyone who attempts to quit smoking will succeed. Based on published literature, with an unaided quit probability of 0.050 and a relative risk of 1.98, the probability of quitting with group therapy is 0.099, or 9.9%.

Thus, based on intention-to-treat calculations, the risk reduction for group therapy with smoking is

$$(0.099 - 0.050) * 7.53\% = 0.37\%$$

The general equation with the other interventions:

$$1 - S_{10} * \exp\,[12.344\ln(age) + 1.797\ln(SBP + SBP\ change) + 11.853\ln(TC + TC\ change) - 7.99\ln(HDL + HDL\ change) + 7.837y - 2.664\ln(age)\ln(TC + TC\ change) + 1.769\ln(age)\ln(HDL) + HDL\ change - 1.795\ln(age) - 61.18]$$

With Mediterranean diet:

$$1 - 0.9144 * \exp[12.344\ ln(45) + 1.797\ ln(160 - 1.70) + 11.853\ ln(200 - 7.35) - 7.99\ ln(40 + 0.94) + 7.837(1) - 2.664\ ln(45)\ ln(200 - 7.35) + 1.769\ ln(45)\ ln(40 + 0.94) - 1.795\ ln(45) - 61.18] = 10.95\%\ risk$$

With walking as aerobic exercise:

$$1 - 0.9144 * \exp[12.344\ ln(45) + 1.797\ ln(160 - 3.80) + 11.853\ ln(200 - 3.48) - 7.99\ ln(40 + 2.32) + 7.837(1) - 2.664\ ln(45)\ ln(200 - 3.48) + 1.769\ ln(45)\ ln(40 + 2.32) - 1.795\ ln(45) - 61.18] = 10.62\%\ risk$$

With yoga:

$$1 - 0.9144 * \exp[12.344\ ln(45) + 1.797\ ln(160 - 4.45) + 11.853\ ln(200 - 17) - 7.99\ ln(40 + 2.87) + 7.837(1) - 2.664\ ln(45)\ ln(200 - 17) + 1.769\ ln(45)\ ln(40 + 2.87) - 1.795\ ln(45) - 61.18] = 9.25\%\ risk$$

Table 2.5. Alternative estimates for effectiveness of lifestyle interventions on reducing CVD risk through changes in risk factors.

	Impact of Lifestyle Changes on Risk Factor due to Interventions			
Risk factor	**Physician advice for smoking cessation**	**Mediterranean diet**	**Aerobic exercise**	**Yoga**
Smoking (% quitting)	8.30* (7.10, 9.70) [28]	--	--	--
Systolic blood pressure (mmHg)	--	-1.70 (-3.35, -0.05) [29]	-3.84 (-4.97, -2.72) [34]	-5.85 (-8.81, -2.89) [25]
Total cholesterol (mg/dl)	--	-6.19‡ (-10.05, -2.32) [32]	1.16 (-9.28, 11.99) [33]	-13.09 (-19.60, -6.59) [25]
HDL cholesterol (mg/dl)	--	0.94 (-1.93, 3.82) [29]	2.32 (1.16, 3.87) [33]	2.94 (0.57, 5.31) [25]

* Probability of quitting smoking with physical advice compared to quitting without intervention. Assume same unassisted rate as base case (5%).[28] The relative proportion of quitting (relative risk) is 1.66 for physician advice versus control (95% CI: 1.42-1.94).[31]

‡ Only this parameter was changed due to data availability.

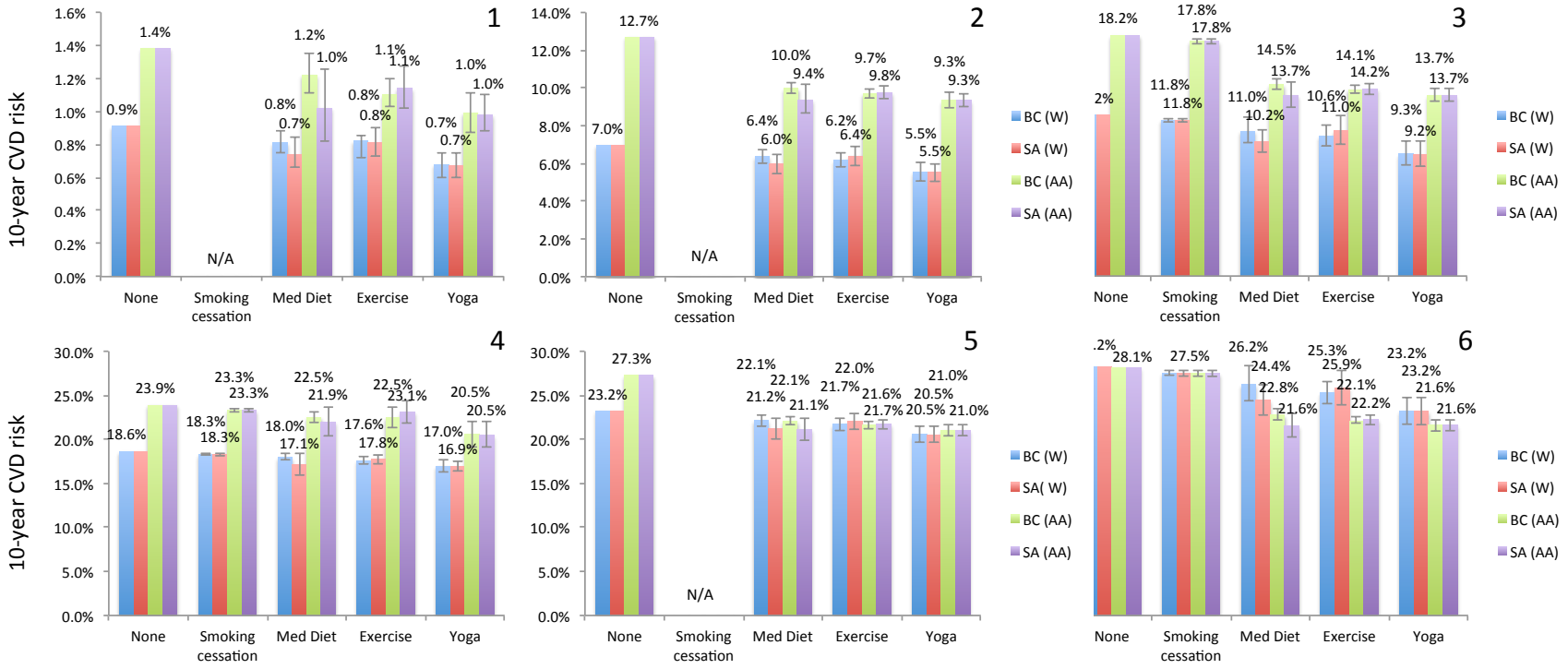


Figure 2.17. Sensitivity analysis with alternate meta-analyses, shown by hypothetical profile (y-axes represent 10-year CVD risk, x-axes represent interventions). Note that the optimal intervention with the lowest 10-year risk with the alternate estimates (red and purple bars) remains the same as that in the base-case (blue and green bars) for each profile and race.

Abbreviations: CVD: cardiovascular disease, Med diet: Mediterranean diet, BC: base case, SA: sensitivity analysis, W: white, AA: African-American, N/A: not applicable

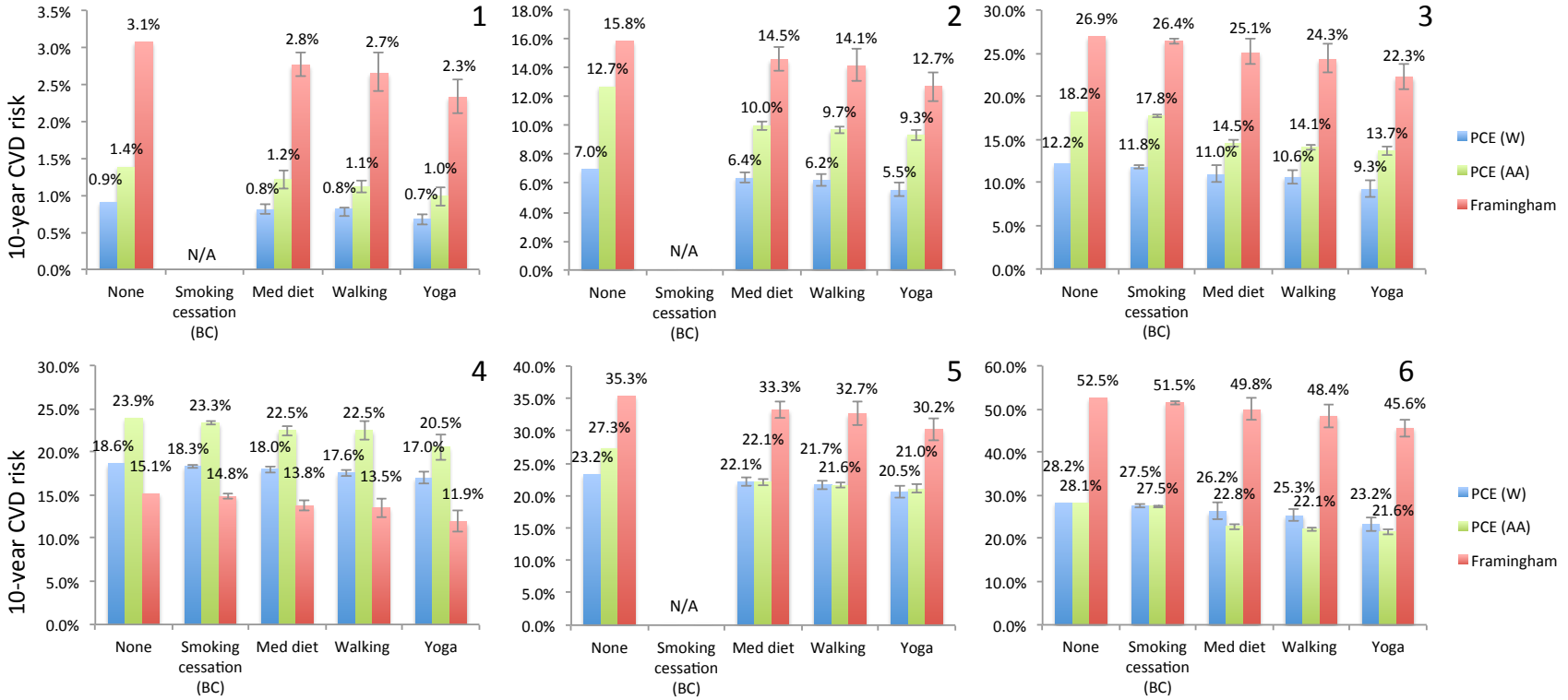


Figure 2.18. Sensitivity analysis with Framingham risk equations, shown by hypothetical profile (y-axes represent 10-year CVD risk, x-axes represent interventions). Note that the optimal intervention with the lowest 10-year risk with the Framingham equations (red bars) remains the same as that in the base-case (blue and green bars) for each profile.

Abbreviations: CVD: cardiovascular disease, Med diet: Mediterranean diet, PCE: Pooled Cohort Equations, W: white, AA: African-American, N/A: not applicable